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GENERAL INTRODUCTION

Head and neck cancer (HNC) and its treatment often leads to acute and long-term consequences, affecting the patient's appearance and physical functions such as eating, speaking, and breathing [1]. These consequences can be monitored in an oncologic setting via patient reported outcome measures (PROMs) [2-11] and, if needed, patients can be referred to rehabilitation services including self-management interventions [12-14]. Patient engagement through self-management is widely recognized as crucial to improve health outcomes for people with a chronic condition [15-18]. Compared with the wealth of evidence for self-management interventions in other chronic diseases, this information in cancer patients is limited [19-25]. Self-management interventions in HNC patients are especially scarce [26]. We set out to investigate the usefulness of monitoring symptoms and quality of life in clinical practice, to evaluate the development, usability and feasibility of self-management interventions supporting rehabilitation in HNC patients, and to acquire insight into the factors influencing the usefulness of these interventions.

EPIDEMIOLOGY AND SYMPTOMS OF HEAD AND NECK CANCER

HNC is the sixth most common site of cancer for men and the eighth for women [27] with nearly 600,000 new cases and 300,000 deaths occurring globally each year [28,29]. In Europe, HNC accounts for an estimated 140,000 new cases [30]. In the Netherlands approximately 3000 patients with HNC are diagnosed each year [31,32]. HNC mainly originates in the oral cavity, oropharynx, hypopharynx, and the larynx. Approximately 85% of HNC tumors is of squamous cell histology. Five-year survival rates range from 30% among patients with a tumor originating in the hypopharynx, 50% in the oropharynx, 60% in the oral cavity [33], and to 69–88% in the larynx [34-36].

HNC is etiologically linked by common exposure to tobacco products and excessive alcohol consumption. Human papillomavirus (HPV) infections play an increasing role in the etiology of HNC, particularly of the oropharynx [37]. The incidence of HNC increases with age, with most patients presenting in their sixth through eighth decade of life, although patients with HPV-associated cancer tend to be younger [33,38,39].

Functionally, the head and neck region supports many fundamental physiologic processes including mastication, deglutition, respiration, and articulation. Tumors often significantly impact on these functions through their involvement of vital structures and treatment related sequelae [40].

TREATMENT

A major challenge in treating cancer is obtaining a high cure rate while preserving vital structures and function. This is especially true for cancers in the anatomically complex region of the head and neck, where important structures and functions are affected by both the cancer and its treatment [41-47]. Early stages (I and II) are generally well treated with single modality (surgery or radiation therapy), whereas the more advanced stages (III and IV) require combined modality treatment, including surgery with postoperative (chemo)radiation ((C)RT) or chemoradiation

(CRT) with surgical salvage if needed [48,49]. With the improvement in HNC detection and intensive multimodality treatments, treatment-related acute and late consequences are an emerging problem [42,50]. These consequences affect critical human functions such as breathing, speech, and the ability to swallow, and psychosocial aspects of the patients' life [51,52].

Surgical treatment

Many patients diagnosed with HNC undergo surgery which may affect one or more functions, and compromises the ability to eat, speak, and swallow, depending on the site and stage of the tumor and the type of surgery required [53,54]. Surgical resection of cancers in the oral cavity can negatively impact speech, mastication, and swallowing [55]. Major surgical treatment for oral or oropharyngeal cancer and microvascular soft tissue reconstruction can result in impaired swallowing [56], and a worse overall speech quality [57]. Surgical resection of pharyngeal and laryngeal tumors can have a negative effect on speech and swallowing, and can compromise the airway [48]. A total laryngectomy results in voice loss, and loss of smell, which decreases the sense of taste. The patient will encounter numerous other issues such as potential oral and airway dryness, communication challenges, changes in activities of daily living (showering/bathing routines), and changes to social and outdoor recreational activities (e.g., swimming, boating) [48]. Removal of lymph nodes in the neck (neck dissection) is associated with significant adverse effects related to appearance and function. Speech and swallowing dysfunctions can occur when the vagus and/or hypoglossal nerves are sacrificed [48,58]. Cosmetic alterations in the contour of the neck, limited range of motions of the shoulder, acute and chronic (neck and/or shoulder) pain, shoulder droop, deteriorated lateral flexion of the neck, and atrophy of the trapezius muscle along with shoulder fixation can occur [48,59-61].

Radiation treatment

Radiotherapy (RT) may cause acute and late toxicities that affect various organs and functions. Common acute toxic effects associated with RT are odynophagia (painful swallowing), dysphagia, muscle weakness, increased secretions, loss of taste, and hoarseness caused by laryngeal edema [54,62-64]. Significant late radiation-induced toxicities include fibrosis (scar tissue), and dysphagia [65]. Fibrosis manifests clinically as a reduction in tissue elasticity and flexibility. Depending on the anatomical location, consequences of fibrosis include distortion of tissues, reduction in range of joint movement, and lymphedema [66,67]. The considerable reduction of saliva leads to persistent dryness of mouth, oral discomfort, sore throat, difficulty in speech, taste alteration, and impairment of chewing and swallowing functions which can lead to nutritional depletion and weight loss [68-70]. Intensity modulated radiotherapy (IMRT) enables to spare some of the salivary tissue (usually at least one parotid gland). Swallowing-sparing IMRT (SW-IMRT) enables to reduce the dose to structures related to swallowing, including the pharyngeal constrictor muscles and the larynx [71,72]. SW-IMRT has therefore the potential to reduce acute and late radiation-induced dysphagia [65,68].

Multimodality treatment

For patients with advanced staged disease, the current preference is often a combination of surgery, radiotherapy and/or chemotherapy [73]. CRT is commonly used as the primary treatment for locally advanced HNC or as adjuvant therapy for tumors with poor clinical features [1]. Although intensive treatment regimens, altered fractionation schedules, and CRT can improve tumor control and patients' survival, they also lead to toxicity (e.g., mucositis, tinnitus, neuropathy, or dysphagia) [63,74,75]. Previous studies showed an increased symptom burden if chemotherapy is added to the treatment [76,77].

HEALTH RELATED QUALITY OF LIFE

With the increased use of aggressive combined modality regimens as primary therapy, HNC patients suffer from a variety of short, and long-term consequences secondary to their initial therapy that impact health related quality of life (HRQOL) [1,42,70,78]. HRQOL is a broad multi-dimensional concept which encompasses the physical, psychological, and social dimensions of mental and functional well-being. In cancer patients, HRQOL can be compromised due to the effects of the initial tumor and the side effects of treatment [79,80]. Given the high rates of acute and late posttreatment side effects in HNC patients, a self-oriented HRQOL evaluation can be a useful aid helping to identify and prioritize preferred outcomes or treatment goals, which otherwise would rely exclusively on endpoint results such as survival and tumor relapse [79-83]. In addition to using conventional pen and paper methods, computer-assisted HRQOL data collection by touch screen technology (e.g., OncoQuest) can be used to self-monitor the consequences of HNC and its treatment, and may improve quality and completeness of data collection [10,11]. Some of the HRQOL domains that are specifically related to HNC are summarized briefly below.

Changes in eating and swallowing

Dysphagia can have a significant impact on HNC patients' everyday lives. A wide range of physical changes to swallowing as well as changes to their emotions, perceptions of food, and to their lifestyles are reported [84]. At the most fundamental level the alterations to oral function often interfere with the kind of food and fluids that can be swallowed. Patients with a restricted mouth opening (trismus) have persistent problems with chewing and eating, dry mouth and lack of taste, all of which result in impaired HRQOL [85]. Numerous patients report that eating requires additional time, which reduces the pleasure of eating. As eating is an essential social activity, eating disorders can result in isolation of the HNC patient and HRQOL impairment [86,87]. RT may induce long-term edema, and fibrosis of several swallowing-related structures causing dysphagia and aspiration, with a significant detrimental effect on HRQOL [70,88-90].

Changes in nutritional status

HNC patients have a high risk of malnutrition secondary to the cancer itself and/or the side effects of treatment. According to a systematic review on the effect of nutritional interventions

on nutritional status, HRQOL and mortality in HNC patients of Langius et al [91], 3-52% of the patients are malnourished in the period before the start of (C)RT. During (C)RT this percentage of malnourished patients rises to 44-88% [92,93]. Acute symptoms such as distortion of taste and smell may limit oral intake and lead to weight loss and dehydration during and directly after CRT [94]. Malnutrition and nutritional deficits have a significant negative impact on mortality, morbidity, and HRQOL [95]. HNC patients are in need of nutritional support and tube feeding for a long time period during and after treatment due to insufficient energy intake [96]. The presence of a long-term gastrostomy feeding tube is a very strong predictor of poorer HRQOL [97].

Changes in taste and smell

When taste is altered by HNC treatment, HRQOL is compromised because both nutrition and emotional well-being are affected [98]. Laryngectomy patients are known to suffer from anosmia, as one would expect, given the absence of nasal airflow after the operation. Among HNC patients treated with RT a statistically significant worse taste function was reported post-treatment than among those who did not receive RT [98].

Changes in speech and voice

Changes in speech and voice are most commonly associated with surgical intervention to the oral cavity [57] or larynx [99]. After total laryngectomy HRQOL decreases initially, and some areas recover slowly over the course of the year after surgery, and some remain significantly worse. Areas that do not recover to baseline level are physical functioning, role functioning, social functioning, fatigue, dyspnea, appetite loss, financial difficulties, senses, social contact and speech [74]. Since speech is highly important for social interaction, reduced speech intelligibility in particular may affect patients' HRQOL to a great extent [100,101]. Higher radiation doses to structures in and adjacent to the larynx result in lower HRQOL scores in the speech domains [102].

Changes in shoulder function

Long-term decreased shoulder flexion and abduction is associated with reduced HRQOL in HNC patients. A study of Eickmeyer et al [103] demonstrated that 5-year survivors of HNC reported persistent impairments in shoulder range of motion (ROM), the ability to perform basic activities of daily living (ADLs), and HRQOL in related domains of shoulder disability, recreation, and employment. Reduced ROM and HRQOL were related to the type of neck dissection and not to RT. In other studies in HNC patients significantly worse HRQOL scores have been reported in patients who received neck dissection compared to those without [104,105].

REHABILITATION AND SUPPORTIVE CARE IN HEAD AND NECK CANCER CARE

Prospective studies suggest a need to develop a more comprehensive healthcare system to support HNC patients' needs [106]. Findings indicate that HNC patients need a plan for the future, need help in navigating the healthcare system, and a healthcare system that better overarches the gap between in and outpatient care [107-109]. To enhance cancer rehabilitation (care targeting physiologic and functional impairments caused by cancer and its treatment) [110,111] and supportive cancer care (care provided to minimize symptom burden, and to prevent, control or relieve complications and side-effects) [109,112], self-management interventions could help to promote successful transition care and follow-up care coordination. Self-management interventions may result in physical and psychological benefits, and in some cases reduce patients' dependence on service use [18]. Studies in patients with chronic conditions have shown that comprehensive interactive interventions that augment medical treatments with self-management lead to better health outcomes and improved HRQOL than care that is strictly medically focused [113,114].

Self-management

Self-management is now a common term in health education and is attached to many health promotion and patient education interventions. There is no 'gold standard' definition of self-management. According to the definition of Barlow [114] self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition. In an attempt to give meaning and substance to the term self-management, Lorig and Holman defined self-management support as a dynamic, interactive and daily process, aimed at helping patients to engage in a set of tasks: medical management of the condition (taking medication, or adhering to a special diet) and emotional management (dealing with the emotional consequences of having a chronic condition). There are six core self-management skills: (1) problem solving, (2) decision making, (3) resource utilization, (4) forming of a patient/health care provider partnership, (5) taking action, (6) self-tailoring [115]. Self-management support interventions with specific instructions for self-care may enable patients to maintain their desired level of independence throughout the HNC care journey. However, interventions and strategies used to support self-management targeting HNC patients are scarce, and relatively little information is known about its usefulness in this patient population [12-14,26,116].

eHealth

As Internet use grows, health interventions including self-management components are increasingly being delivered online [117]. eHealth is an emerging field of medical informatics, referring to the organization and delivery of health services and information using the Internet and related technologies [118,119]. Possible advantages of eHealth include user-centered tailoring,

greater ability to monitor patients' use of intervention components by using electronically delivered prompts [120,121], (travel) cost saving benefits for the patient [122], and provision of a platform for interactive information seeking and sharing [123]. Recent research suggests that various interactive web-based interventions for cancer patients and their caregivers can be used to deliver (supplemental) supportive care [120,123-128]. These interventions can be used to remotely monitor and manage cancer symptoms over time [129], to provide coaching, education and information [130], to offer health-related online community support [131], or to provide e-messages and advice for self-management support [132]. Providing eHealth services can lead to people living with chronic illnesses gaining control of their illness, can improve the survivors' health statuses and quality of life, can promote self-care [118,133,], and can reduce their need for supportive care [134]. However, there are few computerized or web-based self-management interventions to improve HRQOL in cancer survivors [22,24,135-137], and even less in HNC care [116,122,138]. Therefore, we developed (eHealth) self-management interventions to support the rehabilitation of HNC patients, guided by a participatory design approach [139-141].

AIM OF THIS THESIS

The main aim of this thesis is to investigate the usefulness in terms of usability, feasibility, uptake, usage, satisfaction of, and adherence to newly developed (eHealth) self-management interventions supporting the rehabilitation among HNC patients. Furthermore, factors are investigated that may influence the usefulness of these self-management interventions, guiding future research on developing (eHealth) self-management interventions aiming to improve HNC patients' HRQOL.

THESIS OUTLINE

The three main (eHealth) self-management interventions in this thesis are (1) 'OncoQuest' (OQ), an application to monitor HRQOL, (2) 'Head Matters' (HM), a multimodal guided self-care exercise intervention to prevent speech, swallowing and shoulder problems in HNC patients during and after radiotherapy alone or in combination with chemotherapy, and (3) 'In Tune without Cords' (ITwC), a self-care intervention to support the rehabilitation of patients after total laryngectomy.

In **chapter 2**, self-monitoring of speech and swallowing complaints in HNC patients is evaluated. The objective is to evaluate the feasibility of a computerized system OQ as a way to monitor speech and swallowing complaints in relation to HRQOL by HNC patients.

In **chapter 3** the feasibility of a multimodal guided self-care exercise intervention HM to prevent speech, swallowing and shoulder problems in HNC patients during and after treatment with (C)RT is investigated. Several barriers and facilitators to self-care exercise adherence are studied using qualitative research techniques. Six- and 12-week adherence, and performance levels are assessed. Factors related to HM exercise performance are studied in **chapter 4**.

In **chapter 5**, the development and usability of a web-based guided self-care intervention ITwC for patients after a total laryngectomy facilitating (early) rehabilitation is studied. The feasibility of ITwC is investigated in a multicenter study and is described in **chapter 6**.

In **chapter 7** the results obtained in the above described studies are discussed and placed into broader perspective. Strengths and limitations of the studies are discussed, and the implications of the findings for clinical practice, and directions for future research are described.

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