Health-related quality of life and survival in patients with head and neck cancer

First steps towards improved survivorship care

Annette Josephine Wehman - van Nieuwenhuizen

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Ter nagedachtenis aan mijn moeder, Marie-Louise

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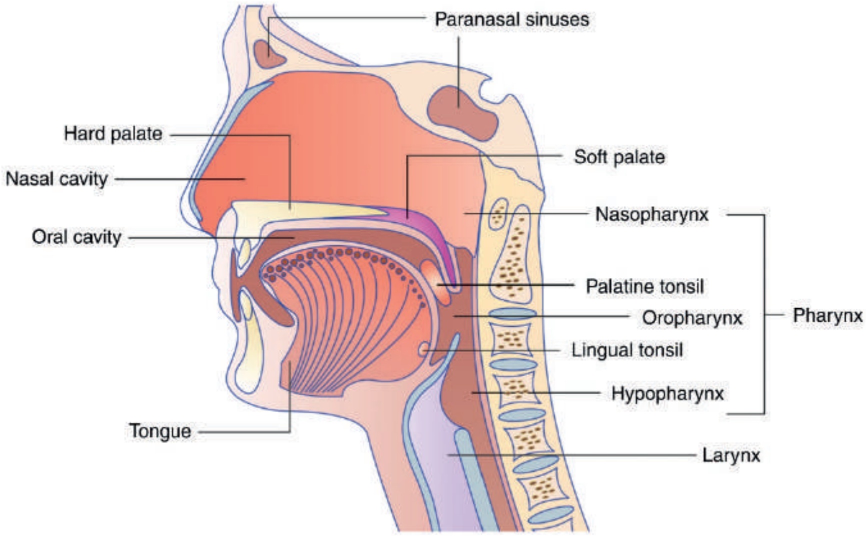
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Encouraging results have been made in the past decades towards improving clinical outcomes in cancer treatment.[1] Nowadays health related quality of life (HRQoL) is recognized as an inseparable factor to account for along the cancer trajectory. Sometimes the medical benefits might even be outweighed by the deleterious impact on HRQoL. A cancer diagnosis and it's treatment can severely impair an individual's HRQoL. Patients are often confronted with various symptoms and toxicities that are associated with cancer diagnosis and treatment such as pain and fatigue, but also physical, emotional, functional, social, and occupational dysfunction.[2-4] Previous research has shown that HRQoL is significantly associated with survival.[5-9] In addition, lifestyle behaviors (e.g. smoking, alcohol use, dietary intake and physical activity) have been shown to be associated with survival.[10-15] In this thesis, the focus is on HRQoL in head and neck cancer (HNC) patients. These patients have to cope with, in addition to generic cancer-related symptoms, specific HNC symptoms, such as oral dysfunction, and speech and swallowing dysfunction.[16-22] This thesis addresses HRQoL in relation to survivor and survivorship in people with head and neck cancer. In this chapter, background information is provided on HNC and its treatment, HRQoL, and HNC survivorship. The aims of this thesis are described and the outline of this thesis is presented.

Head and neck cancer

Head and neck cancer (HNC) encompasses tumors in the upper respiratory or digestive tract. The most common sites in the head and neck region are oral cavity, oropharynx, hypopharynx or larynx. The main tumor histopathology is squamous cell carcinoma which develops in the epithelial layer of the mucosal surfaces from the affected tumor sites.[23] To date, HNC is the sixth leading type of cancer worldwide, with approximately 705.781 new cases and 358.144 deaths in 2018.[24] In Europe and the United States, five year survival rate has slightly improved over the past decades. In The Netherlands, five year survival rate was 59% in 2015.[25] Main risk factors for the development of HNC are tobacco use and excessive alcohol consumption, which seem to have a synergistic effect.[26,27] The presence of the oncogenic human papilloma virus (HPV) infection is another factor that is associated with an increased risk mainly for developing oropharyngeal cancer and to a lesser extent oral carcinoma. [26,27] Male-female ratio of HNC is approximately 1.5. The incidence in men tends to stabilize while the incidence in women still increases due to increased tobacco consumption by females in the 1980s. Most newly diagnosed patients with HNC are over 45 years of age.[26,27]



Schematic representation of the head and neck region relevant for head and neck carcinomas.

Diagnosis and treatment

The first symptoms of a tumor in the head and neck region comprise mouth pain, non-healing ulcers, dysphagia, hoarseness, swelling in the neck or referred otalgia. In general, one third of the patients with HNC are diagnosed with an early stage (I and II) of disease, while two-third are diagnosed with advanced disease (III and IV).[23] Treatment of patients with HNC is multidisciplinary and based on tumor site, TNM stage (the size of the primary tumor (T), presence and number of regional lymph node metastasis (N) and presence of distant metastasis (M)) and overall condition of the patient (i.e. age or cognitive status).[28,29] Treatment for patients with HNC often involves surgery, radiotherapy, chemotherapy or a combination of these modalities. Patients with early stage disease have small tumors confined to the primary site, without metastasis, and are usually treated with single treatment modality (surgery or radiotherapy). Patients with advanced disease have larger tumors and / or locally metastasized tumors. In case of curative treatment, this mostly consists of a combination of surgery and postoperative (chemo)radiotherapy or the concomitant application of chemotherapy combined with locoregional radiotherapy. [28,29]

Heath-related quality of life

HRQoL is a multidimensional concept and encompasses physical, psychological and social well-being and functioning.[30] Patients with HNC may be confronted with specific symptoms, such as oral dysfunction, swallowing and speech problems.[16,17,19-21,31-35] This may have a distinct impact on HRQoL. Previous studies in patients with HNC showed that several domains of HRQoL, including general health, mental health, physical function, appearance, employment and social functioning, decline during and immediately after treatment, but often improve after 6 months.[17,20-22] Previous research also showed that HRQoL seems to stabilize from one year after treatment up to 5-year follow up.[16-22] However, late effects of HNC cancer and its treatment may also occur. [36] To provide individualized (supportive) care, monitoring HRQoL in a structured manner in clinical research and practice is important. HRQoL is typically assessed by patient reported outcome measures (PROMs).[37,38] PROMs supplement clinician rated scores and/or objective testing by revealing the impact of the disease and its treatment on physical, psychological and general functioning of the patient.[39] Wide1y-used PROMs among patients with HNC are the European Organization for Research and Treatment of Cancer, (EORTC) Quality of Life Questionnaires.[39,40] The EORTC Quality of Life Questionnaire (QLQ-C30) provide insight into patients' global quality of life, health related functioning (e.g. physical, emotional, social) and general cancer symptoms (e.g. pain and fatigue).[39,40] The EORTC Head and Neck Module (EORTC QLQ-HN35) is tailored to HNC symptoms such as problems with swallowing and speech.[41] Recently, this PROM was updated and extended into the EORTC QLQ-HN43.[42]

HRQoL in relation to survival

Interestingly the course of HRQoL has shown to be different between HNC survivors and non-survivors during the first 2 years after treatment.[35] Also a recent study demonstrated that overall HRQoL decreased progressively until a year, then recovered toward baseline between 2 and 5 years. However, patients with shorter survival had lower HRQoL pre-diagnosis with a steeper decline in HRQoL during diagnosis and treatment. Higher pre-diagnosis HRQOL was independently associated with improved overall survival.[11]

Other studies investigating the association between HRQoL and survival showed a significant association, independently from other known demographic, lifestyle-related and clinical factors.[43-52] A review of Montazeri et al.[6] revealed a significant association between HRQoL and survival for most cancers, but findings of studies on HNC patients were inconsistent and based on a limited number of studies. The review of Montazeri et al.[6] and a meta-analysis from Quinten et al[53] showed a stronger association between pre-treatment physical functioning and survival compared to other HRQoL domains

in patients with various cancer sites. Quinten et al found a median survival time of 20 months among patients with low physical functioning compared to 65 months among patients with high physical functioning.[53]
However, the observational studies in patients with HNC examining the association between HRQoL and survival had several limitations. For example, relevant confounders were not taken into account in the association between HRQoL and survival, such as co-morbidity[44,46,47,54-61] or lifestyle (e.g. smoking and alcohol consumption).[44,55,58,62-64] Furthermore, most often pre-treatment HRQoL was investigated, whereas also HRQoL after treatment and changes in HRQoL from diagnosis to follow-up may be important in the association with survival. The review of Montazeri et al.[6] showed that for some cancers, HRQoL after treatment was prognostic for survival, where pre-treatment HRQoL was not. Although HRQoL after treatment and change in HRQoL seems to be associated with survival as well, there is only a limited number of studies and there is large variation in these studies concerning assessment time points.[45-47,59,61,64] As a consequence, it remains difficult to draw firm conclusions on the association between HRQoL and survival in HNC patients.

Head and neck cancer survivorship

With the increase in incidence and improved survival rates, more people have to cope with living beyond HNC cancer.[65,66] Cancer and its treatments have long lasting effects, and survivors are at higher risks for comorbidities, physical and psychosocial problems throughout their lifetime.[67] When a patient becomes a cancer survivor is debatable, at diagnosis, after completion of definite treatment or when at least 5 years have elapsed without the sign of any recurrence.[68] From a more individualized perspective it is defined as “living with, through and beyond a cancer diagnosis.[69] For HNC specifically, patients and their families are confronted with profound and numerous disabilities due to the anatomical complexity of the head and neck region. Swallowing and speech impairments are common throughout the entire cancer trajectory. Within the first year of radiotherapy treatment, approximately half of HNC survivors suffer from dysphagia and dysarthria.[70-72] Unfortunately long term effects of radiotherapy are often present on speech and swallowing. For instance, a majority (68%) of HNC survivors reported voice problems even 10 years after radiotherapy.[73] Furthermore, the two-years prevalence of dysphagia is 45% among HNC survivors (all therapies) and 4.6-7.8 times more likely to occur in comparison to non-cancer controls.[74] These findings are reflected in the needs of patients with HNC, where maintaining the ability to swallow and speak as their top 2 functional priorities.[75] These impairments in swallowing and / or speech are primary concerns for HNC survivors and directly associated with reduced HRQoL.[76] In addition HNC symptoms seem to be significantly associated with reduced physical

activity because of dry mouth or throat, difficulty eating, and shortness of breath).[77]
In cancer survivorship promoting a healthy lifestyle is critical. In patients with HNC awareness on lifestyle related factors such as smoking, alcohol use and nutritional status seems to be eminent. However, physical activity seems to be less recognized as an important lifestyle related factor. Studies suggests that only 9% of nurses and from 19% to 23% of oncology physicians refer patients with cancer to exercise programming.[78] Also, in contrast to HNC symptoms and other domains of HRQoL not much is known on physical activity in HNC survivors.
Physical activity can be defined as any bodily movement that results in energy expenditure.[79] In patients with other types of cancer, mainly breast and prostate cancer, physical activity has shown to have beneficial effects on physical and psychosocial function and HRQoL during and after treatment.[80-84] Individualized participant data of 4519 individual patients with cancer revealed that exercise significantly improved physical function and global QoL.[85] Furthermore higher levels of moderate-to-vigorous physical activity have been associated with lower mortality risk in survivors of breast, colon and prostate cancer.[86-90] Also in HNC survivors, higher pre-treatment levels of physical activity and physical function were found to be associated with higher HRQoL.[91,92] Physical activity seems to decrease following HNC diagnosis and during treatment.[92-95] Additionally, little is known on physical activity in HNC survivors in the longer term.

Objectives and outline of this thesis

Summarizing the current literature, there are still important issues that remain to be answered. Two key gaps in knowledge are addressed in this thesis. It is still unclear which HRQoL domains are associated survival in HNC, at which time-point across the cancer journey, and whether absolute values and/or changes in HRQoL are associated with survival. Furthermore, more knowledge on HRQoL in HNC survivorship is needed and especially the role of physical activity.
Therefore, this thesis aims to investigate the association between HRQoL and survival in patients with HNC, and to investigate physical activity and the relationship with HRQoL in long-term HNC survivors.

First, the current knowledge on the value of using HRQoL questionnaires in in patients with HNC is reviewed in-depth. Chapter 2 describes a literature review on the value of HRQoL questionnaires in patients with HNC.
The association between HRQoL and survival in patients with HNC is investigated in the studies described in Chapter 3 and 4. Chapter 3 reports on a systematic literature review of prospective studies on the association between HRQoL and survival in patients with HNC. This study aimed to identify which HRQoL domains are most

strongly associated with survival, adjusting for important clinical, demographic and lifestyle-related factors.

Chapter 4 describes the results of a prospective study among 948 newly diagnosed HNC patients. This study aimed to examine whether pre-treatment, post-treatment or change in HRQoL is associated with survival.

The study described in Chapter 5 aimed to obtain insight into patient reported physical activity in long-term HNC survivors in relation to HRQoL, adjusted for relevant demographic, lifestyle-related and clinical factors.

Chapter 6 describes the feasibility of performing a comprehensive study, including questionnaires (635 items), a home visit (including a (psychiatric) interview, physical tests, blood and saliva collection), and tissue collection.

Chapter 7 discusses the main findings of this thesis, the methodological considerations, implications for clinical practice, recommendations for further research and a conclusion.

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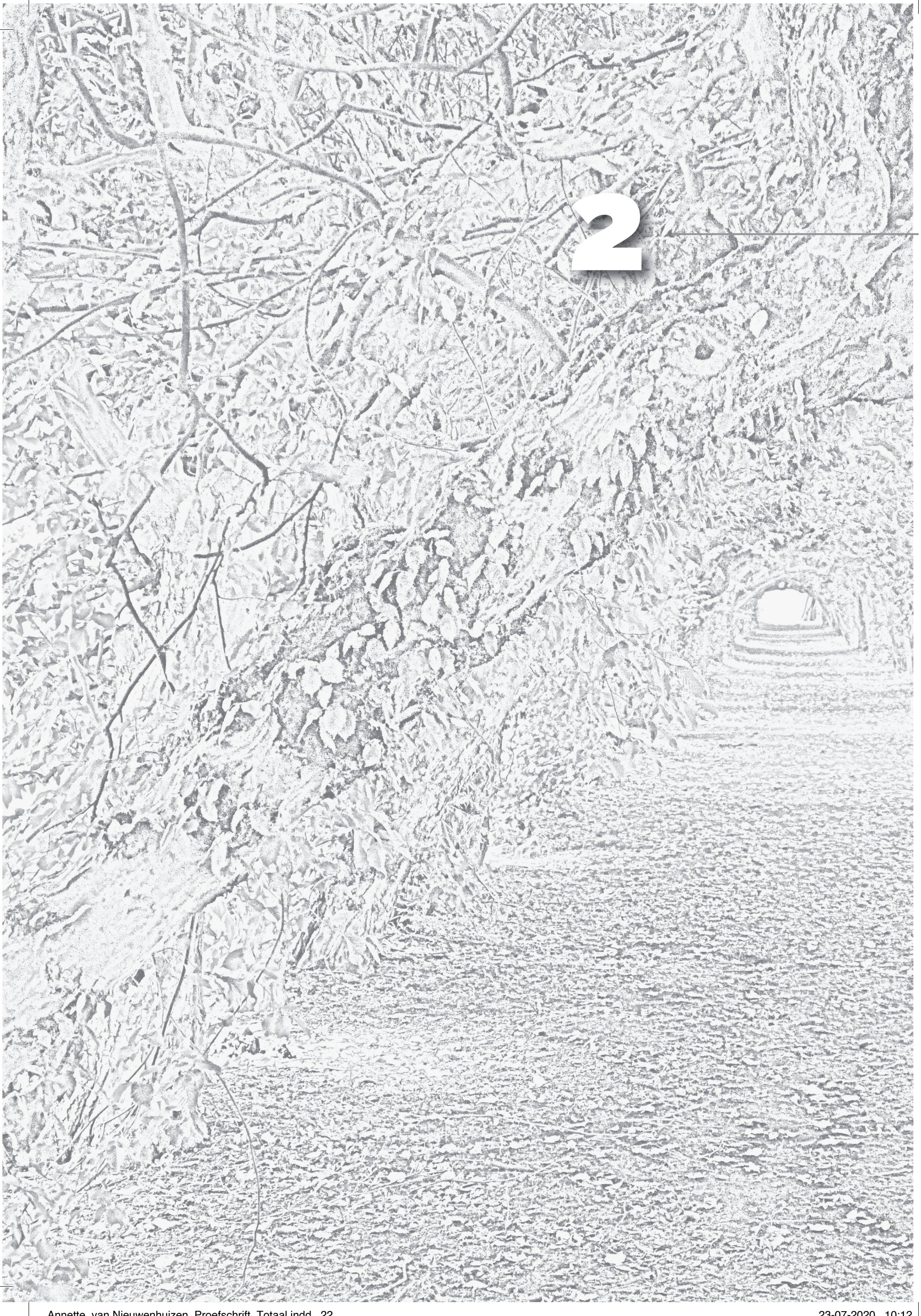

CHAPTER 2

THE VALUE OF QUALITY OF LIFE QUESTIONNAIRES IN HEAD AND NECK CANCER

I.M. Verdonck-de Leeuw
A.J. van Nieuwenhuizen
C.R. Leemans

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ABSTRACT

Purpose of review. To review recent literature on health related quality of life (HRQOL) in head and neck cancer (HNC) patients.

Recent findings. HRQOL is an important part of well-designed clinical trials. HRQOL seems an independent predictor of survival, but this association may be influenced by various cancer-related, personal, biological, and psychobehavioural, physical, lifestyle-related, and social factors. Less is known about the course of HRQOL over time and about the same above mentioned possible factors associated with (change in) HRQOL of HNC patients. Symptom management and psychosocial care may be beneficial for HNC patients to improve HRQOL, but more randomised controlled trials are needed. Studies on HRQOL in HNC are most often based on cross-sectional designs. The variability in outcome measures hampers the generalizability of the results of these studies. Information on HRQOL of caregivers is scarce.

Summary. Better information on all aspects of the course of HRQOL from diagnosis and treatment to long-term survivorship or death is highly needed in both patients and their caregivers enabling reliable and valid predictive modelling. More evidence of efficacy of (new) treatment options, symptom management, and psychosocial care is needed, also in the context of increasing long-term survival and growing attention for cancer survivorship.

INTRODUCTION

Research during the past decades has shown that head and neck cancer (HNC) and its treatment has a specific impact on health related quality of life (HRQOL) compared to other cancer types. In addition to general complaints such as pain and fatigue, HNC patients are often confronted with oral dysfunction, voice, speech and swallowing problems and related social withdrawal and emotional distress. HRQOL is typically assessed by patient reported outcomes such as questionnaires.[1] The past years have shown an improvement in technical, surgical, and medical possibilities available to optimize the functional outcomes of HNC patients and thereby improve HRQOL. Examples are laser surgery, surgical voice restoration after laryngectomy, and novel reconstruction techniques. Growing evidence indicates that the delivery of radiotherapy (RT) alone or with concomitant chemotherapy (CT) yields similar tumour control and survival compared to surgery in HNC patients but possibly to the expense of increased morbidity, such as swallowing, speech, and shoulder dysfunction and hearing problems. To provide individualized supportive care it is clear that it is important to monitor quality of life in a structured manner in clinical practice. Supportive care in cancer is the prevention and management of adverse effects of cancer and its treatment including speech and swallowing rehabilitation, physiotherapy, nutritional support, and psychosocial care. The introduction of new treatments and supportive care options aiming at improving HRQOL are promising but the scientific evidence remains to be determined.

Overview of recent literature

As a first step of this review, a literature search was performed in PubMed on “quality of life”, “questionnaires” and “head and neck cancer” published between January 2010 and September 2011, yielding 160 hits. Based on the following exclusion criteria: patient population other than HNC (n=19), oesophageal cancer (n=16), outcome measure other than patient reported outcome (n=7), study on validation of questionnaire (n=7), and study on small (n<40) patient populations (n=20), 69 studies were excluded. The majority of the remaining 91 studies focussed on patients and only 2 studies on caregivers. There were 3 studies investigating the association between HRQOL and survival.

Regarding study design, a cross-sectional or retrospective design was used in 65 studies, a prospective cohort design in 19 studies, and a randomized controlled trial (RCT) or prospective cross-over trial design in 7 studies. Without defrauding other study designs that may be useful for specific research questions, prospective cohort studies and RCTs are highly needed to obtain reliable and valid insights into HRQOL of HNC patients after various treatment modalities during the whole cancer trajectory from diagnosis to long-term survival or death.

It is striking that among the remaining 93 studies more than 60 different questionnaires were applied. Regarding HNC-specific HRQOL for instance, 4 different questionnaires were used: European Organisation for Research and Treatment of Cancer, Head and Neck Module (EORTC QLQ-HN35), Functional Assessment of Cancer Treatment Questionnaire, Head and Neck Module (FACT-HN), Head and Neck Specific Needs Questionnaire (HNCNQ), and Head and Neck QOL Questionnaire (HNQOLQ). Focussing on symptom specific HROQL, 3 different questionnaires were counted targeting swallowing (Swallowing Quality of Life Questionnaire (SWAL-QOL), MD Anderson Dysphagia Index (MDADI), Sidney Swallow Questionnaire (SSQ)). Kanatas and Rogers[2] recently performed a systematic review on patient reported outcomes in HNC and also concluded that there is a large variety of validated questionnaires available. Their summary is useful when selecting a questionnaire for research projects or clinical practice.

The following sections will review the value of HRQOL as part of recent clinical trials, the association between HRQOL and survival, the prognostic factors associated with HRQOL, and HRQOL in relation to supportive care in both patients and caregivers. Some of the studies from the above mentioned first literature search are selected that fit well in this review.

HRQOL in clinical trials

Including HRQOL to examine the impact of treatment on daily life is considered part of well-designed RCTs. For example, Mesia et al.[3] reported on HRQOL as part of a phase III trial that demonstrated that cetuximab improves survival when added to platinum-based CT for recurrent and/or metastatic HNC. Of 442 patients randomly assigned, 291 patients completed at least one evaluable questionnaire (compliance 65%). They concluded that adding cetuximab to platinum-fluorouracil does not adversely affect HRQOL of patients with recurrent and/or metastatic HNC. Van Herpen et al.[4] reported on HRQOL as part of a phase III study in 358 patients with unresectable locoregionally advanced HNC showing an improved progression-free and overall survival with less toxicity when docetaxel was added to cisplatin and 5-fluorouracil for induction and given before RT. Compliance to HRQOL assessments was 97% at baseline, but dropped to 54% by 6 months. They concluded that induction CT with TPF before RT not only improves survival and reduces toxicity compared with PF but also seems to improve global HRQOL. Information on long-term HRQOL and late effects is scarce, since HRQOL assessment in many studies (as the above mentioned) is limited to the first year after treatment. Ackerstaf et al.[5] reported on the 5-years results of HRQOL among 71 survivors in a randomized phase III trial, assessing intra-arterial versus standard intravenous CRT for inoperable stage IV HNC. No significant differences between 1 and 5 years follow-up were observed, except for “dry mouth” (gradually improving). At 1 year follow-up, survivors reported lower fatigue levels, better voice, and swallowing than patients who could not complete all subsequent follow-up questionnaires.

These examples of recent trials stress the importance of including HRQOL in clinical trials not only to provide evidence on the (positive or negative) impact of new treatment options on HRQOL, but also to enable early supportive care to manage possible adverse events. However, the often low compliance hampers drawing firm conclusions. Random missing data may be handled by organising patient participation in clinical trials in a more structured way to enhance compliance. Advanced statistical analyses including adjustment for survivorship are warranted to analyze non-random missing data (caused by death).

The association between HRQOL and survival

Regarding the association between HRQOL and survival in cancer patients (all cancer types), Montazeri[6] performed a review on 104 citations. With few exceptions, the findings showed that HRQOL or some aspects of HRQOL are significant independent predictors of survival. Global quality of life, functioning domains, and symptoms such as appetite loss, fatigue, and pain, were the most important indicators, individually or in combination, for predicting survival in cancer patients after adjusting for one or more demographic and known clinical prognostic factors.

In the past 2 years, 3 new studies were published investigating this association in HNC patients. Osthus et al.[7] reported that overall survival (mean 75 months) was predicted by HRQOL after treatment in a cohort of 139 HNC patients. Global quality of life, fatigue, dyspnoea, and insomnia predicted overall survival independently from outcome measures as gender, age, neuroticism, coping style, alcohol consumption, smoking status, heart/lung disease, time between diagnosis and inclusion, tumour node metastasis stage, and tumour site. Fang et al.[8] examined the prognostic value of pre-treatment HRQOL on locoregional control, distant metastasis-free survival (DMFS), and overall survival (OS) in 347 patients treated by RT for nasopharyngeal carcinoma. Among various HRQOL variables that significantly predicted OS and DMFS, physical functioning was the most powerful predictor. Oskam et al.[9] investigated the association between HRQOL and survival in a cohort of 80 patients with advanced oral or oropharyngeal cancer after microvascular reconstructive surgery and adjuvant RT. Deterioration of global HRQOL 6 months after treatment compared to pre-treatment levels predicted overall and disease specific mortality independently from sociodemographic and clinical parameters. These 3 studies add up to 7 earlier published studies on the association between HRQOL and survival in HNC.[9] In 8 out of these 10 studies, HRQOL appeared to be an independent predictor of survival. However, study designs differed substantially regarding tumour subsite, treatment modality, and HRQOL outcome measures. Furthermore, new empirical evidence suggests that tumour and patient related biomarkers, psychosocial functioning, and lifestyle may also be related to HRQOL and survival in cancer patients. For instance, several biomarkers of neuroendocrinological and neuroimmunological function have been suggested to play a role in the association between depression, HRQOL, and survival.[10] Neuroimmunological explanations include increased immune responses and increased levels of pro-inflammatory cytokines. IL-6 has also been found to be associated with fatigue, depression, and cognitive impairments.[11] Therefore, large-scaled cohort studies are needed to investigate the association between HRQOL and survival in HNC patients, in relation to broadly defined possible moderating factors as cancer-related, personal, biological, psychobehavioural, physical, lifestyle-related, and social determinants.

Predictive modelling of HRQOL

Previous research has indicated a lack of understanding of the factors that influence HRQOL of HNC patients. Building and testing predictive models of HRQOL contribute to obtain more insight into these factors and may also improve clinical practice and provide directions for future research. In this paragraph some examples of recent prospective studies are reviewed focussing on oral pain, nutrition, swallowing, sleep, depression, and coping style.

Chen et al.[12] focussed on orofacial pain among 72 patients treated with surgery and RT for HNC. They reported that older age, eating difficulty, speech difficulty, and depression were significant predictors of orofacial pain.

Nourissat et al.[13] identified factors associated with weight loss during RT in patients with stage I or II HNC as part of a phase III chemoprevention trial. A total of 540 patients were weighted before and after RT. Eight factors were associated with a greater weight loss: all HNC sites other than the glottic larynx, TNM stage II disease, higher pre-RT body weight, dysphagia before RT, higher mucosa adverse effect of RT, lower dietary energy intake during RT, and worse scores regarding digestion and constipation.

Wilson et al.[14] investigated dysphagia before and after RT or CRT in 167 HNC patients (mostly laryngopharyngeal cancer). Treatment intensity (higher RT dose), younger age, and pre-treatment swallowing problems predicted long-term dysphagia.

Christianen et al.[15] investigated in a group of 354 HNC patients treated with RT or CRT which dose volume histogram parameters and pre-treatment factors predict physician-rated and patient-rated dysphagia at 6 months after treatment. A model based on the mean dose to the superior pharyngeal constrictor muscle and mean dose to the supraglottic larynx was most predictive for physician rated swallowing dysfunction. Regarding patient reported swallowing outcome, models were different and dependent on food intake. Shuman et al.[16] investigated predictors of sleep quality among 457 HNC patients 1 year after diagnosis. Pain, xerostomia, depression, presence of a tracheotomy tube, comorbidities, and younger age were predictors of poor sleep 1 year after diagnosis. Smoking, problem drinking, and female sex were marginally significant ($p < .09$). Type of treatment (surgery, RT and/or CT), primary tumour site, and cancer stage were not significantly associated with 1-year sleep scores. Scharloo et al.[17] investigated the contribution of illness cognitions to the prediction of HRQOL 2 years after diagnosis among 177 HNC patients. Patients' own implicit common sense beliefs about their illness at baseline added little but significantly to the prediction of HRQOL after 2 years. Less belief in own behaviour causing the illness predicted better functioning and better global health. Strong illness identity beliefs predicted worse functioning and worse global health. Negative perceptions about the duration of the illness (chronic timeline beliefs) and more negative perceived consequences also predicted worse HRQOL.

Howren et al.[18] investigated whether pre-treatment depression contributes to predicting HRQOL among 306 HNC patients. Depressive symptoms before cancer treatment significantly predicted (worse) HRQOL at 3 and 12 month follow-up across the 4 HNC-specific domains of speech, eating, aesthetics, and social disruption, independently from age, gender, marital status, cancer site, stage of disease, alcohol and tobacco use, comorbidity status, and pre-treatment HRQOL.

Previous and recent researches on HRQOL show considerable variation between patients: some patients are at risk for poor HRQOL, while others are protected. It is highly relevant to understand risk factors and protective resources that predict HRQOL. This knowledge enables clinicians to identify HNC patients who are at risk for poor HRQOL and enabling referral to supportive care in an earlier stage. Furthermore, understanding of risk-factors and protective resources allows the development of interventions or treatment innovation aiming at improving HRQOL. As already argued in the paragraph on the association between HRQOL and survival, large-scaled studies are also needed to build prognostic models targeting HRQOL. Among others, age, tumour and treatment related characteristics, comorbidity, depression, and coping style, are potential mediators of HRQOL outcome. Some of these factors seem to be treatable. In the reviewed studies the importance was stressed of supportive care to manage symptoms and improve psychosocial functioning that may contribute improving HRQOL after HNC treatment. Predictive modelling helps to identify patients who are most likely to benefit from which supportive care options.

HRQOL and supportive care

There is growing interest in using patient-reported outcomes (PRO's) to screen for physical and psychosocial problems and the need for supportive care in routine clinical practice and several studies have shown that using PRO's in clinical practice facilitates communication about quality of life between doctors and patients. There is less evidence that this approach may affect patient outcome or improve quality of life and additional efforts are needed to enhance the effect of screening, such as advance palliative care planning, survivorship care plans, and improving evidence based supportive care options. In this paragraph, the focus is on studies providing evidence regarding symptom management and supportive care. Bien et al.[19] reported on a RCT (n=80) investigating the effect of Heat and Moisture Exchanger (HME) use on pulmonary symptoms and quality of life aspects in laryngectomized patients. This study confirms the results of previous studies, showing that pulmonary symptoms decrease significantly with HME use and that related aspects such as speech and sleeping tend to improve.

Nibu et al.[20] performed a longitudinal study to assess the impact of rehabilitation and surgical modification on postoperative HRQOL. Patients who had undergone neck dissection (n=224) underwent a rehabilitation program designed for neck dissection. They reported that resection of the sternocleidomastoid muscle (SCM) and spinal accessory nerve (SAN) resulted in shoulder drop. Selective neck dissections and preservation of the SAN and SCM significantly reduced various sensory symptoms of the neck, such as stiffness, pain, numbness, and constriction, and improved shoulder function. Postoperative rehabilitation had a significant effect on arm abduction ability, particularly when the SCM and SAN were resected.

Regarding the need for supportive care among 165 oral cancer patients at time of diagnosis, Chen et al.[21] reported that patients had high supportive care needs, with the highest prevalence of unmet needs in the area of health system and information, followed by psychological care. Precious et al.[22] asked HNC 386 patients about the role fulfilled by their carer(s) and their support. Patients identified the main roles of caregivers as providing emotional support (75%), taking them to healthcare appointments (67%), cleaning the home (62%), and shopping for food (59%). About 60% felt that caring was a considerable burden or very hard for their carers. Patients over 65 years of age and those with low socio-emotional functioning were the most likely to need a considerable amount of care and support.

Shuman et al.[23] carried out a study on the perceived quality of care received by HNC patients at the end of their lives. Results of a survey among families of 58 patients who died of HNC revealed that palliative treatments of HNC, death outside of the hospital, and palliative care team involvement all improve the end-of-life experience in this population.

These studies demonstrate the importance of symptom management and psychosocial care not only in patients but also in their caregivers. Supportive care comes within the responsibility of several care providers: surgeons, radiation and medical oncologists, primary care physicians, and various psychosocial and allied health service providers. These care providers often have disposal over only part of the relevant information and communication between care providers regarding well-being and psychosocial functioning is limited. Because of this fragmentation of continuity of care, patients and families often complain about feelings of powerlessness and a lack of guidance.

There is growing interest in using quality of life questionnaires in clinical practice to monitor quality of life and to facilitate communication about quality of life between doctors and patients. There is less evidence that this approach may affect patient outcome or improve quality of life and it is argued that additional efforts are needed to enhance the effect of screening.[24] For example, the presence of a professional care navigator leads to higher patient satisfaction, shorter duration of hospitalization, fewer cancer-related problems, better emotional quality of life, and patient empowerment.[25]

CONCLUSION

In summary, HRQOL seems a significant predictor of survival. However, this association may be influenced by various cancer-related, personal, biological, psychobehavioural, physical, lifestyle-related, and social factors, which may also interact with each other. These factors are also of influence in predictive modelling of HRQOL as such. Previous research on HRQOL in HNC was often based on cross-sectional designs or often lacked adequate multivariate statistical analyses to adjust for confounding or moderating factors. The large variety of HRQOL questionnaires and variability in predictors between studies and the highly selected inclusion criteria from the RCTs on which most evidence is based, seriously hampers the generalizability of the results of previous studies. In addition, less is known about the course of HRQOL over time and about the (broad range of) possible factors associated with change in (long-term) HRQOL of HNC patients. Insight in the incidence and prevalence of late effects of HNC and treatment and in their associated risk factors is scarce. Better information on all aspects of HRQOL is therefore highly needed as is evidence regarding cost-effectiveness of (new) treatment options, symptom management, and psychosocial care, also in the context of increasing long-term survival and growing attention for cancer survivorship.

Key points:

- HRQOL is an important outcome measure in clinical trials.
- HRQOL is associated with survival, but large-scaled cohort studies are needed investigating possible moderators and mediators such as cancer-related, personal, biological, psychobehavioural, physical, lifestyle-related, and social factors.
- Predictive models of HRQOL are highly needed.
- Organising supportive care by appointing a care coordinator and implementing a survivorship care plan or advanced palliative care planning is beneficial for HNC cancer patients and their caregivers and may improve their HRQOL.
- More evidence is needed on cost-effectiveness of supportive care.

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CHAPTER 3

THE ASSOCIATION BETWEEN HEALTH-RELATED QUALITY OF LIFE AND SURVIVAL IN PATIENTS WITH HEAD AND NECK CANCER: A SYSTEMATIC REVIEW

A.J. van Nieuwenhuizen
L.M. Buffart
J. Brug
C.R. Leemans
I.M. Verdonck-de Leeuw

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ABSTRACT

Objective. To study the association between health-related quality of life (HRQoL) and survival in patients with head and neck cancer (HNC) based on a systematic review of prospective studies.

Methods. A systematic search was conducted in four electronic bibliographic databases. We included studies published up to January 2014, providing data on HRQoL and survival, and the association between HRQoL and survival, among HNC patients. Two researchers independently performed a quality rating. A best evidence synthesis was applied to draw conclusions.

Results. Nineteen studies were included. Twelve studies included all subscales of a HRQoL questionnaire and seven studies focused on specific subscales. The mean quality score was 72 ±17% and 58% of the studies were of high quality. According to the best evidence synthesis, we found strong evidence for a positive association between pre-treatment physical functioning and survival and between change in global QoL from pre-treatment to 6 months after treatment and survival. Due to inconsistent findings, we found insufficient evidence for an association with survival of other HRQoL domains, including role, emotional, cognitive and social functioning, mental health and well-being.

Discussion. This systematic review showed that higher levels of pre-treatment physical function and change in global QoL from pre-treatment to 6 months after treatment are associated with survival in patients with HNC. Future high quality studies with a longitudinal design are needed to examine the complex associations between HRQoL and survival.

INTRODUCTION

Patient reported-outcomes are increasingly used in clinical trials in cancer patients besides the traditional outcome measures as tumor control, overall survival, morbidity and complications.[1-5] This has led to an increased understanding about the course of health-related quality of life (HRQoL) in patients with cancer. It is well known that patients have to deal with various physical and psychosocial side effects of cancer and cancer treatment, including reduced physical fitness and function, reduced self-esteem, increased emotional distress and fatigue, negatively affecting HRQoL.[1-6] Furthermore, there is evidence of a positive association between HRQoL and survival in patients with cancer. Previous reviews and meta-analyses in populations with different types of cancer showed that lower pre-treatment HRQoL was associated with reduced survival.[7-10] Recently, in a pooled analysis, Quinten et al.[10] examined the association between pre-treatment HRQoL and survival separately for 11 different cancers. She concluded that for each cancer, at least one HRQoL domain provided prognostic information additional to clinical and demographic variables such as age, performance status and metastasis, increasing the accuracy of survival prognosis.[10]

Little is known about the association between HRQoL and survival in head and neck cancer patients (HNC). Investigators have found that HNC and its intensive treatment has a distinct impact on HRQoL different from other cancers. In addition to physical and psychosocial problems that patients with all cancers are facing, patients with HNC are often confronted with oral dysfunction, swallowing and speech problems.[11-18] Previous studies showed a decline in general health, mental health, physical function, appearance, employment, and social functioning during and immediately after treatment for HNC.[11;12;14;15;17-27] Also, many HNC survivors continue to suffer from various disease and treatment related physical and psychosocial problems for many years after treatment.[11;12;18;19] Two other prospective cohort studies reported that HRQoL ten years after diagnosis was significantly lower than HRQoL before treatment.[21;28]

In 2008, Mehanna et al.[29] published a systematic review summarizing the available studies examining the association between a broad range of psychosocial factors and survival in patients with HNC. They reported that psychosocial complaints, physical self-efficacy and higher physical functioning were associated with increased survival. In addition, they found that global QoL one year after diagnosis was significantly associated with survival, but this was not the case for global QoL at diagnosis.[29] The review of Montazeri et al.[8] revealed significant associations between HRQoL and survival for most cancers, but findings of studies on HNC patients were inconsistent and based on a limited number of studies. More studies evaluating the association between HRQoL and survival in patients with HNC have been published since the two previous reviews, which warrants a new systematic review of the present evidence.

Furthermore these previous reviews have not applied a best evidence synthesis to summarize the data, which hampers interpretability. Therefore, the objective of this systematic review is to study the association between HRQoL and survival in patients with HNC with profound methodology, and to identify which HRQoL domains are most strongly associated with survival, adjusted for important clinical, demographic and lifestyle-related factors.

MATERIALS AND METHODS:

Selection of studies

A literature search up to 23rd of January 2014 was conducted in four electronic bibliographic databases (PubMed, EMBASE, PsychINFO and CINAHL) in collaboration with a librarian. In order to identify all relevant papers, we used keywords, Mesh terms and free terms for the following search terms including "Head and neck neoplasm", "Quality of life" or "patient reported outcome" and "survival" or "prognostic". The complete search strategy of the literature search is available upon request. The reference lists of all selected papers were screened for additional relevant papers.

Study inclusion criteria

Studies were included if they (1) included patients with HNC, (2) had a prospective study design, (3) assessed HRQoL with a standardized questionnaire, (4) measured mortality and/or survival, (5) analyzed the association between HRQoL and survival, and (6) were full text articles written in English, German or Dutch. Studies focusing on patients with cancer of the thyroid, esophagus, skin or skull base were excluded. We also excluded studies that were part of a supportive care intervention aiming to improve the HRQoL of patients.

Selection procedure and quality assessment

Title and abstract of the references were reviewed to exclude articles out of scope (AN). Full texts of potentially relevant articles were assessed for eligibility by two independent reviewers (AN and LB). Two authors (AN and LB) independently assessed the methodological quality of the included articles. Disagreements were discussed and resolved. The methodological quality of the included studies was scored on a methodological criteria list based on the criteria list suggested by Hayden et al,[30] who developed the list after an extensive review and critical appraisal of systematic reviews of prognostic studies supplemented by recent methodological studies. The list comprises 6 potential biases for prognostic studies i.e. study participation, study attrition, prognostic factors, outcome measurement, confounding measurements and account and analysis. Because most of the included studies focused on HRQoL assessed at only one time point, we excluded the item study attrition. Table 1 presents the methodological scoring list used in the present study. We defined clinical variables (tumor location and stage), demographic variables (age, gender), and comorbidity and lifestyle factors (smoking and alcohol intake) as important confounders that should be accounted for in the analysis, since they are important prognostic predictors for survival. The list contains 11 criteria which can be scored positive (1) or negative (0). A positive score was given when sufficient and adequate information on the criterion was available. A negative score indicates that the paper provided no or insufficient information about this criterion. For the last item in the quality assessment (presentation of points estimates and measures of variability) we gave 0.5 points if all data from the univariate analysis were present but not from multivariate analysis. If the study referred to another publication containing relevant information about the same study, we retrieved the additional publication to score the criterion of concern. The total score is the sum of all criteria that were scored positively, with a maximum score of 11 points. For each study we calculated the percentage of items that a study scored positively on methodological quality. A study was considered of 'high quality' if the quality score was ≥75%.[31]

Data extraction

The following data were extracted (AN): first author, year of publication, number of patients included, cancer location and stage, assessment of HRQoL, subscales included in the analysis, assessment and period of survival, univariate and multivariate association between HRQoL and overall survival (including hazard ratios with 95% confidence intervals (CI) and p-values), and covariates.

Level of scientific evidence

To synthesize the methodological quality of the studies and to be able to draw conclusions regarding the relationship between HRQoL and survival, we applied a best-evidence synthesis.[31;32] The rating system consists of three levels and takes into account the number, methodological quality and consistency of outcomes of these studies as follows: (A) Strong evidence, provided by generally consistent findings in multiple (≥2) high quality studies, (B)

We considered results to be consistent when ≥ 75% of the studies showed results in the same direction, which was defined according to significance ($p<0.05$). If two or more studies were of high methodological quality, we disregarded the studies of low methodological quality in the evidence synthesis. We included the multivariate results in the best evidence synthesis, and it was applied separately for each time point of HRQoL measurements (e.g. pre-treatment, post-treatment), and for different HRQoL domains (e.g. global QoL, functioning, well-being).

Table 1. Quality Assessment

		Coyne-2007 [38]	Curran-2007 [49]	De Graeff-2001 [40]	Fang-2010 [43]	Fang-2003 [50]	Grignon-2007 [55]	Karvonen-2008 [47]	Lango-2013 [41]	Mehanna-2006 [56]	Meyer-2009 [44]	Nordgren-2007 [53]	Nordgren-2006 [52]	Nordgren-2003 [51]	Oskam-2010 [45]	Osthus-2013 [48]	Osthus-2011 [46]	Siddiqui-2007 [39]	Tarsitano – 2012 [42]	Thomplson-2011 [54]	Proportion of positive scores (%)
Study participation																					
A	The sampling frame and recruitment are adequately described (setting and geographic location)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	95
B	Inclusion and exclusion criteria are adequately described	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	95
C	The baseline study sample (participants) are adequately described for key characteristics (age, gender, tumor location and stage)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100
D	There is adequate participation in the study by eligible patients (> 75%) or differences between responders and non-responders is adequately described	1	1	1	1	1	0	0	1	1	0	0	0	0	1	1	1	1	0	0	58
Prospective factor measurement																					
E	HRQoL is assessed with a valid measurement instrument	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100

Table 1. Continued

		Coyne-2007 [38]	Curran-2007 [49]	De Graeff-2001 [40]	Fang-2010 [43]	Fang-2003 [50]	Grignon-2007 [55]	Karvonen-2008 [47]	Lango-2013 [41]	Mehanna-2006 [56]	Meyer-2009 [44]	Nordgren-2007 [53]	Nordgren-2006 [52]	Nordgren-2003 [51]	Oskam-2010 [45]	Osthus-2013 [48]	Osthus-2011 [46]	Siddiqui-2007 [39]	Tarsitano – 2012 [42]	Thompson-2011 [54]	Proportion of positive scores (%)
Outcome measurement																					
F	Survival is clearly defined and measured appropriatelya	0	0	0	0	0	0	1	0	1	1	0	0	0	0	1	0	0	0	0	21
Confounding measurement and account																					
G	All important confounders are measured (key demographic, clinical factors, lifestyle factors and comorbidity)b	0	0	0	1	0	0	1	1	0	1	0	0	0	0	1	1	0	1	0	37
H	Important potential confounders are accounted for in the analysis (appropriated adjustment)	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	1	74
Analysis																					
I	There is sufficient presentation of HRQoL, mean (SD)	0	0	1	1	1	0	1	1	0	1	0	0	0	0	1	1	1	1	0	53
J	There is sufficient presentation of the outcome	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95
K	The strategy for model building is clearly described and appropriate	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	84

Table 1. Continued

		Coyne-2007 [38]	Curran-2007 [49]	De Graeff-2001 [40]	Fang-2010 [43]	Fang-2003 [50]	Grignon-2007 [55]	Karvonen-2008 [47]	Lango-2013 [41]	Mehanna-2006 [56]	Meyer-2009 [44]	Nordgren-2007 [53]	Nordgren-2006 [52]	Nordgren-2003 [51]	Oskam-2010 [45]	Osthus-2013 [48]	Osthus-2011 [46]	Siddiqui-2007 [39]	Tarsitano – 2012 [42]	Thomplson-2011 [54]	Proportion of positive scores (%)
L	Point estimate and measures of variability (HR and 95% CI) were presented(0.5 points if all data were presented of univariate analysis, 1 point for multivariate analysis)	1	0	0	1	0.5	0	1	1	1	1	0	0	0	1	1	1	0	1	0	53
Total quality score, points		9	8	9	10	8.5	6	11	11	7	10	6	6	5	9	12	11	9	9	7	-
Percentage of maximum score (%)		75	67	75	83	71	50	92	92	58	83	50	50	42	75	100	92	75	75	58	72

Moderate evidence, provided by generally consistent findings in one high quality study and (≥1) low quality studies, (C) insufficient evidence, when only one study was available or findings were inconsistent in multiple (≥2) studies. We considered results to be consistent when ≥ 75% of the studies showed results in the same direction, which was defined according to significance ($p<0.05$). If two or more studies were of high methodological quality, we disregarded the studies of low methodological quality in the evidence synthesis. We included the multivariate results in the best evidence synthesis, and it was applied separately for each time point of HRQoL measurements (e.g. pre-treatment, post-treatment), and for different HRQoL domains (e.g. global QoL, functioning, well-being).

RESULTS

Identification and selection of the literature

After removing duplicates, the literature search yielded 2481 unique articles. For 82 potentially relevant articles, we checked full text (Figure 1). The majority of the studies (n=29) were excluded because they lacked information on survival or they did not assess the association between HRQoL and survival (n=29). Of the articles identified in the database search, 14 met the inclusion criteria. We found five additional articles from the reference lists of the included studies. Consequently 19 studies were included in this review comprising 5207 patients. Two articles[33;34] included the same patient population and were counted as one population (n=1093).

Quality assessment

Results of the methodological quality assessment are presented in Table 1. The mean quality score was 72±17% (range 42-100%). Eleven studies[33-43] were of high quality. Of all studies, 79% had shortcomings in the assessment and definition of survival: methods for survival assessment were unknown for 13 studies,[33;34;36-38;40;41;44-49] whereas two studies[35;50] used medical records and. In addition, 63% of the studies had shortcomings in assessments of important confounders: eleven studies[33-35;38;39;41;44;45;47;49;51] did not assess comorbidity, and seven[40;44-48;50] studies did not assess smoking and alcohol consumption. Shortcomings in presenting point estimates and measures of variability were reported in 47% of the studies: Eight studies[34;35;40;44;46-50] reported only significance levels of the association without presenting point estimates and measures of variability and one study[45] presented results of the univariate associations but only reported point estimates and measures of variability of associations that were significant in the multivariate analysis. All studies except for one,[51] adequately described baseline characteristics, recruitment, and in- and exclusion criteria of the study sample.

In addition, all studies used a valid questionnaire to assess HRQoL, and one study[49] used an additional single question on global QoL.

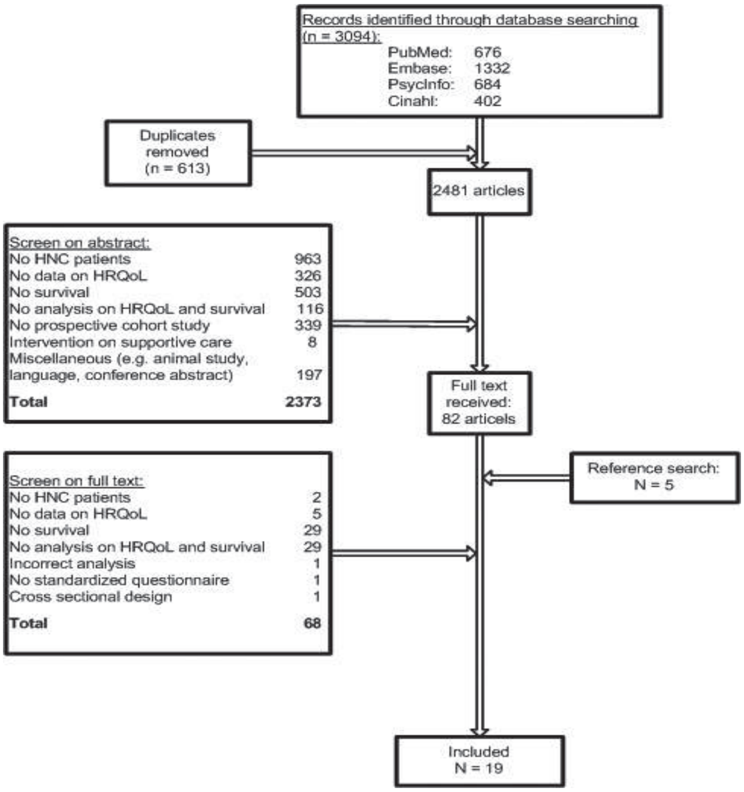

Figure 1. Flowchart of study inclusion

Data extraction

Characteristics of the included studies are presented in Table 2. Sixteen studies[33-40;43-48;50;51] assessed HRQoL before treatment. One study[42] assessed the baseline assessment of HRQoL within 2 years after diagnosis, and two studies[41;49] assessed the HRQoL of patients after a minimal disease free period of 1 year or 2 years. Fifteen studies[33-37;39-45;49-51] included mixed sites of HNC, Nordgren et al.[46-48] published three articles in which the HNC sub-sites oral cavity, pharyngeal and larynx were separately presented (Table 2), and one study[38] included patients with nasopharyngeal carcinomas only. Thirteen studies[35-38;41-43;46-51] included patients with all stages of the tumor, three studies[33;34;40] included patients with tumor stage II, III and IV, two studies[44;45] included patients with tumor stage III and IV, and one study[39] included patients with tumor stage I and II. Twelve studies[35;37-41;43-48] used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) to assess HRQoL, three studies[42;49;50] used the Short Form-36 health survey (SF-36), two studies[33;34] used the Functional Assessment of Cancer Therapy – General (FACT-G), one study[51] the Auckland quality of life questionnaire, one study[36] used the EuroQol 5D (EQ5D), and one study[49] used a self-administered single question on general QoL (a Likert type scaling of overall QoL ranging from 1 (very poor) to 5 (excellent)) in addition to the SF-36.

Pre-treatment HRQoL and the association with survival

Table 3 presents an overview of the associations between survival and HRQoL assessed pre-treatment (top) and during or after treatment (bottom). Pre-treatment global QoL was assessed in thirteen studies, of which six[35;37-40;43] were of high quality. Pre-treatment physical function was assessed in ten studies of which four[35;38;39;43] were of high quality. Nine studies assessed pre-treatment emotional functioning, social functioning, role functioning and cognitive functioning, of which four[35;38;39;43] were of high quality. One high quality study[34] included pre-treatment functional, physical, emotional and social well-being and one high quality study[36] included pre-treatment HRQoL using the EuroQol5D (EQ5D) questionnaire.[52] One low quality study[50] determined pre-treatment mental component summary scores.

Of all high quality studies,75% showed that a higher pre-treatment physical functioning was associated with reduced mortality (HR = 0.64 to 0.99) in the multivariate analysis after adjusting for important clinical, demographic and lifestyle related factors, indicating strong evidence (Table 3). This significant association was supported by 50% of low quality studies.

Table 2. Data extraction from included studies

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
HRQoL assessed pre-treatment												
Coynea 2007 [38]	1093	OC, OP, HP, L	II/III/ IV	FACTG	unknown	Unclear	EWB	1.02 (0.99-1.04)	0.09	1.02(0.99-1.04)	0.13	T, N stage, KPS score, cigarette use, age, income, marital status
Curran 2007 [49]	419	OP, HP, L	III/IV	C30	49m and 29.3m	Unclear	gQoL	n.m.	<0.001	1.66	0.005	T, N stage, tumor site, KPS, age, sex
							PF	n.m.	<0.001	n.m.	n.s.	
							RF	n.m.	n.s.		n.a.	
							EF	n.m.	n.s.		n.a.	
							CF	n.m.	n.s.		n.a.	
							SF	n.m.	n.s.		n.a.	
de Graeffa 2001 [40]	208	OC, OP, HP, L	All	C30	Fu:45m (36-62) surviving patients	At time of analysis survival was checked	gQoL	n.m.	n.s.	n.m.	n.s.	Sex, age, marital status, stage, growth pattern, treatment, radicality and all QoL subscales, smoking, drinking
							PF	n.m.	< 0.05	n.m.	n.s.	
							RF	n.m.	n.s.	n.m.	n.s.	
							EF	n.m.	n.s.	n.m.	n.s.	
							CF	n.m.	< 0.05	1.9 (1.10-3.26)	< 0.05	
							SF	n.m.	< 0.05	n.m.	n.s.	

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
Fanga 2010 [43]	347	NP	All	C30	5y; No survival period	Unclear	gQoL	n.m.	< 0.05	0.83 (0.72-0.94)	0.002	Age, sex, smoking, cancer stage
							PF	n.m.	< 0.05	0.74 (0.64-0.85)	< 0.001	
							RF	n.m.	< 0.05	0.88 (0.79-0.96)	0.005	
							EF	n.m.	n.s.	0.93 (0.82-1.03)	0.16	
							CF	n.m.	< 0.05	0.89 (0.80-0.99)	0.03	
							SF	n.m.	< 0.05	0.87 (0.78-0.95)	0.003	
Fang 2003 [50]	102	OC, OP, HP, L	III/IV	C30	5y; No survival period	Unclear	gQoL	0.99 (0.98-0.99)	0.04	n.m.	n.s.	Stage, KPS, N status
							PF	0.99 (0.97-0.99)	0.03	n.m.	n.s.	
							RF	0.99 (0.99-1.00)	0.22		n.a.	
							EF	0.99 (0.98-1.01)	0.27		n.a.	
							CF	0.99 (0.99-1.01)	0.37		n.a.	
							SF	0.99 (0.98-1.00)	0.14		n.a.	
Grignon 2007 [55]	571	OC, OP, HP, L	All	SF-36	5y; No survival period	Medical record	PCS	n.m.	n.m.	0.97	<0.001	Site, stage, co-morbidity, mental component SF-36
							MCS	n.m.	n.m.	n.m.	0.56	

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
Langoa 2013 [41]	159	HNC	All	EQ5D	Fu:32m (1-71)	Unclear	PRHS	0.02	1.02	2.1 (0.94-5.0)	0.07	T and N classification, performance status, smoking and weight loss
							Mob	1.9	0.19		n.a.	
							Sc	0.006	0.67		n.a.	
							Act	2.7	0.14		n.a.	
							P&D		0.05		n.a.	
							- none	Referent	0.07		n.a.	
							- mod	2.8	0.10		n.a.	
							- sev	8.3	0.03	2.4 (1.1-5.6)	0.05	
							D&A					
							- none	Referent	0.005		n.a.	
							- mod	4	0.01		n.a.	
							- sev	10	0.004		n.a.	
Mehanna 2006 [56]	200	HNC	All	Auckland QoL	10y; Median survival: 6y	Centralized national clinical booking system	GHQ	1.6 (1.10-2.39)	0.02	0.9 (0.5-1.4)	0.26	T, N stage, disease stage, age, gender, smoking, alcohol consumption
							LSS	1.5 (1.02-2.22)	0.04	3.0 (2.1-4.2)	<0.001	
Meyera 2009 [44]	540	HNC (larynx and others)	I/II	C30	5y; Median follow-up: 6.5y	Mortality files, death certificates	gQoL	0.98	0.46		n.a.	Cancer stage, cancer site, age, smoking, alcohol, BMI, trial arm assignment
							PF	0.85	<0.001	0.87 (0.81-0.94)	< 0.001	
							RF	0.94	0.04	0.93 (0.89-0.99)	0.019	
							EF	1.03	0.32		n.a.	
							CF	1.05	0.22		n.a.	
							SF	0.99	0.89		n.a.	

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
Nordgren 2007 [53]	122	OC	All	C30	5y; Survival rate (5y): 52%	Unclear	gQoL	n.m.	n.s.		n.a.	Advanced disease stage (III/IV), co-morbidity present, fatigue, pain C30, pain HN35, sense, speech, teeth, opening mouth wide, dry mouth
							PF	0.98 (0.97-0.99)	< 0.001	n.m.	n.s.	
							RF	n.m.	n.s.		n.a.	
							EF	n.m.	n.s.		n.a.	
							CF	n.m.	<0.05	n.m.	n.s.	
							SF	n.m.	<0.05	n.m.	n.s.	
Nordgren 2006 [52]	89	pharynx	All	C30	5y; Survival rate (5y): 41%-50%	Unclear	gQoL	n.m.	n.s.		n.a.	Advanced disease stage (III/IV), no brachytherapy given, fatigue, dyspnea, speech, coughing, feeling ill
							PF	0.99 (0.98-1.00)	0.027	0.98(0.97-0.99)	0.002	
							RF	n.m.	n.s.		n.a.	
							EF	n.m.	n.s.		n.a.	
							CF	n.m.	n.s.		n.a.	
							SF	n.m.	n.s.		n.a.	
Nordgren 2003 [51]	86	L	All	C30	5y; Survival rate (5y): 62%	Unclear	gQoL	0.98 (0.96-0.99)	0.001	n.m.	n.s.	Radiotherapy / other treatment, stage I + II, stage III +IV, HADS depression, comorbidity and speech scale
							PF	0.97 (0.96-0.98)	< 0.001	0.98 (0.96-0.99)	< 0.001	
							RF	0.98 (0.97-0.99)	< 0.001	n.m.	n.s.	
							EF	n.m.	n.s.		n.a.	
							CF	n.m.	n.s.		n.a	
							SF	0.98 (0.97-0.99)	<0.001	n.m.	n.s.	

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
Oskama 2010 [45]	80	OC, OP	II/III/IV	C30	5y; Median survival: 58m (3.5-102)	Unclear	gQoL	n.m.	n.s.	n.m.	n.s.	Tumor site, stage, surgical status, metastasis, radiotherapy, age, gender, marital status, comorbidity
Osthusa 2013 [48]	106	OC, OP, L, other	All	C30	> 4y; Survival rate (5y): 69.1%	National population register	gQoL	0.31 (0.15-0.61)	0.001	0.47 (0.20-1.10)	0.08	Sex, age, coping by suppression, coping by disengagement, levels of neuroticism, TNM stage, tumor site, alcohol consumption, smoking status, comorbidity
							PF	0.98 (0.96-0.99)	< 0.001	0.97 (0.95-0.99)	< 0.001	
							RF	0.99 (0.98-1.00)	0.18		n.a.	
							EF	0.99 (0.97-1.00)	0.07		n.a.	
							CF	1.00 (0.98-1.01)	0.75		n.a.	
							SF	1.00 (0.98-1.01)	0.79		n.a.	
Siddiquia 2007 [39]	1093	OC, OP, HP, L	II/III/IV	FACT G	Unknown	Unclear	PWB	n.a.		n.m.	n.s.	T, N stage, KPS score, primary site, cigarette use, age, income, marital status
							SWB	n.a.		n.m.	n.s.	
							EWB	n.a.		n.m.	n.s.	
							FWB	n.a.		n.m.	n.s.	
Tarsitanoa 2012 [42]	142	OC	All	C30	5y, OS 55.3% at 60m	unclear	gQoL	0.83 (0.77-0.88)	<0.001	0.86 (0.80-0.93)	<0.001	Age, tumor location, treatment modality, stage

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
HRQoL assessed during or after treatment												
Karvonena 2008 [47]	495	HNC	All	SF-36	FU: 5.1y (13d-7.2y)	Death file for veterans	PCS MCS	0.83(0.77-0.88) 0.96(0.91-1.02)	<0.001 0.158	0.86(0.80-0.93) 0.98 (0.93-1.05)	< 0.001 0.589	Age, time since diagnose, marital status, education, site, stage, comorbidity, smoking
Mehanna 2006 [56]	200	HNC	All	Auckland QoL	10y Median survival: 6y	Centralized national clinical booking system	GHQ LSS	n.m.		1.1 (0.6-2.1) 2.5 (1.4-4.3)	0.72 0.001	disease stage, age, gender, smoking, alcohol consumption, nodal involvement and tumor site
Meyera 2009 [44]	540	HNC (larynx and others)	I/II	C30	5y; Median follow-up: 6.5y	Mortality files, death certificates	Ch-QoL Ch-PF Ch-RF Ch-EF Ch-CF Ch-SF	0.91 0.96 0.91 0.92 0.92 0.91	0.01 <0.001 0.002 0.03 0.03 0.02	0.91)0.84-0.99) 0.75 (0.68-0.83) 0.85 (0.79-0.91) 0.91 (0.84-0.99) 0.91 (0.84-0.99) 0.89 (0.82-0.97)	0.023 <0.001 <0.001 0.024 0.037 0.011	Cancer stage, cancer site, age, smoking, alcohol, BMI, trial arm assignment
Oskama 2010 [45]	80	OC, OP	II/III/ IV	C30	5y Median survival: 58m (3.5-102)	Unclear	QoL6m QoL-deterioration	n.m. n.m.	≤0.01 ≤0.01	0.96 (0.94-0.99) 5.08(2.30-14.60)	0.00 0.00	Tumor site, stage, surgical status, metastasis, radiotherapy, age, gender, marital status, comorbidity

Table 2. Continued

First author and year of publication	Patients (n)	Cancer site	Tumor stage	QoL PRO	Survival Period (mean +SD)	Assessment of survival		Association between QoL and survival				Factors adjusted for
								univariate		multivariate		
								HR (95% CI)	p-value	HR (CI)	p-value	
Osthusa 2011 [46]	139	HN-SCC	All	C30	> 5y; fu: 75m (SD 4m)	Unclear	QoL func. sum score	n.m. n.m.	n.m. n.m.	0.99 (0.97-1.01) 0.97 (0.93-1.01)	0.154 0.085	TNM stage, site, alcohol consumption, currently smoking, heart and lung disease, gender, age, time between diagnosis and inclusion, neuroticism, avoidance focused coping, coping by suppression of competing activity
Thompson 2011 [54]	276	OC, OP, HP, L	All	SF-36	3/4/5y Survival rate (5y): 61.1%	Unclear	PHS QoL	n.m. n.m.	0.01 <0.001	n.m. 4.62	0.29 0.02	Stage, alcohol abuse, tobacco use, age

Abbreviations: Act, problems performing usual activities; BMI, body mass index; C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; CF: cognitive functioning; Ch: change; CI, confidence interval; D&A, depression and anxiety; EF: emotional functioning; EWB: emotional well-being; EQ5D, EuroQol-5d-3L; FACT-G, Functional Assessment of Cancer Therapy – General; fu: follow up; func., functioning; FWB: functional well-being; GHQ, general health questionnaire; gQoL, global quality of life; HADS, Hospital Anxiety and Depression Scale; HN35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck 35; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; HP, hypopharynx; HR, hazard ratio;

Table 2. Continued

KPS, Karnofsky Performance Score; L, larynx; LSS, Life Satisfaction Score; m, months; MCS, mental component summery; Mob, problems with mobility; n, number; n.a., not assessed; n.m., not mentioned; NP, nasopharynx, n.s., not significant; OC, oral cavity; OP, oropharynx; OS, overall survival; P&D, pain and discomfort; PCS, physical component summery; PF, physical function; PHS: physical health score; PRHS, patient related health state; PRO; Patient Reported Outcome; PWB, physical well-being; QoL: quality of life; RF: role functioning; Sc, problems with self-care; SD, standard deviation; SF-36, short form 36 health survey; SF: social functioning; SWB: social well-being; (T)(N)(M)-stage, tumor, node, metastasis; Y: year(s)

[a] indicates the high quality study

Inconsistent findings were found for global QoL, role functioning, cognitive functioning, and social functioning, with 25-50% of the high quality studies reporting significant positive associations with survival, indicating insufficient evidence (level C). Insufficient evidence was also found for the positive associations of emotional function and mental HRQoL with survival, as none of the high quality studies reported a significant association (Table 3). Two separate articles[33;34] on the same patient population reported no significant association of physical, functional, emotional and social well-being with survival. One study[36] using the Eq5D showed that severe pain and discomfort was significantly associated with impaired survival, and no significant associations were found for mobility, self-care, usual activities, and anxiety and depression.

HRQoL during or after treatment and the association with survival

Four high quality studies[39-42] and two low quality studies[49;51] examined the association between HRQoL during or after treatment and survival, in which HRQoL was assessed at different time points varying from during treatment to being disease free for more than 2 years (Table 3). Three studies reported that physical HRQoL assessed within 2 years after diagnosis,[42] global QoL 6 months post-treatment[40] and low QoL one year after treatment[51] were significantly positively associated with survival. Fang et al.[45] reported that improvements in these domains from pre-treatment to HRQoL assessed during radiotherapy were not significantly associated with survival. In patients who were disease free for more than 2 years, Thompson et al.[49] reported a 4 times higher likelihood of death in patients with a higher QoL compared to patients with a lower QoL. In contrast, Osthus et al.[41] found no significant association between global QoL and survival in patients who were disease free for at least one year (Table 2).

In addition, two high quality studies[39;40] included change in HRQoL from pre-treatment to 6 months after treatment. Both studies reported a significant association between change in global QoL and survival, after adjusting for clinical, demographic and lifestyle-related factors indicating strong evidence (Table 3). Regarding the other subscales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), improvement from pre-treatment to 6 months after treatment was also significantly positively associated with overall survival[39] (Table 2).

Table 3. Overview of the level of evidence regarding the associations between HRQoL and survival

	Studies included, n	Association between HRQoL and survival								Level of evidence
		univariate				multivariate				
		n.a.	n.s.	s.	%	n.a.	n.s.	s.	%	
HRQoL assessed pre-treatment										
Global QoL										
All studies	12	0	5	7	58	3	5	4	33	
High quality	6	0	3	3	50	1	3	2	33	Insufficient
Low quality	6	0	2	4	67	2	2	2	33	
Physical function										
All studies	10	1	0	9	90	0	4	6	60	
High quality	4	0	0	4	100	0	1	3	75	Strong
Low quality	6	1	0	5	83	0	3	3	50	
Role function										
All studies	9	0	6	3	33	5	2	2	22	
High quality	4	0	2	2	50	1	2	2	50	Insufficient
Low quality	5	0	4	1	20	4	0	0	0	
Emotional function										
All studies	9	0	9	0	0	7	2	0	0	
High quality	4	0	4	0	0	2	2	0	0	Insufficient
Low quality	5	0	5	0	0	5	0	0	0	
Cognitive function										
All studies	9	0	6	3	33	6	1	2	22	
high quality	4	0	2	2	50	2	0	2	50	Insufficient
Low quality	5	0	4	1	20	4	1	0	0	
Social function										
All studies	9	0	5	4	44	4	4	1	11	
High quality	4	0	2	2	50	2	1	1	25	Insufficient
Low quality	5	0	3	2	40	2	3	0	0	
Mental HRQoL										
All studies	2	1	1	0	0	0	2	0	0	
High quality	1	0	1	0	0	0	1	0	0	Insufficient

Table 3. Continued

	Studies included, n	Association between HRQoL and survival								Level of evidence
		univariate				multivariate				
		n.a.	n.s.	s.	%	n.a.	n.s.	s.	%	
Low quality	1	1	0	0	0	0	1	0	0	
HRQoL assessed after treatment										
Change Global QoL										
All studies	2	0	0	2	100	0	0	2	100	
High quality	2	0	0	2	100	0	0	2	100	Strong
Low quality	0	-	-	-		-	-	-		

Abbreviations: HRQoL, health related quality of life; n.a., not applicable; n.s., not significant; QoL, quality of life; s., significant.

DISCUSSION

This study reviewed the available evidence on the association between HRQoL and survival in patients with HNC using a best evidence synthesis. Our review resulted in two important findings. First, we found strong evidence that higher pre-treatment physical functioning of patients with HNC was associated with increased survival. This finding is in line with studies among patients with other cancers.[7-10] Moreover, Montazeri et al.[8] found a stronger association between pre-treatment physical functioning and survival compared to other HRQoL domains in patients with various cancer sites, although not in patients with HNC, which may be due to the limited number of studies on HNC.

We found insufficient evidence for an association with survival for other pre-treatment HRQoL subscales (global QoL, role functioning, emotional functioning, cognitive functioning, social functioning and mental HRQoL), after applying a best evidence synthesis. Although Mehanna et al.[29] reported in their review an association between cognitive functioning and survival, this finding was based on a single study. Quinten et al.[10] did a pooled analysis using data from randomized controlled trials using the EORTC-QLQ C30. Among patients with HNC no association for the majority of HRQoL subscales and survival was seen, however they found a remarkable association between lower emotional functioning and increased survival. Regarding psychosocial factors, a meta-analysis showed that psychosocial factors were associated with poorer survival in cancer patients.[53] Obviously, future high quality studies are needed to clarify the associations between cognitive functioning or emotional functioning and survival.

Second, we found strong evidence for the association between change in global QoL from pre-treatment to 6 months post-treatment and survival.

These results support the findings of the review of Montazeri et al.[8] who reported for some cancers, that changes in global QoL scores were prognostic for survival, when pre-treatment global QoL was not. Although HRQoL after treatment seems to be associated with survival as well, the limited number of studies and the large variation in assessment time points hampered us to apply a best evidence synthesis.
Future studies focusing on HRQoL should not only focus on pre-treatment HRQoL, but also include HRQoL at different time points after treatment, since they may have predictive value for survival.[8;29;39;40;51]

This systematic review included a quality rating and 58% of the studies were of high quality. Major concerns were the inadequate descriptions of survival assessment, adjustment for possible confounders and presentation of point estimates and measures of variability. As a consequence associations between HRQOL and survival might be biased. Because it is well established that age, tumor location and stage, smoking, alcohol intake and co-morbidity are significantly associated with survival, we selected these variables as confounders to be adjusted for in the reviewed studies.[54-56] However the choice of confounders remains somewhat arbitrary, and it is known that other factors such as more extended tumor characteristics (e.g. extra nodal tumor growth, HPV status, histological grading) and other socio-demographic factors (e.g. marital or socioeconomic status) may be important as well.[35;40;57;58]

Strengths of this study were the methodological quality assessment and best evidence synthesis. the inclusion of only prospective studies, it's solely focus on patients with HNC, and the systematic search in collaboration with a librarian. However some limitations must be noted. The majority of the studies seemed to selectively report the data since they did not report hazard ratios and confidence intervals of non-significant associations. This hampered us to conduct a meta-analysis. Instead we used a best evidence synthesis to summarize the available studies, since this allowed us to take into account non-significant associations as well. In our best evidence synthesis we included only high quality studies to reduce possible bias. However, similar to other reviews and meta-analysis, publication bias endangers the external validity, therefore publication bias cannot be ruled out.
Finally, although in our best evidence synthesis we only included high quality in which the association between HRQoL and survival was adjusted for important demographic, clinical and lifestyle-related factors, some residual confounding may still be present. For instance, although in most high quality studies tumor location and stage were taken into account as possible confounders, it cannot be ruled out that HRQoL may be a reflection of disease severity, and thereby associated with survival.

HRQoL and particularly physical functioning and change in global QoL were independently associated with survival. Improving these HRQoL domains may therefore be an interesting target to improve the survival. However, it is currently unclear whether poorer HRQoL represents a more advance and severe disease, or whether improving these HRQoL domains would result in improved survival.

In conclusion, this systematic review showed that higher levels of pre-treatment physical function and change in global QoL from pre-treatment to 6 months after treatment were associated with increased survival in patients with HNC. There is currently insufficient evidence for an association between other HRQoL domains and survival. Future high quality prospective studies should provide more insight into which time points are most predictive for survival and also determine the role of other HRQoL domains. To obtain a more precise estimate of the association between HRQoL and survival, we recommend that these future studies should more clearly describe how they collected survival data, adjust for relevant confounders and present point of estimates and measures of variability of the association.

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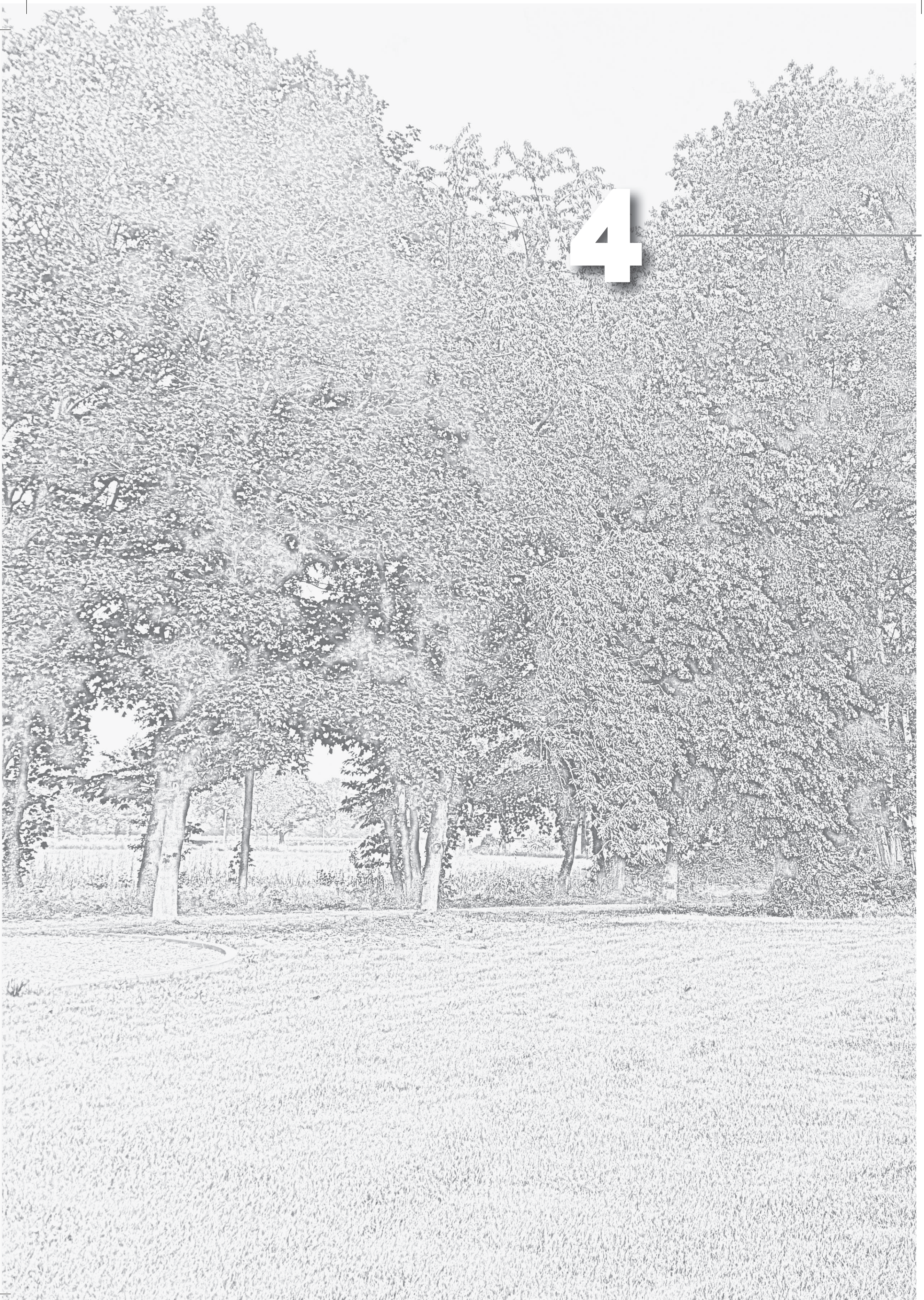

CHAPTER 4

HEALTH RELATED QUALITY OF LIFE AND OVERALL SURVIVAL: A PROSPECTIVE STUDY IN PATIENTS WITH HEAD AND NECK CANCER TREATED WITH RADIOTHERAPY

A.J. van Nieuwenhuizen
L.M. Buffart
J.A. Langendijk
M.R. Vergeer
J. Voortman
C.R. Leemans
I.M. Verdonck-de Leeuw

Submitted to: Quality of Life Research

ABSTRACT

Purpose We aimed to examine whether pre-treatment, post-treatment and change in health- related quality of Life (HRQoL) is associated with survival, in patients with head and neck cancer (HNC).

Methods We included 948 newly diagnosed HNC patients treated with primary or adjuvant (chemo)radiotherapy with curative intent. The EORTC QLQ-C30 questionnaire was assessed pre-treatment and at 6 weeks, 6 months and 12 months post-treatment. Multivariable Cox regression analyses were performed to examine whether HRQoL at all time-points and changes in HRQoL over time were associated with survival, after adjusting for demographic, clinical and lifestyle-related variables.

Results Higher HRQoL scores were significantly associated with improved 5-year overall survival at all time-points, except for the subscale global QoL at 6 weeks. Changes in HRQoL at 6 weeks post-treatment compared to pre-treatment were not significantly associated with survival. Changes in physical (HR: 0.88 95% CI: 0.82-0.96) and emotional functioning (HR: 0.90 95% CI: 0.85-0.96) from pre-treatment to 6 months post-treatment and changes in global QOL, and physical, emotional, and social functioning from pre-treatment to 12 months post-treatment were significantly associated with survival.

Conclusion Higher HRQoL reported pre-treatment and post-treatment (6 weeks, 6 months and 12 months) are significantly associated with improved survival, as well as changes in HRQoL at 6 and 12 months compared to pre-treatment.

Implications for cancer survivors Our results highlight the value of monitoring HRQoL and to identify those patients that report decreased or deteriorated HRQOL. This may help to further improve cancer care in a timely and efficient manner.

INTRODUCTION

Many patients with head and neck cancer (HNC) have to deal with severe physical and psychosocial problems because of the disease and its treatment. Additionally, they are often confronted with HNC specific problems, such as oral dysfunction, swallowing and speech impediments.[1-10] These disorders have a distinct impact on the health-related quality of life (HRQoL) of patients with HNC. It has been shown that the initial course of HRQoL during the first 2 years following treatment is favorable in HNC survivors compared patients who ultimately succumb to the disease. [9] Furthermore, previous observational studies showed a significant association between HRQoL and survival, independently from other demographic, lifestyle-related and clinical factors.[11-20] In a previous systematic review, we found evidence for a significant association between pre-treatment physical functioning and survival, and between change in global QoL from pre-treatment to 6 months follow-up and survival in patients with HNC.[21] However, we noticed that only a small majority (58%) of the existing studies was of high quality. Particularly, 63% of the studies included in that review did not consider relevant confounders (e.g. eleven studies did not assess comorbidity, and seven studies did not assess smoking and alcohol consumption).[21]

As a consequence, it remains difficult to draw firm conclusions on the association between HRQoL and survival. Therefore, the aim of this prospective study was to examine whether pre-treatment HRQoL, HRQoL at 6 weeks, and 6 and 12 months after treatment and change in HRQoL is associated with survival, after adjusting for demographic, clinical, and lifestyle-related factors in patients with HNC.

Patients and Methods

Study population

Between January 1999 and October 2009, all newly diagnosed patients with HNC who were planned to be treated with primary or adjuvant (chemo)radiotherapy in the Amsterdam University Medical Centres, location VUmc, completed questionnaires on HRQoL before treatment, and at 6 weeks, and 6 and 12 months after treatment as part of clinical routine. Patients were eligible for the current analyses if they: 1) were diagnosed with primary squamous cell carcinomas of the mucosal surfaces of the oral cavity, oropharynx, hypopharynx and larynx, 2) were treated with (chemo) radiotherapy or surgery combined with (chemo)radiotherapy with curative intent, 3) were ≥18 years old, 4) were able to read and understand the Dutch language, and 5) completed the pre-treatment questionnaire). Patients were excluded if they had a distant metastasis, were previously treated with surgery or radiotherapy in the head and neck area, or brachytherapy, or had a serious cognitive impairment at baseline.

Health-related quality of life

HRQoL was assessed using the 30-item European Organization for Research and Treatment of Cancer, (EORTC) Quality of Life Questionnaire core module (QLQ-C30) [22]. For the current analyses, we included the global quality of life (QoL) scale and the five function scales (physical, role, emotional, cognitive, and social functioning). Higher scores on the global QoL and functioning scales represent higher HRQoL.

Survival

Five-year survival was assessed by linking medical records to the Dutch death certificate register. Survival was calculated from the date of inclusion (pre-treatment questionnaire) until death.

Demographic, lifestyle-related and clinical factors

Demographic (i.e. gender, age, socio-economic status (SES)), lifestyle-related (i.e. smoking in packyears, smoking history, alcohol use (units per day), alcohol abuse (≥5 units per day)), and clinical factors (i.e. tumor site, stage, HPV status, types of treatment and comorbidity) were obtained from medical records. Socio-economic status was determined using zip codes of patients' living area. Zip codes were translated to SES according to The Netherlands Institute for Social Research [23]. This system describes the social status of a district compared to other districts in The Netherlands using an algorithm based on mean income, percentage of people with low income, percentage of people with low education and percentage of people without a job. Therefore, the mean score of all districts in The Netherlands is zero. We dichotomized SES scores to high (> mean value) versus low (≤ mean value).

Tumor stage was determined according to the American Joint Committee on cancer (AJCC) TNM staging system (seventh ed., 2010). Tumor site was categorized into cancer of the oral cavity, HPV positive oropharynx, HPV negative oropharynx, larynx or hypopharynx. All biopsies of patients with oropharyngeal cancer were tested for HPV on formalin-fixed, paraffin embedded tumor specimen according to a validated test algorithm.[24,25]

Treatment modality was categorized into radiotherapy alone, chemoradiation, or surgery followed by adjuvant (chemo)radiation. Additionally, we recorded whether the patients were treated with 3D-CRT (3-Dimensional Conformal Radiotherapy) or Intensity Modulated Radiotherapy (IMRT), that was introduced in our hospital in 2004. Comorbidity was assessed by a research physician (AvN) using the Adult Comorbidity Evaluation 27 (ACE-27) score,[26] a validated chart built instrument examining the presence of any of the following medical conditions: cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, immunological, previous malignancies, psychiatric disorders, alcohol use, and severe overweight, resulting in a total comorbidity score of none, mild, moderate or severe.

Statistical analysis

Descriptive statistics (mean, standard deviation (SD), or numbers and percentages) were generated for demographic, lifestyle-related, clinical factors, and HRQoL.

Univariable and multivariable Cox proportional hazard regression analyses were used to examine the association between HRQoL and survival. In the multivariable analyses, we adjusted for relevant demographic, lifestyle-related and clinical variables Separate models were built for each HRQoL subscale and for the different time-points (pre-treatment, 6 weeks, 6 months and 12 months after treatment, and change in HRQoL at 6 weeks compared to pre-treatment, change at 6 months compared to pre-treatment, and change at 12 months compared to pre-treatment). In the regression analyses, we divided all HRQoL scores by 10 because such changes are considered clinically meaningful.[27] For all statistical analyses, $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

From January 1999 and October 2009, 948 newly diagnosed patients with HNC met the inclusion criteria for the current analyses. All patients completed the questionnaire pre-treatment. After treatment, questionnaires were completed by 703 patients of the 947 alive (74%) at 6 weeks, 654 patients of the 914 alive (72%) at 6 months and 579 patients of the 838 alive (69%) at 12 months.

Demographic, lifestyle-related and clinical characteristics of the study population are presented in Table 1. The most frequent tumor site was larynx (43%). Among the patients with oropharyngeal cancer, 58% were diagnosed with a HPV negative tumor (HPV status was unknown in 14%). Overall, 60% of patients were alive after 5 years.

Table 1. Pre-treatment demographic, lifestyle-related and clinical characteristics of the study population

Characteristics	Patients (n= 948)
Demographic factors	
Gender, n (%) male	692 (73%)
Age, mean (SD) years	62 (11)
High SES (above average), n (%)	139 (15%)
Lifestyle related factors	
Smoking (packyears), mean (SD)	31 (22)
Former or current smoker, n (%)	806 (85)
Alcohol use (units per day), mean (SD)	3 (3)
Former or current alcohol abuse†, n (%)	262 (28)
Clinical factors	
Tumor site, n (%)	
Oral Cavity	152 (16)
Oropharynx	306 (32)
Oropharynx HPV positive*	86 (28)
Oropharynx HPV negative*	176 (58)
Oropharynx HPV unknown*	44 (14)
Larynx	413 (44)
Hypopharynx	77 (8)
Disease Stage, n (%)	
I	171 (18)
II	193 (20)
III	181 (19)
IV	402 (43)
Comorbidity, n (%)	
None	297 (31)
Mild	322 (34)
Moderate	239 (25)
Severe	90 (10)
Type of treatment, n (%)	
Radiotherapy	522 (55)
Chemoradiation	224 (24)
Primary surgery with adjuvant treatment	203 (21)

Table 1. Continued

Characteristics	Patients (n= 948)
RT technique, n (%)	
IMRT	593 (63)
5 year overall survival rate (%)	570 (60)
Drop-out due to death, n (%)	
6 weeks	10 (1)
6 months	34 (4)
12 months	110 (12)

Health-Related Quality of Life in relation to survival

Mean (SD) scores on the HRQoL subscales and results of Cox regression analyses are presented in Table 2. Adjusted for all included demographic, lifestyle-related and clinical factors, higher (better) scores on all subscales (global QoL, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning) as measured pre-treatment and at 6 and 12 months after treatment were significantly associated with longer survival, (Table 2). At 6 weeks after treatment, higher scores on all subscales were also significantly associated with longer survival, except for global QoL.

Table 2. HRQoL scores and uni- and multivariable Cox regression analyses on the association between HRQoL and survival

	Mean (SD)	Univariable model HR (95% CI)	p-value*	Multivariable model HR (95% CI) †	p-value*
EORTC QLQ-C30 pre-treatment (n=948)					
Global quality of life	66.6 (22.3)	0.89 (0.85-0.93)	0.00	0.91 (0.87-0.96)	0.00
Physical function	82.3 (20.8)	0.84 (0.81-0.88)	0.00	0.87 (0.83-0.91)	0.00
Role functioning	73.4 (32.3)	0.92 (0.90-0.95)	0.00	0.93 (0.90-0.96)	0.00
Emotional functioning	68.3 (23.4)	0.93 (0.90-0.97)	0.00	0.94 (0.90-0.97)	0.01
Cognitive functioning	85.1 (20.9)	0.92 (0.88-0.96)	0.00	0.91 (0.87-0.95)	0.00
Social functioning	82.4 (24.6)	0.92 (0.88-0.95)	0.00	0.91 (0.87-0.95)	0.00
EORTC QLQ-C30 6 weeks (n=703)					
Global quality of life	66.2 (21.5)	0.90 (0.85-0.95)	0.00	0.94 (0.89-1.00)	0.06
Physical function	74.6 (22.3)	0.86 (0.82-0.90)	0.00	0.90 (0.85-0.95)	0.00
Role functioning	66.5 (30.6)	0.91 (0.88-0.95)	0.00	0.93 (0.90-0.97)	0.00
Emotional functioning	76.2 (23.6)	0.93 (0.89-0.98)	0.00	0.94 (0.89-0.99)	0.02
Cognitive functioning	83.1 (21.1)	0.92 (0.87-0.97)	0.00	0.93 (0.88-0.91)	0.01
Social functioning	77.6 (25.1)	0.93 (0.89-0.97)	0.00	0.93 (0.88-0.98)	0.00
EORTC QLQ-C30 6 months (n=654)					
Global quality of life	71.0 (21.7)	0.86 (0.81-0.91)	0.00	0.87 (0.82-0.93)	0.00
Physical function	79.7 (19.9)	0.79 (0.75-0.84)	0.00	0.80 (0.75-0.86)	0.00
Role functioning	73.9 (29.2)	0.89 (0.85-0.93)	0.00	0.90 (0.86-0.94)	0.00
Emotional functioning	78.9 (24.1)	0.88 (0.84-0.92)	0.00	0.88 (0.83-0.93)	0.00
Cognitive functioning	85.2 (21.1)	0.91 (0.86-0.96)	0.00	0.89 (0.84-0.95)	0.00
Social functioning	82.5 (23.9)	0.89 (0.85-0.93)	0.00	0.89 (0.844-0.95)	0.00
EORTC QLQ-C30 12 months (n=579)					
Global quality of life	73.9 (21.5)	0.82 (0.77-0.87)	0.00	0.81 (0.76-0.87)	0.00
Physical function	82.1 (19.5)	0.79 (0.74-0.85)	0.00	0.81 (0.74-0.87)	0.00
Role functioning	78.1 (28.1)	0.86 (0.82-0.91)	0.00	0.86 (0.81-0.91)	0.00
Emotional functioning	81.7 (22.2)	0.86 (0.81-0.92)	0.00	0.82 (0.76-0.88)	0.00
Cognitive functioning	86.2 (19.7)	0.90 (0.84-0.97)	0.00	0.89 (0.82-0.96)	0.00
Social functioning	85.3 (22.2)	0.85 (0.80-0.90)	0.00	0.84 (0.78-0.89)	0.00

†adjusted for age, gender, socio-economic status, smoking (packyears), alcohol abuse (current or history), comorbidity, tumor site, tumor stage, treatment modality

*P of the log likelihood test

Footnote: Higher global QoL and functioning scores indicates higher HRQoL (scale 0-100).

Table 3 presents the mean changes in HRQoL at 6 weeks, 6 months and 12 months after treatment, respectively, compared to pre-treatment. Changes in HRQoL from pre-treatment to 6 weeks after treatment were not significantly associated with survival for any of the subscales (Table 4). Deterioration in physical and emotional functioning at 6 months post-treatment compared to pre-treatment was significantly associated with shorter survival. Deterioration in global QoL, physical, emotional and social functioning at 12 months after treatment compared to pre-treatment was significantly associated with shorter survival.

Table 3. Mean (SD) change scores in HRQoL

	Mean (SD) change
EORTC QLQ-C30 Δ 6 weeks (n=703)	
Global quality of life	-1.4 (23.7)
Physical function	-8.3 (20.8)
Role functioning	-7.2 (37.4)
Emotional functioning	6.9 (24.1)
Cognitive functioning	-2.2 (23.6)
Social functioning	-5.0 (28.1)
EORTC QLQ-C30 Δ 6 months (n=654)	
Global quality of life	3.3 (23.6)
Physical function	-4.2 (18.8)
Role functioning	-1.0 (33.9)
Emotional functioning	9.9 (24.6)
Cognitive functioning	-0.6 (22.1)
Social functioning	-1.0 (28.3)
EORTC QLQ-C30 Δ 12 months (n=579)	
Global quality of life	5.3 (23.5)
Physical function	-2.8 (18.9)
Role functioning	3.6 (34.9)
Emotional functioning	12.2 (23.0)
Cognitive functioning	-0.1 (20.9)
Social functioning	1.5 (27.1)

Δ change compared to pre-treatment. A negative mean change score indicates worsening of HRQoL after treatment compared to pre-treatment.

DISCUSSION

This comprehensive prospective study among a large group of patients with HNC showed that better HRQoL was significantly associated with longer survival, adjusted for demographic, lifestyle-related and clinical factors. This association was found for global QoL, and physical, role, emotional, cognitive, and social functioning before treatment as well as 6 weeks, 6 months and 12 months after treatment. Changes in HRQoL at 6 weeks after treatment compared to pretreatment were not significantly associated with survival. However, deterioration in physical and emotional functioning at 6 and 12 months after treatment compared to pre-treatment was significantly associated with shorter survival, as well as deterioration in global QoL social functioning at 12 months.

Our finding that worse HRQoL before and after treatment is significantly associated with shorter survival supports results from previous observational studies in patients with HNC.[11-16,18-20,28] In contrast to previous studies that reported an association with survival of some HRQoL domains and measured at different time points,[21,29,30] we consistently found that global QoL and all function domains of HRQoL assessed at all time points during the first year after cancer diagnosis were associated with survival. The inconsistent findings across the different subscales and time points in the previous studies may be related to the smaller sample sizes in those studies[12,14,16,17,19,20,31,32] and the heterogeneity of the tumor sites and stages.[13,15,33-41]

Interestingly, where HRQoL measured 6 weeks after treatment was significantly associated with survival, change HRQoL as measured at 6 weeks after treatment compared to pre-treatment was not. This may be explained by the fact that shortly after treatment, many patients still suffer from the acute side effects of treatment and change in HRQoL at short term is not yet a discriminating factor.[6,9] Most of these acute adverse effects are absent from 6 months onwards.[1,2,6,9]

Table 4. Uni- and Multivariable Cox regression analyses on the association between change in HRQoL after treatment compared to pre-treatment and survival

	Univariable model HR (95% CI)	p-value*	Multivariable model HR (95% CI) †	p-value*
EORTC QLQ-C30 Δ 6 weeks (n=703)				
Global quality of life	1.01 (0.96-1.07)	0.62	1.02 (0.96-1.07)	0.59
Physical function	0.98 (0.93-1.04)	0.57	0.98 (0.93-1.04)	0.56
Role functioning	0.99 (0.96-1.02)	0.61	0.99 (0.96-1.03)	0.71
Emotional functioning	0.99 (0.94-1.04)	0.74	1.00 (0.95-1.05)	0.86
Cognitive functioning	1.01 (0.96-1.06)	0.81	1.01 (0.96-1.07)	0.66
Social functioning	1.00 (0.96-1.05)	0.89	1.00 (0.95-1.05)	0.96
EORTC QLQ-C30 Δ 6 months (n=654)				
Global quality of life	0.95 (0.90-1.01)	0.10	0.94 (0.88-1.00)	0.05
Physical function	0.90 (0.84-0.97)	0.01	0.88 (0.82-0.96)	0.00
Role functioning	0.98 (0.94-1.02)	0.33	0.97 (0.93-1.02)	0.23
Emotional functioning	0.91 (0.86-0.97)	0.00	0.90 (0.85-0.96)	0.00
Cognitive functioning	0.96 (0.90-1.03)	0.25	0.96 (0.90-1.03)	0.24
Social functioning	0.96 (0.92-1.01)	0.12	0.97 (0.92-1.03)	0.29
EORTC QLQ-C30 Δ 12 months (n=579)				
Global quality of life	0.93 (0.86-0.99)	0.03	0.90 (0.84-0.97)	0.00
Physical function	0.91 (0.83-0.99)	0.03	0.89 (0.81-0.97)	0.01
Role functioning	0.97 (0.92-1.02)	0.19	0.96 (0.91-1.01)	0.12
Emotional functioning	0.91 (0.84-0.97)	0.01	0.87 (0.81-0.94)	0.00
Cognitive functioning	0.97 (0.89-1.05)	0.45	0.96 (0.88-1.04)	0.33
Social functioning	0.92 (0.86-0.98)	0.01	0.90 (0.84-0.96)	0.00

†adjusted for age, gender, socio-economic status, smoking (packyears), alcohol abuse (current or history), comorbidity, tumor site, tumor stage, treatment

* p-value of the log likelihood

Δ change compared to pre-treatment.

Worse physical and emotional function at 6 and 12 months after treatment compared to pre-treatment was significantly associated with shorter survival. The association between physical functioning and survival has been shown in previous studies, also in patients with cancer types other than HNC.[29,30,42] For instance, a recent study in patients with advanced colorectal cancer revealed that physical functioning assessed with patient-reported outcomes had more prognostic value in predicting overall survival than physician assessed world health organization (WHO) performance status.[43]

The association between emotional functioning and survival corresponds with findings from a previous longitudinal study in a large cohort of patients HNC showing an significant association between depressive symptoms and shorter survival.[44] These findings in HNC patients confirm the association between depression and survival in the community and disease specific populations.[45,46]

In addition to deteriorations in physical and emotional functioning, deteriorations in global QOL and social functioning at 12 months after treatment were also associated with reduced survival. Perhaps, reduced physical and emotional functioning over time also affects global QOL and social functioning. Shortly after diagnoses these problems could be more thoroughly present in patients' lives, where the effects on social or global QoL is postponed. However, when acute symptoms have stabilized after 12 months[1,2,6,9] patients' will be more aware of the persistent effects of HNC and its treatment and the consequences on their social life and global QoL. On the other hand, patients with advanced illness could also not be able to perform in social activities.

Based on our results, monitoring changes in HRQOL (especially physical and emotional functioning) over time in clinical practice seems important, as these scores may be sensitive for signaling clinical deterioration. Symptom monitoring (such as dyspnea, fatigue and pain) in routine care of patients seems to be associated with increased survival compared to usual care.[47] This can be explained by the early responses of nurses to symptom alerts with clinical interventions, and better chemotherapy toleration compared to the usual care group.[47]

Strengths of our study include the large prospective sample of newly diagnosed patient with HNC, allowing to incorporate multiple relevant demographic, lifestyle-related and clinical factors in our statistical models, including HPV status. Another strength is that we investigated the association between survival and HRQoL at different time points before and after treatment. However, some limitations must be noted. We included only patients that received primary or adjuvant (chemo)radiotherapy, and thus excluded patients treated with surgery. Also, the study cohort was treated before 2010, thus not including patients who were treated by recent improvements in (chemo)radiotherapy. These limitations may hamper generalizability of the results. Furthermore, because demographic, lifestyle-related, and clinical variables were retrieved from medical records, we may have missed other important variables that may be predictive for survival such as physical activity, nutritional intake, or marital status, income and occupation.[48] Finally, we were unable to retrieve data on disease-specific survival, which limited our analysis to overall survival.

In conclusion, (change in) HRQoL is significantly associated with survival in addition to demographical, lifestyle-related and clinical measures, not only pre-treatment, but also 6 weeks, 6 months and 12 months after treatment. This highlights the value of monitoring HRQoL in (clinical) practice to identify those patients that report changes in HRQOL at 6 and 12 months after treatment. This may help to further improve cancer care in a timely and efficient manner.

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CHAPTER 5

PATIENT-REPORTED PHYSICAL ACTIVITY AND THE ASSOCIATION WITH HEALTH-RELATED QUALITY OF LIFE IN HEAD AND NECK CANCER SURVIVORS

A.J. van Nieuwenhuizen
L.M. Buffart
C.F. van Uden-Kraan
L.A. van der Velden
M. Lacko
J. Brug
C.R. Leemans
I.M. Verdonck-de Leeuw

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ABSTRACT

Purpose. This study aimed to assess patient-reported levels of physical activity and it's associations with health-related quality of life (HRQoL) adjusted for important demographic, lifestyle-related and clinical factors, among head and neck (HNC) survivors.

Methods. This cross-sectional study included 116 HNC survivors. Physical activity was assessed with the Physical-Activity-Scale-for-the-Elderly (PASE) and HRQoL with the EORTC-QLQ-C30 and EORTC-HN35. Associations were studied using univariable and multivariable regression analyses.

Results. Median PASE score was 100.3 (interquartile range 65.1;170.8) of which 54% were household, 34% leisure time and 12% occupational activities. Younger HNC survivors had higher levels of PA. Higher physical activity was significantly associated with higher global QoL ($p < 0.05$). Findings for physical function, role function, social function, fatigue and pain were in line, but not statistically significant ($0.05 \leq p < 0.10$).

Conclusions. Among HNC survivors, a large proportion of physical activity consists of household activities. Younger HNC survivors had higher physical activity, and higher physical activity levels were associated with higher HRQoL.

INTRODUCTION

Worldwide, the incidence of head and neck cancer (HNC) has increased over the past decades and five year survival rates have improved in Europe[1] and the United States.[2] As a consequence, more HNC survivors have to cope with physical and psychosocial problems and HNC specific symptoms associated with cancer and its treatment, such as oral dysfunction, swallowing and speech problems, severely compromising health-related quality of life (HRQoL).[3-6]

Randomized controlled trials in patients with other types of cancers, mainly breast and prostate cancer, showed that physical activity (PA) can reduce physical and psychosocial problems and improve HRQoL.[7-9] Observational studies showed that higher levels of moderate-to-vigorous PA are associated with lower mortality risk in survivors of breast, colon and prostate cancer.[10-14] Also in HNC survivors, higher pre-treatment levels of PA and physical function were found to be associated with higher HRQoL[15, 16] and survival.[17, 18]

However, PA levels of HNC patients tend to decrease following diagnosis and during treatment.[16, 19-21] Two previous studies[16, 20] examined demographic, clinical and lifestyle correlates of PA and had contradictory results. In a sample of 59 HNC survivors Rogers et al.[20] found that younger age, the absence of comorbidity and abstinence from alcohol were related to higher levels of patient-reported PA. Sammut et al.[16] found no associations of gender, smoking, comorbidity and age with weekly energy expenditure after treatment in a sample of 172 HNC survivors. Insight into demographic and clinical correlates of PA, may help to identify which subgroups of HNC survivors are more likely to have low PA.

At present, the number of studies evaluating the associations between PA and HRQoL in patients with HNC are scarce, especially as compared to patients with other types of cancer such as breast or prostate.[15] Furthermore, these studies could only include leisure time PA and no data on household or occupational activities were included. Rogers at al.[20] found higher levels of leisure time PA, 18.6 (SD 50.9) months after treatment, to be associated with lower fatigue, higher HRQoL and higher functional wellbeing after adjusting for age, presence of comorbidities and alcohol consumption. Sammut et al.[16] reported significant positive correlations between higher levels of PA at 12.9 (SD 12.8) months after treatment and higher HRQoL.

Because of the scarcity of evidence regarding PA levels and the association with HRQoL among HNC survivors, the present study aimed to (1) describe the level of PA among HNC survivors, including leisure-time, household and occupational PA, (2) study demographic, clinical, and lifestyle-related correlates of PA and (3) assess the association between PA and HRQoL adjusted for important demographic, clinical, and lifestyle-related factors.

MATERIALS AND METHODS

Setting and patient recruitment

In this cross-sectional study patients were recruited between January and September 2013 from the Departments of Otolaryngology-Head and Neck Surgery from VU University Medical Center, Amsterdam, Leiden University Medical Center and Maastricht University Medical Center. We included data of PA and HRQoL from two separate studies, the OncoQuest study[22] and the OncoKompas[23] study. At the VU University Medical Center, Amsterdam, the OncoQuest system is implemented as part of standard care, to assess HRQoL in patients with HNC. Additionally, the OncoKompas study was launched, which is an online self-management application where cancer survivors can monitor their HRQoL and get tailored feedback and personalized advice on supportive care services. The HRQoL questionnaires we included for the current study were administered before the online self-management application was carried out. The OncoQuest study and the OncoKompas study included the same HRQoL questionnaires. To be able to answer our research questions on PA in HNC survivors and associations with HRQoL we added the PASE questionnaire for a limited number of time in both studies. Eligibility criteria and patient recruitment of both studies are presented in Figure 1. Patients were eligible for this cross-sectional study if they were 1) diagnosed with HNC, 2) treated with surgery, radiotherapy, chemoradiation or a combination of these treatments,3) aged 18 years or older, and 4) able to write, read and speak Dutch. Patients were excluded if they were diagnosed with basal cell carcinoma's or lymphoma in the head and neck region, or if they suffered from severe psychiatric co-morbidities (e.g. schizophrenia, Korsakov's syndrome, severe dementia). All patients signed an informed consent statement prior to participation. The study was conducted according to regular procedures of the local ethical committee of the VU University Medical Center, Amsterdam.

Outcome measurements

Physical activity

PA was assessed with the 13-item Physical Activity Scale for the Elderly (PASE), a self-administered 1-week recall questionnaire on leisure time, household, and occupational physical activities.[24] The frequency of these activities was recorded as never, seldom (1-2 days a week), sometimes (3-4 days a week) or often (5-7 days a week). The duration of activities was categorized as less than 1 hour, between 1 and 2 hours, between 2 and 4 hours, or more than 4 hours. Paid or volunteer work, except for work that involved mostly sitting activities such as office work, was categorized as less than 1 hour, between 1 and 4 hours, between 5 and 8 hours, or more than 8 hours.[25] The total PASE sum score was computed by multiplying the amount of time spent on each activity (hours/week) by the empirical derived item weights and summing over all activities.[24-26] The PASE was shown to have good to excellent test-retest reliability, and good content validity among patients with cancer with an average age of 50 (SD 12). Its construct validity (with accelerometers as comparison measure) was comparable to other PA questionnaires.[27]

Health-Related Quality of Life

HRQoL was assessed with the European Organization for Research and Treatment of Cancer, (EORTC) Quality of Life Questionnaire core module (EORTC QLQ-C30) and the Tumor specific HRQoL was assessed by the EORTC Head and Neck Module (EORTC HN35).[28] The EORTC QLQ-C30 is a 30-item questionnaire including a global QoL scale, five function scales, three symptom scales and 6 single items, with higher scores presenting higher global QoL and function, and lower scores presenting higher symptom severity.[29] The EORTC HN35 is a 35-item module including HNC specific symptom scales and 10 single items covering several problems.

Demographic, clinical and lifestyle-related factors

Demographic, clinical, and lifestyle-related factors were collected from medical records and included gender, age, zip codes of patients' living area, smoking (pack years, current smoker), alcohol consumption (units per day, current or former abuse (≥5 units a day)), tumor site (oral cavity, oropharynx, hypopharynx, larynx and other), type (squamous cell carcinoma vs. non-squamous cell carcinoma) and stage (I, II, III and IV), tumor recurrence (dichotomized as none versus any, including local, regional and second or third primary tumors), treatment modality (surgery, (chemo) radiotherapy, or surgery followed by (chemo)radiotherapy), time since completion of treatment (months) and comorbidities.

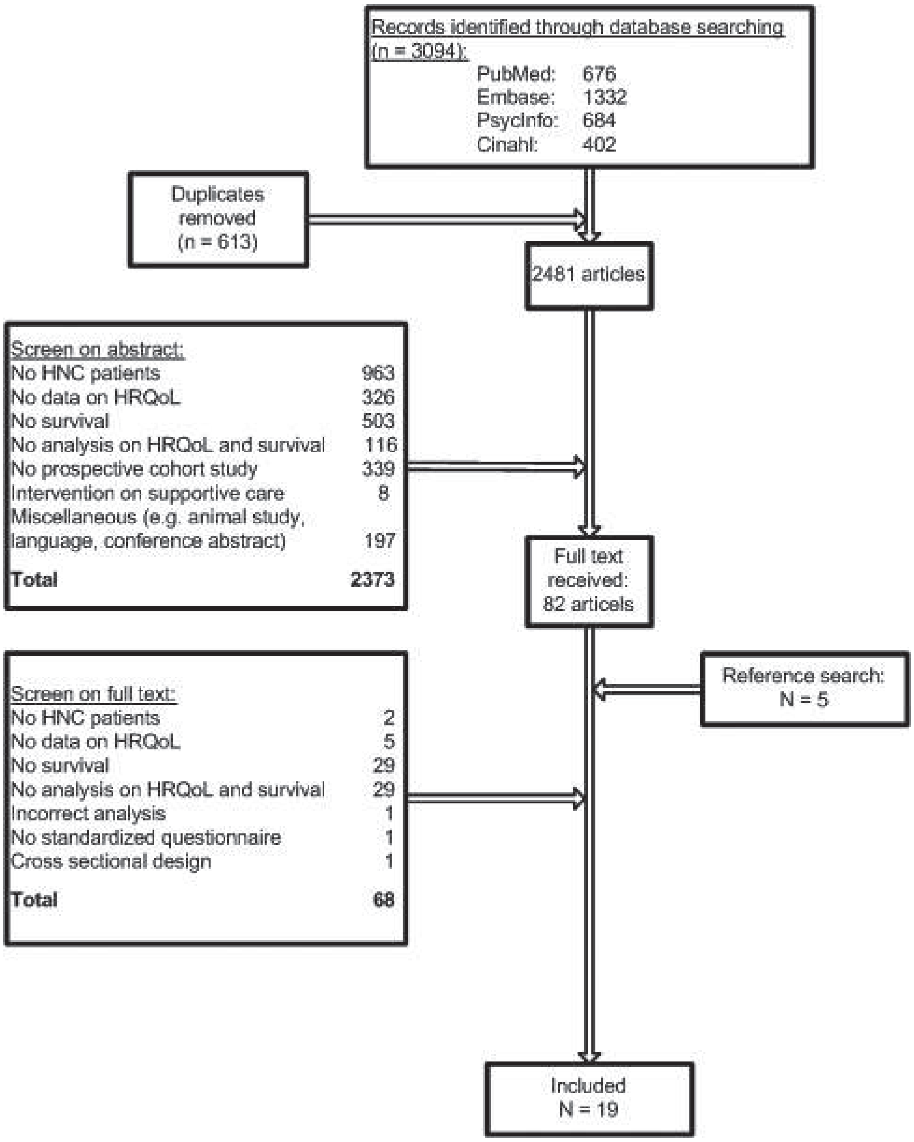
Socio-economic status (SES) was determined using zip codes of patients' living area. Zip codes were translated to SES according to The Netherlands Institute for Social Research.[30] This system describes the social status of a district compared to other districts in The Netherlands using an algorithm based on mean income, percentage of people with low income, percentage of people with low education and percentage of people with without a job. Therefore the mean score of all districts in The Netherlands is zero. We dichotomized SES scores to high (> mean value) versus low (≤ mean value).

Comorbidities were assessed using the Adult Comorbidity Evaluation 27 (ACE-27), a validated chart built instrument examining the presence of any of the following medical conditions: cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, immunological, previous malignancies, psychiatric disorders, alcohol use and severe overweight, resulting in a total comorbidity score of none, mild, moderate or severe.[31]

Statistical analysis

Descriptive statistics (mean, standard deviation (SD), or numbers and percentages) were generated for demographic, lifestyle-related, and clinical factors, PA and HRQoL. For the continuous variables median and interquartile range (IQR) were reported when outcomes were not normally distributed (skewness scores < -1; > 1). Since total PA score was skewed to the right and the residuals obtained in the regression analysis were not normally distributed, we presented data of total PA as median (IQR) and natural log-transformed the data for analyzing the correlates of PA. We conducted univariable and multivariable linear regression analyses (presenting confidence intervals and standardized regression coefficients) to study demographic, lifestyle-related and clinical correlates of PA. No multicollinearity (rp > 0.75) was found. To determine the maximum number of variables to be included in the regression model, we used the rule of thumb of 10 patients per determinant. Consequently, our sample of 116 allowed to include a maximum of 11 variable into the regression model. To prevent overfitting in the multiple linear regression model, we selected variables using a forward selection procedure starting with the variable that most strongly predicted PA. Variables were selected one by one and all variables with $p \leq 0.05$ were inserted in the multiple regression model. We back transformed the results from the final model indicating ratios. The associations between PA and HRQoL were assessed using univariable and multivariable linear regression analyses. For the most accurate estimate of the association, we adjusted for demographic, and lifestyle-related, and clinical characteristics. Due to the maximum number of variables allowed in the regression model, we have chosen tumor stage over tumor location and tumor type because it is more strongly associated with quality of life.[3-6] We explored interactions for the main demographic and clinical characteristics (age, gender, cancer stage and treatment) to study whether the association between PA and HRQoL differed between these subgroups. To limit the number of interactions explored, we tested interactions when the associations between PA and HRQOL had a p-value < 0.10. P-values ≤ 0.05 were considered statistically significant.

Figure 1. Inclusion flowchart



Abbreviations: HNC, head and neck cancer; LUMC, Leiden University Medical Center; MUMC, Maastricht University Medical Center; n, number; VUmc, PRO, patient reported outcome; RR, response rate; VUmc, VU University medical center

Table 1. Demographic, lifestyle-related and clinical characteristics, physical activity(PA) and health-related quality of life (HRQoL)

Characteristics	Participants (n= 116)
Demographic factors	
Gender, n (%) male	73 (63)
Age, mean (SD) years	60 (10)
SES, mean (SD)	0.54 (0.9)
High SES (above average), n (%)	34 (29)
Lifestyle-related	
Smoking (packyears), median (IQR)	20 (0-40)
Smoking at diagnosis, n (%)	63 (54)
Alcohol use (units per day), mean (SD)	1,5 (2.3)
Alcohol abusea at diagnosis, n (%)	23 (20)
Clinical factors	
Tumor location, n (%)	
Oral Cavity and oropharynx	56 (48)
Larynx and hypopharynx	33 (29)
Otherb	27 (23)
Cancer type, n (%)	
Squamous cell	105 (91)
Non-squamous cell	11 (9)
Disease Stage, n (%)	
I and II	41 (35)
III and IV	75 (65)
Type of treatment, n (%)	
Surgery only	21 (18)
Radiotherapy	28 (24)
Chemoradiotherapy	23 (20)
Surgery combined with (chemo)radiation therapy	44 (38)
Recurrence, n (%)	
None	95 (82)
Any	21 (18)
Comorbidity, n (%)	
None or mild	74 (64)
Moderate or severe	42 (36)
Time since treatment, mediam (IQR) months	14 (7-23)
Physical activity	
Total score, median (IQR)	100.3 (65.1-170.8)
Leisure time activities (% of total PA)	34%

Table 1. Continued

Characteristics	Participants (n= 116)
Household activities	54%
Occupational activities	12%
Cancer specific HRQoL, mean (SD)	
Global quality of life	78.2 (15.9)
Physical function	88.0 (13.7)
Role function	85.5 (19.6)
Emotional function	85.9 (14.0)
Cognitive function	89.7 (14.9)
Social function	85.6 (19.0)
Fatigue	23.9 (21.5)
Pain (general)	14.2 (19.9)
Dyspnea	14.4 (22.9)
Insomnia	16.1 (35.4)
Loss of appetite	6.0 (17.9)
Constipation	9.2 (20.9)
Diarrhea	5.2 (13.6)
Financial problems	9.8 (21.1)
Tumor specific HRQoL, mean (SD)	
Pain (mouth)	17.0 (20.9)
Swallowing	16.7 (23.4)
Senses	21.3 (23.4)
Speech problems	16.4 (20.5)
Social eating	15.1 (22.5)
Social contact	5.1 (8.9)
Sexuality	24.5 (29.7)
Teeth	13.9 (24.2)
Opening mouth	13.5 (22.4)
Dry mouth	42.8 (31.3)
Sticky saliva	30.4 (32.3)
Coughing	20.7 (27.3)
Feel ill	9.8 (19.7)

Abbreviations: CRT = chemoradiation; EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30;n: number; RT = radiotherapy; SD: standard deviation; SES: socio-economic status; Surg = surgery;

a) Alcohol abuse defined as ≥ 5 units of alcohol per day

b) Unknown primary, nasopharynx, nasal cavity, nasal sinus, salivary glands, ear and skin

RESULTS

In total, 116 out of 212 HNC survivors met our inclusion criteria and filled out the survey on PA and HRQoL (Figure 1). Mean (SD) age of participants was 60 (10) years and 63% were men. The most frequent tumor site was oropharynx (26%) followed by oral cavity (22%), larynx (22%) and hypopharynx (7%). Most patients were treated by a combination of treatment modalities (58%). Time since completion of treatment was 21 (21) months. Quality of life scores ranged from 78.2 (global quality of life) to 89.7 (cognitive functioning). Regarding cancer specific HRQoL symptom scores ranged from 5.1 (Social contact) to 24.5 (sexuality, Table 1).

Median (IQR) total PASE score was 100.3 (65.1; 170.8), of which 34% consisted of leisure time PA, 54% of household activities, and 12% occupational activities. A younger age was significantly associated with higher levels of PA (β = 0.98, 95% CI = 0.96; 1.00) explaining 5.2% of the variance in PA (Table 2). No significant associations with PA were found for other demographic, clinical, or lifestyle-related variables.

After adjusting for age, gender, SES, smoking, alcohol abuse, comorbidity, tumor stage, treatment modality, recurrence and time since treatment, a higher level of PA was significantly associated with higher global QoL (β: 0.06, 95% CI = 0.03; 0.10). Possible meaningful association were also observed for higher physical function (β: 0.03, 95% CI = -0.00; 0.06), role function (β: 0.04, 95% CI = -0.00; 0.09) and social function (β: 0.04, 95% CI = -0.00; 0.09) and lower level of fatigue (β: -0.05, 95% CI = -0.10; 0.00) and less pain (β: -0.04, 95% CI = -0.09; 0.00), but these associations were not statistically significant ($0.05 \le p < 0.10$, Table 3). Explorative analyses showed that gender was a significant effect modifier in the association between PA and general pain ($\beta_{interaction}$=-0.09, 95% CI = -0.18; -0.005, p= 0.04). Explorative stratified analyses for gender revealed a significant association between PA and general pain in women (β=-0.11, 95% CI = -0.19; -0.03, p= 0.01), while the association was not statistically significant in men (β=-0.02, 95% CI = -0.07; 0.03, p= 0.46). We also found a significant effect modification for age, with a stronger association in patients who were younger ($\beta_{interaction}$=0.005, 95% CI = 0.00; 0.01, p= 0.04).

Table 2. Demographic, lifestyle-related and clinical correlates of physical activity. Results from univariable regression analyses.

	Ratio (95% CI)	P value	Standardized regression coefficients
Demographic factors			
Gender	1.28 (0.93; 1.77)	0.13	0.14
Age, years	0.98 (0.96; 1.00)	0.01	-0.23
SES	0.95 (0.68; 1.34)	0.78	-0.03
Lifestyle-related factors			
Smoking, packyears	1.00 (1.00; 1.01)	0.32	0.09
Smoking at diagnosis	1.20 (0.88; 1.64)	0.25	0.11
Alcohol, units per day	0.99 (1.07; 1.06)	0.79	0.02
Alcohol abusea	0.92 (0.62; 1.36)	0.67	-0.04
Clinical factors			
Tumor location			
OC and OP	1.33 (0.89; 1.98)	0.16	0.17
L and HP	1.22 (0.78; 1.89)	0.38	0.10
Other	Ref		
Cancer type	1.51 (0.88; 2.57)	0.13	0.14
Disease Stage	0.98 (0.70; 1.36)	0.89	-0.01
Recurrence	0.69 (0.46; 1.04)	0.07	-0.17
Comorbidity	0.82 (0.59; 1.14)	0.23	-0.11
Type of treatment			
single vs multiple	0.92 (0.67; 1.27)	0.62	-0.05
Time since treatment (months)	0.99 (0.99; 1.00)	0.10	-0.15

Abbreviations: CI = confidence interval, L and HP = larynx and hypopharynx; OC and OP = oral cavity and oropharynx; SES: socio-economic status. a Alcohol abuse defined as ≥ 5 units of alcohol per day

Gender (0=male, 1=female), SES (0 = other, 1 = high), current smoking (0 = never or former, 1 = current), alcohol abuse (0 = no abuse, 1 = current or former abuse), cancer type (0= no squamous cell carcinoma, 1 = squamous cell carcinoma), disease stage (0 = stage I and II, 1 = stage III and IV), recurrence (0 = no recurrence, 1 = any recurrence), comorbidity (0 = none or mild, 1 = moderate or severe)

Table 3. Independent correlates of physical activity. Results of the multivariable regression analyses

	Ratio (95% CI)	P value	Standardized regression coefficients
Demographic factors			
Age, years	0.98 (0.96; 1.00)	0.01	-0.23

Variables were selected one by one and all variables with p ≤ 0.05 were inserted in the multiple regression model.

Table 4.The association between physical activity and health-related quality of life (HRQoL)

	Univariable analyses	P-value	Multivariable analyses[a]	P-value
HRQoL	β (95% CI)		β (95% CI)	
Global quality of life	0.059 (0.025; 0.092)	0.01	0.061 (0.025; 0.096)	0.00
Physical function	0.034 (0.004; 0.063)	0.03	0.027 (-0.003; 0.057)	0.08
Role functioning	0.040 (-0.003; 0.082)	0.07	0.044 (-0.001; 0.089)	0.05
Emotional functioning	0.011 (-0.020;0.042)	0.49	0.004 (-0.030; 0.038)	0.81
Social functioning	0.034 (-0.008; 0.075)	0.11	0.043 (-0.002; 0.088)	0.06
Cognitive functioning	0.019 (-0.013; 0.052)	0.24	0.018 (-0.019; 0.055)	0.33
Fatigue	-0.043 (-0.090; 0.04)	0.07	-0.050 (-0.103; 0.003)	0.06
Nausea and vomiting	0.000 (-0.017; 0.017)	0.97	-0.004 (-0.024; 0.015)	0.65
Pain (general)	-0.050 (-0.092;-0.007)	0.02	-0.044 (-0.091; 0.003)	0.06
Dyspnoe	0.013 (-0.038; 0.063)	0.62	0.050 (-0.046; 0.056)	0.84
Insomnia	-0.027 (-0.083; 0.029)	0.34	-0.044 (-1.05; 0.017)	0.15
Loss of appetite	0.012 (-0.027; 0.052)	0.54	0.001 (-0.042; 0.045)	0.96
Constipation	-0.026 (-0.072; 0.020)	0.27	-0.021 (-0.072; 0.030)	0.42
Diarrhea	-0.017 (-0.046; 0.013)	0.27	-0.019 (-0.053; 0.015)	0.28
Financial problems	0.09 (-0.037; 0.056)	0.67	0.016 (-0.036; 0.068)	0.54
Tumor specific HRQoL				
Pain (mouth)	-0.015 (-0.061; 0.031)	0.53	-0.009 (-0.060; 0.043)	0.74
Swallowing	-0.022 (-0.074; 0.029)	0.39	-0.022 (-0.073; 0.029)	0.39
Senses	-0.028 (-0.079; 0.024)	0.29	-0.019 (-0.076; 0.038)	0.51
Speech problems	-0.005 (-0.050; 0.040)	0.83	0.004 (-0.045; 0.054)	0.86
Social eating	-0.022 (-0.071; 0.027)	0.38	-0.021 (-0.071; 0.030)	0.42
Social contact	-0.008 (-0.028; 0.012)	0.43	-0.005 (-0.026; 0.017)	0.68
Sexuality	-0.037 (-0.105; 0.031)	0.29	-0.048 (-0.118; 0.022)	0.18
Teeth	0.028 (-0.025; 0.081)	0.30	0.019 (-0.039; 0.077)	0.51
Opening mouth	-0.031 (-0.080; 0.018)	0.21	-0.031 (-0.084; 0.023)	0.26
Dry mouth	0.009 (-0.060; 0.078)	0.80	0.001 (-0.073; 0.075)	0.99
Sticky saliva	0.005 (-0.066; 0.077)	0.88	0.007 (-0.069; 0.083)	0.86
Coughing	-0.028 (-0.088; 0.032)	0.36	-0.026 (-0.090; 0.038)	0.42
Feeling ill	-0.018 (-0.061; 0.026)	0.42	-0.032 (-0.082; 0.016)	0.30

a) adjusted for age, gender, socio-economic status, smoking, alcohol abuse, comorbidity, tumor stage, treatment, recurrence and time since treatment

DISCUSSION

This cross-sectional study describes self-reported PA levels among HNC survivors, the ~~demographic, lifestyle-related and clinical correlates of PA, and the association between~~ PA and HRQoL. Our median PASE score (100.3, IQR 65.1; 170.8) was comparable to the HNC population (n = 283) in a study from Duffy et al,[19] that reported s mean of 115 pre-treatment and a mean of 106 and 110 at 6 and 9 months after treatment, respectively. However, compared to a non-cancer elderly population also using the PASE questionnaire,[24] the population of HNC survivors had lower levels of PA (144.9 vs. 100.3). The findings that HNC survivors are at increased risk for low PA levels and the positive association between PA and HRQoL highlights the relevance for evaluating interventions that aim to improve PA levels in this population.[32]

In the study, total PA mainly consisted of household activity (55%). This is comparable with studies in general populations, reporting that 30-60% of total PA consists of household activities[24, 33, 34] and this proportion tends to increase with age.[33] Because of their significant contribution to total PA levels, it is important to also assess household and occupational activities, and not just leisure time PA as is often the case. Also, for interventions aiming to improve PA levels in HNC survivors, it might be useful to focus on promoting PA during daily routines, especially because HNC survivors reported to prefer exercising alone, unsupervised and at a moderate intensity.[34]

Our finding that older HNC survivors are less physically active is in line with previous studies among HNC survivors[20] as well as in survivors of other types of cancer.[36-38] This illustrates that it is important to promote PA interventions in elderly (head and neck) cancer survivors, particularly, because they are at high risk for functional decline after cancer diagnosis.[39] Unfortunately, current interventions to promote PA may not always reach elderly cancer survivors.[40] We found no significant associations regarding PA and other demographic factors (gender and SES) which is comparable to the studies of Rogers et al.[20] and Sammut et al.[16] However, it should be noted that the information on SES in our study was limited because we estimated SES based on ZIP codes, and did not ask patients to provide data on education or income themselves).

In contrast to previous studies, we found no evidence for an association of smoking ([37, 38]), alcohol consumption[20, 38] or clinical factors with PA.[20, 37, 38, 41] The lack of significant associations for clinical factors (e.g. comorbidity, tumor location, and type of treatment) may indicate that the impact of clinical factors reduces over time and other factors such as motivational factors become more important.[41-44] Future prospective longitudinal studies with objective PA measurements should further clarify whether these associations (demographic, clinical and lifestyle-related) might be present in HNC survivors or if these are only present during or shortly after treatment.

Our finding that a higher PA level was associated with higher global QoL, and possibly better physical function, role function, social function, and less fatigue and pain among HNC survivors is consistent with previous studies.[16, 20] This indicates that improving PA might be an intervention target to improve HRQoL. However, due to the cross-sectional design, it is not possible to make causal inferences and it is unclear whether improving PA levels would improve HRQoL, or whether HNC survivors with lower HRQoL are less physically active. In contrast to general HRQoL, the current study found no support for an association of PA and HNC-specific HRQoL. Due to the cross-sectional nature of this study, it may also suggests that HNC symptoms are not a barrier to PA. Several small studies have shown that PA interventions among HNC survivors are feasible and may improve general and HNC specific HRQoL.[15]

Strengths of our study are the relatively large sample size of an understudied group of cancer survivors, allowing to adjust analysis for important demographic, lifestyle related and clinical factors. We could also include levels of PA originating from household or occupational activities in addition to leisure time PA. However, some limitations must be noted. First, the use of a self-reported questionnaire to assess PA levels is susceptible to recall and social desirability bias.[45] This may have led to an overestimation of PA levels, and therefore the absolute PA level should be interpreted with caution. However, the PASE questionnaire is a valid measure to distinguish active from inactive people,[27] and therefore the direction of the associations may be considered valid. Second we assessed lifestyle-related and clinical factors only at diagnosis, and some of these outcomes might have changed at the time (e.g. smoking, alcohol use, comorbidity) of the questionnaire assessment. Third, the lack of associations of PA with clinical factors may be related to the sample size. However, the wide confidence intervals indicate heterogeneity in the association and standardized regression coefficients were small (≤ 0.23), which makes it is unlikely that associations will be significant and clinically relevant with larger samples. Finally, the cross-sectional design hampered us to draw conclusions about causality, and future studies are needed to investigate whether increasing PA would improve HRQoL.

In conclusion, in this cross-sectional study we found that HNC survivors, and particularly older survivors, are at risk for low levels of PA. Among HNC survivors, a large proportion of PA consists of household activities. HNC survivors with higher levels of PA had higher global QoL and role function. Future studies should investigate the causality of these associations.

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6

CHAPTER 3

A COMPREHENSIVE ASSESSMENT PROTOCOL INCLUDING PATIENT REPORTED OUTCOMES, PHYSICAL TESTS, AND BIOLOGICAL SAMPLING IN NEWLY DIAGNOSED PATIENTS WITH HEAD AND NECK CANCER: IS IT FEASIBLE?

A.J. van Nieuwenhuizen,
L.M. Buffart,
J.H. Smit,
R.H. Brakenhoff,
B.J.M. Braakhuis,
R. de Bree,
C.R. Leemans,
I.M Verdonck-de Leeuw

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ABSTRACT

Purpose: Large cohort studies are needed taking into account cancer-related, personal, biological, psychobehavioural, and lifestyle-related factors, to guide future research to improve treatment and supportive care. We aimed to evaluate the feasibility of a comprehensive baseline assessment of a cohort study evaluating the course of quality of life (QoL).

Methods: Newly diagnosed head and neck cancer (HNC) patients were asked to participate. Assessments consisted of questionnaires (635 items), a home visit (including a (psychiatric) interview, physical tests, blood and saliva collection), and tissue collection. Representativeness of the study sample was evaluated by comparing demographics, clinical factors, depression, anxiety, and QoL between responders and non-responders. Feasibility was evaluated covering the number of questions, time investment, intimacy and physical burden.

Results: During the inclusion period (four months), 15 out of 26 (60%) patients agreed to participate. Less women participated, 13% in responders group versus 63% in non-responders group (p= 0.008). No other differences were found between responders and non-responders. Responders completed more than 95% of the questionnaires items, and rated the number of questions, time investment and intimacy as feasible, and the physical and psychological burden as low. It took on average 3 hours to complete the questionnaires and 1,5 hours for the home visit.

Conclusions: This study reveals that a comprehensive assessment including various questionnaires, physical measurements and biological assessments is feasible according to patients with newly diagnosed HNC. A large prospective cohort study has started aiming to include 739 HNC patients and their informal caregivers in the Netherlands.

INTRODUCTION

Worldwide, each year, head and neck cancer (HNC) accounts for more than 633,000 new cases and over 355,000 deaths.[1] In the Netherlands, the incidence of HNC increased from 2474 in 2001 to 2970 in 2011,[2] mainly due to aging, increased tobacco consumption by females in the 1980s and an increasing number of human papilloma virus related oropharyngeal carcinomas.[3-5] Current five year survival rate of patients with advanced HNC in the Netherlands is approximately 60%.[2] For certain subsites, e.g. oropharyngeal carcinoma, survival is improving.[6] Due to the increasing incidence and improved survival rates, more patients with HNC have to cope with various physical and psychosocial problems associated with the cancer diagnosis and treatment, such as decreased general and mental health, oral dysfunction, swallowing and speech problems and emotional distress, severely compromising health-related quality of life (HRQoL).[7-14] Compared to other types of cancer, including breast, colon and prostate cancer, HNC patients report high levels of distress.[15] At the same time, an increasing number of studies suggest that HRQoL has prognostic value for survival.[16-22] However, most previous studies on HRQoL and survival in HNC patients had some limitations related to relatively small sample sizes, the focus on specific sub-sites of HNC, adjustment for only a few confounders (e.g. lifestyle, demographic and clinical characteristics), or inclusion of only a few aspects of HRQoL.[16-25] Furthermore, little is known about the course of HRQoL of patients with HNC and its determinants across the cancer trajectory. Previous studies showed that several domains of HRQoL, including general health, mental health, physical function, appearance, employment and social functioning declined during and immediately after treatment, and improved after 6 months.[7;8;12-14;23-26] Studies including long term follow-up showed that HRQoL stabilized one year after treatment and was not significantly different from baseline levels at 5-year follow up.[7-9;25;26] However Mehanna et al.[14] reported 10 years after diagnosis, significantly lower HRQoL scores than before treatment, which was recently confirmed by Oskam et al.[27]

A recent review among patients with HNC[28] showed that the majority of studies examining the course of HRQoL over time were limited by their retrospective study design, their focus on only a few aspects of HRQoL instead of all domains,[29] the use of Patient Reported Outcomes (PRO's) only, the small sample size, and lack of pre-treatment measurements of HRQoL.[30] In addition studies examining the association between HRQoL and survival lacked to adjust for all relevant confounders and different study designs were used.[31] Therefore, there is need for a large multi-institutional prospective cohort study evaluating the course of HRQoL in patients with HNC, and its relation with survival integrating all relevant cancer-related, personal, genetic, biological, psychobehavioural, physical, lifestyle-related and social factors. Comprehensive insight in all these factors assessed in a standardized manner is necessary to unravel these complex associations. A study of this magnitude has never been carried out among patients with HNC, and it is unclear whether it is feasible to conduct such an extensive objective assessment of physical and cognitive function, lifestyle, a psychiatric interview, and collection of blood, saliva and tumor tissue, in addition to a large number of PRO's. Thus, the aim of the present study is to assess the feasibility of a comprehensive baseline assessment among patients with HNC.-

MATERIALS AND METHODS

Sample and Setting

As part of clinical routine in our institution, all newly diagnosed HNC patients are asked to fill out questionnaires on HRQoL and emotional distress during their first visit via OncoQuest.[32] OncoQuest is a touch screen computer system to monitor HRQoL in clinical practice and includes three questionnaires: the European Organization for Research and Treatment of Cancer, (EORTC) Quality of Life Questionnaire core module (QLQ-C30),[34;35]) EORTC Head and Neck Module (HN35)[37] and Hospital Anxiety and Depression Scale (HADS).[36]

The 30-item EORTC QLQ-C30 includes a global quality of life scale, 5 function scales regarding physical, role, emotional, cognitive and social functioning, three symptom scales (nausea and vomiting, fatigue and pain) and 6 single items related to dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties.[33;34] The 35-item EORTC QLQ-HN35 is a tumor-specific module addressing symptoms specifically associated with HNC, including pain, swallowing, senses, speech, social eating, social contact and sexuality, as well as 10 single items covering problems with teeth, dry mouth, sticky saliva, cough, opening the mouth wide, weight loss, weight gain, use of nutritional supplements, feeding tubes, and painkillers.[35] The HADS is a 14-item scale for measuring emotional distress and includes a total scale and an anxiety (HADS-A) and depression (HADS-D) subscale [36]. A total score of > 15 is used as an indicator of a high psychological distress. For the subscales, cut off points of ≥ 8 are indicators of high levels of anxiety or depression.

From January to Mid-April 2012, every new patients with HNC was screened for eligibility for the current feasibility study. Patients presenting with oral, oropharygeal, hypopharygeal, laryngeal cancer and patients with neck metastasis of unknown primary tumor with proven squamous cell histology, aged 18 years or older, treated with curative intent), who were able to write, read and speak Dutch were eligible. Patients suffering from severe psychiatric co-morbidities (e.g. schizophrenia, Korsakov's syndrome, severe dementia) were excluded. Eligible patients were asked to participate in this feasibility study by the treating surgeon, and subsequently, the research-physician provided more detailed information about the study and handed out written information. Non-participants were asked for their reason for not participating. All patients signed an informed consent statement prior to participation. The Institutional Review Board of the VU University Medical Center approved the study.

Procedures and assessments

After all eligible patients filled out the three questionnaires (EORTC QLQ C30, EORTC HN35, HADS) as clinical procedure, study participants filled out the comprehensive baseline assessment, consisting of 36 questionnaires and in total 762 items, which took place before the start of treatment. The questionnaires consisted variable sub domains, including general and disease specific QoL, cancer related, personal, psychobehavioural, physical, lifestyle-related, social factors and health care costs (Table 1). According to patient's preference, the PRO's were sent by postal mail, or a link was e-mailed to fill out the PRO's via internet. Subsequently, the research-physician visited the patients at their homes or in the hospital according to preference of the patients, to conduct a (psychiatric) interview, physical tests, and collection of blood. At the end of the visit, patients were instructed to collect 5 saliva samples during the same evening and next morning, and to wear an accelerometer (Actitrainer, Actigraph, Fort Walton Beach, Florida) for the next 7 days. Three to five days after the home visit, a telephone interview was conducted to assess diet using a 24-hour recall. Tumor tissue was gathered during the participants panendoscopic procedure, which is performed as a part of the diagnostic work-up. This procedure aims to determine the field of surgery and to investigate the presence of other tumours. During this panendoscopy a supplemental biopsy was taken for the current study besides the diagnostic tissue collection for the pathology department. An overview of all outcome measures included in the baseline assessment protocol is presented in Table 1. The assessment protocol was developed in collaboration with the coordinator of the Netherlands Study of Depression and Anxiety (NESDA) study.[37] NESDA is a large prospective cohort study which aims to describe the long-term course and consequences of depressive and anxiety disorders.

Table 1. Overview of all outcome measures included in the assessment protocol: patient reported outcome, (home) visit (physical tests and interviews), and biological and clinical factors.

OUTCOMES	Measurement instrument	Number of items
patient reported outcome		
Quality of life		
Generic	EuroQuol-5D (EQ-5D)	6
Disease specific	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-core 30 (EORTC QLQ-C30)	30
Tumor specific	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire module Head and Neck 35 (EORTC QLQ-HN35)	35
Speech	Speech Handicap Index (SHI)	31
Swallowing	Swallowing QoL Questionnaire (SwalQoL)	47
Shoulder	Shoulder Disability Questionnaire (SDQ)	16
Hearing	Caron questionnaire on hearing	19
Malnutrition	Short Nutritional Assessment Questionnaire (SNAQ)	4
Personal factors		
Personality	*Neuroticism-Extroversion-Openness-Five factor inventory (NEO-FFI)*	60
Locus of control	Pearlin & Schooler mastery scale (PSMS)	5
Coping	Mental Adjustment to Cancer scale (MAC)	39
Self efficacy	Generalized self efficacy scale (GES)	10
Well-being	Post traumatic Growth Inventory (PTGI)	21
Physical appearance	Body Image Scale (BIS)	10
Life events	Brugha Questionnaire	13
Coping	Utrechtse Coping List (UCL)	46
Psychobehavioural factors		
Severity anxiety / depression	Hospital Anxiety and Depression Scale (HADS)	14
Fatigue	Multidimensional Fatigue Inventory (MFI)	20
Fatigue	Fatigue Quality List (FQL)	1
Sleep Quality	Pittsburgh Sleep Quality Index (PSQI)	15
Fear of recurrence	Cancer Worry Scale (CWS)	8
Cognition	Cognitive Failure Questionnaire (CFQ)	25
Physical factors		
Sexual function		

Table 1. Continued

OUTCOMES	Measurement instrument	Number of items
Males	International index of Erectile Function (IIEF)	19
Females	Female Sexual Function Index (FSFI)	15
Females	Study specific questionnaire on fertility	16
Lifestyle-related factors		
Alcohol intake	Study specific questions	13
Alcohol dependence	Study specific questions	7
Drug use	Study specific questions	7
Smoking	Study specific questions	8
Nicotine dependence	Study specific questions	5
Physical activity	Physical Activity Scale for the Elderly (PASE)	31
Leisure	Study specific questions	15
Social factors		
Social support	Social Support List Interactions (SSL-I12)	12
Participation	Impact on Participation and Autonomy (IPA)	43
Health care use / costs		
Need and use care	Study specific questionnaire	28
Costs	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TiC-P): Adapted version for HNC	30
(Home) visit		
Personal factors		
Demographic	Standard questions	23
Socioeconomic status / literacy	Standard questions	27
Psychobehavioural factors		
Presence MDD	Composite international diagnostic interview (CIDI) – Major Depressive Disorder (MDD)	Variable
Anxiety disorder	Composite international diagnostic interview (CIDI) – Anxiety disorders (GAD, SOC, PAN, AG)	Variable
Pain	Brief Pain Inventory (BPI)	13

Table 1. Continued

OUTCOMES	Measurement instrument	Number of items
Physical factors		
Speech quality	Speech recording (perceptual and objective analyses)	n.a.
Pulmonary function	Peak flow	n.a.
Strength: upper extremity	JAMAR handgrip dynamometer	n.a.
Strength: lower extremity	30s chair stand test	n.a.
Cardiorespiratory fitness	Chester Step test	n.a.
Body composition	Height, weight, body mass index, waist + hip circumference, thickness of 4 skin folds	n.a.
Blood pressure	Systolic and diastolic blood pressure	n.a.
Visual motor processing speed	Trail making Test part A	n.a.
Executive functioning	Trail making Test part B	n.a.
Activity monitoring	Accelerometer	n.a.
Food	24h recall	n.a.
Social factors		
Loneliness	De Jong-Gierveld Loneliness Scale	11
Health care use / costs		
Work productivity	Productivity and disease questionnaire (PRODISQ)	14
Biological and clinical factors		
Cancer-related factors		
Cancer location / stage	Standard questions, from medical record	n.a.
Treatment modality	Standard questions, from medical record	n.a.
Co-morbidity	Standard questions, from medical record	
Biological factors		
Tumor markers	Tumor tissue	n.a.
Biomarkers	Blood	n.a.
General laboratory	Blood	n.a.
DNA	Blood	n.a.
Proteomics	Blood	n.a.
Gene-expression (RNA)	Blood	n.a.

Abbreviations: MDD: major depressive disorder. N.a: not applicable

Outcome measures

The primary outcome of this study was the feasibility of the baseline assessment protocol, as evaluated by representativeness of the study population, achievability of baseline assessments, and accuracy of the protocol.

Representativeness was assessed by the following questions:

- What percentage of eligible patients is willing to participate?
- What are the main reasons for not participating?
- Are there differences between participants and non-participants regarding age, gender, diagnosis, comorbidity, stage, treatment, HRQoL and emotional distress?

Achievability was evaluated by the following items:

- A study specific questionnaire consisting of 4-point Likert scales (not feasible – a bit feasible – quit feasible – very much feasible) covering the number of items, time investment, intimacy and burden of the PRO's and the home visit.
- The number of items successfully completed was registered as well as the time needed to complete the PRO's, as estimated by patients and the home visits as measured by a research physician.

Accuracy of the assessment protocol was evaluated using the following questions:

- Is the protocol clear to other assessors (i.e. two experienced fieldworkers and a coordinator from the NESDA study)?
- Is the assessment protocol complete, clear and accurate according to the research physician (A.N.)?

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc. Chicago, IL). Descriptive statistics (mean / standard deviation (SD) / proportions) were generated for demographic and clinical characteristics, emotional distress and HRQoL and questions on representativeness and achievability.

Differences in age, gender, diagnosis, comorbidity, stage, treatment, emotional distress, and HRQoL between participants and non-participants were tested with Mann-Whitney U test or χ^2 test. For the comparison of emotional distress and HRQoL we used results from the OncoQuest database.

Results

Representativeness

During a time period of 14 weeks 26 eligible patients were asked, of whom 15 (58%) were willing to participate (Figure 1). The main reason for not participating was the high burden of recently being diagnosed with cancer, leaving no room for additional inconvenience (n= 8; 30%).

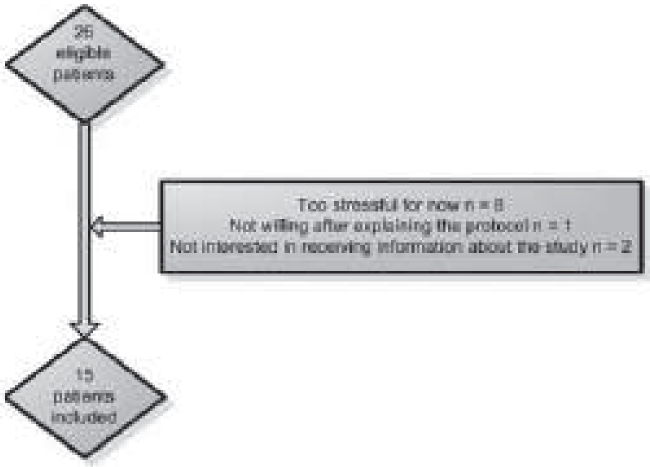

Figure 1. Flowchart of all eligible patients and the reasons for non-participation.

However, all of these patients indicated that they would have been interested in participation at another point in time. Other reasons for non-participation were not willing to participate in any research project (n=2; 8%) or not willing to participate in this specific study protocol (n= 1; 4%).

Except for gender, no differences in demographic and clinical characteristics, emotional distress and HRQoL were found between participants and non-participants. The proportion of women among non-participants (64%) was higher than among participants (13%), p= 0.008 (Table 2).

One participant (7%) and two non-participants (18%) did not fill out OncoQuest, and consequently their data on HRQoL and psychological distress were missing.

Table 2. Differences in demographic and clinical characteristics, psychological distress and health-related quality of life between participants and non-participants.

Characteristics	Participants (n= 15)	Non-participants (n= 11)	Difference (p-value)
Gender, n (%) male	13 (87)	4 (36)	0.008
Age, mean ± SD (range) years	63 ±12 (40-80)	62 ± 8 (52-78)	0.926
Tumor location, n (%)			0.986
Oral Cavity	4 (27)	3 (27)	-
Oropharynx	5 (33)	3 (27)	-
Hypopharynx	0 (0)	0 (0)	-
Larynx	5 (33)	4 (36)	-
Unknown Primary	1 (7)	1 (9)	-
Disease Stage, n (%)			0.749
I	2 (13)	2 (18)	-
II	1 (7)	1 (9)	-
III	5 (33)	3 (27)	-
IV	7 (46)	5 (45)	-
Type of treatment, n (%)			0.486
CHRT	8 (53)	4 (36)	-
RT	4 (27)	2 (18)	-
SURG	1 (7)	3 (27)	-
TOE + SN	2 (13)	2 (18)	-
Comorbidity, n (%)			
None	4 (27)	3 (27)	0.683
Mild	3 (20)	3 (27)	-
Moderate	7 (47)	3 (27)	-
Severe	1 (7)	2 (18)	-
	Participant (n= 14)	Non-participant (n= 9)	
HADS			
Total score, mean ± SD	10 ± 8	11 ± 5	0.587
Depression score ≥ 8, n (%)	3 (21%)	1 (11%)	0.546
Anxiety score ≥ 8, n (%)	3 (21%)	4 (44%)	0.262
Total score > 15, n (%)	3 (21%)	2 (22%)	0.966
EORTC QLQ-C30, mean ± SD			
Global quality of life	78 ± 15	64 ± 29	0.145
Physical function	87 ± 15	81 ± 23	0.480
Role function	88 ± 24	74 ± 30	0.229

Table 2. Continued

Characteristics	Participants (n= 15)	Non-participants (n= 11)	Difference (p-value)
Emotional function	60 ± 22	69 ± 20	0.296
Cognitive function	88 ± 21	94 ± 8	0.402
Social function	92 ± 18	85 ± 28	0.508

Abbreviations: SD: standard deviation; CHRT = chemo radiation therapy; EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS = Hospital Anxiety and Depression Scale; RT = radiotherapy; SURG = surgery; TOE + SN = transoral excision and sentinel node procedure;

Achievability

All participating patients filled out the questionnaires with 95-99% (n=8) to 100% (n=7) of the items completed. Two patients did not fill out the questionnaire on sexuality because they were not sexually active. No problems were detected with other questionnaires. The majority of the patients (80%) preferred the pen-and-paper version over the internet-based method. Completing the PRO's took on average 167 (range 100-270) minutes. All patients filled out the PRO's within one week. One patient needed 270 minutes to complete the PRO's due to concentration problems. Compared to the other patients, this was exceptionally long (range without this particular patient: 100-210 minutes).

Most patients (n= 12) preferred the research physician to conduct the interview, physical tests, and blood collection during a home visit. Assessments of the other three patients were conducted during a hospital visit. The visits took on average 100 (range 60-145) minutes.

Table 3. Achievability of physical tests and biological sample collection.

Physical Assessments	Percentage performed	Reasons for not performing physical assessments
Grip strength	100	-
30 second chair stand test	93	Amputated leg (n = 1)
Step test	80	Amputated leg (n = 1) Cardiac history (n = 1) Severe immobility (n = 1)
Accelerometer	53	Amputated leg (n = 1) Severe immobility (n = 1) PEG* tube placement (n = 2) Lost accelerometer (n = 2) Surgery, within a few days after visit (n = 1)
Biological sample collection	Percentage performed	Reasons for not performing biological assessment
Blood collection	87	Unwillingness (n = 2)
Saliva collection	87	Not returned (n = 2)
Tissue collection	53	Biopsy already taken (n = 1) No extra biopsies, direct surgery (n = 3) No extra biopsies, unknown primary tumor (n = 2) Reason not registered (n = 1)

Abbreviations: PEG (percutaneous endoscopic gastrostomy)

Some of the physical tests and biological sample collections could not be performed (Table 3). The Chester step test was not conducted in three patients due to physical impairments such as an amputated leg, cardiac history or severe mobility problems. Accelerometer data of six patients were missing due to: surgery within a few days after the baseline measurement (n= 1), a percutaneous endoscopic gastrostomy (PEG) tube placement within a few days after baseline assessment (n= 2), wheelchair dependence (n= 1), crutches dependence in daily life (n= 1) and losing the accelerometer (n= 1). All other physical tests were completed by all patients. The cognitive test and the psychiatric interview were conducted in all patients without experiencing any problems. Dietary telephonic interview at the end of the assessments were taken in 11 (73%) patients. Four interviews were missed because treatment already started. Blood and saliva samples were collected in 13 patients (87%) patients; two patients refused to give blood samples, and two patients did not return their saliva samples. Tumor tissue from eight participants (53%) was collected during panendoscopy at the VU University Medical Center. Reasons for not collecting supplemental biopsies were: unknown primary tumor (n= 2), no extra biopsies during panendoscopy because of immediate surgery (n= 3), biopsy already taken in outpatient clinic (n= 1) and unknown (n= 1). Patients evaluated the number of items, the time investment and personal or intimate character of the PRO's and the physical tests as feasible to very much feasible (Table 4). Regarding intimacy of questions, one patient found a questionnaire on sexuality too intimate and therefore rated the item intimacy as 'a bit feasible' for intimacy. One patient found the time investment of the home visit too long. Due to the presence of a child, this home visit took much longer compared to the other patients (145 min).

Table 4. Feasibility of the questionnaires and home visit

Questionnaires, n (%)	Not feasible	A bit feasible	Feasible	Very much feasible
Number of items	-	-	12 (86)	2 (14)
Time investment	-	-	6 (40)	8 (57)
Personal or intimate character of questions	-	1 (7)	7 (50)	6 (43)
Home visits, n (%)				
Number of questions	-	-	3 (21)	11 (79)
Time investment	1 (7)	-	4 (29)	9 (64)
Personal or intimate character of questions	-	-	2 (14)	12 (86)
Burden of physical assessments	-	-	2 (14)	12 (86)

Protocols

Generally, the research-physician reported the home visits to be very pleasant. Concentration problems were present in two patients according to the research-physician. Another patient was somewhat long-winded and expanding to various topics during the (psychiatric) interview, and had to be redirected to the questions continuously. No adverse events occurred during the visits. Furthermore, the protocols were independently judged as clear by the research physician, two other experienced fieldworkers and a research coordinator.

DISCUSSION

This pilot study showed that it is feasible to conduct a comprehensive baseline assessment compromising a large number of PRO's, interviews, physical tests, and biological sample collection among newly diagnosed HNC patients. We found the study sample to be a representative reflection of patients with HNC and the achievability of the assessment protocol was high.

Representativeness

The present study showed that 58% of newly diagnosed HNC patients were willing to participate in a comprehensive assessment. Our response rate was somewhat lower compared to 76%-97% reported in the other prospective cohort studies on HRQoL in HNC patients.7;9;12;38;39 Differences in response rate may be related to the large number of questionnaires included, since only one to three questionnaires were included in the previously mentioned studies. Taking into account our comprehensive assessments, we consider our response rate to be acceptable. Of all eligible patients 30% would like to participate in the study, but not at this specific moment. The most important argument for not participating was that the protocol seems too burdensome. For a future study, we can now better inform eligible patients on the time investments and feasibility of the protocol. The remaining 12% of eligible patients were not willing to participate in any study, and it is likely that this proportion will also be missed in a forthcoming cohort study.

In our study, females were found to be less likely to participate, which is in contrast to the pilot study of Hammerlid et al.40 who found all non-participants to be men. Another prospective study on long term HRQoL in patients with HNC found no significant differences between participants and non-participants in demographic and clinical characteristics.9 Therefore, our under-representativeness of women may be coincidental. On the other hand, it may be related to the higher, but non-significant anxiety levels we found among non-participants, since, in patients with HNC, women are more likely to report higher levels of anxiety than men.41 However, due to the small sample size, the non-significant differences in anxiety between participants and non-participants should be interpreted with caution. Studies among newly diagnosed cancer patients are at risk for selection bias underestimating problems related to emotional distress and HRQoL. Therefore, we will closely monitor differences in main characteristics between responders and non-responders in a future cohort study.

Achievability

Despite the considerable time investment (average of 270 minutes in total), our results showed that almost all patients found the study to be feasible to very much feasible. However, some patients experienced some problems with the questionnaires on sexuality, particularly those who were not sexually active. To avoid unnecessary confrontation with intimate questions in a future cohort study, we will therefore add a remark at the start of this questionnaire that patients can skip this questionnaire if not applicable. Regarding the (home) visits, we noticed that a quiet environment is important to prevent unnecessary delay in conducting the interviews and physical tests.

The home visits were almost fully completed. Blood and saliva was collected in 87% of the patients which we considered to be acceptable. A relatively large proportion (40%) of patients did not wear the accelerometer due to various reasons, of which some were largely unavoidable such as amputated leg and crutches dependence, whereas others may be prevented or (rapidly) solved. In this study, we did not give an accelerometer to patients undergoing a PEG tube placement which potentially hampers physical activities for a certain period of time. However it seems that the patients may be able to wear an accelerometer. Furthermore, a new device may quickly be sent to patients who lost their device. Tissue collection was successful in 53% of the participants. In most cases, supplemental tumor biopsies for this study were not taken due to logistical reasons including immediate surgical treatment of tumor, biopsies already taken in outpatient clinic, or because of an unknown primary tumor. In this pilot study, we did not collect tumor tissue samples from the surgical specimen from the pathology department, but we are planning to do so in a future study if tumor tissue is available.

Strengths and limitations

To our knowledge this pilot study is the first to evaluate a comprehensive assessment protocol of this extent in newly diagnosed HNC patients before treatment. In addition, the inclusion of objective physical tests and biological sample collection in addition to PRO's is a strength of this study. Another strength of this study was the ability to compare data on HRQoL and psychological distress between participants and non-participants, providing a thorough investigation of the representativeness of the included study sample. This study was limited by its focus on baseline assessment only, and we did not collect data on the feasibility of follow-up measurements. However, other longitudinal studies on HRQoL in patients with HNC reported acceptable dropout rates varying between 6 and 14%.[9;38] Whether drop-out rates will be similar in the forthcoming cohort study remains unclear. Furthermore, while almost all single questionnaires were validated it is unclear whether assessment of multiple single valid questionnaires impacts the validity. A previous study examining the influence of the structure of questionnaires on response outcomes showed that changes in order of questionnaires did not substantially affect the outcomes.[42] In the present study, assessments were conducted in a hierarchical order, starting with the main outcome measure health-related quality of life, following by questionnaires assessing covariates. In conclusion, this study showed that it is feasible to conduct a comprehensive assessment protocol including PRO's, interviews, physical tests, and collection of biological samples in newly diagnosed HNC patients before the start of treatment. Therefore, we will set up a large multicentre cohort study in patients with HNC evaluating the course of HRQoL over time starting at diagnosis, and the relationship between HRQoL and survival, taking into account cancer-related, personal, genetic, biological, psychobehavioural, physical, lifestyle-related and social factors, the NETherlands QUality of life and BIomedical Cohort studies in cancer, Head and Neck (NET-QUBIC_HNC).

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CHAPTER 7

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis focused on health-related quality of life (HRQoL) in patients with head and neck cancer (HNC). The research in this thesis aimed to obtain more knowledge on HRQoL in relation to HNC survival, and on the role of physical activity and its relation to HRQoL among patients with HNC. In this final chapter, the most important findings of this thesis are summarized and put into perspective based on current literature. The chapter concludes with implications for clinical practice and recommendations for further research.

Main findings

The literature up to 2012 on HRQoL in patients with HNC was reviewed in Chapter 2. This chapter clearly showed the growing interest in using patient-reported outcome measures (PROMs) to measure HRQoL for research and clinical purposes. Besides, HRQoL seemed to be associated with survival. However, important gaps in knowledge were identified. First, as most of the knowledge on HRQoL in relation to survival was based on cross-sectional studies, little was known about the course of HRQoL over time, and about factors associated with (change in) HRQoL. Second, there is a lack of understanding of the association between HRQoL and survival and how this may be influenced by various cancer-related, personal, biological, and psychological, physical, lifestyle-related, and social factors. Third, data from PROMs are important in clinical trials as well as clinical care for patients. Knowledge on HRQoL may facilitate communication with patients, it can be used to screen and/or monitor physical and psychosocial problems,[1] and to identify patients with HNC with a need for supportive care in routine clinical practice.[2] Fourth, there is a need to develop supportive care interventions to improve HRQoL of patients with HNC and survivors and to evaluate the effectiveness and cost-effectiveness of these interventions.

Health-related quality of life in relation to survival

The association between HRQoL and survival in patients with HNC was further investigated in Chapters 3 and 4. Both studies showed that HRQoL was significantly associated with survival after adjusting for relevant sociodemographic, lifestyle-related and clinical variables. More specifically, there was strong evidence for a positive association between pre-treatment physical function and survival (Chapter 3 and 4) and between change in global QoL (from pre-treatment to 6 months post-treatment) and survival (Chapter 3). Chapter 4 also reported a significant positive association of other domains of HRQoL assessed pre-treatment (global QoL, role function, emotional function, cognitive function and social function) with survival. Moreover, Chapter 4 showed that HRQoL changes in the first 6 weeks of treatment were not associated with survival, while changes in physical and emotional function from diagnosis to 6 months following treatment were associated with survival, as well as changes in global QOL, and physical, emotional, and social function from pre-treatment to 12 months after treatment. Apparently, while HRQoL can be deteriorated shortly after treatment, most likely due to acute side effects of treatment, this short-term deterioration is not likely to be predictive for survival.[3-5] Findings suggest that long-term deterioration of HRQoL, particularly deteriorations in physical and emotional function are likely to be predictive for survival. This predictive value of physical and emotional function has been acknowledged in previous studies.[6-9]

Deterioration in global QoL and social function were only associated with reduced survival one year after treatment. Perhaps, reduced physical and emotional function over time also affects global QoL and social function. On the other hand, patients with advanced illness may not be able to perform social activities. In conclusion, this thesis showed that poor HRQoL at time of diagnosis, as well as a worsening of global quality of life, physical, emotional and social function at 6 and 12 months follow-up compared to time of diagnosis is significantly associated with reduced survival in patients with HNC. Findings from this thesis highlight the importance of monitoring these HRQoL in the first year after diagnosis and treatment, because people with worsening HRQoL might have an increased risk of mortality.

Physical activity and HRQoL

Chapter 5 showed that HNC survivors (mean time after treatment, 21 months), and particularly older survivors, are at risk for low levels of physical activity. A large proportion of physical activity consisted of household activities (54%), followed by leisure time (34%) and occupational activities (12%). Total levels of physical activity in HNC survivors were substantially lower as compared to a non-cancer elderly population also using the PASE questionnaire, i.e. 145 vs. 100 points.[10] The low levels of physical activity in patients with HNC was recently confirmed in a study that measured physical activity objectively using accelerometers.[11] This study reported an average physical activity level of 229 min/day, as compared to 375 min /day) reported in healthy people who were slightly older.[12]

A second important finding of Chapter 5 was the positive association between physical activity and HRQoL. This finding confirm the results of previous smaller studies in HNC survivors.[13,14] The causal direction of this association, however, is unknown due to the cross-sectional design of the study. It is therefore unclear if improving physical activity may improve the HRQL of HNC survivors. There is strong evidence among patients with cancer types other than HNC, such as breast cancer, that exercise interventions during and following cancer treatment can improve HRQoL.[15] However, it is currently unclear whether this is also the case for HNC survivors. At least, the association between physical activity and HRQoL found in the present thesis provides rationale to conduct such exercise trials in HNC survivors. In fact, pilot studies indicated that it is feasible to conduct exercise trials aiming to examine the efficacy of exercise interventions on HRQoL.[16,17] Adherence to the exercise intervention is difficult and may be better when it is administered after treatment completion.[18] In addition to a possible positive association between physical activity and HRQoL as such, observational studies showed that higher levels physical activity are also associated with a 38% lower cancer-specific mortality risk in patients with breast, colon and prostate cancer.[19] One study showed comparable effects for a HNC population.[20] However, currently the number of studies examining the association between physical activity and survival in HNC is limited and more research is needed.[21]

Feasibility a large prospective cohort study examining HRQoL in patients with HNC

To be able to investigate the course of HRQoL from time of diagnosis to long-term follow-up, and to unravel complex associations between the course of HRQoL and survival, in relation to cancer-related, personal, genetic, biological, psychological, physical, lifestyle-related and social factors, a prospective cohort study among a large group of patients with HNC with assessments of all these variables is warranted. Chapter 6 reveals that it is feasible to conduct a comprehensive assessment (with an average time investment of 270 minutes in total) protocol including patient reported outcomes (PROMs), interviews, physical tests, and collection of biological samples in patients that were newly diagnosed with HNC before the start of treatment. Importantly, the study sample appeared to be a representative reflection of patients with HNC and the achievability of the assessment protocol was high. As a result, a large multicenter cohort study in patients with HNC evaluating the course of HRQoL over time starting at diagnosis, and the relationship between HRQoL and survival, taking into account cancer-related, personal, genetic, biological, psychological, physical, lifestyle-related and social factors, the NETherlands QUality of life and BIomedical Cohort studies in cancer, Head and Neck (NET-QUBIC_HNC) was launched. Currently baseline data and samples of 739 patients with HNC, as well as 3-months follow-up data (n=541) and 6 months (n=585) follow-up data and samples are available. Also, baseline of all 262 caregivers are available, as well as 3-months and 6 months follow-up data.[22]

METHODOLOGICAL CONSIDERATIONS

The chapters in this thesis describe literature reviews and observational studies (cross-sectional and longitudinal), to answer the research questions. Both types of studies have methodological shortcomings which are discussed below.

(Systematic) reviews

Reviews and systematic reviews play an essential role in evidence based medicine.[23] Reviews are a high quality source of cumulative evidence, especially when a methodological quality assessment and best evidence syntheses is included.[24] These methods were incorporated in the systematic review presented in Chapter 4. However, the majority of the included studies did not report hazard ratios and confidence intervals of non-significant associations. This hampered the conduct of a meta-analysis. In the best evidence synthesis we included only high quality studies to reduce possible bias. However, similar to other reviews and meta-analysis, publication bias endangers the external validity, and it cannot be ruled out fully.

Observational studies

Data from observational studies, both cross-sectional and longitudinal can be an important source of evidence about patients' true experience and HRQoL of cancer survivorship in addition to randomized controlled trials (RCT's).[25] Furthermore, compared to RCTs, a more heterogeneous group of patients can be included, and therefore findings may be more representative for the total patient population.[25] However, a disadvantage of observational studies is the inability to determine causality. Consequently, from the associations between HRQoL and survival reported in Chapter 3 and 4, it is unclear whether improving HRQoL, and particularly improving physical and emotional function from pre-treatment to 6 months post-treatment, would benefit survival or whether the deteriorations in these HRQoL domains are reflective of the disease severity. Comparably, from the positive association between physical activity and HRQoL reported in Chapter 5, it is unclear whether improving physical activity would improve HRQoL or whether higher HRQoL would result in higher physical activity levels. Nevertheless, these associations emphasize the potential for future RCT's providing information on causality.

Assessment of physical activity

In this thesis, physical activity was assessed by self-report. PROMs are well suited to identify the dimensions and domains of physical activity behaviors.[26] However, they are prone to recall and social desirability bias,[27] and less accurate to estimate light intensity physical activity.[26] This may have resulted in an over- or underestimation of physical activity levels. Nevertheless, the lower physical activity levels that were found in this thesis among patients with HNC as compared to previous findings in the general healthy population using the same questionnaire,[10] has recently been confirmed in a study that assessed physical activity in patients with HNC using objective measurements (i.e. accelerometers).[11] Therefore, the finding from this thesis that patients with HNC have low levels of physical activity is most likely valid. Likewise, there may have been a slight over- or underestimation of the strength of the associations studied. However, because questionnaires are generally able to distinguish physically active from inactive patients, it is unlikely that this would have altered the main findings on the associations.[28]

IMPLICATIONS FOR CLINICAL PRACTICE

Using HRQoL data in clinical practice helps the clinician towards a more holistic approach to the patient. Especially since patients with HNC and survivors often have complex rehabilitation needs due to the anatomical complexity of the head and neck region. Moreover it is important to improve outcomes of people living with and beyond cancer by moving to care pathways with a more patient centred approach opposite from only treating the disease. It is important to stress out choices between potentially morbid but life prolonging interventions versus high quality palliative care.[29] Because (change in) HRQoL is associated with HNC survival (Chapter 3 and 4), monitoring HRQoL in routine care may facilitate identifying patients who might benefit more from palliative care than from survivorship care.[5] Improving communication on HRQoL between doctors and patients, and improving symptom management.[1] is essential, since current literature shows that 68% of patients with HNC have unmet supportive care needs.[2] Often reported concerns of patients with HNC include fear of cancer recurrence, future uncertainties, sadness, and concerns about family or friends.[1] Also, regarding HNC specific problems, even before treatment, patients rank issues related to verbal communication and eating above all other concerns.[2] These unmet needs are closely associated with HRQoL and physical and psychosocial well-being.[30]

PROMs are increasingly used in routine care. However, more uniformity is highly needed. This will provide more comparable results in cancer research and will improve the applicability in clinical practice. When considering implementing PROMs in routine care, important aspects are to limit the time needed to fill out the questionnaires,[31] and reduce the complexity of the questionnaire.[32] The way a questionnaire is completed is important, for instance before the consultation with the physician, at home or in the hospital.[1,33] A tailored implementation strategy for successful integration of PROMs in clinical practice is described in the EORTC manual.[1] Regarding relevant time points along the cancer trajectory, pre-treatment, 6 months and 1 year after treatment seems to be relevant, when PROMs are used to identify patients who might have an increased risk of mortality (Chapter 3 and 4). A recent study in our hospital showed that the use of PROMs in clinical practice is durable, even 5 years after the introduction.[33]

New developments in cancer survivorship are self-monitoring, eHealth, and stepped care. For example, the fully automated self-management application Oncokompas supports cancer survivors to self-monitor HRQoL and symptoms, it provides personalized feedback, information, and a tailored overview of supportive care options. Oncokompas is shown to be effective to improve HRQoL, reduce the burden of symptoms and is cost-effective.[34] Another example is a guided self-help exercise program for head and neck specific symptoms, maintaining mobility of head and neck region as well as the swallowing and speech function.[35-37] Furthermore, a stepped care program that supports HNC survivors to reduce psychological distress was found to be effective and cost-effective.[38,39]

Based on the research in this thesis which showed that physical activity in HNC survivors is low (especially in older survivors) and associated with worse HRQoL, physical exercise might be offered to HNC survivors, via physical therapist-guided or home-based exercise programs.[40] When offering these exercise interventions, medical clearance may be indicated in some cases (e.g. in presence of cardiovascular, renal or metabolic symptoms) prior to high intensity exercise.[41] Additionally, one should be aware of barriers specific to HNC survivors, such as poor health, malnutrition, and lack of interest[42] Tailored advise on physical exercise is vital because patients have to maintain exercising over time. One should be aware of patients' barriers and preferences to increase exercise adherence and maintenance.[18] This can be facilitated by modifiable determinants, such as motivational (e.g. self-efficacy, outcome expectations, action planning and control) and environmental (e.g., access to physical activity) factors.[43]

RECOMMENDATIONS FOR FURTHER RESEARCH

The body of evidence to incorporate HRQoL in clinical practice is substantial, but translation into clinical practice is difficult.[44-47] Likewise, implementation of tailored supportive care programs remains a challenge.[48] Organizations can increase the likelihood of successful routine outcome measurement by providing appropriate training, sufficient administrative support and adequate allocation of resources.[49] Also, as mentioned in Chapter 2 there is a wide variety of PROMs (among 93 studies more than 60 different questionnaires were applied in clinical care and research) and due to the lack of standardization it is difficult to use these data in clinical research and practice.[50] Careful selection of PROMs is important to sustain comparability between findings in clinical practice and applicability towards clinical care, as well as research purposes (e.g. evaluation of treatment and supportive care). Working towards a uniform use of PROMs is necessary to better compare research findings and facilitate clinical. More research is needed to provide a more accessible, uniform platform which is convenient in routine clinical practice.

Manuals and training sessions that aim to support and engage clinicians in PROM based dialogue and patient-centered communication are starting to be developed.[51] Still more research to upscale and implement the use of PROMs is necessary, such as if the use of PROMs is sustainable over time and whether patient-centered communications leads to a beneficial use of PROMs. Concerns from the organization (patient privacy, data security), management (cost-effectiveness) and clinicians (validity of the tools, when should a result be interpreted as clinically relevant) must be taken into account.[52] All relevant stakeholders e.g. patients, nurses, physicians, administrational and technical staff) have to be included in the implementation process.[52] To engage these stakeholders, participatory or qualitative research could be considered.

Health-related quality of life and survival

To better understand the factors that influence the course of HRQoL over time, and the association between HRQoL and survival in patients with HNC, more research is needed. Previous research showed considerable variation between patients who are at risk for poor HRQoL and others that are protected for poor HRQoL.[53] In addition, regarding survival, lower HRQoL pre-treatment and with a steeper decline in HRQoL during diagnosis and treatment is associated with shorter survival.[5] In addition, Chapter 3 and 4 revealed that pre-treatment physical function and changes in physical and emotional function 6 months after treatment are most strongly associated with survival. It is therefore highly relevant to understand the risk factors and the protective resources that predict HRQoL. Unraveling potential determinants of HRQoL is important to identify treatable ones. The multicenter cohort study NET-QUBIC[22] that followed the feasibility study presented in Chapter 6, aims to unravel the complex associations between cancer-related, personal, genetic, biological, psychological, physical, lifestyle-related and social factors, and survival in patients with HNC and, currently, studies on the NET-QUBIC cohort are being conducted.[11,22,54,55]

Physical activity and HRQoL

The positive association between physical activity and HRQoL reported in Chapter 5 indicates the need to conduct a RCT to study potential causal effects of physical activity and exercise interventions on HRQoL in patients with HNC. Currently, RCT's on the (cost-) effectiveness of exercise programs targeting HNC survivors are scarce and limited by a small sample size.[16,17] Although exercise interventions have shown to be effective on HRQoL in patients with cancer,[15,56-60] these studies were primarily based on studies among patients with breast and prostate cancer. It is unknown whether these research findings can be generalized to patients with HNC due to distinct cancer trajectories, symptoms and side effects (e.g. shoulder dysfunction, dry mouth or throat, difficulty eating, and shortness of breath).[61] Additionally, patients with HNC often have an unhealthy lifestyle. Smoking, alcohol use and malnutrition are highly represented in newly diagnosed patients with HNC.[62,63] It can be hypothesized that this could negatively influence the motivation to be physically active. Identifying barriers of physical activity, developing strategies to overcome these barriers and to increase motivation to increase and maintain physical activity is needed. In addition, research needs to be done to learn about the optimal type and dosage of physical activity and the impact of sedentary behavior on HRQoL. Furthermore, evidence on the association between physical activity, and cancer incidence, and mortality is increasing, particularly in patients with breast, colon and prostate cancer.[19,21,41] Yet, the causal effects of physical activity and exercise interventions on clinical outcome is unknown. Previous RCT's have shown that exercise interventions during chemotherapy can benefit chemotherapy completion rates,[64,65] but results are not consistent,[66,67] and studies were limited by a lack of statistical power.[66] Several pre-clinical studies found a direct beneficial effect on exercise on tumor growth.[68,69] If these findings translate from mice to (wo)men is not known. Few RCTs are currently examining the effects of exercise interventions on survival in patients with colon cancer,[70] metastatic prostate cancer,[71] ovarian cancer[72] and allogeneic stem cell transplantation.[73] Future studies should reveal whether exercise interventions can benefit chemoradiation efficacy and potentially survival. When future studies prove a beneficial effect of physical activity intervention among HNC survivors, these interventions can be incorporated in a HNC survivorship care plan along with other programs aiming to improve lifestyle changes (such as smoking and alcohol use).

CONCLUSION

HRQoL is an important outcome in HNC treatment. Two key gaps in knowledge were addressed in this thesis. It was still unclear which HRQoL domains are associated survival in HNC, at which time-point across the cancer journey, and whether absolute values and/or changes in HRQoL are associated with survival. Pre-treatment physical function and changes in physical and emotional function in the first year after treatment are significantly associated with survival. Secondly, more knowledge on HRQoL in HNC survivorship was needed and especially on the role of physical activity.

HNC survivors are not physically active (especially older HNC survivors) in general, and this is associated with lower HRQoL. This thesis contributes to further advancing interdisciplinary research on HRQoL in HNC and may help to develop care pathways with a more patient centred approach.

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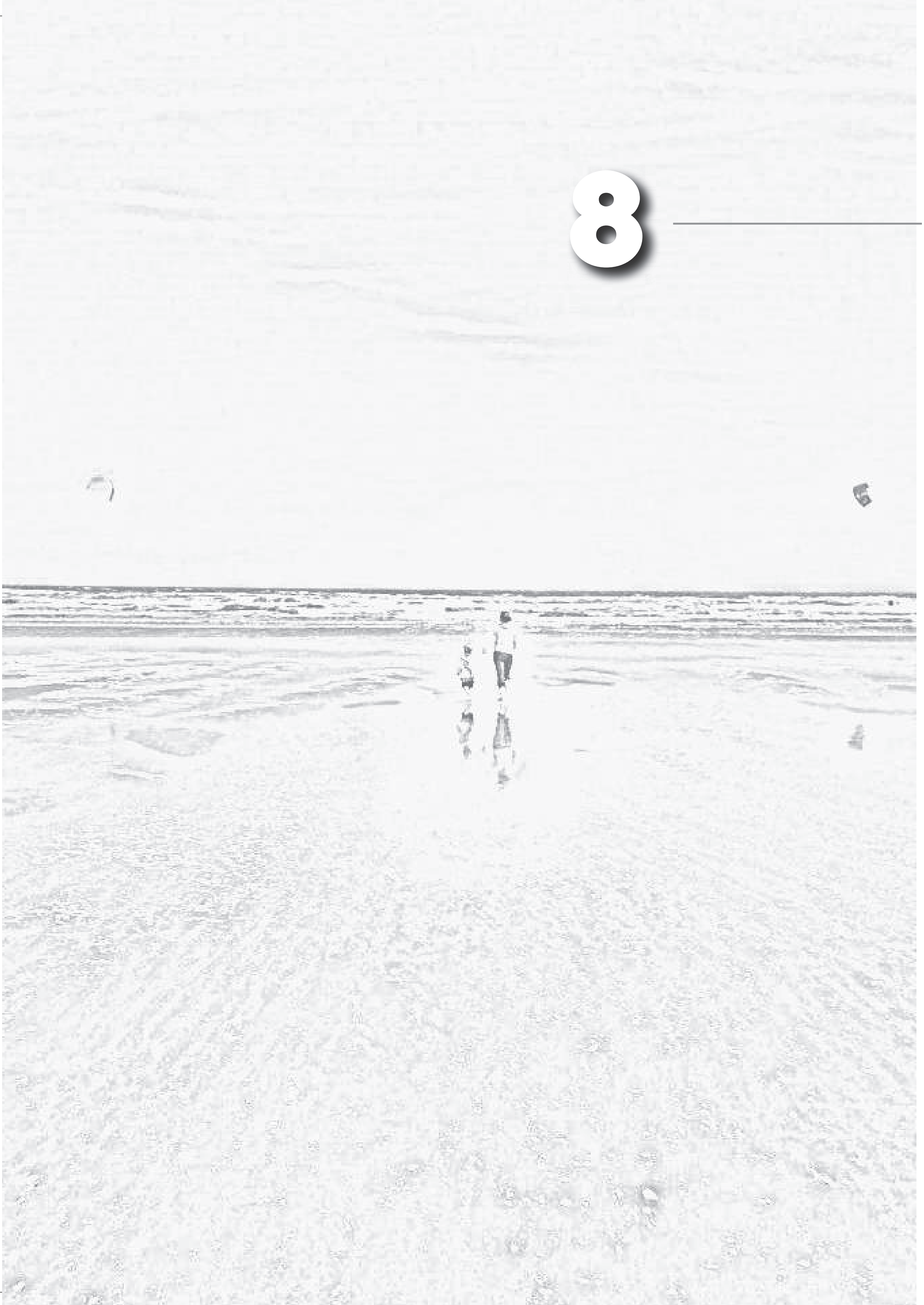


SUMMARY

Chapter 1 provides background information on head and neck cancer (HNC), health related quality of life (HRQoL) and cancer survivorship, with a special focus on physical activity. HNC encompasses tumors in the upper respiratory or digestive tract. To date, HNC is the sixth leading type of cancer worldwide, with approximately 705.781 new cases in 2018 and a 5 year survival rate of approximately 65%. Treatment for patients with HNC often involves surgery, radiotherapy, chemotherapy or a combination of these modalities. As a consequence of HNC and its treatment, many patients face physical and psychosocial problems. Additionally, they may be confronted with very specific problems, such as oral dysfunction, swallowing and speech problems. This may have a distinct impact on the HRQoL of patients with HNC. Interestingly the course of HRQoL has shown to be worse in non-survivors of HNC compared to HNC survivors during the first 2 years after treatment. In addition, previous studies showed an significant association between HRQoL and survival, independently from other known demographic, lifestyle-related and clinical factors.

In cancer survivorship promoting a healthy lifestyle is critical. In patients with HNC awareness of lifestyle-related factors such as smoking, alcohol use and nutritional status seems to be eminent. However, little information is available on physical activity. Two key gaps in knowledge were addressed in this thesis. First, it is still unclear which HRQoL domains are associated with survival in HNC, at which time-point across the cancer journey, and whether absolute values and/or changes in HRQoL are associated with survival. Second, more knowledge on HRQoL in HNC survivorship is needed and especially on the role of physical activity and the association with HRQoL. Therefore, this thesis aims to investigate the association between HRQoL and survival in patients with HNC, and to investigate physical activity levels in long-term HNC survivors and the association with HRQoL.

Chapter 2 reviewed literature on HRQoL in patients with HNC. HRQoL seems an independent predictor of survival, but this association may be influenced by various cancer-related, personal, biological, psychobehavioural, physical, lifestyle-related, and social factors. Less is known about the course of HRQoL over time and about the same above mentioned possible factors associated with (change in) HRQoL in patients with HNC. Symptom management and psychosocial care may be beneficial for HNC patients to improve HRQoL, but more randomised controlled trials are needed. Studies on HRQoL in HNC are most often based on cross-sectional designs. The variability in outcome measures hampers the generalizability of the results of these studies. Information on HRQoL of caregivers is scarce. Better information on all aspects of the course of HRQoL from diagnosis and treatment to long-term survivorship or death is highly needed in both patients and their caregivers. More evidence on the efficacy of (new) treatment options, symptom management, and psychosocial care is needed, also in the context of increasing long-term survival and the growing attention for cancer survivorship.

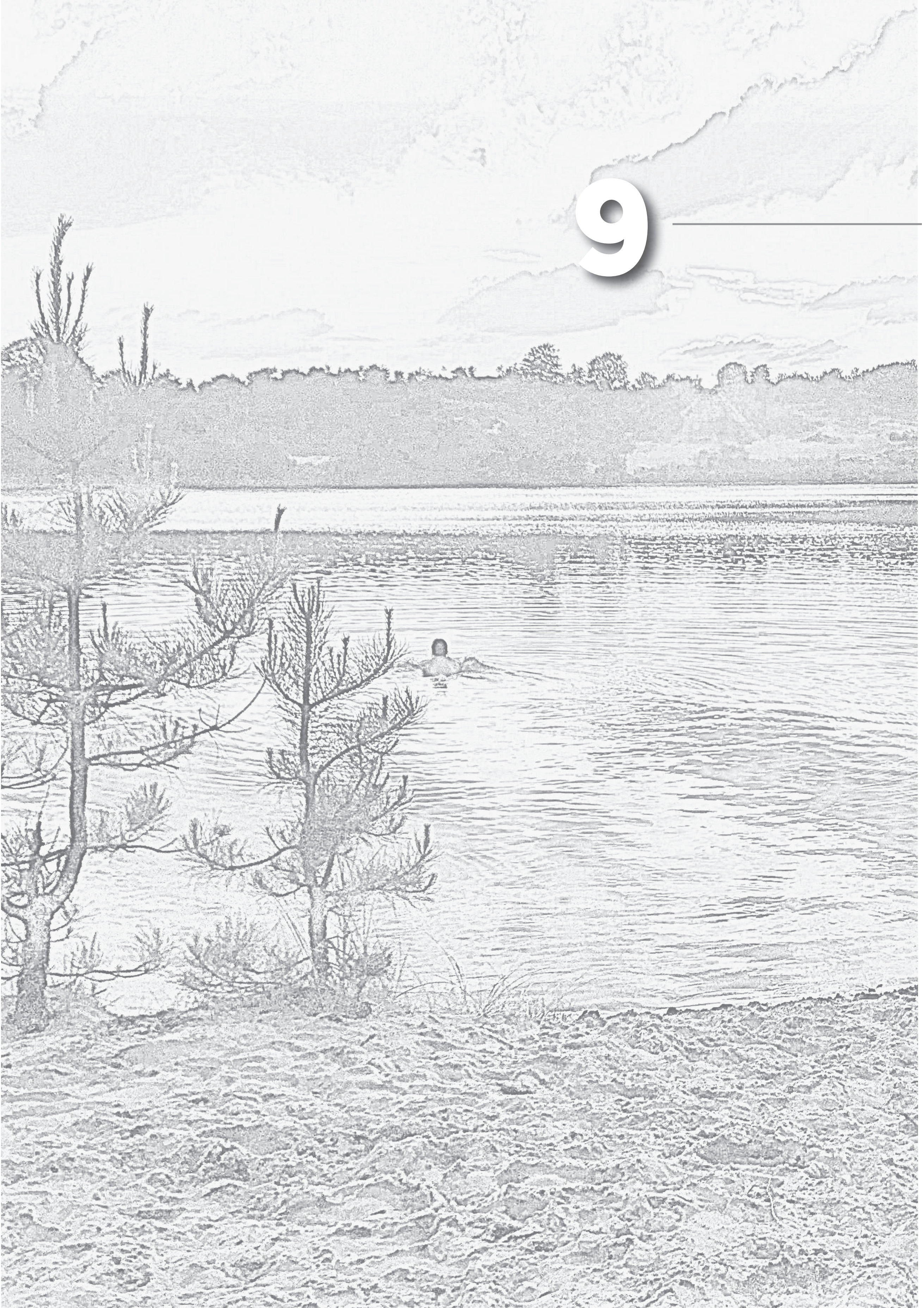
Chapter 3 specifically studied the association between HRQoL and survival in patients with HNC via a systematic review of prospective studies. A systematic search was conducted in four electronic bibliographic databases. We included studies published up to January 2014, providing data on HRQoL and survival, and the association between HRQoL and survival, among HNC patients. Two researchers independently performed a quality rating. A best evidence synthesis was applied to draw conclusions. In total, nineteen studies were included. Twelve studies included all subscales of a HRQoL questionnaire and seven studies focused on specific subscales. The mean quality score was 72 ±17% and 58% of the studies were of high quality. According to the best evidence synthesis, there was strong evidence for a positive association between pre-treatment physical functioning and survival and between change in global QoL from pre-treatment to 6 months after treatment and survival. Due to inconsistent findings, there was insufficient evidence for an association with survival of other HRQoL domains, including role, emotional, cognitive and social functioning, mental health and well-being. This chapter highlights the need for high quality studies with a longitudinal design to examine the complex associations between HRQoL and survival.

Chapter 4 describes a cohort study in which the associations between HRQoL (assessed pre-treatment, post-treatment and change in HRQoL) and survival was examined in patients with HNC. We included different time points along the cancer trajectory (pre-treatment, post-treatment and change in HRQoL). The study included 948 patients newly diagnosed with HNC (oral cavity, oropharynx, hypopharynx and larynx), treated with primary or adjuvant (chemo)radiotherapy with curative intent. HRQoL (EORTC QLQ-C30) was assessed pre-treatment and at 6 weeks, 6 months and 12 months after completion of treatment. Multivariable Cox regression analyses were performed to examine whether pre-treatment HRQoL, post-treatment HRQoL or change in HRQoL were associated with survival, after adjusting for demographic, clinical and lifestyle related variables. HRQoL was significantly associated with survival at all time-points, except for the subscale global QoL at 6 weeks post-treatment. A change in HRQoL in the first 6 weeks was not associated with survival. Changes in physical and emotional functioning from pre-treatment to 6 months post-treatment and changes in global QOL, and physical, emotional, and social functioning from pre-treatment to 12 months post-treatment were significantly associated with survival.

Chapter 5 describes the results of a cross-sectional study that aimed to assess patient-reported levels of physical activity and its association with HRQoL adjusted for relevant demographic, lifestyle-related and clinical factors, among 116 HNC survivors. Physical activity was assessed with the Physical-Activity-Scale-for-the-Elderly (PASE) and HRQoL with the EORTC-QLQ-C30 and EORTC-HN35. Associations were studied using univariable and multivariable regression analyses. Median PASE score was 100.3 (interquartile range 65.1;170.8) of which 54% were household, 34% leisure time and 12% occupational activities. Younger HNC survivors had higher levels of physical activity. Higher physical activity was significantly associated with higher global QoL. Findings for physical function, role function, social function, fatigue and pain were in line, but not statistically significant. These results indicates that improving physical activity might be an intervention target to improve HRQoL. However, due to the cross-sectional design, it is not possible to make causal inferences and it is unclear whether improving physical activity levels would improve HRQoL, or whether HNC survivors with lower HRQoL are less physically active.

To be able to unravel complex associations between cancer-related, personal, genetic, biological, psychobehavioural, physical, lifestyle-related and social factors, and survival in patients with HNC, a cohort study among a large group of patients with HNC with assessments of all these variables is warranted. Chapter 6 aimed to evaluate the feasibility of a comprehensive baseline assessment of a cohort study evaluating the course of HRQoL. Assessments consisted of questionnaires (635 items), a home visit (including a (psychiatric) interview, physical tests, blood and saliva collection), and tissue collection. Representativeness of the study sample was evaluated by comparing demographics, clinical factors, depression, anxiety, and quality of life between patients who participated in the study and those who did not. Feasibility was evaluated covering the number of questions, time investment, intimacy and physical burden. During the inclusion period of four months, 15 out of 26 (60%) patients agreed to participate. Less women participated, 13% in participant group versus 63% in non-participant group (p= 0.008). No other differences were found between participants and non-participants. Study participants completed more than 95% of the questionnaires items, and rated the number of questions, time investment and intimacy as feasible, and the physical and psychological burden as low. It took on average 3 hours to complete the questionnaires and 1,5 hours for the home visit. This study revealed that a comprehensive assessment including various questionnaires, physical measurements and biological assessments is feasible according to patients with newly diagnosed HNC. A large prospective cohort study has started aiming to include 739 HNC patients and their informal caregivers in the Netherlands.

In Chapter 7 the main findings of this thesis are discussed, as well as, the methodological considerations, implications for clinical practice and recommendations for further research. It is concluded that HRQoL is an important outcome in HNC treatment. Two key gaps in knowledge were addressed in this thesis. It was still unclear which HRQoL domains are associated with survival in HNC, at which time-point across the cancer journey, and whether absolute values and/or changes in HRQoL are associated with survival. Pre-treatment physical function and changes in physical and emotional function in the first year after treatment are significantly associated with survival. Secondly, more knowledge on HRQoL in HNC survivorship was needed and especially the role of physical activity. HNC survivors are not physically active (especially older HNC survivors) which is associated with lower HRQoL. This thesis contributes to further advancing interdisciplinary research on HRQoL in HNC and may help to develop care pathways with a more patient centred approach.



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SUMMARY IN DUTCH

Hoofdstuk 1 geeft achtergrondinformatie over hoofd-hals kanker en kwaliteit van leven (KvL) voor, tijdens en na kanker, met een specifieke focus op lichamelijke activiteit. Hoofd-hals kanker bevat tumoren van de bovenste lucht- of voedselweg. Wereldwijd behoort hoofd-hals kanker tot de 6e meest voorkomende vorm van kanker met meer dan 700.000 nieuwe patiënten in 2018. Het overlevingspercentage na 5 jaar is rond de 65%. De behandeling van hoofd-hals kanker omvat in de regel, chirurgie, radiotherapie, chemotherapie of een combinatie van deze behandelmodaliteiten. Als gevolg van de diagnose en behandeling van hoofd-hals kanker worden patiënten geconfronteerd met de fysieke en psychosociale gevolgen ervan. Meer patiënten zullen hiermee om moeten gaan, gezien te toenemende incidentie en overlevingskansen. De algehele en mentale gezondheid verminderen als gevolg van de fysieke en psychosociale problemen die patiënten met hoofd-hals kanker ervaren. Daarbij worden de patiënten met specifieke klachten geconfronteerd, zoals orale dysfunctie, slik- en stemproblemen. Dit heeft een aanzienlijk effect op de KvL voor deze patiëntengroep. Tevens is het beloop van KvL slechter voor patiënten die binnen de eerste 2 jaar na behandeling overlijden. Daarnaast heeft eerder onderzoek aangewezen dat er een significante associatie is tussen KvL en overleven, onafhankelijk van bekende demografische, leefstijl-gerelateerde en klinische factoren.

Het bevorderen van een gezonde leefstijl bij patiënten die leven met of na de diagnose kanker is van groot belang. Hierbij komen adviezen rondom roken, alcohol gebruik en voeding aan bod. Echter, het lijkt erop dat het advies om lichamelijk actief te blijven relatief minder bekend is bij zorgverleners. Daarnaast is het zo dat de kennis rondom lichamelijke activiteit bij patiënten met hoofd-hals kanker relatief achter blijft, met name in vergelijking met de aanwezige kennis rondom hoofd-hals kanker specifieke symptomen van KvL.

Er zijn nog enkele belangrijke vraagstukken onbeantwoord gebleven. Twee specifieke kennishiaten komen in dit proefschrift aan bod. Zo is het nog onvoldoende duidelijk welke domeinen van KvL specifiek samenhangen met overleving, welke momenten in het ziektebeloop het meest van belang zijn en of absolute waarden of juist verandering in KvL geassocieerd zijn met overleven. Tevens is er meer kennis nodig rond KvL bij patiënten die de behandeling van kanker hebben afgerond. De rol van lichamelijke activiteit in de nazorg van patiënten met hoofd-hals kanker is onbekend. Om deze redenen heeft dit proefschrift als doel de associatie tussen KvL en overleving nader te onderzoeken bij patiënten met hoofd-hals kanker en om lichamelijke activiteit en de relatie met KvL te onderzoeken bij patiënten die leven na hoofd-hals kanker.

Hoofdstuk 2 beschrijft een literatuuronderzoek over KvL bij patiënten met hoofd-hals kanker. In dit onderzoek komt naar voren dat KvL een belangrijk onderdeel is van klinische studies. Daarnaast lijkt KvL een onafhankelijke voorspeller te zijn voor overleven, maar dit verband wordt beïnvloed door verscheidene kanker gerelateerde, persoonlijke, biologische, fysieke, leefstijl-gerelateerde en sociale factoren. We weten nog weinig over het beloop van KvL, met name wanneer er rekening wordt gehouden met de eerder genoemde factoren. Het managen van (hoofd-hals specifieke) symptomen en de psychosociale zorg hebben mogelijk een positief effect op KvL bij patiënten met hoofd-hals kanker. Echter om dit te kunnen bewijzen zijn meer gerandomiseerde klinische trials nodig. De studies die tot nu toe zijn gedaan naar KvL bij hoofd-hals kanker bevatten vaak beperkingen. Zo hadden ze meestal een cross-sectioneel ontwerp. Daarnaast was er een grote variatie in de meetinstrumenten waarmee KvL gemeten was, waardoor resultaten lastig met elkaar kunnen worden vergeleken. Bovendien is kennis van KvL bij naasten beperkt. Beter inzicht in het beloop van KvL over de tijd vanaf het moment van diagnose bij zowel patiënten als hun naasten is nodig. Ook is meer kennis nodig omtrent symptoombestrijding en psychosociale zorg, met name in de context van toenemende overlevingskansen en in het kader van de toegenomen aandacht omtrent het leven met en na kanker.

Hoofdstuk 3 beschrijft een systematisch literatuuronderzoek naar de relatie tussen KvL en overleven. Een systematische zoekopdracht werd uitgevoerd in vier elektronische bibliografische databases. Prospectieve observationele studies gepubliceerd tot januari 2014, met gegevens over KvL, overleven en de relatie tussen KvL en overleven bij patiënten met hoofd-hals kanker werden geïncludeerd. De kwaliteit van de studies werd door twee onderzoekers onafhankelijk van elkaar beoordeeld. Daarnaast werd een 'best evidence synthesis' toegepast om conclusies te kunnen trekken. In totaal werden 19 studies geïncludeerd. Twaalf studies includeerde alle domeinen van KvL en 7 studies beschreven alleen specifieke domeinen. De gemiddelde beoordeling van de kwaliteit was 72 ±17% (schaal 0-100) en 58% van de studies waren van hoge kwaliteit. Er werd een sterk bewijs gevonden voor een positieve associatie tussen fysiek functioneren voorafgaand aan de behandeling en overleving. Tevens vonden we sterk bewijs voor een positieve associatie tussen verandering in de algemene KvL, van voor de behandeling tot 6 maanden na de behandeling, en overleving. Door inconsistente bevindingen was er onvoldoende bewijs voor een associatie tussen andere KvL domeinen (zoals rol functioneren, emotioneel functioneren, cognitief functioneren, sociaal functioneren en mentaal welbevinden) en overleving. In de toekomst zijn kwalitatief goede longitudinale studies nodig om de complexe associaties tussen KvL en overleving verder te ontrafelen.

In hoofdstuk 4 werd de associatie tussen KvL en overleving onderzocht in een prospectieve cohort van patiënten met hoofd-hals kanker. Van januari 1999 tot oktober 2009 zijn 948 nieuw gediagnosticeerde patiënten met hoofd-hals kanker (mondholte, orofarynx, hypofarynx en larynx) geïncludeerd, die in opzet curatief behandeld werden middels primaire of adjuvante (chemo)radiotherapie. Tevens hadden deze patiënten de vragenlijst EORTC-QLQ-C30, voorafgaand aan de behandeling, 6 weken, 6 maanden en een jaar na afloop van de behandeling ingevuld om inzicht te krijgen in de KvL. Middels multivariabele Cox regressie analyse werd het verband tussen KvL voor de behandeling, KvL na de behandeling of verandering in KvL enerzijds en overleving anderzijds onderzocht waarin werd gecorrigeerd voor relevante demografische, leefstijl-gerelateerde en klinische variabelen. Hier kwam uit naar voren dat KvL op elk gemeten moment significant geassocieerd was met overleven, met uitzondering van de subschaal algemene KvL gemeten op 6 weken na afronden van de behandeling. Verandering in KvL gemeten van 6 weken na de behandeling ten opzichte van voor de behandeling was niet voorspellend voor overleving. Verandering in fysiek functioneren en emotioneel functioneren van voor de behandeling tot 6 maanden na de behandeling was wel significant geassocieerd met overleving. Evenals verandering in algemene KvL, fysiek functioneren, emotioneel functioneren en sociaal functioneren van voor de behandeling tot 1 jaar na de behandeling.

Hoofdstuk 5 beschrijft een cross-sectionele studie waarin het lichamelijke activiteiten niveau en de relatie met KvL werd onderzocht bij 116 patiënten die zijn behandeld voor hoofd-hals kanker. Lichamelijke activiteit werd gemeten met de ‘Physical-Activity-Scale-for-the-Elderly (PASE) vragenlijst en KvL met de EORTC-QLQ-C30 en EORTC-HN35. Associaties werden bestudeerd middels univariabele en multivariabele regressie analyse. De mediane PASE score was 100.3 (interkwartielafstand 65.1;170.8) waarvan 54% bestond uit huishoudelijke activiteiten, 34% activiteiten in vrije tijd en 12% werk gerelateerde activiteiten. Jongere patiënten waren significant actiever dan oudere patiënten. Patiënten die lichamelijk actiever waren hadden een significant hogere algemene KvL. De verbanden van fysiek functioneren, rol functioneren, sociaal functioneren, vermoeidheid en pijn waren in dezelfde richting maar niet statistisch significant.

Om de complexe associaties tussen kanker gerelateerde, persoonlijke, genetische, biologische, psychosociale, fysieke, leefstijl-gerelateerde en sociale factoren met overleving te ontrafelen bij nieuw gediagnosticeerde patiënten met hoofd-hals kanker is een prospectieve omvangrijke cohort studie noodzakelijk. Hoofdstuk 6 geeft de resultaten weer van de haalbaarheid van een dergelijke omvangrijke meting waarin al deze factoren worden onderzocht. Hierbij werden nieuw gediagnosticeerde patiënten met hoofd-hals kanker gevraagd deel te nemen. De basismeting bestond uit vragenlijsten (635 items), een thuismeting (interview, fysieke testen, verzameling van bloed en speeksel) en verzameling van tumorweefsel. Representativiteit werd bepaald door vergelijking van sociaal-demografische en klinische gegevens en scores op angst, depressie en KvL tussen deelnemers en niet-deelnemers met een Mann-Whitney U test of een Chi-kwadraat toets. Na afloop werd de haalbaarheid van de basismeting geëvalueerd middels een korte studie specifieke vragenlijst. Gedurende de inclusieperiode (4 maanden) participeerden 15 van de 26 (60%) patiënten. Vrouwen participeerden minder vaak, 13% in de deelnemende groep tegenover 63% in de niet deelnemende groep (p= 0.008). Andere patiëntkenmerken verschilden niet tussen de deelnemers en niet-deelnemers. Meer dan 95% van de items in de vragenlijsten werd ingevuld. Het aantal vragen, de tijdsinvestering en de intimiteit van de basismeting waren volgens de deelnemers haalbaar en de fysieke en psychische belasting werd beoordeeld als gering.

De belangrijkste bevindingen van dit proefschrift worden bediscussieerd in Hoofdstuk 7, waarin ook ingegaan wordt op de methodologische overwegingen, de implicaties voor de klinische praktijken de aanbevelingen voor toekomstig onderzoek. Er wordt geconcludeerd dat KvL een belangrijke uitkomstmaat is in de zorg voor patiënten met hoofd-hals kanker. Twee belangrijke kennishiaten zijn in dit proefschrift aan de orde gekomen. Ten eerste was het onvoldoende duidelijk welke KvL domeinen geassocieerd zijn met overleving, welke momenten in het ziektebeloop het meest van belang zijn en of absolute waarden of juist verandering in KvL geassocieerd zijn met overleving. Resultaten van de studies in dit proefschrift laten zien dat fysiek functioneren voorafgaand aan de behandeling, alsook de veranderingen in fysiek functioneren en emotioneel functioneren van voor de behandeling tot 6 maanden na de behandeling sterk geassocieerd zijn met overleving. Ten tweede was de kennis omtrent KvL van lange termijn overlevenden van hoofd-hals kanker en de rol die lichamelijke activiteit daarin heeft onbekend. Patiënten die de behandeling van hoofd-hals kanker hebben afgerond zijn lichamelijk inactief (met name de ouderen), wat geassocieerd is met een lagere KvL. De studies in proefschrift dragen bij aan bevorderen van interdisciplinair onderzoek omtrent KvL bij hoofd-hals kanker. De kennis omtrent patiënten met hoofd-hals kanker die leven met en na de diagnose kanker zal bijdragen aan multidisciplinaire zorg waarbij de patiënt centraal staat.

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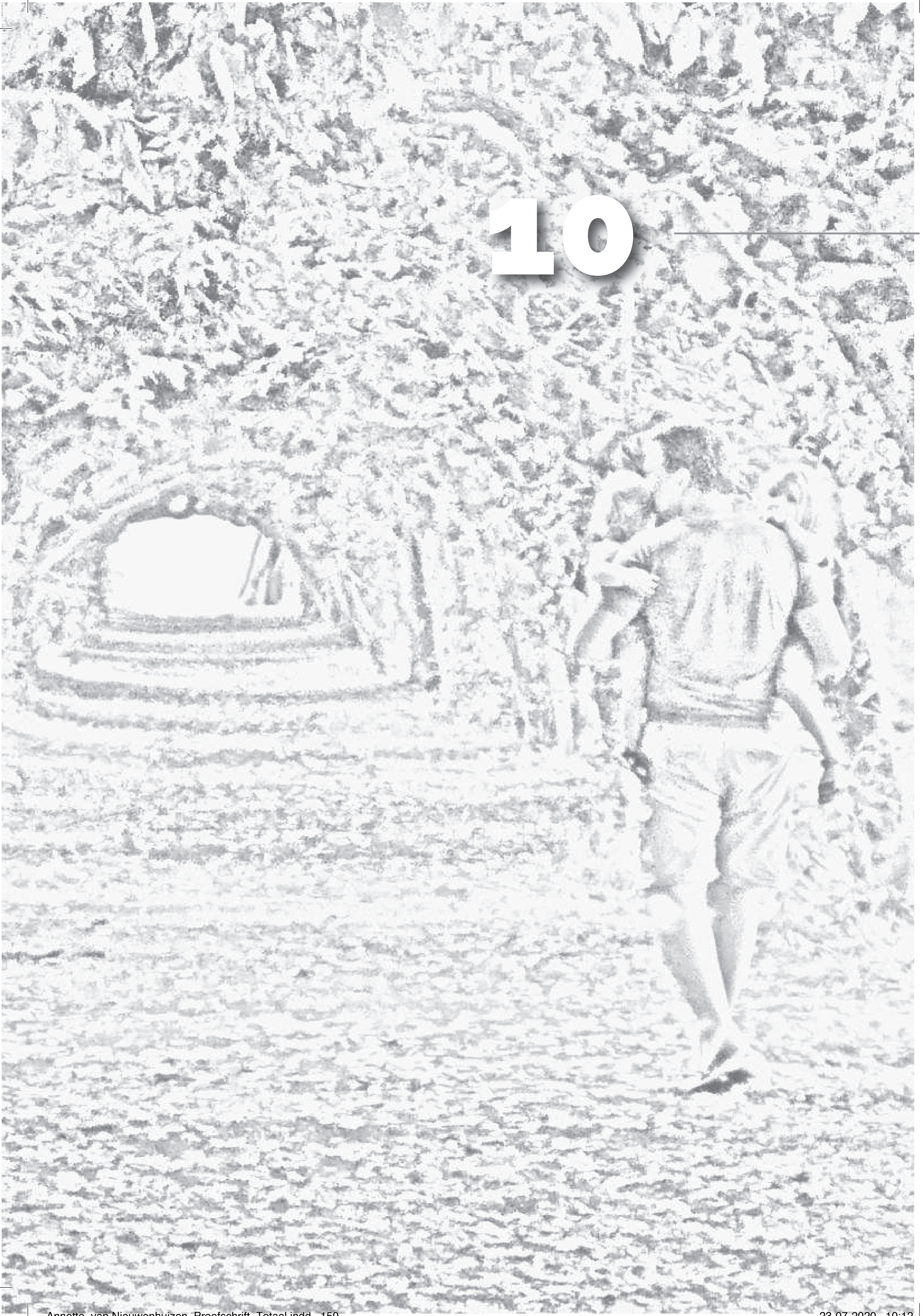

ADDENDUM

DANKWOORD

Eindelijk is het zover, het proefschrift is afgerond. Een lange weg bereikt het eindpunt. Veel is er gebeurt en verandert sinds de aanvang van mijn tijd als onderzoeker in 2011. Nu beginnen met het einde. Het gedeelte wat vanaf de start al in mijn hoofd heeft gezeten en wat gaande weg steeds meer is uitgebreid. Het dankwoord.

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Mijn paranimfen

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CURRICULUM VITAE

Annette van Nieuwenhuizen was born on August 6, 1986 in Oegstgeest, the Netherlands. She attended the Kennemer Lyceum in Overveen, where she received her athenaeum diploma in 2004. In the same year she started her study in medicine at the Vrije Universiteit in Amsterdam. During her study, she studied quality of life in patients with laryngeal papillomatosis, supervised by Rinkel and prof. Verdonck de Leeuw. After obtaining her medical degree in 2011 she started her first research project at the department of Otolaryngology and Head and Neck Surgery of the VU University medical center Amsterdam. She studied health related quality of life in patients with head and neck cancer, which resulted in this thesis. During this period, several chapters of this thesis have been presented in national and international conferences. On june 6, 2013, Annette and her team of colleges climbed the Alpe d'Huez by bike to raise money for the Alpe d'HuZes foundation/Dutch cancer society. In 2014 she commenced her training as resident otorhinolaryngology at the VU University medical center Amsterdam under supervision of prof. dr. C.R. Leemans and Dr. Merkus consecutively. During her residency she worked at the Tergooi ziekenhuis in Blaricum and the Spaarne Gasthuis in Hoofddorp, under supervision of Dr. Borgstein and Dr. E.J.B. van Nieuwkerk, respectively. Currently Annette is in her last year of her specialization in the field of otorhinolaryngology. She is married to Lars Wehman and together they have two children, Elise (2016) and Philip (2019).

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