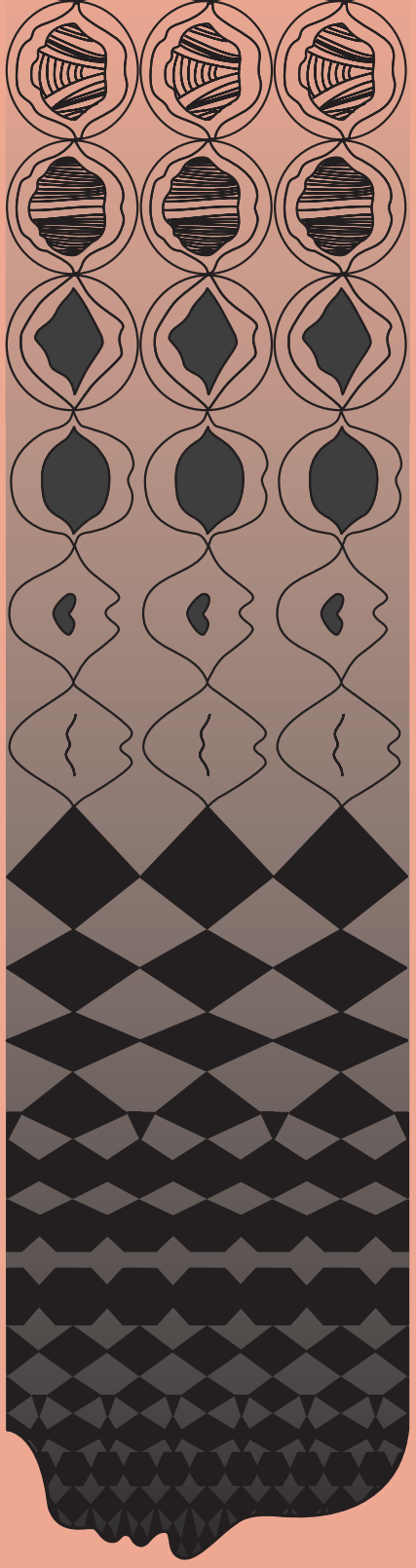

Prognostic Models and Personalized Counselling

Towards Shared Decision Making in Head and Neck Oncology

Emilie A. C. Dronkers

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Prognostic models and personalized counselling; towards shared decision making in head and neck oncology

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Prognostic Models and Personalized Counselling
Towards Shared Decision Making in Head and Neck Oncology

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in de hoofd-hals oncologie
Op weg naar gezamenlijke besluitvorming

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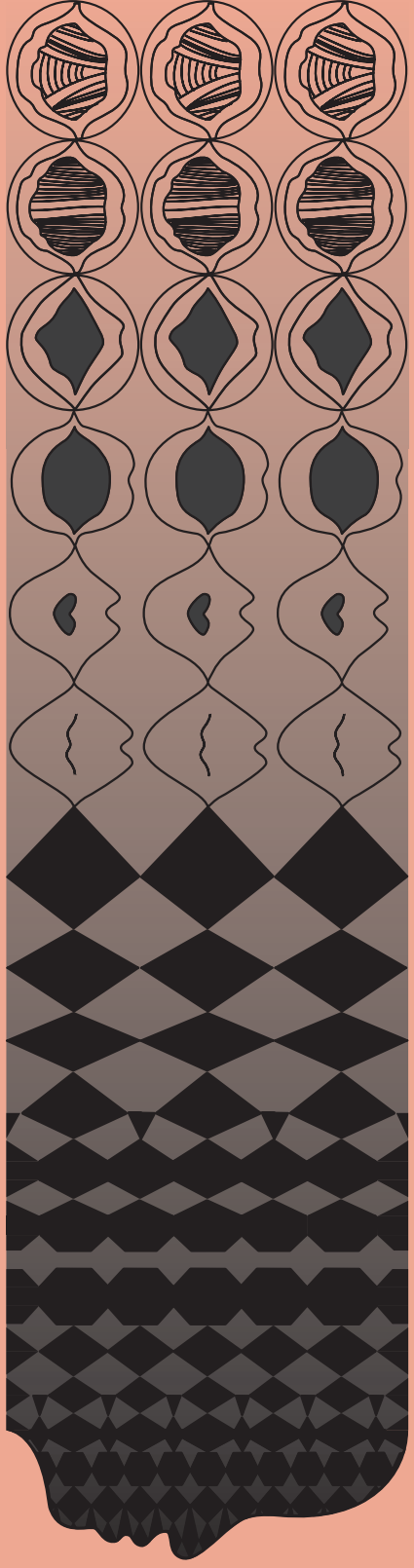
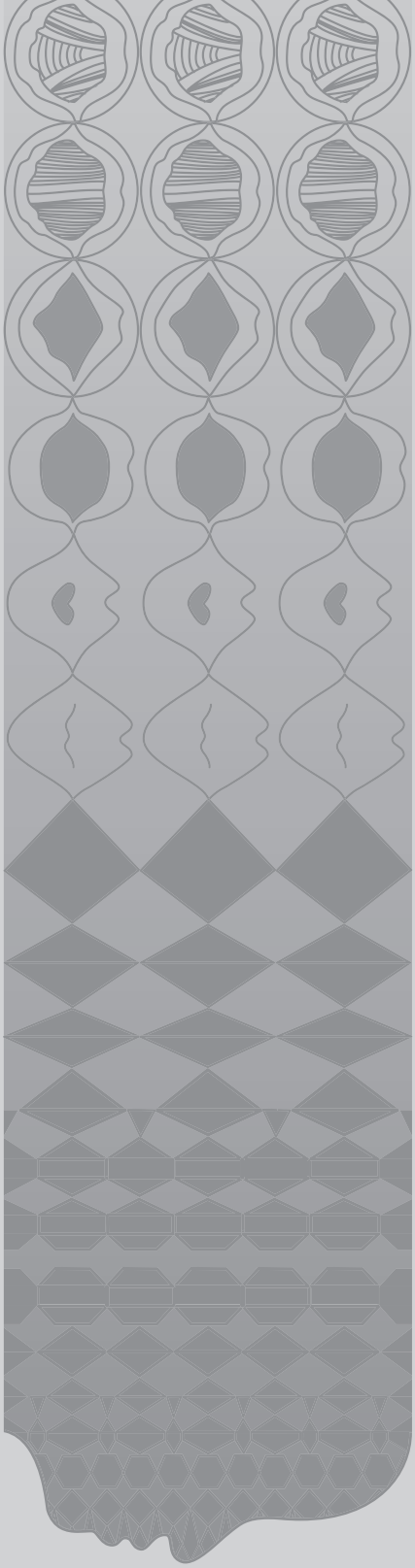


Part I

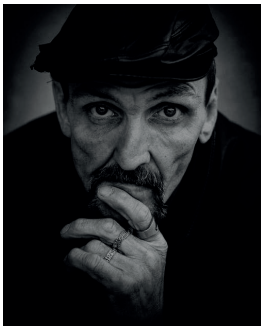
Introduction



Prologue

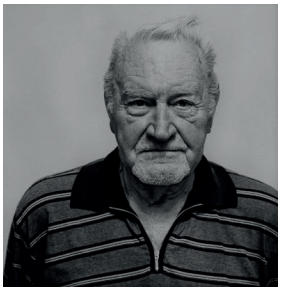
WHY WE STARTED THIS RESEARCH

Mrs. A., an 83-year-old female diagnosed with a cT1bN0M0 carcinoma of the vocal cords. She is widowed and lives in a service flat together with her cat. She loves to sing in a choir together with her friends. During the last years she started to use a rollator due to mobility problems, and she has showed early signs of dementia. She smokes a package of cigarettes each day. Mrs. A. wishes to continue singing in her choir, and she is concerned that treatment of the tumor will withhold her from doing that. She wants her doctor to choose the best treatment for her, as she says "he's the expert".



Mr. B., a 64-year-old male with a large carcinoma of the oral cavity with metastasis to the lymph nodes of the right neck (cT4aN2bM0). He works as a dock worker in the international port of Rotterdam. Mr. B. smokes hand rolled tobacco since the age of 13, and developed alcohol abuse since his wife left him. Every day he drinks 7 half liter cans of beer. He also suffers from type 2 diabetes and had a minor stroke last year. He is proud to avoid doctors' visits as much as possible since he doesn't like other people interfering with his life or pointing out the consequences of his lifestyle. He therefore doesn't want to know anything about survival chances, "let those doctors do their jobs, I'll do mine".

Mrs. C., a 48-year-old female with an HPV (Human Papilloma Virus) related oropharyngeal tumor with metastasis to the neck (cT2N2M0). She has a husband and two kids, boy and girl, aged 16 and 19. She works as an accountant and loves swimming. Mrs. C. consequently seeks to maintain a healthy lifestyle: she has never smoked and rarely drinks alcohol. Besides some issues with hay fever and eczema, she has no other comorbidities. Mrs. C. is anxious about her diagnosis and feels insecure about all that is about to happen. She wants to be informed in detail about her chances of complete cure and the side-effects of the treatment, in order to make a well-considered treatment decision.



Mr. D., a 72-year-old male with a recurrent rT2N1M1 hypopharyngeal carcinoma with metastasis to the lungs. He used to work as a butcher and ran his own store together with his wife for over 40 years. He and his wife have already gone through a lot during the treatment of his primary tumor, including a feeding tube, severe dyspnea and multiple admissions to the hospital. They wish to enjoy each other's company for as long as possible and Mr. D. places equal importance to quality and quantity of life. He wants to be informed about how his life will look like in the forthcoming months.

Despite their differences, all patients do have the same kind of questions at some point of time during their disease trajectory:

"What are my chances to survive?"

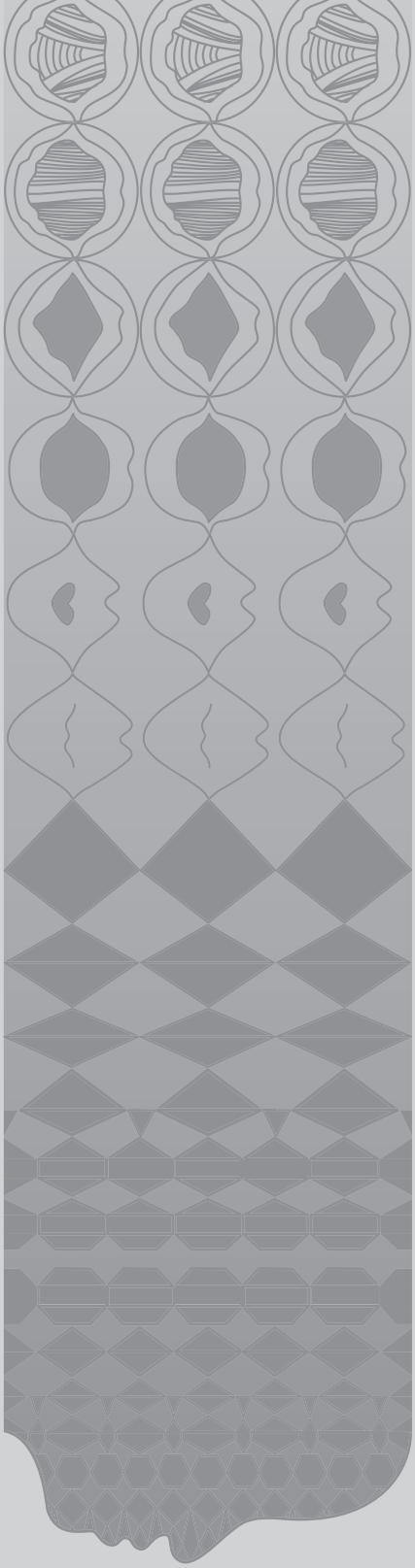
"If I am to proceed with the major surgery or radiotherapy the doctor proposes, what will be the consequences for the quality of my life?"

"Could I imagine living without being able to talk or swallow?"

"What does my diagnosis and upcoming treatment imply for my family and loved ones?"

"How can I best make clear to my doctor what's important to me in life?"

"Do I actually have a choice?"



1

General introduction

THE IMPACT OF BEING DIAGNOSED WITH HEAD AND NECK CANCER

Facts about head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) arises from the epithelium of the head and neck region and frequently manifests as locally advanced disease. Major risk factors are tobacco smoking, alcohol consumption, human papilloma virus (HPV) and Epstein-Barr virus (EBV). The worldwide incidence of these tumors in 2012 was over 680,000 cases, resulting in 4.9% of all malignancies. Despite improvement in treatment, 5-year overall survival rates remain around 50-60%. The majority of HNSCC patients is diagnosed at an advanced stage, and this accounts for the high death rate.[1-3] In the Netherlands annually approximately 2,700 patients are diagnosed with HNSCC and around 800 patients die due to this disease.[1] The peak incidence of HNSCC occurs between ages of 50 and 80, and approximately 25% of HNSCC are diagnosed in elderly patients (>70 years).[4] HNSCC patients are, due to the high incidence of tobacco and alcohol abuse, prone to have significant comorbidity, especially in the respiratory and cardiovascular systems. Comorbidity is an important prognostic factor for overall survival and may influence the choice of treatment.[5-6]

HPV-related HNSCC is a distinct entity within the group of HNSCC.[7] HPV is aetiologically linked to the development of oropharyngeal squamous cell carcinoma (OPSCC). The incidence is increasing over the last decades with varying ranges from 20 -70% in Europe and up to 90% in the United States.[8-10] Patients with HPV-related OPSCC have better locoregional control and superior 5-year survival rates after treatment.[11]

In the majority of cases, treatment for HNSCC consists of surgery, radiotherapy, chemotherapy and combinations of these modalities. All types of treatment are associated with high morbidity that often compromises vital functions, including respiration, swallowing and speech. Despite this multimodality approach, 30%–60% develops local recurrences, and 20%–30% develop distant metastases.[12]

Impact on quality of life

Both disease and its treatment can lead to significant disfigurement and dysfunction with subsequently psychosocial complaints.[13] HNSCC patients experience among the highest rates of major depressive disorders of all oncologic patients, with prevalence rates as high as 46%.[14-15] Also, treatment-related side effects, such as altered speech or swallowing problems, can have an enormous impact on patient's daily life. These side-effects are immediately noticeable in social settings and can negatively affect quality of life, increase levels of psychological distress and put pressure on the spousal relationship.[16-19] Furthermore, conventional treatment with (adjuvant) radiotherapy or chemotherapy may lead to

complications associated with late toxicity, up to 10 or 20 years after treatment. Given the superior prognosis of HPV-related HNSCC, long term quality of life is also at stake in this group of patients.[20] The importance of pre- and post-treatment quality of life in patients with HNSCC is well-recognized in literature.[21,22] Patients' quality of life decreases during treatment, but it starts improving 3-6 months after treatment. Pre-treatment quality of life is associated with survival.[23,24] Good physical functioning and psychological coping abilities are also predictors of survival and disease recurrence.[17]

Impact on decision making

Quality of life research has helped clinicians to become more patient-focused, which is especially important during decision making. Quality of life considerations may affect treatment choices, especially for treatments with similar survival rates.[25] In 2000, a publication by List et al showed that patients' priorities lie in achieving cure, followed by survival for as long as possible.[26] This understanding has been used to support the development of more aggressive treatment modalities, in the hope that those would further improve survival. A recent publication on priorities, concerns and regrets among patients with HNSCC shows that patients still prioritize cure as their most important treatment goal, followed by survival and then followed by quality of life issues. On the other hand, this study also shows that patients who are treated with different treatment modalities suffer from decisional regret regarding their treatment, although they have been cured.[27] Given the consequences of treatment, cure or survival may not always be the main priority for the individual head and neck cancer patient. Especially because an improved cure rate may come at the price of increased short-term and long-term morbidity and decreased quality of life. Months or years after treatment, HNSCC survivors may raise the question: "*Has it been worth it?*".

Prognosis and the use of prognostic models

Therefore, prognosis – or the likely outcome of disease – and quality of life plays an important role in informing patients and choosing treatment at the time of diagnosis. However, at the time of diagnosis, all patients experience uncertainty about the future, and prognostic uncertainty in particular can be distressing.[28] Doctors may also have uncertainties: "*how much does this patient want to know?*" and "*do I have accurate information on the prognosis?*". Prognostic information is a valuable factor in the decision making process.

Prognosis is a key concept in patient care. It can be defined as life expectancy, survival or the prospect of cure as anticipated from the usual course of disease. Besides the natural history of disease, prognosis can be altered by individual patient characteristics, such as comorbidity and medical interventions. Therefore, the prognosis of a specific disease can differ from the prognosis of an individual patient with this disease.

In head and neck oncology, estimation of prognosis is usually based on the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM staging classification. This classification system is an objective and accurate tool that is used to predict prognoses for an entire population of patients. In this classification local tumor spread (T), regional lymph node involvement (N) and presence of distant metastases (M) are combined. However, it is ineffective for predicting outcomes in an individual patient. The classification is unable to take into account the role of other tumor factors and important patient characteristics, such as age, gender and tobacco use, and tumor variables, such as tumor size or histological characteristics.[29] A tool that incorporates these factors to accurately predict patients' outcomes is required. Prognostic models are statistical models that combine data from patients to predict outcome and are likely to be more accurate than simple clinical predictions such as the TNM classification.[30-32]

WHERE WE CAME FROM

The departments of Otorhinolaryngology and Head and Neck Surgery of Erasmus Medical Center (EMC) and Leiden University Medical Center (LUMC) have a long history of two decades of research on prognostication and quality of life in HNSCC.

Prognostic models and prognostication

This line of research was first introduced at LUMC by **Baatenburg de Jong et. al. in 2001**.[33] They presented a 7-variable-prognostic Cox regression model in order to make predictions of prognosis for the individual patient. The following prognostic variables were included: TNM-classification, tumor location, age at diagnosis, prior tumors and gender. **Van der Schroeff (2011)** and **Datema (2012)** extended and improved this model.[6,34-36] Datema enhanced this model with comorbidity as an 8th predictor of prognosis in HNSCC patients, which was confirmed by Van der Schroeff in patients with salivary gland carcinoma. In order to improve the clinical applicability of the updated model Datema performed external validation with a dataset from the USA. Van der Schroeff explored the dynamics of prognosis by introducing the passage of time itself as a new prognostic factor and by developing prognostic models at different time points during follow-up. The updated models were included in *OncologIQ*, a dedicated software package with a user-friendly interface. The individualized 5-year survival charts of HNSCC patients were visualized in this program. The dissertation of Van der Schroeff also showed that prognostic predictions by physicians, in comparison with predictions produced by *OncologIQ*, were generally imprecise and optimistic.

Today, prognostic models and nomograms exist for a wide scale of cancer diagnoses, among which head and neck cancer, breast cancer and prostate cancer. Since 2001, several prognostic models and nomograms for HNSCC patients have been developed (inter) nationally based on multivariate survival analyses of large datasets.[33-35,37,38] The resulting models may divide patients into subgroups (such as 'high risk' or 'low risk'), or predict individual probabilities for survival (e.g. 'the probability of surviving 1 year is 60%'). These programs could help physicians with patient counselling and deciding on treatment options. Today these tools are not yet used on a large-scale. This could be partly explained by the quality of the published models; some models are not validated [a] or show poor performance due to overfitting [b], optimism [c] and miscalibration [d].[39-41] Only since the introduction of the TRIPOD checklist [e], the quality of reporting of published prediction model studies has been improved.[42]

Communication and quality of life research

De Boer (1998), Mehanna (2010) and **Offerman (2013),** from the same research group, contributed to a broader understanding of the psychosocial consequences of HNSCC and quality of life of patients.[43,44] Communication in healthcare is very important in general and especially for patients with a potential live-limiting disease as HNSCC. De Boer started this line of research with a review of the correlation between psychosocial variables and survival and cancer relapse.[45] Offerman focused on improvement of quality of care by a better understanding of psychosocial consequences of HNSCC in both curative and palliative phases of disease. This work also concerns improvement of communication between patients, their partners and healthcare professionals.[19] In depth knowledge on how to best screen and support HNSCC patients during all phases of disease was also obtained.[46]

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a Validation is the process of evaluating the performance of a model. A successfully validated model is one that is somehow certified as fit for purpose. With internal validation parts or all of the dataset on which a model was developed is reused to assess the likely overfit [b] and correct for the resulting optimism [c] in the performance of the model. External validation means assessing the performance of a model already developed when applied to an independent dataset (for example by different investigators in a different geographical location).

b Overfitting is the production of an analysis that corresponds too closely or exactly to a particular set of data and may therefore fail to fit additional data or predict future observations reliably. An overfitted model is a statistical model that contains more parameters than can be justified by the data.

c A prognostic model usually performs better in the sample used to develop the model (development sample) than in other samples, even if those samples are derived from the same population. This 'optimism' is most evident when the development sample is small.

d Calibration reflects prediction accuracy. A miscalibrated prognostic model under- or over-predicts the probability of survival.

e The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) Statement is an evidence-based, minimum set of recommendations for reporting prediction modeling studies in biomedical sciences. This includes both prognostic and diagnostic prediction models as well as prediction model development, validation, updating or extending studies. It offers a standard way for reporting the results of prediction modeling studies and thus aiding their critical appraisal, interpretation and uptake by potential users.

Mehanna reported that HNSCC quality of life questionnaires effectively describe patient's health concerns and can improve patient-clinician communication.[21]

Today, most research in the field of communication about prognosis in cancer care still focuses on end of life or palliative care.[47] However, improving prognostic understanding is especially important in case of treatment decisions where a trade-off between cure and quality of life is at stake. Very little is known about communication of prognosis in HNSCC patients in all stages of disease and about using prognostic models for this purpose.

The way physicians provide prognostic information is of vital importance. Some rely on qualitative statements (e.g. "*I think he is unlikely to survive*"), whereas others use quantitative or numeric expressions (e.g. "*80% of patients in this situation do not survive*").[48] Likewise, the framing of prognostic information, either positive or negative, might be different among physicians (e.g. "*the chance of survival is 20%*" versus "*the chance of death is 80%*"). Inadequate communication can worsen physical and psychological suffering when patients do not fully understand their illness, prognosis and treatment options, and when physicians do not sufficiently elicit their patient's values.[49] Communication of prognosis is difficult, and many physicians experience this particular task as distressing.[50-52] Physicians avoid conversations addressing prognosis for many reasons, but mostly due to uncertainty about the accuracy of prognostication.[47,51]

All five before mentioned dissertations provide recommendations, on which this thesis elaborates.

Recommendations from above mentioned dissertations:

- Further research into the incremental value of new prognostic factors, and biomarkers in particular, in order to make prognostic models for HNSCC patients better. *(dissertation Van der Schroeff 2011)*
- Further research on prognostic communication, especially on how to communicate probability and uncertainty of predicted survival. *(dissertation Van der Schroeff 2011)*
- Efforts should be made to include more recent patients in the database underlying the developed prognostic models, in order to help counter the 'out-of-date principle'. Patients who were diagnosed and treated in a period with comparable diagnostic and treatment standards as today, will have a more representative survival probability than earlier patients. *(dissertation Datema 2012)*
- More research is required to further investigate the relations between psychosocial variables and prognosis. It is advised to define and add relevant confounding factors such as age and stage of disease as well as tumor-specific variables. The point of first

measurement should be as early as possible; at the time of diagnosis or before the revelation of the disease. *(dissertation de Boer 1998)*

- More research is required to make the acquisition process of quality of life data quicker and less laborious for patients. Furthermore, research is needed to evaluate the effects of using quality of life questionnaires on improving communication and clinical outcomes in the consultation. (*dissertation Mehanna 2010)*
- Verbal communication between health care professionals and patients should be regularly evaluated with specific attention for bringing bad news. Systematical evaluation of quality of care is recommended as well. *(dissertation Offerman 2013)*
- It is recommended that HNSCC patients should be structurally screened on different aspects of psychosocial well-being and on relational functioning. The objective of this screening is to detect vulnerable people who will need (extra) treatment and support. *(dissertation Offerman 2013)*

RECENT DEVELOPMENTS: CHALLENGES IN PROGNOSTICATION

Uncertainty in prognostication

While the availability of prognostic models increases, the extent to which physicians communicate prognostic information to patients based on these models remains unclear. Ethical considerations can influence communication of prognosis by using prognostic models. Especially uncertainty in prognostic information, such as standard deviation or confidence intervals, needs an effective communication. Most prognostic models estimate up to 80% of observed survival, leaving 20% of unpredicted course of disease, possibly due to prognostic factors that are not yet identified. [35] As indicated, prognostic models predict the likelihood that a population of similar patients will survive a defined period of time. While there is no certainty on individual survival rates, it can be difficult to make decisions based on this information. There are numerous stories about cancer patients who have received a very poor prognosis, and still live on for decades. The story of world famous biologist Stephen Jay Gould, who lived 20 more years after being diagnosed with mesothelioma, is most exemplary.[53]

Prognosis is a dynamic concept

Prognosis and prognostic modelling is also a dynamic concept. Over time, new prognostic factors will be discovered, and outcomes might change due to improved treatment options. Also, prognosis itself changes over time: the same patient who has survived one year after treatment will have a different prognosis than was predicted before starting the treatment. In order to estimate the 'perfect' prognosis, a timely or even continuous update of already existing prognostic models is required. To measure the improvement of

predictive performance, clarity on the added prognostic value of new prognostic factors is required before adding these factors to existing prognostic models.[54]

How and when to present prognostic information?

In general, the performance of prognostic models is statistically tested by validation of the model with external data. However, a good (statistical) prognostic performance does not qualify the usefulness of a model for clinical practice. Is a graphical display of the data required? And to what extent does a patient need explanation of statistical abstractions, such as median or confidence intervals? Are there any consequences, for example therapeutic ones, when a prognostic model identifies a patient as being 'at risk' for a poor prognosis? Proper interpretation and communication of the prognostic information is key for the clinical applicability of prognostic models. Furthermore, predicting and communicating 'what the future will hold' is not just about life expectation, but also about quality of life while taking into account patients' preferences, personality and further goals in life.

Personalized counselling

Patients need to be well-informed in order to be actively involved in treatment decisions. Prognostic information may be a valuable factor in considering treatment options.[55] Ideally, a treatment decision should reflect patients' preferences with full knowledge of the impact and outcome of all alternatives. In reality, a patient can only choose and undergo one alternative at a time.[56] Clear communication and personalized counselling on all available alternatives is therefore key. This process can be challenging because patients will be informed and need to make choices when they are sick, vulnerable and dependent and have limited time to contemplate.[57]

It takes time and effort to identify patients' preferences of receiving prognostic information. Literature shows that patients desire accurate estimates of prognosis in order to allow them to make decisions that are consistent with their values.[58-60] Patients desire, above all, to maintain hope for their situations and therefore might not want to receive information about their prognosis at all.[58,61,62] Retaining patient's hope allows the physician to take some liberties in communicating prognostic estimates. While no consensus is found in literature, the right timing of sharing prognostic information seems key.[58,63]

Recent developments: challenges in decision making

Since we started our line of research back in 2001 decisions concerning cancer treatment have become more complex. On the one hand, there is a strong tendency to apply standards and guidelines following scientific evidence. On the other hand, cancer patients are considered partners in decision making and incorporate individual perspectives and needs in the decision making process.[64] Accurate information on the individual prognosis,

the expected quality of life and possible consequences of treatment can help patients to make the best possible treatment choice, tailored to their needs, together with their doctor.[26,65,66]

During the last decade patient centred communication and patient involvement in treatment decisions have become an important approach in clinical care.[67] The shared decision making approach (SDM) is considered to be a central component of treatment decision consultations.[64,68] Instead of assuming that decisions should be guided by scientific evidence and physicians' experiences, SDM implies that what matters to patients and families should play a major role in decision making processes.[69] Physicians and patients make decisions together using the best available medical evidence and patient preferences: 'a two-way exchange of information'.[55] Patients consider the likely benefits and harms of each option, communicate their preferences and help select the course of action that best fits these, all in partnership with their physician.[68]

Both physician and patient have an important role in the SDM approach, and this is especially the case in cancer care. Ideally, oncologists determine possible treatments, emphasise the importance of patients' opinion, explain treatment options, get to know patients, guide patients, and provide treatment recommendations. Patients at the same time ask questions, express thoughts and feelings, consider options, offer opinions, and decide or delegate decisions to oncologists.[70]

In current (head and neck oncology) clinical practice, patients are often reluctant to actively participate in consultations. They might worry about being inadequate, bothersome, or claiming too much time from their doctor.[71] They often think that "*the doctor knows best*" or may not feel that it is important to share their personal preferences or circumstances.[72] Physicians might think that the SDM approach will consume extra time or might believe that there is a lack of applicability due to patient characteristics or the clinical situation.[73]

Several initiatives have started to promote the implementation of SDM in daily clinical practice. For example, The Dutch Federation of Patients' Organizations, launched a national campaign together with the Federation of Medical Specialties called "*Improved care starts with a good conversation*" ["*Betere zorg begint met een goed gesprek"*], to improve awareness of SDM among both patients and clinicians (begineengoedgesprek.nl). Secondly, they launched "*Ask3Questions*" to provoke SDM conversations.[74,75]

SURVIVORSHIP CARE IN HNSCC

Including patient preferences and individual factors is not only important while choosing the right treatment, or when sharing prognostic information. In the years following treatment, when HNSCC patients become HNSCC survivors, it is important to include patients' preferences and priorities too.[22] Cancer survivorship is defined as 'living with, through and beyond a cancer diagnosis', and frequently divided into the following phases: acute (initial treatment), extended (recovery and adaptation to a new normal) and long term.[76]

In HNSCC care, surveillance of patients has long focused primarily on successful salvage and detecting loco regional recurrence. HNSCC patients have a relatively high risk of second primary tumors (SPT), due to alcohol and tobacco exposure, and surveillance may detect these malignancies at an earlier stage. However, optimal survivorship care includes issues beyond the detection of cancer: not only cure but also care is important in the post-treatment follow-up phase.[22] As described in the first paragraph of the introduction, HNSCC patients often have to deal with treatment-related side effects that can have an enormous impact on patients' daily life. However, patients can have difficulties sharing a complete health status, including these psychosocial problems, during follow-up visits. There is only a short period of time during these visits and doctors require good communication skills to facilitate this process. Physical impairments and psycho-social problems may go undetected and opportunities to intervene and alleviate suffering can be missed.[77] Value based healthcare - and particularly accurate measurement of patient reported outcomes (PRO) - is increasingly used to facilitate a systematic approach in the follow-up of cancer patients.[78,79] This concept, that was first described by Michael Porter, claims that improvement in both quality and cost of care can be achieved by understanding and integrating the patient perspective into care. Patients actively participate in their own care and clinicians identify critical issues, improving patient management.[80-87] PROs can support patients in coping with the physical and emotional challenges of HNSCC. Structural screening of PROs may help to meet the comprehensive needs of each individual HNSCC survivor and to detect problems earlier.

OUTLINE OF THIS THESIS

This thesis consists of five parts, this general introduction section together with the Prologue forms **Part I.** The purpose of **Part II** is to contribute to a better understanding of HNSCC patient preferences and a better doctor-patient communication regarding prognosis and decision making. In Chapter 2 and 3, the current situation of treatment decision making and prognostic counselling is explored. Given the high morbidity of the different treatment modalities for HNSCC, patients may decline standard, curative treatment. In addition, doctors may propose alternative, nonstandard treatments. In **Chapter 2** factors associated with noncompliance in head and neck cancer treatment for both patients and physicians are determined, and the influence of patient compliance on prognosis is assessed. **Chapter 3** describes whether and how prognostic information on life expectancy is included during communication on diagnosis and treatment plans between physicians and HNSCC patients in different phases of disease. The results presented in this chapter, lead us to the next part of this thesis. Accurate and individual prognostic information is necessary to effectively communicate prognosis.

The potential of prognostic models regarding prognostic counselling and treatment decisions are explored in **Part III**, elaborating on earlier research done by our research group. Two different clinical prediction models for laryngeal and oropharyngeal cancer, including new prognostic markers, are developed (Chapter 4 and 5). In **Chapter 5**, Human Papilloma Virus (HPV) is identified as an important prognostic factor for oropharyngeal squamous cell carcinoma (OPSCC). Patients with HPV positive disease have a favorable prognosis over patients with HPV negative disease. Given this phenomenon, the question rises whether these HPV positive patients should be treated the same way as HPV negative patients. To analyze the potential effect of this new prognostic factor on treatment outcomes, **Chapter 6** focuses on the effect of HPV on nodal response, recurrent disease and survival in patients treated according to the 'Rotterdam protocol'. **Chapter 7** explores the role of the immune response, and especially the role of T-cells, in the beneficial prognostic status of HPV positive OPSCC patients. After these attempts to produce accurate, individualized and up-to-date prognostic models and to connect a new prognostic factor to a potential shift in treatment choices, the next challenge is how to convey prognostic information to patients using prognostic models. In **Chapter 8** this topic is explored in focus groups and some clinical recommendations are given.

Following the results of **Parts II and III**, we learned about patient preferences regarding prognosis, how to calculate and interpret individual prognosis in HNSCC patients, and how to communicate this message. However, taking care of HNSCC patients is not only about including patient preferences and individual factors while choosing the right treatment,

or when sharing prognostic information. Especially in the years following treatment, when HNSCC patients become HNSCC survivors, it is important to include patients' preferences and priorities. In **Part IV** and **Chapter 9** a PRO based clinical support system "*Healthcare Monitor"* is presented which empowers patients and increases patient centered care during follow-up of HNSCC.

We finish this thesis with **Chapter 10 - General Discussion** on the future directions and hurdles that yet have to be overcome in order to truly implement prognostic counselling and shared decision making in head and neck oncologic clinical practice. We present different research initiatives in order to handle the questions that still are to be answered after finishing this thesis and we discuss the implementation of the clinical recommendations provided in this thesis.

Finally, in **Chapter 11 - Epilogue** we will extend our view on future perspectives in patient centered head and neck cancer care to healthcare in general. A paradigm shift seems necessary to engage head and neck cancer patients in treatment decisions and empower them in their own care-process. However this transition is not only advancing in head and neck cancer care, but in general healthcare as well since the role of doctors is changing.[88] From being a traditional doctor choosing what's best for patients, towards a supporting guide choosing wisely together with patients and asking questions like "*what matters most to you?"*. All results are summarized in an **English and Dutch Summary (Chapter 12).**

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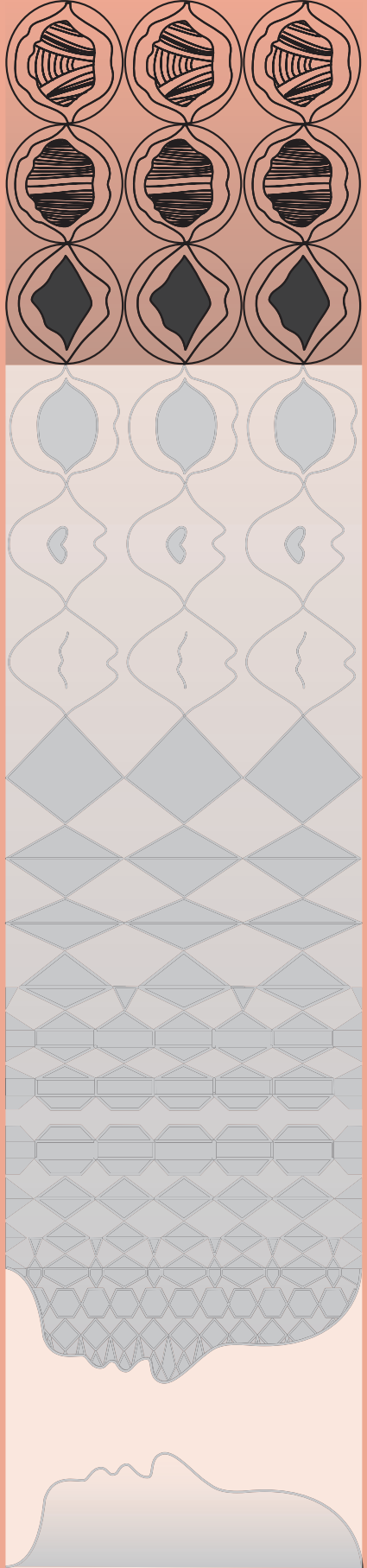
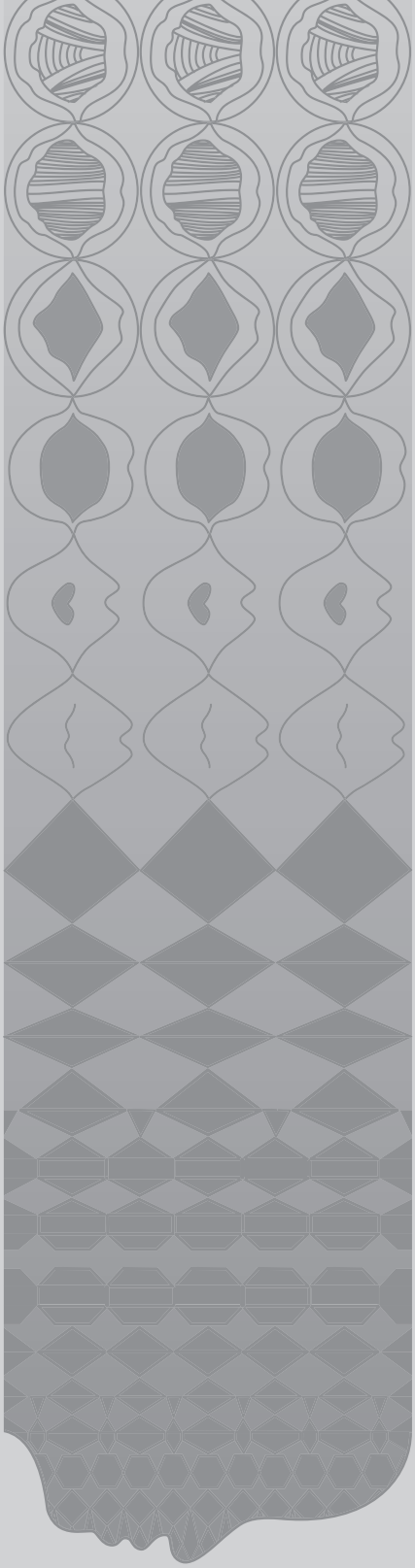


Part II

Patient preferences and current counselling



2

Noncompliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician

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ABSTRACT

Decisions on head and neck squamous cell carcinoma (HNSCC) treatment are widely recognized as being difficult, due to high morbidity, often involving vital functions. Some patients may therefore decline standard, curative treatment. In addition doctors may propose alternative, nonstandard treatments. Little attention is devoted, both in literature and in daily practice, to understanding why and when HNSCC patients or their physicians decline standard, curative treatment modalities. Our objective is to determine factors associated with noncompliance in head and neck cancer treatment for both patients and physicians and to assess the influence of patient compliance on prognosis. We did a retrospective study based on the medical records of 829 patients with primary HNSCC, who were eligible for curative treatment and referred to our hospital between 2010 and 2012. We analyzed treatment choice and reasons for nonstandard treatment decisions, survival, age, gender, social network, tumor site, cTNM classification, and comorbidity (ACE27). Multivariate analysis using logistic regression methods was performed to determine predictive factors associated with non-standard treatment following physician or patient decision. To gain insight in survival of the different groups of patients, we applied a Cox regression analysis. After checking the proportional hazards assumption for each variable, we adjusted the survival analysis for gender, age, tumor site, tumor stage, comorbidity and a history of having a prior tumor. 17% of all patients with a primary HNSCC did not receive standard curative treatment, either due to nonstandard treatment advice (10%) or due to the patient choosing an alternative (7%). A further 3% of all patients refused any type of therapy, even though they were considered eligible for curative treatment. Elderliness, single marital status, female gender, high tumor stage and severe comorbidity are predictive factors. Patients declining standard treatment have a lower overall 3-year survival (34% vs. 70%). Predictive factors for nonstandard treatment decisions in head and neck cancer treatment differed between the treating physician and the patient. Patients who received nonstandard treatment had a lower overall 3-year survival. These findings should be taken into account when counselling patients in whom nonstandard treatment is considered.

BACKGROUND

Decisions concerning cancer treatment are becoming more complex. On the one hand, there is a strong tendency to apply standards and guidelines. On the other hand, cancer patients are considered partners in decision making in order to incorporate individual perspectives and needs. Moreover, patients are better informed about treatment options than they used to be. The fine balance between benefits and side-effects of treatment is increasingly presented and discussed with the patient in an informed or shared decision making process. Still, the use of guidelines is advocated to assure optimal treatment proposals for similar patients.

It is known that a proportion of cancer patients does not receive standard, guideline driven, treatment for cancer that could be curatively treated, either by choice of their physician or by their own choice. Yet, little is known about this specific, non-compliant patient population. How frequently does it occur that patients themselves refuse standard therapy for cancer, even if they are considered eligible for curative treatment by their physician, and what are the reasons for this behavior? This question is particularly interesting if survival rates are low and treatments are associated with morbidity and mortality as well.

Head and neck squamous cell carcinoma (HNSCC) describe a range of squamous cell tumors that arise from the head and neck region, which includes the oral cavity, pharynx, larynx and nasal cavity. The worldwide incidence of head and neck cancer exceeds half a million cases annually, ranking it as the fifth most common cancer worldwide.[1, 2] Five year survival rates for cancers in the head and neck area are about 50%.[1] In the majority of cases, treatment consists of surgery, radiotherapy, chemotherapy and combinations of these modalities. All types of treatment are associated with high morbidity, sometimes compromising vital functions, including respiration, swallowing and speech, and have an enormous impact on the quality of life. Therefore, improved cure rate may come at the price of increased short-term and long-term morbidity and decreased quality of life. Cure is not always the main priority for the head and neck cancer patient. For example, up to 20% of patients would accept a lesser chance of cure to avoid a laryngectomy and to keep their normal voice.[3, 4] Hence, decisions on head and neck cancer treatment are widely recognized as being difficult.[5, 6]

Our primary objective is to determine frequencies of and predictors for receiving a nonstandard treatment in HNSCC and to explore reasons for choosing a nonstandard treatment, either by patients or physicians. As a secondary objective we want to assess the influence on prognosis of receiving nonstandard treatment for curative HNSCC.

MATERIALS AND METHODS

Subjects

This retrospective study, based on medical records, included patients with newly diagnosed HNSCC without distant metastasis. Patients with cancer of the lip, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx which could be treated with curative intent qualified for this study. Recurrent or residual cancer was excluded but patients with second primary HNSCC were deemed eligible. Patients who were enrolled in any clinical trial in this period were also excluded. In the period from January 2010 to December 2012, 829 patients were included. The study was carried out in compliance with the Helsinki declaration and was approved by the ethics committee of the Erasmus Medical Center, including a waiver for informed consent.

All patients were initially set for curative treatment at the Erasmus Medical Center Rotterdam, the Netherlands. The tumor stage at the time of first diagnosis was classified according to the clinical staging system described by the Union for International Cancer Control (UICC). A first treatment proposal was presented at the regional multidisciplinary head and neck tumor conference, where all new patients were discussed. The multidisciplinary tumor board (MDT) consisted of oncologists, head and neck surgeons, and radiotherapists. The treatment proposal was weighed up against the standard treatment protocol, which is based on national guidelines published by the Comprehensive Cancer Centre the Netherlands (IKNL) and regional additions. The final proposal may be according to the guidelines (standard treatment) or deviant (nonstandard treatment). Reasons for nonstandard treatment, either as a result of MDT or patient decision, were collected retrospectively. Solely major deviations of standard guidelines were marked as 'nonstandard' treatment. A change in dose of radiotherapy or chemotherapy was not accepted as a deviation of standard guidelines, but refusing total laryngectomy indeed was.

Outcomes

Following the discussion in the MDT, the treatment proposal was discussed with the patient. In the decision making process, patients may have either accepted or declined the proposal. In this study, we considered the following groups.

1. *Standard treatment according to guidelines (reference group)*
2. *Nonstandard treatment as proposed by the multidisciplinary tumor board*
3. *Nonstandard treatment as desired by the patient:*

a. *Alternative (less extensive)*
b. *No treatment at all*

Different parameters present at the time of diagnosis, were retrospectively collected for every patient. These included age at diagnosis, year of diagnosis, tumor site, tumor stage**,** gender, marital status, having children, comorbidity conditions, prior malignancy (head and neck or other), treating physician (head and neck oncologist, radiotherapist or general oncologist) and survival. The presence of one or more different comorbid ailments was coded for all patients using Adult Comorbidity Evaluation-27 (ACE-27).[7] The ACE-27 grades specific comorbid conditions in different organ systems into one of three levels of comorbidity. The overall comorbid score is graded in four levels, none, mild, moderate or severe and is based on the highest ranked single ailment. Patients with two or more moderate ailments in different organ systems or disease groupings are graded as severe. The ACE-27 is a comprehensive tool, commonly used in head and neck cancer literature, and accurate as a retrospective measuring instrument of comorbidity.

The retrospective analysis of the specified characteristics was performed by the first two authors (EACD an SWM) who were not involved in decision making by the multidisciplinary tumor team.

Statistical analysis

The data was analyzed with IBM SPSS Statistics version 21.0 for Windows. For statistical processing, several variables were converted to dichotomous values, based on experience, evidence from literature, or distribution of data following a normal Gaussian curve with a cutoff point at the mean. This was the case for age (<65 or ≥65 years), marital status (partner or single), comorbidity (ACE-score 0-1 or ACE-score 2-3), tumor site (pharynx, larynx and oral cavity) and tumor stage (stage I-II or stage III-IV). Descriptive statistics, χ^2 tests and simple logistic regression methods were used to compare three groups (reference group, nonstandard treatment by MDT decision and nonstandard treatment by patient's decision). P-values <0.05 were considered to be statistically significant.

Multivariate analysis using logistic regression methods and taking into account interaction terms was performed to determine predictive factors associated with non-standard treatment following MDT or patient decision.[8] A predictor was defined as a predictive factor that contributes independently and significantly (p-value of < 0.05) to the choice of non-standard treatment, done either by the MDT or by patient decision. In general, the limiting sample size in logistic regression analysis is the number of events of interest. The assumption is made that this analysis will produce reasonably stable estimates of the effect of each variable on the outcome if the limiting sample size allows a ratio of approximately 10 to 15 observations per possible predictive factor.[8] To gain insight into the impact of each possible predictor in the model, all variables were entered in the logistic regression analysis at the same time. The following factors were included: age at diag-

nosis, year of diagnosis, gender, marital status, having children, tumor stage, tumor site , comorbidity, prior malignancy and prior head and neck malignancy, and type of initial treatment following national guidelines. Stratification by gender was done following the analysis for interaction terms. To design a final stratified model showing independently and significantly predictive factors associated with non-standard treatment following MDT or patient decisions, a backward selection procedure was applied, accepting predictors with a p-value <0.05. Following this, a forward selection procedure was done to confirm our results.

To gain insight in survival of the different groups of patients, we applied a Cox regression analysis. After checking the proportional hazards assumption for each variable, we adjusted the survival analysis for gender, age, tumor site, tumor stage, comorbidity and a history of having a prior tumor.

RESULTS

The demographics of all included patients and the demographics of the distinguished subgroups of patients are listed in Table 1. 82.9% (n=687) of patients received treatment according to guidelines. The remaining 17.1% (n=142) received nonstandard treatment or no treatment at all. Deviation from protocol in these patients was motivated. In 10.7% (n=89) of all patients the multidisciplinary team decided to propose a nonstandard treatment. The mean age of these patients was 67 years at the time of diagnosis and 22% of them were female. As shown in Table 2 levels of comorbidity, stage of disease, tumor site, initial treatment proposal and marital status differed significantly between this group and the patients who received standard treatment. In multivariate logistic regression analysis many of these characteristics were significantly associated with the outcome of nonstandard tumor board advice. These characteristics are marked by an asterisk in Table 2. A proportion of 7.2% (n=60) of all patients declined a standard treatment proposal given by the multidisciplinary team. The mean age of this group of patients at the time of diagnosis was 72 years and 47% of them was female, whereas the proportion of female subjects of the total population was just 28%. In 4.2% (n=35) of all patients, a part of the treatment was refused by patients themselves and as a result they received less extensive therapy. A further 3% (n=25) of all patients refused any type of therapy, despite being considered eligible for curative treatment by the multidisciplinary team. Gender, age, levels of comorbidity, stage of disease and marital status differed between patients who received standard treatment and those who chose nonstandard treatment against the advice of the MDT (Table 3). Multivariate logistic regression analysis showed that several of these variables were significantly associated with the outcome of patients declining or refusing standard treatment. Following the outcomes,

Table 1. Demographic characteristics of total population and distinguished subgroups

		Nonstandard treatment (*N*=142)*	
	Total population (*N*=829)	**Proposed by the MDT (*N*=89)**	**Desired by the patient (*N*=60)**
Age (years) (mean and standard deviation)	63.9 (11.1)	67.2 (10.9)	71.2 (12.2)
Gender			
Male	596 (72%)	69 (78%)	32 (53%)
Female	233 (28%)	20 (22%)	28 (47%)
Comorbidity score (ACE-27)			
0	182 (22%)	3 (3%)	11 (18%)
1	327 (39%)	30 (34%)	18 (30%)
2	239 (29%)	36 (40%)	22 (37%)
3	81 (10%)	20 (23%)	9 (15%)
Tumor stage			
1	162 (20%)	5 (6%)	8 (13%)
2	180 (22%)	6 (7%)	7 (12%)
3	161 (19%)	26 (29%)	7 (12%)
4	326 (39%)	52 (58%)	38 (63%)
Tumor site			
Lip	24 (3%)	0 (0%)	1 (1%)
Nasopharynx	29 (4%)	4 (4%)	25 (42%)
Oral cavity	255 (31%)	17 (19%)	17 (29%)
Oropharynx	213 (26%)	27 (30%)	6 (10%)
Supraglottic larynx	89 (11%)	13 (15%)	3 (5%)
Glottic larynx	124 (15%)	8 (9%)	8 (13%)
Hypopharynx	95 (11%)	20 (23%)	0 (0%)
Prior malignancy			
No	669 (81%)	70 (79%)	47 (78%)
Other prior cancer yet treated	84 (10%)	7 (8%)	8 (13%)
Prior head and neck cancer yet treated	76 (9%)	12 (13%)	5 (9%)
Marital status			
Partner	569 (69%)	50 (56%)	27 (45%)
Single	260 (31%)	39 (44%)	33 (55%)
Standard treatment according to guidelines			
Radiotherapy	185 (22%)	10 (11%)	4 (7%)
Chemoradiation	183 (22%)	47 (53%)	14 (23%)
Surgery + radiotherapy	208 (25%)	20 (22%)	29 (48%)
Surgery + chemotherapy	12 (1%)	3 (3%)	0 (0%)
Surgery + postoperative radiation (PORT) on indication	116 (14%)	4 (5%)	7 (12%)
Surgery	125 (15%)	5 (6%)	6 (10%)
Year of treatment			
2010	234 (28%)	27 (30%)	21 (35%)
2011	259 (31%)	22 (25%)	21 (35%)
2012	335 (41%)	40 (45%)	18 (30%)

*In seven patients, both MDT and patient were non-compliant to standard treatment guidelines; patients received a proposal of nonstandard treatment by the MDT but however refused any treatment.

stratification by gender was done to specify the influence of the other variables between men and women on decisional behavior. In the group of females who declined standard curative treatment, being older than 65 years at time of diagnosis and being single or widowed were significant predictors. On the other hand, only advanced tumor stage was a significant predictor in male patients who declined standard curative treatment.

Table 2. Unadjusted and adjusted OR's for MDT decision to propose nonstandard treatment

Characteristic		*OR unadjusted*	95% CI	*OR adjusted* [b]	95% CI
Age	< 65 years [a]	1.22	0.7-1.9	1.46	0.9 - 2.4
	≥ 65 years				
Gender	Male [a]	0.72	0.4 - 1.2	0.72	0.4 - 1.3
	Female				
Comorbidity score (ACE-27)	Low (0-1) [a]	3.06*	1.9-4.8	3.40*	2.0 - 5.7
	High (2-3)				
Tumor stage	Early (I-II) [a]	5.74*	3.0-11.0	3.40*	1.4 - 8.5
	Advanced (III-IV)				
Tumor site	Oral cavity [a]				
	Pharynx	2.75*	1.6 - 4.9	0.94	0.4 - 2.2
	Larynx	1.69	0.9 - 3.3	0.85	0.3 - 2.1
Prior malignancy	No [a]				
	Other prior cancer yet treated	0.78	0.3 - 1.6	0.61	0.3 - 1.5
	Prior head and neck cancer yet treated	1.60	0.8 - 3.1	2.56*	1.1 - 5.7
Marital status	Partner [a]	1.83*	1.2 - 2.9	1.68	1.0 - 2.9
	Single				
Children	Yes [a]				
	No	1.23	0.7 - 2.1	1.07	0.6 - 2.0
	Unknown	0.79	0.4 - 1.5	1.31	0.7 - 2.7
	No contact	0.84	0.7 - 1.1	0.90	0.7 - 1.1
Standard treatment according to guidelines	Surgery [a]				
	Radiotherapy	1.37	0.5 - 4.1	1.31	0.4 - 4.5
	Chemoradiation	8.29*	3.2 - 21.5	4.79*	1.3 - 17.1
	Surgery + radiotherapy	2.53	0.9 – 7.0	1.13	0.3 - 4.0
	Surgery + chemotherapy	8.00*	1.6 - 39.0	4.61	0.7 - 29.5
	Surgery + PORT on indication	0.86	0.2 - 3.3	0.98	0.2 - 4.2
Year of treatment	2010 [a]				
	2011	0.71	0.4 - 1.3	0.56	0.3 - 1.1
	2012	1.04	0.6 - 1.7	1.11	0.6 2.0

[a] = reference value, [b] = odds ratio calculated using multivariate logistic regression analysis adjusting for age, gender, comorbidity, tumor stage, tumor site, prior malignancy, marital status, having children, standard treatment proposal according to guidelines, year of treatment, * = p value < 0.05.

Table 3. Unadjusted and adjusted OR's for patient decisions to choose nonstandard treatment and adjusted OR's after stratification for gender

		Not stratified analysis				Stratification for gender			
Characteristic		***OR unadjusted***	**95% CI**	***OR adjusted*** [b]	**95% CI**	***♂OR adjusted*** [c]	**95% CI**	***♀OR adjusted*** [c]	**95% CI**
Age	< 65 years [a]	3.19*	1.8 - 5.7	3.40*	1.8 - 6.4	1.73	0.8 - 3.6	7.22*	2.4 - 22.1
	≥ 65 years								
Gender	Male [a]	2.41*	1.4 - 4.1	2.66*	1.5 - 4.8	-	-	-	-
	Female								
Comorbidity score (ACE-27)	Low (0-1) [a]	1.78*	1.0 - 3.0	1.49	0.8 - 2.7	1.77	0.8 - 3.7	1.39	0.6 - 3.3
	High (2-3)								
Tumor stage	Early (I-II) [a]	2.22*	1.2 - 4.1	1.07	0.4 - 2.9	2.88*	1.2 - 7.1	1.92	0.8 - 4.7
	Advanced (III-IV)								
Tumor site	Oral cavity [a]					-	-	-	-
	Pharynx	0.78	0.4 - 1.4	1.34	0.6 - 3.0				
	Larynx	0.43*	0.2 - 0.9	0.82	0.3 - 2.1				
Prior malignancy	No [a]					-	-	-	-
	Other prior cancer yet treated	1.39	0.6 - 3.1	1.09	0.5 - 2.6				
	Prior head and neck cancer yet treated	0.93	0.4 - 2.4	0.99	0.3 - 2.9				
Marital status	Partner [a]	2.92*	1.7 – 5.0	2.25*	1.2 - 4.1	1.64	0.8 - 3.5	3.63*	1.5 - 9.0
	Single								
Children	Yes [a]					-	-	-	-
	No	2.26*	1.3 - 4.1	2.08*	1.0 - 4.1				
	Unknown	0.78	0.3 - 1.8	1.19	0.5 3.0				
	No contact	1.66	0.4 - 7.5	1.19	0.2 - 5.9				

Table 3. Unadjusted and adjusted OR's for patient decisions to choose nonstandard treatment and adjusted OR's after stratification for gender (continued)

		Not stratified analysis				Stratification for gender			
Characteristic		***OR unadjusted***	**95% CI**	***OR adjusted*** [b]	**95% CI**	***♂OR adjusted*** [c]	**95% CI**	***♀OR adjusted*** [c]	**95% CI**
Standard treatment according to guidelines	Surgery [a]					-	-	-	-
	Radiotherapy	0.44	0.1 - 1.6	0.29	0.07 - 1.2				
	Chemoradiation	1.64	0.6 - 4.4	1.15	0.3 - 4.6				
	Surgery + radiotherapy	3.21*	1.3 – 8.0	2.16	0.6 - 7.6				
	Surgery + chemotherapy	-	-	-	-				
	Surgery + PORT on indication	1.27	0.4 - 3.9	1.10	0.3 - 3.8				
Year of treatment	2010 [a]					-	-	-	-
	2011	0.89	0.5 - 1.7	0.73	0.4 - 1.5				
	2012	0.57	0.3 - 1.1	0.63	0.3 - 1.3				

[a] = reference value, [b] = odds ratio calculated using multivariate logistic regression analysis adjusting for age, gender, comorbidity, tumor stage, tumor site, prior malignancy, marital status, having children, standard treatment proposal according to guidelines, year of treatment, [c] = odds ratio stratified for gender (male versus female) calculated using multivariate logistic regression analysis adjusting for age, comorbidity, tumor stage and marital status, * = p value < 0.05

Solely major deviations from standard treatment guidelines were accepted as being 'non-standard' treatment. Table 4 shows the various reasons the MDT gave for not recommending a standard, guideline-driven treatment for 10% of all patients included in this study. Reasons put forward by 7% of patients declining standard treatment are also shown in Table 4. These patients were all considered eligible for curative treatment, however, chose not to follow proposals of the MDT. In most cases, patients didn't want an extensive type of treatment which would have a great impact on their lives. When the MDT decided to advise a nonstandard therapy their arguments were more about poor physical conditions of the patients, for example cardiovascular disease or insufficient kidney function.

Table 4. Reported reasons of MDT members for not recommending guideline-driven treatment and reported reasons of patients for refusing standard curative treatment proposed by their physician

Reported reasons of MDT members	Number of cases	Percentage
No surgery because of patient conditions	18	20%
No chemotherapy because of patient conditions	28	32%
No radiotherapy because of patient conditions	6	7%
No treatment because of patient conditions	5	6%
No radiotherapy because of medical history	4	4%
Customized chemotherapy because of patient conditions	20	22%
Customized radiotherapy because of patient conditions	5	6%
Customized surgery because of patient conditions	1	1%
Customized therapy because of patient conditions	2	2%
Total	*89*	*100%*

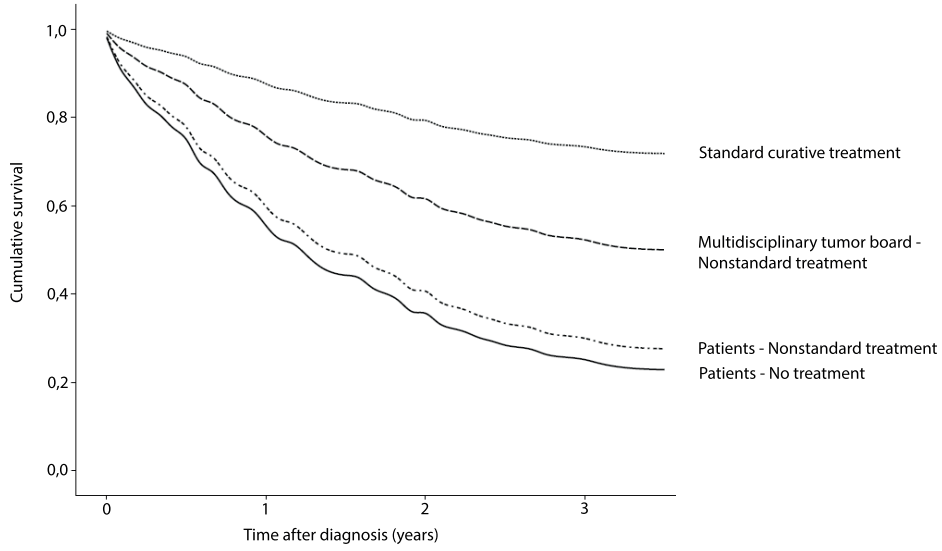
Reported reasons of patients	Number of cases	Percentage
Patient declines any treatment	11	18%
Patient declines surgery	19	32%
Patient declines radiotherapy	12	20%
Patient declines chemotherapy	4	7%
Patient cannot mentally handle therapy	11	18%
Patient declines therapy because of GP recommendation	2	3%
Patient declines therapy because of religious beliefs	1	2%
Total	*60*	*100%*

Survival

Following nonstandard or even non-curative treatment one can imagine that survival will be worse in these patients. Still, it is relevant to know to which extent survival will drop in these patients.

Patients who received nonstandard treatment had a significantly lower overall 3-year survival (34% vs. 70%). Survival for patients who received nonstandard treatment due to a decision made by the multidisciplinary team was decreased (HR 2.1 (1.49 – 3.03), p<0.001). Survival decreased even more in patients who declined standard treatment themselves (HR 3.9 (2.34 – 6.31), p<0.001) or refused any type of treatment (HR 4.5 (2.72 – 7.31), p<0.001). For illustrative purposes we made four separate lines in Figure 1, using the cumulative estimated survival rates per month, calculated with the adjusted Cox regression analysis. These lines represent four categories of patients: those who receive standard curative treatment, those who receive nonstandard treatment due to a decision by the MDT, those who wish for a less extensive though nonstandard type of treatment and those who reject any type of treatment.

Figure 1. Cumulative estimated survival rates per year for 4 distinguished patient groups adjusted for gender, age, tumor site, tumor stage, comorbidity and a history of having a prior tumor



DISCUSSION

One of the major topics in oncology today is to strive for personalized medicine. Decisions on cancer treatment are complex regarding guidelines on the one hand and patients preferences on the other hand. This specifically holds true if survival rates are relatively poor and treatments are associated with morbidity and mortality, as is the case in HNSCC. Counselling of patients and informed decision making is important, and as a result, a proportion of patients will not receive standard curative treatment. Doctors are generally

not aware of the extent of this situation. Our study shows that 17% of all patients with a primary HNSCC did not receive standard curative treatment, either due to a nonstandard treatment advice, or due to the patient choosing an alternative. The MDT decided in 10% of all patients to advise nonstandard treatment in the case of a primary and curable HNSCC. Seven percent of all patients decided themselves to decline standard curative treatment advice. A proportion of 4% wished for a less extensive type of treatment and 3% refused any type of therapy. Reflecting on the various reasons mentioned for choosing a nonstandard treatment for curative HNSCC, there is a difference in argumentation between patients and physicians. Physicians focused more on physical aspects, essentially comorbidity and advanced disease, whereas decisions of patients were based on quality of life and emotional or psychological reasons. We should look at these results with some caution because a retrospective chart review is not an optimal way of identifying reasons of patients to refuse treatment. Patient surveys or interviews appear to be more efficient.[9]

A review of literature on head and neck cancer showed three other studies focusing partly on our objectives.[10-12] In agreement with these studies, we found that a higher comorbidity index and poor physical functioning were associated with nonstandard treatment. Parallel to our results, social factors were also predictive for nonstandard treatment, as widowed persons were more often not treated according to the standard protocol.[10] Still, there were some major differences in methodology between the studied articles and our study. One study did not perform a multivariable analysis and therefore did not adjust for the influence of other predictive factors.[11] In this study patients with recurrent or residual disease were also included. Another study excluded patients with a low tumor stage and patients aged between 60 and 70 years.[10] The last study included only elderly patients.[12] A limitation of our own study would be its retrospective nature, which may have led to some information bias since not all data on the social network of our patients was available. Also, this study was performed in one large center in the Netherlands, and therefore it could be less generalizable for an international population. On the other hand, although national guidelines on head and neck cancer treatment may differ between countries regarding dosages of radiotherapy or details in surgical techniques, the assumption can be made that explicit major deviations of guidelines are comparable. And therefore our results could be applied to an international population of head and neck cancer patients. When comparing our results to previous studies on this subject done in general oncology, there are certain similarities. Various factors claimed to be associated with cancer treatment refusal include: lower social class, higher education, single or divorced, patients living in a rural community, older age group, medical comorbidity, fear of surgery, fear of anesthesia and fear of treatment-related side effects.[13] A recent study in the United States on 113,885 patients showed that nearly 19% of patients with lung/bronchial cancer and non-Hodgkin lymphoma, and more than 16% of patients with prostate cancer received no treatment for

their disease.[14] Not receiving treatment was significantly more common in patients aged >75 years, female patients, in patients from rural areas and patients with an advanced disease stage. 1.1% of all patients refused treatment that was recommended by their physician. This percentage is an average among all cancer types. Patient refusals of treatment appeared to be related to increasing age, comorbid illness, and lack of perceived clinical benefit. These factors, associated with declining curative treatment, are comparable with the results found in our study. However the average percentage of patients who decline standard treatment is far lower than the 7% we found and also lower than the frequencies found in other HNSCC studies.[10-12] Hence, it appears that patients with HNSCC have a higher risk of receiving or choosing nonstandard treatment compared to patients with other types of cancer. A study on patients with advanced colon adenocarcinoma did, however, show quite similar results to our study, with a proportion of 18% of patients that did not receive treatment due to decisions made by their oncologist and 9% of patients that refused treatment themselves.[15] Older patients were more likely to be recommended nonstandard treatment and were more likely to refuse it, if recommended. Patients living alone and patients with a lot of comorbidity were more likely to receive nonstandard treatment due to the decision by their physician or due to their own choice. This is in agreement with the findings from a breast cancer study, which suggested that older unmarried women were more concerned than married women about treatment-related problems after surgery.[16] A possible factor in the behavior of physicians and patients regarding a choice of therapy is probably poor prognosis.

In our study, overall 3-year survival was lower in patients who received nonstandard treatment. The level of comorbidity was higher and general health status was lower in patients in whom the MDT advised nonstandard treatment. This could be an explanation for the lower survival in these patients.[17] However, there was a significant difference in overall survival between patients who received nonstandard treatment due to a decision made by the multidisciplinary team in relation to patients who refused any type of treatment or declined standard treatment themselves.

When patients or physicians are non-compliant with standard treatment guidelines, for whatever reason, it is not surprising that less curative treatment options, and moreover non curative treatment options will be proposed, both leading to worse survival. Hence, it is still relevant to know to what extent survival differs between these groups of patients, especially when focusing on counselling of patients in whom nonstandard treatment options are considered. How should one approach those patients in daily clinical practice? It is possible that patients who are more accepting of their disease and its prognosis may have treatment goals that differ from those who are not. Improved or preserved quality of life instead of an increased chance of cure and survival could be an explanation for

this decisional behavior of patients declining standard treatment options. These findings should be taken into account when counselling patients for whom nonstandard treatment is considered. On the other hand, it is debatable whether these noncompliant patients should be counselled otherwise. Future research should elicit whether the quality of life is improved when patients make more informed choices, independent from what physicians advise.

CONCLUSIONS

Identification of patients with a high risk of receiving nonstandard treatment for curative HNSCC, due to a decision by their physician or themselves, is made possible by this report. Patients living alone, patients with a lot of comorbidity or high tumor stage, females and older patients are more likely to receive nonstandard treatment for curative HNSCC. Therefore we advocate individualized counselling of patients regarding prognosis, quality of life and patient wishes and expectations to achieve shared decision making in treatment for HNSCC.

Our study confirms that the choice of treatment for patients with head and neck cancer should be based on the wishes and motivation of these patients too. In the decision making process, it is important to actively involve the patient and to make sure the patient understands the complexity of the medical problem and the prognosis. Prognostic models based on individual patient characteristics enhance our insight in prognosis of each individual patient. These models can therefore be used in counselling of patients to improve informed decision making.[18-20] We have initiated a prospective trial in our clinic to measure the effect of prognostic counselling using models on treatment outcome, quality of life, patient satisfaction and decisional conflict. In our view, individualized counselling of patients, regarding prognosis, expectations and quality of life, is necessary, before a decision about treatment for HNSCC is made.

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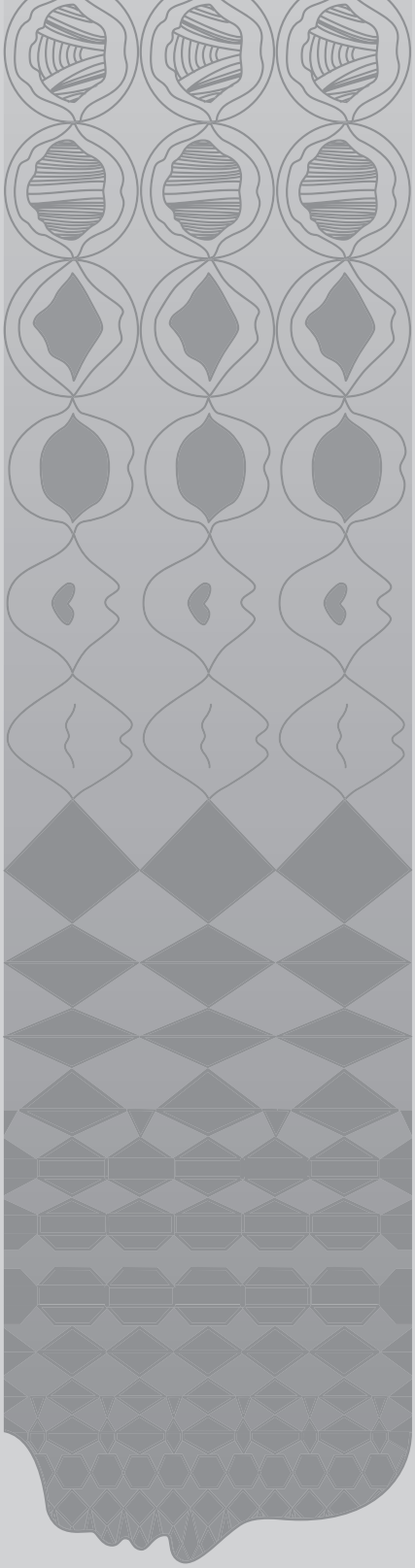

3

Communication of prognosis in head and neck cancer patients; a descriptive qualitative analysis

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ABSTRACT

In shared decision making it is important to adequately, timely and actively involve patients in treatment decisions. Sharing prognostic information can be of key importance. This study describes whether and how prognostic information on life expectancy is included during communication on diagnosis and treatment plans between physicians and head and neck (H&N) oncologic patients in different phases of disease. A descriptive, qualitative study was performed of n=23 audiotaped physician-patient conversations in which both palliative and curative treatment options were discussed and questions on prognosis were expected. Verbatim transcribed consultations were systematically analyzed. A distinction was made between prognostic information that was provided a) quantitatively: by giving numerical probability estimates, such as percentages or years or b) qualitatively: through the use of words such as 'most likely' or 'highly improbable'. In all consultations, H&N surgeons provided some prognostic information. In 5.9% of the provided prognostic information, a quantitative method was used. In 94.1% prognostic information was provided qualitatively, using six identified approaches. H&N surgeons possibly affect patients' perception of prognostic content with two identified communication styles: directive (more physician-centered) and affective (more patient-centered). This study is first in providing examples of how H&N surgeons communicate with their patients regarding prognosis in all stages of disease. They often exclude specific prognostic information. The study outcomes can be used as a first step in developing a guideline for sharing prognostic information in H&N oncologic patients, in order enable the process of shared decision making.

INTRODUCTION

During the last decade patient centered communication and patient involvement in treatment decisions has become an important approach in clinical care.[1] The shared decision making approach (SDM) is considered to be a central component of treatment decision consultations.[2] Patients need to be well-informed in order to be able to be actively involved in treatment decisions.[3] Prognostic information may be a valuable factor in considering treatment options.[4] Besides content, the communication style within the professional setting is also important, especially since patients tend to remember only 20-60% of the information provided by their physician.[5, 7-8] Furthermore, when patients do not fully understand their illness, prognosis and treatment options and physicians do not sufficiently elicit patients' values, this can worsen their physical and psychological suffering.[9]

The SDM approach is getting more attention in treatment decision consultations with head and neck (H&N) cancer patients.[10] The 5-year survival rates of H&N cancer remain around 50%.[11] Also, the commonly used treatment modalities are associated with high morbidity and impact on quality of life.[12] Especially in the case of treatment options with a direct impact on important functions, involving swallowing, taste or speech, there might be a difficult trade-off between life expectation or cure and quality of life. Therefore prognosis, morbidity and quality of life of H&N cancer patients can be significant topics in doctor-patient communication, especially in consultations during which treatment options are discussed.

However, communication on prognosis is difficult. Many physicians experience this particular task as distressing.[13-15] They avoid conversations addressing prognosis for many reasons, most frequently due to uncertainty about the actual prognosis or how to communicate this. Other reasons are lack of training, insufficient time to attend to the patient's emotional needs, and fear of a negative impact on the patient.[14, 16] As a result, some physicians discuss prognosis in vague or in optimistic terms, avoid the topic unless the patient insists, or mainly focus the discussion on treatment options. Estimates of prognosis provided by physicians are also often overly optimistic when compared to actual or predicted outcomes.[17-19] On the other hand, interpretation of prognostic information by patients may range from unrealistic optimism to the belief that one will be the patient who experiences the bad outcome described.[20]

The way physicians provide prognostic information is of vital importance. Some rely on qualitative statements (e.g. *"I think he is unlikely to survive"*), whereas others use quantitative or numeric expressions (e.g. *"80% of patients in this situation do not survive"*).[21] Likewise, the framing of prognostic information, either positive or negative, might be different

among physicians (e.g. *"the chance of survival is 20%"* versus *"the chance that you'll die will be 80%"*). Lastly, physician communication style can differ, either being directive (e.g. telling the patient what to do) or affective (e.g. autonomy supportive).[22] Research has shown that providing sufficient quantitative information allows patients to make fully informed decisions in contrast to providing solely qualitative information.[4, 21, 23] Also, giving numeric expressions of prognosis improves the accuracy of patients' risk perceptions and the comfort with feeling informed.[23]

Most research in the field of communication of prognosis in cancer care focuses on end of life or palliative care. This is also the case for H&N cancer.[24-26] However, improving prognostic understanding is important during all stages of disease. The literature lacks information on communication of prognosis in H&N cancer patients, especially on those with curative treatment options.

This study's primary purpose is to investigate whether prognostic information on life expectancy is included during communication on diagnosis and treatment plans between physicians and H&N oncologic patients in all phases of the disease. We also want to describe the communication style displayed by physicians as this can affect patients' perceptions of prognostic content.

METHODS

We performed a qualitative single-center descriptive study based on audio-taped real physician-patient consultations in which treatment options were discussed and questions on prognosis were to be expected. A qualitative approach is most suitable for in depth investigating health care issues in context and for taking into account interaction, behavior, and perceptions within groups.[27]

Consultations

In this study, n=31 patients were approached to record the consultation with their physician. Patients were eligible if they received a treatment proposal for their recently diagnosed H&N cancer, regardless of the phase (curative/palliative) of their disease. Patients were recruited at the out-patient clinic of the Erasmus MC Cancer Institute and received oral and written counselling about this study by an independent researcher before entering the consultation with their physician. Written informed consent was obtained following guidelines of the Medical Ethical Committee. N=23 patients gave their consent and the consultations between them and n=7 physicians were digitally recorded. Eight patients

declined participation in this study due to privacy reasons. The seven physicians were all H&N cancer surgeons with relevant experience varying between 5 and 30 years.

Definition of prognostic information

Prognosis was defined as life expectancy, survival and the prospect of cure as anticipated from the usual course of disease. We made a distinction between prognostic information that was provided quantitatively by giving numerical probability estimates such as percentages or years or qualitatively through use of words or phrases such as 'most likely', 'frequent' or 'highly improbable'.

Analytic procedures

All verbatim transcribed consultations were analyzed by three independent researchers (ED, MB and MO) using a constant comparative technique.[28] Two researchers (ED and MO) who were trained in this technique, initially made independent assessments of the first 7 consultations separately, assuring that all audiotaped H&N surgeons were included at least once. Both researchers detected prognostic information provided by H&N surgeons and wrote short descriptions of the different phrases used to share prognostic information (quantitatively or qualitatively). All highlighted passages have been reviewed and discussed in detail by the researchers in order to reach consensus. In the next assessment saturation of the qualitative study approach was reached after discussing 13 more consultations. No additional prognostic content besides the known qualitative and quantitative approaches regarding prognosis could be identified. Apart from the method of providing prognostic information, the communication style or professional attitude of H&N surgeons that can affect patients' perception of prognostic content, was described. We made a distinction between directive and affective communication styles. The directive communication style is more physician-centered, while the affective communication style is more supportive and patient-centered.[21, 23] A third researcher (MB) verified the results by coding n=7 transcribed consultations that were randomly selected.

At the end of this procedure, the researchers found a few examples that were classified differently by each researcher. After an in-depth discussion, consensus was reached. The results were subsequently rationalized into a coding frame that was applied to all transcripts, using NVivo qualitative software (version 10). Furthermore, the primary initiator of the discussion about prognosis in each consultation was documented, either being the patient, the caregiver or the H&N surgeon. Also the time used to communicate the prognosis in the consultation was recorded.

RESULTS

Characteristics of participants and consultations

Twenty three patients participated in this study, with an average age of 68 years. Most patients (87%) received a curative treatment plan (Table 1).

Mean total duration of consultations was 14 minutes and 21 seconds (SD 9 minutes 1 second). The mean time used for discussing a quantitative prognosis was 38 seconds (SD 35 seconds), accounting for 4.4% of the consultations. H&N surgeons were the primary initiators in 58% of discussions about prognosis, patients in 18% and caregivers in 24%.

Table 1. Patient characteristics

	Number of patients	% of total number of patients
Men	17	74%
Women	6	26%
Age (years):		
50-59	6	26%
60-69	9	39%
70-79	5	22%
>80	3	13%
Intention of treatment:		
Curative	20	87%
Palliative	3	13%

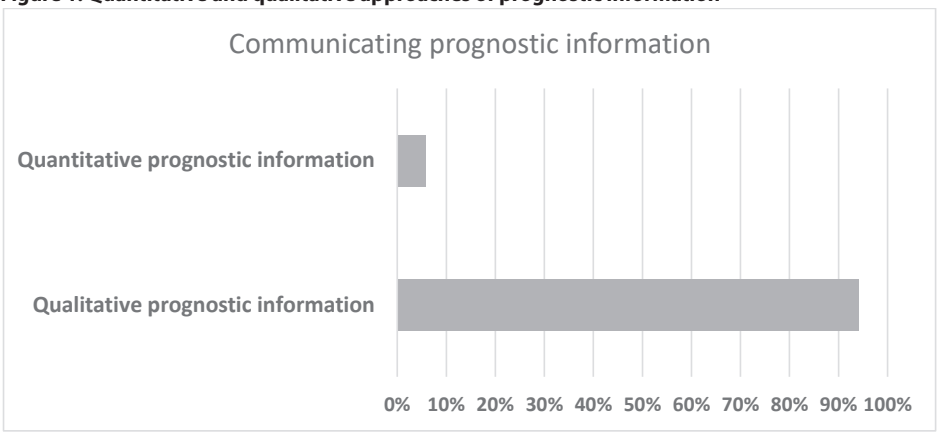
Provision of prognostic information

In all n=23 consultations, H&N surgeons provided some prognostic information. We found a total of n=222 quotations containing prognostic information. In seven interviews, n=13 quotations (5.9%) demonstrating a quantitative method using clear numerical probabilities were identified. An example of this method:

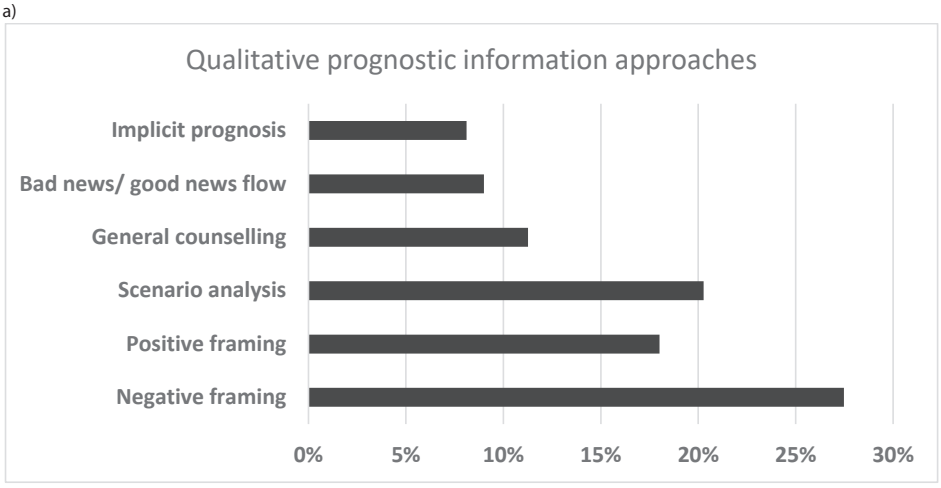
> *H&N surgeon:*
> *"You can say that the probability of you living for one more year is not big. That chance that you will live to 90 is considerably smaller. If I had to predict, I would say that you have a 30% to 40% more chance compared to those in your age group who presently get nothing. Not 0 though if it was at 0 we would not do anything."*

In all n=23 consultations, prognosis of the disease and its treatment was provided in a qualitative manner (n=209 quotations, 94.1%) (Figure 1a) In 30% of the interviews quantitative and qualitative methods were combined to deliver the prognostic message. In case of a qualitative method H&N surgeons varied communication approaches to share the prognostic content. We identified six different qualitative prognostic communication approaches: 1) bad news / good news flow (9%), 2) positive framing (18%), 3) negative framing (28%), 4) implicit prognosis (8%), 5) general counselling (11%) and 6) scenario analysis (20%) (Figure 1b). Examples are shown in Table 2.

Figure 1. Quantitative and qualitative approaches of prognostic information



a)



b)

The *'bad news / good news flow'* approach is characterized by good news and bad news being used in an alternating order resulting in possible uncertainty about the prognostic tendency of the provided information: positive or negative? (example 1, Table 2)

In the '*positive framing'* approach the positive aspects of prognosis are emphasized (example 2, Table 2) The negative aspects regarding prognosis are underlined in the '*negative framing'* approach (example 3, Table 2). The use of an 'implicit prognosis' approach (example 4, Table 2) is illustrative for a qualitative method of providing prognostic information. An approximation or ambiguous description of prognosis of the individual patient is used, thus implicitly providing prognostic information without being specific. An example of this method:

Table 2. Identified prognostic communication approaches used by physicians.

Approach 1) Bad news good news flow: *Example: "The last time I saw you, you were not looking well. Tthat is the reason for the scan and ultrasound. The tongue looks good and the throat is also completely fine, only in the scan there is still a small lymph node visible in the neck."*
Approach 2) Positive framing: *Example: "Now luckily for you radiation treatment only will probably be enough".*
Approach 3) Negative framing: *Example: "You see the only thing I can do is a big operation with a lot of risk and a small chance of success and I do not think that that is realistic as we are then making you worse than you are now. The risk are.. that there are huge blood vessels...you may become paralyzed on one side…you will end up in a wheel chair and a nursing home."*
Approach 4) Implicit prognosis: *Example: "Now that means that, yes, your life expectancy through this has naturally changed slightly. Look, for you is has become like heads or tails either you will survive or you will not. However if you look at it with a group of patients then there will obviously be a few patients that will indeed pass away because of this problem…that is exactly what is happening now."*
Approach 5) General counselling: *Example: "You have stopped smoking right? Yes thankfully, as that is very important…as that gives you a greater chance of getting back into the good group, as we know that people that continue to smoke have worse expectancies."*
Approach 6) Scenario analysis: *Example: "Another option is not a curative treatment. You can decide only to radiate but that will be to keep the tumor under control, reduce symptoms and slow it down. However because of the tongue tumor we do not expect you to survive."*

> *H&N surgeon:*
> *"Now that means that… yes… your life expectancy through this has naturally changed slightly. Look, for you is has become like heads or tails; either you will survive or you will not. However if you look at it with a group of patients then there will obviously be a few patients that will indeed pass away because of this problem…that is exactly what is happening now."*

In the *'general counselling'* approach general information about the course disease or treatment in a general population with regard to prognosis is given. The final qualitative approach that could be identified is *'scenario analysis'* (example 6, Table 2). Prognostic information on a 'what if' scene is provided. In this situation general conditions are outlined that could be the case for the individual patient.

Examples of different communication styles displayed by physicians

H&N surgeons possibly affect patients' perception of prognostic content with two identified communication styles: directive (more physician-centered) and affective (more

patient-centered). Several examples of the directive communication style were found (Table 3), such as the paternalistic professional attitude and the use of medical jargon during patient-physician communication.

Table 3. Examples of directive communication style

Example 1 – Paternalistic professional attitude: H&N surgeon: *"In the meantime many things have been set in motion for you...I had already requested the surgery and there is already a date planned for you."*
Example 2 – Use of medical jargon: H&N surgeon: *"Yes it is now at the T3 stage so the protocol will without a doubt say PORT."*

In the first example, the H&N surgeon has already decided – with best intentions – which treatment option is the best for the patient. The second example shows the use of medical jargon which can lead to one-way communication in which patients might feel by-passed.

We found examples of the more patient-centered affective communication style that were characterized by giving hope or by a compassionate tone of voice. Diminutive words were used along with the affective communication style. Those words appeared to alleviate the harsh message, but could also be misleading when serious subjects such as 'tumor' or 'treatment plan' were discussed (Table 4). In example 1, the physician supports the patient to take part in the decision process. In example 2, the physician is trying to provide hope to the patient. Finally, example 3 illustrates the use of diminutive words as discussed above.

Table 4. Examples of affective communication style

Example 1 – Patient empowering professional attitude: H&N surgeon: *"So we think that yes we can consider the radiation treatment. If this is what you want… as you are naturally the boss… if we say something and you do not want that, that is also fine. It is your life."*
Example 2 – Giving hope: H&N surgeon: *"One abnormality yes but again it could be a false alarm."*
Example 3 – Use of diminutive words and euphemisms: H&N surgeon: *"Yes…the X-ray was naturally not made for nothing as there are some small problems with your lungs…and…"* Patient: *"Of course, I coughed up blood."*

DISCUSSION

To our knowledge, this study is first in describing whether and how prognostic information is included during communication on diagnosis and treatment plans between H&N surgeons and their H&N oncologic patient in all phases of disease. Research has shown that providing sufficient quantitative information on life-expectancy allows patients to

make fully informed decisions.[2, 21, 23] In this study our qualitative analysis revealed that only 5.9% of the provided prognostic information included in the treatment and decision consultations was given quantitatively. In the majority of cases (94.1%) a variety of qualitative methods was used. Positive and negative framing were mostly used (46%). The same prognostic content could be interpreted differently using these framing approaches. With positive framing patients might interpret the information unrealistically optimistic and with negative framing patients might believe that they will be the ones with the bad outcome. A combination of these two approaches is found in the 'bad news / good news flow' (9%), where good and bad news are used in an alternating order, potentially resulting in insecurity about the prognostic tendency of the provided information*: "am I going to be all right or not?"*. The same might happen with a '*general counselling*' approach (11%) or '*scenario analysis'* approach (20%) where the prognostic information is general and not tailor-made to the patients specific situation. The '*implicit prognosis*' approach was seen in the minority (8%) of the qualitative approaches, while being closest to the prognostic value of the explicit quantitative approach.

Overall, we found that different communication approaches were used during one encounter in a rapid alternating order. Given the fact that patients tend to remember only 20-60% of the information provided by their physician, they may feel so overwhelmed by the amount of information, one can question if they adapted the useful part.[8]

Why is an explicit quantitative prognostic communication strategy being used in a minority of the cases? Given the 4.4% of the total time of conversations that H&N surgeons communicate prognostic information in numerical probabilities, there might be a reluctance to do so.

First, this could be due to a lack of reliable prognostic information, which is in agreement with earlier research. Prognostic judgments by physicians tend to be inaccurate and optimistically biased.[18-19] In H&N oncology, estimation of prognosis is based on the American Joint Committee on Cancer (AJCC) TNM staging classification. This objective and accurate tool is used to predict prognosis for an entire population of patients. However, it is ineffective for predicting outcomes in an individual patient, not taking into account the role of other tumor factors and important patient characteristics such as comorbidity or tobacco use.[19, 29] In order to improve predictions, prognostic models for H&N oncologic patients are developed based on multivariate survival analyses of large datasets.[30-32] These tools could help physicians with patient counselling and deciding on treatment options.

Secondly, it will take time and effort to identify patients' preferences about receiving prognostic information. Literature shows that patients desire accurate estimates of prognosis

in order to allow them to make decisions that are consistent with their values.[5, 33-34] On the other hand, patients desire, above all, to maintain hope for their situations, or do not want to receive information about their prognosis at all.[5, 35-36] That 'management of hope' permits the physician to take some liberties with prognostic estimates. Obviously, there is some tension between these two views and as mentioned before the majority of available studies focus on patients in the palliative phase of their disease.[33-36] As we used a qualitative study design, no deductions could be made about predisposing factors that could predict patient preferences on wanting prognostic information or not.

Furthermore, the right timing of sharing prognostic information is key. This is part of the professional attitude each physician possesses and the relationship built with the patient. However it is difficult for physicians to predict patients' values or preferences.[37] There is no consensus in literature on this topic. One study reported that 84% of patients with metastatic disease wanted to discuss treatment goals and options when first diagnosed, and only 59% wanted to discuss survival at that time.[5] Another study showed that common sense or intuition should guide physicians when to raise prognostic discussions.[6] Patients preferred their doctors to raise the topic of prognosis early on, as not to question the timing of raising it themselves. Physicians see communicating prognosis as a process rather than a conversation triggered by certain circumstances, such as upon diagnosis.[25] Literature shows that younger and more educated patients are associated with wanting a high level of prognostic information.[38-40] Caregivers favored full patient involvement in decision making, while patients were divided between wanting autonomy and a more passive approach.[24]

Finally, professional communication skills explain the limited use of explicit prognostic communication. Communication styles may differ and might affect patients' perception of the prognostic content. Most studies emphasize the importance of the communication style as frequently as the content.[5-7] This is underlined by our findings on professional attitude. For physicians, it sometimes seemed to be a struggle finding the right words and tone of voice. Accurate information is preferred, as long as it is not delivered bluntly or with too much hard factual or detailed information.[5-7] It is reasonable that physicians try to offer hope to cancer patients. However, a realistic perspective, including a small amount of 'negative' information about the course of disease, can help patients gain a more balanced perception of their prognosis and subsequently experience less anxiety and distress.[33, 39, 41] In confirmation with literature, patients favor information conveyed in a compassionate and empathic manner.[42] Patients prefer information given in a digestible manner using appropriate language, avoiding medical jargon.[43] In addition, information may need to be repeated on different occasions to meet patient's individual needs and to

prevent the 'one-way-process' of overwhelming the patient with information and different communication strategies.[44]

Strengths and limitations

The major strength of this study is that it gives a unique insight behind closed doors. Insight is gained in otherwise private consultations between H&N surgeons and their patients. Another strength is that we included patients with all stages of disease. At the same time this is a limitation of the study because life expectancy and therefore prognosis is inevitably worse in patients in the palliative phase of disease. As patients volunteered to partake in this study it is possible that the results of this study represent the more 'engaged' patients and caregivers; those who are interested in prognosis and quality of life, and present a participating attitude during the consultation. Additionally bias could be introduced as physicians are aware their conversations are registered. Despite these limitations, the study results add to an underexposed subject and enabled us to better understand communication of prognosis in patients with H&N cancer.

PRACTICE IMPLICATIONS

Based on our results and discussion of the topic, we prepared first steps for a guideline for sharing prognostic information in H&N oncology practice (Table 5). These suggested steps are meant as a stimulus to encourage sharing prognostic communication in a clinical setting. We recommend to provide written information on treatment options to assist patients and caregivers with retaining information and to overcome the 'one-way-process' whereby a physician provides a large amount of information to patients.[45] Additionally, the presence of a case manager or an additional visit to an oncology nurse could be of added value to both patient as H&N surgeon. This is an easy accessible professional who can take some more time with the patient in order to clarify and confirm the physician's message.

Table 5. Guideline for sharing prognostic information in H&N oncology practice.

Step 1: Explore patient preferences on receiving prognostic information
Step 2: Assure there is accurate or as personal as possible information on the prognosis of the individual patient
Step 3: Initiate a conversation about life expectancy
Step 4: Use prognostic information in an empathic, honest and digestible way
Step 5: Avoid use of a directive communication style; yet give a realistic perspective of prognosis
Step 6: Recognize prognostic communication as a process and if needed repeat information on different occasions

CONCLUSION

This study is first in providing examples of how H&N surgeons communicate with their patients regarding prognosis in all stages of disease. Understanding the difficulties of communicating prognosis will take us a step further into our strive for patient-centered counselling and shared decision making. This study points out that specific quantitative prognostic information is often not included in communication between H&N oncologic surgeons and their patients and different qualitative methods are used instead. Doctors should be aware of both their communication approach for discussing prognosis and their communication as this might affect patients' understanding and perception of information provided. Prognostic models can contribute to knowledge and thus enhance patient empowerment and make shared decision possible.

Future research

With this study we add to an underexposed subject of research on prognostic communication in head and neck oncologic patients. However there is a need for creating patient-preference studies, starting research on the efficacy of our suggested approach of prognostic communication and developing decision aids for patients and caregivers. In our clinic we have started a study based on focus group methodology to discover patient preferences in prognostic communication. There is limited data on effective teaching methods to promote long-term change of communication skills. Research should focus on whether feedback is an essential element and how best to incorporate decision aids into conversations. Finally, development of reliable, internally and externally validated sophisticated prognostic models is needed to support physicians in providing tailor-made prognostic information to their patients.

Acknowledgements

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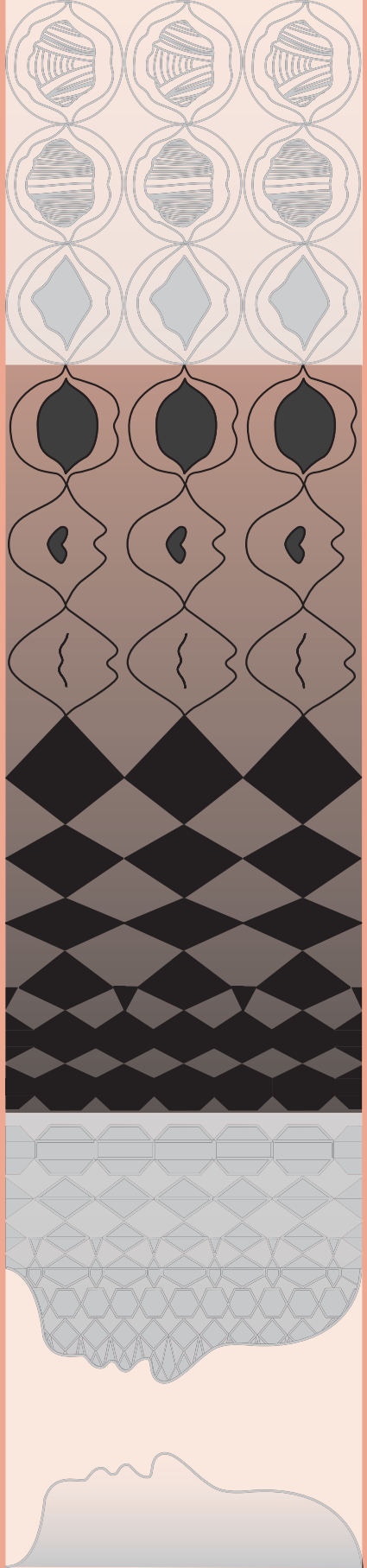
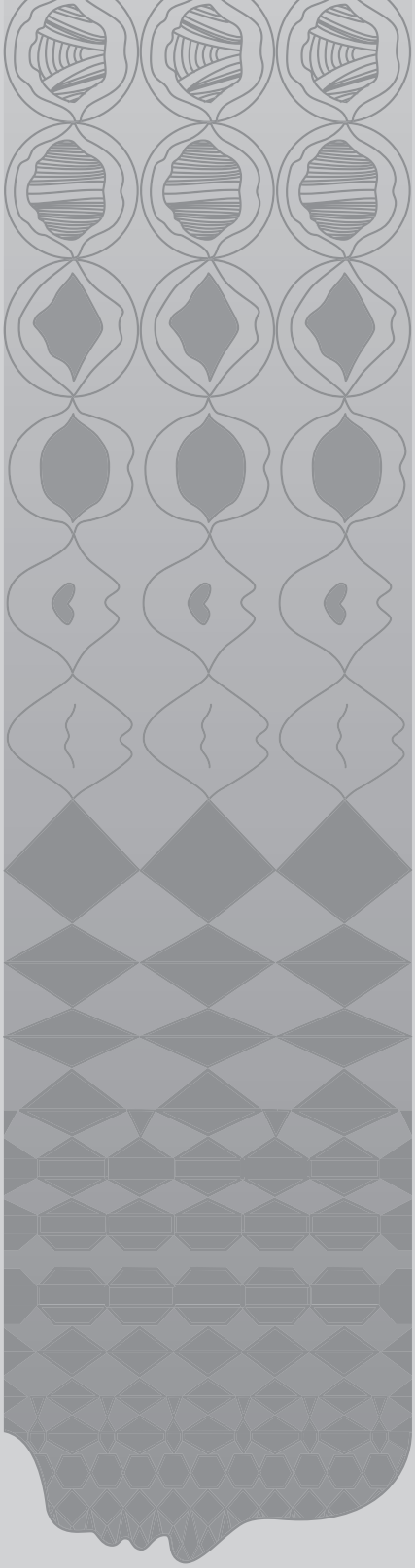


Part III

Tools for personalized counselling: development of prognostic models



4

Influence of anemia and BMI on prognosis of laryngeal squamous cell carcinoma: development of an updated prognostic model

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** Both authors contributed equally to this work.*

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ABSTRACT

The objective of this study was to study the impact of anemia and body mass index (BMI) on survival, and development of a prognostic model for overall survival for patients with laryngeal squamous cell carcinoma (LSCC). A retrospective cohort study was performed including all consecutive patients with LSCC diagnosed and treated at the Erasmus Medical Center between January 2006 and December 2013. Patient- and tumor-specific data were collected using data from the Netherlands Comprehensive Cancer Organization and supplemented with data from patient records available in the Erasmus MC. All comorbidities were scored at the time of diagnosis. In total 788 patients were included. Mean follow-up time was 50 months (SD: ± 30), during which 298 patients (37.8%) died. In both univariate and multivariate analysis BMI and anemia were significant predictors for overall survival. Multivariate analysis was performed using known predictors such as age, TNM-stage and comorbidity (ACE-27). The hazard ratio of anemia was 1.41 (95% CI: 1.05 - 1.90) and of BMI was 0.97 (95% CI: 0.94 - 0.99). BMI had an inverse association with overall survival in both univariate and multivariate survival analysis. Updating and validating an existing prognostic model with addition of anemia and BMI enhanced the performance of the prognostic model (C-statistic) from 0.77 (95% CI: 0.74 – 0.79) to 0.79 (95% CI: 0.77 - 0.82). Anemia and BMI are predictors of overall survival for LSCC, independent of other known predictors of overall survival. Adding anemia and BMI to an existing prognostic model provides better prediction of overall survival.

INTRODUCTION

Malignancies of the head and neck are predominantly located in the oral cavity (including the lips), pharynx (including nasopharynx) and the larynx. The worldwide incidence of these tumors was over 680,000 cases in 2012, resulting in 4.9% of all malignancies. Mortality of head and neck tumors made up 4.6% of all mortality due to a malignant disease.[1]

In the Netherlands, over 38% of all head and neck squamous cell carcinoma (HNSCC) originates from the larynx.[2] Also, laryngeal squamous cell carcinoma (LSCC) has a favorable prognosis compared to HNSCC as a whole.[2] Treatment of LSCC can impair speech, swallowing and breathing, which have a profound impact on the quality of life.[3,4] Prognosis and morbidity of LSCC are therefore significant topics in communication between physicians and their patients.

In the recent past, our research group developed prognostic models to estimate patients' individual prognosis to support decision making.[5,6] In these models, besides cTNM stage and age, comorbidity, scored with the Adult Comorbidity Evaluation 27 (ACE-27), turned out to be an important prognostic factor for overall survival.[7,8]

However, more recent studies show that the presence of anemia and low Body Mass Index (BMI) also negatively impact patient survival of HNSCC. [9,10] A systematic review on the impact of BMI on survival shows better survival for patients with a BMI above 25.0.[10] However, other comorbidities (as measured by ACE-27) or weight loss were not addressed in this study. In addition, the presence of anemia is known to negatively impact the efficacy of radiotherapy [11], but the effect of anemia on overall survival of patients with HNSCC treated otherwise is presently not known. Furthermore, anemia is not taken into account in comorbidity indexes nor in existing prognostic models.

As prognosis is an important factor during patient counseling, insight in the influence of anemia and BMI amongst other comorbidities on survival of head and neck malignancies is needed. Therefore, the purpose of this study is to report on the impact of anemia and BMI on overall survival of LSCC, independent of other comorbidities. The secondary objective is to determine whether adding anemia and BMI improves the existing prognostic model.

METHODS

This study was approved by the ethics committee of the Erasmus Medical Center (Erasmus MC) (MEC number: MEC-2016-751). Patients with glottic and supraglottic squamous cell carcinoma who were diagnosed and treated at the Erasmus MC between January 1st, 2006 and December 31st , 2013, were included in this retrospective study. Patients were excluded in case of a synchronous primary tumor in the head and neck region, when a patient died before completion of diagnostics or when records were incomplete.

Primary outcome of this study was overall survival and the secondary outcome was Harrell's concordance statistic for internal validation of an updated prognostic model.

Data collection

Tumor- and patient-specific data regarding these patients were obtained from the Netherlands Comprehensive Cancer Organization (NCCO) and merged with corresponding data from the patient records of Erasmus MC. Subsequently, the data were manually checked for each patient using available data from the patient records. Incorrect or missing data was either revised or supplemented by the research staff.

If there was any doubt on the validity of the data collected, the patient was discussed by the research staff until a consensus was reached. A log was kept in which the inclusion of patients was recorded.

Definitions

Information on patient specific comorbidities, anemia, intoxications, length, weight and weight loss was scored Both patient- and disease specific data was scored at the time of diagnosis. Comorbidity was scored using the Adult Comorbidity Evaluation-27 (ACE-27). This ACE-27 index consists of 27 different endpoints in 9 organ systems. Severity of comorbidity was classified into four categories: none, slight, moderate and severe (ACE-27 score 0, 1, 2, and 3 respectively). [6,11]

Anemia was defined as hemoglobin levels below 8.5 mmol/L for men and below 7.5 mmol/L for woman, which corresponds to 13.7 and 12.1 g/dL respectively. Length and weight was used to calculate the Body Mass Index (BMI). Patients were categorized in underweight (BMI < 18.5), normal weight (BMI ≥18.5 and <25), overweight (BMI ≥25 and <30), obese (BMI ≥30 and <38) and morbid obese (BMI ≥38). A BMI ≥38 was chosen as the cut-off for morbid obesity (instead of BMI ≥35) as this corresponds to a moderate comorbidity in the ACE-27 comorbidity index.

Weight loss was defined as the percentage of weight patients lost within 6 months prior to diagnosis of the tumor. It was subdivided in no- to mild weight loss (0-5%), moderate weight loss (5 – 10%) and severe weight loss (>10%).

Intoxications were defined as tobacco- and alcohol use. Data on (former) use at the time of diagnosis was collected. If tobacco use had occurred in any time in the past, the total pack years was registered. Marital status was defined as having a partner (either married or having a durable long term relationship), or being either single or widowed. Finally, we recorded if the received therapy was in accordance with standard treatment protocol at the time of diagnosis.

Data on patient follow-up was obtained using the Dutch Civil Registry and data available in the Erasmus MC. Final day of follow-up time for a patient was defined as the final date that the patient was confirmed to be alive. Follow-up ended on the 31st of December 2015, resulting in a minimum follow-up duration of 2 years.

Statistical analysis

The data was analyzed using IBM SPSS (version 21.0) and R (version 3.4.0) statistical software. Descriptive statistics were performed for all variables and, if applicable, the assumption of a Gaussian distribution was verified. Associations between the collected covariates were studied using the Pearson Chi-square test for categorical data and Student t-test or Wilcoxon rank test for continuous data. During univariate analysis, BMI was analyzed as both a continuous and categorical variable. Univariate analysis of overall survival was performed on all available variables by applying Kaplan-Meier analysis (log-rank test) and the Cox proportional hazard regression model was used to calculate the univariate hazard ratios.

Some data were missing for the variables anemia, BMI, weight loss and variables related to intoxications, see Table 1. After analyzing patterns of our missing data, data were considered missing at random (MAR).[12] Since the MAR assumption was plausible, we found multiple imputation (MI) to be the best way to handle our missing data. After analyzing patterns of the missing data, data were considered missing at random. We performed MI using the Markov Chain Monte Carlo (MCMC) function in SPSS and used 5 iterations to account for possible simulation errors. Therefore the missing data were imputed using multiple imputation with the iterative Markov Chain Monte Carlo (MCMC) method. A total of five iterations were performed. Multivariate statistical analysis was performed by using the pooled data of all five iterations in a Cox proportional hazard regression model. Multiplicative interaction terms were taken into account. Covariate selection was performed using all available variables and subsequently eliminating variables using backward

stepwise elimination until all variables left had a p-value below 0.10. Continuous variables used were age at time of diagnosis, pack years and BMI. All other variables used were categorical. For both univariate and multivariate analysis, a p-value lower than 0.05 was considered significant.

After performing multivariate Cox proportional hazard regression analysis of overall survival, we created a prognostic model using all variables previously defined as prognosticators by our study group (Datema et al. in 2010 and Van der Schroeff in 2012).[5,6] The following variables were included for the prior model: gender, tumor site, age at time of diagnosis, TNM-stage and ACE-27 comorbidity score. The prior model was then updated with freshly defined significant prognosticators from our current study. Afterwards, Harrell's concordance statistic (C-statistic) was used to internally validate the model. After creation of the two prognostic models, C-statistic was used to assess the discriminative ability of the model. Internal validation by bootstrapping our data 1000 times corrected for optimism. After internal validation, the C-statistic was used to compare the new model with the prior model. For estimating the C-statistic of this prior model the data of the current study was used.

RESULTS

A total of 819 patients with primary LSCC between January 2006 and December 2013 were identified. Ten patients were excluded for having synchronous primary head and neck tumors. Another sixteen patients were excluded due to the origin of index tumor being subglottic or unspecified. Finally, three patients died before the diagnostic process was completed and two patients were lost to follow-up while it was unknown whether they received therapy. The remaining 788 patients were included in this study. Patient demographics are presented in Table 1.

Mean duration of follow-up was 50 months (SD: ± 30 months), during which 298 patients (37.8%) died. Two-year survival was 79.4% (SD: ± 2,7%) and five year survival was 63.7% (SD: ± 3.5%).

Overall survival

After univariate analysis, the following variables showed a significant correlation with overall survival: age, tumor localization, clinical TNM-staging, received treatment (yes/no), treatment according to standard treatment protocol (yes/no), ACE-27 score, marital status, BMI, weight loss, anemia and pack years. Of these variables, the following variables have hazard rates which increase by year or unit increase: age, pack years and BMI. See Table 2 for an overview of the univariate survival analysis.

Table 1. Demographics of the total patient population (n = 788)

Variables		No. of patients (%)	Missing (%)
Gender	Men	651 (82.6)	-
	Woman	137 (17.4)	
Mean age at time of diagnosis (years)		66 ± 10	-
Tumor localization	Glottis	530 (67.3)	-
	Supraglottis	258 (32.7)	
T – stage	1	19 (2.4)	-
	1A	260 (33.0)	
	1B	52 (6.6)	
	2	183 (23.2)	
	3	192 (24.4)	
	4A	82 (10.4)	
N – stage	0	661 (83.9)	-
	1	55 (7.0)	
	2	68 (8.6)	
	3	4 (0.5)	
M - stage	0	786 (99.7)	-
	1	2 (0.3)	
Treatment given	Yes	765 (97.1)	-
	No	23 (2.9)	
Treated according to protocol	Yes	698 (88.6)	-
	No	90 (11.4)	
Smoking	Current	477 (60.5)	5 (0.6)
	Former	266 (33.8)	
	Non-smoker	40 (5.1)	
Mean pack years		41 ± 22	183 (23.2)
Alcohol	Current	545 (69.2)	6 (0.8)
	Former	178 (22.6)	
	Non-drinker	59 (7.5)	
ACE-27 total score	0 (none)	224 (28,4)	-
	1 (mild)	273 (34.6)	
	2 (moderate)	204 (25.9)	
	3 (severe)	87 (11.0)	
Marital status	With partner	542 (68.8)	35 (4.4)
	No partner	211 (26.8)	
Body Mass Index	< 18.5	28 (3.6)	65 (8.1)
	≥ 18.5 and < 25	294 (37.3)	
	≥ 25 and < 30	275(34.9)	
	≥ 30 and < 38	106 (13.5)	
	≥ 38	21 (2.7)	
Weight loss	< 5%	526 (66.8)	158 (20.0)
	≥ 5% and < 10%	56 (7.1)	
	≥ 10%	48 (6.1)	
Anemia	Yes	121 (15.4)	55 (7.0)
	No	612 (77.7)	

Table 2. Univariate analysis of overall survival of patients with LSCC

Variables		Hazard Ratio (95% CI)	Overall P-value
Gender	Men*	-	0.462
	Women	0.89 (0.65 - 1.22)	
Age at time of diagnosis (years)**		1.05 (1.04 - 1.06)	0.000
Tumor localization	Glottis*	-	0.000
	Supraglottis	2.49 (1.98 - 3.13)	
T-stage	1A + 1*	-	0.000
	1B	1.82 (1.06 - 3.13)	
	2	1.98 (1.39 - 2.82)	
	3	3.84 (2.78 - 5.30)	
	4A	4.47 (3.04 - 6.57)	
N-stage	0*	-	0.000
	1	2.76 (1.94 - 3.94)	
	≥2	2.64 (1.92 - 3.64)	
Treatment given	Yes*	-	0.000
	No	46.40 (27.78 - 77.48)	
Treatment according	Yes*	-	0.000
to protocol	No	3.38 (2.55 - 4.48)	
Smoking	Never*	-	0.965
	Yes	0.98 (0.58 - 1.66)	
	Former	1.02 (0.59 - 1.75)	
Pack years**		1.01 (1.01-1.02)	0.000
Alcohol	Never*	-	0.113
	Yes	0.95 (0.72 - 1.25)	
	Former	1.44 (0.92 - 2.24)	
ACE-27 score	0 (none)*	-	0.000
	1 (mild)	1.86 (1.33 - 2.61)	
	2 (moderate)	2.21 (1.55 - 3.13)	
	3 (severe)	5.95 (4.09 - 8.66)	
Marital status	With partner	-	
	No partner	1.32 (1.03 – 1.69)	0.030
Body Mass Index**		0.96 (0.94 - 0.99)	0.004
Weight loss	<5%*	-	0.000
	≥ 5% and < 10%	2.47 (1.70 - 3.57)	
	≥ 10%	2.53 (1.68 - 3.81)	
Anemia	No*	-	0.000
	Yes	2.81 (2.16 - 3.67)	

*: reference value, **: hazard ratio per unit or year increase.

An increase in BMI was related to a decrease in mortality (Figure 1A). In contrast to the inverse relationship between high BMI and mortality, a J-shaped relationship between BMI and comorbidity could be seen (Figure 2). Both underweight patients and overweight/obese patients showed an increase in moderate to severe comorbidity. Nearly 76.8% of patients who lost more than 5% of their weight in the six months prior to diagnosis had a BMI below 25.0.

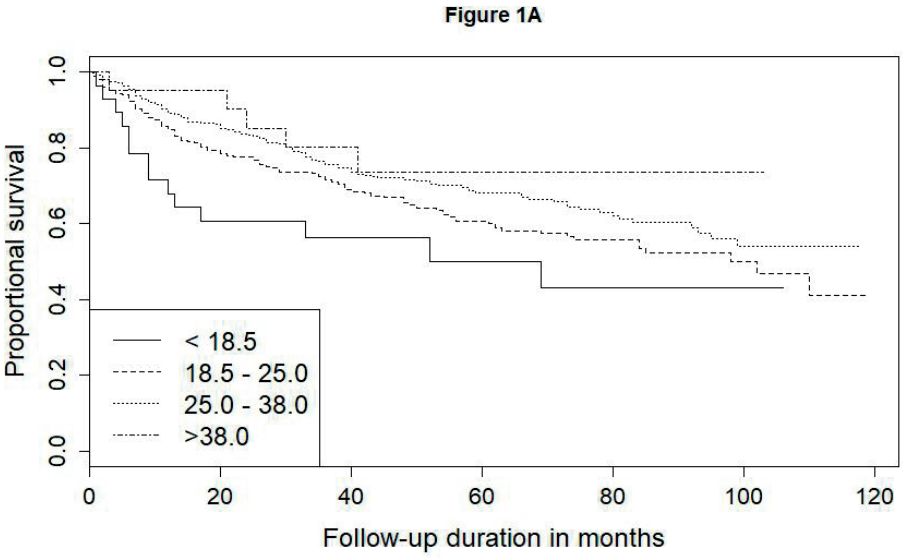
The presence of weight loss showed to be a significant predictor for worse overall survival, with the prognosis of moderate and severe weight loss being similar (Figure 1B). Furthermore, patients with over 5% weight loss had significantly higher T-stage and N-stage (p=0.000). No significant correlation between weight loss and comorbidity could be found.

Presence of anemia showed to have a negative impact on overall mortality (Figure 1C). Anemia was found in 11.3% of all patients with T1-2 LSCC, which is lower when compared to T3 and T4 tumors (23.0 and 32.1% respectively, p=0.000). Additionally, patients with loco-regional lymph node metastasis more often suffered from anemia compared to patients without nodal metastasis (14.8% vs 25.0%, p=0.020). Anemia occurred in 29.6% of patients with moderate to severe weight loss and in 13.1% of patients without weight loss (p=0.000). Finally, anemia had a higher prevalence in patients with severe comorbidity, when compared to patients with no- to moderate comorbidity scores (35.3% versus 14.0%, p=0.000). For an overview of the effect of comorbidity on survival, see Figure 1D.

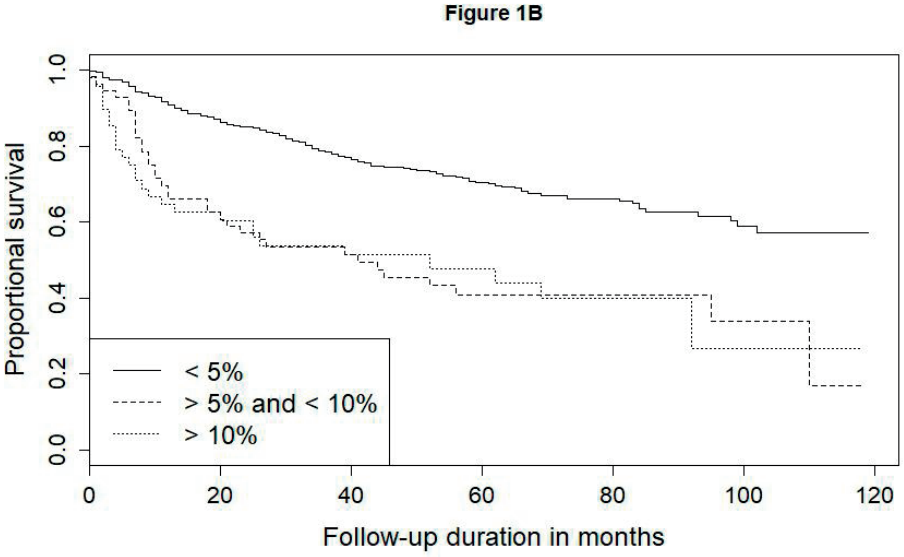
Of all patients, only 90 did not receive treatment according to standard treatment protocols. Of these, 38 patients (38.9%) refused treatment according to guidelines, while the remaining patients (n=52; 61.2%) did not receive therapy according to protocol on the basis of expert opinion. Of the underweight patients, significantly more patients (28.6%) were not treated according to guidelines compared to normal weight (12.2%) or overweight (8.7%) patients (p=0.000). Also anemia was significantly associated with not receiving treatment according to protocol (75.2%) versus 91.2% of all patients without anemia (p=0.000). Similarly, in patients with no- to moderate comorbidity only 9.7% did not receive treatment according to protocol, compared to 26.3% in patients with severe comorbidity (p=0.000).

After establishing the univariate relationship between the tumor- and patient-specific variables mentioned above, multivariate Cox regression survival analysis was performed. A multiplicative interaction term was found between tumor localization and T-stage. All variables except M-stage, pack years, weight loss and 'treatment according to protocol' remained significant after correcting for each variable in the multivariate analysis. An overview of the multivariate analysis is given in Table 3.

Figure 1. Kaplan Meier survival curves for overall survival

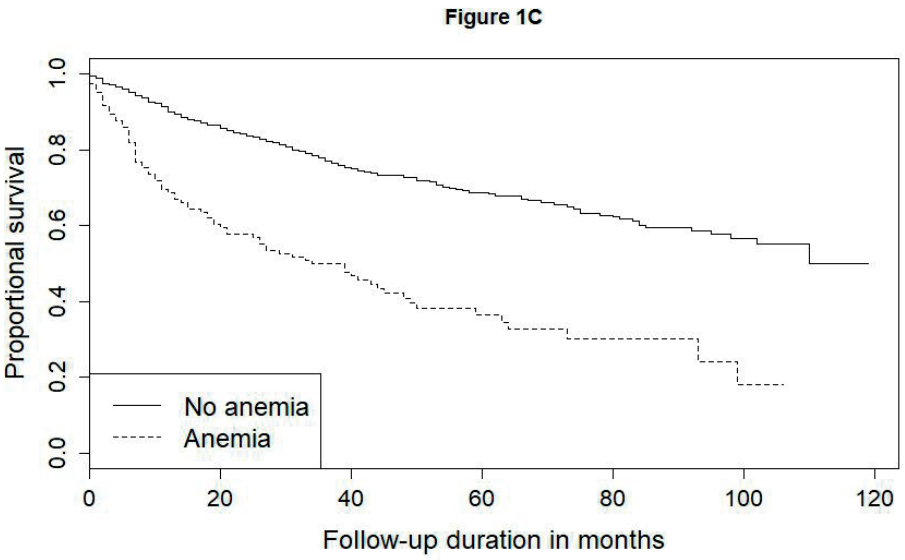


1A. Body Mass Index (categorical),

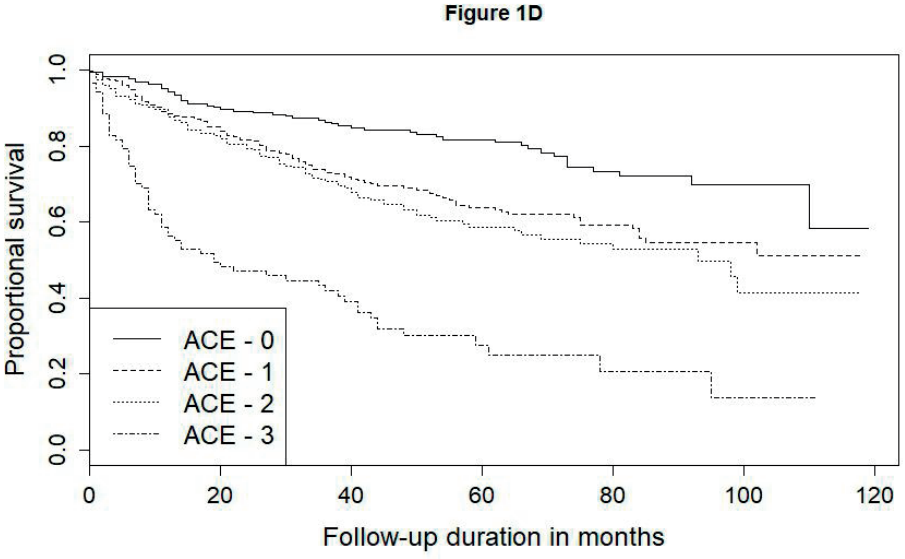


1B: weight loss (in %),

Figure 1. Kaplan Meier survival curves for overall survival

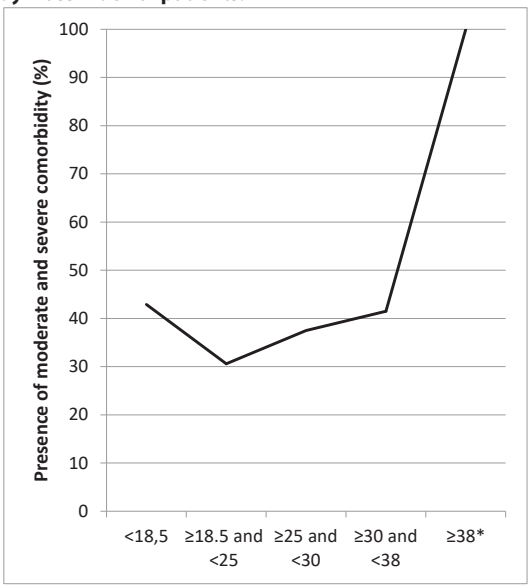


1C: presence of anemia,



1D: comorbidity scored according to the ACE-27 comorbidity index.

Figure 2. Presence of moderate and severe comorbidity scored using the Adult Comorbidity Index – 27, set against the Body Mass Index of patients.



*: in the ACE-27 comorbidity index, a BMI ≥38 is scored as a moderate comorbidity. Therefore all patients had a total comorbidity score of moderate or severe.

Prognostic model comparison

First, we performed a multivariate Cox proportional hazard regression analysis with our LSCC data, using the variables presented in the model as proposed by Datema et al. and Van der Schroeff et al. (gender, 'age at time of diagnosis', tumor localization, cTNM-stage and ACE-27 comorbidity score). [5,6] We bootstrapped our data 1000 times to internally validate this model, We performed internal validation by bootstrapping our data, which resulted in a C-statistic of 0.77 (95% CI: 0.74 – 0.79).

Then, we fitted our new multivariate model, including: gender, 'age at time of diagnosis', tumor localization, cT- and N-stage, ACE-27 comorbidity score, treatment given (yes/no), pack years (continuous), BMI (continuous), weight loss and anemia. Again, we performed internal validation by bootstrapping our data 1000 times, leading to a C-statistic of 0.79 (95% CI: 0.77 – 0.82). The difference between these C-statistics (0.77 and 0.79) was borderline significant.

Table 3. Multivariate analysis of overall survival of patients with LSCC

Variables		Hazard Ratio (95% CI)	P-value
Age at time of diagnosis (years)**		1.05 (1.03 - 1.06)	0.000
Tumor localization	Glottis*	-	-
	Supraglottis	3.03 (1.48 - 6.26)	0.003
T-stage	1A and 1*	-	-
	1B	2.27 (1.29 - 3.99)	0.004
	2	1.93 (1.51 - 2.97)	0.003
	3	3.89 (2.41 - 6.28)	0.000
	4A	4.95 (2.93 - 8.36)	0.000
N-stage	0*	-	-
	1	1.35 (0.90 - 2.04)	0.150
	≥2	1.13 (1.63 - 2.40)	0.013
Treatment given	Yes*	-	-
	No	12.80 (6.94 - 23.60)	0.000
Pack years**		1.006 (1.000 - 1.012)	0.069
Total ACE-27 score	0 (none)*	-	-
	1 (mild)	1.33 (0.93 - 1.89)	0.121
	2 (moderate)	1.57 (1.07 - 2.30)	0.019
	3 (severe)	3.32 (2.18 - 5.08)	0.000
Body Mass Index**		0.97 (0.94 - 0.99)	0.033
Weight loss	< 5%*	-	-
	≥ 5%	1.38 (0.99 - 1.90)	0.054
Anemia	No*	-	-
	Yes	1.41 (1.05 - 1.90)	0.024

*: reference value, **: hazard ratio per unit or year increase.

DISCUSSION

In this study, we demonstrated that anemia and low BMI both have a significant impact on overall survival independently of the presence of comorbidity as measured by the ACE-27 index. Addition of both anemia and BMI to an existing prognostic model showed a borderline significant improvement of the predictive power of the model.

Two recent reviews discussing the relationship between BMI and survival concluded that BMI had a J- or a U-shaped relationship with mortality. Both excessively low and high BMI resulted in a worse prognosis.[13,14] In contrast, univariate survival analysis of BMI in our study showed an inverse relationship with overall survival.

We observed a J-shaped relationship between BMI and comorbidity. The difference between this J-shaped relationship and the inverse relationship between BMI and survival

suggest that the impact of BMI on survival was independent of comorbidity. This was confirmed by our multivariate analysis, in which we adjusted for comorbidity . The cause for this may be related to the obesity paradox.[15] In this paradox the presence of high BMI is a favorable prognostic factor for patients with chronic disease, such as malignancies.

In a review on the impact of BMI on survival of head and neck malignancies, published in 2015, BMI was also inversely correlated with survival.[10] This review stated that patients with high BMI may have higher nutritional reserves. This may be beneficial during treatment, as treatment (such as chemo-radiation therapy) may lead to less intake. Furthermore, Hollander et al. mentioned that pre-existing illnesses and weight loss could be a confounder to the presence of low BMI.[10] However, they did not report on the prevalence of these variables. After we took into account both the ACE-27 comorbidity index and weight loss, BMI still had a significant negative association with overall survival. Gama et al. also found that BMI remained a predictor of overall survival after adjusting for presence of comorbidity.[16]

In the ACE-27 comorbidity index, BMI above 38 is classified as a moderate comorbidity. No comorbidity score is given to underweight patients. This is not in accordance with the inverse relationship between BMI and survival found in our study. In addition, no multiplicative interaction term was found between BMI and the ACE-27 comorbidity index. Therefore, our results suggest that the ACE-27 comorbidity index may be sub-optimal in evaluating the prognosis of patients with LSCC.

According to literature, 20.2% of all patients with head and neck cancer have ≥5% weight loss within 1 month or ≥10% in the last 6 months at the time of diagnosis.[17] In our study 15% of all patients had ≥5% weight loss in the 6 months prior to diagnosis. Patients with malignancies of the glottis are known to show less than 10% weight loss at the time of diagnosis.[17] This group made up nearly two thirds of our study, which may explain the lower prevalence of weight loss. Weight loss is known to have higher prevalence at the time of treatment initiation then at the time of diagnosis (32.2% versus 20.2%) and prevalence shows high discrepancy between early and late stages of disease.[17]

In univariate survival analysis moderate and severe weight loss had a similar influence on overall survival. Langius et al. reported that weight loss has a negative impact on prognosis in both univariate and multivariate analysis. However, they had not taken comorbidity or BMI into account.[18] In a similar study which included HNSCC from all tumor sites, Datema et al. reported that weight loss (classified as >10% of total body weight) was a predictive factor for overall survival in univariate but was no longer significant in multivariate survival analysis.[19] This is in line with our study, as after performing multivariate survival analysis in our study, the association between ≥ 5% weight loss and survival was no longer signifi-

cant after multivariate survival analysis. However, we measured weight loss at the time of diagnosis, while prevalence is known to be higher at the start of treatment.[17] Therefore, new studies should be performed in order to further investigate the relationship between weight loss, BMI and survival in both LSCC and head and neck cancer in general.

Prevalence of anemia in this study was far lower than reported in several recent studies. Hoff et al. reported a prevalence of 41.3% and Baumeister et al. reported 53.7%, compared to 15.4% in our study.[20,21] Several differences in study population may explain this finding. Hoff et al. reported significantly more regional metastases (N+; prevalence of 54.8% versus 16.1%) and more T3 and T4 tumors (52.4% versus 47.6%). Furthermore, his study population consisted of 69.8% pharyngeal- and 30.2% supraglottic malignancies.[20] Baumeister et al. focused on oropharyngeal malignancies, and reported 66% moderate and severe comorbidity versus 36.9% in our study.[21] In our study comorbidity, T- and N-stage have shown to be significantly correlated with the presence of anemia. Furthermore, Baumeister et al. included low hematocrit levels and low red blood cell count as independent variables for defining anemia, which could also explain the discrepancy in prevalence of anemia.[21]

During univariate analysis, presence of anemia proved to have a significantly negative influence on overall survival. This association persisted after adjusting for other known predictors of overall survival, including T-stage, N-stage and comorbidities. The hazard ratio of anemia (HR = 1.41) is very similar to the hazard ratio of a moderate comorbidity (HR = 1.57). Reasoning behind the impact of anemia on overall survival may be because of the impact of anemia on treatment, but also because it may be a marker for underlying tumor cachexia.

While we did not have data on patient treatment, anemia is known to decrease the effectiveness of radiotherapy.[11] It results in a reduction of overall survival and local control of head and neck cancer treated with radiotherapy.[22-24] Furthermore, blood transfusions or administration of erythropoietin do not improve prognosis.[22,25,26] However, transfusions temporarily lessen symptoms such as fatigue and breathlessness, and therefore may improve quality of life. [27]

A study on the effect of anemia on outcomes of surgical treatment of oral SCC also reported that a decrease in pre-treatment hemoglobin levels lead to an increase in local recurrence and lymph node metastasis.[28] A second study, in which all 336 patients received surgical therapy and only 30% received post-operative radiotherapy, concluded that patients who were not anemic have better overall survival and relapse-free survival. [9]

Finally, anemia is known to be one of the diagnostic criteria for tumor cachexia, along with weight loss.[17,29] Presence of tumor cachexia is known to negatively impact overall survival and thus may be an underlying confounder.[17,29] Therefore, more research is needed on the role of tumor cachexia and anemia as independent variables for survival.

Our research group develops prognostic models for head and neck carcinoma since 2001, with the intention to help reduce the gap between scientific studies and clinical practice.[30] The prognostic model created in the current study showed to be able to predict overall survival with LSCC fairly good, with a reasonably good C-statistic of 0.79. The C-statistic was a slight improvement over the previous model by Datema et al. and van der Schroeff et al. (C-statistic of 0.77 with our LSCC data). The previously published model of Datema et al. for head and neck cancer originating from all head and neck regions, reported a lower C-statistic of 0.73.[5] The article published by Van der Schroeff et al., again reporting on a prognostic model for all head and neck HNSCC, stated a C-statistic ranging from 0.76 for 1 year survival to 0.69 for 5 year survival.[6] Reason for the higher C-statistic in the current study may be due to the homogenous population of only laryngeal carcinomas.

All data on BMI and weight loss was scored at the time of diagnosis. It is known that prevalence of weight loss at the time of diagnosis is lower than at the start of treatment, which also affects patient BMI.[17] This may have led to an overestimation of patient BMI and as a result an underestimation of the impact low BMI has on patient survival. In a similar way, presence of anemia may be affected by the time delay between diagnosis and start of treatment. However, more research is needed to confirm this.

Study strengths and limitations

A major strength of this study is the large consecutive patient population with only a minimum of missing data. Also this study is first in describing the relationship between BMI, general comorbidities and survival in patients with LSCC.

However, there are several limitations to this study. First of all, we did not take socio-economic status (SES) into account. Several studies have shown the importance of SES in head and neck carcinoma.[31-35] However, the variables marital status, comorbidities, smoking status and TNM stage at time of diagnosis are related to SES.[31-33] Several studies show that after taking all these variables into account during multivariate analysis, survival of LSCC is no longer associated with SES.[34,35]

A second study limitation is the moment of data inclusion. All data on anemia, BMI and weight loss was scored at the time of diagnosis. It is known that prevalence of weight loss at the time of diagnosis is lower than at the start of treatment. Not only does this affect

weight loss, it also affects patient BMI.[17] This may have led to an overestimation of patient BMI and, as a result, an underestimation of the impact low BMI has on patient survival. Presence of anemia may also be affected by the time delay between diagnosis and start of treatment.

Additionally, anemia is known to be one of the diagnostic criteria for tumor cachexia, along with weight loss.[17,29] Presence of tumor cachexia is known to negatively impact overall survival and thus may be an underlying confounder.[17,29] Therefore, more research is needed on the role of tumor cachexia and anemia as independent variables for survival.

CONCLUSION

Our study has shown that the presence of anemia and low BMI have an independent negative effect on overall survival of LSCC. During patient counseling, physicians should take presence of anemia and low BMI into account before deciding on patient treatment proposal. The new improved prognostic model presented in this study, which includes both anemia and BMI, may help to improve estimation of prognosis in patients suffering from laryngeal carcinomas. Future research should focus on updating prognostic models for all head and neck cancer localizations with inclusion of anemia and BMI.

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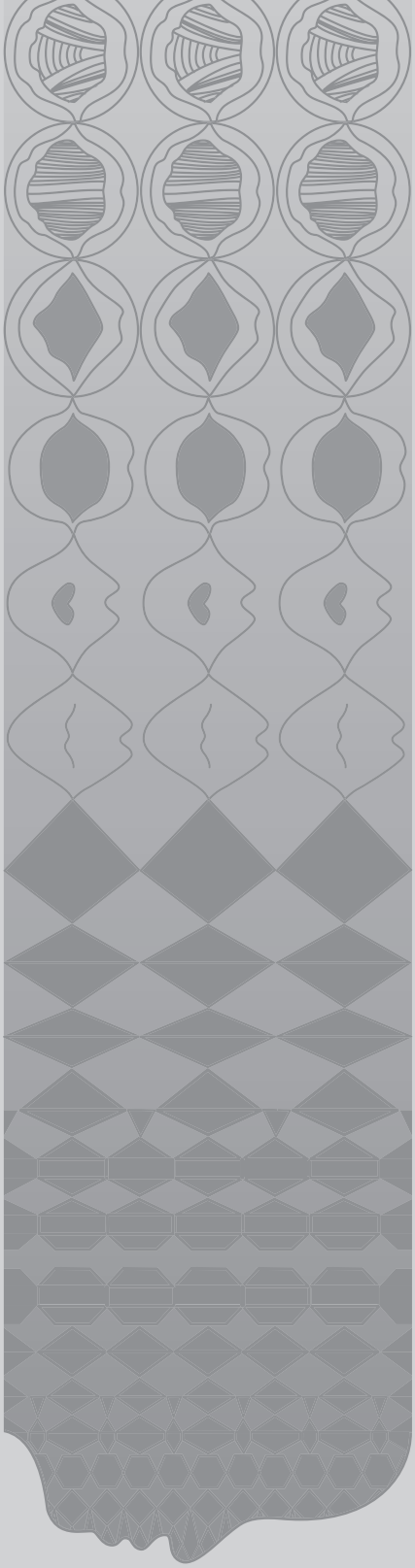

5

Value of Human Papilloma Virus (HPV) as a marker of prognosis for oropharyngeal cancer: validation and decision curve analysis of an updated prognostic model for patients in Western Europe and the USA

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ABSTRACT

Human Papilloma Virus (HPV) infection is a prognostic factor in oropharyngeal squamous cell carcinoma (OPSCC). We developed an updated prognostic model for OPSCC, including HPV status, based on a large consecutive series of patients diagnosed and treated in three international multi-institutional cohorts. An internal- external cross validation procedure was followed and decision curve analysis (DCA) was performed to evaluate the reliability of decisions based on predictions derived from the prognostic model. The updated prognostic model, including 8th TNM classification and a separate variable for HPV, performs reasonably good and very similar to the original model in terms of calibration and discrimination. DCA however shows an improved clinical utility in comparison with the original model. The updated model could therefore be used for counselling patients about their individual prognosis.

INTRODUCTION

Over the last decades, rising incidence rates of oropharyngeal squamous cell carcinoma (OPSCC) in several geographical areas have been reported. Infection with human papillomavirus (HPV) is the major cause of these rising incidence rates.[1,2] The prevalence of HPV-positive OPSCC varies between studies. Ranges from 20 -70% in Europe and up to 90% in the United States have been reported.[1,3,4] HPV-related OPSCC is a distinct entity in contrast to tobacco- and alcohol related head and neck cancer, with regard to cellular, biologic and clinical characteristics.[5] Patients with HPV related OPSCC have an advanced N-status, better loco regional control and improved 5-year survival rates after treatment.[6] Therefore, HPV status has emerged as the main prognostic factor in OPSCC.

Recently the 8th edition UICC/AJCC TNM staging of OPSCC has been divided into two different staging systems for both HPV related OPSCC and non-HPV related OPSCC.[7] The new staging rules permit a more appropriate depiction of the prognosis of HPV-positive disease than is supplied by the 7th edition TNM classification. The discrimination of stages is especially better in HPV related OPSCC patients with smaller tumors and advanced N-status.[8]

The 8th edition of the UICC/AJCC TNM staging of OPSCC uses the immunohistochemical detection of p16 as a surrogate marker for HPV-induced carcinogenic transformation. p16 is a relatively easy, low-cost measurement, which can be easily performed on formaldehyde fixed and paraffin embedded pretreatment (FFPE) tumor samples and is readily available in routine histopathology laboratories.[9,10] However, while the test has a high sensitivity (94%), there is a moderate specificity (82%), especially in comparison with the 'gold standard' technique of HPV-DNA detection.[11] Therefore, positive immunostaining of p16 can occur in the actual absence of HPV. An estimated 10-20% of all OPSCC are p16 positive, but HPV-DNA negative.[12] Studies have shown that the prognosis of patients with p16 positive but HPV-DNA negative OPSCC is almost identical to the prognosis of 'true' HPV (both p16 and HPV-DNA) negative OPSCC patients.[13,14] Several research groups therefore strongly advise to determine HPV status by a bimodal approach with both p16 immunostaining and HPV-DNA or mRNA detection.[13-16]

The favorable prognosis of HPV positive OPSCC has lead towards a need for more specific, or rather individualized, information for both patients and doctors. In general, TNM stage alone is ineffective for predicting outcomes in individual patients, because other tumor factors and patient characteristics such as age, gender, tobacco use or comorbidity are not taken into account in the classification system.[17] Prognostic models are statistical models that calculate the cumulative effect of several prognostic variables on survival. Earlier

studies presented models for HPV related OPSCC designed to stratify patients in to risk categories, mostly for the purpose of clinical trials.[3,18-21] However, most of these models are based on clinical trial populations instead of consecutive patient series, do not include combined HPV-DNA and p16 status or have not been externally validated in cohorts from different geographical areas.

In 2010 we presented a prognostic model and internal model validation for patients with newly diagnosed head and neck cancer.[22] This model is based on a Dutch cohort of n=1371 consecutive patients, treated with curative intent between 1981-1999, and externally validated with data from a large referral center in the USA. The model includes the predictors age, gender, 7th TNM classification, prior tumors and comorbidity. Discrimination of this model is good with a Harrel's C-index of 0.73.

With this study we aim to extend, update, improve and validate this prognostic model for OPSCC patients by incorporating the newly published UICC/AJCC 8th TNM staging system (cN status), and both p16 and HPV-DNA status. Our goal is to use this model in clinical practice for counselling of patients.

MATERIALS AND METHODS

This retrospective cohort study was conducted after approval was given by the Medical Ethical Committee. Tissue samples were used and analyzed according to the FEDERA guidelines. Data were analyzed with IBM SPSS Statistics 21.0 and R software V 3.1.1 (packages foreign, mice, rms, survival, Hmisc, stdca). All tests were 2-sided with a significance level of 0.05.

Study design

Five different centers provided data for this retrospective cohort study. Three were located in the Netherlands (Leiden University Medical Center, Erasmus University Medical Center Rotterdam and Amsterdam Medical Center – location VUMC). Two were located in the USA (The Siteman Cancer Center at Barnes-Jewish Hospital St. Louis, Missouri and Washington University School of Medicine). All patients with primary OPSCC curatively treated in the period 1984 – 2011 were deemed eligible for inclusion. The data provided by the five different centers were aggregated in three independent multi institutional cohorts. The characteristics of the different cohorts are described below.

The reference cohort

The prognostic model we presented in 2010 was based on 1371 consecutive patients. Within the original cohort we used back in 2010 for our prognostic model, 15% (n=204) patients were diagnosed with OPSCC. The data were retrieved from the hospital-based cancer registry (ONCDOC) of the Leiden University Medical Center (LUMC). For this study we expanded our search in ONCDOC for all primary OPSCC, diagnosed between 1981 and 2011. Patients of whom FFPE tumor samples were available in the archives of the Pathology Department of the LUMC were included. N=341 pretreatment tumor samples of patients diagnosed with primary OPSCC between 1984 and 2011 were available in the archives. A senior pathologist with elaborate experience in histologic analysis of OPSCC analyzed the tumor samples again on the presence of malignant cells. 311 of 341 (91.2%) tumor samples contained OPSCC.

The external validation cohorts

The Dutch external validation cohort (NL external cohort: Erasmus University Medical Center Rotterdam and VUMC Amsterdam) comprised n=723 patients, diagnosed with primary OPSCC between 2000-2006. The patients were identified through the Dutch Cancer Registries and the data within this cohort were earlier described and used for the development of a prognostic model.18 The USA external validation cohort (USA External Cohort: Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine) consisted of N=305 patients with primary OPSCC, diagnosed and treated between 1996-2009.

Variables

Data of a total of n=1339 consecutive OPSCC patients could be collected from the development and validation cohorts. Variables extracted for each patient were gender, age at diagnosis, date of diagnosis, anatomic subsite of the tumor, cTNM classification (with both 7th and 8th cN classification), comorbidity, prior tumor, smoking behavior, recurrent disease, last date of follow-up and survival. Comorbidity was classified according to the Adult Comorbidity Evaluation 27 (ACE27) index calculator. This classification divides comorbidity into four categories: none, mild, moderate and severe.[23] Main study endpoint was overall survival (OS), calculated from the day of diagnosis. Data were considered right-censored if patients were still alive at the time of last follow-up.

HPV analysis

In all three cohorts the immunohistochemical (IHC) analysis was performed for p16 INK4A (Roche MTM Laboratories AG, Heidelberg, Germany or MTM Laboratories CINTEC, Westborough, MA) on 4 um thick FFPE tumor sections, using a fully automated Ventana BenchMark ULTRA Stainer (Ventana, Tucson Arizona, USA) according to manufacturers'

instructions at the pathology department. In all cohorts, stains were reviewed by two independent observers. Strong and diffuse nuclear and cytoplasmic immunostaining in more than 70% of the carcinoma tissue was considered as p16 positive. Partial staining of <70% or no reactivity was considered to be p16 negative. This definition of p16-positivity is consistent with previously published articles.[24] In the Dutch cohorts, DNA was extracted from all p16 positive cases using an automated silica-based extraction system. PCR was performed using the HR HPV GP 5+/6+ PCR with enzyme-immuno-assay.[25] Information on high risk HPV DNA was not available for the USA external cohort.

Statistical methods

Differences in patient characteristics between the three cohorts were assessed using Pearson's χ^2 test and ANOVA with Bonferroni correction. Missing data were handled following the missing at random assumption (MAR). Multiple imputation (MI) was performed with n=30 imputations based on the percentage of incomplete cases. The pooled imputed data were used in all analyses.

The significance of 8th TNM classification (cN status), p16 and HPV-DNA as a marker of prognosis in OPSCC was estimated by the Kaplan-Meier approach in the combined development and validation cohorts and all three cohorts separately. With these data a new Cox proportional hazards regression model was fitted. This model included the same predictors as the previously defined model. The following variables were used in the previously published model: age at diagnosis, gender, cTNM, comorbidity and subsite of the tumor.[22]

The incremental value of adding 8th TNM and HPV status (tested by p16 or PCR) to the previously defined model variables was tested in all cohorts using Wald-test in a nested models analysis. Based on literature, smoking was assumed to be an effect modifier of the incremental prognostic value of HPV.[26] Therefore, adding smoking as an interaction term to the model was also tested using Wald-test.

Cox proportional hazards regression analysis was used to evaluate the effects of all covariates on OS in an internal – external cross validation design. In prognostic modelling, the use of the maximal sample size is preferred. When multiple small datasets are available, an internal – external cross validation design is advised to combine the strength of external validation with the strength of prediction model development on all available data.[27] In an internal-external cross validation design one cohort is non-randomly left out at the time to cross-validate the model developed in the other cohorts. Because the split is not at random, this qualifies as external validation.

In this study different full models were developed by adding one new variable (8th TNM classification, p16, HPV-DNA or smoking) at a time. For each full model, three performance assessments of cross-validation were done based on the three (development and validation) cohorts. Calibration plots and ROC curves for 5 year survival probability were made for all cross-validated models. The area under the ROC curve (AUC) was calculated to evaluate the concordance between predicted and observed responses of individual subjects separately in all nine different cross-validated models. We tested for heterogeneity in baseline risk and performed interaction tests across the different cohorts.

Decision curve analysis (DCA) was performed in order to evaluate the clinical usefulness of the model for decision making. Although the AUC has been the standard for evaluating the discriminating ability of a prognostic model, it has been increasingly recognized that changes in AUC are not sensitive when a new prognostic factor (such as a biomarker) is added to a model that already comprises standard prognostic factors.[28] The AUC typically shows only a small improvement, but the clinical utility of a model including this new prognostic factor may be large. To overcome this limitation, DCA as described by Vickers et al. can be used to summarize the performance of the model in supporting decision making.[29,30]

In this study we used DCA to examine the theoretical relationship between the threshold survival probability at 5 years after diagnosis (for example 5-year survival probability of 65%) and the relative value of benefits (predicting a true positive case) and harms (predicting a false positive case) associated with the different full prognostic models.

The final model was fitted on all data (n=1339). The extent of any overfitting was estimated in an internal validation procedure using 500 bootstrap samples. A shrinkage factor was calculated and used to shrink the regression coefficients to obtain well-calibrated predictions of prognosis for new patients. The bootstrap procedure also yielded an optimism-corrected Harrell's Concordance Index.

RESULTS

Patient characteristics

Patient characteristics of all three cohorts are shown in Table 1. The baseline patient and tumor characteristics differed significantly between the USA cohort and both Dutch cohorts. Especially regarding cT status, cM status, tobacco use and p16 analysis, large differences are shown between the Dutch cohorts and the USA cohort. Over 70% of patients in the USA cohort were p16 positive, in comparison with approximately 30% of patients in

Table 1. Demographic characteristics

		Reference cohort (Dutch, NLREF) 1984-2011		External cohort (Dutch, NLEXT) 2000-2006		External cohort (USA, USEXT) 1996-2009		p- value
		N=311	Table Total %	N=723	Table Total %	N=305	Table Total %	
Age	Mean (SD)	59.7 (49.5 – 69.9)		60.2 (50.8 – 69.6)		55.6 (46.4 – 64.8)		p<0.001*
Gender	male	206	66.2%	482	66.7%	266	87.2%	p<0.001**
	female	105	33.8%	241	33.3%	39	12.8%	
cT	1	58	18.6%	114	15.8%	78	25.6%	
	2	96	30.9%	230	31.8%	110	36.1%	
	3	81	26.0%	243	33.6%	51	16.7%	p<0.001**
	4	76	24.4%	134	18.5%	57	18.7%	
	NA	0	0%	2	0.3%	9	3.0%	
cN (7th TNM)	0	122	39.2%	271	37.5%	39	12.8%	
	1	49	15.8%	101	14.0%	48	15.7%	
	2	119	38.3%	317	43.8%	194	63.6%	p<0.001**
	3	21	6.8%	33	4.6%	21	6.9%	
	NA	0	0%	1	0.1%	3	1.0%	
cN (8th TNM)	0	122	39.2%	271	37.5%	39	12.8%	
	1	60	19.3%	120	16.6%	81	26.6%	
	2	108	34.7%	298	41.2%	157	51.5%	p<0.001**
	3	21	6.8%	33	4.6%	20	6.6%	
	NA	0	0%	1	0.1%	8	2.6%	
cM	0	302	97,1%	714	98.8%	300	100.0%	
	1	9	2,9%	4	0.6%	0	0%	p=0.054***
	NA	0	0%	5	0.7%	0	0%	
Comorbidity (ACE27)	None	133	42.8%	292	40.4%	123	40.3%	
	Mild	63	20.3%	219	30.3%	113	37.0%	
	Moderate	72	23.2%	176	24.3%	42	13.8%	p<0.001**
	Severe	39	12.5%	34	4.7%	22	7,2%	
	NA	4	1.3%	2	0.3%	5	1.7%	
Smoking	never	36	11.6%	64	8.9%	81	26.6%	
	ever	126	40.5%	653	90.3%	212	69.5%	p<0.001**
	NA	149	47.9%	6	0.8%	12	3.9%	
Death	No	123	39.5%	274	37.9%	208	68.2%	p<0.001**
	Yes	188	60.5%	449	62.1%	97	31.8%	
Recurrent disease	No	199	63.9%	385	53.2%	243	79.6%	p<0.001**
	Yes	112	36.1%	338	46.7%	62	21.3%	
P16 analysis	<70% immunostaining	213	68.5%	544	75.2%	70	23.0%	
	≥70% immunostaining	98	31.5%	179	24.8%	230	75.4%	p<0.001**
	NA	0	0%	0	0%	5	1.6%	

Table 1. Demographic characteristics (continued)

		Reference cohort (Dutch, NLREF) 1984-2011		External cohort (Dutch, NLEXT) 2000-2006		External cohort (USA, USEXT) 1996-2009		p- value
		N=311	Table Total %	N=723	Table Total %	N=305	Table Total %	
HPV DNA analysis	negative	241	77.5%	571	79.0%	NA	NA	
	positive	70	22.5%	152	21.0%	NA	NA	p=0.652***
	NA	0	0%	0	0%	305	100%	

*as defined by one way ANOVA using bonferroni p-value adjustment, ** as defined by the $\chi 2$ test, *** no data for USA available therefore $\chi 2$ test was performed between NL reference and NL external cohort.

the Dutch cohorts. The characteristics of both Dutch cohorts were nearly comparable. The 5-year OS estimates were 70.7% in the p16 positive group and 38.7% in the p16 negative group.

In the Dutch reference cohort, 28.6% (n=28) of patients were p16 positive but HPV-DNA negative. In the Dutch external validation cohort, 15.1% (n=27) of patients were p16 positive but HPV-DNA negative. Since HPV-DNA analysis was not available in the USA external validation cohort, the percentage of true positive HPV cases could not be defined. Figure 1 shows OS as estimated by the Kaplan Meier approach for the significance of p16 and HPV-DNA as a marker for prognosis in all 3 cohorts separately. Log-rank test showed for both factors a significant result regarding the non-equality of survival distributions ($p<0.001$).

In Table 2 the univariate hazard ratio's (HR's) of all new possible prognostic factors are outlined. The differences in HR in cN status between the Dutch and USA cohorts can be explained by the higher percentage of p16 positive patients in the USA cohort, and thus a different distribution of N-stages. The differences in HR between p16 and HPV-DNA can be explained by the percentage of 'false-positive' p16 cases (p16 positive, but HPV-DNA negative).

The incremental value of adding 8th TNM and HPV status (tested by p16 or PCR) to the previously defined model variables was tested in all cohorts using Wald test in a nested models analysis. Both in the Dutch reference cohort as in the combined internal – external cohort, the Wald test revealed significant results for adding HPV to the previously defined model ($p<0.001$). This was the case for p16 and HPV-DNA-analysis. Testing for interaction between smoking and HPV positivity did not show significant interaction ($p=0.09$).

Figure 1. Overall survival in all 3 cohorts

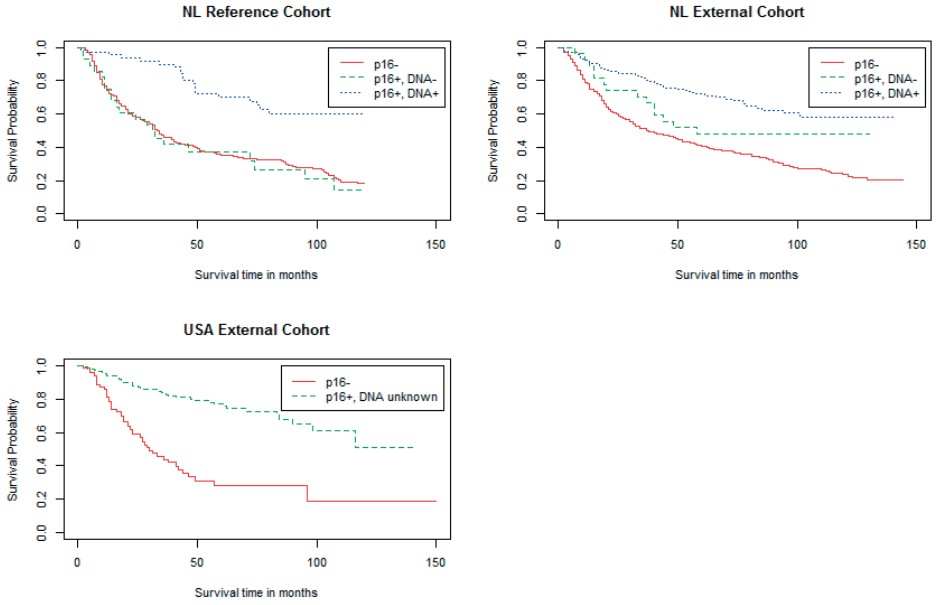

Table 2. Univariate analysis showing unadjusted Hazard Ratio's (HR) for prognostic value of new model variables.

		Dutch reference cohort (LUMC)		Dutch external cohort (EMC/VUMC)		USA external cohort (USA)	
		HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
cN (8th TNM)	N0	-	-	-	-	-	-
	N1	0.93 (0.61 – 1.43)	0.74	0.91 (0.68 – 1.22)	0.519	0.87 (0.44 – 1.72)	0.685
	N2	1.696 (1.22 – 2.37)	0.002	1.48 (1.20 – 1.83)	0.000	1.02 (0.55 – 1.89)	0.954
	N3	2.33 (1.41 – 3.87)	0.001	2.83 (1.91 – 4.25)	0.000	2.72 (1.21 – 6.14)	0.016
P16	Negative	-	-	-	-	-	-
	Positive	0.48 (0.34 – 0.69)	0.000	0.417 (0.32 – 0.54)	0.000	0.247 (0.164 – 0.37)	0.000
HPV-DNA	Negative	-	-	-	-	NA	
	Positive	0.303 (0.19 – 0.48)	0.000	0.390 (0.29 – 0.52)	0.000	NA	

Following these results, four different prognostic models were fitted:

1. *age + gender + comorbidity + 7th cTNM (original model)*
2. *age + gender + comorbidity + 8th cTNM classification*
3. *age + gender + comorbidity + 8th cTNM classification + P16*
4. *age + gender + comorbidity + 8th cTNM classification + HPV DNA*

The four different prognostic models were cross-validated over the three cohorts using Cox proportional hazards regression analysis, leading to a total of 11 performance assessments. Since HPV-DNA analysis was not available in the USA external validation cohort, a model with HPV DNA could not be validated for this cohort. The calibration of the 11 different models was assessed graphically with a calibration plot. (Figure 2a). The results of 11 model performance assessments (HR's and 95% CI) are presented in Table 3a-c. The Harrell's Concordance Indices of all models differed between 0.64 and 0.74. Models containing 8th TNM and a separate variable for HPV as a prognostic factor performed better than models without HPV.

To summarize the performance of the model in supporting decision making, DCA was performed. Decision curves of 11 model performance assessments for the relationship between threshold survival probability at 5 years after diagnosis and the relative value of benefits and harms are displayed in Figure 2b. Interpretation of the decision curve depends on comparing the net benefit of the different models with that of a strategy of "treat all" (the thin grey line) and "treat none" (parallel to the x axis at net benefit of zero). "Treating" in this setting means any treatment decision that could be made for OPSCC patients dependent on expected survival rate, such as adjuvant chemotherapy, or dose-escalating radiotherapy. The strategy with the highest net benefit at a particular point is optimal, irrespective of the size of the difference. Net benefits of all models were superior at wide range of "decision to treat" thresholds. Across all threshold probabilities, models with a variable for HPV (either p16 or HPV DNA) performed better than models with only the 8th TNM classification. The HPV DNA prognostic model had a slightly greater net benefit compared with the HPV p16 prognostic model.

Regarding the results of internal – external cross validation and the decision curve analysis, we chose to fit the final model in the combined data (n=1339), based on the following variables: gender, age at diagnosis, 8th cTNM classification, comorbidity (ACE27) and p16 analysis. The choice for p16 analysis as a measurement of HPV positivity was also emphasized because of the easy accessibility of this surrogate marker in routine histopathological laboratories. We tested for heterogeneity in baseline risk and performed interaction tests across the different cohorts for the final model. Wald test showed a significant result for comparing the final model with and without an interaction term for the three different cohorts (p=0.021). Therefore, the interaction term for cohorts was also fitted in the updated final model. Harrell's Concordance Index for this model was 0.72. The extent of overfitting was estimated in an internal validation procedure using 500 bootstrap samples. The bootstrap procedure yielded an optimism-corrected Harrell's Concordance Index of 0.70.

3a) Reference cohort (LUMC)

Factors	Model 1 (7th TNM)			Model 2 (8th TNM)			Model 3 (8th TNM + p16)			Model 4 (8th TNM + p16 + DNA)		
	C-stat= 0.672			C-stat= 0.674			C-stat= 0.693			C-stat = 0.703		
	Hazard Ratio	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*
Male	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
Female	1.19	0.98 -1.44	0.073	1.18	0.98 -1.43	0.083	1.01	0.83 - 1.22	0.90	1.02	0.84 - 1.23	0.85
Age	1.02	1.01 -1.03	<0.001	1.02	1.01 - 1.03	<0.001	1.02	1.01 - 1.03	<0.001	1.02	1.01 - 1.03	<0.001
cT1	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
cT2	1.15	0.87 - 1.51	0.334	1.13	0.86 - 1.49	0.382	1.08	0.82 - 1.42	0.592	1.06	0.81 - 1.40	0.685
cT3	1.69	1.29 - 2.22	<0.001	1.67	1.27 - 2.19	<0.001	1.39	1.06 - 1.84	0.017	1.39	1.05 - 1.83	0.021
cT4	2.69	2.02 - 3.59	<0.001	2.62	1.97 - 3.49	<0.001	2.12	1.58 - 2.84	<0.001	2.08	1.55 - 2.79	<0.001
cN0	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
cN1	0.99	0.75 - 1.31	0.96	0.93	0.71 - 1.21	0.59	1.22	0.93 - 1.59	0.149	1.25	0.95 - 1.63	0.11
cN2	1.23	1.01 - 1.51	0.042	1.29	1.05 - 1.59	0.014	1.77	1.43 - 2.19	<0.001	1.80	1.46 - 2.23	<0.001
cN3	2.76	1.93 - 3.95	<0.001	2.76	1.93 - 3.94	<0.001	3.56	2.49 - 5.10	<0.001	3.70	2.58 - 5.32	<0.001
cM0	1.0	-		1.0	-	-	1.0	-	-	1.0	-	-
cM1	4.75	1.50 - 14.98	0.007	4.54	1.43 - 14.32	0.009	5.74	1.83 - 18.0	0.003	6.04	1.91 - 18.95	0.002
ACE27 Score 0	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
ACE27 Score 1	1.33	1.07 - 1.65	0.008	1.33	1.07 - 1.65	0.009	1.24	0.99 - 1.54	0.052	1.23	0.99 - 1.52	0.065
ACE27 Score 2	2.11	1.68 - 2.66	<0.001	2.09	1.66 - 2.63	<0.001	1.69	1.34 - 2.13	<0.001	1.68	1.33 - 2.12	<0.001
ACE27 Score 3	2.62	1.84 - 3.72	<0.001	2.60	1.84 - 3.69	<0.001	2.65	1.87 - 3.75	<0.001	2.58	1.81 - 3.67	<0.001
p16 negative	-	-	-	-	-	-	1.0	-	-	1.0	-	-
p16 positive	-	-	-	-	-	-	0.34	0.28 - 0.43	<0.001	0.56	0.35 - 0.89	0.017
PCR DNA HPV negative	-	-	-	-	-	-	-	-	-	1.0	-	-
PCR DNA HPV positive	-	-	-	-	-	-	-	-	-	0.55	0.32 - 0.94	0.032

3b) Dutch external validation cohort (EMC/VUMC)

Factors	Model 5 (7th TNM)			Model 6 (8th TNM)			Model 7 (8th TNM + p16)			Model 8 (8th TNM + p16 + DNA)		
	C-stat= 0.643			C-stat= 0.647			C-stat= 0.679			C-stat= 0.678		
	Hazard Ratio	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*
Male	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
Female	1.12	0.85 - 1.48	0.430	1.14	0.86 - 1.51	0.354	1.03	0.77 - 1.36	0.852	1.01	0.76 - 1.34	0.934
Age	1.02	1.01 - 1.03	0.0021	1.02	1.01 - 1.03	0.0025	1.02	1.01 - 1.03	0.0025	1.02	1.01 - 1.03	0.0041
cT1	1.0	-	-	1.0	-	-	1.0	v		1.0	-	-
cT2	1.81	1.20 - 2.73	0.0046	1.78	1.18 - 2.69	0.006	1.74	1.15 - 2.63	0.0081	1.71	1.12 - 2.58	0.012
cT3	2.38	1.55 - 3.65	<0.001	2.35	1.53 - 3.61	<0.001	2.06	1.34 - 3.17	<0.001	1.97	1.27 - 3.03	0.0023
cT4	4.03	2.68 - 6.06	<0.001	3.96	2.62 - 5.96	<0.001	3.17	2.09 - 4.78	<0.001	2.93	1.93 - 4.43	<0.001
cN0	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
cN1	1.11	0.76 - 1.62	0.597	0.97	0.68 - 1.39	0.887	1.36	0.95 - 1.96	0.095	1.45	1.01 - 2.09	0.0439
cN2	1.09	0.82 - 1.44	0.565	1.15	0.86 - 1.54	0.331	1.69	1.25 - 2.28	<0.001	1.78	1.31 - 2.40	<0.001
cN3	1.84	1.21 - 2.81	0.0047	1.85	1.21 - 2.83	0.0042	2.53	1.65 - 3.88	<0.001	2.53	1.64 - 3.89	<0.001
cM0	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
cM1	8.12	3.76 - 17.5	<0.001	7.89	3.65 - 17.06	<0.001	6.71	3.09 - 14.54	<0.001	6.81	3.13 - 14.82	<0.001
ACE27 Score 0	1.0	-	-	1.0	-	-	1.0	-	-	1.0	-	-
ACE27 Score 1	0.79	0.58 - 1.08	0.147	0.80	0.58 - 1.09	0.152	0.80	0.58 - 1.09	0.164	0.81	0.58 - 1.11	0.195
ACE27 Score 2	1.44	1.06 - 1.95	0.018	1.42	1.05 - 1.93	0.023	1.11	0.81 - 1.52	0.504	1.07	0.78 - 1.47	0.655
ACE27 Score 3	1.39	0.95 - 2.03	0.083	1.39	0.95 - 2.02	0.089	1.15	0.78 - 1.69	0.467	1.11	0.75 - 1.64	0.589
p16 negative	-	-	-	-	-	-	1.0	-	-	1.0	-	-
p16 positive	-	-	-	-	-	-	0.35	0.27 - 0.47	<0.001	0.65	0.43 - 0.99	0.045
PCR DNA HPV negative	-	-	-	-	-	-	-	-	-	1.0	-	-
PCR DNA HPV positive	-	-	-	-	-	-	-	-	-	0.41	0.25 - 0.67	<0.001

3c) USA external validation cohort (St. Louis)

Factors	Model 9 (7th TNM)			Model 10 (8th TNM)			Model 11 (8th TNM + p16)		
	C-stat= 0.677			C-stat= 0.674			C-stat= 0.735		
	Hazard Ratio	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*	*Hazard Ratio*	*95% CI*	*p-value*
Male	1.0	-	-	1.0	-	-	1.0	-	
Female	1.05	0.87 - 1.25	0.556	1.06	0.89 - 1.25	0.530	1.02	0.86 - 1.21	0.796
Age	1.03	1.02 - 1.03	<0.001	1.03	1.02 - 1.03	<0.001	1.03	1.02 - 1.04	<0.001
cT1	1.0	-	-	1.0	-	-	1.0	-	-
cT2	1.22	0.94 - 1.59	0.142	1.20	0.92 - 1.56	0.178	1.19	0.92 - 1.56	0.189
cT3	1.59	1.22 - 2.06	<0.001	1.55	1.19 - 2.01	<0.001	1.45	1.12 - 1.88	0.0053
cT4	2.39	1.81 - 3.13	<0.001	2.29	1.74 - 3.01	<0.001	1.97	1.49 - 2.59	<0.001
cN0	1.0	-	-	1.0	-	-	1.0	-	-
cN1	1.01	0.78 - 1.29	0.949	0.94	0.74 - 1.20	0.625	1.11	0.86 - 1.41	0.430
cN2	1.38	1.15 - 1.67	<0.001	1.47	1.22 - 1.76	<0.001	1.79	1.47 - 2.16	<0.001
cN3	2.61	1.89 - 3.60	<0.001	2.63	1.90 - 3.63	<0.001	3.23	2.33 - 4.48	<0.001
cM0	1.0	-	-	1.0	-	-	1.0	-	-
cM1	4.25	2.29 - 7.88	<0.001	4.13	2.23 - 7.66	<0.001	4.35	2.33 - 8.11	<0.001
ACE27 Score 0	1.0	-	-	1.0	-	-	1.0	-	-
ACE27 Score 1	1.36	1.11 - 1.66	0.0033	1.36	1.11 - 1.66	0.0028	1.23	1.01 - 1.51	0.0442
ACE27 Score 2	1.89	1.54 - 2.31	<0.001	1.87	1.53 - 2.29	<0.001	1.60	1.31 - 1.96	<0.001
ACE27 Score 3	2.59	1.93 - 3.48	<0.001	2.61	1.95 - 3.51	<0.001	2.25	1.67 - 3.02	<0.001
p16 negative	-	-	-	-	-	-	1.0	-	-
p16 positive	-	-	-	-	-	-	0.43	0.35 - 0.53	<0.001

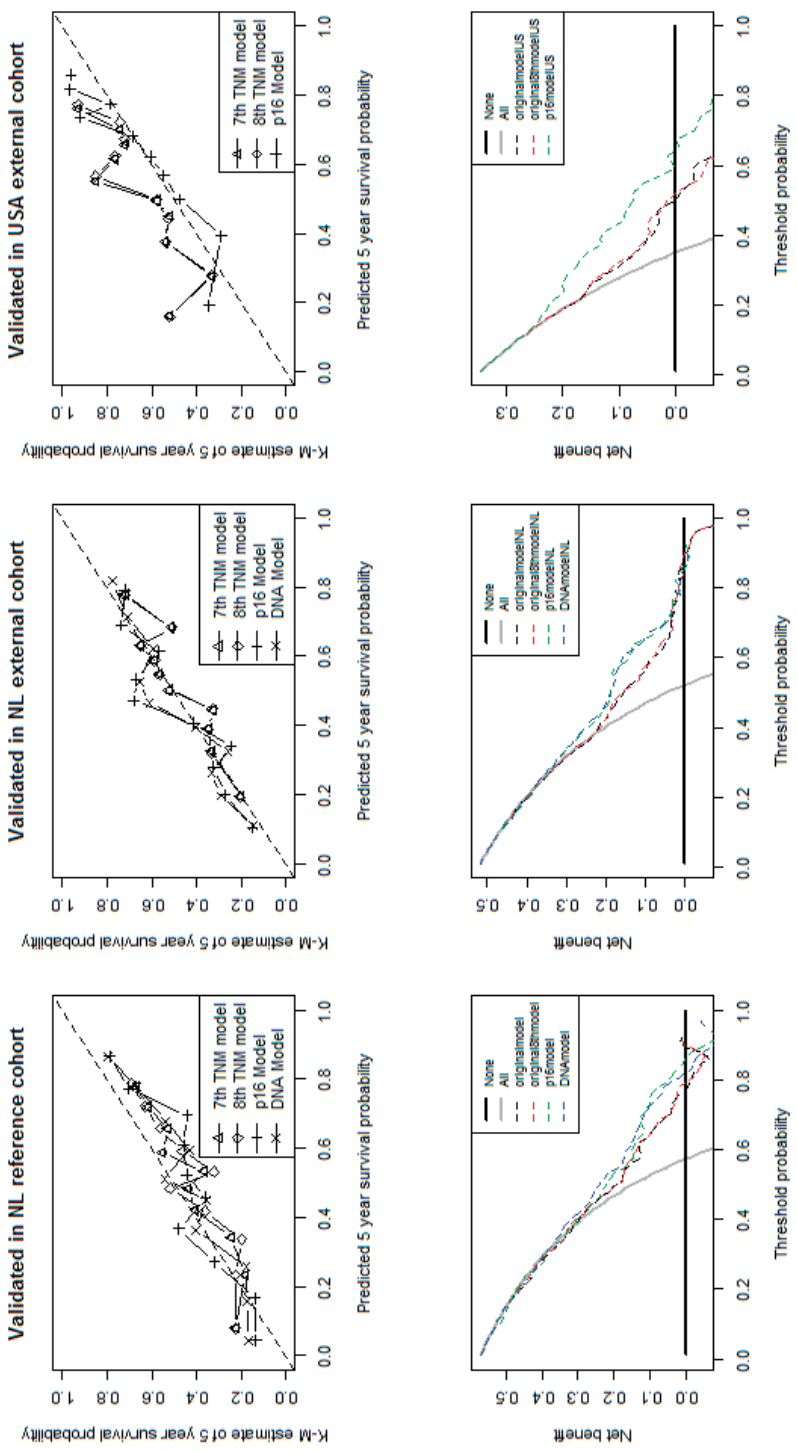

Figure 2. a) calibration plots of all models, b) decision curves of all models

DISCUSSION

This study describes the update, improvement and validation of an existing prognostic model for OPSCC patients by incorporating the newly published UICC/AJCC 8th TNM staging system (cN sta-tus), and both p16 and HPV-DNA status. Three independent multi-institutional cohorts with OPSCC patients from Western Europe and the USA (period 1984 – 2011) were used in an internal-external cross validation design. In all cohorts HPV, either detected by p16 or PCR DNA, was an independent prognostic factor for overall survival in OPSCC patients. Models with 8th TNM and a separate variable for HPV (PCR DNA or p16) as a prognostic factor performed better than models without HPV. Harrell's Concordance Indices were reasonably good. The final updated prognostic model, including 8th TNM classification and a separate variable for HPV, performs very similar to the original model in terms of calibration and discrimination. Decision curve analysis (DCA) however showed an improved clinical utility in comparison with the original model. To our knowledge, this study is first to report on DCA in prognostic models for head and neck cancer patients. Models with a separate variable for HPV (either p16 or HPV DNA) performed better in terms of supporting decision making, than models with only the 8th TNM classification, despite the incorporation of p16 in this classification system. This statistical method for summarization of model performance in supporting decision making is very interesting given the ongoing studies on de-escalation therapies and other treatment modifications for patients with HPV positive OPSCC.[31] The updated model could be used for counselling patients about their individual prognosis and treatment options. Besides de-escalation therapies for HPV positive patients, tailor-made treatment proposals based on the predicted overall survival for HPV negative patients (with a likely unfavorable prognosis) are of interest.

This study shows that with the introduction of the 8th TNM classification, predictions based only on TNM are improved, but not precise enough for individual patients. Also comorbidity, age, gender and HPV-DNA status should be taken into account. One of the strengths of this study is the joint use of PCR DNA and p16 for scoring HPV positivity in OPSCC patients. The large sizes of the development and validation cohorts, the heterogeneity due to different geographical areas, and the consecutive population based aspect diminishes the risk of selection bias. The same heterogeneity however is a limitation of this study, and is shown best in de USA cohort. The USA cohort might perform better due to several factors: a higher HPV prevalence, lower smoking and a lower share of patients in advanced stage (no M1 disease). Furthermore, there was no information on PCR DNA in this cohort and therefore false-positive (e.g. p16 positive but HPV DNA negative) tumors could have affected the results. This kind of heterogeneity in patient populations can lead to poor calibration in comparison to the derivation cohort. However, internal validation

of the full model corrected for optimism using bootstrapping showed reasonably well performance of the model with Harrell's Concordance Index of 0.70.

There was a slight difference in favor of the performance of models with HPV positivity measured by PCR DNA in comparison with the surrogate biomarker p16. Positive immunostaining for p16 can occur in the actual absence of HPV.[12] And since the prognosis of p16 positive but HPV-DNA negative OPSCC is almost identical to the prognosis of double negative patients, a bimodal approach of p16 and HPV-DNA detection is advised for most accurate determination of HPV status.[13-16] The results of our study, and especially the calibration and AUCs of the different models, are in alignment with this recommendation. Alternatively, in terms of DCA and clinical applicability of prognostic models in a decision making process, p16 is a very representative prognostic marker. P16 is readily available in routine histopathology laboratories and not expensive to measure. The easy access to p16 measurements, the reasonably good performance of a model with p16 and the more imprecise prediction of individual prognosis using only 8th TNM classification are arguments to use our proposed updated model with p16 as a marker of HPV positivity. We recommend the use of our model in a clinical setting, especially when counselling patients about their individual prognosis. This could facilitate a shared decision making process. Evidently, when considering de-escalation therapies, one should be sure about HPV positivity and also perform an HPV-DNA analysis.

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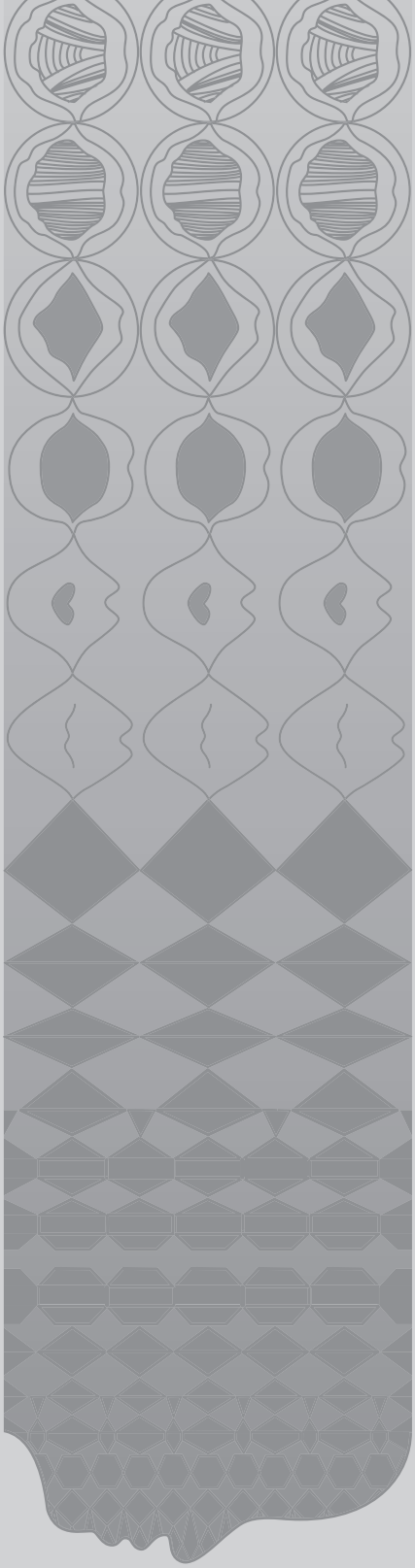

6

Nodal response after 46 Gy of intensity-modulated radiotherapy is associated with human papillomavirus-related oropharyngeal carcinoma.

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ABSTRACT

This study aimed to analyze the effect of human papillomavirus associated T1-2 node positive oropharyngeal carcinoma (HPV+ OPSCC) on nodal response, recurrent disease and survival in patients treated according to the Rotterdam protocol. In total 77 patients with T1-2 OPSCC with nodal disease, treated between 2000-2012, were included in this study. Patients were treated according to 'the Rotterdam protocol': 46 Gy of IMRT followed by a local boost using cyberknife or brachytherapy (22 Gy) and neck dissection. The presence of HPV was determined by p16 INK4A immunostaining. Outcomes were overall survival, disease free survival and the extent of nodal response. Nodal stage was determined following 7th and 8th AJCC/UICC classification. 68.4% of patients had p16 positive disease. 35.4% of all patients achieved complete nodal response (pN0) after 46 Gy of IMRT. Based on the 7th TNM classification, nodal response (partial or complete) was significantly associated with HPV status (p=0.002). Patients with p16-positive OPSCC had an OR of 4.6 to achieve complete nodal response. However, smoking interacted with this effect. Applying the 8th TNM classification, complete or partial response was associated with HPV status, however not significant (OR 1.7, p=0.138). Complete nodal response lead to 100% overall survival in p16-positive OPSCC. HPV-related OPSCC are associated with complete nodal response after 46 Gy of IMRT. Patients with full regional control (pN0) after IMRT and subsequent neck dissection show a significantly better overall survival, but smoking negatively interacts with this effect.

INTRODUCTION

Currently, over 70% of oropharyngeal squamous cell carcinoma (OPSCC) in Europe is associated with Human Papilloma Virus (HPV).[1] Patients with HPV-positive OPSCC tend to be young and fit at presentation. Also, HPV-positive OPSCC has a 58% reduction in the risk of death compared to HPV-negative OPSCC.[2] A common presentation of HPV-related OPSCC is that of an early primary tumor (T1-2) along with advanced nodal disease (N2-3).[3,4] Disease control rates for patients with HPV-positive OPSCC are significantly better than that seen in HPV-negative OPSCC. Several studies have also shown that HPV associated OPSCC is more radio-sensitive than HPV-negative OPSCC.[2,5]

Due to their advanced nodal disease, patients with HPV-positive OPSCC are considered advanced stage (III-IVb) disease. Therefore patients with HPV-positive disease traditionally are treated with intensive multimodality regimens. However, the reality is that their outlook is actually more favorable.[2] Therefore, recently the 8th edition UICC/AJCC TNM staging of OPSCC has been divided into two different staging systems for both HPV associated (p16 positive) OPSCC and non-HPV associated (p16 negative) OPSCC. [6] This staging system specifically results in a change of nodal stage categories, both clinical and pathological, and represent a significant change for HPV-positive OPSCC from the non-HPV associated OPSCC. [7] Hence, it permits a more appropriate depiction of the prognosis of HPV-positive disease than is supplied by the 7th edition TNM classification.[8]

The optimal treatment of nodal disease in (HPV-positive) OPSCC has therefore become controversial. Planned neck dissection following definitive radiotherapy has been considered standard of care in the past. However, data suggest that patients with a complete clinical and radiographic response to primary nonsurgical treatment can be observed without neck dissection and followed with imaging studies.[2,9] Some institutions do not perform neck dissection if a complete response of the neck is achieved after radiotherapy (70Gy), regardless of the original size of the metastasis. Other studies recommend neck dissection in patients with N2-N3 disease regardless of response to the oncologic treatment, but also show an improved disease-free survival.[10-13] This leads to the fundamental question if and when to perform a neck dissection in patients with OPSCC. In addition to this question, several clinical trials, such as ECOG 311 and Pathos, are currently investigating de-intensification strategies, aiming to maintain a high cure rate while limiting short and longer term treatment related side effects.[14-16]

In 2000, 'the Rotterdam protocol' was introduced at our institution for patients with T1-2 OPSCC. This is an organ function preservation protocol and includes intensity modulated radiotherapy (IMRT) of 46 Gy to the primary tumor and the neck nodes in 23 fractions,

followed by a local boost using brachytherapy 22 Gy in 8 fractions (BT) or cyberknife 16.5 Gy in 3 fractions (CK) and a neck dissection in case of node positive (N+) disease. The local tumor is therefore treated with at least 66 Gy and nodal disease with 46 Gy. Patients with T3-4 tumors or advanced nodal disease (N3) receive concomitant chemoradiation with cisplatin.[17] Although two radiation techniques (IMRT and BT or CK) are used, the Rotterdam protocol aims for low toxicity and therefore could be considered in line with other de-intensification strategies.

We reported earlier that the Rotterdam protocol results in excellent local control rates compared to 46 Gy of 2-dimensional (2D) or 3D conformal radiotherapy followed by a BT boost, a technique we used from 1990 until 2000. In N+ disease, neck dissection after a relatively low dose of IMRT to the involved neck resulted in excellent regional control, because no regional failure was reported in those patients.[17] However, we did not collect HPV data on patients in this series. It is possible that the improved oncologic outcomes are not only attributable to the Rotterdam protocol, but also related to HPV-positive disease. Especially since an increased incidence of HPV-positive OPSCC was seen in the past decade compared to 1990 and 2000.

The objective of this study is therefore to describe the role of HPV status in patients with T1-2 node positive OPSCC, treated according to the Rotterdam protocol. Furthermore we want to analyze the effect of HPV-positive disease on nodal response, recurrent disease and survival in the study population, taking into account both 7th and 8th TNM classification. Finally we want to answer the earlier formulated question if and when to perform a neck dissection in patients with OPSCC, especially in case of smaller primary tumors with advanced nodal disease.

PATIENTS AND METHODS

This retrospective cohort study was conducted after approval was given by the institutional Medical Ethical Committee (MEC-2015-171). A waiver of informed consent was also given by the same ethics committee. Tissue samples were used and analyzed according to the FEDERA guidelines.

Patient demographics

Between 2000 and 2012, n=131 patients were identified who were treated according to the Rotterdam protocol for T1-T2 node positive OPSCC. Diagnosis of squamous cell carcinoma was confirmed according to histopathology; carcinoma in situ was excluded. Only patients of whom FFPE (formaldehyde fixed and paraffin embedded) pretreatment

samples were available in the archives of the Pathology department were included. Patients were excluded in case there was not enough previously untreated tissue sample left to perform HPV analysis. A total of n=77 patients remained for evaluation.

Demographic and clinical characteristics of patients were collected by a detailed medical chart review. Variables included were age, gender, comorbidity, clinical and pathological tumor- and nodal stage (both 7th and 8th UICC/AJCC TNM classification), extranodal extension (ENE), smoking habits, acute toxicity following radiotherapy, complications following surgery, survival status and cancer recurrence. Acute toxicity was scored based on chart reviews using the RTOG/EORTC criteria.[18] Complications following surgery were scored based on the Clavien-Dindo classification.[19]

Analysis of HPV

Immunohistochemical (IHC) analysis was performed for p16 INK4A. Strong and diffuse nuclear and cytoplasmic immunostaining in more than 70% of the tumor cells was considered as p16-positive. p16 staining is a well-established cost-effective surrogate for HPV status in oropharyngeal cancer compared with other methods (e.g. in-situ hybridisation or PCR), if scored and interpreted appropriately. [21-23]

Analysis of primary tumor and nodal disease

Tumor stage classification was determined according to both the 7th and the 8th UICC/AJCC TNM staging. Staging was performed by physical examination, CT or MRI, endoscopy and fine needle aspiration of pathological nodes, and/or biopsy of the primary tumor site. The histopathological examination of the neck dissection sample included identifying the number and location of the lymph nodes containing active metastatic disease, that is remaining viable tumor cells with presence of mitosis in tumor cells. The amount of viable tumor was estimated and percentage of viable tumor cell was given, which was correlated to the clinical response. Patients were considered to have complete nodal response in case no viable tumor cells were seen in their neck dissection sample (pN0). If viable tumor cells were identified in the neck dissection sample, but less lymph nodes were affected in comparison to the clinical TNM staging, patients were considered to have partial nodal response (pN < cN).

Statistical analysis

Data were analyzed with IBM SPSS Statistics 24.0 for Windows and R statistical software version 3.4.2. All tests were 2-sided with a significance level of 0.05. Univariate analysis of associations between categorical variables, HPV status and nodal status was done using Pearson chi-square tests. Multivariate analysis was performed by binary logistic regression analysis using complete or partial nodal response as outcome of interest. Overall survival (OS) was calculated from the date of diagnosis to the date of death. Disease free survival

(DFS) was defined as recurrent locoregional disease or distant metastasis. Survival was first examined using Kaplan-Meier univariate survival analysis followed by the log-rank test. Multivariate Cox Proportional Hazards Regression Analysis was then performed using OS and DFS as outcomes.

Table 1. Patient characteristics

		p16 negative			p16 positive		
		Mean (SD)	N	%	Mean (SD)	N	%
Age (years)		59 (8)			58 (9)		
Gender	Male		16	28.1%		41	71.9%
	Female		8	40.0%		12	60.0%
ACE27	None		8	26.7%		22	73.3%
	Mild		6	25.0%		18	75.0%
	moderate		9	47.4%		10	52.6%
	Severe		1	25.0%		3	75.0%
Tobacco use	No smoking history		0	0.0%		16	100.0%
	Former smoker		12	33.3%		24	66.7%
	Current smoker		12	48.0%		13	52.0%
Clinical T stage	T1		7	20.6%		27	79.4%
	T2		17	39.5%		26	60.5%
Clinical N stage (7th TNM classification)	N0		0	0.0%		0	0.0%
	N1		13	48.1%		14	51.9%
	N2a		2	14.3%		12	85.7%
	N2b		7	25.0%		21	75.0%
	N2c		1	16.7%		5	83.3%
	N3		1	50.0%		1	50.0%
Clinical N stage (8th TNM classification)	N0		0	0.0%		0	0.0%
	N1		13	21.7%		47	78.3%
	N2		0	0.0%		5	100.0%
	N3		0	0.0%		1	100.0%
	N2a		2	100.0%		0	0.0%
	N2b		5	100.0%		0	0.0%
	N2c		0	0.0%		0	0.0%
	N3a		1	100.0%		0	0.0%
	N3b		3	100.0%		0	0.0%
Extranodal extension	No		21	29.2%		51	70.8%
	Yes		3	60.0%		2	40.0%
Interval between last day of radiation and neck dissection (days)		14 (9)			14 (9)		
Recurrent disease	No recurrent disease		15	22.7%		51	77.3%
	(Loco)regional recurrence		5	100.0%		0	0.0%
	Distant metastasis		4	66.7%		2	33.3%
Deceased	No		11	19.0%		47	81.0%
	Yes		13	68.4%		6	31.6%
Follow up time (months)		54 (45)			69 (36)		

RESULTS

Patient characteristics

Table 1 shows the descriptive characteristics of the included patients. The majority of patients (68.8%) had p16-positive disease. Mean age at diagnosis was 58 years, and most patients were male (74.0%). Advanced disease was seen in over 70% of patients and the mean interval between last day of radiation therapy and day of neck dissection was 14 days (SD 9 days). Acute toxicity after radiation was low while 48.1% of patients had mild complications after neck dissection (Table 2).

Table 2. Acute toxicity after radiation and complications after neckdissection

Acute toxicity		
	N	%
grade 0	6	7.8%
grade 1	23	29.8%
Xerostomia	22	
Mucositis	1	
grade 2	37	48.1%
Xerostomia	2	
Mucositis	31	
Pain	4	
grade 3	8	10.4%
Dysphagia	6	
Pain	1	
Dyspnea	1	
grade 4	3	3.9%
Dyspnea	1	
ulceration of the skin	2	
Complications after neckdissection		
Grade 0 (no complications)	40	51.9%
Grade 1 (wound infections, hematoma, shoulder complaints requiring physiotherapy)	25	32.5%
Grade 2 (wound infections requiring antibiotics, wound dehiscence)	9	11.7%
Grade 3b (bleeding requiring revision surgery)	3	3.9%

Effect of the Rotterdam protocol for OPSCC on nodal response

Clinical nodal stage compared to pathological nodal stage after neck dissection resulted in 36.4% (n=28) of patients with complete nodal response (pN0) after 46 Gy of IMRT. The majority of the patients with pN0 necks, 82.1% (n=23), had p16-positive disease.

A proportion of patients had partial nodal response: 19.5% (n=15) using the 7th AJCC TNM classification and only 5.2% (n=4) using the 8th AJCC TNM classification. Using the 8th TNM classification the majority of patients did not have any significant change in their nodal disease after 46 Gy of IMRT (54.5%, n=42) and a minority of them showed a larger N-status after radiation (3.9%, n=3). Table 3 outlines the differences between cN an pN after IMRT, and the effect of p16-positive disease on nodal response while Figure 1 shows an overview of the differences in nodal response following tumor staging using the 7th and 8th TNM classification

Figure 1. UICC/AJCC Stage grouping, cN compared to pN after 46 Gy of IMRT

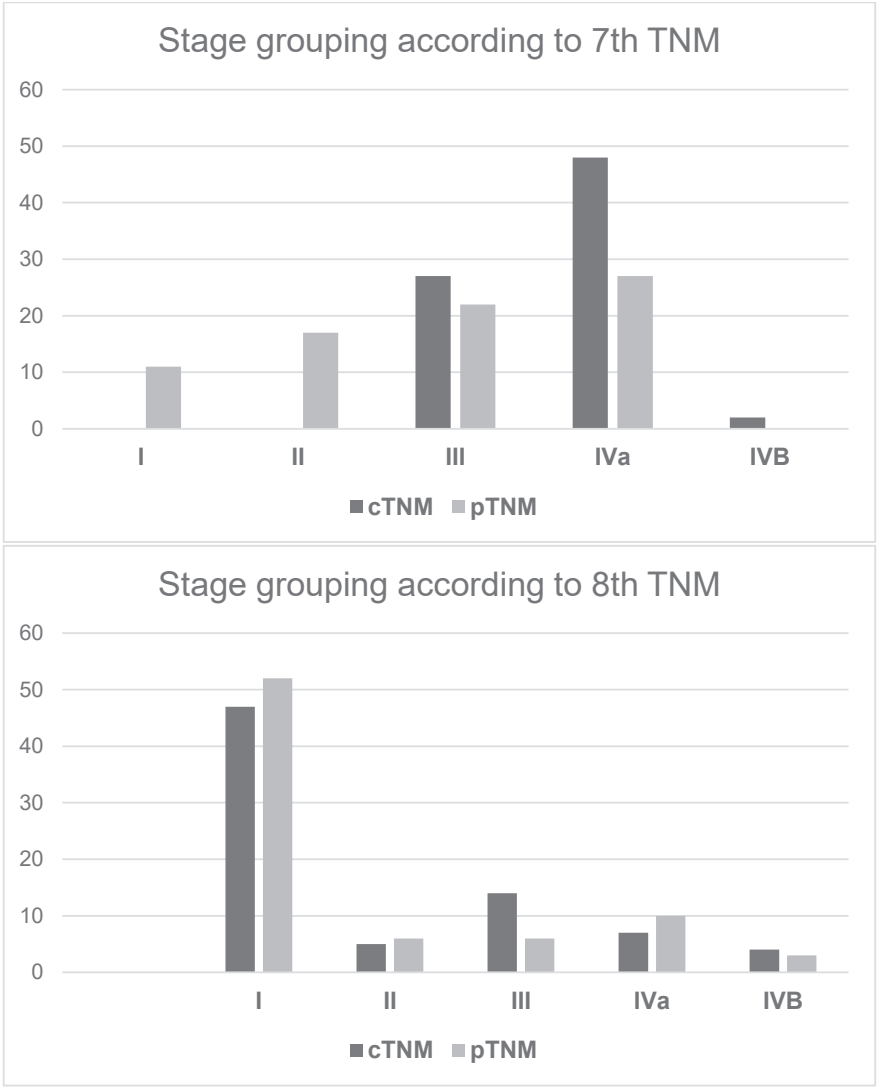


Table 3a. cN compared to pN after 46 Gy of IMRT using 7th TNM classification

p16 positive OPSCC – 7th TNM classification

		Pathological nodal stage (after neckdissection)										
Clinical nodal stage		**pN0**		**pN1**		**pN2a**		**pN2b**		**pN2c**		**Total**
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*
	cN1	7†		5		0		0		0		12
	cN2a	6†		4‡		0		0		0		10
	cN2b	7†		6‡		1‡		11		0		25
	cN2c	3†		1‡		0		0		1		5
	cN3	0		0		0		1‡		0		1
Total		23	43.4%	16	30.2%	1	1.9%	12	22.6%	1	1.9%	53

† *Full nodal response (pathologically cancer free),* ‡*Partial nodal response (pN < cN)*

p16 negative OPSCC – 7th TNM classification

		Pathological nodal stage (after neckdissection)										
Clinical nodal stage		**pN0**		**pN1**		**pN2a**		**pN2b**		**pN2c**		**Total**
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*
	cN1	5†		5		0		3§		0		13
	cN2a	0		0		2		0		0		2
	cN2b	0		1‡		0		6		0		7
	cN2c	0		0		0		0		1		1
	cN3	0		0		1‡		0		0		1
Total		5	20.8%	6	25%	3	12.5%	9	37.5%	1	4.2%	24

† *Full nodal response (pathologically cancer free),* ‡*Partial nodal response (pN < cN),* §*Nodal progression (pN > cN)*

Table 3b. cN compared to pN after 46 Gy of IMRT using 8th TNM classification

p16 positive OPSCC – 8th TNM classification

		Pathological nodal stage (after neckdissection)						
Clinical nodal stage		**pN0**		**pN1**		**pN2**		**Total**
		N	*%*	*N*	*%*	*N*	*%*	
	cN1	20†		27		0		47
	cN2	3†		1‡		1		5
	cN3	0		1‡		0		1
Total		23	43.4%	29	54.7%	1	1.9%	53

† *Full nodal response (pathologically cancer free),* ‡*Partial nodal response (pN < cN)*

p16 negative OPSCC – 8th TNM classification

		Pathological nodal stage (after neckdissection)												
Clinical nodal stage		**pN0**		**pN1**		**pN2a**		**pN2b**		**pN3a**		**pN3b**		**Total**
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*
	cN1	5†		5		0		3§		0		0		13
	cN2a	0		0		2		0		0		0		2
	cN2b	0		1‡		0		4		0		0		5
	cN3a	0		0		0		1‡		0		0		1
	cN3b	0		0		0		0		0		3		3
Total		5	20.8%	6	25.0%	2	8.3%	8	33.3%	0	0%	3	12.5%	24

† *Full nodal response (pathologically cancer free),* ‡*Partial nodal response (pN < cN),* §*Nodal progression (pN > cN)*

Using the 7th TNM classification, nodal response (partial or complete) was significantly associated with HPV status (p=0.002). 67.9% (n=36) of p16-positive patients had complete or partial response compared to 29.2% (n=7) of p16-negative patients (Supplementary Table A1). Multivariate logistic regression analysis was performed to estimate the adjusted Odds Ratio (OR) of the effect of HPV status on nodal response, adjusted for UICC/AJCC tumor stage and tobacco use. p16-positive patients had an OR of 4.6 (95% CI 1.4 – 15.5, p=0.012) to achieve complete nodal response after 46 Gy of IMRT. However, smoking interacts with this effect. Patients with p16-positive OPSCC who were non- or former smokers had an OR of 6.3 (95% CI 1.4 – 28.4, p=0.017), whereas p16-positive current smokers had an OR of 4.5 (95% CI 0.7 – 25.7, p=0.089) to achieve complete nodal response.

When applying the 8th TNM classification, complete or partial response seemed to be related to HPV status, however not significantly (p=0.138) (Supplementary Table A2). Of the p16-positive patients, 47.2% (n=25) compared to 29.2% (n=7) of the p16-negative patients had nodal response. The same association was seen in multivariate analysis, adjusted for UICC/AJCC tumor stage and tobacco use, with an OR of 1.7 (p=0.314). Using the 8th TNM classification, the correlation between nodal response and p16 positivity does not hold.

Effect of the Rotterdam protocol, HPV status and nodal response on overall and disease free survival

Mean 5-year OS was 77.8%. The log rank test for OS significantly favored patients with p16-positive OPSCC (5-year OS 87.5%) versus p16-negative OPSCC (5-year OS 55.8%, p<0.001). The same result was found for 5-year DFS of patients with p16-positive OPSCC (98%) versus 54.5% DFS for p16-negative OPSCC (p<0.001), see Figure 2a-b. When HPV status was stratified for smoking status OS was significantly better in never or former smokers (5-year OS p16-positive disease 95% versus 71.6% p16-negative disease), then in current smokers (5-year OS p16-positive disease 62.5%, p16-negative disease 41.7%, p<0.001).

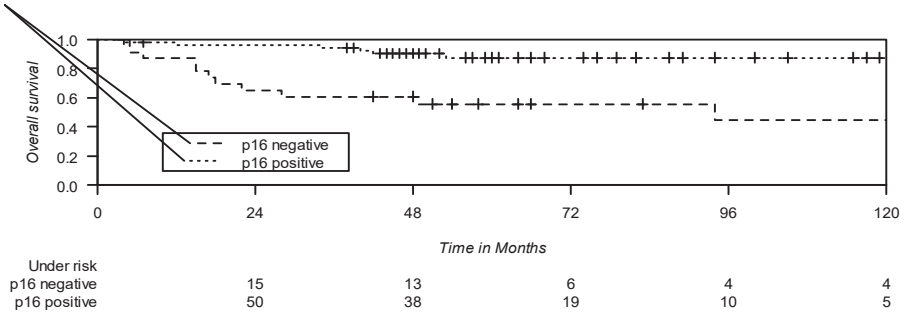
Patients with complete nodal response after 46 Gy of IMRT had a 5-year OS of 96.3% versus 67.0% for patients with partial or no nodal response (p= 0.003).

5-year OS for p16-positive patients with complete nodal response was 100%, and 80% for p16-negative patients. 5-year OS for p16-positive patients with partial or no nodal response was 78.5% and for p16-negative patients 51.5%. Both are significant results (p< 0.001). Similar trends were seen for DFS, but these findings did not reach statistical significance.

Figure 3 shows the difference between 7th and 8th TNM classification in classifying p16-positive OPSCC patients in prognostic subgroups with regards to nodal response.

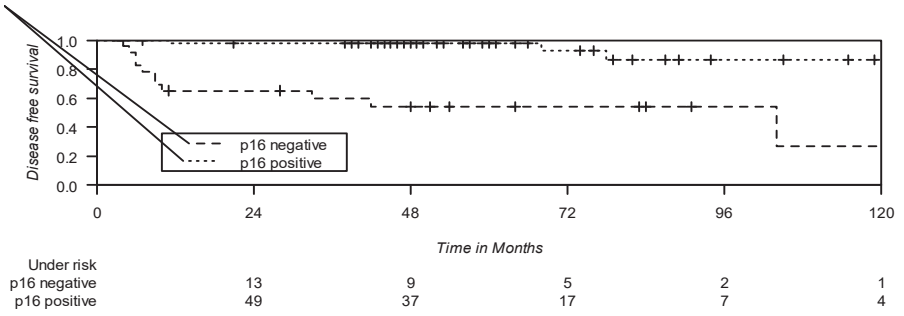
Figure 2. Kaplan Meier curve of overall (2a) and disease free survival (2b) as a function of p16 immunostaining

2a.



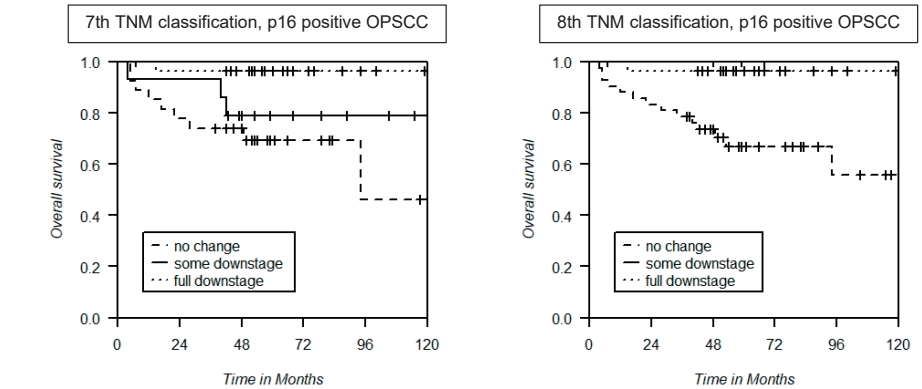
Under risk					
p16 negative	15	13	6	4	4
p16 positive	50	38	19	10	5

2b.



Under risk					
p16 negative	13	9	5	2	1
p16 positive	49	37	17	7	4

Figure 3. Kaplan Meier curve of overall survival as a function of p16 immunostaining and nodal response according to 7th and 8th TNM classification respectively



Under risk					
no change	21	17	6	2	1
some downstage	13	9	5	3	1
full downstage	26	22	13	9	7

Under risk					
no change	35	25	12	5	2
some downstage	3	3	0	0	0
full downstage	26	22	13	9	7

The Kaplan Meier curves illustrate that the use of the 8th TNM classification provides a more realistic effect of nodal response on cumulative survival for patients with p16-positive OPSCC compared to the 7th edition. By classifying nodal stage (cN and pN) according to the 8th edition, both partial and complete nodal response lead to a 100% survival, even after 10 years. This is in contrast to the 7th edition where overall survival of p16-positive patients with partial nodal response is over 90%.

DISCUSSION

In this study we observed that the majority of our patients with T1-2 node positive OPSCC had p16-positive disease. Treatment with the Rotterdam protocol for OPSCC resulted in excellent loco regional control and overall survival was significantly better in this group compared to patients with p16-negative OPSCC.

This current study shows that p16-positive disease is associated with increased nodal response after a relatively low dose of IMRT to the involved neck. Patients with complete nodal response after IMRT had a significantly increased survival compared to patients with partial nodal response. However, this association is affected by the TNM classification that is used. In the 8th TNM classification, stage grouping for T1-2 OPSCC is based entirely on the extent of nodal disease, and permits a more appropriate depiction of the prognosis of HPV positive disease.[7] Our hypothesis of the favorable effect of HPV positive disease on nodal response after 46 Gy of IMRT holds true using the 7th TNM classification but is obscured by the use of the 8th TNM classification. This finding is not that remarkable since advanced nodal disease for p16-positive OPSCC is literally down-staged in the 8th TNM classification, for both cN and pN.[7,8] However, this finding does point out that the 8th TNM provides a more realistic effect of nodal response on overall survival for p16-positive OPSCC patients. Classification of nodal stage by the 8th edition shows a 100% overall survival for p16-positive patients with both partial and complete nodal response in contrast with over 90% overall survival for patients with partial nodal response that are staged using the 7th edition.

Yet, our results also show a proportion of p16-positive OPSCC patients with no nodal response after 46 Gy of IMRT. These patients also have a reduced 5 year overall survival (75.7%). There are two possible explanations for these results: false positivity of p16 analysis and smoking. Since we did not carry out HPV DNA-detection, some p16-positive tumors may have been HPV negative, with relatively worse prognosis. Furthermore, not all FFPE's were available of all patients treated according to the Rotterdam protocol between 2000 and 2012, and therefore selection bias might have occurred. In addition, in our study

we also found that smoking negatively interacts with the effect of p16-positive OPSCC on prognosis. This finding is in conjunction with the study by Platek et al., where smoking was found to be a prognostic factor independent of HPV.[24] They show that current smoking during radiotherapy in OPSCC patients is associated with a four- to sevenfold increase in risk of mortality for HPV positive and HPV negative patients respectively. Our study confirms that every effort should be made to motivate current smokers with OPSCC to stop smoking.

Our results on p16-positive disease being significantly associated with increased nodal response even after 46 Gy radiotherapy are in line with those found in literature. Bird et al., showed that only 9% of HPV-positive patients underwent neck dissection within 6 months of radiation completion (54-65 Gy of IMRT) because of suspected residual disease.[25] In addition, Garden et al. found that 80% of HPV-positive patients had no neck dissection based on their response after 70 Gy of IMRT.[26] They concluded that only 2% of HPV-positive OPSCC patients benefit from a neck dissection.

However, Marklund et al. found that HPV-positive tumors had the same proportion (23%) of viable tumor cells in the neck specimen, 6-8 weeks after radiotherapy (64-68 Gy) as HPV-negative tumors.[10] In our study, neck dissection was performed within 3 weeks after radiation. An explanation for the difference between these results could be that HPV-positive tumors have a more rapid early response after radiotherapy followed by tapered response such that it may take longer for HPV-positive nodes to regress. Other studies performed weekly CT scans to measure the volume of positive lymph nodes.[27,28] They found that in HPV-positive patients with node positive OPSCC, spontaneous shrinkage was seen before radiotherapy, during treatment enlargement of nodes was seen and shortly after treatment there was a poor response on IMRT (25.3% failed to show complete response after 12 weeks). This finding suggests that complementary neck dissection still seems necessary for a subgroup of these patients. Our data also support this suggestion following the decreased overall- and disease free survival in patients who had no nodal response 3 weeks after 46 Gy of IMRT.

CONCLUSION

The Rotterdam protocol for T1-2 OPSCC results in excellent local control rates with low toxicity. In node-positive disease, neck-dissection after a relatively low dose of IMRT to the involved neck results in excellent regional control and a low severe complication rate. p16-positivity is associated with complete nodal response. Smoking, however, negatively interacts with this effect. There is a significant difference between HPV-positive tumors

with complete nodal response (pN0) and HPV-negative tumors in terms of survival. Despite these results, we believe there is not enough evidence to omit neck dissection yet. On the one hand due to the relatively large fraction of p16-positive patients in this study that did not show nodal response. On the other hand due to the fact that p16-positivity does not equal HPV positivity and p16-positive/HPV DNA negative OPSCC do not have the HPV-related favorable prognosis.[29] Therefore, additional HPV DNA testing should be considered when looking at decisions regarding treatment deintensification. Nevertheless, the results of this and other studies suggest that a number of OPSCC patients do not necessarily need the current gold standard of 70 Gy of radiotherapy to obtain locoregional control of their disease. Currently proceeding treatment de-intensification trials may provide a proof of this principle.[14-16] In addition, our center is embarking on a prospective study using functional MRI to assess the neck prior to neck dissection for OPSCC patients.

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Supplementary Table A1. Univariate analysis of associations between variables and nodal response, based on 7th TNM classification

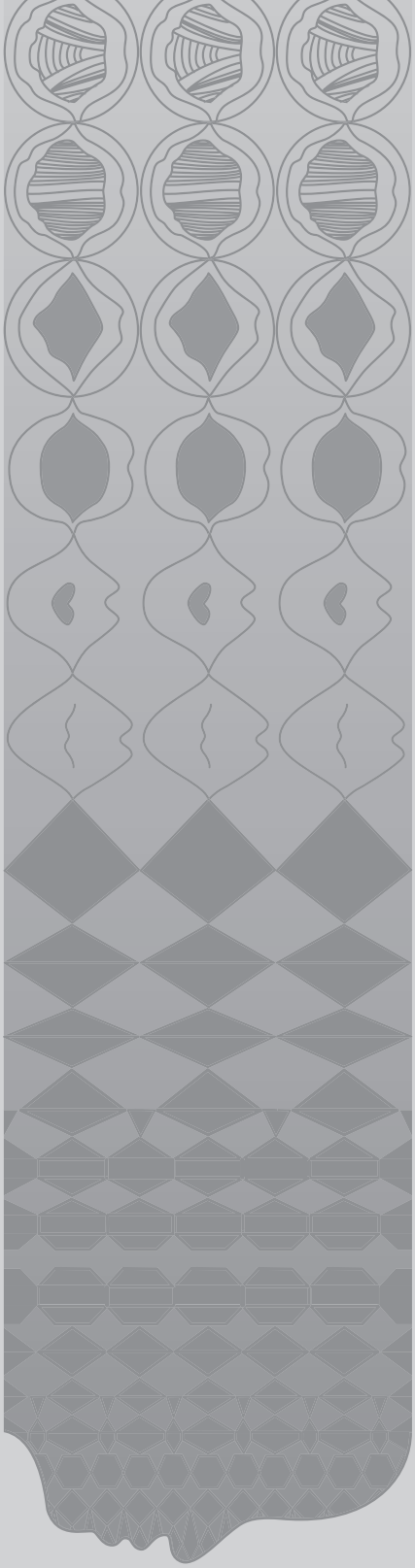
		Complete or partial nodal response						
		No			yes			
		Mean	N	%	Mean	N	%	p-value*
Age		60			57			0.304
Gender	Male		23	67.6%		34	79.1%	0.256
	Female		11	32.4%		9	20.9%	
ACE27	None		14	41.2%		16	37.2%	0.609
	Mild		8	23.5%		16	37.2%	
	Moderate		10	29.4%		9	20.9%	
	Severe		2	5.9%		2	4.7%	
Tobacco use	No smoking history		4	11.8%		12	27.9%	0.149
	Former smoker		16	47.1%		20	46.5%	
	Current smoker		14	41.2%		11	25.6%	
Clinical tumor stage (7th UICC/AJCC classification system)	I		0	0.0%		0	0.0%	0.182
	II		0	0.0%		0	0.0%	
	III		15	44.1%		12	27.9%	
	Iva		19	55.9%		29	67.4%	
	IVb		0	0.0%		2	4.7%	
p16 immunostaining	Negative		17	50.0%		7	16.3%	**0.002**
	Positive (>70% staining)		17	50.0%		36	83.7%	
Acute toxicity	Low (0-2)		28	82.4%		38	88.4%	0.454
	High (3-4)		6	17.6%		5	11.6%	
Recurrent disease	No recurrent disease		25	73.5%		41	95.3%	**0.025**
	(Loco)regional recurrence		4	11.8%		1	2.3%	
	Distant metastasis		5	14.7%		1	2.3%	
Deceased	No		20	58.8%		38	88.4%	**0.003**
	Yes		14	41.2%		5	11.6%	

*univariate analysis by chi-square test independent samples t-test, $p < 0.05$ is considered significant result

Supplementary Table A2. Univariate analysis of associations between variables and nodal response, based on 8th TNM classification

		Complete or partial nodal response						
		No			yes			
		Mean	N	%	Mean	N	%	p-value*
Age		60			56			0.092
Gender	Male		31	68.9%		26	81.3%	0.223
	Female		14	31.1%		6	18.8%	
ACE27	None		17	37.8%		13	40.6%	0.578
	Mild		12	26.7%		12	37.5%	
	Moderate		13	28.9%		6	18.8%	
	Severe		3	6.7%		1	3.1%	
Tobacco use	No smoking history		7	15.6%		9	28.1%	0.307
	Former smoker		21	46.7%		15	46.9%	
	Current smoker		17	37.8%		8	25.0%	
Clinical tumor stage (8th UICC/AJCC classification system)	I		27	60.0%		20	62.5%	0.225
	II		1	2.2%		4	12.5%	
	III		8	17.8%		6	18.8%	
	IVa		6	13.3%		1	3.1%	
	IVb		3	6.7%		1	3.1%	
p16 staining	Negative		17	37.8%		7	21.9%	0.138
	positive (>70% staining)		28	62.2%		25	78.1%	
Acute toxicity	Low (0-2)		36	80.0%		30	93.8%	0.089
	High (3-4)		9	20.0%		2	6.3%	
Recurrent disease	No recurrent disease		36	80.0%		30	93.8%	0.235
	(Loco)regional recurrence		4	8.9%		1	3.1%	
	Distant metastasis		5	11.1%		1	3.1%	
Deceased	No		28	62.2%		30	93.8%	**0.002**
	Yes		17	37.8%		2	6.3%	

*univariate analysis by chi-square test independent samples t-test, $p < 0.05$ is considered significant result



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A beneficial tumor microenvironment in oropharyngeal squamous cell carcinoma is characterized by a high T cell and low IL-17+ cell frequency

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ABSTRACT

Patients with HPV-positive oropharyngeal squamous cell carcinomas (OPSCCs) have a better prognosis than patients with non-HPV-induced OPSCC. The role of the immune response in this phenomenon is yet unclear. We studied the number of T cells, regulatory T cells (Tregs), T helper 17 (Th17) cells and IL-17+ non-T cells (mainly granulocytes) in matched HPV-positive and HPV-negative OPSCC cases (n = 162). Furthermore, the production of IFN-γ and IL-17 by tumor-infiltrating T cells was analyzed. The number of tumor-infiltrating T cells and Tregs was higher in HPV-positive than HPV-negative OPSCC ($p < 0.0001$). In contrast, HPV-negative OPSCC contained significantly higher numbers of IL-17+ non-T cells ($p < 0.0001$). Although a high number of intratumoral T cells showed a trend toward improved survival of all OPSCC patients, their prognostic effect in patients with a low number of intra-tumoral IL-17+ non-T cells was significant with regard to disease-specific ($p = 0.033$) and disease-free survival ($p = 0.012$). This suggests that a high frequency of IL-17+ non-T cells was related to a poor immune response, which was further supported by the observation that a high number of T cells was correlated with improved disease-free survival in the HPV-positive OPSCC ($p = 0.008$). In addition, we detected a minor Th17 cell population. However, T cells obtained from HPV-positive OPSCC produced significantly more IL-17 than those from HPV-negative tumors ($p = 0.006$). The improved prognosis of HPV-positive OPSCC is thus correlated with higher numbers of tumor-infiltrating T cells, more active Th17 cells and lower numbers of IL-17+ non-T cells.

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) can be divided into subtypes with different etiologies, one subtype due to alcohol and tobacco use and another due to persistent infection with high-risk human papillomavirus (HPV).[1,2] The incidence of OPSCC and the prevalence of HPV-associated tumors are increasing in Europe and the USA.[3-7] The reported proportion of HPV-positive OPSCC ranges from 20 to 90%. This high variation between studies may be related to the time period in which HPV prevalence was investigated as well as to the lack of a standardized HPV detection assay.[8] Remarkably, patients with HPV-positive OPSCC have a significantly better prognosis than patients with non-HPV-induced tumors.[8-11] However, heavy smoking habits seem to undo the beneficial effect of HPV positivity on survival.[12]

A different type of cancer, arising in the cervix uteri, is practically always initiated by a persistent HPV infection.[13] From studies on cervical HPV infections, HPV is known to be cleared in over 90 % of cases.[14] In case of cervical cancer development, the tumor cells are thought to manipulate the immune response such that it facilitates tumor growth.[15] In addition, the immune response present in the tumor microenvironment is critical for clinical outcome. As OPSCC can be divided in virally induced and non-virally induced subtypes, this tumor type provides a means to study the relationship between the immune response and clinical outcome as a function of viral etiology. A high frequency of intratumoral CD8+ cytotoxic T cells has been found to be correlated with improved survival in OPSCC.[16] However, data are still limited for other T cell subsets in OPSCC, including regulatory T cells (Tregs).

The role of Tregs in cancer in general seems to be context and tumor type dependent[17], with correlations reported between a high Treg frequency and poor prognosis[18-20] but also improved prognosis.[21-24] The role of T helper 17 (Th17) cells and other IL-17 expressing cells is unclear, with contradictory functions attributed to this cell type in cancer.[25] We have recently shown that Th17 cells tend to be correlated with improved survival, while total IL-17, predominantly expressed by granulocytes, correlated with poor survival in cancer patients.[26,27]

The aim of this study was to elucidate the role of the immune response in virally induced versus non-virally induced OPSCC. We determined the distribution of intra-epithelial and stromal T cells, Tregs, Th17 and IL-17+ non-T cells with regard to HPV status in a large series of OPSCC cases and analyzed the correlations with patient survival. The IL-17+ non-T cells were included in these analyses, because we previously found that on average only 6% of the tumor-infiltrating IL-17+ cells in head and neck cancer were Th17 cells, while 45% were

granulocytes.[26] In addition, the production of IFN-γ and IL-17 by tumor-infiltrating lymphocytes upon mitogenic stimulation was compared in HPV-positive and HPV-negative tumors. Because of the differences in survival based on HPV status, the differences in immune response between OPSCC groups may indicate markers of a beneficial immune response. We hypothesized that HPV-positive tumors are characterized by a different quantity and composition of immune cell infiltrates. We expect that total T cells and Th17 cells are correlated with improved clinical outcome, while Tregs and IL-17+ non-Th17 cells are correlated with poor outcome for patients.

MATERIALS AND METHODS

Patient material

For this study, we searched the hospital-based cancer registry Oncology Documentation (ONCDOC) of the LUMC for all primary oropharyngeal tumors, diagnosed between 1970 and 2011. Trained data managers scored all patient, treatment and follow-up data. These data were retrieved from the patients' medical record and hospital-based data system. ONCDOC also performs an independent and active follow-up. Formaldehyde fixed, paraffin-embedded (FFPE) pretreatment tumor samples from 341 patients were obtained from the archives of the Pathology Department of the LUMC. A dedicated pathologist (Senada Koljenović) analyzed the tumor samples for the presence of malignant cells. Thirty tumor samples (8.8 %) were excluded for further analysis due to the absence of malignant cells. All included patients were treated following standard guidelines that applied in the year of diagnosis. Patient and tumor characteristics are listed in Table 1. The median follow-up time of the 162 patients selected for final analysis was 37 months. Patient samples were handled according to the medical ethical guidelines described in the Code of Conduct for Proper Secondary Use of Human Tissue of the Dutch Federation of Biomedical Scientific Societies (www.federa.org).

p16 and HPV detection

FFPE tumor specimens from 311 patients were cut into 4-µm-thick sections, deparaffinized and stained for p16 (INK4A; Roche MTM Laboratories AG, Heidelberg, Germany) using a fully automated Ventana BenchMark ULTRA Stainer (Ventana, Tucson Arizona, USA) according to the manufacturers' instructions. Binding of peroxidase-coupled antibodies was visualized using 3,3'-diamino-benzidinetetrahydrochloride (DAB). Slides were counterstained with hematoxylin. P16 immunostained samples were scored independently by two dedicated pathologists (Senada Koljenović, Elisabeth Bloemena). The tumor samples were scored as 'p16 positive' when >70 % of the tumor cells showed both nuclear and cytoplasmic staining.

Table 1. Patient and tumor characteristics

Clinical-pathological parameter	Category	HPV-negative tumors (%) (N = 99)	HPV-positive tumors (%) (N = 63)
Age	Median (years)	60	57
	Range (years)	41-86	43-90
Sex	Female	32 (32)	25 (40)
	Male	67 (68)	38 (60)
Tumor location	Tongue base	23 (23)	16 (25)
	Tonsil	25 (25)	31 (49)
	Tonsillar fossa	26 (26)	9 (14)
	Oropharyngeal wall	13 (13)	4 (6)
	Soft palate	8 (8)	1 (2)
	Vallecula	1 (1)	2 (3)
	Uvula	3 (3)	0 (0)
Tumor morphology	Squamous cell (unspecified)	35 (35)	32 (51)
	Keratinizing squamous cell	45 (45)	14 (22)
	Non-keratinizing squamous large cell	16 (16)	16 (25)
	Papillary squamous cell	2 (2)	1 (2)
	Squamous spindle cell	1 (1)	0 (0)
TNM stage[1]	T1	16 (16)	19 (30)
	T2	33 (33)	27 (43)
	T3	26 (26)	13 (21)
	T4	24 (24)	4 (6)
	N0	38 (38)	9 (14)
	N1	22 (22)	13 (21)
	N2	33 (33)	38 (60)
	N3	6 (6)	3 (5)
	M0	97 (98)	62 (98)
	M1	2 (2)	1 (2)
Local recurrence	No	83 (84)	55 (87)
	Yes	16 (16)	8 (13)
Regional recurrence	No	82 (83)	57 (90)
	Yes	17 (17)	6 (10)
Distant metastasis	No	84 (85)	57 (90)
	Yes	15 (15)	6 (10)
Deceased	No	29 (29)	45 (71)
	Yes	70 (71)	18 (29)
Follow-up time	Median (months)	28	55
Prior tumor	No	93 (94)	55 (87)
	Yes	6 (6)	8 (13)

[1]Clinical TNM classification of the tumor size (T) and the involvement of regional lymph nodes (N) and distant metastases (M).

High-risk HPV DNA detection was performed on the p16-positive cases. DNA was extracted from all p16 positive cases using an automated silica-based extraction system, and PCR was performed using the HPV-Risk assay (Self-Screen BV, Amsterdam, the Netherlands).[28] The HPV-Risk assay is a novel real-time PCR assay targeting the E7 region of 15 high-risk HPV types (i.e., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67 and 68) and provides additional genotype information for HPV16 and HPV 18. The HPV-Risk assay is clinically validated and meets the cross-sectional clinical and reproducibility criteria of the international guidelines for HPV test requirements.

Matching

All p16 positive cases (n=94) were included in this study as well as n=94 p16 negative cases that were matched for tumor T stage, N stage, location, patient gender and decennium of diagnosis. Hence, a subset of n=188 out of n=311 patients was selected for the present study.

Immunofluorescent stainings

Part of the selected n=188 tumor samples could not be analyzed due to insufficient tumor material to obtain at least one microscopic image (n=26). Triple immunofluorescent staining for CD3 (ab828, Abcam, Cambride, UK), FoxP3 (ab20034, Abcam) and IL-17 (AF-317-NA, R&D Systems, Abingdon, UK) was performed on 162 tumor samples as described before.[29] These comprised 86 p16 positive and 76 p16 negative tumors. Images were obtained using an LSM700 confocal laser scanning microscope containing an LCI Plan-Neofluar 25×/0.8 Imm Korr DIC M27 objective (Zeiss, Göttingen, Germany). One to four random images sampled a total vital tumor (epithelium + stroma) area of up to 1.0 mm^2. Total tumor epithelium and stroma surface area and double or triple positivity of cells were determined in each image using LSM Image Browser (version 4.2.0.121, Zeiss). Single-, double- and triple-positive cells were scored separately in the tumor epithelial and stromal areas using ImageJ version 1.47 (http://rsb.info.nih.gov/ij). Cells within blood vessels and largely autofluorescent areas were not scored.

TIL isolation and cytokine analysis

Fresh OPSCC tissue was cut into small pieces of ~1 mm^3 and cultured in IMDM (Lonza), supplemented with 10% human AB serum (Life Technology) and two–three times a week 1000 IU/mL IL-2 (Novartis Aldesleukin). TIL were cultured for two–four weeks to obtain sufficient cells for testing their response to PHA stimulation (in triplicate wells). Unstimulated T cells were used as a negative control. Supernatant (50 µl/well) was harvested after 4 days of stimulation and used for cytokine analysis. The production of IFN-γ (Sanquin) and IL-17A (eBiosciences) was analyzed according to the manufacturers' ELISA kit guidelines.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, USA) and R version 3.1.1. (packages: foreign, mice, rms, survival). Differences in the numbers of positive cells between patient groups were tested using the Wilcoxon Mann–Whitney tests. Correlations (r) between cell frequencies were tested using the Spearman's rank correlation rho test. For each disease-free (time from diagnosis until local or distant recurrence or death to disease) and disease-specific (time from diagnosis until death to disease) survival, Kaplan–Meier curve generation and log rank analysis, the cell numbers were divided into four equal quartiles and the lowest quartile (low frequency) was compared with the other quartiles (high frequency). For comparisons based on a ratio or other combination of cell frequencies, patients were divided into a high and low group based on the median. Missing values for the variable smoking status were handled by performing multiple imputation using the package 'mice' in R. All variables included in Table 1 were used for imputation. N=5 imputations were performed, and the pooled imputed data were used in multivariate analyses. Multivariate analysis was performed using Cox proportional hazard regression analysis. All tests were two-sided, and p values below 0.05 were considered statistically significant.

RESULTS

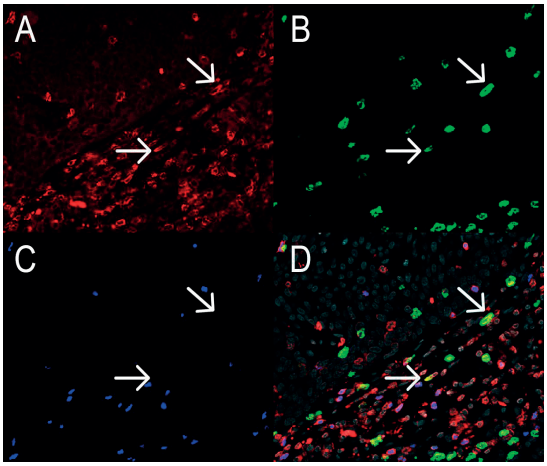
HPV analysis

Of the initial 311 tumor samples that were evaluated for HPV status, 94 (30%) were scored 'p16 positive.' The inter-observer variability between the scoring of all tumor samples by two pathologists was 0.867 (kappa statistic, $p < 0.001$). Of the p16 positive cases, 70 (74.4%) contained high-risk HPV DNA, of which 63 (90%) were HPV 16 positive, and 7 (10%) contained HPV 18 or other types of high-risk HPV. The variability between the p16 and PCR analyses was 0.774 (kappa statistic, $p < 0.001$). After matching all p16 positive cases (n=94) for tumor T stage, N stage, location, patient gender and decennium of diagnosis with an equal amount of p16 negative cases, only 162 samples were suitable for further analysis by immunofluorescence. Of this subset of tumor samples, 86 were p16 positive and 76 were p16 negative. A proportion of 73.3 % (n=63) of the p16 positive cases contained high-risk HPV DNA. Only these 63 cases were taken into account as HPV positive in further analysis. As a result, p16 positive but HPV DNA negative cases were considered HPV negative (n=21). N stage, location of tumor, patient gender, patient age and level of comorbidity were not significantly different between the HPV-positive and HPV-negative cases. A higher T stage was observed in the HPV-negative patients, which might be due to the p16 positive HPV-negative patients to be considered HPV negative in the final analysis. However, adding T stage to the multivariate analyses did not influence the significance of the results.

HPV-positive tumors are more heavily infiltrated by T cells and less by IL-17+ non-T cells

Irrespective of HPV status, all tumor samples were infiltrated by CD3+ T cells, which comprised a substantial population of CD3+FoxP3+ Tregs (Figure 1, Supplementary Figure 1 and Supplementary Table 1). IL-17+ cells represented another substantial infiltrating immune cell population, whereas only a minor population of CD3+IL-17+ Th17 cells was observed. FoxP3+ cells were always positive for CD3. FoxP3+IL-17+ cells were observed very infrequently—at maximum five cells in all samples comprising 0.01% of FoxP3+ cells—and were thus not further analyzed.

Figure 1. Representative image of an oropharyngeal cancer specimen stained by triple immunofluorescence for IL-17

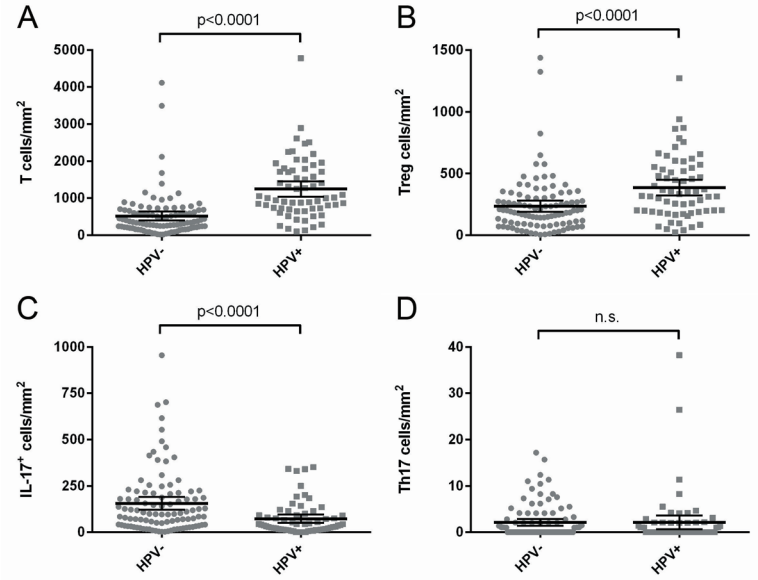


(A), CD3 (B) and FoxP3 (C), with the combined stainings together with DAPI counterstain (grey) shown in D. Different IL-17+ cells and CD3+FoxP3+ Tregs are present. The arrows indicate two Th17 cells double positive for IL-17 and CD3.

HPV-positive tumors contained significantly higher numbers of CD3+ T cells infiltrating in the tumor epithelium ($p < 0.0001$) and the tumor stroma ($p < 0.0001$). Because the increase in T cells in HPV-positive tumors was similar in the epithelium, stroma and the combined tumor epithelium and stroma field, the significantly increased numbers of CD3+ T cells in the HPV-positive compared to the HPV-negative tumors are shown in Figure 2a for the combined area ($p < 0.0001$). The number of CD3+FoxP3+ Tregs infiltrating in the tumor epithelium ($p < 0.0001$) and stroma ($p < 0.0001$) was also significantly higher in HPV-positive tumors. The increased number of Tregs in the tumor epithelium and stroma combined in HPV-positive tumors is shown in Figure 2b ($p < 0.0001$). However, the average ratio of total T cells over Tregs was twice as high in HPV-positive tumors compared to HPV-negative tumors (Supplementary Table 1). Non-Treg T cells were thus particularly increased in HPV-positive tumors. In contrast, the number of IL-17+ non-T cells was signifi-

cantly higher in the tumor epithelium (p = 0.003), the stroma (p = 0.004) and the tumor epithelium and stroma combined (p < 0.0001, Figure 2c) of HPV-negative compared to HPV-positive tumors. The frequency of Th17 cells was not significantly different between HPV-positive and HPV-negative tumors (Figure 2d).

Figure 2. Tumor infiltrating T cells and IL-17+ cells in HPV-positive and HPV-negative tumors.



The number of total CD3+ T cells (A), FoxP3+CD3+ Tregs (B), CD3-IL-17+ cells (C) and CD3+IL-17+ Th17 cells (D) infiltrating in the tumor epithelium and stroma per mm2 is shown for HPV-negative tumors and HPV-positive tumors. The bars indicate the mean and 95% confidence interval; n.s. = not significant.

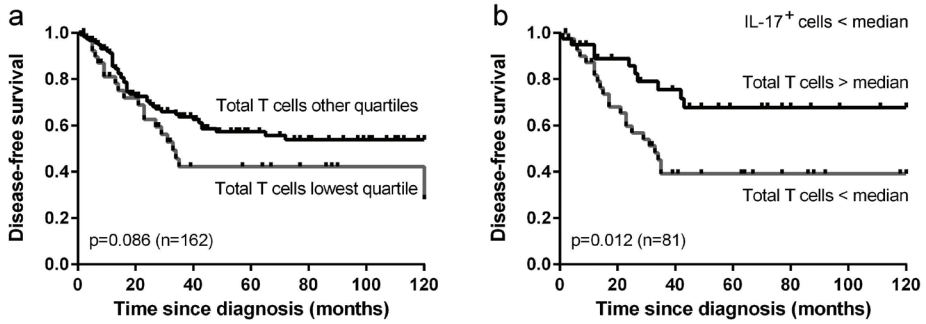
The frequency of infiltrating Tregs was significantly correlated with the frequency of total infiltrating T cells in both HPV-positive (r = 0.676, p < 0.0001) and HPV-negative tumors (r = 0.877, p < 0.0001). The frequency of infiltrating IL-17+ cells was not significantly correlated with the frequency of total infiltrating T cells (data not shown).

Infiltrating T cells are correlated with improved survival in combination with low IL-17+ non-T cell frequencies

We subsequently studied the correlations between the infiltrating immune cell frequencies and patient survival. Since the correlations for stromal and total cell numbers were similar, the correlations for intra-epithelial and total cell numbers are discussed. A high number of infiltrating total T cells in all patients combined showed a trend toward correlation with improved disease-specific (p = 0.089, data not shown) and disease-free survival (0.086, Figure 3a) compared to a low number of T cells (i.e., lowest quartile). Previously, we found that cervical cancer-infiltrating IL-17+ cells, representing mainly granulocytes, were

associated with poor survival.[26] We, therefore, divided the patients based on the median number of IL-17+ cells. Among patients with a low number of IL-17+ cells, a high number of total infiltrating T cells was correlated with improved disease-specific (p = 0.033, data not shown) and disease-free survival (p = 0.012, Figure 3b) when compared to a low T cell frequency. The prognostic effect of tumor-infiltrating T cells was lost in the group of patients with an above number of tumor-infiltrating IL-17+ cells (data not shown).Thus, the effect of tumor-infiltrating T cells in OPSCC may be related to the low number of IL-17+ cells present.

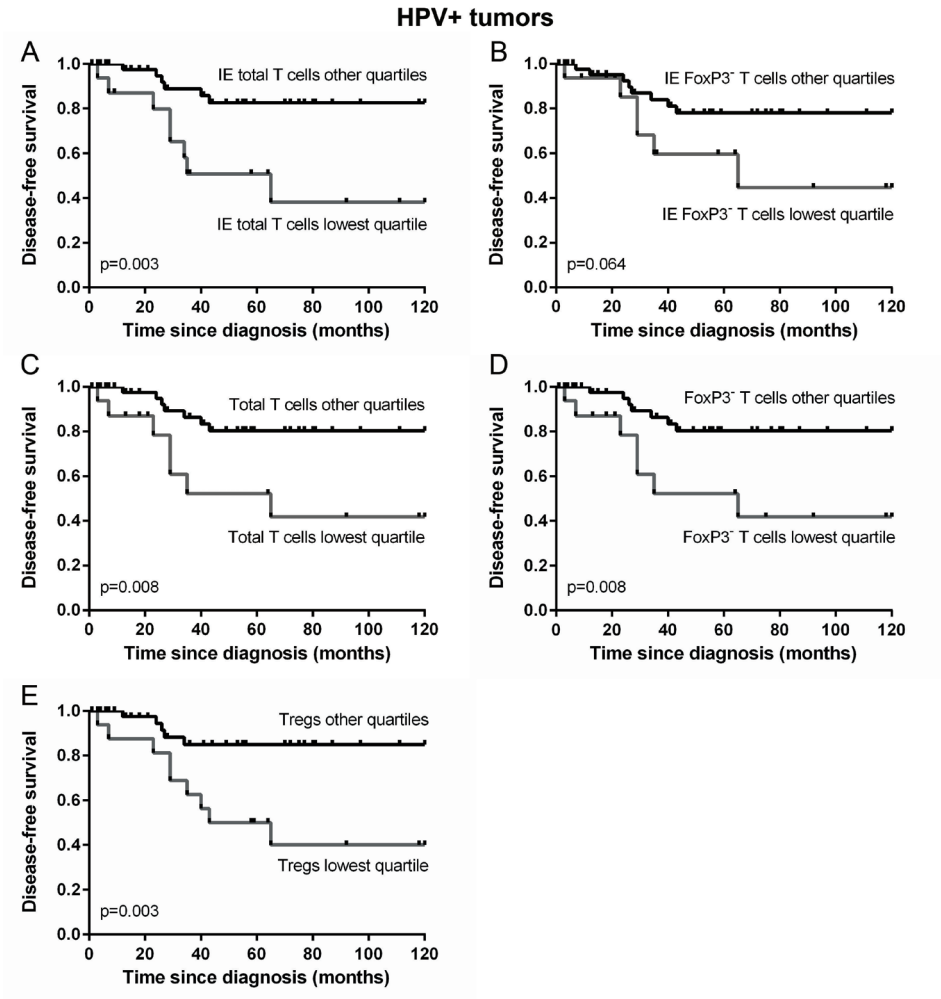
Figure 3. Kaplan-Meier disease-free survival curves for a low (i.e. lowest quartile) versus higher number of total T cells among all patients (A) and a low (i.e. below median) versus high number of total T cells among the patients with a below median number of IL-17+ cells/mm2 (B).



We further studied the survival correlations among patients with HPV-positive tumors. The presence of HPV in OPSCC tumors was significantly correlated with improved disease-specific (p = 0.0001) and disease-free survival (p < 0.0001, data not shown), corresponding to earlier studies.[30,31] Since p16-positive tumors were matched to p16-negative tumors for factors that may contribute to prognosis, these factors were equally distributed over the groups of HPV-positive and HPV-negative tumors and similarly correlated with survival. When corrected for comorbidity, prior tumor occurrence and smoking status, the hazard ratio, for a recurrence or death to disease with an HPV-positive compared to an HPV-negative tumor was 0.334 (95% CI: 0.185-0.605, p < 0.0001). Analysis of the correlation between tumor-infiltrating immune cells and survival revealed that among patients with HPV-positive tumors, which displayed significantly lower numbers of IL17+ cells than the HPV-negative tumors, a high number of intra-epithelial T cells was indeed correlated with improved disease-free survival (p = 0.003, Figure 4a) compared to a low intraepithelial T cell frequency (i.e., lowest quartile). Similarly, a high non-Treg intra-epithelial T cell frequency showed a trend toward a correlation with improved disease-free survival (p = 0.064, Figure 4b). Furthermore, a high T cell frequency, a high CD3+FoxP3− non-Treg T cell frequency and a high Treg frequency infiltrating the total tumor area (epithelium and stroma combined) of HPV-positive tumors were all significantly correlated with improved disease-free survival (p = 0.008, p = 0.008, p = 0.003, respectively; Figure 4c–e). We also

found a trend toward a positive correlation between a high Treg frequency in the total tumor area and disease-specific survival (p = 0.055, data not shown). We did not find significant correlations between the IL-17+ cell frequencies and disease-free or disease-specific survival among patients with HPV-positive tumors, probably because in most cases the numbers were low when compared to HPV-negative tumors. Only a high intra-epithelial T cell frequency remained significantly correlated with disease-free survival when corrected for comorbidity, prior tumor occurrence and smoking status in a multivariate analysis (Supplementary Table 2).

Figure 4. Among patients with HPV-positive tumors, Kaplan-Meier curves are shown for a low versus high number of total T cells (A) and non-Treg T cells (B) within the tumor epithelium and a low versus high T cell (C), non-Treg T cell (D) and Treg (E) frequency in the total tumor area (epithelium and stroma combined).



For patients with HPV-negative tumors, we only found a significant correlation for a high T cell/IL-17+ non-T cell ratio and improved disease-specific survival (p = 0.043, data not shown). No significant direct correlations between the T cell, Treg or IL-17+ cell frequencies and disease-free or disease-specific survival were found (Supplementary Table 2), while the effect of other factors that may contribute to prognosis (comorbidity, prior tumor occurrence and smoking status) remained similar to the effect in patients with HPV-positive tumors (data not shown).

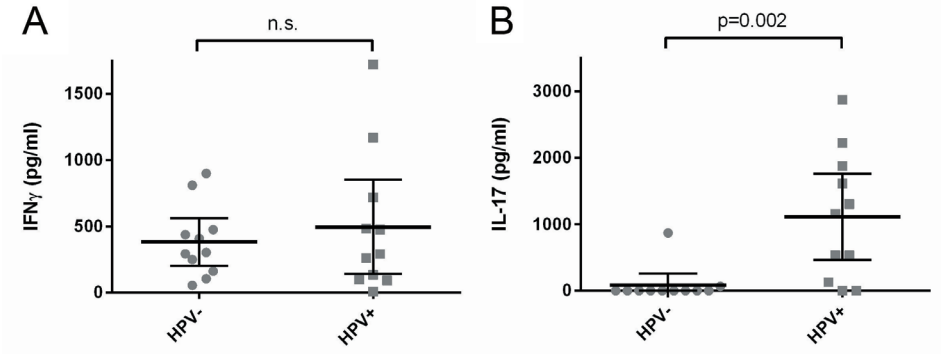
Epithelium infiltrating T cells in HPV-positive tumors are inversely correlated with smoking status

Because of the correlation described between smoking habits and prognosis in HPV-positive tumors[12], we wondered whether smoking habits may directly influence the tumor infiltration of T cells. Indeed, HPV-positive tumors of heavy smokers (>24 pack-years) were significantly correlated with a lower intra-epithelial T cell frequency compared to tumors of never smokers (p = 0.003, Supplementary Figure 2). The other cell type studies were not significantly correlated with smoking status (data not shown).

HPV-positive tumor-infiltrating T cells produce IL-17 upon activation

To study whether the production of effector molecules was influenced by the presence of HPV, we isolated the tumorinfiltrating T cells from 11 HPV-negative OPSCC and 11 HPV-positive OPSCC and assessed cytokine production after 4 days of stimulation with PHA. We studied IFN-γ production as a measure for effector non-Treg T cells, and IL-17 production as a measure for Th17 cells. While IFN-γ was produced in all cases, the TILs isolated from HPV-positive tumors produced IL-17 more frequently (p = 0.006) (Figure 5a, b), suggesting that functional Th17 cells are especially present in HPV-positive tumors.

Figure 5. Production of IFNγ (A) and IL-17 (B) by tumor infiltrating lymphocytes stimulated with PHA.



The bars indicate the mean and 95% confidence interval; n.s. = not significant.

DISCUSSION

HPV-positive OPSCC contained more tumor-infiltrating T cells and less IL-17+ non-T cells compared to HPV-negative tumors in both the epithelial and stromal part of the tumor. An increased number of CD3+, CD8+ and Treg cells[32-34] and a trend toward a decreased number of IL-17+ cells[35] infiltrating HPV-positive compared to HPV-negative OPSCC have been shown previously.[36] Although correlations between a high tumor-infiltrating lymphocyte frequency and improved survival in both patients with HPV-positive[37] and HPV-negative tumors[16,33,38] have been described before, data regarding the T cell subtypes involved have been limited and inconclusive. The current study revealed that a high number of intra-tumoral T cells showed a trend toward better survival of all (HPV-positive and HPV-negative) OPSCC patients. Since we have shown before that a high frequency of IL-17+ non-T cells, representing mainly granulocytes is correlated with poor survival in early-stage squamous cervical cancer[26], here we studied the effect of tumor-infiltrating T cells stratified for a high or low number of infiltrating IL-17+ cells. In patients with a below median number of intra-tumoral IL-17+ non-T cells, a high tumor-infiltrating T cell frequency was correlated with improved disease-free and disease-specific survival, suggesting that a high frequency of IL-17+ cells is related to a poor immune response. No significant correlation was observed in tumors with a high number of IL-17+ non-T cells. The hypothesis was further substantiated by the observation that in the HPV-positive OPSCC, which contained less IL-17+ cells than HPV-negative OPSCC, a high number of T cells was correlated with improved disease-free survival. This suggests that IL-17+ non-T cells may be correlated with an unfavorable immune response. Such a tumor-promoting role can be explained by the role of IL-17 in driving inflammation, angiogenesis and tumor growth, and studies so far have indeed described correlations between IL-17 and poor survival in cancer patients.[27] Thus, the beneficial effect of infiltrating T cells might be overruled if a high number of IL-17+ cells are present.

Among patients with HPV-positive tumors, we specifically found correlations with improved disease-free survival for high frequencies of both non-Treg T cells and Tregs. A high number of Tregs also showed a trend toward a correlation with improved disease-specific survival in HPV-positive OPSCC. The role of Tregs is controversial in OPSCC.[16] We have shown before that a high T cell infiltration in cervical cancer is correlated with improved prognosis[39], with specifically a low T cell/Tregs ratio within the tumor epithelium being correlated with poor survival.[40,41] Indeed, only a high intra-epithelial total T cell frequency remained significantly correlated with disease-free survival in the multivariate analyses performed here. Because we now show that the intra-tumoral Treg frequency was increased and strongly correlated with the total T cell frequency in a ratio that favors the infiltration of non-Treg T cells in HPV-positive OPSCC, the positive role of Tregs in oropha-

ryngeal cancer may also rely on their coinfiltration with effector T cells. The current data suggest that a high T cell infiltrate, including Tregs, is correlated with improved prognosis in HPV-positive OPSCC.

A minor Th17 cell population was observed, which was not significantly different between HPV-positive and HPV-negative tumors. However, we showed that T cells infiltrating HPV-positive tumors produced significantly higher amounts of IL-17 compared to T cells infiltrating HPV-negative tumors. This activated state may be an indication that Th17 cells are associated with a tumor-targeting immune response. In agreement, Partlová et al.[34] also showed that cell suspensions prepared from HPV-positive head and neck squamous cell carcinoma produced more IL-17 than cell suspensions from HPV-negative tumors. These data together strongly suggest that Th17 cells are more active in HPV-positive tumors. The seemingly opposing small population size and large potential of Th17 cells might be explained by their stem cell-like phenotype[42] and potential for plasticity[43]. This corresponds with the correlations described between Th17 cells and improved cancer patient survival[27], including our study in squamous cervical cancer.[26]

We did not find any direct correlations between the infiltrating immune cell frequencies investigated and disease-free or disease-specific survival in HPV-negative tumors. Only the T cell/IL-17+ non-T cell ratio was significantly correlated with disease-specific survival, again suggesting that the beneficial effect of T cells may be lost because of the higher numbers of IL-17+ non-T cells present in HPV-negative OPSCC.

To conclude, HPV-positive OPSCC contain higher numbers of tumor-infiltrating T cells, more active Th17 cells and lower numbers of IL-17+ non-T cells. Future studies should evaluate whether this is a general signature of a beneficial tumor-targeting immune response. This would provide a rationale to study the role and potential of T cell administration or IL-17 blockade.

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Supplementary Table 1. Number of T cells, Tregs and IL-17$^+$ cells present in squamous oropharyngeal carcinoma

	Location	Total T cells		Tregs		IL-17$^+$ (non-Th17) cells		Th17 cells		Total T cells/Tregs	
		Mean (range)	Median	Mean (range)	Median	Mean (range)	Median	Mean (range)	Median	Mean (range)	Median
HPV-negative tumors	Epithelium	251 (0-1767)	151	98 (0-863)	49	92 (0-730)	41	1 (0-9)	0	4 (1-37)	2
	Stroma	1237 (47-7042)	971	624 (16-2596)	520	343 (0-2613)	237	6 (0-70)	0	2 (1-8)	2
	Total	519 (21-4113)	362	237 (4-1438)	193	156 (3-956)	99	2 (0-17)	0	2 (1-8)	2
HPV-positive tumors	Epithelium	738 (30-2596)	545	226 (12-1272)	150	47 (0-389)	14	1 (0-17)	0	6 (1-84)	3
	Stroma	2985 (295-7831)	2633	1017 (0-3437)	972	229 (0-1479)	121	7 (0-85)	0	4 (1-35)	3
	Total	1251 (104-4775)	1005	387 (24-1272)	335	73 (0-351)	39	2 (0-38)	0	5 (1-63)	3

The mean, minimum, maximum and median number of total CD3$^+$ cells, FoxP3$^+$CD3$^+$ Tregs, CD3$^-$IL-17$^+$ cells and CD3$^+$IL-17$^+$ Th17 cells observed infiltrating in the tumor epithelium, tumor stroma and combined total area per mm^2 is indicated for HPV-negative and HPV-positive tumors.

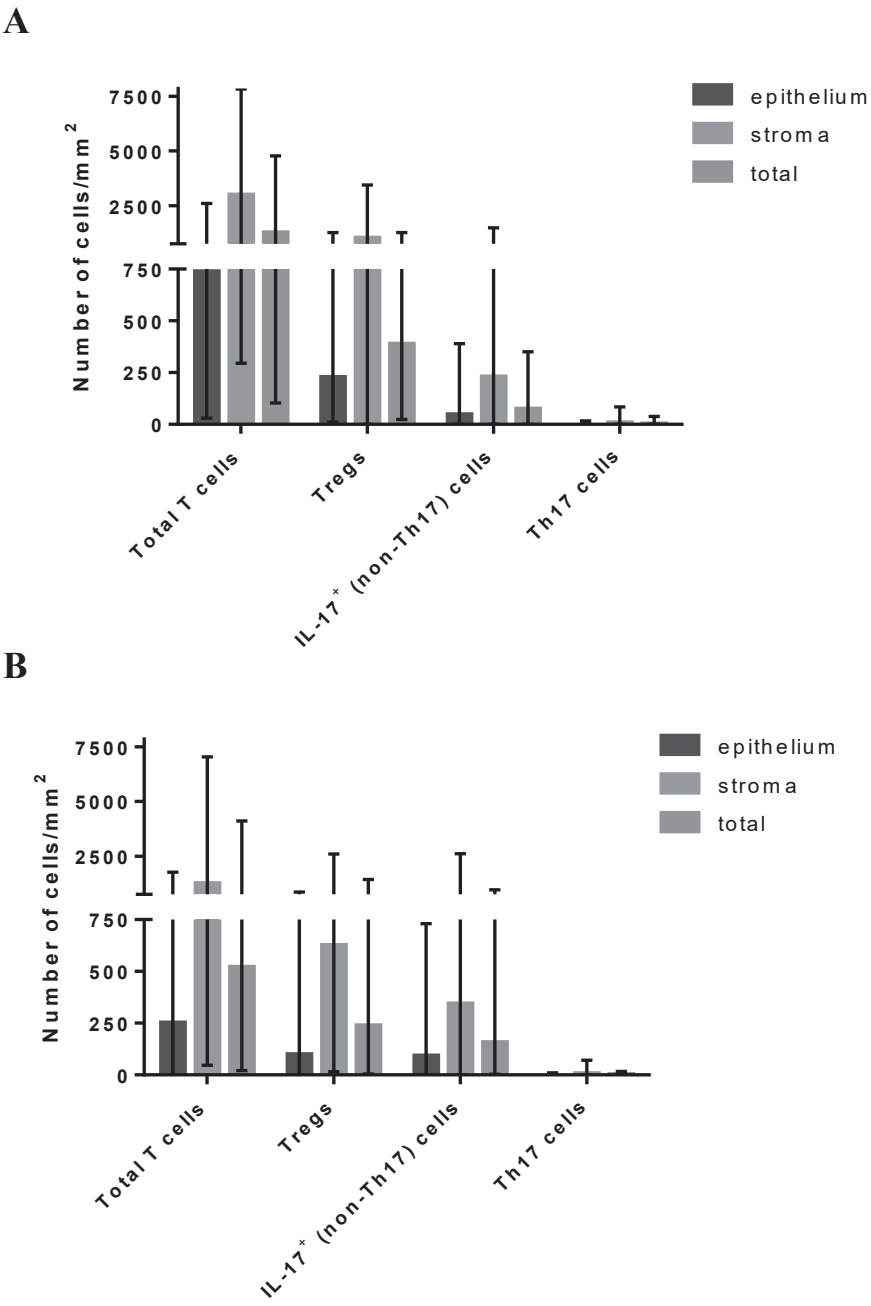
Supplementary Table 2. Effect of 6 different types of T cell infiltrations on disease-free survival regarding HPV status

	High intraepithelial T cell frequency		High total T cell frequency		High total Treg frequency		High total nonTreg T cell frequency		High intraepithelial nonTreg T cell frequency		High total IL-17^{+} cell frequency	
Univariate Hazard Ratio	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*
HPV negative (p16-)	1.46 (0.73-2.93)	0.282	1.11 (0.58-2.12)	0.751	1.65 (0.81-0.36)	0.165	1.62 (0.81-3.26)	0.174	1.15 (0.89-1.50)	0.292	0.96 (0.51-1.82)	0.912
HPV positive (p16+/PCR+)	0.22 (0.08-0.64)	**0.006**	0.28 (0.10-0.82)	**0.021**	0.21 (0.07-0.64)	**0.006**	0.27 (0.09-0.78)	**0.015**	0.35 (0.12-1.03)	0.056	0.50 (0.17-1.51)	0.220
Multivariate Hazard Ratio*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*	*HR (95%CI)*	*p-value*
HPV negative (p16-)	1.52 (0.74-3.18)	0.256	1.13 (0.57-2.21)	0.721	1.77 (0.83-3.74)	0.134	1.66 (0.81-3.41)	0.168	1.16 (0.84-1.88)	0.258	1.09 (0.54-2.18)	0.806
HPV positive (p16+/PCR+)	0.25 (0.07-0.95)	**0.043**	0.34 (0.10-1.13)	0.080	0.28 (0.08-1.02)	0.054	0.40 (0.12-1.32)	0.135	1.18 (0.24-5.97)	0.835	0.53 (0.17-1.69)	0.284

*Adjusted for comorbidity, prior tumor and smoking status using Cox proportional hazards regression analysis. This analysis was performed 6 times, entering a different type of T cell infiltration each time, but adjusting for the same variables (comorbidity, prior tumor and smoking status).

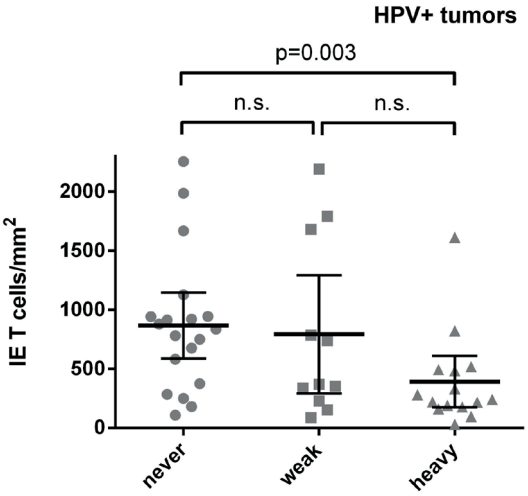
HR= hazard ratio, 95%CI = 95% confidence interval. 'High'= upper 3 qrt vs lowest qrt.

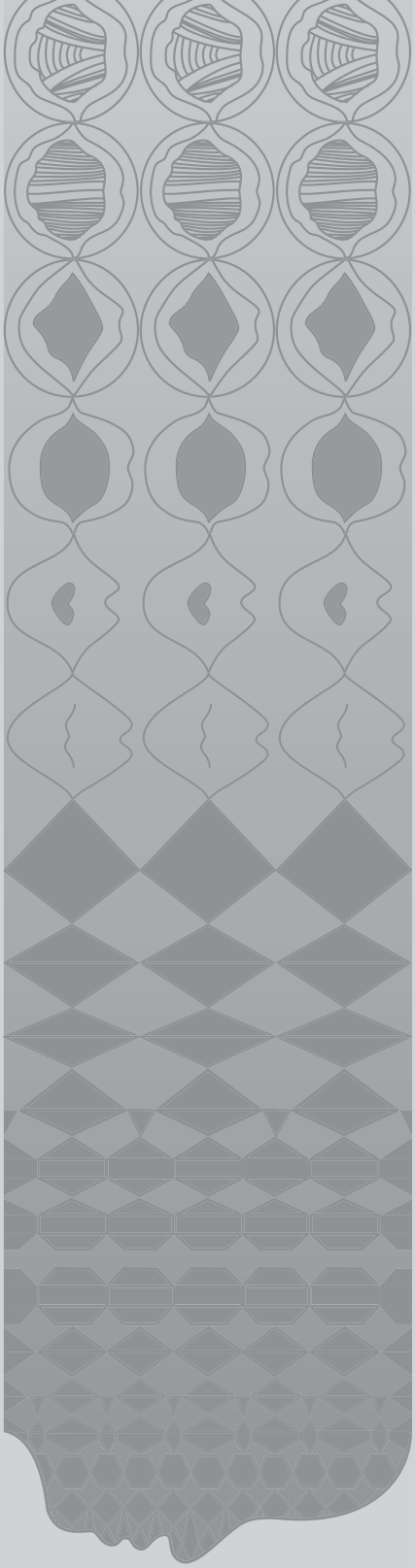
Supplementary Figure 1. Quantification of tumor infiltrating cells.



The mean and range of the number of CD3+ T cells, FoxP3+CD3+ Tregs, CD3-IL-17+ cells and CD3+IL-17+ Th17 cells infiltrating in the tumor epithelium, tumor stroma and combined total area per mm2 is shown in HPV-negative tumors (A, n=99) and HPV-positive tumors (B, n=63).

Supplementary figure 2. The number of total CD3+ T cells infiltrating in the tumor epithelium per mm2 in HPV-positive tumors is shown for never, weak (1-24 packyears) and heavy smokers (>24 packyears). The bars indicate the mean and 95% confidence interval; n.s. = not significant.





8

Head and Neck cancer patients' preferences for individualized prognostic information: a focus group study.

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ABSTRACT

Head and Neck cancer (HNC) is characterized by significant mortality and morbidity. Treatment is often invasive and interferes with vital functions, resulting in a delicate balance between survival benefit and deterioration in quality of life (QoL). Therefore, including prognostic information during patient counseling can be of great importance. The first aim of this study was to explore HNC patients' preferences for receiving prognostic information: both qualitative (general terms like 'curable cancer'), and quantitative information (numbers, percentages). The second aim of this study was to explore patients' views on 'OncologIQ', a prognostic model developed to estimate overall survival in newly diagnosed HNC patients. We conducted a single center qualitative study by organizing five focus groups with HNC patients (n=21) and their caregivers (n=19), categorized in: 1) small laryngeal carcinomas treated with radiotherapy or laser, 2) extensive oral cavity procedures, 3) total laryngectomy, 4) chemoradiation, 5) other treatments. The patients' perspective was the main focus. The interview guide consisted of two main topics: life-expectancy and the prognostic model OncologIQ. All focus groups were recorded, transcribed and coded. Themes were derived using content analysis. While all patients considered it somewhat to very important to receive information about their life-expectancy, only some of them wanted to receive quantitative information. Disclosing qualitative prognostic information like 'the cancer is curable' would give enough reassurance for most patients. Overall, patients thought life-expectancy should not be discussed shortly after cancer diagnosis disclosure, as a certain time is needed to process the first shock. They had a stronger preference for receiving prognostic information in case of a poor prognosis. Prognostic information should also include information on the expected QoL. The pie chart was the most preferred chart for discussing survival rates. The participants found it important to receive information on their life-expectancy. While most patients were enough reassured by qualitative prognostic information, some wanted to receive quantitative information like OncologIQs' estimates. A tailor-made approach is necessary to provide customized prognostic information. A clinical practice guideline was developed to support professionals in sharing prognostic information, aiming to improve shared decision making and patient-centered care.

BACKGROUND

Head and Neck cancer (HNC) is an aggressive type of cancer characterized by significant mortality and morbidity.[1-4] Treatment is often invasive and interferes with vital functions such as breathing, swallowing, and speech. In addition, patients often face psychosocial problems and experience body image dissatisfaction as a result of the mutilating procedures.[2,5] On the one hand physicians aim for cure and prolonging life, while on the other hand they strive for optimization of quality of life (QoL). This often results in a delicate balance between survival benefit and the functional, and psychosocial disabilities a patient is willing to accept after treatment. Therefore adequate counseling of patients including prognostic information can be of great importance. Previous research focused on whether or not to disclose the prognosis.[6] More recently the focus has shifted more in-depth to what information to provide, and how to do this.[6-8] This is in line with the increased attention for shared decision making (SDM). Patients need to be well-informed before they can be actively involved in treatment decisions.[9-10] As patients may not be able to make well-informed treatment decisions without understanding their prognosis, providing prognostic information is a key factor in SDM.

We recently published the results of a qualitative research, focusing on treatment discussions among HNC patients and their doctors. We found that in only 6% of the consultations doctors provided quantitative prognostic information, by discussing numbers, such as percentages. In 94% qualitative prognostic information was provided, by using words such as 'curable' and 'good prospect'.[11] The current study is the second step in our qualitative research by exploring HNC patients' preferences and views on receiving prognostic information. Relatively little attention has been paid to this topic. Some cancer patients want to know everything, while others are overwhelmed by too much information. Furthermore, each patient group has its own characteristics and preferences. For example, patients with breast cancer are considered to have high information needs.[12] To our knowledge, there are no studies published that explore HNC patients' views on receiving quantitative prognostic information. Therefore, research is needed on *what* these patients want to know about their prognosis and in which *manner* they wish this information to be conveyed to enable better counseling and patient-centered care.

Physicians are often unable to forecast an individual's life-expectancy and tend to overestimate survival.[13,14] This can lead to concerns of being proved inaccurate and therefore reluctance to discuss the prognosis.[15] Survival rates of cancer are traditionally based on the TNM-classification of the tumor. These are however general estimates of a heterogeneous group of patients and not tailored to an individual's prospect. Prognostic models that include patient specific predictors, like age and co-morbidity, could help doctors to provide

a more personalized prognosis. Over the last years, an internally and externally validated prognostic model named "OncologIQ" has been developed. This model estimates the 1- to 10-year overall survival (OS) of patients with primary HNC, based on the average treatment effect.[16-18] Besides tumor location and TNM-classification, OncologIQ includes age, sex, and the Adult Comorbidity Evaluation 27 (ACE-27) as prognostic factors for OS (see also Figure 1).[16-18] The benefit of having a HPV-positive tumor or receiving chemotherapy were added by an adaptation method. This model could support doctors with prognostication during patient encounters, by providing more personalized estimates of the OS. However, it remains unclear if, how, and when this prognostic information should be shared with HNC patients? Furthermore, how should one visualize the individual survival estimates and in which manner should healthcare providers explain the results? While more prognostic models are developed, there is a dearth of evidence on the impact of the use of such models in clinical practice[19], and to what level patients appreciate and understand the information provided.[20] Our study fills this gap by exploring patients thoughts on OncologIQ.

The aim of the current study was to explore 1) HNC patients' preferences for receiving prognostic information, 2) and their views on the prognostic model OncologIQ. By assessing patients' views on these topics, we can optimize counseling between physicians and patients. In addition, a clinical practice guideline on how to use OncologIQ for individualized prognostic counseling was developed.

METHODS

We conducted a single center qualitative study by organizing five focus groups with HNC patients and their caregivers between December 2016 and February 2017. Methods and results are described using the Consolidated Criteria for Reporting Qualitative Research (COREQ).[21]

Definition of prognosis

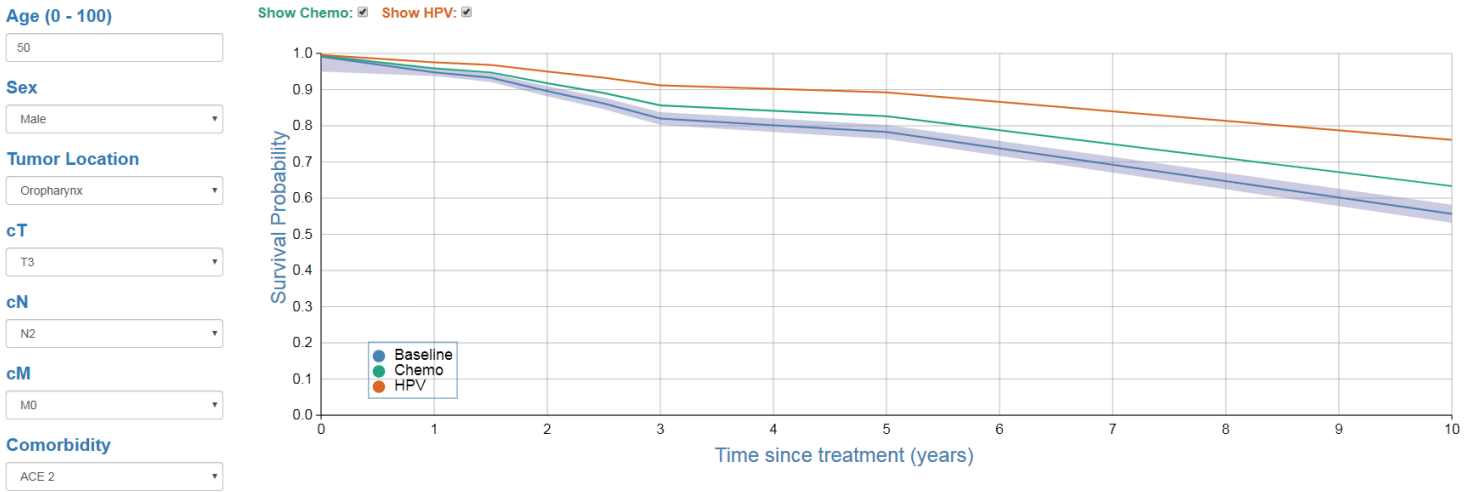
In this study we refer to the concept of prognosis from two different angles:

- *Qualitative information: general terms like 'the cancer is curable'*
- *Quantitative information: numbers or percentages, like survival rates.*

Research team & reflexivity

The research team consisted of three investigators. M.P.J. Offerman (MO), PhD, is a psychologist and has several years of experience with focus group research. The second inves-

Figure 1. An example of OncologIQ's estimates, as presented during the focus groups



tigator, A. Hoesseini (AH), MD, is a physician, clinical epidemiologist, and PhD candidate. The third investigator, E.A.C. Dronkers (ED), MD, is also a physician, clinical epidemiologist, and PhD candidate. MO and AH conducted the focus groups. There was no relationship established with the participants prior to the beginning of the study. Treating physicians were not allowed to attend the focus groups, so participants would not feel reluctant to share their thoughts.

Study design

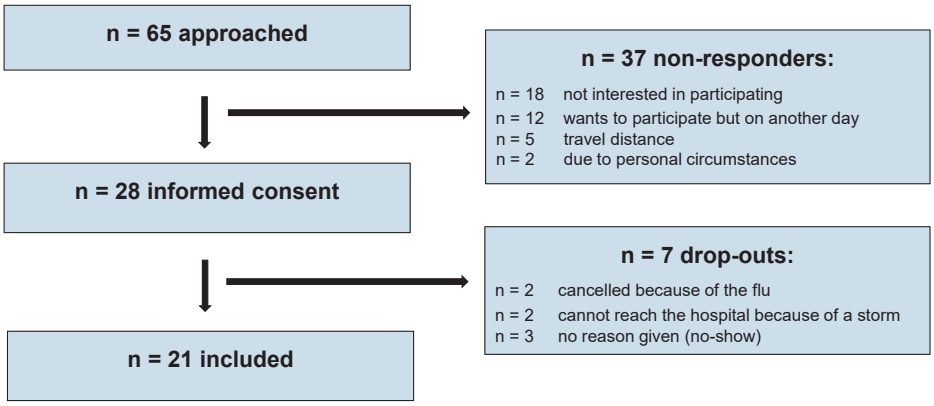
This study was approved by the ethics committee of the Erasmus Medical Center (MEC-2013-052). After consulting experienced head and oncologists on how the groups should be selected, we divided patients in five common treatment groups, which is a reflection of the patient population we treat in our hospital: 1) small laryngeal carcinomas treated with radiotherapy or laser, 2) extensive oral cavity procedures, 3) total laryngectomy, 4) chemoradiation, 5) other treatments (local resection, neck dissection etc.). In this way, we selected patients who had a shared experience and thus were more likely to feel understood by each other. Based on the theory of social comparison[22], patients with a similar background feel more recognized and consequently less reluctant to share their thoughts.

Participants were consecutively selected by AH if they had undergone treatment for HNC in the Erasmus MC Cancer Institute, 6 to 18 months before selection. Patients were approached by telephone and information about the content and the working procedure of the focus groups was given. They were told that we wanted to learn from their experiences, with a main focus on how they had experienced the counseling by the healthcare providers. In order to limit selection bias, specific information on OncologIQ was not given in advance. Caregivers were encouraged to accompany patients. See Figure 2 for the patient selection and exclusion criteria. Also, information on non-participants in shown in Figure 2. In total 21 patients gave their informed consent and participated. All focus groups were held in the same conference room in the Erasmus MC Cancer Institute. Two volunteers were present during each focus group to welcome the patients. The volunteers did not know the patients and did not actively participate in the focus groups. Data were stored anonymously by study ID and were only accessible by the research team.

Interview guide

An interview guide was made prior to the start of the focus groups (see Supplementary Material). The main topics were 1) life-expectancy, and 2) the prognostic model OncologIQ. Each topic was first briefly introduced by AH and MO using a PowerPoint presentation (see Supplementary Material). Subsequently closed-ended questions, using small cards, were answered by patients themselves. This enabled patients to react individually without being affected by the opinion of the other participants and their caregivers. The closed-ended

Figure 2. Patient selection procedure.



Exclusion criteria were: aged 80 years or older; a carcinoma in situ; Korsakoff syndrome or dementia; severe alcohol and/or drugs abuse; possible recurrent or metastatic disease; recent hospitalization; simultaneous tumor outside of the head and neck region

questions were followed by open-ended questions to stimulate the group discussion, and caregivers were also encouraged to participate to a certain extent, as patients' perspective was the main focus. Caregivers were invited as they are the main source of support for the patient and are often present during treatment decision consultations. Similar to these conversations, in the end the patient decides what kind of prognostic information is shared. OncologIQ was introduced only after the topic 'life-expectancy' was thoroughly discussed. This order was deliberately chosen as we wanted to explore life-expectancy unbiased before introducing the prognostic tool. The model was demonstrated by showing a hypothetical patient with a different kind of tumor than the patients present in the focus group. The interview guide and presentation were adjusted once after the first focus group. In this first focus group we introduced quantitative terms like '5-year survival' directly after discussing life-expectancy in qualitative terms such as 'curable'. This resulted in confusion among patients and caregivers. They interpreted the 5-year survival rate as *"being told you only have five more years left to live"* or confused it with the 5-year follow-up after the diagnosis. Therefore, we decided to introduce life-expectancy in qualitative terms more extensively before the break and introduce quantitative terms like 5-years survival after the break in the next focus groups. We also added one quantitative question on whether the physician should use a chart when explaining survival rates. After these adjustments no problems were encountered in focus group two until five, and therefore no further adjustments were made. All focus groups were digitally recorded. The mean duration of the focus groups was 2 hours and 7 minutes. The focus groups were transcribed by AH and one of our volunteers.

Data analysis

The grounded theory approach was used to analyze the data. This implies that the researcher moves back and forth between the population under study and analysis of the data, so that an explanatory theory evolves through an iterative process.[23] Two researchers (AH and MO) coded all transcripts and discussed the coding for each group until consensus was reached. Themes were derived from the coded data by AH and MO individually. These themes were discussed and if necessary rearranged, starting with one focus group, and adding the others one by one. When there was no agreement on the themes or on the matching of quotations with the themes, consensus was reached after an in-depth discussion. After discussing the fourth focus group, no new themes were identified and therefore data saturation occurred. The next step was verification of the results by the third researcher (ED). She was given parts of coded transcripts and was asked to match them with the identified themes, and if deemed necessary suggest new themes or codes. No new themes were identified by ED, however some (sub)themes were rearranged. Finally, one quotation per (sub)theme was jointly chosen to include in the results section. NVivo 12 was used to manage the data. The participants did not provide feedback on the findings.

RESULTS

Participants

Table 1 shows an overview of the number of patients and caregivers in each focus group, and patient characteristics. In total 17 patients (81%) were accompanied by their caregiver(s). In 15/17 of the cases (88.2%) this was a partner. One patient took a sibling with her and one patient was accompanied by both his partner and two children. Education level was categorized according to the International Standard Classification of Education.[24,25] Patients' age and sex were similar to national HNC data gathered in the Netherlands Cancer Registry (NCR) by the Netherlands Comprehensive Cancer Organization (IKNL).[26] Patients education level was more or less similar to a recent study among 2189 consecutive HNC patients in our tertiary center.[27] This did not apply to marital status: while in the latter study 28% of patients were single[27], in the focus groups only 10% were.

1) Life-expectancy

After the introduction of the main topic life-expectancy, we first asked patients the closed-ended question: To what extent do you think it is important to receive information about your life expectancy? (4-point Likert-scale: 'not at all important' to 'very important', see also Attachment 1). 62% of patients answered 'very important', the remaining eight (38%) answered 'somewhat important'. Hereafter, open-ended questions were asked (see interview

Table 1. Number of participants and patient characteristics.

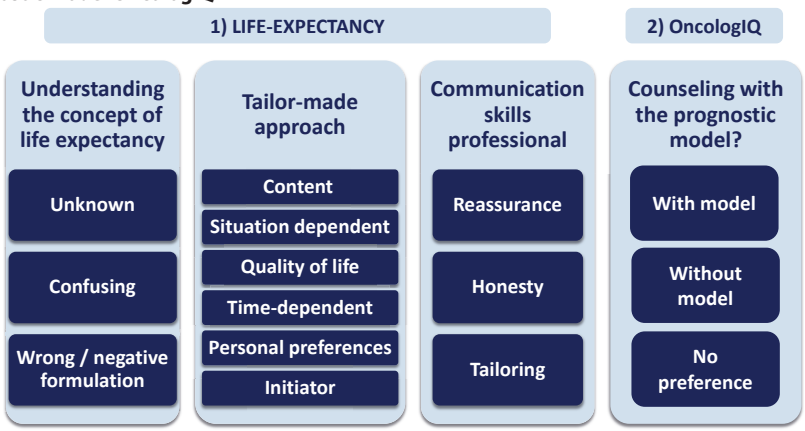
Focus groups	Patients	Caregivers
1. small laryngeal carcinomas treated with radiotherapy / laser	6 (28.6%)	6 (31.6%)
2. extensive oral cavity surgical procedures	2 (9.5%)	2 (10.5%)
3. total laryngectomy	4 (19.0%)	6 (31.6%)
4. chemoradiation	5 23.8%)	3 (15.8%)
5. other treatments**	4 (19.0%)	2 (10.5%)
Total no. of participants per focus group (%)*	21 (100%)	19 (100%)
Patient characteristics	No. (%) / median (Q1-Q3)	
Age, years	65.0 (53.5 – 68.5)	
Age range, years	33 – 78	
Sex		
male	12 (57.1 %)	
female	9 (42.9 %)	
Tumor localization		
larynx	9 (42.9%)	
hypopharynx	2 (9.5%)	
oral cavity	3 (14.3%)	
oropharynx	6 (28.6%)	
unknown primary	1 (4.8%)	
Tumor stage		
I	5 (23.8%)	
II	3 (14.3%)	
III	5 (23.8%)	
IVa	7 (33.3%)	
IVb	1 (4.8%)	
Marital status		
married / durable relationship	19 (90.5%)	
single	2 (9.5%)	
Education level		
lower (primary education or less / lower secondary)	7 (33.3%)	
intermediate (upper secondary / post-secondary non-tertiary)	9 (42.9%)	
tertiary (short cycle tertiary / bachelor / master / doctoral)	4 (19.0%)	
missing	1	
Median time between end of treatment and participation in the focus group (Q1 – Q3)	47 weeks (35 – 64)	

*Two patients were treated for cancer recurrence by a total laryngectomy, the remaining were treated for a primary head and neck tumor.

** For example neck dissection or local resection.

guide) to stimulate the group discussion. From the transcripts of these discussions in total three themes and 12 subthemes were derived (see Figure 3 for the code tree and Table 2 for the contents).

Figure 3. Code trees of themes and subthemes derived from the topics 1) life-expectancy and 2) the prognostic model OncologIQ



2) The prognostic model OncologIQ

Table 3 gives an overview of the themes that were derived from the discussions on OncologIQ (see also Figure 3 for the code tree). In addition, several recommendations were shared. Table 4 shows several visual formats of communication and patients' preferences for the selected charts. The pie chart was the most preferred chart. All patients in focus group two until five (n=15) preferred the combination of verbal explanation of survival rates and a visual presentation with a chart, over a verbal explanation solely. This was deemed easier to understand.

DISCUSSION

To our knowledge, this is the first study offering in-depth understanding of HNC patients' preferences for disclosure of prognostic information, and the use of a prognostic model during treatment decision consultations.

1) Life-expectancy

Understanding the concept and using a tailor-made approach

While all patients considered it somewhat to very important to receive information about their life-expectancy, only some of them wanted to receive this in a specific quantitative

manner, like 5-year survival rates. This is in line with previous research among patients with advanced or incurable cancer.[28,29] The majority of patients wanted to receive prognostic information from their doctor in general terms, like "*your cancer can be well treated*". This kind of qualitative information would give these patients enough reassurance for the first moment. Even though doctors generally use the concept *5-year survival rate*, participants often did not understand this concept or confused it with other terms, for example chances of cure, and thought it had a negative connotation. Overall, little is known about patients' awareness, and understanding of prognosis.[6] Previous research stressed that in some cases cancer patients misunderstand or fail to absorb the information given, cannot recall the status of their disease and often overestimate their survival chances.[6,30-32]

The need for receiving prognostic information was dependent on different circumstances. This means that sharing prognostic information requires a tailor-made approach. Patients had a stronger preference for quantitative information like months or survival rates, in the hypothetical case of cancer recurrence and/or a poor prognosis. This kind of information would enable them to weigh whether undergoing a second treatment to prolong survival would be worth the 'costs'.

Prognostic information is not a standalone concept according to patients and caregivers. Patients also expressed the need for information about their expected QoL, since this would be of significant importance in the decision making process. Fried et al. asked 226 patients with a limited life expectancy whether they would choose a treatment with survival, but with severe functional or cognitive impairment. 74.4% of patients answered they would not accept severe functional impairment and 88.8% would not accept cognitive impairment, and thus rather face death.[33] However, more recent research by Blanchard et al. among HNC patients showed that they overall prioritize survival over functional endpoints.[34] Although we did not explicitly ask patients to prioritize survival and QoL, they did however mention that at a certain point the survival benefits would not weigh against the deterioration in QoL. On the other hand they mentioned that patients are prone to keep pushing their boundaries, and increasingly accept functional limitations in order to stay alive.

In case patients want to receive quantitative information, what would be the right timing to share this? Our focus group results suggest that the right timing and phasing are of key importance. It seems that life-expectancy should be best discussed after the conversation in which the cancer diagnosis is given. According to most patients and their caregivers, it would be too stressful to discuss this all at once. Several patients addressed that it depends on personal preferences whether a patient wants to receive prognostic information. While on the one hand some patients gain an increased sense of control by receiving more infor-

Table 2. Explanation of (sub)themes and quotations, derived from the focus group discussions on topic 1) life-expectancy

THEME - SUBTHEME		SUBCATEGORY	QUOTATION*
Understanding the concept of life expectancy	**1. Unknown**. Participants are not familiar with the concept life expectancy.		*I have never heard of the 5-year survival rate. (pt 3, f4)*
What are patients' views on the concept of prognosis, life-expectancy and 5-year survival rates?	**2. Confusing.** Participants don't understand the different terms that are used alternately. This can be confusing.		*But what is actually meant by life expectancy? Do they mean survival chances, cure or life expectancy after treatment? (pt 2, f4) Or quality of life? (pt 1, f4)*
	3. Wrong / negative formulation. The 5-year survival term sounds negative. When talking about survival rates it should be emphasized that we are talking about chances, not certainties.		*It really should be said differently, but I do not know how… When you get home you only hear 'five years, five years'. (pt 5, f1)*
Tailor-made approach	**1. Content**. Prognostic information can be divided in 1) qualitative information: general terms without numbers or percentages, like "the cancer is curable", and 2) quantitative information: numbers or percentages, like months, years or survival rates. All patients wanted to receive information in general terms. However, quantitative information was not desired by all patients. Some felt empowered by prognostic information expressed in numbers or percentages, and others were in doubt or did not want to receive quantitative information at all.	**1) qualitative information desired**	*If you say 'well treatable' I do not think that life expectancy is important. Well treatable is well treatable. Therefore that means the end result is also good. In that case I do not need to hear a percentage. (pt 6, f1)*
How should a professional provide customized prognostic information?		**2) quantitative information…**	
		… desirable	*I want to know what my chances are and find the percentages important. If you say 'it is 3%', it becomes somewhat more difficult. If I would hear 80% then I would think 'all right, I'm definitely going to make it'. (pt 5, f4)*
		… value unclear	*I find it somewhat difficult. You can say 'I am part of the 70%', but it could also be that you're part of the 30% (…) What do you gain from those percentages? How can I tell you there is a 100% chance you will not be hit by a tram when you cross the road? (caregiver 1, f5).*
		… not desired	*I can imagine that someone just doesn't want to know. Apart from the fact that the percentage says nothing, I can imagine that you do not want to hear it. If I would be in this situation again, I would not ask and say 'I don't need to know' (pt 1, f2).*

Table 2. ***(continued)***

THEME - SUBTHEME		SUBCATEGORY	QUOTATION*
	2. Situation dependent. The need for quantitative prognostic information depends on the situation. In case of a poor prognosis patients have a strong preference for receiving quantitative prognostic information, while in case of a relative good prognosis patients are equally divided between wanting or not wanting to receive this information.	**1) good prognosis**	*In the case that positive results are expected, the doctor does not need to procrastinate and should just tell me. (pt 2, f1)*
		2) poor prognosis	*Suppose the cancer spreads and they say 'there is no more treatment possible, if you want to know, you have six months left.' Then I think it is important to know. (pt 4, f1)*
	3. Quality of life. Prognostic information alone is not enough. Also information on the expected quality of life, with or without treatment, should be provided.		*You have to have a life. (pt 2, f3) At least a certain level of quality. (…) And you are always going to push your boundaries. You start with radiation and say 'if the larynx goes, it is over for me.' You keep pushing that boundary, since an individual wants to stay alive. (caregiver 3, f3) Up to a certain limit. (caregiver 4, f3)*
	4. Time-dependent. If patients want to know more about their life-expectancy, for example survival rates, when should we discuss this? Overall, patients think this should not be discussed shortly after receiving the cancer diagnosis, because receiving the diagnosis is already an incredibly stressful event that first needs to be processed.		*At the time when I was at the doctor and heard I had a tumor, that information would be too much for me. (pt 4, f4)*
	5. Personal preferences. It depends on personal preferences whether a patients wants to receive prognostic information.		*First of all there are two patients groups. Some patients don't want to know anything and say 'just treat me and I'll see'. Others want to know everything. (caregiver 4, f1)*
	6. Initiator. Who should take the initiative? How do you find out which patients want prognostic information, and what kind of information? Some patients will take the lead, while others aren't capable or don't want to, as they trust the doctor to do the right thing being the expert.		*I think the first step is that the patient says 'yes I want to know' or 'I don't want to know' and that he or she is also the one to say 'I want or do not want the family to know'. (caregiver 1, f5)*

Table 2. ***(continued)***

THEME - SUBTHEME	SUBCATEGORY	QUOTATION*
Communication skills professional	**1. Reassurance**. Reassuring the patient and giving hope.	*You all want to hear: 'everything will be alright'. Although I know that's not realistic. (pt 2, f5)*
A customized approach requires certain communication skills of professionals. Which communication skills should a physician use when discussing the prognosis?	**2. Honesty**. Being honest while providing prognostic information.	*To me it should be very clear. Just how it is and then I can see for myself what I will do with it. (pt 5, f1) Yes for me too. Do not sugar coat it and tell it straightforward, so I know what I am in for. (pt 2, f1)*
	3. Tailoring. Tailor prognostic information after exploring patients' needs and preferences or decide not to share prognostic information at all when a patient isn't ready for it.	*I think the doctor needs to look carefully at the patient. Can the patient handle the news at that time? (pt 1, f4) This means that you have a little more time with the doctor and that the doctor needs to know more of the personal history of the patient. (pt 2, f4)*

* pt = patient, f = focus group

mation about their disease and prognosis, others want to receive very little information. The latter group often wants the doctor to take control and is not interested in the details on treatment or prognosis. Receiving unwanted prognostic information could destroy hope and therefore patients' needs should be explored beforehand[35], instead of bluntly confronting them with unwanted information.

Who should take the initiative in exploring prognostic information needs? While some patients will take the lead, others aren't capable or don't want to. Therefore, according to the participants, the healthcare provider should be the one to introduce the topic, while the patient is given the opportunity to decide whether he or she wants to receive the information. This is in agreement with a qualitative research among advanced cancer patients: most patients and caregivers in this study said a physician should offer to discuss the prognosis, if the option to decline the information was also provided.[36]

Communication skills professional

According to our participants, doctors should be honest while discussing the prognosis without taking away hope, and tailor prognostic information after exploring patients' needs. The importance of being realistic and honest while maintaining hope is also identified in previous literature on patients with advanced or incurable cancer.[37-40] For example, Kutner et al. found that while 100% of patients in their survey wanted honesty from clinicians, 91% also wanted them to be optimistic.[37] Balancing between honesty while disclosing prognosis and maintaining hope can be a challenging task for healthcare providers.[39,41]

2) The prognostic model OncologIQ

After fully exploring patients thoughts and believes on the topic life-expectancy, the prognostic model OncologIQ was introduced. Some patients would appreciate counseling with OncologIQ as they thought it was clear and more personalized, while others were in doubt. Some patients didn't want counseling with OncologIQ at all because of the need to maintain some ambiguity about the future. This need to maintain ambiguity about outcomes, is also identified in previous research among advanced or incurable cancer patients.[29,35,38] Ambiguity could help to maintain hope and avoids a blunt confrontation with the facts. Participants shared several recommendations to improve the model. In three focus groups caregivers were concerned that the monthly health insurance premium would rise, if the insurance companies would also have access to an individuals' prognostic estimate. Questions on this topic should be considered when using a prognostic model for counseling.

Table 3. Explanation of (sub)themes, recommendations and quotations, derived from the focus group discussions on topic 2) prognostic model OncologIQ

THEME - SUBTHEME		QUOTATIONS
Counseling with the prognostic model? ***How do patients feel and think about counseling with OncologIQ?***	**With model**. Some patients want to be counselled with the prognostic model. They think it gives a clear overview of their survival chances, and provides a personal estimate of their survival rates.	*It makes it more personal I think. It applies more to you personally. (caregiver 2, f3)*
	Without model. Some patients don't want to be counselled with the model. They find it too confronting, or just don't feel the need to receive counselling with a prognostic model. Others think the model doesn't include enough prognostic factors yet.	*If I'm part of the big group, I have more alternative possibilities.(pt 1, f5)*
	No preference. Some patients don't have a specific preference, as they see both advantages and disadvantages of receiving prognostics information with a model.	*I sit on the fence a little. I think it is more confronting, but also somewhat more realistic. It is close to home and that can be frightening. So I am not sure whether I want it like that. (pt 4, f5)*

RECOMMENDATIONS	QUOTATIONS
Add additional prognostic factors, in order to make the prediction more individualized.	*I actually think it's pretty unreliable. You should fill in many more things, like does the patient smoke, drink, and exercise? (pt 2, f4)*
Add treatment modalities if possible.	*Can you add radiotherapy in this model? (caregiver 1, f2)*
Include quality of life as an outcome in the model.	*This model says nothing about the quality of life. (caregiver 3, f3)*
Provide structural information to make sure every patient is informed about the possibility to discuss the individual prognosis with OncologIQ.	*People should be able to indicate in advance whether they want to know this or not. (pt 4, f5)*
This prognostic information should be given by someone else than the physician, as the participants thought this task would be too time-consuming and stressful for the physician. They opted to trust this task to a specialized nurse. In addition, one caregiver suggested to integrate this in our Healthcare Monitor.	*I think it's too much for a doctor. You become a doctor to help patients, but to really get to know the human psyche is something else. (caregiver 2, f5)*
Take concerns about the health insurance into account. In three focus groups caregivers shared their concerns about hypothetical consequences for the health insurance.	*Then the premium will increase. (caregiver 2, f3)*
Show and explain all variables that are included in OncologIQ. This enables patients to understand which variables are used to calculate their prediction.	*I think you should show the variables. This enables you to see what the prediction is based on. (pt 3, f3)*
Use the 5-year survival rate. When discussing survival rates, participants prefer using the 5-year survival rates instead of 1- or 10-year survival rates, unless the individual patient prefers otherwise.	
Create the possibility to view OncologIQ in a patient portal.	

Visual formats of communication

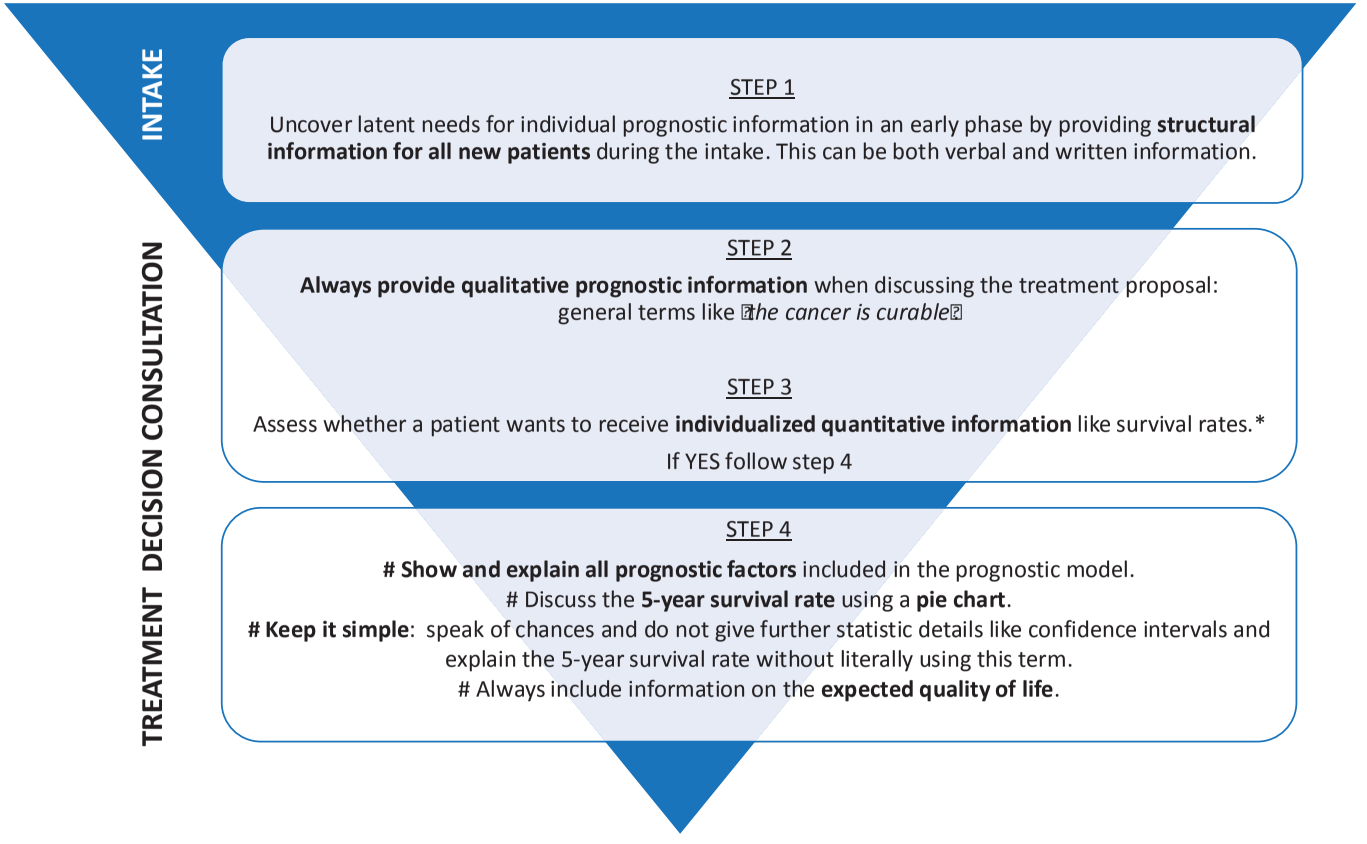
Prognosis can be presented in various formats. While previous research showed that most persons find numbers and 100-person diagrams easiest to understand[42,43], the HNC patients in this study preferred the pie chart. The pie chart was a favorite because they thought it was clear at a glance (see table 4) and less confronting than some of the other formats. The 100-person diagram was considered too confronting by both patients and caregivers. This is in line with previous research that explored this by using a 100-faces diagram.[43] In addition, Davey et al. stated that the survival graph was considered negative, since it showed the constantly increasing mortality. In the current study, patients' thoughts on the survival graph were also mostly negative. They found it too mathematical, since one must first must interpret the X- and Y-axis. Davey et al. also tested cancer patients' understanding of the survival graph: only six out of 26 patients correctly interpreted the graph.[43] Furthermore, we assessed that the included patients' preferred to combine verbal explanation with visual prognostic information over a verbal explanation solely. This is also reported in previous research on this topic.[44] Furthermore, it remains unclear as to what extent patients understand the uncertainty around prognostic models' estimates.[45] Presenting data uncertainty is difficult and there is no consensus in literature about the optimal way to communicate different types of uncertainty.[45,46]

Practice implications: a guideline for individualized prognostic counseling

OncologIQ could take away physicians reluctance to discuss the prognosis and reduce ambiguity in case of conflicting opinions among healthcare professionals by providing individual estimates. Previous research showed physicians' willingness to use prognostic models in end-of-life care, aiming to improve prognostic confidence.[15] It also enabled physicians' to take a more directive role in specific cases where the expected prognosis significantly differs from patients' expectations, and it reduced ambiguity in case of conflicting opinions about prognosis among colleagues.[15]

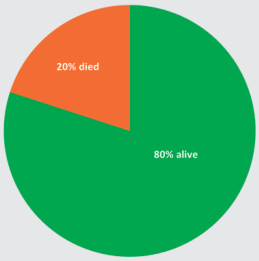
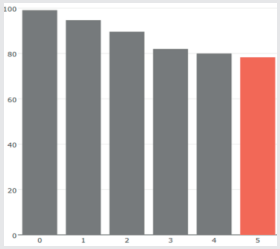
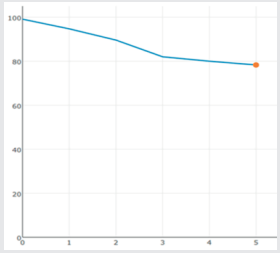
Based on the results of this focus groups study, especially the recommendations discussed in Table 3, a clinical practice guideline was developed that includes basic steps for sharing individualized prognostic information (see Figure 4). While our earlier published guideline for professional communication focuses on general aspects of sharing prognostic information with HNC patients[11], this guideline specifically focuses on how to share the information provided by the prognostic model OncologIQ. It could also be used for other similar prognostic models in HNC. Since the term '5-year survival rate' seemed to confuse patients and caregivers, we recommend not to use it literally. We asked patients which survival period would be most appropriate if a patient wants quantitative prognostic information. Most patients preferred five years, as they deemed two years 'too short' and 10 years 'too far ahead'.

Figure 4. Clinical practice guideline for individualized prognostic counseling.



*Keep the following in mind: do not to discuss life-expectancy in the same consult in which the cancer diagnosis is discussed but hereafter

Table 4. Visual formats of communication: chart preferences and patient quotations. Patients were asked which figure they would prefer when talking about life-expectancy.*

		Quotations
1st pie chart (91 points)		pro: *Black and white situation where you see at a glance "oh that's it". You do not have to think about it. (pt 2, f1)* con: *I only see "died". Deceased and gone. (pt 1, f5)*
2nd bar chart (62 points)		pro: - con: *I don't like it. (pt 4, f1)*
3rd 100-person diagram (58 points)		pro: *It is clear at a glance. (pt 2, f4)* con: *Too confronting. (pt 4, f5)* *These are just like people. (pt 3, f5)*
4th survival graph (56 points)		pro: *The graph is less harsh. I think it's the nicest and most positive one. (caregiver 2, f5)* con: *You always have a X-axis and Y-axis that you first need to interpret. (pt 6, f1) I find it too mathematical. (pt 2, f4)*
5th 100- square chart (48 points)		pro: - con: *I don't like it at all (several patients).*

*First choice nomination resulted in five points, last choice nomination in one point. In total 315 points were divided. Figure 2 until 5 also included captions with the '% died' versus '% survive', and if applicable captions of the x- and y-axis (not shown in this table).

Strengths and limitations

One must first listen to patients' preferences and needs, to be able to provide patient-centered care. The use of a qualitative methodology provided us with rich data on HNC patients' preferences on these vital but unexplored topics. However, it is difficult to make assumptions on its generalizability. This study focused on patients with HNC in the curative setting. Since each setting has its own concerns, the generalizability of these results to the incurable setting is not desirable. Also, our results may be different in other, non-Western, cultures or countries. A certain selection bias may have occurred as the included patients are willing to participate in a focus group with other patients and caregivers. In addition, while almost one third of the patient population in our center is single[27], only 10% of patients in the focus group were. The presence of family members or other caregivers adds complexity to prognostic discussions since they may have different information needs.[47] However, we purposely chose to include caregivers in the focus groups, as they are also present during the treatment decision consultation.

Future perspectives

The results of the current study have been used to improve OncologIQ. Recently, the prognostic model has been updated. [27] In the first place because the original model was based on outdated data as the survival of HNC patients has improved in the past years.[48] The second aim of the update was to test whether adding new prognostic factors would improve model performance, as recommended during the focus groups. Also, a visual format for patients has been developed, including a pie chart of the 5-year survival rate. The updated model can be found on www.oncologiq.nl. The next step will be to evaluate the clinical impact of OncologIQ in a prospective clinical trial. The primary outcome of this trial is decisional conflict among HNC patients who are counselled with and without the model during treatment decision consultations. The effect of the use of OncologIQ in our multidisciplinary tumor board meetings is also recently assessed in a pilot study.

A future aim would be to develop a prognostic model that includes both survival and QoL for HNC patients. Despite not addressing this future prospective during the focus groups, several patients stressed the importance of combining both survival and QoL, rather than focusing solely on survival. Due to the implementation of our Healthcare Monitor we will be able to meet this need soon.[49] With this monitor we are collecting electronically patient reported outcomes (ePRO) on physical and psychosocial functioning since 2013, from intake until the last follow-up visit. In the first place this is done to improve patient care and counseling, although these data could also be used for research purposes.

CONCLUSIONS

This study is first in examining HNC patients' preferences for disclosure of prognostic information, and the use of a prognostic model. Overall, the findings of the current study highlight the importance of exploring patients' thoughts and needs, in order to enhance patient-centered care. The participants found it important to receive information on their life-expectancy. While disclosing prognostic information in general terms like "the cancer is curable" gave enough reassurance for most patients, some also wanted numerical information like OncologIQ's prognostic estimates. A tailor-made approach is necessary to provide this prognostic information in a customized manner. A clinical practice guideline was developed to support the healthcare professional in sharing individualized prognostic information, aiming to improve shared decision making.

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Supplementary material 1. Interview guide: overview of the topics and corresponding questions.

Topics	Answer type	
Treatment decision consultation (warm-up topic)		
1. What do you think is a good treatment proposal?	open-ended	
2. To what extent do you want to be involved by your doctor when it comes to treatment choices?	multiple choice*	*A: patient and doctor should decide together* *B: the patient decides* *C: the doctor decides*
Life-expectancy (main topic 1)		
1. To what extent do you think it is important to receive information about your life expectancy?	multiple choice*	*4-point Likert-scale: "not at all important" to "very important"*
2. Do you think that life-expectancy should be discussed with each patient?	open-ended	
3. Should the doctor share survival rates with the patient?	open-ended	
The prognostic model OncologIQ (main topic 2)		
1. Which view would you prefer? (see table 4)	multiple choice*	*see table 7: all patients were asked to choose a preferred order*
2. What would your preference be: 1) only verbal explanation of the percentages or 2) verbal explanation and showing a chart?	multiple choice*	
3. What do you think of this model? (see figure 1)		
4. What would you change?	open-ended	
5. Do you think you would be better informed with the information in this model?	open-ended	
6. Do you think that the information in this model would be appropriate for everyone?	open-ended	
	open-ended	

* All multiple choice questions were answered by patients themselves. During open-ended questions caregivers were encouraged to participate in the group discussion to a certain extend as the patients' perspective was the main focus.

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC
University Medical Center Rotterdam

Focus group meeting

date

dr. Marinella Offerman
drs. Arta Hoesseini

Erasmus MC

Welcome & aim

- Aim: to improve head and neck cancer patient care for future patients
- We want to learn from your experiences: you can say anything you want!
- Although there are some similarities, your situation and treatment is not identical with other patients in this room
- Data will be anonymised
- Turn off mobile phones

Supplementary material 2. PowerPoint presentation that was used during the focus groups

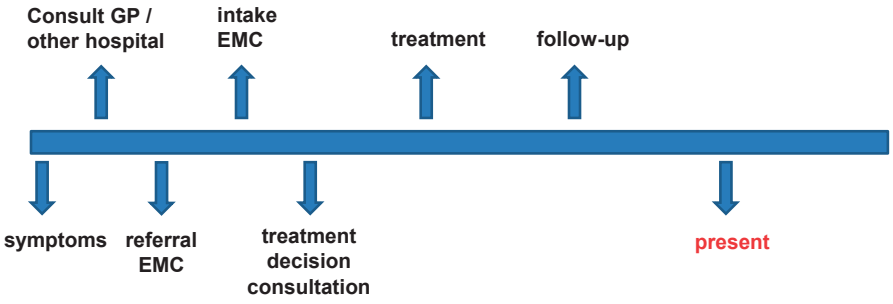
Erasmus MC

Agenda

19:00	welcome & aim
19:10	treatment decision consultation
19:30	shared decision making
19:40	life-expectancy (1)
20:00	**break**
20:10	life-expectancy (2)
21:20	closing
21:30	end

Erasmus MC

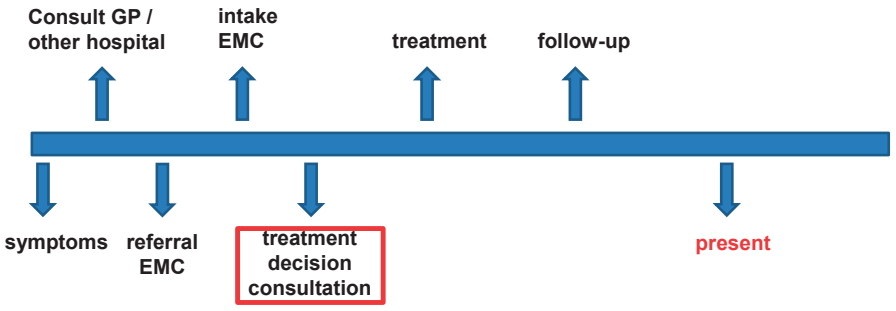
Time line



Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

Time line



Erasmus MC

- What do you think is a good treatment proposal?

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

Shared Decision Making

- Patient & doctor decide together

Erasmus MC

- To what extent do you want to be involved by your doctor when it comes to treatment choices?

❑ Patient and doctor should decide together
❑ The patient decides
❑ The doctor decides

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

Life-expectancy

- Not always discussed
- Hard to predict → **probability**
- One of the ways to discuss this is in a ''qualitative manner'', general terms like: '*the cancer is curable*'
- Another way is quantitative, like specific numbers or percentages

Erasmus MC

- To what extent do you think it is important to receive information about your life expectancy?

❑ Not at all important
❑ Not important
❑ Somewhat important
❑ Very important

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

- Do you think that life-expectancy should be discussed with each patient?

Erasmus MC

- BREAK (20:00 – 20:10)

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

Life-expectancy

- A specific way to discuss life-expectancy is with numbers / percentages
- Percentage of patients who are alive at 2-, 5- or 10-years after treatment
- **Probability** calculation, large group of patients with different characteristics

Erasmus MC

Life-expectancy

Example: a patient with a 5-years survival probability of 70%

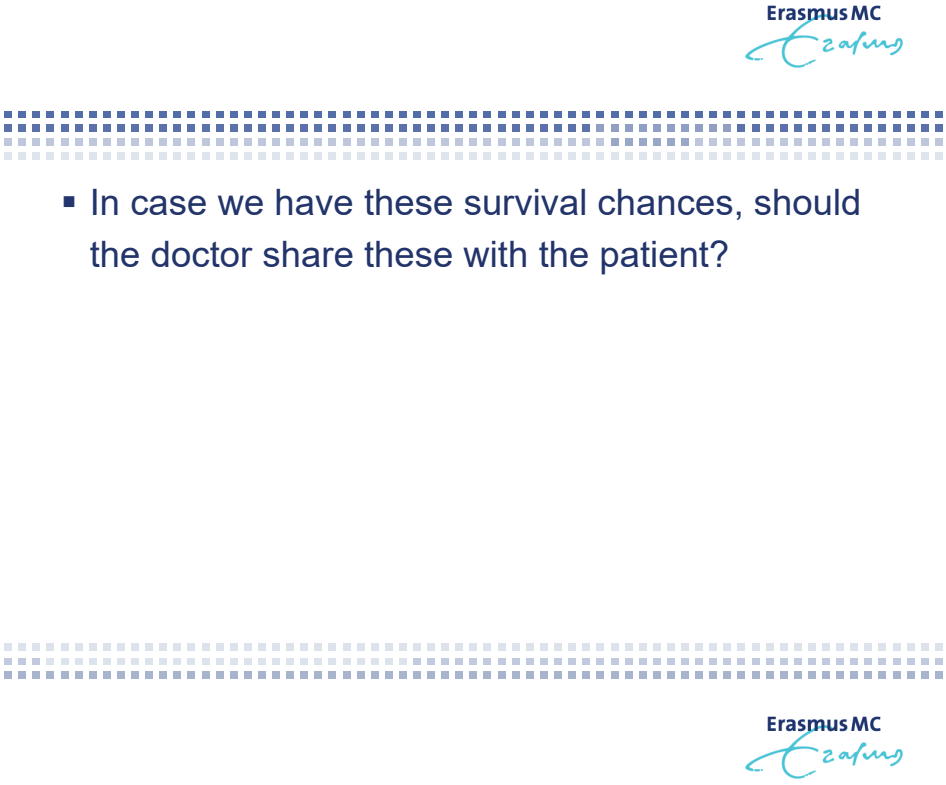
=

the **probability** that after 5 years 70 out of 100 patients are still alive

=

the **probability** that the patients is alive after 5 years is 70%

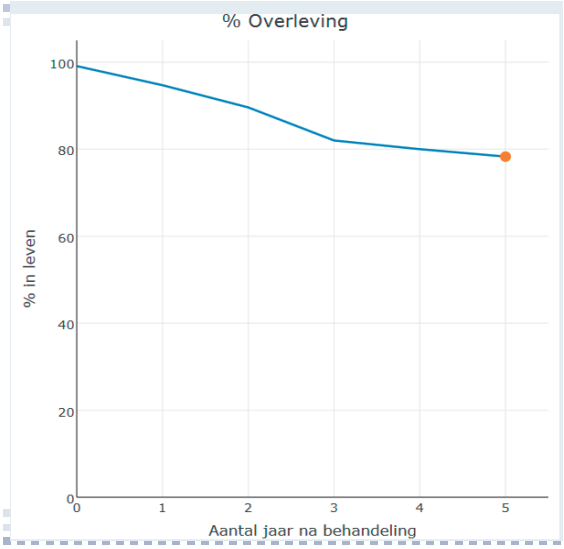
Supplementary material 2. PowerPoint presentation that was used during the focus groups



Supplementary material 2. PowerPoint presentation that was used during the focus groups

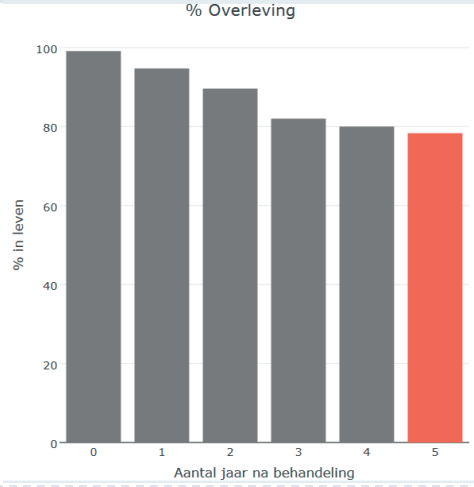
Erasmus MC

5-year survival rate



Erasmus MC

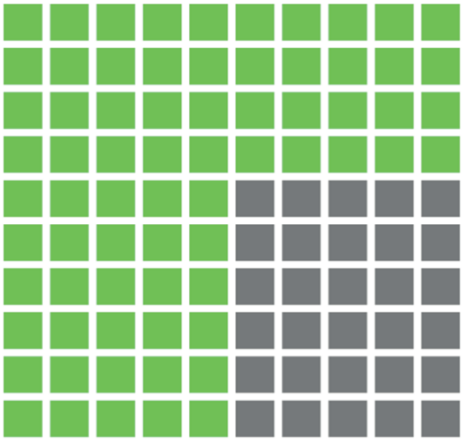
5-year survival rate



Supplementary material 2. PowerPoint presentation that was used during the focus groups

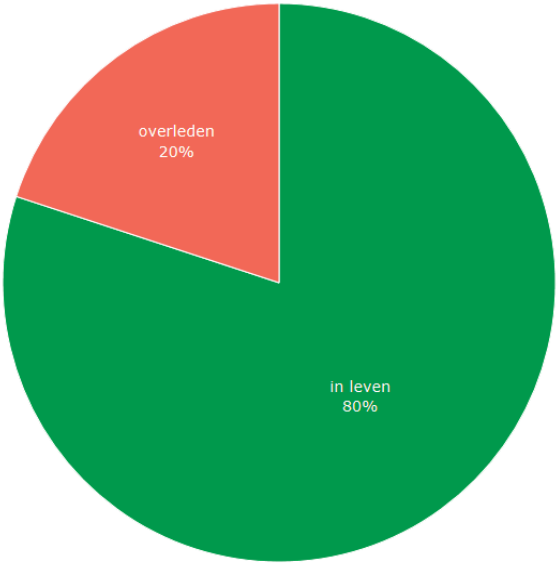
Erasmus MC

5-year survival rate



Erasmus MC

5-year survival rate



Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

5-year survival rate

Erasmus MC

What would you prefer:

- Only verbal explanation of the %

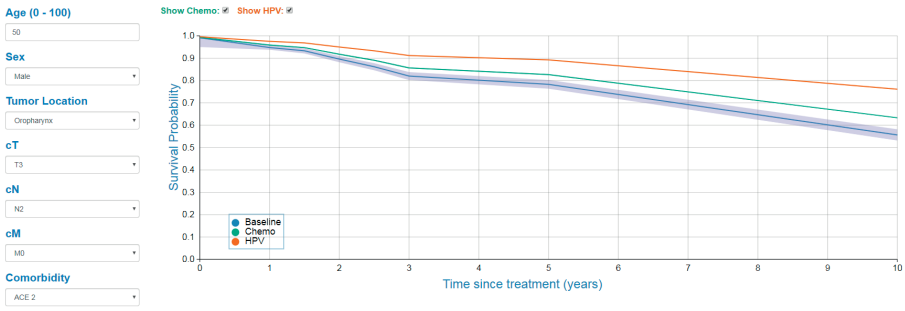
OR

- Verbal explanation and showing a chart

Supplementary material 2. PowerPoint presentation that was used during the focus groups

Erasmus MC

Model



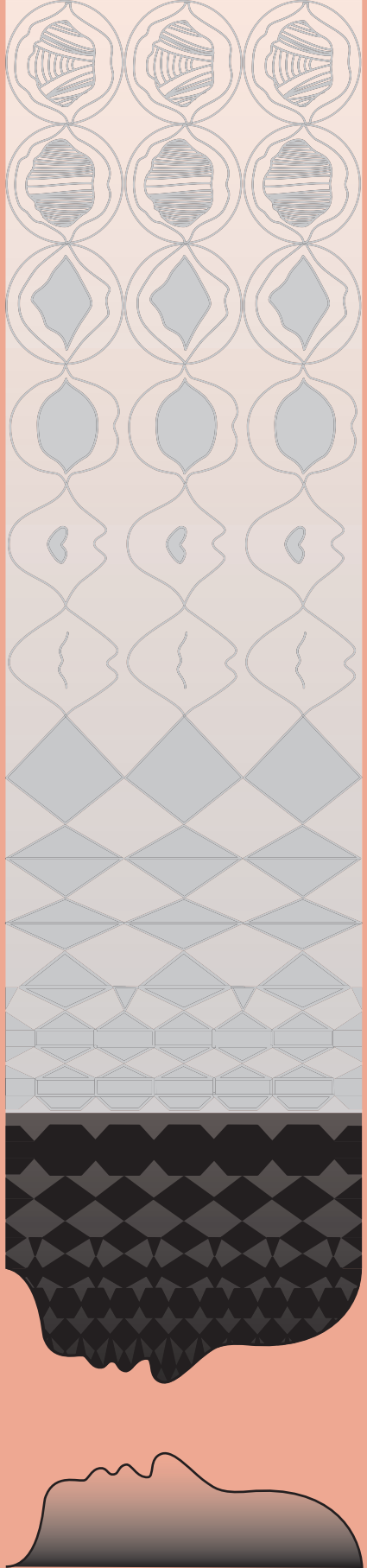
Erasmus MC

- What do you think of this model?

Supplementary material 2. PowerPoint presentation that was used during the focus groups

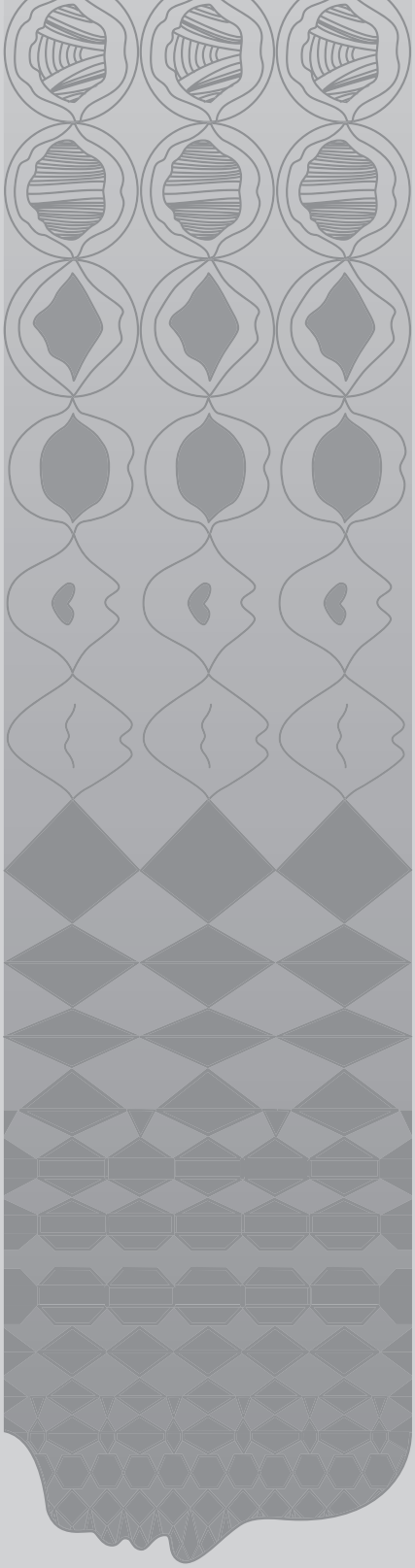
Erasmus MC

- What would you change?
- Do you think you would be better informed with the information in this model?
- Do you think that the information in this model would be appropriate for everyone?



Part IV

Tools for shared decision making: development of a value based clinical support system



9

Keys to successful implementation of routine symptom monitoring in head and neck oncology with *'Healthcare Monitor'* and patients' perspectives of quality of care

Emilie Dronkers, Robert Baatenburg de Jong, Egge van der Poel, Aniel Sewnaik, Marinella Offerman.

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ABSTRACT

Value based healthcare is increasingly used to facilitate a systematic approach during follow-up of patients. We developed Healthcare Monitor (HM): an ePRO (electronic patient reported outcome measures)-structure for the longitudinal follow-up of head and neck cancer (HNC) patients. This study shares key-lessons from implementation and seeks to provide insight into how patients experience HM. We conducted a mixed-methods study using quantitative data from a nonrandomized retrospective survey of patients who received HM (n=45) vs. standard care (n=46), and qualitative data from structured interviews (n=15). Implementation of HM included significant challenges. Finding common ground among clinicians, administrators, and IT staff was most important. Qualitative findings suggest that patients experienced better doctor-patient communication and increased efficiency of the consultation using HM. Patients felt better prepared and experienced more focus on critical issues. Quantitative analysis did not show significant differences. Integration of HM into routine care for HNC patients may have increased patient centred care and facilitates screening of symptoms. However, future research is needed to analyze the potential benefits more extensively.

INTRODUCTION

Value based healthcare is increasingly used to stimulate patient centered care and to empower patients during doctor-patient encounters.[1-3] This concept, that was first described by Michael Porter, claims that improvement in both quality and cost of care can be achieved by understanding and integrating the patient perspective into care.[2] To help clinicians better understand the patient perspective, use of patient reported outcome measurements (PROMs) is recognized as essential.[3] They are defined as standardized, validated questionnaires completed by patients to measure their perception of their functional well-being and health status.[4] Electronic PROMs (ePROs) allow for efficient standardized assessment and improved ease of use in comparison to paper-based PROMs.[4-6]

Understanding the patient perspective is important during follow-up of cancer patients, since doctor-patient communication can be challenging for both patients and doctors. Patients can have difficulties sharing a complete health status in a short period of time and doctors also need to have good skills to facilitate this process.[7, 8] Physical impairments and psycho-social problems may go undetected and opportunities to intervene can be missed.[9, 10] By using ePROs, patients might actively participate in their own care and clinicians identify critical issues, improving patient management.[4, 6, 9, 11-14]

ePROs focus on physical problems, psychosocial problems and/or the impact on global health related quality of life (HRQoL).[4] They provide data detailing the patient's own view on the impact of having cancer, and its treatment. Furthermore, ePROs can capture a more holistic view on individual health outcomes. There is evidence from general cancer care that clinical interventions following the routine use of ePROs in clinical practice may improve patients' HRQoL, enhance doctor-patient communication, and may even lengthen survival, for example among patients with advanced cancers.[1, 12] ePROs can also play a role in shared decision making.[15, 16] However, monitoring of ePROs alone does not improve patients' outcomes.[8, 17, 18] Providing individual feedback to the patient can help to for example discuss the need for supportive care.[4, 19-21]

The ePRO approach is also getting more attention in head and neck cancer (HNC) care.[22, 23] Due to advancements in diagnosis and treatment the number of HNC survivors have increased.[24] However, HNC patients often have to deal with treatment-related side effects that can have an enormous impact on patients' daily life. Some of these side-effects are immediately noticeable in social settings and can negatively affect HRQoL and increase levels of psychological distress and on the spousal relationship.[25-27] ePROs might support patients in coping with the physical and emotional challenges of HNC by providing themselves and their clinicians better insight into their condition.

In 2013 we developed Healthcare Monitor (HM), an ePRO based clinical support system, which uses simple and internationally validated questionnaires regarding HNC to measure physical and psychosocial functioning from day of diagnosis until 5 years after. Since 2015, HM has been structurally embedded in our care for HNC patients.

The overall aim of this study was to provide a first evaluation of HM after implementation. We (1) review the challenges we experienced during the initial implementation phase (i.e. clinical impressions). In addition, (2) we evaluate patients' experiences with HM in practice and the perceptions of quality of care among patients receiving standard care versus those receiving HM care.

MATERIALS AND METHODS

'Healthcare Monitor': description and organizational setting

The Erasmus Medical Center (Erasmus MC) houses the largest HNC center in the Netherlands with over 600 new patients annually. In 2013, we developed Healthcare Monitor (HM) (see Figure 1). This is an ePRO based clinical support system, designed with health care professionals and technology providers for follow-up and management of HNC patients. Our vision behind the development of HM is threefold:

1) improve overall quality of patientcare
2) support research in general
3) improve transparency of healthcare for the purpose of national registries and audits

Internationally validated questionnaires (Table 1)[28-34], measuring physical problems, psychosocial symptoms and HRQoL of HNC patients, are routinely collected with HM from the first visit at the day of diagnosis to the final consultation (5 years after end of treatment). A dedicated nurse practitioner counsels patients on the way of working with HM . Patients suffering from disorders affecting cognitive abilities (e.g. dementia, Korsakoff syndrome) may be excluded from participation in HM. All patients complete questionnaires before every outpatient clinic visit. They do this either in the comfort of home via internet or with an iPad at the clinic. In case patients want assistance with filling out the questionnaires, for example due to illiteracy, trained volunteers are available to help. These volunteers are already part of our specialized outpatient clinic team for HNC patients. They help patients with the logistic procedures during diagnosis.

Figure 1. Infographic Healthcare Monitor

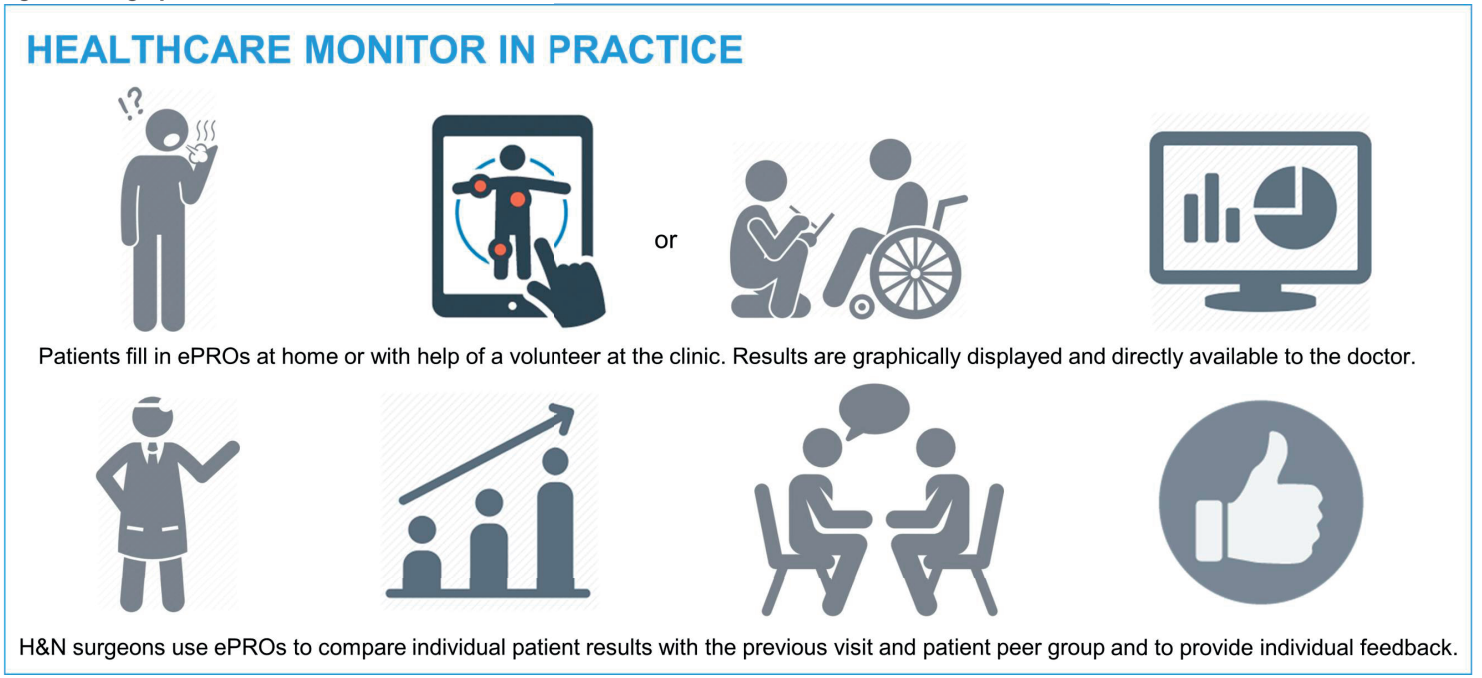

Table 1. Generic and specific Patient Reported Outcome Measurements used in Healthcare Monitor

General questionnaire: items on lifestyle, socio-economic status and civil status.
EORTC QLQ-C30: assess the quality of life of cancer patients.
EORTC H&N35 module: measure the quality of life specifically in head and neck cancer patients
Hospital Anxiety and Distress Scale (HADS): measure symptoms of anxiety and distress in patients.
10 item Eating Assessment Tool (EAT10): assessment of swallowing function.
Voice Handicap Index (VHI): assessment of function of voice and speech.
EQ5D-3L: generic standardized measure of health status.

Clinicians have real-time access to the results which are graphically displayed inside the electronic health record (EHR). Clear graphics help to systematically monitor symptoms, and allow clinicians to compare individual patient results during the course of time and with their peer group. Firstly, published norms from questionnaires (Table 1) were used as peer group information.[28-32] Since 2018, we also evaluate scores from all other HNC patients treated at Erasmus MC as the amount of data is becoming sufficient to make a valid comparison from that time onwards. Scores from HNC patients evaluated at the same point in post-treatment follow-up care, with the same tumor type and stage are used for this purpose.

Literature shows us that monitoring of symptoms alone is not enough.[35] Our HM concept therefore includes both monitoring and sharing the results with patients. Clinicians use graphs to provide direct individual feedback to each patient. All patients receive further clinical or diagnostic evaluation or referral to specialty care as needed. HM data and the conversation following the individual feedback can thus further guide health care providers and patients on supportive care needs.

Patients' informed consent to use their data for peer group information and for broader research and benchmark purposes is requested before and after treatment. Since the time between diagnosis and first regular follow-up visit after treatment can easily reach up to 6 months, we believe it is more conscientious to ask patients again for their consent after treatment.

We started HM with a pilot phase from November 2013 to March 2015 among 260 patients with small (T1-2) laryngeal carcinoma, treated with (laser) surgery. Patients were included at any point during their diagnostic, treatment or post-treatment trajectory (up to 5 years after diagnosis). Total response was 97% at intake and 90% in follow-up phase. As a first (non-scientific) evaluation these patients were asked after their visit at the out-patient clinic if they thought HM to be an improvement of care and 70% agreed. Physicians also found HM an useful tool to respond better to patients' needs. After concluding the initial

pilot phase, HM has been structurally embedded in our care for HNC patients since April 2015.

First evaluation of HM: key lessons and mixed-methods design

In the current report, we review the challenges we experienced during the initial implementation phase by sharing barriers and facilitators based on pragmatic experience in implementing HM initiative. Some of these impressions are briefly summarized in narrative and tabular form in the beginning of the Results section. In addition, to evaluate patient experiences, we conducted a mixed-methods study using quantitative data from a self-developed patient reported experience measures (PREM) questionnaire and qualitative data from interviews. Ethical approval was not necessary according to the Dutch Medical Research Involving Human Subjects Act, as this study evaluated standard care.

Quantitative method

We invited n=151 patients diagnosed with HNC between October 2014 and April 2016 to anonymously complete a survey on the care they received during follow-up visits at our outpatient clinic. This number of patients invited was not based on a power-analysis, but was determined by the number of patients actively using HM at that time. In the accompanying letter provided to patients, informed consent was requested to use the data anonymously for the purpose of this evaluation study. There was no overlap in participants between the pilot phase and this evaluation study.

Two groups were distinguished: 1) HNC patients that were diagnosed prior to implementation of HM (standard care group), and 2) HNC patients that were diagnosed after implementation of HM (HM care group). Patients in group 2 were treated more recently than those in group 1. No other patient characteristics then age and gender were available due to the anonymous response. In the standard care group symptoms were discussed during standard clinical encounters. In the HM care group patients filled out ePRO questionnaires before their doctors visit, and the results were directly discussed during the consultation.

We developed a 12-item PREM questionnaire with a 4-point Likert scale for both groups of patients. Six extra items were developed specifically for the HM care group, based on questions on functioning of HM raised in our research meetings and meetings with health care professionals. In this survey for HM patients (Supplementary Table 1a), we asked about the burden of filling out HM questionnaires and about the congruity of items addressed in HM and experienced by patients themselves. Both groups of patients were asked to answer questions on doctor-patient communication, their preparation to discuss their individual conditions, physicians' awareness of individual patient conditions and efforts made to improve these individual patient conditions. (Supplementary Table 1b) We also

asked questions about the length of the consultation and asked patients to rate their subjectively experienced quality of care ranging between 1 and 10. A higher score means a higher experienced level of quality of care.

Qualitative method

Structured interviews (N= 15) were conducted in 2016 during one full consultation day of one HNC surgeon at the outpatient clinic. Only patients who received HM care and were in the early follow-up phase, several months after curative treatment, were approached to take part in the interviews. Patients were selected randomly from physician's consultation visits at our outpatient clinic. The interviews were held by a female senior researcher with PhD degree (MO). There was no relationship established with participants prior to start of the interview, nor did participants have knowledge of the interview. Interviews were held either directly after the consultation with the HNC surgeon or after the moment patients filled in the HM ePROs at our outpatient clinic prior to the visit with their HNC surgeon. All interviews were held at the outpatient clinic of the Erasmus Medical Center. All approached patients agreed to cooperate with the interview, and they gave oral informed consent to use the interview for the purpose of this evaluation study. Patients were interviewed on the added value of HM and on how they think of HM in general. A semi-structured interview guide was made which consisted five key questions, all with an open character, followed by more elaborate questions to follow-through on the subject (Table 2) The questions were asked in a fixed order for all the interviews.

Table 2. Interview guide for structured interviews

1.	What are your general experiences with 'Healthcare Monitor'?
2.	Do you find the way of working with 'Healthcare Monitor' a good thing? And if so or not, why?
3.	'Healthcare Monitor' provides your doctor with direct insight into you symptoms. What is your opinion about this?
4.	Do you experience added value by filling healthcare questionnaires upfront to your doctor s control visit? If so, what is the added value in your opinion?
5.	Do you have any suggestions for us to further improve our working method with Healthcare Monitor?

Data analyses

All statistical analyses were performed using SPSS version 22 (IBM Corp. Armonk, NY, USA). The quantitative data from the nonrandomized retrospective survey were analyzed using descriptive statistics. To compare patients in the HM care group to those in the standard care group on items 1-7 of the PREM questionnaire, statistical analysis of categorical data was performed by chi-square test and analysis of continuous data by students t-test. Only four patients in the standard care group did not fill out the complete survey. Since these data were missing not at random, we left the data out of the analysis by performing a complete case analysis. Logistic regression analysis, adjusted for age and gender, was done to analyze differences in

experienced quality of care (items 8-12) between HM care and standard care. The answers patients provided on the 4-point Likert scale were dichotomized to 'agree' and 'disagree' for this purpose. P-values <0.05 were considered significant.

The semi-structured interviews were thematically analyzed by a trained senior researcher with no relationship with the patients (MO). Qualitative content analysis was used for analysis of the data and inductive categories were derived. Based on the answers provided by patients during the interviews, three themes were identified from the data and clearly presented in the results.

RESULTS

Key clinical impressions from the setup and implementation of Healthcare Monitor

The implementation of an ePRO structure in clinical practice includes significant challenges.[4, 36, 37] Our experienced barriers and facilitators are summed up in Table 3.

First of all, common ground is needed. One must gain support from every member of the team, including healthcare providers, administrative employees and technology providers This task will take some effort, but we believe the common goal of improving patient care makes it worthwhile.

We found conducting a pilot phase to be very helpful in reducing any 'teething problems'. As of January 2019, 1737 patients have taken part in HM from their day of diagnosis and routinely receive this care, with 95% patient compliance at intake and over 80% at the different moments of follow-up.

In comparison with literature regarding use of PROs in oncology settings, our compliance rates are uncommonly high.[4] We believe that the way we integrated ePROs in regular patient care leads to this high compliance. Reported data of the patient are directly used for the benefit of the patient, and the online system facilitates a better preparation for clinical consultation given the opportunity to fill out ePROS when it suits the patient.

Illiteracy, not having access to internet and advanced age are known barriers for participation of patients in an ePRO structure.[4, 23] We chose to train our already available group of volunteers in assisting patients with filling out HM questionnaires. This role is important for the sustainability of HM since the volunteers encourage patients to fill out the questionnaires themselves by showing the ease of the system. An important group of vulnerable

Table 3. Facilitators and barriers for implementation of 'Healthcare Monitor' care

Facilitators of '*Healthcare Monitor*':
- Patients can fill out the questionnaires via internet at the comfort of their homes.
- Trained volunteers can assist patients with filling out the questionnaires before the doctor's visit.
- Clinicians have real-time access to the results which are graphically displayed inside the hospital information system.
- Clinicians capture a holistic view of the patient including both physical and psychosocial functioning.
- Review of longitudinal ePRO reports is possible to identify the course of physical and psychosocial complaints and to compare patients individual results with their peer group.
- Clinicians use the results to provide direct individual feedback to the patient on the need for supportive care.
- Clinicians can identify critical issues earlier.
- Better counselling of patients is possible leading to better quality of care.
- Patients can actively participate in their own care which strengthens patient empowerment.
Barriers to use '*Healthcare Monitor*':
- The implementation of HM consumes time and energy whilst the organization still runs all the other activities it has going.
- Dedication and support is needed from every member of the team.
- For successful implementation, it takes effort to motivate all healthcare providers, administrative employees and technology providers.
- Many workplace and organizational adjustments are necessary.
- A sustainable and robust technical environment is necessary.
- Adequate resources are necessary so that patients who screen positive subsequently will receive diagnostic or clinical evaluation, and referral to specialty care as needed.
- The extra costs needed to implement HM care are not reimbursed by health insurers or government yet.
- Evaluation of the work process as a whole is needed in order to adapt user needs.

patients who generally don't have access to digital solutions and may have problems with phrasing their complaints is thus supported to take part in HM care.

The graphical display of HM results inside the hospital information system is also helpful. The course of symptoms can be identified and patients' individual results can be compared with their peer group.

However, we also experienced that the implementation of HM consumes time and energy. Organizational and workplace adjustments were necessary, and the close cooperation with health care and technology providers was essential. For example, all medical staff (including secretaries, nurses, doctors and case managers) was trained in using and/or interpreting HM. A small renovation of our outpatient clinic was necessary to have a private space available for filling out HM questionnaires on the iPad. Furthermore, after two years we had to hire a new secretary to manage the HM system working schedules of the volunteer group and to oversee that every patient fills in the HM questionnaires beforehand (either at home

or at the clinic). The provision of a powerful IT network and the assurance of data safety was necessary in order to facilitate a more efficient and safe work process.

Quantitative results from the mixed methods study

Within the HM group, 45 of 71 patients (63.4%) completed this survey, and 46 of 66 patients (69.7%) completed the survey in the standard care group. No information was available on reasons for declining participation. Both groups of patients showed comparable distribution of age and gender. Within the HM group, we found that 31 69% of patients completed the HM questionnaires at home, and 12 (27%) used the help of a volunteer to complete the HM questionnaires at the outpatient clinic. The time needed to complete HM questionnaires as perceived by patients was on average 19 minutes (SD 8 minutes). A majority of 41 patients (91.1%) indicated that this time was not too short nor too long. A minority of patients found the HM questionnaires unclear (n=2, 4%) and irrelevant (n=2, 4%). The reasons these patients mentioned were: "*they're asking me to answer the same questions using different wording 20 times in a row*" and "*I have to answer questions on pain management that are not related to my tongue cancer*".

In univariate analysis no significant differences on any of the 17 items were seen between the two groups of patients (Table 4). In comparison with standard care, more patients indicated that the use of HM helped physicians to have a more complete picture of patients and to have a focus on their specific condition, however these were non-significant results.

Table 4. Perceptions of quality of care among patients receiving standard care vs. those receiving electronic patient-reported symptom monitoring

			***Standard care* (n=42)**		***Healthcare Monitor* (n=45)**		***p-value****
			Mean (SD) / Frequency	**%**	**Mean (SD) / Frequency**	**%**	
1	Age (years)		67.5 (11.3)		63.7 (9.7)		0.092
2	Gender	Male	30	71.4%	34	75.6%	0.740
		Female	12	28.6%	11	24.4%	
3	Did the doctor discuss your most common health complaints?	yes	37	88.1%	43	95.5%	0.636
		no	5	11.9%	2	4.5%	
4	Has the doctor taken action when it comes to treating your complaints?	yes	34	80.9%	41	91.1%	0.375
		no	8	19.1%	4	8.9%	
5	Did you miss topics during the consultation?	yes	12	28.6%	10	22.2%	0.243
		no	30	71.4%	35	77.8%	
5A	Did you miss a topic on symptom burden during the consultation?	yes	34	81.0%	39	86.7%	0.286
		no	8	19.0%	6	13.3%	

Table 4. Perceptions of quality of care among patients receiving standard care vs. those receiving electronic patient-reported symptom monitoring (continued)

			Standard care (n=42)		*Healthcare Monitor* (n=45)		*p-value**
			Mean (SD) / Frequency	%	Mean (SD) / Frequency	%	
5B	Did you miss a topic on psychosocial distress during the consultation?	yes	37	88.1%	39	86.7%	0.621
		no	5	11.9%	6	13.3%	
5C	Did you miss a topic on comorbidity during the consultation?	yes	40	95.2%	42	93.3%	0.662
		no	2	4.8%	3	6.7%	
5D	Did you miss a topic on medication during the consultation?	yes	40	95.2%	42	93.3%	0.662
		no	2	4.8%	3	6.7%	
5E	Did you miss a topic on influence of disease on your partner during the consultation?	yes	37	88.1%	40	88.9%	0.748
		no	5	11.9%	5	11.1%	
5F	Did you miss a topic on influence of disease on your occupation during the consultation?	yes	39	92.9%	43	95.6%	0.645
		no	3	7.1%	2	4.4%	
5G	Did you miss a topic on influence of disease on your social life during the consultation?	yes	39	92.9%	40	88.9%	0.725
		no	3	7.1%	5	11.1%	
6	Subjective rating (1-10) of experienced quality of care		8.2 (SD1.3)		8.1 (SD 1.1)		0.695
7	Length of consultation (minutes)		12 (SD 6)		11 (SD 4)		0.149
8	I felt well prepared for the consultation with my treating physician	yes	41	97.6%	45	100%	0.458
		no	0	0%	0	0%	
		missing	1	2.4%	0	0%	
9	My treating physician was focused on my specific complaints	yes	39	92.9%	42	93.3%	0.398
		no	3	7.1%	2	4.4%	
		missing	0	0%	1	2.3%	
10	My treating physician had a complete picture of me	yes	30	71.4%	38	84.4%	0.554
		no	8	19%	7	15.6%	
		missing	4	9.6%	0	0%	
11	My treating physician paid attention to my specific complaints	yes	37	88.1%	41	91.1%	0.291
		no	5	11.9%	3	6.6%	
		missing	0	0%	1	2.3%	
12	My treating physician undertook action in response to my specific complaints	yes	33	78.6%	40	88.8%	0.585
		no	4	9.5%	4	8.8%	
		missing	5	11.9%	1	2.4%	

* Categorical data analyzed by chi-square test, continuous data by students' t-test, equal variances not assumed.

Also the length of the consultation as perceived by patients was shorter when using HM, but this was also not a significant difference. Logistic regression analysis showed that age and gender were not significant predictors for the experienced quality of care in both groups (items 8-12). The subjectively overall experienced quality of care (item 6) was equally high in both groups.

Qualitative results from the mixed methods study

The answers provided by patients during the interviews were categorized into three themes. The themes are: 1) patient preparation for the consultation, 2) doctor-patient communication, and 3) patient experience with HM care. A summary of the results including verbatim examples are provided in Table 5. Patients also shared their views of the pros and cons of HM and suggestions for improvement (Table 6).

Table 5. Verbatim examples of three overall themes regarding patients' views of 'Healthcare Monitor' experience in practice

Theme	Verbatim example*
Better preparation patient Patients see HM as a tool to be better prepared for their visit to the doctor. Patients forget less and because they have been through all the questions beforehand, they are more conscious on how they really feel.	*'This system makes it easier for us as a patient to come to the doctor, because you have been through all the questions yourself.'* *'If I didn´t have this preparation with the questionnaires when going to my control visit, I would close the door after my consult thinking ´I should have asked my doctor this or that!'* *'It is good for me, as a patient, to fill out these questionnaires because I need to think myself how I really feel, so that I can ask my doctor the right questions.'* *'You already shared upfront (with the questionnaires) how you are doing'*
Better doctor patient communication A good preparation to the doctor's visit generally contributes to the quality of the conversation and HM seems to play an important role in that process. Patients mentioned that the doctor can see at one glance how they are doing. The fact that the doctor has this complete overview of the patient in advance, makes it easier for them to speak to their doctor.	*'When you fill out the questionnaires, I understand what the doctor wants to know from me, so I don´t feel overwhelmed by the doctor as I know now what to expect.'* *'It is good that the doctor has a complete overview of how I am doing and how I cope with it.'* *'You can be more efficient in your talk with the doctor and it might result in shorter waiting times.'* *'I don't have to think so hard anymore (how I am doing) during the doctor's visit'*
Positive patient experience The way of working with HM contributes to a positive experience and a sense of security and peace. Patients are feeling heard, taken seriously and they felt there is room to share both their physical and mental complaints.	*'By filling out the questionnaires I feel that the doctor looks at me in a professional manner. There is a good overall control.'* *'The doctor can directly follow through at my complaints and that is a good thing'* *'It is a nice feeling that they pay attention to me'* *'I think the 'Healthcare Monitor' is a good thing, especially sometime after treatment, when you reflect on the whole trajectory and how you feel about that.'*

* All quotes are based on responses from varied patients.

Table 6. Patient perceptions of pros and cons of Healthcare Monitor and suggestions for improvement, from the structured interviews.

PROS	CONS
- I experience a more efficient doctors visit; - I love to fill out the questionnaires: it is easy and quick, so I am happy with it; - The *'Healthcare Monitor'* gives me insight in how I really feel; - I feel much better prepared! - A big advantage is that I can fill out the questionnaires at home via internet - I feel a greater commitment of my doctor in this way - I feel at ease with the help of a volunteer at the hospital when filling out the questionnaires - It is very well organized in comparison to other hospitals	- *It is a fuss: so many questionnaires* - *Questionnaires sometimes look alike* - *Every time when I fill out the questionnaires, I feel confronted with the disease I had…*

SUGGESTIONS FOR IMPROVEMENT
- *It is important to emphasize that the 'Healthcare Monitor' is beneficial for you as an individual patient.* - *Would be better if questions are not only related to the last week, however, to the period in between the control visits.*

DISCUSSION

The overall aim of this study was to provide insight into our key lessons on the set-up and implementation of HM and into how HNC patients experience and value HM care in clinical practice.

We believe that the implementation of HM included significant challenges, but also had demonstrated to be a worthwhile investment. The results of the qualitative analyses look very promising. However, the quantitative analyses did not show any significant results. Quantitative analyses showed that HM users scored higher on some questions of the PREM questionnaire than those who had received standard care. HM users experienced more often that their physician had a complete picture of them and undertook action in response to their specific complaints. The differences in these percentages were not statistically significant but they exceeded 10 points and thus appear to be clinically meaningful results worthy of further research. No significant difference regarding the perceived quality of care could be found between groups possibly because of a ceiling effect. Also, the standard care patients were further along in their recovery than patients in the HM group and this might have introduced confounding by time since treatment.

Qualitative analyses suggested that HNC patients who received HM care noticed more focus on critical issues and an increased efficiency of the consultation. Patients felt better prepared and were more conscious on how they really feel, and mentioned their clinicians had a more holistic view on their symptoms. Furthermore, structurally monitoring ePROs and discussing the results with individual patients contributed to a positive experience and a sense of security. These qualitative findings are in line with earlier (both qualitative as well as quantitative) studies on the value of using PROMs in HNC clinical practice to improve communication between doctors and patients and to facilitate screening of symptoms and psychological distress.[16, 22, 23, 35] In our study, HNC patients also experienced a better doctor-patient communication with HM.

The results from our evaluation indicate that HM might be useful in identifying the latent needs of patients. The ePRO questions stimulate patients to think about issues in relation to their disease they might not have thought about before. As a result, awareness of symptoms and a sense of the normal course of disease can be raised , leading to patient empowerment.

Besides the improvement of perceived patient care as suggested by the qualitative results, we learned that conducting scientific studies can benefit from the existing ePRO structure within HM as well. The logistic set-up, including organizational and workplace adjustments, and the relationship of trust between patients and trained volunteers, creates opportunities to counsel patients on research projects. Longitudinal ePRO data can enhance benchmarking on an individual level in our clinic as well as in larger, multicenter, studies. We would like to share our lessons with other HNC clinics, in order to improve patient care and create benchmark possibilities. Therefore we prepared a guideline with eight questions that might be helpful to address before implementing an ePRO structure into daily clinical practice (see Table 7).

Table 7. Toolkit: with eight essential questions towards implementation of an ePRO structure in HNC clinics

Step 1:	'Why do I want to measure outcome in this patient group?'
Step 2:	'What are the right outcomes measures for this patient group?'
Step 3:	'What questionnaires should I use, are those validated and readily available?'
Step 4:	'What are the right moments to measure ePROs?
Step 5:	'Are there any workspace or organizational adjustments necessary?'
Step 6:	'How do I take data-integrity into account?'
Step 7:	'What will I do with the obtained data?'
Step 8:	'Do I have adequate resources available for patients in need of extra care?'

Future perspectives

Although we experienced that the implementation of HM took a lot of effort, the experienced value made it worthwhile. This positive balance contributed to a sustainable system. In order to maintain this balance, we believe two areas of focus for the future are important.

One way of achieving a lower experienced effort might be by exploring computer adaptive testing methods (CAT) in HM, since the use of traditional PROMs often requires patients to answer items that are not directly applicable to them.[38, 39] CAT has several advantages including reduced patient burden and increased question relevance to individual patients.[40] Another way HM might be improved is the optimization of the graphical display of the results. We are currently developing a dashboard including HM results which can help physicians to efficiently get an overview of all data. In order to achieve a higher experienced value, research is needed to obtain more insight into the referral and uptake of supportive care services following the individual feedback from doctors to patients using HM.

An ePRO setup such as HM may also have direct influence on health care costs. On the one hand, one can imagine that when more symptoms (for example psycho-social) are being recognized due to HM, this will also lead to more diagnostics or involvement of other health care providers (e.g. psychiatrist), and therefore probably to higher costs. On the other hand, HM could also contribute to lower rather than higher costs, due to earlier identification of conditions and reduced frequency of regular outpatient clinic visits. A cost effectiveness study seems appropriate, especially in the context of value based healthcare.

Study limitations

The mixed methods design we used for this study was sufficient as a first step and forms a useful foundation for further research. However, this study has some limitations. Both the structured interviews as well as the retrospective nonrandomized survey have a small sample size. Although the questions of the structured interview all have an open character, they may have introduced a positive bias as some of the questions already include the suggestion of HM being beneficial. The small sample size of the quantitative analysis and absence of a power analysis might explain the non-significant results. Also, clinical characteristics or demographic variables other than age and gender were not available. Another limitation of this study is that we did not evaluate the experience of healthcare providers on the use of HM. Therefore, we are currently preparing a yearly evaluation questionnaire for patients and professionals.

CONCLUSION

Our qualitative data suggest that integration of our ePRO clinical support system 'Healthcare Monitor' into routine care for HNC patients may lead to increased patient centred care and an improved perception of doctor-patient communication, and may enable a holistic approach, and enhance patient empowerment.

Structurally monitoring ePROs and discussing the results with each patient appears to contribute to a positive patient experience and facilitates screening and follow up of symptoms including psychological distress. However, future research is needed to analyze the potential benefits more extensively.

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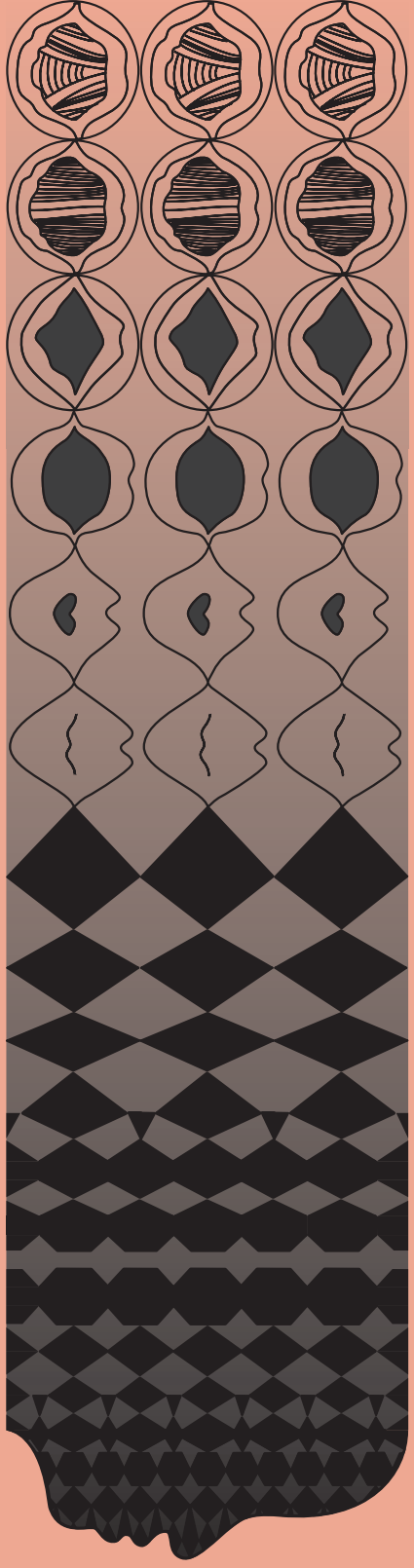
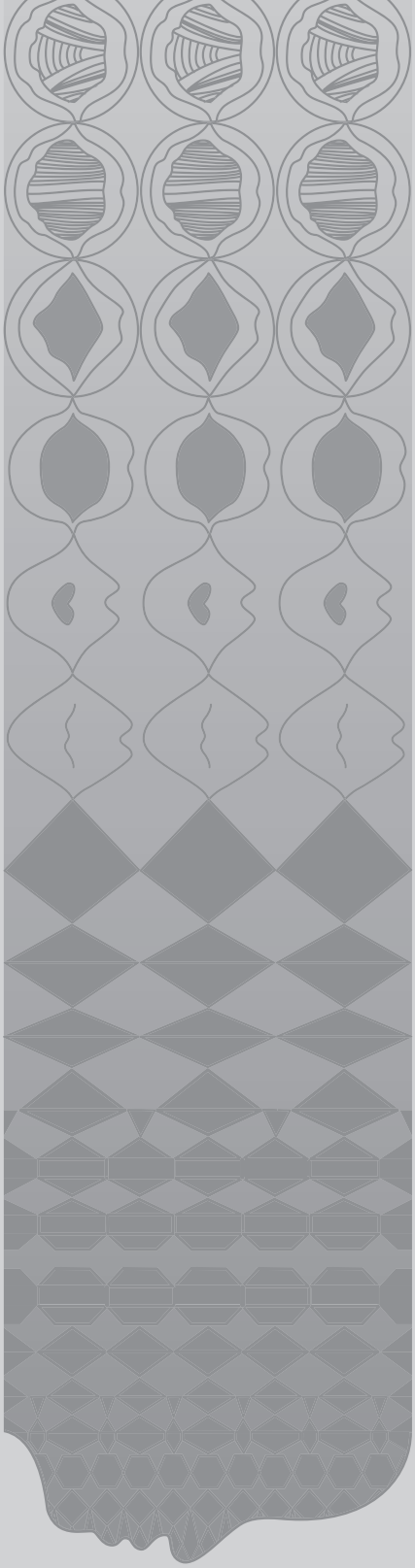


Part V

General discussion and future perspectives



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General discussion

WHY WE STARTED THIS RESEARCH

The **Prologue** of this thesis outlines four fictitious cases of patients with Head and Neck Squamous Cell Carcinoma (HNSCC). Four individuals with very specific characteristics, preferences and goals in life. Despite their differences these patients have similar questions at some point in their disease trajectory: "*What are my chances to survive?*", "*Do I actually have a choice to make?*" and "*How will this impact my future?*"

These questions are characterized by the individual outlook and the same goes for information requirements. One patient is eager to gain as much detailed information as possible. Another patient just wants to hear his doctor saying "*it's okay, people get through this*". Coping and communication styles differ as much as personality styles. There is no 'one-size-fits-all solution' regarding patient counselling and decision making. Physicians require good communication skills to understand the personalities of these patients and assess their needs accordingly. To establish good communication, a relationship of mutual trust between physician and patient is crucial. In the last decade, the classical model of paternalism has been shifting towards a model based on patient autonomy.[1,2] Simultaneously, societal developments are shifting towards a more individual point of view. Integrating personalized counselling and enabling shared decision making in HNSCC care therefore is vital.

This thesis provides steppingstones for the introduction and implementation of personalized counselling and shared decision making in head and neck oncology, elaborating on previous research done by our department on doctor-patient communication and prognostic modelling.

THE QUESTIONS ADDRESSED IN THIS THESIS

The research as presented in this thesis focuses on personalized counselling, improving prognostic models and implementing these models in clinical practice with one core aim: shared decision making. All these topics are addressed in the three parts of this thesis.

Part I: Patient preferences and current counselling

What are patient preferences on decision making and receiving prognostic information and how is patient counselling on these topics currently done?

Part II: Tools for personalized counselling: development of prognostic models

Disclosure of relevant decision making information to patients seems important, but how should physicians communicate prognostic information? And how should physicians use and interpret prognostic models for this purpose? Are modifications required to the existing prognostic models, such as adding biomarkers? And what consequences do the use of clinical prediction models for clinical practice have?

Part III: Tools for shared decision making: development of a value based clinical support system

Not merely patient preferences and individual factors determine the right treatment of head and neck cancer patients, nor sharing prognostic information. Especially in the years following treatment, when HNSCC patients become HNSCC survivors, it is important to include patients' preferences and priorities. How can we gather this information by structurally screening different aspects of psychosocial well-being? And would including this information into a clinical support system improve the quality of care and patient autonomy?

KEY LEARNINGS

The above mentioned themes and questions are addressed in **Chapters 2- 9** and summarized in **Chapter 10**. The three central themes of this thesis will be discussed on a scientific level ("*what have we learned and added to the literature?"),* and a more practical level ("*what may change in clinical practice due to this research?*"). The strengths and limitations of the research presented in this thesis are evaluated, leading to plans and recommendations for (future) research projects.

WHAT WE HAVE LEARNED AND ADDED TO THE LITERATURE

Part I: Patient preferences and current counselling

- Standard curative treatment is not received by 17% of patients with a primary HNSCC: either due to a nonstandard treatment advice, or due to the patient choosing an alternative. (**Chapter 2**)
- Patients declining standard treatment have a lower overall 3-year survival (34 % vs. 70 %). (**Chapter 2**)
- Patients living alone, patients with a lot of comorbidity or high tumor stage, females and older patients are more likely to receive nonstandard treatment for curative HNSCC. (**Chapter 2**)
- Physicians focus more on physical aspects (essentially comorbidity and advanced disease), and patients base their decision more on quality of life and emotional or psychological reasons. (**Chapter 2**)
- In treatment-decision consultations physicians provide some prognostic information. Only 5.9% of the provided prognostic information is quantitative (e.g. numerical probability estimate such as percentages or years). (**Chapter 3**)
- In 94.1% prognostic information is provided qualitatively (e.g. through the use of words such as 'most likely' or 'highly improbable), using six identified approaches. (**Chapter 3**)
- Head and neck surgeons affect patients' perception of prognostic content with their communication styles (**Chapter 3**)

These studies add to an underexposed subject of research on patient preferences and prognostic communication in head and neck oncologic patients. We have learned that 17% of patients with initially curable HNSCC refrain from curative treatment. In 7% of cases the choice for nonstandard treatment is based on explicit patient wishes. We found that overall survival is worse in patients who do not receive treatment according to guidelines. The survival of patients who refused standard treatment options is significantly worse in comparison with patients for whom physicians make a nonstandard treatment decision. Therefore, we raise the question: should these patients be counselled differently to stimulate compliance to guidelines with the aim of improving overall survival? Or, are patients who decline standard treatment options in fact patients who make an informed and deliberate choice based on their preferences? Future research should elicit whether quality of life is improved when patients make more informed choices, independent of their physicians' advice.

Earlier literature showed that providing sufficient quantitative information on life-expectancy allows patients to make fully informed decisions.[3,4] Our study provided a unique insight behind closed doors in otherwise private consultations between HNSCC surgeons and their patients. We learned that currently just 5.9% of the provided prognostic information in treatment-decision consultations is provided quantitatively (i.e. numbers). In the majority of cases (94.1%) a variety of qualitative methods is used, such as positive and negative framing (46%): with positive framing patients might interpret the information unrealistically optimistic and with negative framing patients might believe that they will be the ones with the bad outcome. Physicians can affect patients' perception of prognostic content with their communication styles. Given the discrepancy in survival between patient who do and don't adhere to treatment guidelines, it is important to make sure the patient understands the complexity of their medical problem and their prognosis. However, there is limited data on effective teaching methods to promote long-term change of communication skills. Research should focus on whether patient feedback is an essential element in clinical quality and how best to incorporate decision aids into conversations.

Part II: Tools for personalized counselling: development of prognostic models

The use of prognostic models

- Anemia and BMI are predictors of overall survival for LSCC, independent of other known predictors of overall survival. (**Chapter 4**)
- Adding anemia and BMI to an existing prognostic model for LSCC provides better prediction of overall survival (C-statistic 0.79). (**Chapter 4**)
- An updated prognostic model, including 8th TNM classification and a separate variable for HPV (PCR DNA or p16), performs reasonably good and very similar to the original model (C-statistic 0.70). (**Chapter 5**)
- HNSCC patients find it important to receive prognostic information. A tailor-made approach is necessary to provide this in a customized manner. (**Chapter 8**)
- Patients often do not understand the concept of "5-year survival rate". (**Chapter 8**)
- In most cases patients want to receive prognostic information from their doctor in general, qualitative terms, like *'your cancer can be treated…'* (**Chapter 8**)
- HNSCC patients prefer a pie chart to visualize prognosis: it is clear at a glance and less confronting. (**Chapter 8**)

In **Chapters 4 and 5** new prognostic factors for predicting overall survival in HNSCC are introduced: anemia, BMI and HPV positivity. New (more recent) patient data was used, contributing to better and more up-to-date predictions. Nonetheless, prognosis and

prognostic modelling remains a dynamic concept: over time, new prognostic factors will be explored, and improved treatment options might change outcomes.

In **Chapter 5**, a new statistical method is introduced into our prognostic modelling research line: Decision Curve Analysis (DCA). More and more studies on the development and validation of a predictive model are using DCA.[5] However, this type of study is at risk for overfit, as is ours. The cross validation method corrects for an overoptimistic evaluation of our model's performance and DCA. Typically, DCA is used to help with decisions regarding treatment or diagnostics, for example in prostate cancer.[6] In these decisional conflicts, there is a clear choice between 'treatment or no treatment' and there is a clearly defined treatment threshold. The use of DCA as we propose is not that intuitive. Interpretation of our decision curve depends on comparing the net benefit of the different models with that of a strategy of 'treat all' and 'treat none'. 'Treating' in this setting means any treatment decision that could be made for OPSCC patients dependent on expected survival rate, such as adjuvant chemotherapy or dose-escalating radiotherapy. The strategy with the highest net benefit at a particular point is optimal, irrespective of the size of the difference. This method of interpretation leaves a great deal of risk assessment to the user of the prognostic model.

To our knowledge, **Chapter 8** is the first study examining HNC patients' preferences to disclose prognostic information, and utilize a prognostic model during treatment decision consultations. The results highlight the importance of exploring patients' thoughts and needs, in order to enhance patient centered care. While disclosing prognostic information in general terms like ''*the cancer is curable*" gives sufficient reassurance to most patients, some patients require numerical information like *OncologIQ*'s prognostic estimates as well. A tailor-made approach is necessary to provide prognostic information in a patient-centered way.

In line with available literature, we found that patients with HPV positive disease have a favorable prognosis over patients with HPV negative disease. Furthermore, lower recurrence rates and an higher sensitivity to chemotherapy and radiotherapy are reported.[7] HPV positive OPSCC is primarily associated with the tonsil or base of tongue, where the crypts and the reticulated epithelium play key roles in the immune responses.[8] This indicates that the immune system might play an important role in HPV related OPSCC. Given these phenomena, the question rises whether these HPV positive patients should be treated the same way as HPV negative patients.

The shift in treatment of HPV related OPSCC

- HPV, either detected by p16 or PCR DNA, is an independent prognostic factor for overall survival in OPSCC patients. (**Chapter 5**)
- HPV-related OPSCC are associated with complete nodal response after 46 Gy of IMRT. (**Chapter 6**)
- Patients with small OPSCC and full regional control (pN0) after IMRT and subsequent neck dissection show a significantly better overall survival, but smoking negatively interacts with this effect. (**Chapter 6**)
- The improved prognosis of HPV-positive OPSCC is correlated with higher numbers of tumor-infiltrating T cells, more active Th17 cells and lower numbers of IL-17+ non-T cells. (**Chapter 7**)

Firstly, there is a need for more specific, individualized information for both patients and physicians, as provided by the prognostic model developed in **Chapter 5**. Adding HPV as a prognostic factor to our model is of incremental value, as is shown by decision curve analysis (DCA). DCA - a statistical method for summarization of model performance in supporting decision making - showed an improved clinical utility in comparison with the original model. This model is cross-validated in 3 heterogenic cohorts, and as such applicable for both high and low HPV areas (Europe and the North America).

Secondly, there is a need for individualized treatment protocols, which is reflected by the ongoing studies on de-escalation therapies and other treatment modifications for patients with HPV positive OPSCC.[9] The results of **Chapters 6 and 7** contribute to the knowledge on this topic. **Chapter 6** suggest that a number of OPSCC patients do not necessarily need the current gold standard of 70 Gy of radiotherapy to obtain locoregional control of their disease. The results of **Chapter 7** indicate the possibility of immunotherapy for HPV positive OPSCC, given de relationship between improved prognosis and higher numbers of tumor-infiltrating T cells. This has been confirmed in a large systematic review.[10] However, in order to develop efficient immunotherapy for clinical treatment – that can both inhibit the repression role and also enhance the promotion of the immune system – requires a far more detailed understanding of the immune microenvironment of HNSCC.[11]

Part III: Tools for shared decision making: development of a value based clinical support system

- Integration of *Healthcare Monitor* into routine care for HNSCC patients has increased patient centred care, improved doctor-patient communication, enabled a holistic approach, and enhanced patient empowerment. (**Chapter 9**)
- *Healthcare Monitor* facilitates screening of symptoms and enhances research projects and benchmarking. (**Chapter 9**)

Predictive, personalized, preventive, and participatory medicine - so-called P4 medicine - has been proclaimed as a way to transform cancer care by optimizing the wellness of patients with cancer.[12] This approach requires both the engagement of patients in self-management and of physicians in providing targeted interventions on the basis of access to personalized information about patients' needs. Routine screening of symptoms is a means of providing such information. Developing a tool which integrates PROMs into routine care is difficult.[13] Within the field of head and neck cancer care, there is a lot of research on the routine use of ePROs in clinical practice in order to improve patients' quality of life and enhance doctor-patient communication.[14-16] Nonetheless, monitoring of ePROs alone does not improve patients' outcomes. Providing individual feedback to the patient can help to discuss the need for supportive care and particularly to have a more focused consultation. *Healthcare Monitor* is the first ePRO based clinical support system for HNSCC patients in the Netherlands to monitor ePROs during all follow-up visits and to enable patients to get direct and personalized feedback from their treating physician.

WHAT WE HAVE LEARNED: CHANGES IN (FUTURE) CLINICAL PRACTICE

Part I: Patient preferences and current counselling

- Awareness of a subset of patients who incline towards nonstandard treatment for curative HNSCC is raised. (**Chapter 2**)
- A guideline for sharing prognostic information in HNSCC practice is available. These suggested steps are meant as a stimulus to encourage sharing prognostic communication in a clinical setting. (**Chapter 3**)

It is important for a physician to be conscious of frail patients. Female patients, elderly and patients with a single marital status are more likely to receive non-standard treatment for curative HNSCC and prefer dedicated counselling with a focus on tailor-made prognostic information. Physicians should explore patient preferences on receiving prognostic information and assure there is accurate, personal information on the prognosis of the individual patient. It is important to recognize prognostic communication as a process and to avoid the use of a directive communication style while giving a realistic perspective of prognosis.

Available literature and our research indicate patients need to be well-informed to be actively involved in treatment decisions.[17-19] A treatment decision should reflect patients' preferences with full knowledge of the risks, benefits and consequences of all alternatives. However, patients often want a treatment recommendation from their physician.[20] The way physicians provide information on prognosis and quality of life is therefore of vital importance.[21] Communication and personalized counselling is key, given that the shared decision making process can be confusing. Physicians need to remember that patients need to make these decisions when they are sick, vulnerable, dependent and reflection time is limited.[22]

Part II: Tools for personalized counselling: development of prognostic models

The use of prognostic models

- Two accurate and up to date prognostic models for laryngeal (LSCC) and oropharyngeal cancer (OPSCC), including new prognostic markers, are developed and validated and available for clinical practice. (**Chapter 4 and 5**)
- The prognostic information from these models is best conveyed to patients using a pie chart. (**Chapter 8**)

Most prognostic models are not used on a large-scale and certainly not in daily clinical practice. This could be partly explained by the quality of the published models and partly by the unfamiliarity of physicians to use prognostic models in their consultations with patients. The two prognostic models presented in this research form a (validated) update of the already existing model (*OncologIQ*[23]), in order to approximate the 'perfect' estimation of prognosis. By default, prognostic models will be 'imperfect'. As such, patients and physicians need to understand probability and uncertainty. After all, prognostic models predict the likelihood that a population of similar patients will survive a defined period of time, but gives no certainty to the individual patient. Proper interpretation and communication of the prognostic information is essential for the clinical applicability of prognostic models. Our study among focus groups showed that physicians should assess whether a patient wants to receive individualized prognostic information. The suggestions made to improve prognostic counselling are very straightforward: assess if patients want to receive prognostic information and if so, keep it simple. The results of **Chapter 8** will first be used to improve the graphical visualization of *OncologIQ*.

The prognostic impact of HPV related OPSCC

- Decision curve analysis (DCA) shows that models including HPV performed better in terms of supporting decision making, than models with only the 8th TNM classification. (**Chapter 5**)
- HPV-related OPSCC are associated with complete nodal response after 46 Gy of IMRT and patients with full regional control (pN0) after IMRT and subsequent neck dissection show a significantly better overall survival. (**Chapter 6**)
- The improved prognosis of HPV-positive OPSCC is correlated with higher numbers of tumor-infiltrating T cells, more active Th17 cells and lower numbers of IL-17+ non-T cells. (**Chapter 7**)

The updated prognostic model for OPSCC patients (**Chapter 5**) and the evaluation of our 'Rotterdam protocol' (**Chapter 6**) contributes to an increased attention towards HPV positive OPSCC patients in our clinical practice. Given the results of our own research, the recently updated 8th AJCC TNM classification and the extensive reviews and de-escalation studies in literature, it will not be long before a change of treatment protocols for HPV positive OPSCC patients will become active. In addition, our center is embarking on a prospective study using functional MRI to assess the neck prior to neck dissection for OPSCC patients.

Part III: Tools for shared decision making: development of a value based clinical support system

- Integration of *Healthcare Monitor* into routine care for HNSCC patients has increased patient centred care, improved doctor-patient communication, enabled a holistic approach, and enhanced patient empowerment. (**Chapter 9**)
- The implementation of HM included significant challenges, but also had demonstrated to be a worthwhile investment. (**Chapter 9**)

We learned about patient preferences regarding prognosis, how to calculate and interpret individual prognosis in HNSCC patients, and how to communicate this message. Our ePRO based clinical support system '*Healthcare Monitor'* forms the foundation of a real paradigm shift in HNSCC care. The results from our evaluation indicate that Healthcare Monitor anticipates in the latent needs of patients. The ePRO questions stimulate patients to think about issues in relation to their disease they may never have thought about before. As a result, patients get better awareness of symptoms and an understanding of the expected course of their disease, leading to patient empowerment. Discussing the results contribute to a more focused conversation and eventually a better way of coping with their disease. The longitudinal ePRO data - collected from a consecutive and heterogeneous group of patients without hardly any exclusion criteria - enhances benchmarking on an individual level and in larger studies, such as national cancer registries. Physicians have real-time access to the graphically displayed results and can visually review longitudinal ePRO reports. The course of physical and psychosocial symptoms can be identified and patients individual results can be compared with their peer group, enhancing direct individual feedback to the patient on their need for support.

WHAT IS LACKING IN THIS RESEARCH

This thesis covers a range of topics through quantitative and qualitative research methods on the themes of personalized counselling and shared decision making in HNSCC care. Large retrospective cohort studies, several qualitative research methods, immunofluorescent and histopathological techniques as well as extensive statistical methods are included.

This thesis lacks a prospective study focusing on the actual use of prognostic models in clinical practice. Given the results of our research (**Chapter 2, 3 and 8**), we advocate individualized counselling of patients regarding prognosis, quality of life and patient wishes and expectations to achieve shared decision making in treatment for HNSCC. In the decision making process, it is important to actively involve the patient and to make sure the

patient understands the complexity of the medical problem and the prognosis. Prognostic models based on individual patient characteristics enhance our insight in prognosis of each individual patient. We believe that these models can therefore be used in counselling patients to improve informed decision making. Does our hypothesis that individualized counselling of patients based on a prognostic model improves decision making indeed hold true? This hypothesis is best tested in a prospective study.

In **Chapters 4 and 5**, new prognostic variables were introduced. Despite the improvement of prognostic estimates, these models lack three important aspects of disease: quality of life, treatment morbidity and the dynamic aspects of prognosis. Physicians and patients are not only interested in prognosis in terms of 'life -expectancy' and in quality of life and short- and long-term morbidity following treatment. This is further indicated in **Chapters 2, 3, 6 and 8**. An update of the existing models including data on quality of life and treatment related morbidity is of high importance. In order to make well-founded decisions, information on the evolution of quality of life and treatment related morbidity during time, balanced against survival rates, is necessary. Information on the evolution of prognosis during time is important in order to weigh quality of life against survival rates. Van der Schroeff already published on the dynamic aspects of prognosis.[24] All prognostic estimates change when during follow-up a patient develops a tumor recurrence or metastasis. But when the patient remains tumor-free the prognosis will change as well: the prognosis of cancer patients who for instance survive the first two years improves. This is caused by the fact that they survived the first critical period.

The very promising results of **Chapter 9** are based on a single-center experience and the generalizability of our results is questionable. Successful implementation of a value based clinical support system is easier said than done. The implementation consumes time and energy as the organization continues its other key activities. Many organizational, technical and workplace adjustments will be required, and the close cooperation with health care providers and technology providers is crucial. Common ground needs to be defined for the implementation of these new working methods. Besides the investment in organizational changes, the implementation of a value based clinical support system requires a financial investment. A cost-effectiveness study, preferably in a multi-center design, is necessary.

PLANS AND RECOMMENDATIONS

In view of the conclusions, strengths and limitations of the research as presented in this thesis, new research initiatives are proposed or have already started.

ProVo study

In the section 'what is lacking in this research', we proposed a prospective study to test the incremental value of the use of prognostic models in clinical practice. In 2014 we have initiated a prospective trial with sequential cohorts (*ProVo* study – *'Prognostisch Voorlichten'*) in our clinic to measure the effect of prognostic counselling using models on treatment outcome, quality of life, patient satisfaction and decisional conflict. Within this study protocol, we investigate decisional conflict, treatment choices and quality of life in patients with HNSCC after individualized prognostic counselling, in comparison with the current prognostic counselling. Besides the effect of prognostic counselling on decisional conflict in HNSCC patients, the effect of the use of *OncologIQ* in our multidisciplinary tumor board meetings will be investigated by evaluating treatment proposals and healthcare providers therapeutic confidence scores with and without the use of the model. The results of the first cohort (current counselling) are currently being analyzed. The second cohort (counselling using *OncologIQ* prognostic model) has started in the fall of 2019. The results of this study may help to improve a shared (or informed decision) making process, empower patients and lead to a tailor-made proposal for each patient.

Update of OncologIQ

How to proceed with prognostic research when the *ProVo* study is finished? An update of our existing models including data on quality of life and treatment related morbidity is of high importance in order to further personalize counselling on treatment options and survival. The data collected within *Healthcare Monitor* are a great source. Repeated measurement data on QoL, psychosocial and physical symptoms from a consecutive cohort will make valid and reliable predictions of QoL and morbidity in relation to survival possible.

Besides quality of life, time is an important factor that needs to be included further in our prognostic models. Prognosis certainly is a dynamic concept.[24] Therefore a dynamic prognostic model including continuous updates on prognostic markers, quality of life, morbidity and survival time would be of great value. Besides a very complete database, automatization of the survival analysis itself and periodic feedback on the model performance is necessary.

Rotterdam Oncological Documentation

Such a vessel seems far on the horizon. When accurate, complete and up-to-date data on survival, morbidity and quality of life is available this will mean a giant step forward. Our original models [23-25] are all build using data from *ONCDOC*. The data in *ONCDOC* were structurally collected and safeguarded by dedicated oncological data managers at LUMC, who also monitored events during follow-up. Elaborating on our experience

with *ONCDOC,* we set up a similar database in 2015: *RONCDOC* (Rotterdam Oncological Documentation). This is a database that compromises all HNSCC patients treated in the Erasmus MC Cancer Institute since 1995. Patient, tumor and therapy data are acquired from the Netherlands Comprehensive Cancer Organization and merged with data from the electronic patient files (EPF). Data are extensively collected on (among others) cause of death, comorbidity, prior malignancies, tobacco and alcohol consumption, BMI, clinical and histopathological tumor stage and type and intent of treatment (curative/palliative). Dedicated medical students check the data on validity and discuss them in the research staff if there is any doubt. Hereafter, data are checked again using a cleaning algorithm. This leads to a high degree of classification accuracy and a low risk of bias. Besides these clinical variables, there is also a biobank with TMAs (Tissue Micro Arrays) connected to RONCDOC. With TMAs included in RONCDOC it is possible to easily add molecular and other biomarkers to our prognostic models. Currently, we are providing steps to connect the currently retrospective RONCDOC database with the prospective Healthcare Monitor data and an automated input of clinical data from the EPF (using data mining) and the Netherlands Comprehensive Cancer Organization.

Expansion of Healthcare Monitor

We have plans to expand on *Healthcare Monitor:*

1. We already made the first steps to set up an HNSCC patient panel in cooperation with the Dutch national head and neck cancer patient organization. This panel will considerate new PROMs, PREMs and other extensions of the *Healthcare Monitor*. This is very important in order to really reflect patient's desires and preferences.

2. As diagnosis and treatment of HNSCC requires a multidisciplinary team, we want to extend questionnaires for specific health care providers, e.g. late toxicity after radiotherapy and esthetic consequences after flap reconstruction.

3. We want to explore Item Response Theory (IRT) and Computer Adaptive Testing (CAT) methods. PROMs are typically static, standardized questionnaires. To achieve precise measurements for all patients, traditional PROMs often require a substantial number of items. These questionnaires are often perceived as too long. Patients need to complete the same questions at all times, but not all questions are relevant to all patients (or not in all cases).[26] Furthermore, scores are difficult to interpret because of the ordinal nature of most scales, and scores may also be incomparable across different PROMs as each PROM has its own scale. Item banks, based on IRT methods, preferably used as a CAT, propose a solution. During a CAT assessment, item selection is done by the computer, based on answers to previous questions. Patients will get more relevant questions and

will need to complete less questions.[27] CAT has several advantages including reduced patient burden and increased question relevance to individual patients. One of the major advantages of CAT is that the content of questionnaires can be adapted to the individual patient without compromising the comparability of scores across patients, based on IRT.[28] To develop an item bank, large datasets and multiple analyses (Differential Item Functioning analyses) are needed to check if the item parameters are consistent across subgroups and populations. Although CAT has several advantages, there are also some disadvantages. For patients, it might not be possible to return to questions they already filled in, as the CAT has since adapted and it cannot unadapt. For clinicians and researchers, it might be difficult to compare longitudinal results within one patient or patient groups when a CAT method is used.

4. We wonder as well if *Healthcare Monitor* can have direct influence on health care costs. One can imagine that when more symptoms (for example psycho-social) are recognized by the *Healthcare Monitor*, this will lead to more diagnostics or involvement of other health care providers (e.g. psychiatrist), and therefore probably to higher costs. On the other hand, *Healthcare Monitor* may reduce costs, due to earlier identification of conditions and reduced frequency of regular outpatient clinic visits. A cost effectiveness study or analysis of cost-benefit ratio seems appropriate, especially in the context of value based healthcare. Other studies suggest a direct correlation between improved HRQoL by ePROs and an improved survival.[29] It would be of high interest to analyze this relationship among HNSCC patients.

5. To gain insight in *Healthcare Monitor* results, we are working on a real-time dashboard which graphically displays the results for both physicians and patients. Clear graphics can help to systematically monitor symptoms, and allow clinicians to compare individual patient results: 1) during the course of time, 2) with their peer group and 3) with control groups from literature. In the future, algorithms may predict patient symptoms based on their individual characteristics. Furthermore, a 'continuous improvement dashboard' is being developed to learn from our data and improve our working methods.

6. Finally, we would like to share our learnings on implementing *Healthcare Monitor* care in other head and neck cancer clinics. Our results are based on a single-center experience and the generalizability of our results may be questionable. Therefore, wider dissemination of our value-based healthcare concept is key in improving patient care on a national level and create benchmark possibilities.

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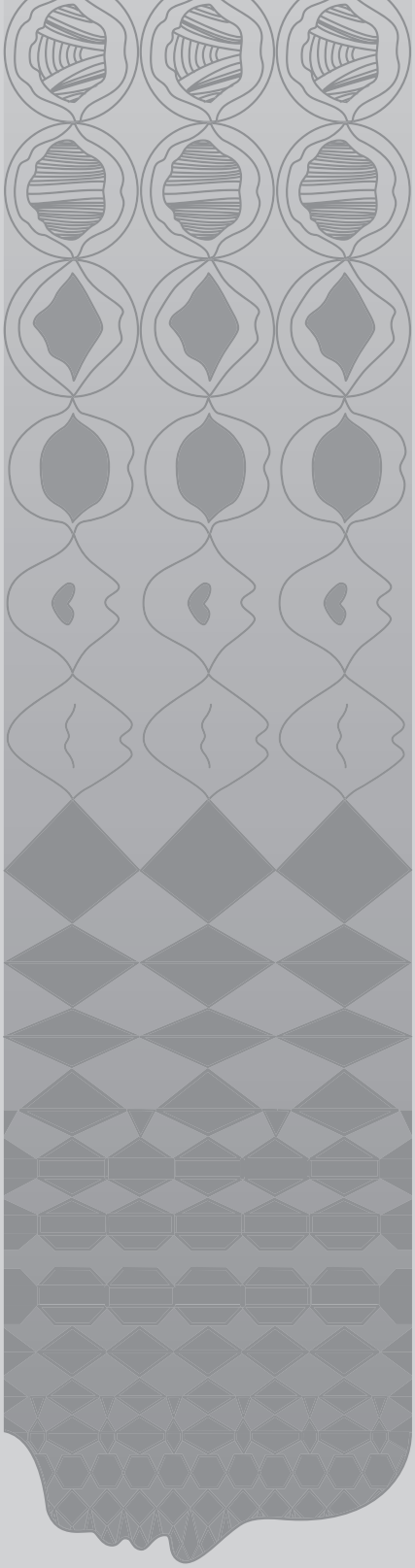

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Epilogue

The results as presented in this thesis contribute to the further implementation of prognostic counselling, shared decision making and value based healthcare in head and neck oncologic clinical practice. Still, there are some hurdles to overcome. In order to truly involve head and neck cancer patients in treatment decisions and to empower them in their own care-process, a paradigm shift seems necessary. This transition is not only ongoing in head and neck cancer care, but in general healthcare as well. In this final chapter, we will contemplate on the future perspectives of patient centered care in head and neck cancer care and general healthcare.

OUTLINE OF A FUTURE CASE: PATIENT WITH HNSCC IN 2040

Mrs. E., a 47 year old female with cT2N2M0 HPV related cancer of the left tonsil. She lives together with her husband and three children aged 8, 11 and 13 years. She works as a data scientist at a large consultancy agency. When she first experience symptoms (pain in her left throat and a lump in her neck), she searches on '*IBM Watson for patients*' the chances of having a serious disease. She makes an appointment with her general practitioner (GP), and fills out some personalized questions on the health-app on her smartphone. Her GP is also worried, given the answers to the Computer Adaptive Testing (CAT) questionnaire and her findings at physical examination. She enters Mrs. E.'s data into a webportal, and a diagnostic protocol is set in motion.

Mrs. E. is referred to a dedicated head and neck cancer team, with surgeons, radiotherapists, oncologists, paramedics and data scientists all working closely together. During the first appointment speech recognition software is used to register all necessary medical and psychosocial details of the conversation between Mrs. E. and her doctor. The data are used in an algorithm that predicts the best diagnostic-, treatment- and communication strategy. Also, a personalized prehabilitation program enables her and her family to prepare for treatment by exercise, nutrition and psychological interventions.

After diagnostic imaging and some blood tests, Mrs. E. is diagnosed with regionally advanced HPV related oropharyngeal cancer. Mrs. E. has several appointments with the team members to discuss diagnosis, prognosis and treatment options. Her immune response and genetic profile as well as the molecular characteristics of the tumor and clinical characteristics of Mrs. E are entered into *OncologIQ*. This dynamic prognostic model is continuously updated with data from national cancer registries, *RONCDOC* and from *Healthcare*

Monitor (which is incorporated in the *National Head and Neck Audit*). Costs and benefits of different treatment options are also taken into account in this model. Together with her husband, physicians and a dedicated case manager she chooses the treatment (proton therapy) that best suits her genetic profile and the molecular aspects of the tumor, and adheres best to her preferences regarding survival, quality of life and morbidity of treatment.

The follow-up phase during and after treatment is guided via the e-Health module of *Healthcare Monitor* on her smartphone. Mrs. E. uses wearables for physical self-measurement on a daily basis. If any abnormalities are sensed by the system she also answers personalized questions on her well-being. Mrs. E. may also answer these personalized questions any time she feels insecure or in need of support. The data are sent to the multidisciplinary team. An algorithm – based on tens of thousands of HNSCC patients all over the world – calculates every single day if medical care is needed. If necessary, direct feedback is provided to Mrs. E. herself and the most appropriate healthcare provider for the specific condition on that particular day. If needed, a large network of patients is available for online peer support.

HOW DO WE BECOME FUTURE-PROOF?

The future case of a Mrs. E. describes many technical and data-driven innovations. Several techniques will continue to make their way into medicine in the coming years.

Machine learning

Machine learning (ML) describes a subset of artificial intelligence (AI) that enables computers to continuously learn from historical data and make predictions about data using the information learned. Predictions about unknown variables are made, based on past experiences using large sets of data. ML is highly accurate and precise beyond the abilities of standard statistical techniques or human judgement to make predictions about outcomes in medicine.[1] ML has the potential to enable physicians to make actionable decisions based on all digitized health information 'big data'. Due to the vast amount of data, there is a lower risk of having outliers, but the risk of bias and confounding is still relevant.

ML is also known as 'a black box'. The input data can be seen, and the final outcome as analyzed by the algorithm can be seen as well. Traditional statistics still provide measures of effect size of individual variables, such as odds ratios. ML does not generate this kind of measures due to complex non-linear calculations. Therefore, it may be impossible, or at least very difficult for physicians, to interpret how ML actually progresses towards an

outcome.[2] However, whilst an algorithm based on ML is easy to use for physicians, the 'black box' phenomenon might not be an enduring obstacle. Direct and visual attractive implementation of ML algorithms in the electronic health record (EHR) would be very helpful to ease the use. Currently most EHRs contain gigantic amounts of patient data, but the majority of these data is not structured and therefore not directly usable by ML algorithms. A different set up of EHRs is necessary, with special attention being given to privacy of patient information and an efficient information exchange.

It is necessary to think about the ethical and educational consequences of the implementation of ML algorithms in healthcare. When computers predominantly influence clinical decisions, who is responsible when a harmful decision is made? And will this change how medical students are trained, when an algorithm may offer a repertoire of academical expert opinions due to its exposure to rare pathologies? Would the position of the omniscient professor become a thing of the past? Other aspects such as communication training and courses on interpretation and analysis of data will become essential.

Evidence for value based healthcare

New technology, increased patient wishes and changing population demographics all lead to an increased drive to spend more resources on keeping people alive and in good health for as long as possible. To ensure affordability, our attention will be increasingly focused on the value of healthcare. Evidence-based medicine (EBM) forms the basis of value based healthcare (VBHC). It became the dominant medical paradigm after 1990. In EBM, clinical decision making is based on the best available research evidence, instead of physicians' expertise, with the randomized clinical trial (RCT) as gold standard.[3] However, the highest quality evidence is most often based on standardized groups of male, Caucasian adults and doesn't take into account individual patient values. VBHC integrates patient preferences (values) and scientific research into clinical practice by achieving maximum benefit per cost. And by seeing patients as medical consumers who participate in their own decision making process (SDM), patient centered care is made possible. Nevertheless, to be able to achieve the best value for a population, we must ensure that all interferences also have strong evidence of cost-effectiveness. Have available resources been divided fairly and optimally between different conditions? In the debate in general healthcare regarding SDM it is often presumed that SDM is only relevant for well-educated middle class health literate patients and is only a luxury for high income countries.[4] It is important to feed our different experiences with decision making in (generally low-educated and lower class) HNSCC patients into this debate.

From God to guide

The case of Mrs. E. shows that the role of doctors will change.[5] From being a traditional doctor choosing what's best for patients , towards a supporting guide choosing wisely together with patients while interpreting ML algorithm outcomes and asking questions like "*what matters most to you?*". 'Choosing wisely' is key since not everything that is possible (treatment wise), should be done. On the one hand because 'doing good' and 'doing harm' is not a binary decision and individual patients could have their own perspectives on this matter. On the other hand because of the financial aspects of an expanding healthcare system. After all, ML algorithms might help to improve both quality and cost of care by identifying effective and economical treatments. However, ethical issues may arise when an algorithm predicts that a certain treatment would be beneficial for an individual patient, but undesirable from an economic point of view.

While the role of doctors will change in the near future, 'the patient centered approach' will remain. After all, people like to be treated as 'people' instead of 'numbers'. In the current yearning for data-driven technological innovations lurks the danger of losing the real patient-centered approach. Even if algorithms meticulously could predict all individual aspects of diagnosis, treatment and prognosis, a need for personal attention will persist. Not only by helping patients to understand terms like probability or uncertainty of ML predictions, but mostly by offering a listening ear and by ensuring patients that a professional is taking care of them. Also, some patients will need more guidance than others, especially in case of health illiterate or severely ill patients.

The wise patient

Finally, the role of patients will change too. Having access to the right information, at the right time, delivered in the right way, leads to an increase in patients' abilities to take a more active role in their decision making and healthcare in general. This patient empowerment is really achieved when patients realize they can improve their medical outcomes by taking responsibility for their own healthcare decisions in partnership with their healthcare providers. This responsibility goes beyond taking care of the body by lifestyle changes or by adhering to decisions. It also means to be a smart healthcare consumer with an eye for both the individual as well as the altruistic perspective.

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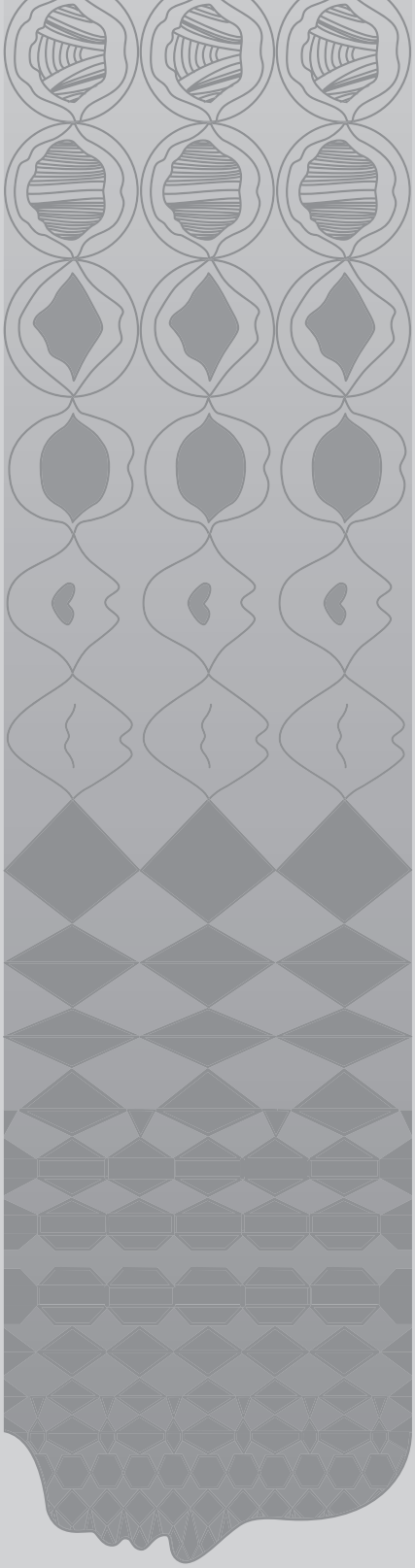

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Summary

English summary

Nederlandse samenvatting

ENGLISH SUMMARY

PART I: INTRODUCTION

The research in this thesis focused on personalized counselling, improving prognostic models and implementing these models in clinical practice with one core aim: shared decision making. All these topics are addressed in the five parts of this thesis.

In the **Prologue** four fictitious patients with Head and Neck Squamous Cell Carcinoma (HNSCC) are presented, providing perspective why we started this research. All four individuals have their specific characteristics, preferences and goals in life. Despite their differences these patients have similar questions at some point: "*What are my chances to survive?*", "*Do I actually have a choice to make?*" and "*How will this impact my future?*" **Chapter 1** provides a general introduction to this dissertation.

PART II: PATIENT PREFERENCES AND CURRENT COUNSELLING

The purpose of **Part II** of this thesis was to contribute to a better understanding of HNSCC patient preferences and better doctor-patient communication regarding prognosis and decision making. In **Chapter 2 and 3**, the current situation of treatment decision making and prognostic counselling was explored. Given the high morbidity of treatment modalities for HNSCC, patients may decline standard, curative treatment. In addition, doctors may propose alternative, nonstandard treatments.

In **Chapter 2** factors associated with noncompliance in head and neck cancer treatment for both patients and physicians were explored. Also, the influence of patient compliance on prognosis was assessed. In our retrospective cohort of n=829 patients (diagnosed between 2010-2012) 17% of all patients with a primary HNSCC did not receive standard curative treatment. This was due to a nonstandard treatment advice, or because the patients' wish for an alternative. The multidisciplinary tumor board (MDT) advised in 10% of all patients nonstandard treatment in case of a primary and curable HNSCC. Seven percent of all patients decided themselves to decline standard curative treatment advice. A proportion of 4% wished for a less extensive treatment and 3% refused any therapy. Patients who are more likely to receive nonstandard treatment for curative HNSCC had the following characteristics: living alone, extensive comorbidity, high tumor stage, females and elderly (>65 years). Reflecting on the various reasons mentioned for choosing a nonstandard treatment for curative HNSCC, there is a difference in argumentation between

patients and physicians. Physicians focused more on physical aspects, as comorbidity and advanced disease, whereas patients focused on quality of life and emotional or psychological reasons. Patients declining standard treatment had a lower overall 3-year survival (34% vs. 70%).

Chapter 3 describes whether and how information on life expectancy is included in communication between physicians and HNSCC patients in different phases of disease. We performed a descriptive, qualitative study in which n=23 audiotaped physician-patient conversations concerning prognosis, curative and palliative treatment options were verbatim transcribed and systematically analyzed. A distinction was made between prognostic information that was provided a) quantitatively: by giving numerical probability estimates, such as percentages or years or b) qualitatively: through the use of words such as '*most likely*' or '*highly improbable*'. In all consultations, physicians provided some prognostic information. Only in 5.9% of the provided prognostic information, a quantitative method was used. In 94.1% prognostic information was provided qualitatively, using six identified approaches. The exclusion of specific prognostic information resulted in uncertainty about the essence of the information provided. Head and neck surgeons possibly affect patients' perception of prognostic content with two identified communication styles: directive (more physician-centered) and affective (more patient-centered). Based on the results and discussion of the topic, we prepared first steps for a guideline for sharing prognostic information in HNSCC practice.

The results presented in this chapter, leads us to the next part of this thesis. Accurate and individual prognostic information is necessary to effectively communicate prognosis.

PART III: TOOLS FOR PERSONALIZED COUNSELLING: DEVELOPMENT OF PROGNOSTIC MODELS

The potential of prognostic models regarding prognostic counselling and treatment decisions were explored in **Part III**, building further on earlier research done by our research group. Two different clinical prediction models for laryngeal and oropharyngeal cancer, including new prognostic markers, were developed (**Chapter 4 and 5)**.

Chapter 4 focusses on the development of a prognostic model for overall survival for patients with laryngeal squamous cell carcinoma (LSCC) and evaluates the impact of anemia and body mass index (BMI) on survival. A retrospective cohort study was performed including all consecutive patients with LSCC diagnosed and treated between 2006-2013. Patient- and tumor-specific data of n=788 patients were collected from the Netherlands

Comprehensive Cancer Organization and supplemented with data from patient records in the Erasmus MC. We demonstrated that anemia (HR 1.41) and low BMI (HR 0.97) both have a significant impact on overall survival independently of the presence of comorbidity as measured by the ACE-27 index. With addition of anemia and BMI to our existing prognostic model the performance of the prognostic model (C-statistic) improved from 0.77 (95% CI: 0.74 – 0.79) to 0.79 (95% CI: 0.77 - 0.82).

Chapter 5 describes the update, improvement and validation of an existing prognostic model for oropharyngeal squamous cell carcinoma (OPSCC) patients by incorporating the newly published UICC/AJCC 8th TNM staging system (cN status), and both p16 and HPV-DNA status. HPV-related HNSCC is a distinct entity within HNSCC. Patients with HPV-related OPSCC have better loco-regional control and superior 5-year survival rates after treatment. Three independent multi-institutional cohorts with OPSCC patients in Western Europe and the USA (period 1984 – 2011, n=1339) were used in an internal-external cross validation design. In all cohorts HPV, either detected by p16 or PCR DNA, was an independent prognostic factor for overall survival in OPSCC patients. The 5-year OS estimates were 70.7% in the HPV positive group and 38.7% in the HPV negative group. The updated prognostic model, including 8th TNM classification and a separate variable for HPV (PCR DNA or p16), performs reasonably good and very similar to the original model in terms of calibration and discrimination with an optimism-corrected Harrell's Concordance Index of 0.70. Decision curve analysis (DCA) however showed an improved clinical utility in comparison with the original model. Models with a variable for HPV (either p16 or HPV DNA) performed better in terms of supporting decision making, than models with only addition of the 8th TNM classification. This statistical method for summarization of model performance in supporting decision making is very interesting given the ongoing studies on treatment modifications (e.g. de-escalation therapies) for patients with HPV positive OPSCC.

This chapter showed us that patients with HPV positive disease have a favorable prognosis over patients with HPV negative disease. Given this phenomenon, the question rises whether these HPV positive patients should be treated the same way as HPV negative patients. The potential effect of this new prognostic factor on treatment outcomes is addressed in **chapter 6 and 7**.

In **Chapter 6** we analyzed the effect of treatment according to 'the Rotterdam protocol' on nodal response, recurrent disease and survival in patients with HPV associated T1-2 node positive OPSCC. This study included n=77 patients with T1-2 OPSCC with nodal disease, treated between 2000-2012. Patients were treated according to 'the Rotterdam protocol': 46 Gy of intensity modulated radiotherapy (IMRT) followed by a local boost

using cyberknife or brachytherapy (22 Gy) and neck dissection. The presence of HPV was determined by p16 INK4A immunostaining. Outcomes were the extent of nodal response, disease free survival and overall survival. Nodal stage was determined following 7th and 8th AJCC/UICC classification. 68.4% of patients had p16 positive disease. 35.4% of all patients achieved complete nodal response (pN0) after 46 Gy of IMRT. The nodal response (partial or complete) was significantly associated with HPV status (p=0.002). Complete nodal response led to 100% overall survival in p16-positive OPSCC. HPV-related OPSCC are thus associated with complete nodal response after 46 Gy of IMRT. Patients with full regional control (pN0) after IMRT and subsequent neck dissection showed a significantly better overall survival, but smoking negatively interacts with this effect.

Chapter 7 explores the role of the immune response, and especially the role of T cells, in the beneficial prognostic status of HPV positive OPSCC patients. Patients with HPV-positive OPSCC have a better prognosis than patients with non-HPV-induced OPSCC. The role of the immune response in this phenomenon is yet unclear. We studied the number of T cells, regulatory T cells (Tregs), T helper 17 (Th17) cells and IL-17+ non-T cells (mainly granulocytes) in matched HPV-positive and HPV-negative OPSCC cases (n=162). Furthermore, the production of IFN-γ and IL-17 by tumor-infiltrating T cells was analyzed. The number of tumor-infiltrating T cells and Tregs was higher in HPV-positive than HPV-negative OPSCC ($p < 0.0001$). In contrast, HPV-negative OPSCC contained significantly higher numbers of IL-17+ non-T cells ($p < 0.0001$). Although a high number of intratumoral T cells showed a trend toward improved survival of all OPSCC patients, their prognostic effect in patients with a low number of intra-tumoral IL-17+ non-T cells was significant with regard to disease-specific ($p = 0.033$) and disease-free survival ($p = 0.012$). This suggests that a high frequency of IL-17+ non-T cells was related to a poor immune response, which was further supported by the observation that a high number of T cells was correlated with improved disease-free survival in the HPV-positive OPSCC ($p = 0.008$). In addition, we detected a minor Th17 cell population. However, T cells obtained from HPV-positive OPSCC produced significantly more IL-17 than those from HPV-negative tumors ($p = 0.006$). The improved prognosis of HPV-positive OPSCC is thus correlated with higher numbers of tumor-infiltrating T cells, more active Th17 cells and lower numbers of IL-17+ non-T cells.

After these attempts to produce accurate, individualized and up to date prognostic models, and to connect a new prognostic factor to a potential shift in treatment choices, the next challenge is how to convey prognostic information to patients using prognostic models.

Chapter 8 describes a focus group study that examines HNSCC patients' thoughts, preferences and needs for disclosure of prognostic information. Secondly, patients' views on the

use of the prognostic model *OncologIQ*, during treatment decision consultations were explored. All HNSCC patients find it important to receive prognostic information and a tailor-made approach is necessary. Some patients wanted quantitative information, for example *OncologIQ*'s estimates of '5-year survival rates'. However, patients often misunderstood this concept or confused it with other terms, for example chances of cure. Most patients wanted to receive prognostic information from their doctor in general terms, like *"your cancer can be treated…"* Above all, according to our participants, physicians should be honest while discussing the prognosis, without taking away hope, and tailor prognostic information after exploring patients' needs. Prognosis can be presented in various formats, including verbal explanation and graphs. The HNSCC patients in this research preferred the pie chart to discuss survival rates. The pie chart was a favorite because they thought it was clear at a glance and less confronting. The 100-person diagram was considered too confronting by both patients and caregivers. A clinical practice guideline was developed for sharing individualized prognostic information. This guideline could support the healthcare professional during the treatment decision consultation.

PART IV: TOOLS FOR SHARED DECISION MAKING: DEVELOPMENT OF A VALUE BASED CLINICAL SUPPORT SYSTEM

Following the results of **Parts II and III**, we learned about patient preferences regarding prognosis, calculation and interpretation of individual prognosis, and how to communicate this message. However, taking care of HNSCC patients is not only about including patient preferences and individual factors regarding prognosis and treatment options. It is also important to include patients' preferences and priorities in the years after treatment, when HNSCC patients become HNSCC survivors. Value based healthcare and measurement of electronically patient reported outcomes (ePROs) in particular, is increasingly used to facilitate a systematic approach in the follow-up of cancer patients. In **Part IV** an ePRO based clinical support system "*Health Care Monitor"* is presented which empowers patients and increases patient centered care during follow-up of HNSCC.

Chapter 9 elaborates on *Healthcare Monitor*: an ePRO based clinical support system we developed in 2013 for the longitudinal follow-up of HNSCC patients. In 2019 already more than 1700 HNSCC patients were included. *Healthcare Monitor* measures physical, functional and psychosocial functioning from diagnosis until end of follow-up. Clinicians have real-time access to the results which ensures direct patient feedback. A mixed methods design was used to provide insight into how HNSCC patients experience *Healthcare Monitor* in clinical practice. N=151 patients were invited to anonymously complete a self-developed patient reported experience measurement (PREM) questionnaire on the care

process at our outpatient clinic. Directly after consultation with their clinician, n=15 patients were interviewed on the added value of our ePRO method. Integration of *Healthcare Monitor* into routine care for HNSCC patients has increased patient centred care, improved doctor-patient communication, enabled a holistic approach, and enhanced patient empowerment. *Healthcare Monitor* facilitates screening of symptoms and enhances research projects and benchmarking.

PART V: GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The presented thesis aimed to contribute to the further implementation of prognostic counselling, shared decision making and value based healthcare in head and neck oncologic clinical practice. In **Chapter 10 – General Discussion** lessons learned both on a scientific level ("*what have we learned and added to the literature?"),* and a more practical level ("*what may change in clinical practice due to this research?*") are discussed. Future research should focus on the usage of prognostic models in treatment decisions and the update of prognostic models with quality of life data. Furthermore, studying cost-effectiveness of initiatives such as *Healthcare Monitor* and wider dissemination of the value-based healthcare concept is key in improving patient care on a (inter)national level. In **Chapter 11 – Epilogue** a view on the future is shared: what will patient centered head and neck cancer care and healthcare in general look like in 2040, and how do we become future proof?

NEDERLANDSE SAMENVATTING

DEEL I: INTRODUCTIE

Het onderzoek in dit proefschrift richt zich op het individualiseren van prognostische voorlichting, het verbeteren van prognostische modellen en het implementeren van deze modellen in de klinische praktijk met één duidelijk doel: gedeelde besluitvorming. Deze onderwerpen komen aan bod in de vijf delen van dit proefschrift.

In de **Proloog** worden vier fictieve casus van patiënten met hoofd-hals kanker gepresenteerd. Deze casus illustreren het achtergrond perspectief vanuit de patiënt en vormen de aanleiding voor ons onderzoek. De vier individuen hebben zeer specifieke kenmerken, voorkeuren en doelen in het leven. Ondanks hun verschillen hebben deze patiënten op een bepaald punt in hun ziektetraject vergelijkbare vragen: "*Wat zijn mijn kansen om te overleven?*", "*Heb ik eigenlijk wel een keuze?*" En "*Welke invloed heeft dit op mijn toekomst?*" **Hoofdstuk 1** geeft een algemene inleiding op het proefschrift.

DEEL II: PATIËNTVOORKEUREN EN HUIDIGE VOORLICHTING

Met **deel II** van dit proefschrift wordt bijgedragen aan een beter begrip van de voorkeuren van hoofd-hals kanker patiënten met betrekking tot informatie over prognose en besluitvorming. Ook wordt ingegaan op de communicatie tussen arts en patiënt. In **hoofdstuk 2 en 3** wordt de huidige situatie rondom behandelbeslissingen en prognostisch voorlichten onderzocht. Door de hoge morbiditeit van de verschillende behandelmodaliteiten voor hoofd-hals kanker kan de keuze voor al dan niet behandelen kan lastig zijn. Patiënten kunnen de volgens het standaard protocol aangewezen curatieve behandeling weigeren. In deze gevallen kunnen artsen echter ook alternatieve, niet-protocollaire behandelingen voorstellen.

In **hoofdstuk 2** wordt onderzocht welke factoren van invloed zijn op het kiezen van een niet-protocollaire behandeling door zowel hoofd-hals kanker patiënten als artsen. Ook de invloed van de behandelkeuze op de prognose wordt beoordeeld. Met een retrospectieve cohortstudie onder n = 829 patiënten werd aangetoond dat 17% van alle patiënten met een primaire hoofd-hals tumor, gediagnosticeerd tussen 2010-2012, geen protocollaire curatieve behandeling onderging. Dit was te wijten aan een niet-protocollair behandeladvies, of aan de patiënt die een alternatief koos. De multidisciplinaire tumorwerkgroep besloot bij 10% van alle patiënten om een niet-protocollaire behandeling te adviseren

bij patiënten met een curatief te behandelen primaire hoofd-hals tumor. Zeven procent van alle patiënten weigerde het volgens het protocol aangewezen curatieve behandelvoorstel. Van deze groep koos 4% voor een minder uitgebreide vorm van behandeling en 3% weigerde elke vorm van therapie. Patiënten die alleen wonen, patiënten met veel comorbiditeit of een hoog tumorstadium, vrouwen en oudere patiënten ondergingen vaker een niet-protocollaire behandeling voor een in principe curatief te behandelen hoofd-hals tumor. Reflecterend op de verschillende redenen die worden genoemd voor het kiezen van een niet-protocollaire behandeling voor hoofd-hals tumoren die curatief kunnen worden behandeld, wordt er een verschil gezien in de redenen om af te wijken van het protocol tussen patiënten en artsen. Artsen concentreerden zich meer op fysieke aspecten, voornamelijk in het kader van comorbiditeit en gevorderde ziekte, terwijl beslissingen van patiënten vaker gebaseerd waren op kwaliteit van leven en emotionele of psychologische redenen. Patiënten die zelf een protocollaire behandeling weigerden hadden een veel slechtere drie-jaar overleving (34% vs. 70%).

Hoofdstuk 3 beschrijft of en hoe prognostische informatie over de levensverwachting besproken wordt tijdens zogenaamde 'diagnose en behandeladvies' gesprekken tussen artsen en hoofd-hals kanker patiënten in verschillende fasen van hun ziekte. Voor deze beschrijvende kwalitatieve studie werden opnames gemaakt van n=23 arts-patiënt gesprekken. In deze gesprekken werden zowel palliatieve als curatieve behandelopties besproken en konden vragen van patiënten over de prognose worden verwacht. Deze gesprekken werden woordelijk getranscribeerd, en vervolgens systematisch geanalyseerd. Er werd onderscheid gemaakt tussen prognostische informatie die kwantitatief werd verstrekt (door het geven van numerieke schattingen van de prognose, zoals percentages of jaren) of die kwalitatief werd verstrekt (door het gebruik van woorden zoals '*hoogstwaarschijnlijk*' of '*zeer onwaarschijnlijk*'). In alle consulten werd door artsen enige prognostische informatie met patiënten gedeeld. In slechts 5,9% van de gesprekken werd bij het verstrekken van prognostische informatie een kwantitatieve methode gebruikt. In de overige 94,1% werd een kwalitatieve methode gebruikt, waarbij zes verschillende benaderingen werden geïdentificeerd. Het niet bespreken van specifieke prognostische informatie resulteerde in onzekerheid over de essentie van de verstrekte informatie. Mogelijk beïnvloeden artsen de perceptie van de patiënt door de manier waarop ze prognostische informatie communiceren. Twee communicatiestijlen konden hierbij worden onderscheiden: directief (meer arts-gericht) en affectief (meer patiëntgericht). De resultaten van deze studie en het bespreken van dit onderwerp hebben geleid tot een richtlijn voor het delen van prognostische informatie in de klinische praktijk.

De resultaten in dit hoofdstuk leiden naar het volgende deel van dit proefschrift. Om de prognose effectief te kunnen communiceren is exacte en individuele prognostische informatie van groot belang.

DEEL III: TOOLS VOOR GEPERSONALISEERDE VOORLICHTING: DE ONTWIKKELING VAN PROGNOSTISCHE MODELLEN

Voortbouwend op eerder onderzoek van onze onderzoeksgroep wordt in **deel III** het potentieel van prognostische modellen met betrekking tot het prognostisch voorlichten en het maken van behandelbeslissingen onderzocht. Twee verschillende klinische predictiemodellen voor larynx- en oropharynxcarcinoom, inclusief nieuwe prognostische markers, zijn ontwikkeld (**hoofdstuk 4 en 5**).

Hoofdstuk 4 richt zich op de ontwikkeling van een prognostisch model om de overleving van patiënten met plaveiselcelcarcinoom van de larynx (LSCC) te voorspellen en gaat in op de impact van anemie en body mass index (BMI) op de overleving. Hiertoe werd een retrospectief cohortonderzoek uitgevoerd onder alle patiënten met LSCC die tussen 2006-2013 zijn gediagnosticeerd en behandeld. Patiënt- en tumorspecifieke gegevens van n=788 patiënten werden verzameld met data van het Integraal Kankercentrum Nederland (IKNL) en werden aangevuld met gegevens uit patiëntendossiers van het Erasmus MC. Anemie (HR 1,41) en een lage BMI (HR 0,97) bleken beiden een significant effect te hebben op de overleving, onafhankelijk van de mate van comorbiditeit (gemeten met de ACE-27). Het toevoegen van anemie en BMI als prognostische factor aan het reeds bestaande prognostische model verbeterde de prestaties van het prognostische model (C-statistiek) van 0,77 (95% BI: 0,74 - 0,79) tot 0,79 (95% BI: 0,77 - 0,82).

Hoofdstuk 5 beschrijft de update, verbetering en validatie van het reeds bestaande prognostische model voor patiënten met plaveiselcelcarcinoom van de oropharynx (OPSCC). Drie prognostische factoren werden aan het bestaande model toegevoegd: de nieuwe 8e UICC/AJCC TNM-stadiëring (cN-status) en zowel p16 als HPV-DNA-status. HPV-gerelateerde hoofd-hals kanker is een aparte entiteit. Patiënten met HPV-gerelateerde OPSCC hebben namelijk een betere locoregionale controle en superieure overleving 5 jaar na de behandeling. Drie onafhankelijke multi-institutionele cohorten met OPSCC-patiënten uit West-Europa en de VS (periode 1984 - 2011, n = 1339) werden gebruikt voor een interne-externe kruisvalidatie analyse. In alle cohorten was HPV, gedetecteerd met p16 of PCR-DNA, een onafhankelijke prognostische factor voor algehele overleving bij OPSCC-patiënten. De 5-jaars overleving was 70,7% in de HPV positieve groep en 38,7% de HPV negatieve groep. Het aangepaste prognostische model, inclusief de 8e TNM-classificatie

en een afzonderlijke variabele voor HPV (PCR DNA of p16), presteert redelijk goed en lijkt qua kalibratie en discriminatie erg op het originele model met een voor optimisme gecorrigeerde Harrell's Concordance Index van 0,70. Een decision curve analysis (DCA) toonde echter een hoger klinisch nut in vergelijking met het oorspronkelijke model. Modellen met een variabele voor HPV (p16 of HPV-DNA) presteerden beter ten aanzien van de ondersteuning in de besluitvorming dan modellen met alleen de 8e TNM-classificatie. Deze statistische methode, waarbij een samenvatting wordt gegeven van modelprestaties ten aanzien van de ondersteuning in de besluitvorming, is zeer interessant gezien de lopende onderzoeken naar behandelaanpassingen (bijvoorbeeld de-escalatietherapie) voor patienten met HPV-positief OPSCC.

Dit hoofdstuk laat zien dat patiënten met HPV-positieve ziekte een gunstigere prognose hebben ten opzichte van patiënten met HPV-negatieve ziekte. Dit leidt tot de vraag of deze HPV-positieve patiënten op dezelfde manier moeten worden behandeld als HPV-negatieve patiënten. Het potentiële effect van deze nieuwe prognostische factor op de behandelresultaten wordt behandeld in **hoofdstuk 6 en 7**.

In **hoofdstuk 6** wordt gekeken naar het effect van de behandeling volgens het 'Rotterdam-protocol' op de nodale respons, het krijgen van een recidief en de overleving bij patiënten met HPV-geassocieerde T1-2 OPSCC met positieve lymfklieren. Voor dit doel werden n=77 patiënten met T1-2 OPSCC met positieve lymfklieren geïncludeerd, die waren behandeld tussen 2000-2012. Patiënten werden behandeld volgens 'het Rotterdam-protocol': 46 Gy IMRT gevolgd door een lokale boost met cyberknife of brachytherapie (22 Gy) en een halsklierdissectie. De aanwezigheid van HPV werd bepaald door p16 INK4A-immunokleuring. Uitkomsten waren: algehele overleving, ziektevrije overleving en de mate van nodale respons. De mate van regionale metastasering werd bepaald volgens de 7e en de 8e AJCC / UICC-classificatie. 68,4% van de patiënten had p16-positieve ziekte. 35,4% van alle patiënten bereikte een volledige nodale respons (pN0) na 46 Gy IMRT. Bovendien was een (gedeeltelijke of volledige) nodale respons significant geassocieerd met de HPV-status (p = 0,002). Volledige nodale respons leidde tot 100% algehele overleving in p16-positief OPSCC. HPV-gerelateerde OPSCC zijn dus geassocieerd met volledige nodale respons na 46 Gy IMRT. Patiënten met volledige regionale controle (pN0) na IMRT en daaropvolgende halsklierdissectie vertoonden een significant betere algehele overleving, maar roken had een negatieve invloed op dit effect.

Hoofdstuk 7 onderzoekt de rol van de immuunrespons, en met name de rol van T-cellen, op de gunstige prognostische status van HPV-positieve OPSCC-patiënten. Patiënten met HPV-positief OPSCC hebben een betere prognose dan patiënten met niet-HPV-gerelateerd OPSCC. De rol van de immuunrespons op dit fenomeen is nog onduidelijk. Voor dit onder-

zoek is het aantal T-cellen, regulatoire T-cellen (Tregs), T-helper 17 (Th17) -cellen en IL-17 + niet-T-cellen (voornamelijk granulocyten) bestudeerd in gematchte HPV-positieve en HPV-negatieve OPSCC casus (n=162). Verder werd de productie van IFN-γ en IL-17 door tumor-infiltrerende T-cellen geanalyseerd. Het aantal tumor-infiltrerende T-cellen en Tregs was hoger in HPV-positief OPSCC vergeleken met HPV-negatief OPSCC ($p < 0,0001$). Daarentegen bevatte HPV-negatief OPSCC aanzienlijk hogere aantallen IL-17 + niet-T-cellen ($p < 0,0001$). Hoewel het hebben van een groot aantal intratumorale T-cellen een trend naar verbeterde overleving van alle OPSCC-patiënten vertoonde, was hun prognostisch effect bij patiënten met een laag aantal intra-tumorale IL-17 + niet-T-cellen significant met betrekking tot ziektespecifieke ($p = 0,033$) en ziektevrije overleving ($p = 0,012$). Dit suggereert dat een hoge frequentie van IL-17 + niet-T-cellen gerelateerd is aan een slechte immuunrespons, wat verder wordt ondersteund door de waarneming dat het hebben van een groot aantal T-cellen gecorreleerd is met een verbeterde ziektevrije overleving in de HPV-positieve OPSCC groep ($p = 0,008$). Verder werd een kleine Th17-celpopulatie gedetecteerd. T-cellen verkregen van HPV-positief OPSCC produceerden echter significant meer IL-17 dan die van HPV-negatieve tumoren ($p = 0,006$). De verbeterde prognose van HPV-positief OPSCC is dus gecorreleerd met hogere aantallen tumor-infiltrerende T-cellen, actievere Th17-cellen en lagere aantallen IL-17 + niet-T-cellen.

Na het streven om nauwkeurige, geïndividualiseerde en up-to-date prognostische modellen te produceren en een nieuwe prognostische factor te verbinden met een mogelijke verschuiving in behandelstrategieën, is de volgende uitdaging hoe prognostische informatie afkomstig van prognostische modellen op een begrijpelijke wijze kan worden gedeeld met patiënten.

Hoofdstuk 8 beschrijft een studie die in focusgroepen is uitgevoerd waarin de gedachten, voorkeuren en behoeften van hoofd-hals kanker patiënten ten aanzien van het delen van prognostische informatie werden onderzocht. Ook werden de opvattingen van patiënten over het gebruik van het prognostische model *OncologIQ* in de spreekkamer onderzocht. Alle hoofd-hals kanker patiënten vonden het belangrijk om prognostische informatie te ontvangen, een op maat gemaakte aanpak is hierbij noodzakelijk. In sommige gevallen wilden patiënten juist kwantitatieve informatie, bijvoorbeeld *OncologIQ*'s schatting van de '5-jaars overlevingskans'. In andere gevallen begrepen patiënten begrepen dit concept vaak niet of verwarden het met andere termen, zoals genezingskans. In de meeste gevallen wilden patiënten algemene prognostische informatie van hun arts ontvangen, zoals *'uw kanker kan worden behandeld ...'* Volgens de deelnemers aan de focusgroepen moeten artsen eerlijk zijn tijdens het bespreken van de prognose, zonder hoop weg te nemen, en prognostische informatie aanpassen naar gelang de behoeften van patiënten. Prognose kan in verschillende vormen worden gepresenteerd, inclusief verbale uitleg en grafieken.

De hoofd-hals kanker patiënten in dit onderzoek gaven de voorkeur aan het cirkeldiagram om overlevingskansen te bespreken. Het cirkeldiagram was favoriet omdat de kansen hiermee in één oogopslag duidelijk waren en minder confronterend. Het 100-poppetjes diagram werd door zowel patiënten als zorgverleners als te confronterend beschouwd. Voor het delen van geïndividualiseerde prognostische informatie werd een richtlijn voor de klinische praktijk ontwikkeld. Deze richtlijn kan de beroepsbeoefenaar in de gezondheidszorg ondersteunen tijdens een behandelbeslissingsgesprek.

DEEL IV: TOOLS VOOR GEDEELDE BESLUITVORMING: ONTWIKKELING VAN EEN WAARDEGEDREVEN KLINISCH HULPMIDDEL

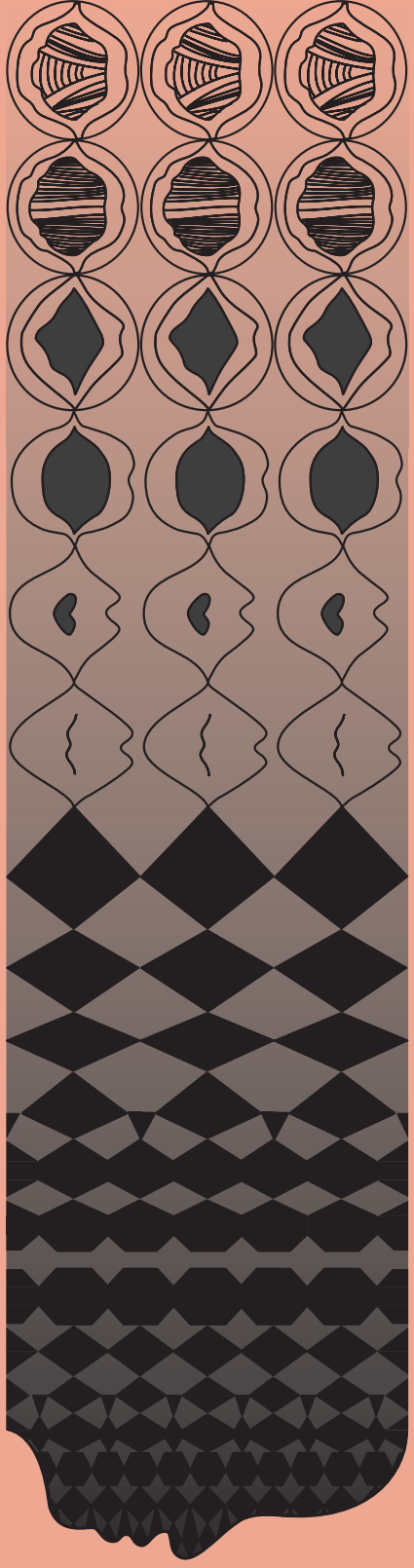
De resultaten zoals gepresenteerd in **deel II en III** geven informatie over de voorkeuren van patiënten met betrekking tot de prognose, het berekenen en interpreteren van individuele prognoses bij hoofd-hals kanker patiënten en hoe deze prognostische informatie het beste kan worden gecommuniceerd. De zorg voor hoofd-hals kanker patiënten gaat echter niet alleen over het includeren van patiëntvoorkeuren en individuele factoren bij het kiezen van de juiste behandeling of het delen van prognostische informatie. Vooral in de jaren na de behandeling, wanneer hoofd-hals kanker patiënten, hoofd-hals kanker overlevenden worden, is het belangrijk om de voorkeuren en prioriteiten van patiënten mee te nemen. Waardegedreven zorg - en in het bijzonder het nauwkeurig meten van elektronisch gerapporteerde patiëntresultaten (ePRO's) - wordt steeds vaker gebruikt om een systematische aanpak van de follow-up van kankerpatiënten mogelijk te maken. In **Deel III** wordt een op ePRO's gebaseerd klinisch hulpmiddel '*Zorgmonitor*' gepresenteerd dat patiënten in staat stelt zelfstandiger te zijn en krachtiger op te treden en de patiëntgerichte zorg verhoogt tijdens de follow-up van hoofd-hals kanker.

Hoofdstuk 9 gaat dieper in op de '*Zorgmonitor*': een op ePRO's gebaseerd klinisch hulpmiddel dat in 2013 is ontwikkeld voor de longitudinale follow-up van hoofd-hals kanker patiënten. In 2019 zijn al meer dan 1700 hoofd-hals kanker patiënten geïncludeerd. De '*Zorgmonitor*' meet het fysiek, functioneel en psychosociaal functioneren vanaf de diagnose tot het einde van de follow-up. Artsen hebben directe toegang tot de resultaten, wat zorgt voor directe feedback aan de patiënt. Een combinatie van kwalitatieve en kwantitatieve onderzoeksmethoden werd gebruikt om inzicht te verkrijgen in hoe hoofd-hals kanker patiënten de '*Zorgmonitor*' in de klinische praktijk ervaren. N=151 patiënten werden uitgenodigd om anoniem een zelf ontwikkelde PREM-vragenlijst in te vullen over de ervaren zorg op onze polikliniek. Ook werden (direct na het consult met hun arts) n=15 patiënten geïnterviewd over de toegevoegde waarde van onze ePRO-methode. Integratie van de '*Zorgmonitor*' in de standaard zorg voor hoofd-hals kanker patiënten heeft patiëntgerichte

zorg en de arts-patiëntcommunicatie verbeterd, een holistische aanpak mogelijk gemaakt en de patiënt meer zelfstandigheid en kracht gegeven. De '*Zorgmonitor*' vergemakkelijkt de screening op symptomen en de dataverzameling draagt bij aan onderzoeksprojecten en benchmarking met andere klinieken.

DEEL V: ALGEMENE DISCUSSIE EN TOEKOMSTPERSPECTIEF

Dit proefschrift draagt bij aan de verdere implementatie van het prognostisch voorlichten van hoofd hals kankerpatiënten, gedeelde besluitvorming en waardegedreven zorg. In **hoofdstuk 10 - Algemene discussie** worden de lessen besproken die geleerd zijn op een wetenschappelijk niveau (*"wat hebben we geleerd en toegevoegd aan de literatuur?"*) en op een meer praktisch niveau (*"wat kan er door dit onderzoek in de klinische praktijk veranderen?"*). Toekomstig onderzoek moet zich richten op het gebruik van prognostische modellen bij het maken van behandelbeslissingen en op de update van prognostische modellen met gegevens over de kwaliteit van leven. Verder is het bestuderen van de kosteneffectiviteit van initiatieven zoals de *Zorgmonitor* en een bredere verspreiding van het waardegedreven zorg concept van cruciaal belang om de patiëntenzorg op (inter) nationaal niveau te kunnen verbeteren. In **hoofdstuk 11 - Epiloog** wordt een visie op de toekomst gedeeld: hoe ziet patiëntgerichte hoofd-hals kankerzorg en gezondheidszorg er in het algemeen uit in 2040 en hoe maken we ons klaar voor de toekomst?



Addendum

List of abbreviations

Affiliations of contributing authors

PhD portfolio

List of publications

Dankwoord

Curriculum vitae

LIST OF ABBREVIATIONS

ACE-27	Adult Comorbidity Evaluation-27
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
AUC	Area Under the Curve
BMI	Body Mass Index
BT	Brachytherapy
CAT	Computer Adaptive Testing
CI	Confidence Interval
CK	Cyberknife
COREQ	Consolidated Criteria for Reporting Qualitative Research
C-statistic	Harrell's concordance statistic
DCA	Decision Curve Analysis
DFS	Disease free survival
EBM	Evidence Based Medicine
EBV	Epstein-Barr virus
ENE	Extranodal Extension
EHR	Electronic Health Record
EPF	Electronic Patient Files
ePRO	Electronic Patient Reported Outcome
FFPE	Formaldehyde Fixed and Paraffin Embedded Pretreatment
GP	General Practitioner
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
IHC	Immunohistochemical
IKNL	Comprehensive Cancer Centre the Netherlands
IMRT	Intensity Modulated Radiotherapy
IRT	Item Response Theory
LSCC	Laryngeal Squamous Cell Carcinoma
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MDT	Multidisciplinary Tumorboard
MEC	Medical Ethical Committee

MI	Multiple Imputation
ML	Machine learning
NCCO	Comprehensive Cancer Centre the Netherlands
NCR	Netherlands Cancer Registry
ONCDOC	Oncology Documentation
OPSCC	Oropharyngeal Squamous Cell Carcinoma
OR	Odds Ratio
OS	Overall survival
PREM	Patient Reported Experience Measures
PRO	Patient Reported Outcome
QoL	Quality of Life
RCT	Randomized Clinical Trial
ROC	Receiver Operating Characteristic
RONCDOC	Rotterdam Oncological Documentation
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SDM	Shared Decision Making
SES	Socio Economic Status
Th17	T helper 17
TMA	Tissue Micro Arrays
Tregs	Regulatory T cells
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
UICC	Union for International Cancer Control
VBHC	Value Based Healthcare

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PHD PORTFOLIO

Name:	E.A.C. Dronkers
Department:	Otolaryngology and Head & Neck Surgery
Research School:	Erasmus Medical Center
PhD period:	2012 – 2020

PHD TRAINING (107 ECTS) YEAR

Master of Science in Clinical Epidemiology (NIHES)	2013 – 2015

Advanced Courses	
Repeated Measurements in Clinical Studies	2014
Missing Values in Clinical Research	2014
Advanced Analysis of Prognosis Studies	2014
Quality of Life Measurement	2014
Introduction to Bayesian Methods in Clinical and Epidemiological Research	2014
Psychology in Medicine	2015
Joint Models for Longitudinal and Survival Data	2016

General Academic Courses	
Endnote course	2013
Pubmed course	2013
Biomedical English Writing and Communication	2013
Basic course on Regulations and organization for Clinical Investigators (BROK)	2013
NvvO: Introduction in clinical and fundamental oncology	2013
Basic surgical exam	2015
Reregistration BROK	2017

Other ENT-related courses	
Advanced Trauma Life Support (ATLS) Provider Course	2012
Head and neck anatomy (dissection)	2012,2014,2016, 2019
Desiderius school (teamwork, communication, health law, evidence-based medicine, management)	2015-2019
Course on endoscopy and laryngology	2016
Course on functional endoscopic sinus surgery	2016

Course on ear surgery in 3D models	2017
Course on mouth pathology	2018
Course on radiology	2019
Course nasal surgery	2019
Course on ear surgery	2020

Presentations on (inter)national conferences	
Otolaryngology Annual Research Day Erasmus MC (4 oral presentations)	2013 – 2018
6th IFHNOS, Buenos Aires (poster)	2018
Invited speaker lustrum scientific meeting of Dutch society for ENT (oral)	2018
230th Scientific meeting of Dutch society for ENT (oral)	2017
229th Scientific meeting of Dutch society for ENT (poster)	2016
Invited speaker biannual 'Speerpuntencursus' Dutch society for ENT (oral)	2016
9th AHNS, Seattle (2 oral presentations)	2016
227th Scientific meeting of Dutch society for ENT (oral)	2015
5th IFHNOS, New York (oral)	2014
223th Scientific meeting of Dutch society for ENT (oral)	2014
NWHHT young researcher's day (oral)	2014
5th WIN, Paris (poster)	2013
222th Scientific meeting of Dutch society for ENT (oral)	2013
NWHHT Rotterdam (oral and poster)	2013

TEACHING ACTIVITIES (31 ECTS) YEAR

Lecturing	
Supervising various workgroups for 1st, 3rd and 5th year medical students	2012 – 2020
Supervising various workgroups for ER, OR, oncology nurses in training	2012 – 2017

Supervision	
Supervising graduation research of several MSc students:	2013 – 2020
Steven Mes (2013), Mejrem Ahmetaj (2014),	
Denise van Beekveld (2016), Anri Maharadze (2016),	
Roderick te Riele (2016), Rens Woudenberg (2018), Diako Berzenji (2019)	
Supervising PhD research of Maarten Dorr and Eveline Dieleman	2018-2020

OTHER	YEAR
Awards	
1st Prize Posterpresentation 229th scientific meeting of Dutch society for ENT	2016
Yearly NVWPO-prize (Dutch Flemish Pediatric Otorhinolaryngology Society)	2020
Nominee ValueBased HealthCare Prize Europe	2020

Other activities	
Co-developer and project manager of RONCDOC	2015-2020
Co-developer of 'Zorgmonitor' (Healthcare Monitor)	2013-2020
Chairman of Greenteam Erasmus MC	2018-2020
Member Linnean initiative coalition	2018-2020
Review of four papers for Head Neck Journal	2018-2020

LIST OF PUBLICATIONS

Dronkers EAC, Baatenburg de Jong RJ, van der Poel EF, Sewnaik A, Offerman MPJ. *Keys to successful implementation of routine symptom monitoring in head and neck oncology with 'Healthcare Monitor' and patients' perspectives of quality of care.* Accepted for publication, Head&Neck (August 2020), doi: 10.1002/hed.26425

Offerman MPJ, **Dronkers EAC,** Baatenburg de Jong RJ. *Zorgmonitor ondersteunt uitkomstgerichte zorg voor patiënten met hoofd-halskanker.* Hoofdstuk in het boek *'Gepersonaliseerde medische zorg'* NFU-consortium Kwaliteit van Zorg, redactie van Weert NJHW en Hazelzet JA, Juni 2020, ISBN: 9789090331836

Hoesseini A, **Dronkers EAC**, Sewnaik A, Hardillo JAU, Baatenburg de Jong RJ, Offerman MPJ. *Head and Neck cancer patients' preferences for individualized prognostic information: a focus group study.* BMC Cancer. 2020 May 7;20(1):399. doi: 10.1186/s12885-020-6554-8.

Hoesseini A*, van Leeuwen N*, Offerman MPJ, Zhang J, **Dronkers EAC**, Sewnaik A, Lingsma H, Baatenburg de Jong RJ. *Predicting survival in head and neck cancer: external validation and update of the prognostic model OncologIQ in 2189 patients.* Submitted to Head Neck May 2020

Berzenji D, Monserez DA, Verduijn GM, **Dronkers EAC**, Jansen PP, Keereweer S, Sewnaik A, Baatenburg de Jong RJ, Hardillo JAU. *Treatment of head and neck carcinoma of unknown primary: cracking a nut with a sledgehammer.* Submitted to the Laryngoscope May 2020

Dronkers EAC, Nieboer D, Mes SW, van der Schroeff MP, Koljenovic S, Bloemena E, Brakenhoff RH, Snijders PJ, Lewis J, Steyerberg EW, Baatenburg de Jong RJ. *Value of Human Papilloma Virus (HPV) as a marker of prognosis for oropharyngeal cancer: validation and decision curve analysis of an updated prognostic model for patients in Western Europe and the USA.* To be submitted.

Bugter O*, van Iwaarden DLP*, **Dronkers EAC**, Wieringa MH, Verduijn GM, Mureau MAM, ten Hove I, van Meerten E, Hardillo JAU, Baatenburg de Jong RJ. *Survival of head and neck cancer patients with metachronous multiple primary tumors is surprisingly favorable.* Head Neck. 2019 Jun;41(6):1648-1655. doi: 10.1002/hed.25595.

Dronkers EAC, Vanden Driessche KSJ, Veder LL. *Otomastoïditis op basis van actinomycose.* Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde. November 2019, Volume: 25, Number: 4

Govers TM, Rovers MM, Brands MT, **Dronkers EAC**, Baatenburg de Jong RJ, Merkx MAW, Takes RP, Grutters JPC. *Integrated prediction and decision models are valuable in informing personalized decision making.* J Clin Epidemiol. August 2018.

Smits RWH*, Ten Hove I*, **Dronkers EAC**, Bakker Schut TC, Mast H, Baatenburg de Jong RJ, Wolvius EB, Puppels GJ, Koljenović S. *Evaluation of bone resection margins of segmental mandibulectomy for oral squamous cell carcinoma.* Int J Oral Maxillofac Surg. August 2018.

Dronkers EAC, Hoesseini A, de Boer MF, Offerman MPJ. *Communication of prognosis in head and neck cancer patients; a descriptive qualitative analysis*. Oral Oncology. July 2018.

Caspers CJI, **Dronkers EAC**, Monserez D, Wieringa MH, Baatenburg de Jong RJ, Hardillo JAU. *Adjuvant radiotherapy in sinonasal mucoasal melanoma: a retrospective analysis.* Clin Otolaryngol. April 2018.

Dronkers EAC, Koljenovic S, Verduijn GM, Baatenburg de Jong RJ, Hardillo JAU. *Nodal response after 46 Gy of intensity-modulated radiotherapy is associated with human papillomavirus-related oropharyngeal carcinoma.* Laryngoscope. March 2018.

Te Riele RJLM*, **Dronkers EAC***, Wieringa MH, De Herdt MJ, Sewnaik A, Hardillo JA, Baatenburg de Jong RJ. *Influence of anemia and BMI on prognosis of laryngeal squamous cell carcinoma: development of an updated prognostic model*. Oral Oncology. March 2018.

van Overveld LFJ, Takes RP, Vijn TW, Braspenning JCC, de Boer JP, Brouns JJA, Bun RJ, van Dijk BAC, Dortmans JAWF, **Dronkers EAC**, van Es RJJ, Hoebers FJP, Kropveld A, Langendijk JA, Langeveld TPM, Oosting SF, Verschuur HP, de Visscher JGAM, van Weert S, Merkx MAW, Smeele LE Hermens RPMG. *Feedback preferences of patients, professionals and health insurers in integrated head and neck cancer care*. Health Expect. December 2017.

Rothuizen LT, **Dronkers EAC**, van der Schroeff MP. *Nabloedingen bij tonsillectomie in het Erasmus MC: is de huidige postoperatieve observatieperiode adequaat?* Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde. Juli 2016, Volume: 22, Number: 3

Punt S*, **Dronkers EAC***, Welters MJ, Goedemans R, Koljenović S, Bloemena E, Snijders PJ, Gorter A, van der Burg SH, Baatenburg de Jong RJ, Jordanova ES.*A beneficial tumor*

microenvironment in oropharyngeal squamous cell carcinoma is characterized by a high T cell and low IL-17+ cell frequency. Cancer Immunology Immunotherapy. February 2016.

Dronkers EAC, Baatenburg de Jong RJ. *De waarde van prognostische modellen in de voorlichting en behandeling bij patiënten met hoofd-halstumoren*. Oncotherapie Nieuwsbrief Augustus 2015.

Dronkers EAC, Mes SW, Wieringa MH, van der Schroeff MP, Baatenburg de Jong RJ. *Noncompliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician.* BMC Cancer. July 2015.

Smits RW, Koljenović S, Hardillo JA, Ten Hove I. Meeuwis CA, Sewnaik A, **Dronkers EAC**, Bakker Schut TC, Langeveld TP, Molenaar J, Hegt VN, Puppels GJ, Baatenburg de Jong RJ. *Resection margins in oral cancer surgery: room for improvement.* Head and Neck, April 2015.

*= equally contributed

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Tot slot, lieve René. "Is dat boekje al af?" Ja, het is af. Dank voor je geduld, je wijze woorden, je liefde, je vertrouwen en alle vrolijke avonturen die we samen beleven. De wereld veroveren samen met jou en met de kleine reisgenoot die Team R&E in december zal versterken is hetgeen wat mij het meest gelukkig maakt.

CURRICULUM VITAE

Emilia (Emilie) Annette Cornelie Dronkers werd geboren op 5 juli 1988 te Breda. Met de huisartsenpraktijk van haar ouders aan huis werd al op jonge leeftijd de interesse voor de geneeskunde gewekt. Muziek, literatuur, klassieke talen en filosofie hadden echter haar grote aandacht. Naast haar scholing aan het Stedelijk Gymnasium te Breda, volgde zij daarom de vooropleiding klassiek piano aan het Conservatorium te Tilburg en het pre-university program for top-students in klassieke talen aan de Universiteit Leiden. In 2005 behaalde ze haar Gymnasium diploma (cum laude) en in hetzelfde jaar startte zij met de studie Geneeskunde aan de Universiteit Leiden, waar zij in 2011 het artsexamen behaalde (cum laude).

Na werkervaring te hebben opgedaan als ANIOS op de afdeling Chirurgie van het Haga Ziekenhuis te Den Haag werd in 2012 aangevangen met dit promotie-onderzoek aan de afdeling KNO/Hoofd-hals chirurgie van het Erasmus Medisch Centrum Rotterdam. Het onderzoek werd gecombineerd met klinische werkzaamheden als ANIOS KNO en met een opleiding tot klinisch epidemioloog (Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences).

In december 2015 begon zij met de opleiding tot KNO-arts onder leiding van prof. dr. R.J. Baatenburg de Jong en dr. R.M. Metselaar. De perifere stages deed zij in het Haga Ziekenhuis Den Haag (opleiders: dr. H.M. Blom en dr. J.P. Koopman) en het Reinier de Graaf Gasthuis Delft (opleiders: drs. F.W. Peek, mw. dr. H.C. Hafkamp). De opleiding volgt zij in deeltijd, zodat daarnaast tijd beschikbaar is voor de verschillende projecten waar zij als onderzoeker nauw bij betrokken is. Emilie begeleidt meerdere promovendi en medisch studenten bij hun onderzoek naar waardegedreven zorg en prognostische modellen. Verder is zij bestuurlijk actief als voorzitter van het Greenteam van het Erasmus MC en verbonden aan het Linnean-initiatief: een landelijke denktank op het gebied van Value Based Healthcare.

Naar verwachting zal de opleiding tot KNO-arts worden afgerond in juni 2021. Zij wil zich onder meer specialiseren in stem-, slik- en luchtwegchirurgie, met als doel rehabilitatie van deze vitale functies bij aangeboren afwijkingen en na (oncologische) behandelingen.

Emilie is in 2019 getrouwd met René de Rooij. In december 2020 verwachten zij hun eerste kindje.