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 loco-regional 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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