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Erasmus MC
Erasmus Medisch Centrum Rotterdam



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 HN-SCC: 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 the 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 models²³⁻²⁵ 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 comprises 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 consider 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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