Supportive care in head and neck cancer patients

Patient-reported needs and costs

Femke Jansen

SUPPORTIVE CARE IN HEAD AND NECK CANCER PATIENTS
PATIENT-REPORTED NEEDS AND COSTS

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General introduction and outline of this thesis

Due to cancer and its treatment, cancer patients may face several physical and psychological symptoms as well as adjustments in daily living. To address these symptoms and to help patients to adjust to their new situation, supportive care is often needed. Optimal supportive care is tailored to the needs of the individual patient (patient-centered care), is effective (quality care), and is cost-effective (affordable care). This thesis focuses on supportive care in head and neck cancer (HNC) patients, especially on patients' need for supportive care and its cost-effectiveness or cost-utility.

In this first chapter, background information on HNC and its treatment is outlined, followed by current knowledge on HNC patients' need for supportive care and innovative supportive care interventions. In addition, an economic perspective on cancer and supportive care is provided, including information on the economic burden of cancer, and the cost-effectiveness or cost-utility of supportive care interventions. This chapter finishes with presenting the aim and outline of this thesis.

HEAD AND NECK CANCER

Epidemiology

In the Netherlands over 100,000 patients are diagnosed with cancer each year[1]. Head and neck cancer (HNC) is the seventh most common cancer diagnosis in men and the ninth in women[1], and encompasses cancers of the oral cavity, oropharynx, hypopharynx, and larynx (Figure 1). Also more rare cancers in the head and neck region, including cancers of the mucosal side of the lips, nasopharynx, paranasal sinuses, nasal cavity, and salivary glands, are categorized as HNC. Annually, over 139,500 patients are diagnosed with HNC in Europe[2], including almost 3,200 from the Netherlands[1]. The overall five-year survival rate of advanced stage HNC patients is approximately 50%[1]. For the main HNC locations, the five-year survival rates are 31% (hypopharynx), 47% (oropharynx), 61% (oral cavity), and 68% (larynx)[1].

Well-known risk factors for HNC are tobacco smoking and excessive alcohol consumption[3], with almost three quarters of all HNCs being attributable to these environmental risk factors[4]. In addition, infection with the high-risk Human Papillomavirus (HPV) is increasingly being reported as a causative factor for oropharyngeal cancer[5].

Treatment

Treatment of HNC patients is multidisciplinary and based on tumor location, TNM stage (i.e., the size of the primary tumor (T), presence and number of regional lymph node metastasis (N), and presence of distant metastasis (M))[6], overall condition of the patient, patient preferences, and sometimes institutional factors[7,8]. HNC treatment often involves surgery, radiation, chemotherapy (including biological therapy), or a combination of these treatments. Immunotherapy, which uses the immune system to attack the cancer, is also increasingly being reported to be a promising option in combination with other modalities[9,10]. Radiation with or without chemotherapy is treatment of choice for the oropharyngeal and hypopharyngeal cancer patient, while patients with a tumor of the oral cavity are usually treated with surgery with or without (chemo)radiation. In laryngeal cancer, small tumors are often treated by laser surgery or radiation, while more invasive tumors or tumor recurrences are treated by major surgery (i.e., total laryngectomy) or organ-preserving chemoradiation protocols.

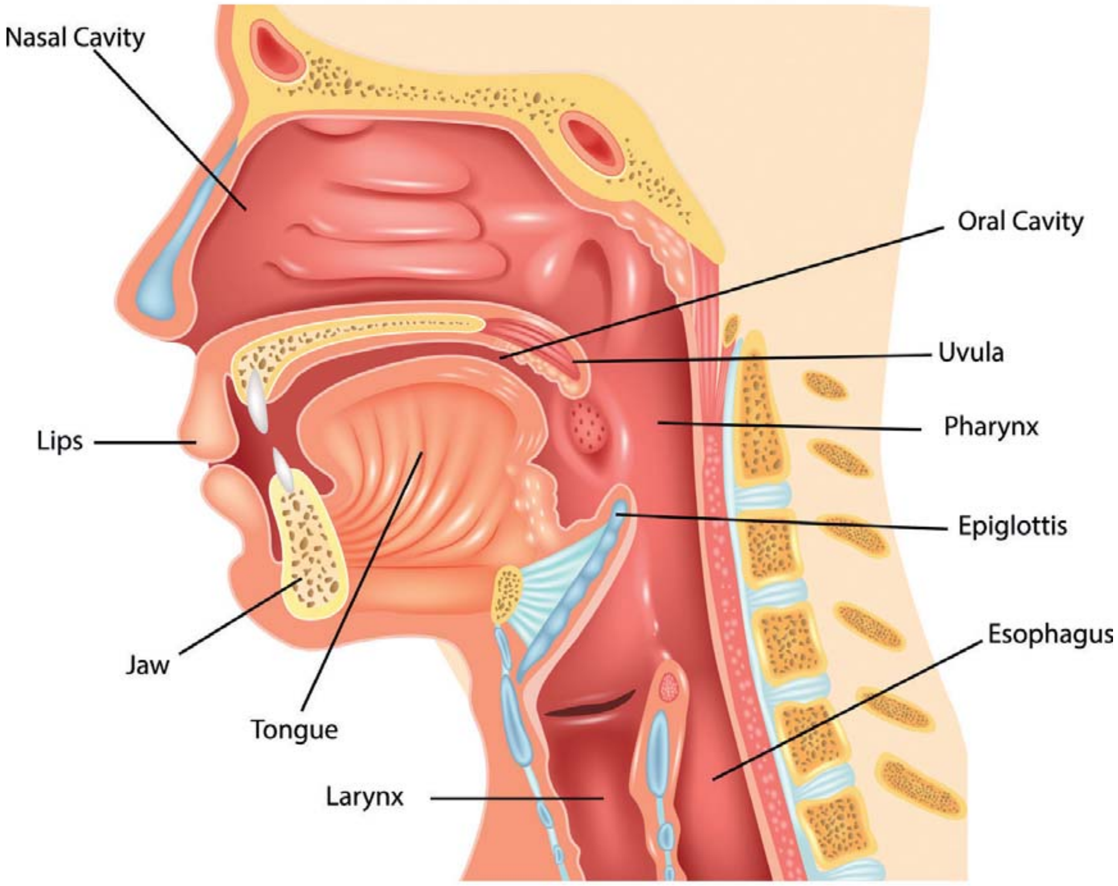

Figure 1. Head and neck region

Total laryngectomy is performed about 150 times a year in the Netherlands[11]. Patients treated with a total laryngectomy are often seen as a distinct subgroup of HNC patients, due to the specific adjustments in normal daily functioning they encounter, including changes regarding breathing, speech, swallowing and smell[12-15].

Experienced symptoms and health-related quality of life

Due to the cancer and its treatment, HNC patients often experience generic and HNC-specific symptoms. Symptoms that are often reported are fatigue, insomnia, dry mouth (xerostomia), difficulty swallowing (dysphagia), change in smell, problems with nutrition, speech problems, hearing difficulties and neck and shoulder problems[16-20]. Also, psychological symptoms are often reported, including psychological distress, depression, anxiety, and fear of cancer recurrence[21-23].

These general and HNC-specific symptoms can have a major influence on patients' health-related quality of life (HRQOL)[16,19]. HRQOL is a multidimensional concept and encompasses physical, role functioning, social, and psychological aspects of well-being and functioning[24]. HNC patients' HRQOL has been found to decline with treatment, but often recovers to baseline HRQOL level (i.e., level at cancer diagnosis) at medium-term follow-up[25,26]. Some specific HRQOL domains, however, may be impaired up to long-term follow-up, including for example, xerostomia and dysphagia[25,26]. Also, workforce participation may be impaired up to long-term follow-up[27].

SUPPORTIVE CARE TARGETING HEAD AND NECK CANCER PATIENTS

To improve symptoms and HRQOL and to adapt to changes in daily living, supportive care is often provided to HNC patients. Supportive care is defined as the prevention and management of adverse effects of cancer and its treatment[28], and encompasses, for instance, information and care related to physical functioning, daily living, psychological functioning, sexuality, and lifestyle[29-31]. In order to provide optimal supportive care, insight into HNC patients' supportive care needs is required.

Supportive care needs

Previous studies found that 60% to 74% of HNC patients experience unmet supportive care needs[32-35]. Often reported (unmet) supportive care needs among HNC patients are information needs, psychological needs (e.g., depression or fear of recurrence), needs related to physical functioning and daily living (e.g., pain or fatigue), and HNC-specific needs (e.g., dry mouth and speech problems)[33-42]. A previous study among newly diagnosed oral cavity cancer patients reported that overall supportive care needs were highest two months after the start of (chemo)radiation, after which it reduced to pre-treatment levels[39]. However, although reduced, supportive care needs may remain up to long-term follow-up[34,35,41]. To target these needs, HNC patients reported to be interested in, for example, internet support groups, information and education, caregiver support, but also help with coping with changes in voice and sleep problems[33,40].

Measuring supportive care needs

Several patient-reported outcome measures exist that question patients on their impairments in daily functioning or experienced symptoms, and impact on their HRQOL, hereby gaining insight into patients’ potential (but not actual) need for supportive care. Widely-used patient-reported outcome measures that measure HRQOL and experienced symptoms among HNC patients are for example the distress thermometer and problem list[43,44] and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires[45-47]. The EORTC Quality of Life Questionnaire-Core 30-questions (QLQ-C30) and the EORTC HNC-specific module (EORTC QLQ-H&N35) provide insight into patient’s global quality of life, health-related functioning (e.g., physical functioning and emotional functioning), and general cancer (e.g., pain and fatigue) and HNC-specific symptoms (e.g., swallowing and speech)[45-47]. Both EORTC questionnaires are often used in scientific research as well as in daily clinical practice[48-53]. It has been found that usage of patient-reported outcome measures in clinical practice may improve communication between patients and healthcare professionals and improve patient outcomes[54]. Usage of the EORTC QLQ-C30 and QLQ-H&N35 in Dutch clinical care has also been found to be appreciated by HNC patients[55]. To facilitate usage of these patient-reported outcome measures in daily clinical practice, however, guidance on interpretation of individual scores is needed. In other words cutoff scores are needed to interpret when a score represents a problem for an individual patient that requires clinical attention or additional supportive care[50,56].

Also, recently, several patient-reported outcome measures have been developed which measure the actual (unmet) need for supportive care, including the Cancer Needs Questionnaire (CNQ)[57], the Cancer Survivors’ Unmet Needs Measure (CaSUN)[58], the Survivors Unmet Needs Survey (SUNS)[59], the Patient Concerns Inventory (PCI)[60], and the Supportive Care Needs Survey (SCNS)[31,61,62]. Especially the SCNS is currently often used[30,63]. The SCNS is based on the CNQ, and has been developed in Australia. Three different versions of the SCNS exist: a long-form (SCNS-LF59)[61], a short-form (SCNS-SF34)[31], and a screening tool (SCNS-ST9)[62], of which the SCNS-SF34 is most often used. The SCNS-SF34 measures 34 different supportive care needs related to psychological functioning, health system and information, patient care and support, physical and daily living, and sexuality[31]. Translations of the SCNS-SF34 are available in English[31,64], French[65], German[66], Italian[67], Mexican[68], Chinese[69,70], and Japanese[71]. In addition, several supplementary modules for use in conjunction with the SCNS-SF34, such as a breast cancer module[72,73] or prostate cancer module[74], have been developed. So far, no Dutch translation of the SCNS-SF34 has been validated in (HNC) patients. Also, no HNC-specific module for use in conjunction with the SCNS-SF34 has been developed and validated. Usage of a Dutch translation of the SCNS-SF34 combined with an HNC-specific module will be of high value to provide insight into (unmet) supportive care needs of Dutch HNC patients, especially those groups that are currently still understudied (e.g., patients treated with total laryngectomy).

Innovative supportive care interventions

After identifying HNC patients in need for additional supportive care, it is of utmost importance that effective supportive care is available and provided to the patients. Current healthcare systems increasingly focus on self-management interventions to target patients' supportive care needs[75-78]. Self-management has been defined as "those tasks that individuals undertake to deal with the medical, role, and emotional management of their health condition(s)"[76]. Also eHealth interventions, defined as "information and communications technology, especially the Internet, to improve or enable health and health care"[79], are increasingly being developed[80,81]. A previous study in mixed cancer patients found that patients themselves have a positive attitude towards both self-management and eHealth[29].

Several supportive care interventions, including self-management and eHealth interventions, have been developed specifically for HNC patients[82-89]. An example is a stepped care intervention targeting psychological distress in HNC and lung cancer patients, in which self-management, eHealth and traditional types of supportive care are combined[82]. This stepped care program consists of four steps, namely: two weeks of watchful waiting (step 1), five weeks of guided self-help by a book or by the Internet (step 2), five weeks of face-to-face problem-solving therapy (step 3), and specialized psychological interventions and/or psychotropic medication (step 4). Patients stepped-up to the next step only when symptoms of psychological distress did not resolve. Krebber et al. found that this stepped care program was effective in improving psychological distress compared to care-as-usual[90,91].

ECONOMIC PERSPECTIVE ON CANCER AND SUPPORTIVE CARE IN (HEAD AND NECK) CANCER PATIENTS

Several supportive care interventions have thus been developed targeting supportive care needs of HNC patients[82-89]. Besides improving patients' outcomes, optimal supportive care needs to provide good value for money, as the economic burden of cancer is high.

The economic burden of cancer

Total healthcare expenditures in the Netherlands have increased from 10.9% of the gross domestic product (GDP) in 2001 to 12.2% in 2007 to 14.0% in 2015[92]. In comparison, in 2007, total healthcare expenditure as percentage of the GDP was 8.4% in the United Kingdom, 10.4% in Germany, 11.0% in France, and 15.7% in the United States[93]. The total healthcare costs of cancer are estimated to be accountable for on average 4% of the total healthcare expenditures[94]. In the Netherlands, total healthcare costs of cancer are accountable for 5% of the total healthcare expenditures[95]. In comparison, cardiovascular diseases are accountable for 8% and endocrine disorders (e.g., diabetes) for 2% of the total healthcare expenditures[95]. HNC also involves high healthcare expenditures[96,97].

Besides its influence on healthcare expenditures, cancer and its treatment also impact on other types of costs, for example productivity losses or informal care costs[94,98]. Although clear insight into employment rates of HNC patients at time of diagnosis are missing, it is estimated that about 30% to 47% of HNC patients are employed at time of diagnosis[27,90]. A previous study among Dutch HNC patients employed at time of diagnosis found that median sick leave after cancer diagnosis was 6 months[99]. More than half (53%) of these employed patients returned to the same work after treatment, 30% returned to changed work, and 17% did not return to work at all. In a study among HNC patients from Ireland, it was found that 77% of patients employed at time of HNC diagnosis took time off work after diagnosis, of which 32% had not start working again at time of the survey (which was on average 6 years post-diagnosis)[27,100]. Productivity losses in HNC patients can thus be high[100]. Also, the potential costs due to the burden placed on informal caregivers of HNC patients is estimated to be high. In a previous study by Hanly et al.[101] it was found that long-term carers (> 1 year) of HNC patients spent on average 17.8 hours per week caring, of which most hours concerned help with household tasks. However, 31.3% also reported to provide help with other activities of daily living, including for example personal care, and 17.4% reported to provide cancer-specific care. In total, it has been estimated that 60% of the total economic burden of cancer is due to non-healthcare costs, such as productivity losses (due to morbidity and mortality) and informal care costs[94].

Cost-effectiveness and cost-utility of supportive care interventions

As the economic burden of cancer is thus high and the total healthcare expenditures are increasing, choices have to be made regarding resource allocation. Supportive care interventions are expected to have the potential to provide good value for money, and some supportive care interventions are hypothesized to even help reduce the total costs of cancer[102-104]. Carlson et al. hypothesized that psychosocial oncology care may, besides improving patient outcomes, reduce total costs, due to long-term cost savings as a consequence of less utilization of other types of care[102,103]. Also self-management interventions targeting patients with long-term conditions have been reported to have the potential to reduce total costs without harming patient outcomes[104].

To investigate whether specific supportive care interventions provide good value for money, economic evaluations (e.g., cost-effectiveness and cost-utility analyses) are performed. In cost-effectiveness and cost-utility analyses the difference in total costs between different interventions, or a new intervention and care-as-usual, are weighted against the difference in effects[105,106]. When health effects, such as life years gained or improvement in psychological distress, are compared the analyses are called cost-effectiveness analyses. When a utility measure is used, such as quality-adjusted life years (QALYs), it is called a cost-utility analysis. So far, however, only few studies have investigated the cost-effectiveness or cost-utility of supportive care interventions targeting cancer patients[107,108]. More studies focusing on the cost-effectiveness or cost-utility of supportive care interventions targeting HNC patients are, therefore, warranted.

AIM OF THIS THESIS

This thesis focuses on supportive care targeting HNC patients. The first part of this thesis aims to obtain knowledge on supportive care needs of HNC patients, using psychometrically assessed patient-reported outcome measures. The second part aims to provide an economic perspective on supportive care interventions, including insight into the potential association between patient activation for self-management and costs, and insight into the cost-effectiveness and cost-utility of psychosocial supportive care interventions.

Outline of this thesis

The first part of this thesis (chapter 2, 3 and 4) focuses on measuring the need for supportive care using patient-reported outcome measures. In *chapter 2*, cutoff scores are identified on the EORTC QLQ-C30 and QLQ-H&N35 questionnaires, which can be used in clinical practice to identify HNC patients with potential unmet supportive care needs. In *chapter 3* the psychometric characteristics of the Dutch translation of the SCNS-SF34 in HNC patients are investigated. In addition, an HNC-specific module (SCNS-HNC) for use in conjunction with the SCNS-SF34 is developed and psychometrically evaluated. In *chapter 4*, the SCNS-SF34 and SCNS-HNC are used to measure (unmet) needs for supportive care in a specific group of HNC patients, namely patients treated with total laryngectomy.

The second part of this thesis (chapter 5, 6 and 7) provides an economic perspective on supportive care interventions. *Chapter 5* provides insights into healthcare utilization and total costs from a societal perspective among patients treated with total laryngectomy, and its association with patient activation for self-management. *Chapter 6* reviews the literature on the cost-effectiveness and cost-utility of psychosocial supportive care in cancer patients in general, and in *chapter 7* the cost-utility of a stepped care program targeting anxiety and depression among HNC and lung cancer patients is evaluated by means of a randomized controlled trial. Finally, in *chapter 8* results of all studies are discussed. In addition, strengths and limitations, implications for clinical practice and recommendations for further research are provided.

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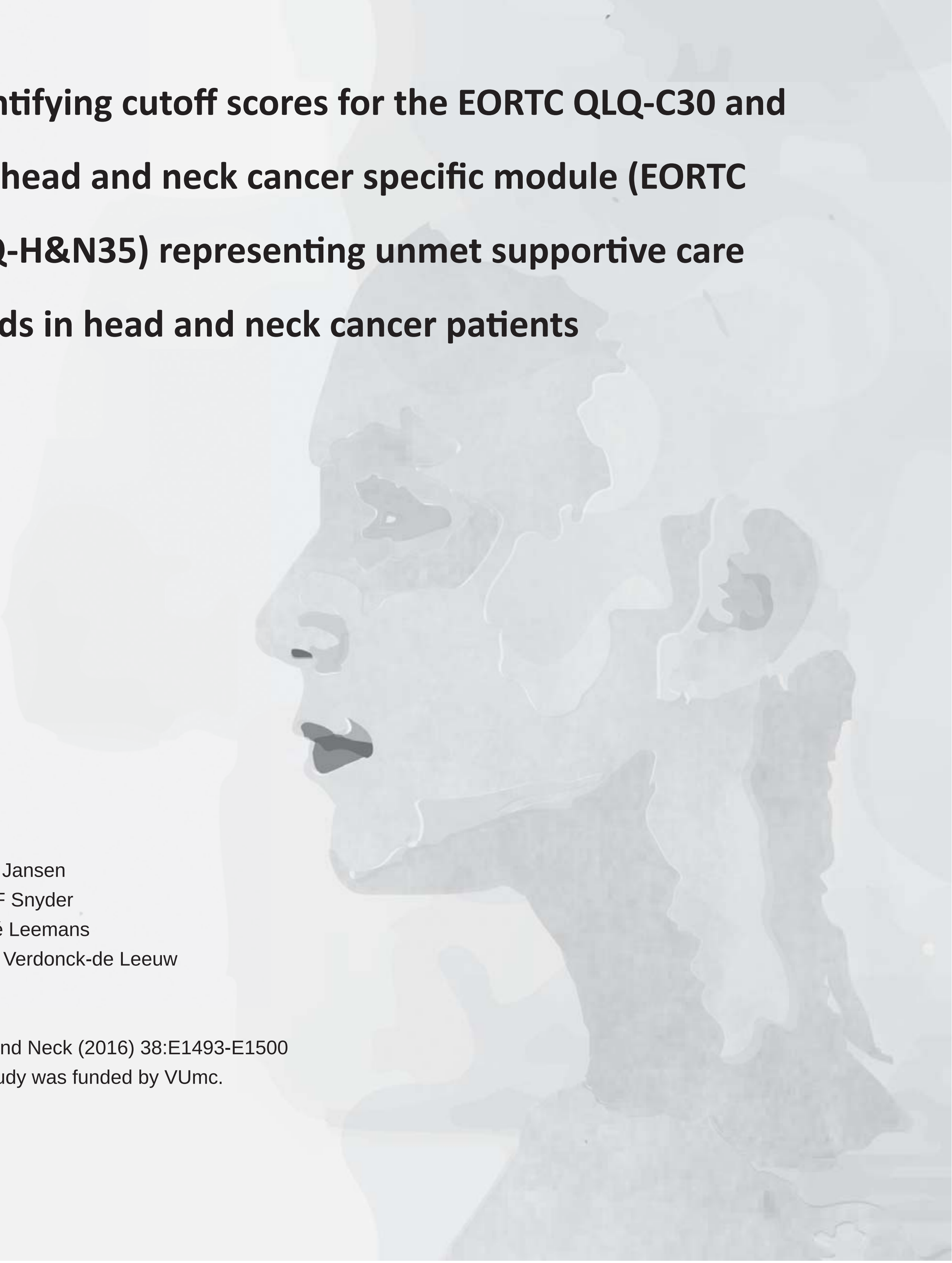
2

Identifying cutoff scores for the EORTC QLQ-C30 and the head and neck cancer specific module (EORTC QLQ-H&N35) representing unmet supportive care needs in head and neck cancer patients



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ABSTRACT

Background. For use of the European Organization for Research and Treatment of Cancer generic health-related quality of life module (EORTC QLQ-C30) and head and neck cancer (HNC)-specific module (QLQ-H&N35) in clinical practice, guidance on interpretation of individual patients' scores is needed.

Purpose. This study investigates cutoff scores for the EORTC QLQ-C30 and QLQ-H&N35 to identify HNC patients who may require clinical attention.

Methods. Ninety-six HNC patients completed the EORTC QLQ-C30, QLQ-H&N35 and questions on supportive care needs. For all EORTC domains with the ability to discriminate between patients with and without unmet needs (area under the receiver operating characteristic curve (AUC) ≥ 0.70), the accuracy (e.g., sensitivity and specificity) of potential cutoff scores were calculated.

Results. Cutoff scores (sensitivity ≥ 0.80 and specificity ≥ 0.60) of 90 (functioning domains) and 5 - 10 (symptom domains) were found on seven of 28 continuous EORTC QLQ-C30 and QLQ-H&N35 domains. Borderline cutoff scores (sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50) were found on five other domains.

Conclusion. This study provided cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 based on patients' perceptions of their needs for supportive care. Future research is needed on the replicability of these cutoff scores.

INTRODUCTION

Head and neck cancer (HNC) patients are often confronted with general cancer or HNC-specific problems caused by the tumor or its treatment, such as fatigue[1], anxiety[2], depression[3], swallowing problems[4], restrictions in speech[5] and nutrition[6]. These problems can significantly impair patients' health-related quality of life (HRQOL)[1,6,7].

Several patient-reported outcome measures (PROMs) have been developed for research purposes to gain insight into patients' functioning and problems influencing their HRQOL. The European Organization for Research and Treatment of Cancer (EORTC) generic (EORTC QLQ-C30)[8,9] and HNC-specific (EORTC QLQ-H&N35)[10] module are frequently used PROMs measuring HRQOL in research targeting HNC patients. Nowadays, PROMs – including the EORTC measures – are also being used in clinical practice for individual patient management (i.e., screen for problems and monitor progress)[11-16]. Usage of PROMs in clinical practice may improve patient-clinician communication and may improve patient outcomes[17].

For use of the EORTC measures in clinical practice, guidance on interpretation of individual patients' scores is needed. In other words, information on scores representing a problem for an individual patient that requires attention is needed[18]. One approach is to compare patients' scores with normative data from other patient populations or the general population. While normative data for the EORTC QLQ-C30 and QLQ-H&N35 in the general Dutch population have been reported[19,20], these normative data do not necessarily represent the score that discriminates between individual cancer patients with and without a perceived unmet need for supportive care. Therefore, Snyder et al.[21-23] identified cutoff scores on the EORTC QLQ-C30 that can discriminate between patients with and without perceived unmet needs as measured using the Supportive Care Needs Survey Short-Form 34 (SCNS-SF34)[24].

However, the previous studies of Snyder et al.[21-23] did not include HNC patients and did not include disease-specific modules, such as the EORTC QLQ-H&N35. The aim of the present study was to investigate whether the earlier defined cutoff scores on the EORTC QLQ-C30 from other cancer populations are replicable in HNC patients and to identify cutoff scores on the EORTC QLQ-H&N35 that discriminate between HNC patients with and without unmet needs as perceived by the patients themselves.

MATERIALS AND METHODS

Design and study measures

Patients in the post-treatment phase using OncoQuest at the Department of Otolaryngology – Head and Neck Surgery of VU University Medical Center (VUmc) in Amsterdam, the Netherlands from April to September 2013 were asked to participate in this cross-sectional study. OncoQuest is a touch-screen computer-assisted system aiming to monitor HRQOL in clinical outpatient practice[12,13]. Patients participating in OncoQuest are asked to complete several PROMs (including the EORTC QLQ-C30 and QLQ-H&N35) at their first visit to the outpatient clinic and at follow-up visits after treatment. Patients were included in this study when they were treated for cancer of the oral cavity, pharynx, larynx, nasal cavity or major salivary glands with curative intent, were in the post-treatment phase, and were older than 18 years. Patients were excluded when they had cognitive impairments or did not understand the Dutch language. According to the Dutch Medical Research Involving Human Subjects Act, ethical approval was not necessary, because patients were not subjected to procedures or required to follow rules of behavior.

Patients participating in OncoQuest were asked to participate in this study after they completed OncoQuest[12,13]. Patients willing to participate were asked to complete a questionnaire at home and return it in a pre-addressed and pre-stamped envelope. The questionnaire included items on HNC patients' need for supportive care.

The SCNS-SF34 was used to measure supportive care needs from the patient's perspective in the last month on 34 items representing physical & daily living, psychological, sexuality, patient care & support and health system & information needs[24,25]. Evidence supporting the validity of the SCNS-SF34 has been reported among English[25,26], French[27], German[28], Chinese[29,30] and Japanese[31] cancer populations. For usage in Dutch studies (including this study), the SCNS-SF34 has been translated into Dutch according to the EORTC translation guideline[32].

In addition to the SCNS-SF34, we used the SCNS-HNC, a PROM on the need for supportive care concerning eleven HNC-specific issues (e.g., problems with chewing and/or swallowing or problems with speech), developed by a multidisciplinary team consisting of a psychologist, speech pathologist, linguist, physician and health scientist. The SCNS-HNC has not yet been validated, whereas the SCNS-SF34 has been validated as previously reported, however, not among Dutch HNC patients. Only separate SCNS items were used and no combination of items (i.e., SCNS domains) to define cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35. The usage of SCNS items instead of domains, corresponds to previous studies by Snyder et al. in which SCNS items were shown to have better discriminative ability than SCNS domains[21-23].

On both the SCNS-SF34 and the SCNS-HNC, patients were asked to report their need for supportive care on a 5-point, two-level response scale[24]. The first level consists of two broad categories of need, i.e., ‘no need’ and ‘some need’. The ‘no need’ scale is further subdivided into ‘1 = not applicable’ for issues that were no problem to the patient and ‘2 = satisfied’ for issues on which a patient needed support but the support was satisfactory. The ‘some need’ level has three categories indicating the level of need for additional care: 3 = low, 4 = moderate and 5 = high. Thus scores ≤ 2 indicate no unmet need and scores > 2 indicate some level of unmet need.

In addition, all patients included in this study completed the EORTC QLQ-C30 and QLQ-H&N35[8-10] using OncoQuest[12,13]. The 30-item EORTC QLQ-C30 (version 3.0) includes 15 different domains, namely a global HRQOL domain (2 items), five functioning domains: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items) and social functioning (2 items), three symptom domains: nausea/vomiting (2 items), fatigue (3 items) and pain (2 items) and six single items relating to dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties[8,9]. The EORTC QLQ-H&N35 module covers specific issues on HNC and comprises 18 different domains, namely seven symptom domains: oral pain (4 items), swallowing (5 items), senses (2 items), speech (3 items), social eating (4 items), social contact (5 items) and sexuality (2 items) and 11 single items covering problems with teeth, dry mouth, sticky saliva, cough, opening the mouth wide, feeling ill, weight loss or weight gain, use of nutritional supplements, feeding tubes, and painkillers[10]. For functioning domains and the global HRQOL domain, a higher score indicates a better level of functioning, while for the symptom domains, a higher score represents higher levels of symptoms or problems[8-10]. The EORTC QLQ-C30 and QLQ-H&N35 have both shown good psychometric properties (i.e., validity, reliability and responsiveness) in cancer patients[9,10].

Finally, socio-demographic characteristics (i.e., age and gender) were patient-reported and clinical characteristics (i.e., tumor site and disease stage) were retrieved from patients’ medical records.

Table 1. Overview of hypothesized relationships between the EORTC QLQ-C30 and QLQ-H&N35 domains and SCNS-SF34 and SCNS-HNC items, and the resulting area under the ROC curve

EORTC QLQ-C30	Item of the SCNS-SF34 or SCNS-HNC and the corresponding area under the ROC curve
Hypothesized AUC < 0.70[1]	
Global quality of life	Item ‘Feeling unwell a lot of the time (AUC = 0.812)’
Physical functioning	Items ‘Pain (AUC=0.652)’, ‘Lack of energy/tiredness (AUC = 0.779)’, ‘Feeling unwell a lot of the time (AUC = 0.614)’, ‘Work around the home (AUC = 0.819)’, ‘Not being able to do the things you used to do (AUC = 0.730)’ or ‘Problems with mobility of head, neck and shoulders (AUC = 0.705)’
Role functioning	Items ‘Work around the home (AUC = 0.788)’ and ‘Not being able to do the things you used to do (AUC = 0.724)’
Emotional functioning	Items ‘Anxiety (AUC = 0.861)’, ‘Feeling down or depressed (AUC = 0.850)’, ‘Feelings of sadness (AUC = 0.853)’, ‘Fears about the cancer spreading (AUC = 0.792)’, ‘Worry that the results of treatment are beyond your control (AUC = 0.804)’, ‘Uncertainty about the future (AUC = 0.750)’, ‘Learning to feel in control of your situation (AUC = 0.846)’, ‘Keeping a positive outlook (AUC = 0.759)’, ‘Feelings about death and dying (AUC = 0.769)’ or ‘Concerns about the worries of those close to you (AUC = 0.728)’
Fatigue	Item ‘Lack of energy/tiredness (AUC = 0.847)’
Pain	Item ‘Pain (AUC = 0.666)’
Hypothesized AUC < 0.70[1]	
Cognitive functioning	Item ‘Not being able to do the things you used to do (AUC = 0.646)’
Social functioning	Item ‘Not being able to do the things you used to do (AUC = 0.875)’
Nausea/vomiting	Items ‘Feeling unwell a lot of the time (AUC = 0.710)’ and ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.617)’
Dyspnea	Items ‘Feeling unwell a lot of the time (AUC = 0.626)’ and ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.633)’
Insomnia	Items ‘Lack of energy/tiredness (AUC = 0.569)’, ‘Feeling unwell a lot of the time (AUC = 0.647)’ and ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.663)’
Loss of appetite	Items ‘Feeling unwell a lot of the time (AUC = 0.629)’, ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.642)’ or ‘Being informed about nutrition (AUC = 0.572)’
Constipation	Items ‘Feeling unwell a lot of the time (AUC = 0.448)’ and ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.524)’
Diarrhea	Items ‘Feeling unwell a lot of the time (AUC = 0.612)’ and ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.563)’
Financial problem	None

Table 1. Continued

EORTC QLQ-H&N35	Item of the SCNS-SF34 or SCNS-HNC
Hypothesized AUC ≥ 0.70[1]	
Oral pain	Item ‘Pain (AUC = 0.739)’
Swallowing	Item ‘Problems with chewing and/or swallowing (AUC = 0.814)’
Speech	Item ‘Problems with speech (AUC = 0.840)’
Sexuality	Items ‘Changes in sexual feelings (AUC = 0.822)’, ‘Changes in sexual relationships (AUC = 0.805)’ or ‘To be given information about sexual relationships (AUC = 0.567)’
Dry mouth	Item ‘Problems with a dry mouth and/or sticky saliva (AUC = 0.754)’
Sticky saliva	Item ‘Problems with a dry mouth and/or sticky saliva (AUC = 0.791)’
Hypothesized AUC < 0.70[1]	
Senses	Item ‘Being informed about nutrition (AUC = 0.625)’
Social eating	Item ‘Problems with chewing and/or swallowing (AUC = 0.741)’
Social contact	Items ‘Problems with speech (AUC=0.639)’ or ‘Problems with hearing (AUC = 0.637)’
Teeth	Item ‘Oral hygiene (AUC = 0.555)’
Opening mouth	Item ‘Problems with chewing and/or swallowing (AUC = 0.649)’
Coughing	Item ‘Being given information about aspects of managing your illness and side-effects at home (AUC = 0.629)’
Feeling ill	Item ‘Feeling unwell a lot of the time (AUC = 0.717)’
Pain killers	None
Nutrition supplement	None
Feeding tube	None
Weight loss	None
Weight gain	None

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer generic health-related quality of life module; EORTC QLQ-H&N35, EORTC head and neck cancer-specific health-related quality of life module; SCNS-SF34, Supportive Care Needs Survey Short-Form 34; SCNS-HNC, Supportive Care Needs Survey Head and Neck Cancer Module; ROC, receiver operating characteristic; AUC, area under the ROC curve.

Underlined items are the items of the SCNS-SF34 or SCNS-HNC with best discriminative ability, which were used in further analyses.

[1] An AUC ≥ 0.70 is considered to indicate acceptable to excellent discriminative ability[33].

Statistical analyses

All analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 20 (IBM Corp., Armonk, NY USA). Socio-demographic and clinical characteristics of the study population were summarized using descriptive statistics (e.g., frequencies and percentages).

Based on previous studies on cutoff scores for the EORTC QLQ-C30 and researchers' expectations, we formulated *a priori* hypotheses on the EORTC QLQ-C30 and QLQ-H&N35 domains' ability to discriminate between patients with and without unmet needs based on items of the SCNS-SF34 and SCNS-HNC (i.e., item score > 2 versus score ≤ 2) (Table 1). For EORTC domains with content similar to items on the SCNS-SF34 or SCNS-HNC (e.g., the EORTC fatigue domain and the SCNS-SF34 item on lack of energy/tiredness) a better discriminative ability was hypothesized than for domains with less similar content (e.g., EORTC teeth domain and the SCNS-HNC item on oral hygiene). The ability of the EORTC domains to discriminate between HNC patients with and without unmet needs was investigated by calculating the area under the receiver operating characteristic curve (AUC). Although there are no firm cutoffs for AUC values that represent good discriminative ability, a score ≥ 0.70 is suggested to indicate acceptable to excellent discriminative ability[33].

In total, 37 hypotheses were formulated on 14 EORTC QLQ-C30 domains: 21 relationships on six EORTC QLQ-C30 domains were expected to demonstrate acceptable discriminative ability (i.e., an AUC ≥ 0.70), whereas 16 relationships on eight other EORTC QLQ-C30 domains were expected to show poor discriminative ability (i.e., an AUC < 0.70). In addition, 16 hypotheses were formulated on 13 EORTC QLQ-H&N35 domains: eight relationships on six EORTC QLQ-H&N35 domains were expected to demonstrate acceptable discriminative ability, whereas eight relationships on seven other EORTC QLQ-H&N35 domains were expected to demonstrate poor discriminative ability. Some SCNS-SF34 and SCNS-HNC items were hypothesized to be related to several different EORTC domains (e.g., the SCNS-SF34 item on 'Work around the home' was hypothesized to be related to physical functioning and role functioning), therefore, only 19 of the 34 SCNS-SF34 items and seven of the 11 SCNS-HNC items were used in this study.

For all EORTC domains with AUCs ≥ 0.70, the sensitivity, specificity, positive and negative predictive value of potential cutoff scores were calculated using descriptive statistics. For this study, potential cutoff scores were defined as candidate cutoff scores when sensitivity

≥ 0.80 and specificity ≥ 0.60 or as borderline candidate cutoff scores when sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50. In addition, Pearson's correlation coefficient of the EORTC domain and the SCNS item was presented.

RESULTS

From April to September 2013, 139 patients who used the OncoQuest system for routine PROM assessment (including the EORTC QLQ-C30 and QLQ-H&N35) as part of standard clinical care during follow-up consultations were asked to participate in this study. In total 107 of 139 (77%) patients completed the questionnaire on their supportive care needs; these responders were comparable to non-responders regarding age, gender and clinical characteristics. For this particular study, 96 of 107 patients were included; 11 patients were excluded since they had a tumor other than HNC (n = 5), had lymph node metastasis of an unknown primary (n = 3), had a benign tumor (n = 1), received palliative treatment (n = 1) or EORTC data was not available (n = 1). Median time between completion of EORTC measures using OncoQuest and the questionnaire on their supportive care needs was 6 days (inter quartile range = 1 - 20). Most of the patients were male (61%) and were younger than 65 years (58%) (Table 2). The majority of patients had a tumor of the pharynx (35%), followed by the oral cavity (26%), larynx (25%), nasal cavity (7%) and major salivary glands (6%). More than half of all patients had stage III or IV disease (52%).

In total, 45 of the 53 (85%) *a priori* formulated hypotheses on the ability to discriminate between patients with and without unmet needs based on the SCNS-SF34 and SCNS-HNC were supported by the findings of this study. Of the six EORTC QLQ-C30 domains hypothesized to have acceptable discriminative ability to identify unmet needs based on the SCNS-SF34 or SCNS-HNC items (i.e., AUC ≥ 0.70), five domains (global quality of life, physical functioning, role functioning, emotional functioning, fatigue) showed acceptable discriminative ability (0.79 ≤ AUC ≤ 0.86). On the sixth domain, pain, a borderline AUC of 0.67 was found. Acceptable discriminative ability was (unexpectedly) also found on the EORTC QLQ-C30 social functioning (AUC = 0.88) and nausea/vomiting domains (AUC = 0.71). On the EORTC QLQ-H&N35, six domains were hypothesized to demonstrate acceptable discriminative ability (oral pain, swallowing, speech, sexuality, dry mouth and sticky saliva), all of which were supported by our findings (0.74 ≤ AUC ≤ 0.84). Acceptable discriminative ability was (unexpectedly) also found on social eating (AUC = 0.74) and feeling ill (AUC = 0.72).

Table 2. Patient characteristics

Characteristics (n = 96)	No. of patients (%)
Age	
- < 65 years	56 (58%)
- ≥ 65 years	40 (42%)
Sex	
- Male	59 (61%)
- Female	37 (39%)
Living arrangements	
- Living alone	18 (19%)
- Living with a partner	57 (59%)
- Living with (a partner and) children	19 (20%)
- Living in an institution	1 (1%)
- Other arrangements (e.g., living with parents)	1 (1%)
Education level	
- Elementary and lower education	43 (45%)
- Secondary education	31 (32%)
- Higher education	22 (23%)
Tumor site	
- Oral cavity	25 (26%)
- Pharynx	34 (35%)
- Larynx	24 (25%)
- Nasal cavity	7 (7%)
- Major salivary glands	6 (6%)
Disease stage (UICC)	
- Stage I	21 (22%)
- Stage II	21 (22%)
- Stage III	18 (19%)
- Stage IV	34 (33%)
- Unknown	2 (2%)
Type of treatment	
- Surgery	24 (25%)
- Radiotherapy	23 (24%)
- Surgery and (chemo)radiation	29 (30%)
- Chemoradiation	20 (21%)
Time since last cancer treatment	
- < 6 months	19 (20%)
- 6 - 18 months	18 (10%)
- 18 - 30 months	11 (11%)
- > 30 months	48 (50%)

Abbreviations: UICC, International Union Against Cancer.

For all 15 EORTC QLQ-C30 and QLQ-H&N35 domains with acceptable discriminative ability and the pain domain with a borderline acceptable discriminative ability, the sensitivity, specificity and positive and negative predictive value of various cutoff scores were calculated. On the EORTC domains on which multiple SCNS-SF34 or SCNS-HNC items showed an AUC ≥ 0.70, the SCNS-SF34 or SCNS-HNC item with the highest AUC was used in further analyses. Since the SCNS-SF34 items found to have the strongest association with the EORTC QLQ-C30 emotional functioning domain in this study (i.e., 'anxiety') was different from the item ('feelings of sadness') in two previous studies[21,22], the sensitivity, specificity and positive and negative predictive value of various cutoff scores on the EORTC QLQ-C30 emotional functioning domain was calculated using both items.

In Table 3, candidate cutoff scores (sensitivity ≥ 0.80 and specificity ≥ 0.60) and borderline candidate cutoff scores (sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50) on all domains with acceptable discriminative ability are presented. On four of the eight EORTC QLQ-C30 domains with acceptable discriminative ability (physical functioning, role functioning, emotional functioning and social functioning), we were able to identify candidate cutoff scores with sensitivity ≥ 0.80 and specificity ≥ 0.67. On the global quality of life and fatigue domain, borderline candidate cutoff scores were found (with sensitivity = 0.70 and specificity = 0.78 and sensitivity = 0.90 and specificity = 0.58, respectively). On the pain and nausea/vomiting domains no (borderline) candidate cutoff scores were identified, since the highest reachable sensitivity scores were respectively 0.62 and 0.50.

Of the eight EORTC QLQ-H&N35 domains with acceptable discriminative ability, for three domains (swallowing, sexuality and sticky saliva) candidate cutoff scores were identified with sensitivity ≥ 0.85 and specificity ≥ 0.62. On the EORTC QLQ-H&N35 domain on oral pain, speech and social eating borderline candidate cutoff scores were identified (all of which had sensitivity ≥ 0.72 and specificity ≥ 0.61 or sensitivity = 0.90 and specificity = 0.56). On the domains dry mouth and feeling ill no candidate cutoff scores were identified.

Table 3: Sensitivity, specificity and positive and negative predictive value of different cutoff scores on various EORTC domains

EORTC domain	SCNS-SF34 or SCNS-HNC item	Correlation	Cut-off[1]	Sensitivity	Specificity	PPV	NPV
EORTC QLQ-C30							
Global quality of life[2]	Feeling unwell a lot of the time[3]	-0.501	60	0.50	0.97	0.63	0.94
			70	0.60	0.87	0.35	0.95
			80	0.70	0.78	0.27	0.96
			90	0.90	0.47	0.16	0.98
Physical functioning[2]	Work around the home[3]	-0.435	80	0.45	0.91	0.56	0.86
			85	0.60	0.87	0.55	0.89
			90	0.85	0.67	0.41	0.94
			100	0.95	0.49	0.33	0.97
Role functioning[2]	Work around the home[3]	-0.443	60	0.30	0.88	0.40	0.83
			80	0.65	0.82	0.48	0.90
			90	0.85	0.71	0.44	0.95
Emotional functioning[2]	Anxiety	-0.618	70	0.53	0.90	0.53	0.90
			80	0.65	0.81	0.42	0.91
			90	0.82	0.71	0.38	0.95
			100	1.00	0.53	0.32	1.00
	Feelings of sadness[3]	-0.610	70	0.59	0.91	0.59	0.91
			80	0.71	0.82	0.46	0.93
			90	0.82	0.71	0.38	0.95
			100	0.94	0.52	0.30	0.98
Fatigue[2]	Lack of energy/tiredness[3]	0.737	**20**	0.90	0.58	0.49	0.93
			30	0.63	0.83	0.63	0.83
			40	0.50	0.97	0.88	0.81
Pain[2,4]	Pain[3]	0.376	10	0.62	0.69	0.24	0.92
			20	0.39	0.82	0.25	0.90
Social functioning	Not being able to do the things you used to do	-0.706	80	0.52	0.99	0.93	0.85
			90	0.80	0.92	0.77	0.93
Nausea/ vomiting	Feeling unwell a lot of the time	0.434	10	0.50	0.91	0.39	0.94
			20	0.30	0.98	0.60	0.92

Table 3: Continued

EORTC domain	SCNS-SF34 or SCNS-HNC item	Correlation	Cut-off[1]	Sensitivity	Specificity	PPV	NPV
EORTC QLQ-H&N35							
Oral pain	Pain	0.302	5	0.85	0.45	0.19	0.95
			10	0.77	0.61	0.24	0.94
			20	0.62	0.80	0.32	0.93
			30	0.46	0.87	0.35	0.91
Swallowing	Problems with chewing and/or swallowing	0.580	**5**	0.88	0.62	0.45	0.94
			10	0.72	0.75	0.50	0.88
			20	0.52	0.86	0.57	0.84
Speech	Problems with speech	0.619	**10**	0.90	0.56	0.33	0.96
			20	0.74	0.77	0.44	0.92
			30	0.74	0.87	0.58	0.93
			40	0.37	0.97	0.78	0.86
Sexuality	Changes in sexual feelings	0.440	**10**	0.88	0.71	0.28	0.98
			20	0.75	0.74	0.27	0.96
			40	0.63	0.89	0.42	0.95
			60	0.38	0.92	0.38	0.92
Dry mouth	Problems with a dry mouth and/or sticky saliva	0.474	10	0.94	0.31	0.43	0.91
			40	0.62	0.81	0.64	0.79
			70	0.18	0.97	0.75	0.68
Sticky saliva	Problems with a dry mouth and/or sticky saliva	0.535	**10**	0.85	0.65	0.57	0.89
			40	0.47	0.89	0.70	0.75
Social eating	Problems with chewing and/or swallowing	0.420	**5**	0.72	0.63	0.41	0.87
			10	0.64	0.82	0.55	0.87
			20	0.36	0.93	0.64	0.81
Feeling ill	Feeling unwell a lot of the time	0.464	10	0.50	0.92	0.42	0.94
			40	0.20	1.00	1.00	0.92

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; SCNS-SF34, Supportive Care Needs Survey Short-Form 34; SCNS-HNC, Supportive Care Needs Survey Head and Neck Cancer Module; QLQ-C30, generic health-related quality of life module; QLQ-H&N35, head and neck cancer-specific health-related quality of life module; PPV, positive predictive value; NPV, Negative predictive value.

[1] Cutoff scores are underlined and in bold when sensitivity ≥ 0.80 and specificity ≥ 0.60 (candidate) and in bold when sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50 (borderline candidate). When applicable, potential cutoff scores surrounding the candidate cutoff scores were also presented.

[2] Cutoff scores on these domains based on the SCNS-SF34 have been reported in previous studies on breast, prostate, colorectal and lung cancer patients[21-23].

[3] Same SCNS-SF34 or SCNS-HNC item as used in previous studies[21-23].

[4] Although discriminative ability was borderline (AUC = 0.67) the sensitivity, specificity and positive and negative predictive values of cutoff scores were reported, since previous studies reported an acceptable discriminative ability (0.74 ≤ AUC ≤ 0.78) on this domain[21-23].

DISCUSSION

This study aimed to investigate whether the earlier defined cutoff scores on the EORTC QLQ-C30 in breast, prostate, colorectal, and lung cancer patients are replicable in HNC patients and to identify cutoff scores on the EORTC QLQ-H&N35. Cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 are helpful in clinical practice for identifying HNC patients who require more attention[18].

Results showed that the cutoff scores on the EORTC QLQ-C30 domains that represent in our opinion the most optimal trade-off between sensitivity and specificity in the present study (i.e., sensitivity ≥ 0.80 and specificity ≥ 0.60 or sensitivity ≥ 0.70 and specificity ≥ 0.60 (borderline) or sensitivity ≥ 0.80 and specificity ≥ 0.50 (borderline)) were partly similar to previously defined cutoff scores[21-23]. We found cutoff scores of 90 on physical functioning, role functioning and emotional functioning and additional borderline cutoff scores on global quality of life (80) and fatigue (20), which were similar to the cutoff scores in previous studies[21-23]. On the pain domain, no cutoff scores were identified with acceptable sensitivity and specificity in our study, while cutoff scores of 10 and 20 were proposed in previous studies[21-23]. Besides the defined cutoff scores on these five domains, we also identified a cutoff score of 90 on the domain on social functioning for use in HNC patients. In previous studies no cutoff scores were identified for this domain, since the discriminative ability on social functioning was borderline unacceptable (i.e., AUC = 0.64 - 0.68)[21-23]. In addition to cutoff scores on the EORTC QLQ-C30, we also identified cutoff of scores of 5 or 10 on the swallowing, sexuality and sticky saliva domain of the EORTC QLQ-H&N35 and borderline cutoff scores ranging from 5 - 30 on the domains on oral pain, speech and social eating. For external validation purposes, future studies are recommended to investigate whether these newly defined cutoff scores on the EORTC QLQ-H&N35 are replicable in other Dutch and non-Dutch HNC patients. Also, future studies are recommended on the replicability of the newly defined cutoff score on the EORTC QLQ-C30 social functioning domain in HNC populations and whether it results in an acceptable trade-off between sensitivity and specificity in other cancer populations as well. Besides, it should be investigated whether use of the defined cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 also identify patients with problems, who do not identify the corresponding unmet needs themselves. These patients may not identify their need for supportive care, perhaps since they are not aware of potential care available for their problem (e.g., regarding fatigue or insomnia), or are focused on other issues; however, they may still benefit from supportive care.

In the present study, the defined cutoff scores on the EORTC QLQ-H&N35 domain of oral pain was higher compared to mean scores in a reference group of the Dutch general population[20]. At least one of the defined cutoff scores on all other EORTC QLQ-C30 and QLQ-H&N35 domains were comparable to normative data[19,20]. When using our defined (higher) cutoff score on the domain of oral pain, patient scores will be less often identified as potentially concerning compared to using the normative data[20]. This may be appropriate, since this study aimed to target patients with unmet needs for supportive care and did not aim to target patients who experience problems but do not have a need for additional supportive care.

On seven of the 28 continuous EORTC QLQ-C30 and QLQ-H&N35 domains (physical functioning, role functioning, emotional functioning, social functioning, swallowing, sexuality and sticky saliva), we were able to identify cutoff scores with sensitivity ≥ 0.80 and specificity ≥ 0.60. In addition, five other domains (global quality of life, fatigue, oral pain, speech and social eating) had at least one cutoff score with sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50, which we regarded as borderline. This was largely in line with expectations, since we had hypothesized acceptable discriminative ability on only 12 domains; for two of these domains (pain and dry mouth) no (candidate) cutoff scores were identified. Future studies should focus on identifying cutoff scores on these two domains, as well as the other domains on which, as hypothesized, no cutoff scores were found.

The appropriateness of a cutoff score involves a trade-off between sensitivity and specificity and depends on the action taken in response to scores highlighted as potentially concerning. When the PROM only signals a need for further evaluation of the potential problem, followed by additional supportive care if required, sensitivity may be favored over specificity. In contrast, specificity may be favored over sensitivity if a deviating score is directly followed by an action (e.g., prescription of medication or other treatment decisions) without further evaluation by a clinician or nurse specialist. Since PROMs measuring HRQOL mostly have a signaling function, it may be acceptable to favor sensitivity over specificity.

Besides making a trade-off between sensitivity and specificity, the appropriateness of cutoff scores can be evaluated based on positive and negative predictive values. In this study, negative predictive values of both candidate and borderline cutoff scores were high (ranging from 0.88 to 1.00), indicating that 88 to 100% of patients were correctly identified as having no problem. The positive predictive value of most cutoff scores was quite low (most positive predictive values were ≤ 0.45; range: 0.24 to 0.77), indicating that for several cutoff scores > 55% of patients were signaled with a deviating score while not perceiving an unmet need. We believe that this low positive predictive value may not be especially concerning, since a deviant score is expected to be followed by non-intensive further evaluation (e.g., asking the patient about the potential concerning problem). However, as previously reported[21], it is important to minimize alert fatigue caused when a high proportion of signaled patients do not need additional care.

A potential limitation of this study is that cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 are defined using the SCNS-SF34 and SCNS-HNC as the anchor. Although the SCNS-SF34 is validated in other non-Dutch studies[25-31], this PROM has not yet been validated among Dutch HNC patients. The SCNS-HNC is newly developed and has not yet been validated. Further research to validate the SCNS-SF34 in Dutch HNC patients and the SCNS-HNC generally is needed to confirm the findings reported here.

Another limitation is the discrepancy in recall period, since patients did not complete the EORTC questionnaires and SCNS-SF34 and SCNS-HNC at the same time (median difference was 6 days), and the EORTC and SCNS questionnaires have different recall periods (1-week compared to 1-month). However, since patients completed the SCNS-SF34 and SCNS-HNC after completion of the EORTC measures, the different recall periods of the questionnaires may partly counteract the discrepancy due to differences in when the questionnaires were completed. In addition, patients were recruited after primary treatment for HNC via OncoQuest[12,13], which may have resulted in selection bias, and the sample size of this study was small. Future studies should therefore be performed to confirm the results of this study regarding cutoff scores on especially the EORTC QLQ-H&N35 in larger HNC populations including patients at time of diagnosis, during treatment, and in the palliative or end-of-life phase of the disease.

In summary, we were able to replicate previously defined cutoff scores on four of the functioning domains (80 - 100) and fatigue domain (20) of the EORTC QLQ-C30 and to identify new cutoff scores on the EORTC QLQ-C30 social functioning domain (90) and several EORTC QLQ-H&N35 domains (5 - 30) in HNC patients. These cutoff scores may assist in interpretation of individual patient's scores in clinical practice. Future research is needed to investigate whether the newly defined cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 can be replicated in other patient cohorts, and the usefulness of the cutoff scores in clinical practice.

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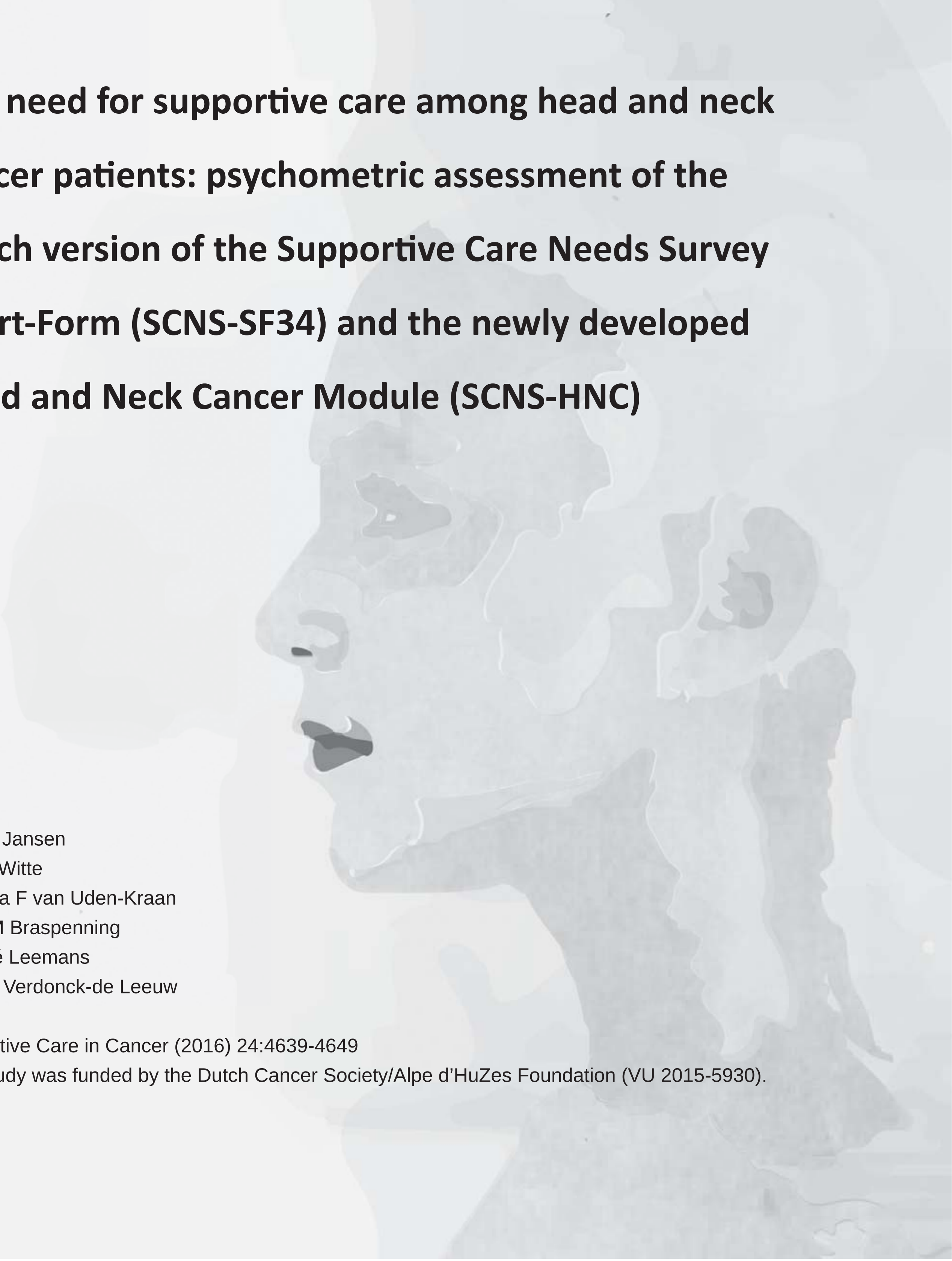
The need for supportive care among head and neck cancer patients: psychometric assessment of the Dutch version of the Supportive Care Needs Survey Short-Form (SCNS-SF34) and the newly developed Head and Neck Cancer Module (SCNS-HNC)



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ABSTRACT

Background. In order to provide adequate supportive care tailored to patients' wishes and needs, insight into their perceived need for supportive care is required. A frequently used patient-reported outcome measure on generic cancer-related supportive care needs is the 34-item Short-Form Supportive Care Needs Survey (SCNS-SF34).

Purpose: To assess the psychometric properties of the Dutch version of SCNS-SF34 and the newly developed module for head and neck cancer (HNC) patients (SCNS-HNC).

Methods: HNC patients were included from two cross-sectional studies. Content validity of the SCNS-HNC was analyzed by examining redundancy and completeness of items. Factor structure was assessed using confirmatory and exploratory factor analyses. Cronbach's alpha, Spearman's correlation, Mann-Whitney U test, Kruskall-Wallis and intraclass correlation coefficients (ICC) were used to assess internal consistency, construct validity and test-retest reliability.

Results: Content validity of the SCNS-HNC was good, although some HNC-topics were missing. For the SCNS-SF34 a 4-factor structure was found: physical & daily living, psychological, sexuality and health system, information & patient support (alpha = 0.79 to 0.95). For the SCNS-HNC a 2-factor structure was found: HNC-specific functioning and lifestyle (alpha = 0.89 and 0.60). Respectively 96% and 89% of the hypothesized correlations between the SCNS-SF34 or SCNS-HNC and other patient-reported outcome measures were found; 57% and 67% also showed the hypothesized magnitude of correlation. The SCNS-SF34 domains discriminated between treatment procedure (physical & daily living: $p = 0.02$ and psychological: $p = 0.01$) and time since treatment (health system, information & patient support: $p = 0.02$). Test-retest reliability of SCNS-SF34 domains and HNC-specific functioning domain were above 0.70 (ICC = 0.74 to 0.83), and ICC = 0.67 for the lifestyle domain. Floor effects ranged 21.1% to 70.9%.

Conclusion: The SCNS-SF34 and SCNS-HNC are valid and reliable instruments to evaluate the need for supportive care among (Dutch) HNC patients.

INTRODUCTION

Head and neck cancer (HNC) patients often experience generic cancer-related problems, such as pain, fatigue[1], anxiety[2] and depression[3] as well as HNC-specific problems such as dysphagia[4], or problems with speech[5], nutrition[6] and hearing[7] influencing their quality of life[1,6]. Supportive care, defined as the prevention and management of adverse effects of cancer and its treatment[8], can help to improve these problems.

In order to provide adequate supportive care tailored to patients' wishes and needs, insight into their perceived need for supportive care is required. A frequently used patient-reported outcome measure (PROM) on generic cancer-related supportive care needs is the 34-item Short-Form Supportive Care Needs Survey (SCNS-SF34). The SCNS-SF34 measures the need and level of need for supportive care, including physical and daily living, psychological, sexuality, patient care and support and health system and information needs[9,10].

Currently, the SCNS-SF34 has been translated and validated in English[9,11], French[12], German[13], Italian[14], Mexican[15], Chinese[16,17] and Japanese[18] populations, including breast[12,16,18], colorectal[17], prostate[11] and mixed[9,13-15] cancer patients. A Dutch translation of the SCNS-SF34 has not been validated so far. In addition, the SCNS-SF34 has not yet been validated among HNC patients. Cross-validation of PROMs when translated into a different language or used in a different cancer population is of importance, since lingual, cultural and population differences may affect psychometric characteristics.

Supplementary modules for use in conjunction with the SCNS-SF34 have been developed to measure supportive care needs specific for breast[19,20], melanoma[21] and prostate[22] cancer patients. Henry et al.[23] added four items (alcohol cessation, smoking cessation, feeling better about my appearance and finding meaning and purpose in life) to the SCNS-SF34 which were expected to be relevant to HNC patients, however these items were not validated. Therefore, we developed a HNC-specific module (SCNS-HNC) by multidisciplinary team discussions consisting of a physician, speech pathologist, linguist, psychologist, and health scientist, which we previously used to identify cutoff scores on the EORTC HNC-specific quality of life questionnaire (EORTC QLQ-H&N35)[24].

The aim of this study was to assess the psychometric properties (i.e., internal consistency, validity and test-retest reliability) of the Dutch version of the SCNS-SF34 and SCNS-HNC in HNC patients.

PATIENTS AND METHODS

Design and study participants

Patients were included from two cross-sectional studies conducted at the department of Otolaryngology – Head and Neck Surgery of the VU University Medical Center (VUmc), Amsterdam, the Netherlands. The first study included HNC patients who visited the department from April to September 2013 and who participated in an evaluation study of a touch screen computer-assisted PROM system, which is part of standard clinical practice (called OncoQuest)[25]. After completing OncoQuest, all eligible patients were asked to fill in a questionnaire at home using paper and pencil (including the SCNS-SF34 and SCNS-HNC). In addition, all patients who discussed the results of OncoQuest with an oncology nurse (also part of standard clinical practice) were asked whether they agreed to have a researcher present during this nursing consultation. The researcher completed a study-specific report form regarding this consultation.

The second study included HNC patients who visited the department in February or March 2015. All eligible patients were asked to fill in a questionnaire at home using paper and pencil (including the SCNS-SF34 and SCNS-HNC). In addition, all patients who completed the first questionnaire in this second study were asked to complete the SCNS-SF34 and SCNS-HNC a second time 1 - 2 weeks later (for test-retest analyses).

Completed questionnaires were sent back to VUmc. In case of missing data, clarifications were sought over the telephone. Patients were included in this particular study when they (i) were treated with curative intent for cancer of the oral cavity, pharynx, larynx, nasal cavity or major salivary glands; (ii) were between 3 months and 5 years after last treatment; and (iii) were ≥ 18 years. Patients were excluded when they had cognitive impairments or did not understand the Dutch language. According to the Dutch Medical Research Involving Human Subjects Act, ethical approval was not necessary, because patients were not subjected to procedures or required to follow rules of behavior.

Measures

SCNS-SF34

The SCNS-SF34 measures the need and level of need for supportive care in the last month on 34 items on a 5-point, two-level response scale[9,10]. The first response scale consists of two broad categories of need, i.e., ‘no need’ and ‘a need’. The ‘no need’ scale is further subdivided into ‘not applicable’ for issues that were no problem to the patient and ‘satisfied’ for issues on which a patient needed support but the support was satisfactory. The ‘need’ category has three subcategories indicating the level of need for additional care: ‘low need’, ‘moderate need’ and ‘high need’. According to the original study of Boyes et al. among mixed cancer patients[9] supportive care needs can be subdivided into five underlying domains: physical & daily living, psychological, sexuality, patient care & support and health system & information. An alternative factor structure was suggested by Au et al. among breast cancer patients[16], who found four underlying domains using 33 items: physical & daily living, psychological, sexuality and health system, information & patient support. A total score per domain can be calculated and converted to a standardized 0 - 100 score, with a higher score indicating a higher level of need[10].

The SCNS-SF34 was translated into Dutch according to the European Organization for Research and Treatment of Cancer (EORTC) guideline[26]. A translator and a nurse specialist (both Dutch native speakers) translated the SCNS-SF34 into Dutch. The translations were compared by two of the authors (FJ and IV) and slight discrepancies were solved by discussion in order to provide one Dutch version. By means of back-translation the Dutch version was converted into English by two independently working native English-speaking persons and compared by the two authors to the original English version.

SCNS-HNC

The SCNS-HNC measures the need for supportive care concerning eleven HNC-specific issues using the same response scale as the SCNS-SF34. In addition, a single free-text item was added where patients could report any additional needs, which were not yet taken into account in the SCNS-SF34 or SCNS-HNC. This free-text item was added to analyze whether supportive care needs were missing from the patient perspective. Reading age of the SCNS-HNC calculated using the formula of Douma (formula of Flesch–Kincaid Grade adjusted for Dutch situation) was 13 - 15 years[27].

Other PROMs and clinical measures

All HNC patients also completed the EORTC generic (EORTC QLQ-C30)[28] and HNC-specific (EORTC QLQ-H&N35)[29] quality of life measure, the Hospital Anxiety and Depression Scale (HADS)[30], the Speech Handicap Index (SHI)[31] and a PROM evaluating swallowing problems (SWAL-QOL)[32]. In the first study these PROMs were completed using OncoQuest[25], while in the second study they were assessed concurrently with the SCNS-SF34 and SCNS-HNC. Besides, in the first study a study-specific report form was completed by an observing researcher who was present during the nursing consultation following OncoQuest. This report form included information on topics, information and supportive care options discussed during the nursing consultation.

Finally, socio-demographic characteristics were patient-reported and clinical characteristics were retrieved from patients' medical records.

Data analyses

Content validity of the SCNS-HNC was analyzed by examining redundancy and completeness of items. Items were considered redundant if < 10% of the patients reported a need (or in case of SCNS-HNC item 6 < 10% of patients treated with total laryngectomy). Completeness of the SCNS-HNC was examined by analyzing supportive care needs reported on the free-text item of the SCNS-HNC and analyzing needs discussed during the nursing consultation as assessed in the study-specific report form. If ≥ 5% of patients reported or discussed an additional supportive care need, adding this specific need to the SCNS-HNC should be considered.

Confirmatory factor analysis was used to analyze whether the original 5-factor[9] or alternative 4-factor structure[16] of the SCNS-SF34 could be replicated, as proposed by Terwee et al.[33]. Criteria for an acceptable fit were: 1) Root Mean Square Error of Approximation (RMSEA) < 0.06 and Comparative Fit Index (CFI) and Tucker-Lewis Index-Non-Normed Fit Index ≥ 0.9. Principal component analysis with varimax rotation of factors with eigenvalues > 1.0 was used to analyze the factor structure of the SCNS-HNC. Appropriateness of principal component analysis was examined using Bartlett's test of sphericity ($p < 0.05$) and the Kaiser, Meyer Olkin index of sampling adequacy (KMO ≥ 0.60). Internal consistency was assessed using Cronbach's alpha coefficient; a value between 0.70 and 0.95 is considered good[33].

To analyze construct validity, a priori hypotheses were formulated regarding the correlation between the SCNS-SF34 (31 hypotheses) or SCNS-HNC (9 hypotheses) and other PROMs (EORTC QLQ-C30, EORTC QLQ-H&N35, HADS, SHI and SWAL-QOL) (presented in Table 1), and expected differences between groups of HNC patients (13 hypotheses). Hypotheses were based on previous studies[9,11-13,16,18,34-36] and researchers' expectations. Regarding expected differences, it was expected that: 1) younger patients (18 - 60 years) reported a higher level of need than older patients (> 60 years) on all domains except for physical & daily living[12,13,16,18,35]; 2) females reported a higher level of need on the physical &

daily living and psychological domain[13], while males reported a higher level of need on the sexuality domain[13,35]; 3) patients with multimodality treatment reported a higher level of need on all domains but sexuality than patients who received single treatment; and 4) patients longer after treatment reported a lower need on the patient care & support and health system & information domains[36]. Correlations were analyzed using Spearman's correlation coefficient, since needs were non-normal distributed. Magnitude of the correlations were defined as moderate ($r = 0.30$ to 0.50) or strong ($r > 0.50$)[37]. Differences between groups of HNC patients were analyzed using Mann-Whitney U test or Kruskall-Wallis. A p-value < 0.05 was considered statistically significant. The SCNS-SF34 and/or SCNS-HNC were found to be valid if at least 75% of the hypotheses were in correspondence with the a priori defined hypotheses[33].

Test-retest reliability was analyzed using intraclass correlation coefficients with absolute agreement (ICC) in patients who completed the second questionnaire within one month after the first. An ICC value ≥ 0.70 has been considered good[33]. Finally, floor or ceiling effects (> 15% of patients with the lowest or highest possible score) was investigated using frequency tables.

All analyses were performed using the IBM Statistical package for the Social Science (SPSS) version 22 (IBM Corp., Armonk, NY USA) and Mplus version 6.11 (Muthen & Muthen, Los Angeles, CA USA)[38].

Sample size calculation

For this study, at least 170 patients were needed for factor analyses (5 times the number of SCNS-SF34 items), 50 patients per subgroup for construct validity analyses, and 50 patients for test-retest reliability[33].

Table 1. A priori defined hypotheses regarding the (magnitude of the) correlation of domains of the SCNS-SF34 and items of the SCNS-HNC with other patient-reported outcome measures and the found correlation

	SCNS-SF34					SCNS-HNC				
	P&DL	PSY	SEX	PC&S HSI & PS^{1}	HS&I^{1}	Chewing or swallowing	Dry mouth and/ or sticky mucus	Problems with weight	To be informed on nutrition	Difficulty speaking
HADS										
Anxiety	0.48^{+}	0.65^{++}	0.34^{+}	0.51^{+}	$^{+}$					
Depression	0.61^{+}	0.64^{++}	0.33^{+}	0.57^{+}	$^{+}$					
EORTC QLQ-C30										
Physical functioning	-0.50^{--}									
Role functioning	-0.63^{-}									
Emotional functioning	-0.56^{-}	-0.64^{--}		-0.47^{-}	$^{-}$					
Cognitive functioning	-0.43^{-}	-0.47^{-}								
Social functioning	-0.54^{-}									
Global quality of life	-0.55^{--}	-0.51^{-}								
Fatigue	0.64^{++}	0.55^{+}		0.52^{+}						
Pain	0.47^{++}			0.42^{+}						
Dyspnea				0.19^{+}						
Sleep/insomnia	0.42^{+}									
Appetite loss		0.44^{+}		0.38^{+}						

EORTC QLQ-H&N35						
Swallowing		0.62^{++}				
Dry mouth			0.55^{+}			
Sticky saliva			0.57^{+}			
Weight loss				0.40^{+}		
Weight gain				0.08^{+}		
Speech						0.61^{++}
Sexuality	0.47^{+}					
SWAL-QOL						
Symptom		0.62^{++}				
Food selection					0.48^{+}	
SHI total score						0.64^{++}

Abbreviations: SCNS-SF34, Supportive Care Needs Survey Short-Form 34; SCNS-HNC, Supportive Care Needs Survey Head and Neck Cancer Module; P&DL, physical & daily living; PSY, psychological; SEX, sexuality; PC&S, patient care & support; HS&I, health system & information; HSI&PS, health system, information & patient support; HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer generic health-related quality of life module; EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer Head and Neck Cancer Module; SWALQOL, swallowing quality of life; SHI, Speech Handicap Index.

$^{+}$: a positive moderate (r = 0.30 - 0.50) association was expected;

$^{++}$: a positive strong (r > 0.50) association was expected;

$^{-}$: a negative moderate (r = -0.30 - -0.50) association was expected;

$^{--}$: a negative strong (r < -0.50) association was expected.

If the a priori defined hypothesis was supported, the coefficient was underlined.

[1] Since a 4-factor structure was found, we only present correlations of the combined HIS & PS domain.

RESULTS

Study sample

In total, 201 patients were included for content analyses, factor analyses and construct validity analyses; 110 patients for test-retest analyses; and 69 patients for content analysis using the study-specific report forms. Socio-demographic and clinical characteristics are presented in Table 2.

Table 2. Characteristics of the study samples

Characteristics	**Factor analyses and construct validity** n = 201	**Test-retest reliability** n = 110	**Content validity (study specific report form)** n = 69
	%	**%**	%
Age			
- 18 – 60 years	31.3%	25.5%	46.4%
- > 60 years	68.7%	74.5%	53.6%
Sex			
- Male	66.7%	72.7%	63.8%
- Female	33.3%	27.3%	36.2%
Living arrangements			
- Living alone	24.4%	30.0%	14.3%[1]
- Living with partner	58.7%	59.1%	59.2%
- Living with partner and children	15.4%	10.0%	22.4%
- Other (e.g., with children)	1.5%	0.9%	4.1%
Education			
- Elementary education	6.5%	3.6%	5.8%[1]
- Lower education	37.8%	40.0%	24.6%
- Secondary education	26.9%	25.5%	23.2%
- Higher education	28.9%	30.9%	17.4%
Employment status			
- Employed (paid/unpaid)	35.8%	30.9%	42.9%[1]
- Unemployed	12.5%	11.8%	16.3%
- Housewife/houseman	3.5%	3.6%	4.1%
- Retired	48.3%	53.6%	36.7%

Table 2. Continued

Characteristics	**Factor analyses and construct validity** n = 201	**Test-retest reliability** n = 110	**Content validity (study specific report form)** n = 69
	%	**%**	%
Tumor site			
- Oral cavity	31.3%	33.6%	30.4%
- Pharynx	36.8%	35.5%	36.2%
- Larynx	19.9%	20.9%	17.4%
- Nasal cavity	6.0%	4.5%	8.7%
- Major salivary glands	6.0%	5.5%	7.2%
Disease stage (UICC)			
- Stage I	27.9%	30.9%	23.2%
- Stage II	13.4%	10.0%	21.7%
- Stage III	16.4%	16.4%	18.8%
- Stage IV	36.8%	34.5%	34.8%
- Unknown	5.5%	8.2%	1.4%
Type of treatment			
- Surgery	25.4%	25.5%	27.5%
- Radiotherapy	20.4%	21.8%	23.2%
- Surgery and chemoradiation	8.5%	7.3%	5.8%
- Surgery and radiation	22.4%	22.7%	23.2%
- Chemoradiation	23.4%	22.7%	20.3%
Time since last treatment			
- < 1 year	38.8%	34.5%	44.9%
- 1 - 2 year	29.9%	31.8%	26.1%
- > 2 year	31.3%	33.6%	29.0%

Abbreviations: UICC, International Union Against Cancer.
[1] Living arrangement, education and employment status is missing in 20 patients.

Content validity of the SCNS-HNC

On all SCNS-HNC items, ≥ 10% of the patients reported a need, indicating there were no redundant items. Regarding completeness, two of the 201 patients who filled in the SCNS-HNC reported on the free-text item that they had an additional need not yet taken into account in the questionnaire, one indicated to have needs regarding pain and one regarding psychological distress. The study-specific report form of the nursing consultation following OncoQuest revealed some frequently discussed HNC-specific issues not yet included in the SCNS-HNC: coughing and breathlessness (23%), difficulty eating or eating in company (19%), taste and olfaction (16%), changes in appetite (9%), and mobility of the tongue (6%).

Factor analysis and internal consistency

The 5-factor structure as well as the 4-factor structure of the SCNS-SF34 could not be replicated in our study sample using confirmatory factor analysis (Table 3). Under either the assumption of correlated factors or of uncorrelated factors, both factor structures had a negative residual variance on item 16 “Changes in your sexual relationships”. Therefore, we also performed an analysis in which item 16 was deleted. In that case, both factor models could not be estimated when assuming correlated factors. When assuming correlated factors, both factor models showed inadequate RMSEA-scores. Therefore, an exploratory principal component analysis was performed to investigate the factor structure for use in HNC patients. At first a new 5-factor structure was generated (Table 4), replicating the physical & daily living and sexuality domains and almost replicating the psychological needs and health system, information & patient support domain as reported in Au et al.[16]. However, the fifth factor comprised 4 items (item 17 - 19 and 24) without clear cohesion. Since 3 out of these 4 items had high cross-loadings (cross loadings 0.34 to 0.51), a second principal component analysis was performed without item 19 (which did not have any cross-loadings) and forced into 4 factors, resulting in the same factor structure as in Au et al. [16]. Although this 4-factor structure (Bartlett’s test of sphericity ($p < 0.001$) and KMO = 0.93) did not have a good fit of the model using confirmatory factor analyses, this model is nevertheless proposed to be the best model for use in HNC patients with good internal consistency (Cronbach’s alpha ranging from 0.79 (sexuality domain) to 0.95 (psychological)) (Table 5).

Principal component analysis of the SCNS-HNC showed two underlying constructs, namely HNC-specific functioning and lifestyle (Bartlett’s test of sphericity ($p < 0.001$) and KMO = 0.88) (Table 6). Item 6 was not included in the principal component analysis, since it was not correlated ($r < 0.30$) with the other items. Internal consistency of HNC-specific functioning domain was good (Cronbach’s alpha = 0.89), while below 0.70 for the two-item lifestyle domain (Cronbach’s alpha = 0.60).

Construct validity

In total, 27 of the 28 (96%) hypothesized correlations (seven hypotheses on health system, information & patient support were investigated instead of 11 hypotheses when the 5-factor structure would have been replicated) between the SCNS-SF34 and other PROMs, were found (Table 1). Sixteen correlations (57%) also supported the a priori hypothesized magnitude of correlation. Regarding expected differences, three of the ten hypotheses were confirmed (30%) (Table 7). Patients treated with multi-modality treatment reported a higher need on the physical & daily living (p = 0.015) and psychological domain (p = 0.009), while no difference was found for health system, information & patient support (p = 0.070). Patients longer after treatment reported less need for health system, information & patient support than patients shorter after treatment (p = 0.015). No significant differences were found regarding gender or age.

Of the SCNS-HNC, 8 of the 9 (89%) hypothesized correlations were found (Table 1). Six correlations (67%) also supported the a priori hypothesized magnitude of correlation.

<u>Test-retest reliability</u>

Test-retest reliability of the SCNS-SF34 domains was good (ICC ranged from 0.74 (sexuality) to 0.83 (physical & daily living)). Test-retest reliability for HNC-specific functioning was also good (ICC = 0.83), while it was slightly lower than 0.70 for the lifestyle domain (ICC = 0.67).

<u>Presence of floor and/or ceiling effects</u>

On all SCNS-SF34 and SCNS-HNC domains floor effects were present (Table 5 and 6). Floor effects (no need for care) ranged from 21.1% (health system, information & patient support) to 70.9% (lifestyle). No ceiling effects were present.

Table 3: Goodness-of-fit indices for the Supportive Care Needs Survey Short-Form 34 (SCNS-SF34) using confirmatory factor analysis (n = 201)

Model		χ^2 statistic	Df	p-value	RMSEA	CFI	TLI
5 factor model	uncorrelated factors[1]	10017.44	527	≤ 0.001	0.299	0.476	0.442
	uncorrelated factors without item 16	Model could not be estimated					
	correlated factors[1]	901.112	517	≤ 0.001	0.061	0.979	0.977
	correlated factors without item 16	867.861	485	≤ 0.001	0.063	0.978	0.976
4 factor model	uncorrelated factors[1]	8210.269	495	≤ 0.001	0.278	0.567	0.538
	uncorrelated factors without item 16	Model could not be estimated					
	correlated factors[1]	854.928	489	≤ 0.001	0.061	0.979	0.978
	correlated factors without item 16	823.389	458	≤ 0.001	0.063	0.979	0.977

Abbreviations: χ2, Chi-Square Df, degrees of freedom; RMSEA, Root Mean Square Error of Approximation; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index-Non-Normed Fit Index.

[1] Model in which item 16 had a negative residual variance

Table 4: First factor structure generated for the SCNS-SF34 in head and neck cancer patients using principal component analysis (n = 201)

	Factor Loadings[1]				
Item	**1**	**2**	**3**	**4**	**5**
1. Pain		0.38	0.39	0.48	
2. Lack of energy/tiredness	0.30	0.52		0.58	
3. Feelings unwell a lot of the time		0.55		0.65	
4. Work around the home				0.75	
5. Not being able to do the things you used to do	0.38	0.41		0.69	
6. Anxiety		0.79		0.30	
7. Feeling down or depressed	0.30	0.78			
8. Feelings of sadness		0.81			
9. Fears about the cancer spreading		0.84			
10. Worry that the results of treatment are beyond your control		0.73			
11. Uncertainty about the future		0.82			
12. Learning to feel in control of your situation	0.31	0.68		0.39	
13. Keeping a positive look		0.52		0.41	
14. Feelings about death and dying		0.78			
15. Changes in sexual feelings		0.47			0.73
16. Changes in your sexual relationships		0.35			0.83
17. Concerns about the worries of those close to you		0.37	0.51		
18. More choice about which cancer specialists you see		0.34	0.73		
19. More choice about which hospital you attend			0.74		
20. Reassurance by medical staff that the way you feel is normal	0.55	0.32	0.35		
21. Hospital staff attending promptly to your physical needs	0.63		0.44		
22. Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs	0.68		0.35		
23. Being given written information about the important aspects of you care	0.64		0.50		
24. Being given information (written, diagrams, drawings) about aspects of managing your illness and side-effects at home	0.51		0.58		

Table 4: Continued.

	Factor Loadings[1]				
Item	**1**	**2**	**3**	**4**	**5**
25. Being given explanations of those tests for which you would like explanations	0.67	0.31	0.31		
26. Being adequately informed about the benefits and side-effects of treatments before you choose to have them	0.74		0.30		
27. Being informed about your test results as soon as feasible	0.76	0.31			
28. Being informed about cancer which is under control or diminishing (that is, remission)	0.78	0.36			
29. Being informed about things you can do to help yourself to get well	0.74				
30. Having access to professional counselling (e.g., psychologist, social worker, counsellor, nurse specialist) if you, family or friends need it	0.65	0.34			
31. To be given information about sexual relationships					0.77
32. Being treated like a person not just another case	0.82				
33. Being treated in a hospital or clinic that is as physically pleasant as possible	0.74				
34. Having one member of hospital staff with whom you can talk to about all aspects of you condition, treatment and follow-up	0.77			0.31	

[1] loadings > 0.3 are presented, and main (i.e., highest) loading is underlined.

Table 5. Floor and ceiling effects of the SCNS-SF34 and suggested factor structure in head and neck cancer patients (n = 201)

			Factor Loadings[1]			
Item	**% Lowest score**	**% Highest score**	**1**	**2**	**3**	**4**
Physical & daily living	*38.8%*	*0%*				
1. Pain	70.9%	2.5%		0.39	0.54	
2. Lack of energy/tiredness	51.0%	4.5%	0.33	0.51	0.60	
3. Feelings unwell a lot of the time	74.6%	1.0%		0.53	0.67	
4. Work around the home	58.4%	3.0%			0.76	
5. Not being able to do the things you used to do	57.7%	7.5%	0.39	0.39	0.69	
Psychological	*29.7%*	*0%*				
6. Anxiety	68.0%	2.5%		0.78	0.31	
7. Feeling down or depressed	67.7%	1.0%	0.32	0.78		
8. Feelings of sadness	66.7%	2.0%		0.81		
9. Fears about the cancer spreading	51.5%	8.5%		0.85		
10. Worry that the results of treatment are beyond your control	59.7%	3.5%	0.34	0.74		
11. Uncertainty about the future	50.0%	5.5%	0.33	0.82		
12. Learning to feel in control of your situation	58.0%	1.5%	0.35	0.68	0.41	
13. Keeping a positive look	54.2%	3.5%	0.31	0.52	0.42	
14. Feelings about death and dying	65.0%	4.5%		0.79		
17. Concerns about the worries of those close to you	60.5%	2.5%	0.38	0.42	0.30	
Sexuality	*69.9%*	*0.5%*				
15. Changes in sexual feelings	75.3%	3.0%		0.48		0.74
16. Changes in your sexual relationships	77.8%	2.5%		0.36		0.84
31. To be given information about sexual relationships	85.4%	0.5%				0.76
Health system, information & patient support	*21.1%*	*0%*				
18. More choice about which cancer specialists you see	67.5%	1.5%	0.47	0.41		
20. Reassurance by medical staff that the way you feel is normal	43.5%	2.5%	0.62	0.34	0.31	
21. Hospital staff attending promptly to your physical needs	57.5%	2.0%	0.73			

Table 5. Continued

Item	% Lowest score	% Highest score	Factor Loadings[1]			
			1	2	3	4
22. Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs	55.0%	1.5%	0.75			
23. Being given written information about the important aspects of you care	58.0%	2.0%	0.75			
24. Being given information (written, diagrams, drawings) about aspects of managing your illness and side-effects at home	61.5%	4.0%	0.65		0.30	
25. Being given explanations of those tests for which you would like explanations	46.2%	2.5%	0.72	0.31		
26. Being adequately informed about the benefits and side-effects of treatments before you choose to have them	47.2%	4.5%	0.79			
27. Being informed about your test results as soon as feasible	43.3%	11.9%	0.74	0.31		
28. Being informed about cancer which is under control or diminishing (that is, remission)	38.3%	10.4%	0.77	0.37		
29. Being informed about things you can do to help yourself to get well	50.2%	8.5%	0.78	0.30		
30. Having access to professional counselling (e.g., psychologist, social worker, counsellor, nurse specialist) if you, family or friends need it	66.7%	4.5%	0.67	0.35		
32. Being treated like a person not just another case	53.2%	9.5%	0.79			
33. Being treated in a hospital or clinic that is as physically pleasant as possible	44.3%	6.5%	0.72			
34. Having one member of hospital staff with whom you can talk to about all aspects of you condition, treatment and follow-up	47.3%	6.5%	0.78			
19. More choice about which hospital you attend	68.5%	2.0%	-	-	-	-
Eigenvalue			16.69	3.34	1.67	1.23
Variance			50.58	10.11	5.05	3.71
Cronbach's alpha			0.95	0.95	0.89	0.79

[1] loadings > 0.3 are presented, and main (i.e., highest) loading is underlined.

Table 6. Floor and ceiling effects of the SCNS-HNC and suggested factor structure In head and neck cancer patients (n = 201)

			Factor loadings[1]	
Item	**% Lowest score**	**% Highest score**	**1**	**2**
HNC-specific functioning	*21.3%*	*1.0%*		
1. Problems with chewing and or swallowing	47.0%	8.0%	0.84	
2. Problems with dry mouth and/or sticky mucus	36.0%	10.0%	0.85	
3. Problems with weight (underweight or overweight)	47.0%	6.5%	0.74	
4. To be informed on nutrition	57.5%	5.0%	0.78	
5. Difficulty speaking	54.8%	5.0%	0.77	
7. Problems with hearing	71.5%	2.5%	0.59	
8. Oral hygiene	56.6%	4.5%	0.75	
9. Problems with mobility of neck or shoulders	58.8%	7.0%	0.70	
Lifestyle	*70.9%*	*0.5%*		
10. Quit smoking	81.4%	5.0%		0.84
11. Quit drinking	78.5%	0.5%		0.85
6. Care of your stoma and/or voice prosthesis[2]	20.0%	30.0%	-	-
Eigenvalue			4.76	1.39
Variance			47.63	13.94
Cronbach's alpha			0.89	0.60

Abbreviations: HNC, head and neck cancer.

[1] loadings > 0.3 are presented, and main (i.e., highest) loading is underlined.

[2] Percentage lowest score and percentage highest score calculated for patients treated with total laryngectomy only.

Table 7. Differences in SCNS-SF34 domain scores between different patient groups

		SCNS domain							
		Physical & daily living n = 196		Psychological n = 195		Sexuality n = 196		Health system, information & patient support n = 199	
Characteristics	N	Median [range]	p	Median [range]	p	Median [range]	p	Median [range]	p
Age					0.67		0.31		0.72
18 - 60 years	63			7.5 [0 - 92.5]		0 [0 - 75.0]		13.3 [0 - 83.3]	
> 60 years	138			10.0 [0 - 85.0]		0 [0 - 100.0]		15.0 [0 - 91.7]	
Gender			0.11		0.67		0.55		
Male	134	10.0 [0 - 95.0]		10.0 [0 - 92.5]		0 [0 - 100.0]			
Female	67	12.5 [0 - 95.0]		10.0 [0 - 85.0]		0 [0 - 66.7]			
Treatment procedure			0.02		0.01				0.07
Single treatment	92	5.0 [0 - 95.0]		5.0 [0 - 85.0]				11.7 [0 - 85.0]	
Multi modality treatment	109	10.0 [0 - 95.0]		15.0 [0 - 92.5]				18.3 [0 - 91.7]	
Time since last treatment									0.02
0 - 1 year	78							19.2 [0 - 91.7]	
1 - 2 years	60							13.3 [0 - 81.7]	
> 2 years	63							7.5 [0 - 76.7]	

Abbreviations: SCNS, Supportive Care Needs Survey.

DISCUSSION

This study is the first study that investigated the psychometric properties of the Dutch version of the SCNS-SF34 and newly developed SCNS-HNC among HNC patients. Psychometric properties assessed were content validity, factor structure, internal consistency, construct validity and test-retest reliability.

Content validity analyses of the SCNS-HNC showed that there were no redundant items, but that some HNC issues may need to be added: taste and olfaction, difficulty eating, eating in company and changes in appetite, coughing and breathlessness, and mobility of the tongue. For some of these problems the need for supportive care was already addressed indirectly, e.g., the problems on difficulty eating, eating in company and changes in appetite were addressed partly by the question on being informed about nutrition, and the problems on mobility of the tongue is addressed by the question on chewing and swallowing, and speech. For the other problems/needs (taste and olfaction, and coughing and breathlessness), multidisciplinary discussions are needed on the necessity to update the SCNS-HNC. In the present study we aimed to include only those problems/needs for which supportive care is available. However, we realize that this aim is not consistent with the tenets of supportive care needs assessment. One of the purposes is to assist in identifying, guiding and designing the range of services that ought to be available to patients[39]. Although an item on taste and olfaction, and on coughing and breathlessness may be added, the SCNS-HNC is a comprehensive PROM.

Appropriateness of the SCNS-HNC was further supported by the identified 2-factor structure: HNC-specific functioning which comprises of 8 items on needs related to HNC-specific functioning and problems, and a lifestyle domain which comprises of 2 items related to quitting smoking and drinking. Internal consistency of HNC-specific functioning was good (Cronbach's alpha = 0.89), while somewhat low for the lifestyle domain (Cronbach's alpha = 0.60), which can be explained by the fact that this domain includes only two items. We acknowledge that a domain with two items is generally recognized as less stable and thereby less reliable and less construct valid than a domain with more items[40].

Regarding the SCNS-SF34, confirmatory factor analyses showed that the 5-factor structure of Boyes et al.[9] and the 4-factor structure of Au et al.[16] could not be replicated in this study. Nevertheless, exploratory factor analyses showed that the 4-factor structure in which item 19 is deleted and the domains on health systems & information and patient care & support were combined in one domain (i.e., health system, information & patient support)[16] was the best model for use in HNC patients with good internal consistency (Cronbach's alpha ranged from 0.79 to 0.95). Up till now, this 4-factor structure has only been proposed by Au et al.[16]. Other validation studies proposed the (slightly-adjusted) 5-factor structure of Boyes et al.[9], although these studies also acknowledged some difficulties or inconsistencies when replicating the 5-factor structure[11-13,15,17,18]. Okuyama et al.[18] for instance showed that items 21 and 22 had stronger cross loadings on the health system & information domain, while originally allocated to the patient care & support domain. The same holds for Lehmann et al.[13] who found that item 30 had stronger cross loadings on the psychological domain, while originally allocated to the health care & information domain. In addition, Schofield et al.[11] reported that items 18 and 19 originally allocated to the patient care & support domain did not load (loading < 0.30) to one of the domains at all and Doubova et al.[15] excluded item 31 due to high cross loadings. Finally, Brédart et al.[12] and Li et al.[17], the only two studies that performed confirmatory factor analyses, reported that residuals were correlated indicating redundancy among items. Based on these validation studies and our results, as already hypothesized by Li et al.[17], it can be assumed that one universal factor structure for the SCNS-SF34 is unlikely. The factor structure of the SCNS-SF34 may potentially differ regarding for example age, gender or cancer diagnosis.

To assess construct validity of both the SCNS-SF34 and SCNS-HNC, we defined clear a priori hypotheses regarding the (magnitude of) correlation with other PROMs and expected differences between groups of HNC patients. In our study 96% and 89% of the hypothesized correlations were found for the SCNS-SF34 and SCNS-HNC respectively, however, only 57% and 67% (respectively) showed the hypothesized magnitude of correlation. In 11 of the 16 cases in which the correlation as such was supported but not the magnitude of correlation, a stronger correlation was found than a priori hypothesized based on previous validation studies[9,11-13,16,18] and researchers' expectations. Regarding discriminative construct validity, patients treated with multi-modality treatment in our study reported higher levels of physical & daily living and psychological needs and patients longer after treatment reported less health system, information & patient support needs. No significant differences in supportive care needs were found between different gender and age groups. This is in contrast to previous studies which have repeatedly shown such differences[12,13,16-18,35].

A possible explanation for the stronger correlations and absence of differences in supportive care needs regarding age and gender is that all patients included in our study were at least 3 months after treatment and in general had low levels of supportive care needs, as shown by the high floor effects of 21.1% to 70.9%. These high floor effects may have resulted in limited variation in outcomes and consequently in higher correlations and the absence of differences between groups. Another explanation may be that supportive care needs are different in HNC patients compared to other cancer populations (i.e., breast, prostate and mixed cancer populations) on which our hypotheses were mainly based[9,11-13,16,18,34,35]. Our results are in line with the results of Henry et al. which was published after our hypotheses formulation[23], who found relatively high correlations between total SCNS-SF34 score and HADS-D and HADS-A of r = 0.44 and 0.53 and no association with gender and age in HNC patients.

Finally, test-retest reliability of the SCNS-SF34 and SCNS-HNC was overall shown to be good (ICC ranged from 0.67 to 0.83). Only two previous validation studies[12,15] also assessed test-retest reliability of the SCNS-SF34. They also showed good test-retest reliability, except for the physical & daily living domain in breast cancer patients[12].

A limitation of this study is that we included HNC patients after treatment limiting generalizability to HNC patients undergoing treatment or other Dutch cancer populations. Therefore we encourage the validation of the SCNS-SF34 and SCNS-HNC in patients during treatment and other Dutch cancer populations. Another limitation of this study is that although patients were asked to report any additional needs not yet included in the SCNS-HNC, patients did not participate in the developmental stage by interview or focus group. Also, critically reviewing to assess whether all of the items were relevant for the construct being measured and cognitive interviews to determine how the items were perceived or understood by HNC patients were not performed. Main strengths of this study are the development of the SCNS-HNC which can be used in conjunction with the SCNS-SF34, and the assessment of a wide range of psychometric characteristics including content validity, factor structure, internal consistency, construct validity and test-retest reliability. In conclusion, in this study, a module was developed for use in conjunction with the SCNS-SF34 that measures supportive care needs specific for HNC patients (i.e., SCNS-HNC). The SCNS-SF34 and SCNS-HNC are valid and reliable PROMs to evaluate the need for supportive care among HNC patients. More research on the validation of the SCNS-SF34 and SCNS-HNC in other populations, including HNC patients undergoing treatment is, however, warranted.

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4

Supportive care needs in patients treated with total laryngectomy and its associated factors

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ABSTRACT

Background. A group of head and neck cancer (HNC) patients who specifically may have a high need for supportive care are patients treated with total laryngectomy (TL).

Purpose. To investigate (unmet) supportive care needs in TL patients, and its associated factors.

Methods. TL patients (n = 283) completed questions on supportive care needs (SCNS-SF34 and SCNS-HNC). The prevalence of (unmet) supportive care needs, and its associated factors were investigated using logistic regression analyses.

Results. Supportive care needs were highest for HNC-specific functioning (76%), followed by health system, information & patient support (69%), psychological (66%), physical and daily living (62%), sexuality (38%) and lifestyle (19%). Seventy-one percent reported at least one low, moderate or high unmet need, especially regarding HNC-specific functioning (53%). Female gender, living alone, and having a voice prosthesis were significantly positively associated with unmet needs on at least one domain ($p < 0.05$). A worse health-related quality of life was associated with unmet needs on all domains.

Conclusion. The majority of TL patients report at least one low, moderate or high unmet need for supportive care.

INTRODUCTION

Unmet supportive care needs have been reported in 60% to 74% of head and neck cancer (HNC) patients[1-4]. This is higher than the 25% found among Dutch mixed cancer patients[5], while it fits into the wide range of 1% - 93% reported in a previous systematic review[6]. Often reported supportive care needs among HNC patients are psychological needs (e.g., distress), health system and information needs (e.g., being provided with written information on important aspects of your care), and needs regarding physical and daily living (e.g., pain)[2-4,7-14]. Also HNC-specific supportive care needs are often reported, for instance, dry mouth, dental health, eating and speech problems[4,7,9,10,12]. Although highest in the treatment and early follow-up phase[2,9-11], SC needs may remain through the long-term follow-up[3,4,10,12,14].

A group of HNC patients who specifically may have a high need for supportive care are patients treated with total laryngectomy (TL). These patients encounter several adjustments in normal daily functioning, with which they have to live for the rest of their lives, including adjustments in airway management, smell, swallowing and speech[15-17]. In addition, they have often been treated with (chemo)radiation and/or neck dissection, which may induce problems, such as dysphagia and shoulder complaints[15,18]. In a focus-group study among TL patients (2 to 22 years after TL surgery) several supportive care needs were identified, psychosocial care needs and needs related to treatment-related changes in physical functioning, including eating, swallowing, neck and shoulder pain, speech and tracheostomy and voice prosthesis care[19]. No study has, however, quantitatively investigated the prevalence of (unmet) supportive care needs among patients treated with TL in particular.

The aim of this study was to investigate the need for supportive care and unmet needs for supportive care in patients treated with TL. In addition, the association of socio-demographic, clinical and lifestyle factors, and health-related quality of life (HRQOL) with unmet needs was investigated. Based on previous studies among HNC patients, it was hypothesized that a shorter time since diagnosis or treatment[2,9,11,20] and a lower HRQOL[2,3] is associated with a higher prevalence of unmet needs. Also, living alone[4], being unemployed[11], and more intensive type of treatment[2,11,20] were hypothesized to be associated with a higher prevalence of unmet needs. Age[2,10,20], gender[2-4,8,20], having children[3], education level[2], smoking status[2,4,11], and alcohol consumption[2,4] were not expected to be associated with unmet needs. Insight into unmet supportive care needs of TL patients and its associated factors provides knowledge necessary to tailor care for this specific patient group.

MATERIALS AND METHODS

Design and study population

All 914 members of the Dutch Patient Association for Laryngectomees were asked to participate in this cross-sectional study in November 2014. All members were approached by regular post. The post included an information letter, an informed consent form and a paper-and-pencil questionnaire, which they could complete at home. All approached patients were treated with TL and were older than 18 years. In total, 288 patients (32%) completed the questionnaire. According to the Dutch Medical Research Involving Human Subjects Act, ethical approval was not necessary, because patients were not subjected to procedures or required to follow rules of behavior. All data was collected and analyzed anonymously.

Patient-reported outcome measures

Supportive care needs were measured using the 34-item Short-Form Supportive Care Needs Survey (SCNS-SF34)[20-22], the HNC-specific module (SCNS-HNC)[20], and six additional single items (Table 1). The SCNS-SF34 consists of 34 items which were originally reported to have five underlying domains; physical & daily living, psychological, sexuality, patient care & support, and health system & information needs[21,22]. Recently, we translated this measure into Dutch and assessed its psychometric characteristics among Dutch mixed HNC patients (between 3 months and five years after treatment)[20]. In this previous study, we found four underlying domains using 33 items: physical & daily living needs (5 items), psychological needs (10 items), sexuality needs (3 items), and health system, information & patient support needs (15 items)[20]. This four-factor structure also showed good internal consistency in the present study (Cronbach's alpha ranged from 0.83 to 0.95), and was used in this study. The one item not included in one of the four domains (i.e., more choice about which hospital you attend) was measured as a single item. Besides assessing its factor structure and internal consistency, the previous study among mixed HNC patients also reported that the SCNS-SF34 was construct valid and had good test-retest reliability[20].

The SCNS-HNC contains 11 items on two underlying domains, namely HNC-specific functioning (8 items) and lifestyle needs (2 items), and one single item on stoma care and/or voice prosthesis care. The SCNS-HNC has also previously been validated among Dutch mixed HNC patients[20]. Internal consistency using Cronbach's alpha in this TL population was 0.84 (HNC-specific functioning needs) and 0.54 (lifestyle needs). In addition, the previous study showed evidence for its construct validity and test-retest reliability[20].

Content validity, however, showed that some additional items may need to be added which may be relevant in a general HNC population[20], but especially in a TL population. This is the reason why we added six additional single items (last six items of Table 1).

Table 1. Supportive care needs and unmet needs among patients treated with total laryngectomy

SCNS-SF34 and SCNS-HNC domains and items	% with a need	% with an unmet need	Median total score [IQR]
Physical & daily living	62.1%	37.1%	10 [0 - 25]
Pain	20.9%	8.8%	
Lack of energy/tiredness	41.6%	27.1%	
Feelings unwell a lot of the time	16.9%	8.5%	
Work around the home	44.0%	20.2%	
Not being able to do the things you used to do	45.4%	22.9%	
Psychological	66.3%	39.2%	8 [0 - 25]
Anxiety	20.6%	14.0%	
Feeling down or depressed	28.8%	18.5%	
Feelings of sadness	29.4%	18.3%	
Fears about the cancer spreading	35.3%	24.2%	
Worry that the results of treatment are beyond your control	29.4%	14.5%	
Uncertainty about the future	37.9%	21.0%	
Learning to feel in control of your situation	36.2%	12.5%	
Keeping a positive outlook	47.6%	12.2%	
Feelings about death and dying	27.2%	16.2%	
Concerns about the worries of those close to you	41.2%	18.7%	
Sexuality	38.0%	23.0%	0 [0 - 17]
Changes in sexual feelings	31.9%	19.0%	
Changes in your sexual relationships	31.0%	18.6%	
To be given information about sexual relationships	19.3%	9.1%	

Table 1. Continued.

SCNS-SF34 and SCNS-HNC domains and items	% with a need	% with an unmet need	Median total score [IQR]
Health system, information & patient support	69.1%	34.9%	13 [0 - 25]
More choice about which cancer specialists you see	30.9%	6.9%	
Reassurance by medical staff that the way you feel is normal	44.4%	12.4%	
Hospital staff attending promptly to your physical needs	46.5%	10.6%	
Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs	43.8%	9.4%	
Being given written information about the important aspects of you care	47.8%	14.2%	
Being given information (written, diagrams, drawings) about aspects of managing your illness and side-effects at home	38.0%	10.6%	
Being given explanations of those tests for which you would like explanations	42.9%	13.9%	
Being adequately informed about the benefits and side-effects of treatments before you choose to have them	47.8%	16.1%	
Being informed about your test results as soon as feasible	40.6%	15.2%	
Being informed about cancer which is under control or diminishing (that is, remission)	39.4%	15.0%	
Being informed about things you can do to help yourself to get well	39.4%	15.0%	
Having access to professional counselling (e.g., psychologist, social worker, counsellor, nurse specialist) if you, family or friends need it	34.8%	14.3%	
Being treated like a person not just another case	50.2%	17.5%	
Being treated in a hospital or clinic that is as physically pleasant as possible	52.0%	17.2%	
Having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up	50.5%	17.8%	

Table 1. Continued.

SCNS-SF34 and SCNS-HNC domains and items	% with a need	% with an unmet need	Median total score [IQR]
<u>HNC-specific functioning</u>	75.9%	53.2%	16 [3 - 31]
Problems with chewing and/or swallowing	45.8%	26.0%	
Problems with dry mouth and/or sticky saliva	46.8%	27.3%	
Problems with weight (underweight or overweight)	46.6%	19.1%	
To be informed on nutrition	33.3%	13.4%	
Difficulty speaking	52.5%	27.9%	
Problems with hearing	37.5%	16.6%	
Oral hygiene	36.1%	7.8%	
Problems with mobility of neck or shoulders	51.8%	27.7%	
<u>Lifestyle</u>	18.8%	5.4%	0 [0 - 0]
Quit smoking	4.7%	1.8%	
Quit drinking	18.4%	5.1%	
<u>Single items</u>			
More choice about which hospital you attend	33.9%	8.8%	
Care of your stoma and/or voice prosthesis	49.6%	16.4%	
Problems with taste and olfaction	60.9%	35.0%	
Problems with coughing	44.3%	23.2%	
Difficulty eating	48.9%	26.4%	
Shortness of breath	44.0%	23.8%	
Problems with social eating	50.5%	30.2%	
Loss of appetite	27.6%	12.0%	

Abbreviations: SCNS-SF34, 34-item Short-Form Supportive Care Needs Survey; SCNS-HNC, the SCNS head and neck cancer-specific module; IQR, interquartile range

All SCNS-SF34, SCNS-HNC and single items are answered on a 5-point scale[22], namely: '1 = not applicable' for issues that are no problem to the patient; '2 = satisfied' for issues on which a patient needs support but the support is already satisfactory fulfilled; and '3 = low unmet need', '4 = moderate unmet need' and '5 = high unmet need' for issues on which a patient reports respectively a low, moderate or high need for additional supportive care. Patients are asked to take the last month into account when answering the questions. In this study an item score ≥ 2 was used to identify patients with a need, while an item score ≥ 3 was used to identify patients with unmet needs. In addition, a total score per domain was calculated and converted to a 0 - 100 score, with a higher score indicating a higher level of supportive care needs.

Besides questions on (unmet) supportive care needs, several factors potentially associated with unmet needs were measured via patient self-report using study-specific questions. Socio-demographic factors included age, gender, having children, living arrangements, education level, and employment status. Clinical factors included time since TL, treatment (TL with or without (chemo)radiation) and current speech method (voice prosthesis, injection method, electrolarynx or other (multiple answers were possible)). Lifestyle factors included smoking (is not a smoker, is a smoker or quitted smoking) and drinking behavior (does not drink, does drink or quitted drinking). HRQOL was measured using the EuroQoL-5 dimensions (EQ-5D) questionnaire. The EQ-5D measures current problems on five dimensions of HRQOL, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants can answer they have no problems, some problems or extreme problems. Based on these five dimensions, an EQ-5D total score was generated using the Dutch Index Tariff[23]. A higher score indicated a better HRQOL. Pickard et al.[24] previously presented evidence on the validity and reliability of this measure in different groups of cancer patients.

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 22 (IBM Corp., Armonk, NY USA). Socio-demographic, clinical and lifestyle factors and HRQOL were described using frequencies, percentages, means and standard deviations (SD) or medians and (interquartile) ranges. The need for supportive care among TL patients was assessed by calculating the total score per domain converted to a 0 - 100 score. Missing data on the SCNS-SF34 and SCNS-HNC was imputed by the mean score of the other items of the particular domain in case less than half of the items within the domain were missing[22]. In addition, the prevalence of supportive care needs (one or more items with a score ≥ 2) and unmet needs (one or more items with a score ≥ 3) was assessed in total and per supportive care domain. To assess factors associated with at least one overall low, moderate or high unmet need and at least one low, moderate or high unmet need per domain, forward multivariate logistic regression analyses were used. The p-value for entry in the model was < 0.10. In case the p-value in the final model was < 0.05 the factor was also considered to be statistically significantly associated with the outcome. Included factors were age, gender, having children, living arrangements, education level, employment status, time since TL, treatment, having a voice prosthesis, smoking, drinking and HRQOL. Factors associated with unmet lifestyle needs were not assessed, since the percentage of unmet needs and Cronbach's alpha were too low. Also, factors associated with the total 0 - 100 score were not assessed, since data were heavily skewed to the right.

RESULTS

Of the 288 TL patients who participated in the study, 5 patients did not complete any of the supportive care needs questions and were excluded. Most of the 283 TL patients were men (84%) and the mean age was 70 (SD = 9) (Table 2). Most TL patients had a lower education level (49%), followed by a secondary (25%), higher (18%) or elementary education level (9%). Time since TL ranged from 0 to 37 years (median = 7). Most TL patients also received radiation (72%) or chemoradiation (9%) prior to or after TL.

Need for supportive care

The highest need concerned the HNC-specific functioning domain (76%), followed by health system, information & patient support (69%), psychological (66%), physical and daily living (62%), sexuality (38%) and lifestyle needs (19%) (Table 1). Most reported HNC-specific functioning needs were needs regarding difficulty speaking (53%), problems with mobility of neck and shoulders (52%), and problems with dry mouth and/or sticky saliva (47%). Being treated in a hospital or clinic that is as physically pleasant as possible (52%), having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up (51%), and being treated like a person not just another case (50%) were the most important health system, information & patient support needs. Most reported psychological needs were keeping a positive outlook (48%) and concerns about the worries of those close to you (41%). Regarding physical and daily living, not being able to do the things you used to do (45%), work around the home (44%) and lack of energy/tiredness (42%) were the most important needs. For sexuality, changes in sexual feelings (32%), and for lifestyle, quit drinking were most important (18%). Furthermore, high needs were reported on several (HNC and TL-specific) single items, such as problems with taste and olfaction (61%), problems with social eating (51%) and care of your stoma and/or voice prosthesis (50%).

Unmet needs for supportive care

Over all questions on supportive care needs, 71% of TL patients reported at least one low, moderate or high unmet need. The highest percentage of unmet need concerned the HNC-specific functioning domain (53%), followed by the psychological (39%), physical & daily living (37%), health system, information & patient support (35%), sexuality (23%) and lifestyle domain (5%) (Table 1). For all domains and items, the percentage of patients that reported an unmet need was much lower than the percentage of patients that reported a need. The top 10 unmet needs were: problems with taste and olfaction (35%), problems with social eating (30%), difficulty speaking (28%), problems with mobility of neck or shoulders (28%), problems with dry mouth and/or sticky saliva (27%), lack of energy or tiredness (27%), difficulty eating (26%), problems with chewing and/or swallowing (26%), fears about the cancer spreading (24%), and shortness of breath (24%).

Table 2: Patient characteristics

	Patients treated with total laryngectomy n = 283
Mean [SD] age[1]	70 (9)
Sex[2]	
- men	84%
- women	16%
Having children[3]	
- no	15%
- yes	85%
Living arrangements[3]	
- living alone	21%
- living with partner	68%
- living with partner and children	7%
- other (e.g., with children or in an institution)	3%
Education level[4]	
- elementary	9%
- lower	49%
- secondary	25%
- higher	18%
Employment status	
- employed in paid work	11%
- not employed/not able to work	15%
- retired	74%
Smoking status[4]	
- is not a smoker	67%
- is a smoker or quitted smoking	33%
Drinking status[4]	
- does not drink	31%
- drinks	60%
- quitted drinking	9%

Table 2: Continued.

	Patients treated with total laryngectomy n = 283
Median [IQR] years since total laryngectomy[2]	7 [2 - 14]
Received other treatments[5]	
- no	19%
- yes, radiation	72%
- yes, chemoradiation	9%
Current speech method*	
- voice prosthesis	83%
- injection method	18%
- electrolarynx	5%
- other (e.g., cannot speak)	3%
Median [IQR] health-related quality of life (EQ-5D utility score)	0.89 [0.81 - 1.00]

Abbreviations: SD, standard deviation; IQR, interquartile range; EQ-5D, EuroQol-5 dimensions
[1] Age is missing in two patients.
[2] Gender and time since total laryngectomy are missing in four patients.
[3] Having children, living situation and health-related quality of life are missing in seven patients.
[4] Education level, smoking status, drinking status are missing in three patients.
[5] Received other treatment and current speech method are missing in six patients.
* Multiple answers possible

Factors associated with unmet needs

Several factors were, based on a p-value for entry < 0.10, included in the final model (Table 3). The explained variance (via Nagelkerke's R^2) ranged from 0.10 (total supportive care needs and sexuality needs) to 0.29 (physical & daily living needs). Patients with a lower (worse) HRQOL reported significantly more often unmet needs on all supportive care needs domains and the overall domain, compared to patients with a higher (better) HRQOL (all p-values ≤ 0.002). In addition, psychological unmet needs were significantly more often reported in women (p = 0.029), and in patients with a voice prosthesis (compared to patients without a voice prosthesis, p = 0.022). Health, system, information & patient support unmet needs were found to be significantly more prevalent in patients living alone (compared to patients living together, p = 0.017).

Table 3. Factors associated with unmet needs among patients treated with total laryngectomy[1]

	Total	**SCNS-SF34**				**SCNS-HNC**[2]
		Physical & daily living	**Psychological**	**Sexuality**	**Health, system, information & patient support**	**HNC-specific functioning**
	n = 276	n = 267	n = 252	n = 266	n = 260	n = 265
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Age					P = 0.068	
- < 63 years					1.44 [0.61 – 3.40]	
- 64 – 69 years					1.93 [0.85 – 4.37]	
- 70 – 76 years					2.91 [1.29 – 6.60]	
- ≥ 77 years					Reference	
Sex			P = 0.029			
- men			Reference			
- women			2.36 [1.10 – 5.10]			
Living arrangements					P = 0.017	
- living alone					Reference	
- living together					0.44 [0.22 – 0.86]	
Education level						P = 0.065
- elementary						1.79 [0.59 – 5.40]
- lower						2.34 [1.10 – 4.95]
- secondary						3.01 [1.30 – 7.01]
- higher						Reference

Smoking status				P = 0.059		
- is not a smoker				Reference		
- current smoker or quitted smoking				1.78 [0.98 – 3.23]		
Years since total laryngectomy			P = 0.066			
- last year			1.88 [0.77 – 4.58]			
- 1 – 2 years ago			2.51 [1.15 – 5.48]			
- 3 – 4 years ago			2.11 [0.87 – 5.14]			
- ≥ 5 years ago			Reference			
Other treatment						P = 0.062
- no						Reference
- yes, (chemo)radiation						1.92 [0.97 – 3.82]
Voice prosthesis			P = 0.022		P = 0.069	
- without a voice prosthesis			Reference		Reference	
- with a voice prosthesis			2.97 [1.17 – 7.52]		2.21 [0.94 – 5.19]	
Health-related quality of life	P < 0.001	P < 0.001	P < 0.001	P = 0.002	P < 0.001	P < 0.001
- < 0.80	Reference	Reference	Reference	Reference	Reference	Reference
- 0.80 – 0.89	0.51 [0.22 – 1.21]	0.40 [0.20 – 0.80]	0.34 [0.16 – 0.71]	0.65 [0.32 – 1.31]	0.30 [0.15 – 0.62]	0.34 [0.16 – 0.73]
- 0.90 – 1.00	0.21 [0.10 – 0.47]	0.07 [0.03 – 0.15]	0.14 [0.07 – 0.30]	0.25 [0.13 – 0.58]	0.20 [0.10 – 0.40]	0.14 [0.07 – 0.28]
Explained variance[3]	0.10	0.29	0.27	0.10	0.20	0.22

Abbreviations: SCNS-SF34, 34-item Short-Form Supportive Care Needs Survey; SCNS-HNC, the SCNS head and neck cancer-specific module; OR, odds ratio; CI, confidence interval.

[1] Only those factors are presented which showed a multivariate association (p-value for enter < 0.10) on at least one of the domains or on the overall unmet need domain.

[2] The SCNS-HNC lifestyle domain is not presented in this table, since internal consistency was low and only a small group of TL patients reported an unmet need.

[3] Calculated using Nagelkerke R^2

DISCUSSION

This study aimed to provide insight into (unmet) needs for supportive care in TL patients. In addition, the association of socio-demographic, clinical and lifestyle factors, and HRQOL with unmet needs was investigated. We found that many TL patients have supportive care needs, especially regarding HNC-specific functioning (76%), health system, information & patient support (69%), psychological (66%) and physical and daily living needs (62%). For many of these patients their need for supportive care was satisfactorily fulfilled, since reported unmet needs on the abovementioned domains were much lower, with respectively 53%, 35%, 39% and 37%. Nevertheless, 71% of all TL patients reported at least one low, moderate or high unmet need. Patients with a worse HRQOL reported significantly more often unmet needs on all supportive care domains compared to patients with a better HRQOL. Also socio-demographic and clinical factors were found to be associated with unmet needs.

Our finding that more than seven out of ten TL patients have at least one low, moderate or high unmet need for supportive care is supported by previous studies in mixed HNC patients in which unmet needs of 60% - 74% were reported[1-4]. Clear comparison of our findings to previous studies on (unmet) supportive care needs in HNC patients is, however, limited. Only four of the previous studies also used the SCNS-SF34[1,3,13,14], while the other studies used the Cancer Needs Questionnaire Short Form (CNQ-SF)[7,9,10], the Cancer Survivors' Unmet Needs Measure (CaSUN)[2], the Survivors Unmet Needs Survey (SUNS)[11], the Patient Concerns Inventory (PCI)[4] or a study-specific questionnaire[12]. We favored the SCNS-SF34 over the other patient-reported outcome measures as this measurement instrument is most frequently used, and has previously been validated in Dutch among HNC patients specifically[20].

Another reason why the comparison of findings is limited is the multiple ways used to calculate domain scores on the SCNS-SF34, as shown in the different SCNS-SF34 studies[1,3,13,14]. Previous studies investigated factors associated with moderate or high unmet needs[1], factors associated with number of low, moderate or high unmet needs[14], or factors associated with continuous outcomes of the SCNS-SF34[3,13]. In our study the continuous outcomes of the SCNS-SF34 were heavily skewed to the right, which is why we decided to dichotomize between patients with at least one low, moderate or high unmet need and patients without such a need. In contrast to Boyes et al.[1] we thus also categorized low unmet needs as unmet needs. We hypothesize that besides focusing on patients with moderate or high unmet needs, it is of importance to focus on patients with low unmet needs as well, as the provision of low-intensive supportive care (e.g. the provision of information or self-management interventions) may prevent the development to more serious needs, for which more-intensive (and more costly) supportive care interventions may be necessary. More research on this matter is, however, warranted.

We found that HNC-specific and TL-specific unmet needs were highly prevalent among TL patients, as 53% reported low, moderate or high unmet needs on the HNC-specific functioning domain and 12% to 35% reported unmet needs on HNC-specific or TL-specific single items. Eight of the 10 most prevalent unmet needs were HNC or TL-specific. These results are in contrast to two previous studies in respectively newly diagnosed oral cancer patients[9] and mixed HNC patients up to 5 years after diagnosis[3], which found no HNC-specific unmet needs among its top 10. This may, however, be explained by their use of a more limited HNC measurement instrument. In the study of Wells et al.[4] in mixed HNC patients 3 months to 5 years after treatment, comparable to our findings, multiple HNC-specific unmet needs were reported among its top 10, including needs regarding dry mouth, dental health, swallowing, speech, chewing and eating, and taste loss. Based on these results it seems that regular care may not always fit the needs of individual patients, and that it is important to provide TL patients with tailored supportive care. To facilitate TL patients to have an active role themselves to manage these HNC-specific and TL-specific problems, we recently developed and tested a self-help application consisting of information and self-care advice on stoma care, voice prosthesis care, speech, smelling, nutrition and mobility of neck or shoulders, and of a guided self-help exercise program targeting speech, swallowing and neck and shoulder problems. Previous research showed that this application is feasible and valued by both TL patients and their care providers[19,25]. Currently, the (cost)effectiveness of the exercise program is being investigated among TL patients[26].

In addition to HNC and TL-specific unmet needs, psychological and physical and daily living unmet needs were often reported in our study (respectively 39% and 37% of all patients reported at least one low, moderate or high unmet need). A psychological unmet need reported by almost one out of five TL patients was concerns about the worries of those close to them. Caregivers of TL patients often help TL patients with daily care, which may place a burden on the caregiver's daily life[27]. Although recently published research among caregivers of HNC patients indicated that the perceived burden from the caregivers' perspective was relatively low[28], about half of all caregivers report at least one moderate to high unmet need[28-29]. Whether these needs among HNC caregivers are comparable to those of caregivers of a more homogeneous group of TL-patients need, however, to be further investigated. A currently ongoing Dutch longitudinal cohort study measures supportive care needs among caregivers of HNC patients using the caregivers version of the SCNS (i.e., the SCNS-P&C)[30], enabling the opportunity to investigate supportive care needs of both HNC and TL caregivers in more detail (over time)[31,32].

To investigate which TL patients have a particular need for additional supportive care, we investigated factors associated with unmet needs. As hypothesized[2,4,9,11,20], time since diagnosis or treatment, living alone, and a more intensive type of treatment were based on a p-value for entry of < 0.10 included in the final model of at least one supportive care domain, of which living alone was also found to be significantly associated. Also, comparable to previous research in HNC patients[2,3], a worse HRQOL was consistently found to be significantly associated with unmet needs. In addition, although not hypothesized, female gender, and patients with a voice prosthesis (compared to patients without a voice prosthesis) were sigificantly positively associated with unmet needs. These results indicate that some TL patients are in higher need for additional supportive care than others, which should be taken into account when tailoring care to the individual needs of patients. However, it should also be noted that the explained variance of our results were with 10% - 29% relatively low, further research is, therefore, recommended to investigate explanatory factors (e.g. other clinical factors, personal factors or social support) in more detail (over time).

A strength of the current study is that this is the first study that specifically focused on (unmet) supportive care needs in TL patients. Also, HNC and TL-specific needs were measured using the recently validated SCNS-HNC[20] and some single items targeting TL patients specifically. Only half of the previous studies measured HNC-specific needs[3,4,7,9,10], mostly limited to a few questions on HNC-specific coping needs[7,9,10] or needs regarding smoking cessation, alcohol cessation, feeling better about appearance, or finding meaning and purpose in life[3]. Another strength is the sample size of 283 TL patients, which is quite high when taking into account that on average only 150 patients are treated by TL each year in the Netherlands[33]. However, it should be taken into account that the patients were selected via the Dutch Patient Association for Laryngectomees, and that the response rate was rather low (32%), which may have resulted in selection bias and reduced generalizability to all TL patients. The low response rate may be due to the fact that study procedures were anonymized, and we were, therefore, not able to send reminders to non-responders. Because of these study procedures, we were also not able to collect data from the medical file. We had to rely on patient self-report for clinical information, which is also why some potential relevant clinical information was not collected. Another limitation is the cross-sectional design, hampering the ability to draw conclusions on causality of findings and to distinguish (unmet) supportive care needs at different moments in the cancer trajectory. Also, although this study sample was homogeneous regarding the study sample (i.e. TL patients only), time since TL was quit heterogeneous.

In conclusion, the majority of TL patients have supportive care needs, especially regarding HNC-specific functioning, health system, information & patient support, psychological, and physical and daily living needs. In total, 71% of all TL patients reported at least one low, moderate or high unmet need. Several socio-demographic and clinical factors were found to be associated with unmet needs on at least one supportive care domain. Also, patients with a worse HRQOL reported significantly more often unmet needs on all domains compared to patients with a better HRQOL. More research is needed on the course of (unmet) supportive care needs over time.

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5

Costs from a healthcare and societal perspective among cancer patients after total laryngectomy: are they related to patient activation?

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ABSTRACT

Purpose. To investigate the associations between patient activation and total costs in cancer patients treated with total laryngectomy (TL).

Methods. All members of the Dutch Patients' Association for Laryngectomees were asked to participate in this cross-sectional study. TL patients who wanted to participate were asked to complete a survey. Costs were measured using the medical consumption and productivity cost questionnaire and patient activation using the patient activation measure (PAM). Socio-demographic and clinical characteristics were self-reported, and health-related quality of life (HRQOL) measured using the EQ-5D. The difference in total costs from a healthcare and societal perspective among four groups with different PAM levels were compared using (multiple) regression analyses (5,000 bootstrap replications).

Results. In total, 248 TL patients participated. Patients with a higher (better) PAM (level 2, 3 and 4) had a probability of 70%, 80% and 93% that total costs from a healthcare perspective were lower than in patients with the lowest PAM level (difference €-375 to €-936). From a societal perspective this was 73%, 87% and 82% (difference €-468 to €-719). After adjustment for time since TL, education and sex, the probability that total costs were lower in patients with a higher PAM level compared to patients with the lowest PAM level changed to 62% - 91% (healthcare) and 63% - 92% (societal). After additional adjustment for HRQOL, the probability to be less costly changed to 35% - 71% (healthcare) and 31% - 48% (societal).

Conclusion. A better patient activation is likely to be associated with lower total costs from a healthcare and societal perspective.

INTRODUCTION

Current healthcare systems increasingly focus on the ability of cancer patients to manage and cope themselves with the consequences of being treated for cancer, defined as self-management[1-4]. Several self-management interventions, including eHealth interventions, have been developed to guide cancer patients in their self-management[2,5-14]. It has been hypothesized that self-management may improve patients' health outcomes and reduce (healthcare) costs[4,15].

A previous systematic review of Panagioti et al.[16] indeed found that self-management interventions for different populations with chronic illnesses may reduce healthcare utilization without compromising patients' health outcomes. In cancer patients specifically, only few studies focused on the impact of self-management interventions on (healthcare) costs so far, although several researchers are planning to[8-10,12]. A recent study comparing psychologist-led care with a nurse-led self-management intervention in distressed cancer patients, showed no evidence for cost-effectiveness of the self-management intervention[13]. However, a stepped care program targeting psychological distress in cancer patients consisting of four steps, including a self-help intervention, was found to be more effective and highly likely to be less costly compared to care-as-usual[14,17].

Although previous studies thus indicated that self-management interventions have the potential to be cost-effective or even cost saving, the pathway via which self-management may influence costs is still partly unknown. A recent study by Howell et al.[7] provided a conceptual framework to assess performance of self-management education support in clinical practice. This framework conceptualizes that self-management interventions influence patients' acquired skills, such as self-efficacy, problem-solving skills, and self-monitoring behavior, which in turn may influence patients' confidence to manage (e.g., manage symptoms, emotional impact of illness, and role and relationship changes). Patients' acquired skills as well as patients' confidence to manage may consequently influence patient outcomes, such as increased health-related quality of life (HRQOL) and lower healthcare use and costs.

Previous studies in non-cancer populations indeed found that patients' knowledge, confidence and ability to manage the disease, defined as patient activation[18], may influence healthcare usage and costs[19-27]. It was generally found that patients with better patient activation levels used preventive care (e.g., mammography screening, care for feet and eyes or low density lipid-protein cholesterol testing in diabetes patients) more often than less activated patients[19-23], while other forms of healthcare use (e.g., hospitalization) was reduced[19,21,23-26]. In addition, activated patients had lower total healthcare costs than less activated patients[19,27]. This suggests that although activated patients may use preventive healthcare more often, total healthcare costs of these activated patients are lower, because they use other (and potentially more expensive) types of healthcare less often. However, these studies did not take costs from a societal perspective into account. Also, no such studies have yet been performed among cancer patients.

Therefore, this study aimed to investigate the associations between patient activation and total costs in cancer patients from both a healthcare and societal perspective. To answer this research question, we studied patients with laryngeal or hypopharyngeal cancer treated with total laryngectomy (TL). As a consequence of TL, several body functions including breathing, smell, swallowing and voice production are changed[28-32]. In addition, many TL patients experience head, neck and shoulder mobility problems as well as more generic cancer-related problems such as fatigue, anxiety and depression[30,31,33]. As a result of these problems and changes in body functions, TL patients are expected to report high healthcare and societal costs, even a long time after treatment, as was also reported in a previous study among laryngeal cancer patients in general [34,35]. We hypothesized that TL patients with a better patient activation level report lower costs from both a healthcare and a societal perspective, compared to patients with lower levels of patient activation.

PATIENTS AND METHODS

Design and study population

All members of the Dutch Patients' Association for Laryngectomees were asked to participate in a cross-sectional study in November 2014. Patients willing to participate were asked to complete a survey comprising of validated questionnaires on healthcare utilization, productivity losses, patient activation, and HRQOL, and study-specific sociodemographic and clinical questions. Patients were included when they were treated with TL, were older than 18 years, and completed the survey. The study was performed in accordance with the Dutch Medical Research Involving Human Subjects Act. Ethical approval was not necessary, as patients were not subjected to procedures or required to follow rules of behavior.

Measures

Direct medical healthcare utilization, direct non-medical service utilization and productivity losses in the previous three months were measured using the medical consumption questionnaire (iMCQ)[36] and productivity cost questionnaire (iPCQ)[37] of the Institute for Medical Technology Assessment of the Erasmus University Rotterdam, the Netherlands. The questionnaire was slightly adapted for usage in this population of TL patients. Direct medical costs in the previous three months were calculated by multiplying resource use by the integral cost price[38]. All prices were adjusted to 2014 prices using the consumer price index. Productivity losses from paid work were calculated by multiplying productivity losses by gender and age-specific costs[38] using the friction cost approach. Thus productivity losses were only included if start date of absence from work was less than the friction period of 160 days before completion of the questionnaire.

The patient activation measure (PAM) was used to measure patient activation. The PAM consists of 13 statements on self-reported knowledge, skills and confidence for self-management of one's health or chronic condition[18]. Patients can answer that they: 1. strongly disagree, 2. disagree, 3. agree, or 4. strongly agree with the statement, or can indicate that the statement is not applicable. A total score is calculated by summing scores of all applicable items and transforming it to a standardized activation score ranging of 0 (low patient activation) to 100 (high patient activation). In this study, a total score was calculated when at least 10 items were completed with a valid score. Patients' total score is categorized into four levels: PAM 1 (score ≤ 47.0), PAM 2 (score between 47.1 and 55.1), PAM 3 (score between 55.2 and 67.0) and PAM 4 (score > 67.0).

In addition, HRQOL was measured using the EuroQol-5 dimensions (EQ-5D). The EQ-5D consists of five items measuring problems on five domains, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients are asked to report their level of problems on each of these domains: no problems, some problems or extreme problems[39]. The resulting profile of answers can be transformed to a value given by the Dutch general public using the EQ-5D index[40]. Also, sociodemographic and clinical characteristics were measured, namely age, sex, living situation, having children, education level, work situation, smoking, drinking, time since TL surgery, treatment with (chemo)radiation and current speech method.

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 22 (IBM Corp., Armonk, NY USA) and STATA version 12.1. Descriptive statistics were used to provide insight into sociodemographic characteristics, clinical characteristics and direct medical healthcare utilization, direct non-medical service utilization and productivity losses. Chi-squared tests, Fisher's Exact tests, independent samples T-tests and Mann-Whitney tests were used to compare sociodemographic and clinical characteristics among TL patients. A p-value < 0.05 was considered statistically significant.

To investigate the association between patient activation and total costs from a healthcare and societal perspective, mean costs of the four PAM groups were compared using both unadjusted and adjusted analyses. All analyses were performed using (multiple) regression analyses with dummy coding for PAM level. The analyses were performed twice, once with total costs from a healthcare perspective and once with total costs from a societal perspective (including direct medical, direct non-medical and productivity losses) as dependent variable. In the adjusted analyses, analyses were adjusted for variables that differed among the PAM groups (education level) and for variables found to have a major univariate influence (a change of ≥ 20%) on incremental costs. Variables which were assessed for eligibility were age (continuous), sex (male/female), having children (yes/no), living alone (yes/no), employment status (employed vs. not employed or retired), smoking status (no vs. yes or quitted smoking), drinking status (no vs. yes or quitted drinking), time since total laryngectomy (continuous), additional treatment with (chemo)radiation (no additional treatment vs. (chemo)radiation) and having a voice prosthesis (yes/no).

Besides abovementioned analyses, an additional multiple regression analysis was performed in which we adjusted for HRQOL (in addition to the other variables included in the second analysis). We adjusted for HRQOL in a separate analysis since patient activation and HRQOL are likely to be strongly associated[41], and both may be associated with total costs.

Since cost data is usually characterized by its non-normal distribution and high variance, studies are seldom powered to detect significant differences in costs among groups. Therefore, as accepted in current state of economic evaluations, a probabilistic approach was used rather than reliance upon significance levels to investigate the association between PAM level and total costs[42]. The probability that groups with a higher PAM level (level 2, 3 and 4) had lower costs compared to the group with the lowest PAM level (level 1) was assessed by replicating the regression analyses using bias-corrected accelerated bootstrapping with 5,000 replications.

RESULTS

In total 288 of the 914 (32%) approached patients actually participated. In this study only those patients (n = 248) were included for whom PAM data and data on direct medical healthcare utilization, direct non-medical service utilization and productivity losses were available. There were some significant differences between the included (n = 248) and the excluded patients (n = 40) (Table 1). Included patients were significantly younger (mean = 70 years, standard deviation (SD) = 9 versus mean = 73 years, SD = 10; p = 0.043) and had a significantly shorter time since TL (median = 6 years, range 0 - 34 versus median = 11 years, range 0 - 37; p = 0.025).

Of the 248 patients, the mean PAM score was 59 (SD = 17). Most patients (n = 104) had a PAM score between 55.2 and 67.0 (PAM level 3), 56 patients had a low PAM score (PAM level 1), 43 patients had a somewhat higher PAM score (PAM level 2) and 45 patients were in the group with the highest PAM score (PAM level 4). There were no significant differences between these four groups regarding socio-demographic and clinical characteristics, except for education level (p = 0.041) and HRQOL (p = 0.004) (Table 1). The group with the highest PAM level had on average the highest percentage of higher educated patients as well as the highest HRQOL, while the group with the lowest PAM level had the lowest.

Direct medical healthcare utilization, direct non-medical service utilization, and productivity losses

Results of direct medical healthcare utilization, direct non-medical service utilization and productivity losses in the previous three months among TL patients are presented in Table 2. In general, more than half of all TL patients visited their general practitioner in the past 3 months (54%). In addition, 55% of patients reported that they visited a specialist in an academic center, while 42% visited a specialist in a general practice. A quarter of all TL patients received care from a physiotherapist, 18% received care from a speech pathologist, 17% from an oral hygienist and 14% from a dietitian. Only 3% received care from a social worker, 2% received psychologic or psychiatric help in a private practice and 1% received psychologic or psychiatric help in a mental healthcare center. About one out of 10 TL patients (11%) were admitted to a hospital in the previous three months, while 26% received day treatment. Several TL patients received personal care (6%), nursing care (6%), or home care (8%) by a professional. Also, 15% of the TL patients reported to receive informal care. Two percent of all TL patients reported to have productivity losses, which is 18% of the employed TL patients.

Table 1. Patient characteristics

	Included patients n = 248	**Not included patients** n = 40	**PAM 1** n = 56	**PAM 2** n = 43	**PAM 3** n = 104	**PAM 4** n = 45	**Significance level included patients**	**Significance level PAM groups**
Mean [SD] age[1]	70 [9]	73 [10]	70 [9]	70 [9]	68 [9]	72 [9]	0.043	0.206
Sex[2]							0.183	0.067
- men	85%	77%	75%	84%	89%	91%		
- women	15%	23%	25%	16%	11%	9%		
Having children[3,4]							0.526	0.982
- no	15%	11%	16%	16%	15%	14%		
- yes	85%	89%	84%	84%	85%	86%		
Living arrangements[3]							0.920	0.459
- living alone	21%	22%	29%	19%	19%	18%		
- living together (with partner, children or in an institution)	79%	78%	71%	81%	81%	82%		
Education level[5]							0.784	0.041
- elementary	10%	8%	7%	14%	12%	7%		
- lower	47%	55%	64%	49%	43%	30%		
- secondary	25%	23%	18%	26%	24%	36%		
- higher	18%	15%	11%	12%	22%	27%		
Employment status							0.164	0.650
- employed in paid work	11%	13%	7%	14%	11%	16%		
- not employed/not able to work	17%	5%	14%	21%	18%	11%		
- retired	72%	83%	79%	65%	71%	73%		
Smoking status[5]							0.486	0.750
- is not a smoker	67%	73%	66%	60%	69%	70%		
- current smoker or quitted smoking	33%	28%	34%	40%	31%	30%		

Drinking status[5]							0.302	0.269
- does not drink	29%	38%	39%	26%	28%	23%		
- drinks or quitted drinking	71%	62%	61%	74%	72%	77%		
Median [range] years since total laryngectomy[6]	6 [0 - 34]	11 [0 - 37]	6 [0 - 34]	4 [0 - 27]	5 [0 - 28]	10 [0 - 33]	0.025	0.094
Received other treatments[7]							0.557	0.259
- no	19%	15%	11%	23%	20%	25%		
- yes, (chemo) radiation	81%	85%	89%	77%	80%	75%		
Current speech method[4,7]								
- voice prosthesis	84%	78%	87%	84%	83%	84%	0.285	0.917
- injection method	17%	25%	13%	19%	18%	16%	0.194	0.830
- electrolarynx	5%	10%	2%	7%	5%	5%	0.242	NS
- other (e.g., cannot speak)	2%	8%	4%	2%	2%	0%	0.089	NS
Median [range] health-related quality of life[8] (EQ-5D utility score)	0.89 [0.07-1.00]	1.00 [0.24-1.00]	0.83 [0.07-1.00]	0.86 [0.65-1.00]	0.90 [0.19-1.00]	1.00 [0.32-1.00]	0.297	0.004

Abbreviations: PAM, patient activation measure; SD, standard deviation; EQ-5D, EuroQol-5 dimensions; NS, non-significant

[1] Age is missing in 2 patients.

[2] Sex is missing in 4 patients.

[3] Having children and living situation are missing in 7 patients.

[4] Multiple answers possible.

[5] Education level, smoking status and drinking status are missing in 3 patients.

[6] Time since total laryngectomy is missing in 14 patients.

[7] Information on other received treatments and current speech method is missing in 6 patients.

[8] Health-related quality of life is missing in 9 patients.

Table 2: Description of direct medical healthcare utilization, direct non-medical service utilization and productivity losses among patients after total laryngectomy with different levels of patient activation

	All patients n = 248		**PAM 1** n = 56	
	% patients using service	Mean (SD) number of contacts/ hours or days[1]	% patients using service	Mean (SD) number of contacts/ hours or days[1]
Direct medical				
General practitioner (phone)	38%	1.9 (1.3)	41%	1.7 (0.6)
General practitioner (home visit)	13%	1.9 (1.1)	14%	1.9 (0.8)
General practitioner (practice)	54%	1.8 (1.3)	64%	2.0 (1.4)
Company doctor	5%	1.3 (0.5)	2%	1.0 (-)
Social worker	3%	1.6 (0.9)	5%	1.3 (0.5)
Physiotherapist	25%	11.9 (8.9)	29%	13.6 (10.2)
Ergotherapist	1%	2.5 (2.1)	0%	-
Dietitian	14%	1.6 (0.9)	14%	1.9 (1.5)
Speech pathologist	18%	4.3 (5.5)	21%	6.8 (8.8)
Oral hygienist	17%	1.3 (0.9)	16%	1.7 (1.3)
Psychologic or psychiatric help (private practice)	2%	2.8 (2.2)	2%	6.0 (-)
Psychologic or psychiatric help (mental healthcare center)	1%	2.0 (1.0)	2%	1.0 (-)
Specialist (general practice)	42%	1.9 (1.4)	41%	2.0 (1.1)
Specialist (academic center)	55%	2.2 (2.2)	63%	1.9 (1.9)
Spiritual counsellor	1%	1.3 (0.6)	2%	1.0 (-)
Alternative medicine	1%	2.0 (1.4)	0%	-
Emergency care visit	12%	2.0 (2.6)	16%	1.4 (0.5)
Personal care by a nurse	6%	78.5 (46.7)	11%	71.3 (54.4)
Nursing care by a nurse	6%	54.8 (42.8)	9%	87.1 (35.1)
Admission medical center (day treatment)	26%	4.6 (7.7)	32%	3.1 (3.3)
Admission medical center (multiple days)	11%	6.7 (6.0)	14%	4.3 (2.6)
Medication	84%	NA	84%	NA
Direct non-medical				
Home care	8%	37.6 (16.3)	16%	37.2 (11.7)
Support groups	2%	24.9 (36.6)	4%	2.0 (1.4)
Informal care	15%	83.7 (151.8)	25%	59.7 (42.2)
Productivity losses (presenteeism and absenteeism)	2%	NA	2%	NA

Abbreviations: PAM, patient activation measure; SD, standard deviation.

[1] Of all patients who used the service or had productivity losses. Most direct medical costs and support groups were measured per contact. Personal care, nursing care, home care, informal care and productivity losses were measured per hour. Admission to a medical center was measured in days.

PAM 2 n = 43		**PAM 3** n = 104		**PAM 4** n = 45	
% patients using service	Mean (SD) number of contacts/ hours or days[1]	% patients using service	Mean (SD) number of contacts/ hours or days[1]	% patients using service	Mean (SD) number of contacts/ hours or days[1]
44%	1.9 (2.1)	38%	2.0 (1.3)	31%	2.1 (1.2)
19%	1.3 (0.5)	11%	2.6 (1.5)	13%	1.7 (0.8)
44%	1.9 (1.3)	59%	1.7 (1.1)	38%	2.0 (1.5)
2%	2.0 (-)	8%	1.3 (0.5)	7%	1.3 (0.6)
2%	3.0 (-)	3%	1.7 (1.2)	0%	-
35%	12.3 (9.1)	22%	11.7 (8.8)	18%	8.8 (5.7)
0%	-	0%	-	4%	2.5 (2.1)
12%	2.0 (0.7)	16%	1.5 (0.6)	11%	1.4 (0.9)
16%	4.0 (3.9)	17%	3.7 (3.9)	16%	2.0 (1.8)
21%	1.1 (0.3)	19%	1.3 (0.9)	9%	1.0 (0.0)
2%	1.0 (-)	3%	3.0 (2.0)	2%	1.0 (-)
0%	-	1%	3.0 (-)	2%	2.0 (-)
42%	1.9 (1.2)	48%	1.9 (1.6)	31%	1.4 (0.6)
47%	2.5 (3.2)	61%	2.2 (1.8)	40%	2.3 (2.8)
0%	-	1%	2.0 (-)	2%	1.0 (-)
0%	-	2%	2.0 (1.4)	0%	-
9%	1.5 (0.6)	13%	1.5 (1.1)	7%	6.0 (7.8)
7%	83.3 (64.3)	5%	71.2 (26.1)	2%	143 (-)
7%	15.3 (7.6)	5%	43.0 (31.4)	4%	62.5 (77.1)
28%	5.3 (11.0)	22%	4.5 (6.7)	24%	6.4 (10.6)
7%	11.7 (12.7)	13%	8.3 (5.3)	7%	1.3 (0.6)
88%	NA	84%	NA	82%	NA
9%	34.3 (16.0)	4%	47.3 (24.8)	9%	32.1 (18.6)
5%	12.3 (16.6)	0%	-	4%	60.5 (50.2)
19%	62.6 (54.7)	12%	54.1 (35.1)	9%	287.5 (434.6)
2%	NA	3%	NA	0%	NA

Table 3: Association between patient activation level and direct medical costs and total costs from a societal perspective (n = 248)

	Total costs from a healthcare perspective	**Difference is costs from a healthcare perspective** € [95% CI]		
	Mean (SD)	Unadjusted	Adjusted[1]	Adjusted including health-related quality of life
PAM level 1	€2,282 (3,798)	Reference	Reference	Reference
PAM level 2	€1,908 (3,314)	€-375 [€-1,748 to €1,026]	€-204 [€-1,496 to €1,114]	€264 [€-875 to €1,670]
PAM level 3	€1,781 (2,978)	€-501 [€-1,779 to €537]	€-624 [€-1,731 to €324]	€-19 [€-932 to €881]
PAM level 4	€1,346 (2,597)	€-936 [€-2,282 to €288]	€-770 [€-1,954 to €397]	€-263 [€-1,278 to €823]

Abbreviations: PAM, patient activation measure; SD, standard deviation; CI, confidence interval
[1] Adjusted for time since TL, sex, and education level.

<u>Patient activation in relation to total costs from a healthcare and societal perspective</u>

Total costs from a healthcare perspective in the previous 3 months ranged from €1,346 (SD = 2,597) in the group with the highest PAM level to €2,282 (SD = 3,798) in the group with the lowest PAM level (Table 3). Total costs from a societal perspective ranged from €1,909 (SD = 3,855) in the group with the highest PAM level to €2,627 (SD = 4,147) in the group with the lowest PAM level. In the unadjusted analysis, patients in the group with the highest PAM level had a 93% probability that total costs from a healthcare perspective were lower than costs in the group with the lowest PAM level (Table 3 and 4). This probability was 82% for total costs from a societal perspective. For the other two groups, probabilities of respectively 80% and 87% (PAM 3 vs. PAM 1) and 70% and 73% (PAM 2 vs. PAM 1) were found. After adjusting for potential confounders (time since TL, sex, and education level), these probabilities changed to respectively 91% and 79% (PAM 4 vs. PAM 1), 88% and 92% (PAM 3 vs. PAM 1), and 62% and 63% (PAM 2 vs. PAM 1). After adjusting for potential confounders and HRQOL, the probabilities were reduced to respectively 71% and 45% (PAM 4 vs. PAM 1), 52% and 48% (PAM 3 vs. PAM 1), and 35% and 31% (PAM 2 vs. PAM 1). No statistically significant differences were found.

Total costs from a societal perspective	Difference in costs from a societal perspective € [95% CI]		
Mean (SD)	Unadjusted	Adjusted[1]	Adjusted including health-related quality of life
€2,627 (4,147)	Reference	Reference	Reference
€2,159 (3,431)	€-468 [€-1,970 to €998]	€-251 [€-1,659 to €1,156]	€344 [€-891 to €1,782]
€1,933 (3,104)	€-694 [€-2,045 to €427]	€-801 [€-2,039 to €240]	€35 [€-999 to €1,059]
€1,909 (3,855)	€-719 [€-2,282 to €921]	€-541 [€-1,898 to €955]	€146 [€-1,060 to €1,583]

Table 4: Probability[1] that costs are lower compared to the group with the lowest PAM score

		Total costs from a healthcare perspective	Total costs from a societal perspective
Unadjusted	PAM 2 vs PAM 1	70%	73%
	PAM 3 vs PAM 1	80%	87%
	PAM 4 vs PAM 1	93%	82%
Adjusted[2]	PAM 2 vs PAM 1	62%	63%
	PAM 3 vs PAM 1	88%	92%
	PAM 4 vs PAM 1	91%	79%
Adjusted including EQ-5D	PAM 2 vs PAM 1	35%	31%
	PAM 3 vs PAM 1	52%	48%
	PAM 4 vs PAM 1	71%	45%

Abbreviations: PAM, patient activation measure

[1] The probability that total costs were lower in a certain PAM group compared to the first PAM group was investigated by replicating the regression analyses using bias-corrected accelerated bootstrapping with 5,000 replications. The percentage described in this Table presents the percentage of the 5,000 bootstrap replications that showed lower total costs.

[2] Adjusted for time since TL, sex, and education level.

DISCUSSION

This study aimed to investigate the associations between patient activation and total costs from a healthcare and societal perspective in cancer patients. To answer this research question, TL cancer patients were studied. We found that TL patients with a better patient activation reported less costs from a healthcare and societal perspective compared to patients with lower patient activation (probability of 70% to 93%). This finding remained present when adjusting for sociodemographic and clinical characteristics (probability of 62% to 92%).

Our findings on total costs from a healthcare perspective are in line with previous cross-sectional analyses of Hibbard et al.[27] and Greene et al.[19] conducted in primary care patients. Hibbard et al.[27] reported that the predicted total healthcare costs were 8% higher in the group with the lowest patient activation compared to the group with the highest patient activation, even when adjusted for several sociodemographic characteristics and a risk score for future costs. In the study of Greene et al.[19] predicted total healthcare costs were 8% higher in the lowest patient activation group and 12% higher in the second lowest group, compared to the highest patient activation group.

Besides healthcare costs, our study also included other important costs from a societal point of view, such as informal care costs and productivity losses. It was previously estimated that about 60% of the economic burden of cancer in the European Union is caused by productivity losses (including mortality and morbidity) and informal care costs[43], emphasizing the importance of conducting analyses from a societal perspective. In our study, we found that 15% of all TL patients received informal care, 8% received home care, 2% made use of support groups, and 2% (or 18% of all employed TL patients) had productivity losses. Of these cost categories, especially informal care usage seemed to decrease with better patient activation (PAM 1 = 25%, PAM 2 = 19%, PAM 3 = 12%, and PAM 4 = 9%). However, no clear influence of the inclusion of these costs on the association between patient activation and total costs was found; the adjusted probability to be less costly was 62% - 91% from a healthcare perspective compared to 63% - 92% from a societal perspective. Further research should look at the association between patient activation and different cost categories (e.g., healthcare costs, informal care costs and productivity losses) in more detail.

As an additional analysis, we investigated the potential confounding role of HRQOL on the association between patient activation and total costs from a healthcare and societal perspective. We found that after adjustment for HRQOL no association seemed to be present anymore (probability to be less costly was 31% - 71%). Due to the cross-sectional design of the study, no conclusions can be drawn regarding causality of the association between HRQOL, patient activation and total costs. However, based on the conceptual framework of Howell et al.[7], it can be hypothesized that self-management interventions may improve patient activation, which in turn may improve patient health outcomes, such as HRQOL, and costs. So far, however, only a few randomized controlled trials have investigated the effectiveness of self-management interventions on patient activation, including one study in cancer patients[44], which showed inconclusive results[44-47]. Also, none of these studies investigated cost-effectiveness or cost-utility. One previous (non-randomized) prospective study in primary care patients, nevertheless, reported that primary care patients with a positive change in patient activation (e.g., from level 3 to 4) had lower total healthcare costs compared to patients who remained at PAM level 3[19]. Further research should investigate whether patient activation can be improved in cancer patients, and whether this affects HRQOL and total costs. A currently ongoing Dutch randomized controlled trial on the (cost-)effectiveness of a guided self-help program in TL cancer patients may provide further information regarding this association[10].

This study provides novel insights into the associations between patient activation and total costs, as no such study has previously been performed in cancer patients. Also, this is the first study that investigated the association between patient activation in relation to costs from a societal perspective. Some potential limitations, however, need also to be kept in mind. First, information on healthcare utilization, service utilization and productivity losses were obtained using self-report, which may have resulted in recall bias. Besides, missing data was not entirely missing at random; patients in the final study sample were significantly younger and had a significantly shorter time period since TL, which might influence representativeness of findings for the entire TL population. Also, the relative low response of 32% and the selection of patients via the Dutch Patients' Association for Laryngectomees may have influenced the representativeness of findings. In conclusion, patient activation is likely to be associated with total costs from both a healthcare and societal perspective in TL patients. TL patients with better patient activation reported less costs compared to patients with lower patient activation, even after adjusting for sociodemographic and clinical characteristics. However, after adjusting for HRQOL, no such association seemed to be present anymore. More research on the causality of the association between patient activation, HRQOL and total costs from both a healthcare and a societal perspective in cancer patients is warranted.

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A review on cost-effectiveness and cost-utility of psychosocial care in cancer patients

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ABSTRACT

Several psychosocial care interventions have been found effective in improving psychosocial outcomes in cancer patients. Nowadays there is increasingly being asked for information on the value for money of this type of intervention. This review therefore evaluates current evidence from studies investigating cost-effectiveness or cost-utility of psychosocial care in cancer patients. A systematic search was conducted in PubMed and Web of Science yielding 539 unique records, of which 11 studies were included. Studies were mainly performed in breast cancer populations or mixed cancer populations. Studied interventions included collaborative care (4 studies), group interventions (4 studies), individual psychological support (2 studies) and individual psycho-education (1 study). Seven studies assessed the cost-utility of psychosocial care (based on quality-adjusted life years (QALYs)), while three studies investigated its cost-effectiveness (based on Profile of Mood States (mood), Revised Impact of Events Scale (distress), 12-item Health Survey (mental health) or Fear of Progression questionnaire (fear of cancer progression)). One study did both. Costs included were intervention costs (3 studies), intervention costs and direct medical costs (5 studies) or intervention costs, direct medical costs and direct non-medical costs (3 studies). In general, results indicated that psychosocial care is likely to be cost-effective at different, potentially acceptable, willingness-to-pay thresholds. Further research should be performed to provide more clear information as to which psychosocial care interventions are most cost-effective and for whom. In addition, more research should be performed encompassing potential important cost drivers from a societal perspective, such as productivity losses or informal care costs, in the analyses.

INTRODUCTION

Many cancer patients experience psychosocial problems during or after treatment, including depression, anxiety, fear of cancer progression or problems with coping[1-3]. The prevalence of depression in cancer patients has been estimated at 8% to 24%[1] and the prevalence of anxiety at 18%[2]. Unmet care needs regarding these psychosocial problems have been reported in up to 89% of cancer patients[4,5].

Several psychosocial care interventions have been developed in recent years aiming to target these problems and care needs in cancer patients, ranging from relatively low-intensive interventions (e.g., self-help or group interventions) to high-intensive interventions (e.g., individual cognitive behavioral therapy)[6]. Also stepped care (i.e., an approach in which effective, yet least resource-intensive treatment is delivered first, followed by, when necessary, more resource-intensive treatments) and collaborative care interventions (i.e., a care model in which different healthcare disciplines closely collaborate in order to provide systematic treatment and follow-up) have been developed[7-9]. In general, psychosocial care interventions have been found effective in improving psychosocial outcomes, such as distress and quality of life, in cancer patients[6,10].

Carlson and Bultz[11,12] hypothesized that providing psychosocial care to cancer patients may not only be effective in improving outcomes, but may also lead to cost savings in the long-term. Cancer patients benefitting from psychosocial care are hypothesized to make less use of other healthcare services (i.e., visits to the general practitioner or oncologist) called cost offset, due to, for example, an increased ability to adhere to demanding treatments or lifestyle recommendations resulting in an improved overall health. In addition, productivity losses may be reduced due to an increased ability to work. Previous studies have indeed found such an association between better psychosocial outcomes and less healthcare utilization or costs[13-16] and higher rates of return to work[17,18]. However, other studies did not found such an association[19,20].

Whether providing psychosocial care to cancer patients indeed is economically attractive can be assessed by performing economic evaluations, such as cost-effectiveness or cost-utility analyses[21,22]. The current health care system increasingly asks for this kind of evaluations[23,24], since the economic burden of cancer care is high[25] and choices have to be made regarding optimal resource allocation.

In cost-effectiveness and cost-utility analyses, the difference in total costs between different interventions or between a new intervention and care-as-usual are weighted against the difference in effectiveness, such as improvement in psychological distress or fear of cancer progression (called cost-effectiveness analyses), or differences in quality-adjusted life years (QALYs) (called cost-utility analyses)[21,22]. This results in a ratio of the incremental costs for an incremental unit of effect, called incremental cost-effectiveness ratio (ICER). Cost-effectiveness and cost-utility analyses can be performed from different perspectives (e.g., a healthcare perspective or a societal perspective), which determines the cost categories taken into account in the analyses. In a healthcare perspective, costs of the healthcare system are taken into account, while in a societal perspective, a broader spectrum of costs are measured including, for example, productivity losses and informal care costs.

Two systematic reviews[26,27] on the economic evaluation of psychosocial interventions have been published so far, one of which included studies up to 2013[27]. This last review revealed that psychosocial care interventions have the potential to be cost-effective[27]. However, also studies combining exercise interventions and psychosocial support, or on the most optimal follow-up strategy were included[27], which hampers firm conclusions on the value for money of psychosocial care among cancer patients. Moreover, because new developments in psychosocial care are ongoing and studies on the cost-effectiveness and cost-utility of psychosocial care are increasingly being published in the past two years, a new search updating current evidence is warranted. The aim of this review was, therefore, to assess current evidence on the cost-effectiveness and cost-utility of psychosocial care interventions in cancer patients.

METHODS

Literature search

A literature search was conducted in two electronic bibliographic databases, namely PubMed (dates of coverage 1950 - present) and Web of Science (1900 - present) from inception to January 2016. Search terms included different terms for economic evaluations (e.g., cost-effectiveness or cost-utility analyses), cancer (e.g., neoplasm), psychosocial care (e.g., psychological care or supportive care) and psychosocial outcomes (e.g., depression or anxiety). Table 1 provides a detailed overview on the combinations of search terms used. In addition to this literature search, reference lists from eligible articles were manually searched and authors were asked for additional studies.

Table 1. Search strategy

PubMed (MedLine)	**Web of Science**
(Neoplasms[MeSH] OR neoplasm[ti] OR Cancer[ti] OR "chronic cancer patients"[ti] OR "cancer survivors"[ti]) AND (((cost* OR economic[ti]) AND (analysis OR analyses OR effectiveness OR utility OR evaluation OR benefit)) OR (cost-analysis OR cost-analyses OR cost-effectiveness OR cost-utility OR cost-benefit OR cost-evaluation OR cost-effectiv*)) AND ("supportive care"[ti] OR "psychosocial care"[ti] OR "psychological care"[ti] OR "after care"[ti] OR anxiety[ti] OR depression[ti] OR social[ti] OR psychosocial[ti] OR cognitive[ti] OR stress[ti] OR mood[ti] OR pain[ti])	TITLE: (neoplasm OR Cancer OR chronic cancer patients OR cancer survivors) AND TITLE: (supportive care OR psychosocial care OR psychological care OR after care OR anxiety OR depression OR social OR psychosocial OR cognitive OR stress OR mood OR pain) AND TITLE: (cost* OR economic) AND TITLE: (analysis OR analyses OR effectiveness OR utility OR evaluation OR benefit OR cost-analysis OR cost-analyses OR cost-effectiveness OR cost-utility OR cost-benefit OR cost-evaluation OR cost-effectiv*)

Abbreviation: MeSH, medical subject heading; ti, title

Study inclusion and exclusion criteria

Research articles were included if they: (a) presented results on the cost-effectiveness or cost-utility of psychosocial care interventions; (b) used QALYs or a psychosocial outcome measure as outcome; (c) included adult cancer patients only; and (d) full-text was available in English or Dutch. Research articles were excluded if they assessed the cost-effectiveness or cost-utility of an exercise intervention; were not yet published as full-text; or were reviews (although reference lists were checked). No limits were set for year of publication.

Selection procedure and data extraction

Screening of the databases for relevant articles was performed by two of the authors (FJ and VvZ). First, title and abstract of all identified records were screened for potential relevance. Consequently, full-text of potentially relevant articles were assessed for eligibility based on the inclusion and exclusion criteria. Differences in study selection between the two authors were solved by discussion. When needed a third person (IVdL) was consulted.

All studies found eligible for inclusion in this review were thoroughly read and relevant data was extracted. Data extracted included general information (i.e., name of the author, year of publication, country in which the study was conducted), study design, study population (i.e., cancer diagnosis, important eligibility criteria and number of patients), intervention and control treatment (i.e., type of treatment and treatment duration), follow-up period, outcome measure(s), study perspective (e.g., healthcare perspective or societal perspective), included cost categories (i.e., intervention costs, direct medical, direct non-medical, indirect medical or indirect non-medical costs), and study results. All costs identified were converted to dollar-prices using the exchange rate of the index year reported in the article. In case the index year was not reported, the assumed index year was used.

Main findings of the included studies regarding the cost-effectiveness or cost-utility of psychosocial care interventions were summarized in a permutation matrix with nine possible cost-effectiveness/cost-utility outcomes[28]. All studies were allocated to one of the nine possibilities based on main evidence for incremental costs (lower costs, equal costs or higher costs) and incremental effects (lower effects, equal effects or higher effects).

Quality assessment

The quality of the included studies was assessed using the 10-item checklist of Drummond et al.[21,22]. One author (FJ) conducted the quality assessment. When an article referred to previous publications (e.g., design paper or study on effectiveness) for additional information, this study was retrieved as well for quality assessment. A total score per study was calculated by counting the numbers of items scored positively (+ 1) or partly positive (+ 0.5), resulting in a score ranging from 0 - 10. In addition, the percentage of studies that met a particular criterion was calculated.

RESULTS

Identification and selection of the literature

In total 539 records were screened for eligibility based on title and abstract, of which 25 were selected for full-text review (Figure 1). In addition, two articles were added based on reference checking or authors knowledge. After full-text review, 11 studies were included.

Table 2 provides an overview of the selected studies. Studies were published between 2006 and 2015, of which seven recently (i.e., 2014 or 2015)[29-35]. Most studies were conducted in the United Kingdom[34-36] and the United States[31,32,37] (both three studies), followed by Canada[38], Germany[39], Sweden[29], the Netherlands[33] and Australia[30] (all one study). Nine studies were cost-effectiveness or cost-utility studies conducted alongside a randomized controlled trial (RCT) on effectiveness of psychosocial care[29,32,35,39], while two studies used a decision analytic model, in which the cost-utility was estimated based on multiple sources of data[33,34].

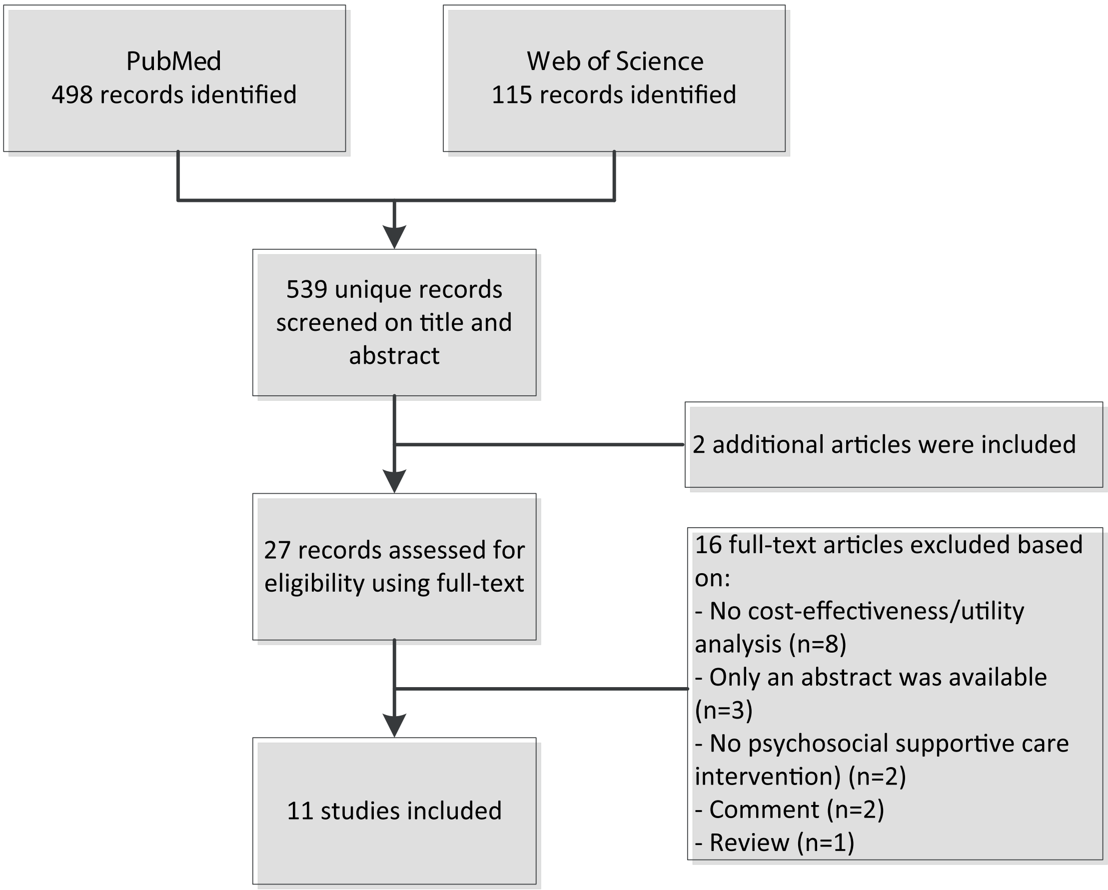


Figure 1: Flow diagram

Study populations and psychosocial care interventions

Of all nine studies that were performed alongside an RCT, four studies were conducted in breast cancer patients[29,32,37,38], and five studies were conducted in a mixed cancer population[30,31,35,36,39], which also consisted mainly of breast cancer patients. The two model studies used a hypothetical cohort of 1,000 breast cancer patients[33] or one hypothetical female cancer patient[34]. In six studies all patients were included regardless of baseline scores on psychosocial outcomes[29,32,34,37,38], while in five studies selection criteria for psychosocial outcomes were set[30,31,35,36,39]. In Strong et al. and Duarte et al.[35,36] patients were included when they had a diagnosis of major depressive disorder (based on screening followed by a structured clinical interview). In Choi Yoo et al.[31] patients screened with clinical significant depression or pain were included. Sabariego et al.[39] included patients screened with increased fear of cancer progression. Finally, Chatterton et al.[30] included patients with elevated levels of distress measured using the distress thermometer.

Table 2. Characteristics of the included studies

	Design	Study population	Treatment
Lemieux (2006)[38] Canada	RCT	Women with metastatic breast cancer (n = 125).	1) Weekly supportive-expressive psychosocial group therapy plus standard care. Patients were asked to attend group sessions for at least one year. Control: Care-as-usual, which comprised of educational materials and psychosocial treatment when deemed necessary.
Mandelblatt (2008)[37] United States	RCT	Women treated with surgery for invasive breast cancer four to six weeks ago (n = 389).	1) An educational video addressing re-entry challenges in physical health, emotional well-being, interpersonal relations and life perspectives plus the control-booklet. 2) Individual psycho-educational counselling (one face-to-face and one telephone session) plus the educational video and control-booklet. Control: A booklet-control condition.
Strong (2008)[36] United Kingdom	RCT	Mixed cancer patients with a prognosis > 6 months and screened for major depressive disorder (HADS ≥ 15 and major depressive disorder assessed in a Structured Clinical Interview) (n = 200).	1) Nurse-delivered collaborative care intervention (DCPC) comprising of education about depression and its treatment (including antidepressant medication), problem-solving therapy, and communication with each patient's oncologist and general practitioner. A maximum of 10 individual sessions of 45 minutes were provided over 3 months followed by additional sessions when necessary. Control: Care-as-usual. Each patient's general practitioner was informed about the major depression diagnosis and was provided with advice on antidepressant drug, if requested.
Sabariego (2010)[39] Germany	RCT	Mixed cancer patients with increased fear of cancer progression and treated with a 3-week inpatient rehabilitation program (n = 174).	1) Four sessions of 90 minutes of cognitive behavioral group therapy (CBT) in addition to the standard rehabilitation program. Control: Four sessions of 90 minutes of supportive-experiential group therapy (SET) in addition to the standard rehabilitation program.

Follow-up	Outcome(s)[1]	Perspective	Results
2-year (mean)	Mood (POMS)	Healthcare perspective, including intervention costs and direct medical costs.	Intervention costs were on average $1,394 per patient. Psychosocial group therapy was more costly ($+3,526, NS) and more effective (POMS effect size of 0.32, sig) than care-as-usual. ICER was $5,550 for an effect size of 0.5 in mood.
6-month	Distress (IES-R)	Societal perspective, including intervention costs (which includes patient opportunity costs) and direct medical costs. Only intervention costs were included in the CEA analyses.	Intervention costs were $11 (control), $26 (video) and $134 (video plus counseling) per participant. Individual counselling was most costly, while equally effective as the educational video condition and therefore dominated. The educational video condition was more costly ($+15) and more effective (IES-R incremental effect -0.002, NS) than a booklet-control condition. ICER was $7,275 per unit improvement in IES-R.
6-month	QALYs (EQ-5D)	Healthcare perspective, including intervention costs and direct medical costs.	Intervention costs were on average $487 (£262) per patient. DCPC was more costly ($+623 (£335), sig) and more effective (incremental QALYs +0.063, sig) than care-as-usual. ICER was $9,818 (£5,278) per QALY gained.
1-year	Fear of progression (FoP-Q); Mental health (SF-12 mental).	Societal perspective, including intervention costs, direct medical costs, direct non-medical and indirect non-medical costs. Indirect non-medical costs were not included in the CEA analyses.	Incremental intervention costs were on average $57 (€47) per patient (or $345 (€282) per group). CBT was less costly ($-2,889 (€-2,362) or $-3,322 (€-2,716) depending on analyses, both NS), while almost equal in effectiveness (FoP-Q incremental effect +0.03, NS and SF-12 incremental effect +0.16, both NS) compared to SET. ICER was $-96,309 (€-78,742) per unit improvement in FoP-Q. ICER was $-20,763 (€-16,976) per unit improvement in SF-12.

Table 2. Continued

	Design	Study population	Treatment
Arving (2014)[29] Sweden	RCT	Breast cancer patients about to start adjuvant treatment (n = 168).	1) Individual psychological support from a nurse trained in psychological techniques (INS). 2) individual psychological support from a psychologist (IPS). No maximum number of sessions were set. Control: Care-as-usual including referral to a psychiatrist or social worker when needed.
Choi Yoo (2014)[31] United States	RCT	Mixed cancer patients with clinical significant depression (PHQ-9 ≥ 10 and endorsement of depressed mood and/or anhedonia) or pain (definitely or possibly cancer-related and BPI worst pain score ≥ 6) (n = 405).	1) Centralized telecare management for pain and depression coupled with automated home-based symptom monitoring. Control: Care-as-usual, which comprised of informing patients on their depressive and pain symptoms and providing screening results to the oncologist.
Walker (2014)[34] United Kingdom	Decision analytic model	Hypothetical patient diagnosed with cancer (female 63-years) attending specialist cancer outpatients services (base-case).	1) Systematic identification for major depressive disorder (HADS ≥ 15 and major depressive disorder assessed in a Structured Clinical Interview), followed by a nurse-delivered collaborative care intervention (DCPC). DCPC comprised of education about depression and its treatment (including antidepressant medication), problem-solving therapy, and communication with each patient's oncologist and general practitioner, in addition to care-as-usual. A maximum of 10 individual sessions of 45 minutes were provided over 4 months, followed by additional sessions when necessary. Control: Care-as-usual, consisting of identification and treatment of major depression by patient's general practitioner.
Mewes (2015)[33] The Netherlands	Decision analytic model	Hypothetical cohort of 1,000 breast cancer patients with matched clinical characteristics as in the RCT.	1) A 6-week cognitive behavioral group therapy (CBT) program of 90 minutes each 2) A 12-week home-based exercise program, individually tailored during an intake with a physiotherapist[2]. Control: A care-as-usual, waiting-list control group.

Follow-up	Outcome(s)[1]	Perspective	Results
2-year	QALYs (EORTC QLQ-C30 mapped into EQ-5D)	Healthcare perspective, including intervention costs and direct medical costs.	Intervention costs were per patient on average $690 (€560) for the INS group and $805 (€653) for the IPS group. INS as well as IPS were less costly ($-8,786 (€-7,130) and $-6,630 (€-5,381), both sig) and more effective (incremental QALYs +0.09, NS and +0.16, both NS) compared to care-as-usual. INS and IPS were dominant compared to care-as-usual.
1-year	QALYs (disease free days; SF-12 converted to SF-6D; modified EQ-5D and a VAS scale)	Healthcare perspective, including intervention costs.	Intervention costs were on average $953 (all patients) or $1189 (depressed patients only) per patient. Centralized telecare management was more costly ($+953) and more effective (incremental QALYs +0.088, sig (EQ-5D) or +0.013 (SF-12)) than care-as-usual. ICER was $10,826 or $73,287 per QALY gained. In depressed patients (n=309) the ICER ranged from $19,72 to $26,95 per disease-free day gained or from $18,018 to $49,549 per QALY gained.
5-year	QALYs	Healthcare perspective, including intervention costs.	Intervention costs were per patient $676 (£464) for the intervention group and $532 (£365) for the control group. DCPC was more costly ($+144 (£99)) and more effective (incremental QALYs +0.009) than care-as-usual. ICER was $17,132 (£11,765) per QALY gained.
5-year	QALYs (SF-36 converted to EQ-5D).	Healthcare perspective, including intervention costs and direct medical costs.	Intervention costs were $247 (€190) per patient. CBT was more costly ($239 (€+184)) and more effective (incremental QALYs +0.008) than the weight-list control group. ICER was $29,266 (€22,502) per QALY gained.

Table 2. continued

	Design	Study population	Treatment
Lengacher (2015)[32] United States	RCT	Breast cancer patients who completed treatment within 2 years prior to study enrollment (n = 104).	1) A 6-week mindfulness stress reduction program, which consisted of 2-hour group sessions once a week. Control: A care-as-usual, waiting-list control group. Care-as-usual comprised of standard post-treatment clinic visits.
Chatterton (2015)[30] Australia	RCT	Mixed cancer patients with elevated levels of distress (score ≥ 4 on the distress thermometer) (n = 336).	1) Psychologist-led, individual cognitive behavioral intervention (PI) (max. 5 sessions). Control: Nurse-led, single-session self-management intervention (NI).
Duarte (2015)[35] United Kingdom	RCT	Mixed cancer patients with a prognosis > 12 months and screened for major depressive disorder (HADS ≥ 15 and major depressive disorder assessed in a Structured Clinical Interview) (n = 500).	1) Nurse-delivered collaborative care intervention (DCPC) comprising of education and its treatment (including antidepressant medication), problem-solving therapy, and communication with each patient's oncologist and general practitioner, in addition to care-as-usual. A maximum of 10 individual sessions of 45 minutes were provided over a 4 month-period, followed by some additional sessions when necessary. Control: Care-as-usual, patient's general practitioner and oncologist were informed about the major depression diagnosis and ask to treat their patients as they normally would.

Abbreviations: RCT, randomized controlled trial; POMS, Profile of Mood States; NS, not significant; sig, significant; ICER, incremental cost-effectiveness ratio; IES-R, Revised Impact of Events Scale; CEA, cost-effectiveness analyses; HADS, Hospital Anxiety and Depression Scale; DCPC, Depression Care for People with Cancer; QALYs, quality-adjusted life years; EQ-5D, EuroQol 5-dimensions; CBT, cognitive behavioral therapy; SET, supportive-experiental therapy; FoP-Q, Fear of Progression Questionnaire; SF-12, 12-item Health Survey; INS, individual psychosocial support from a trained nurse; IPS, individual psychosocial support from a psychologist; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions; PHQ, Patient Health Questionnaire; BPI, Brief Pain Inventory; SF-6D, Short-Form 6-dimensions;

Follow-up	Outcome(s)[1]	Perspective	Results
12-week	QALYs (SF-12)	Societal perspective, including intervention costs and direct non-medical costs (i.e., patient opportunity costs).	Intervention costs were $666 per patients. The mindfulness program was more costly ($+666 (intervention costs) and $+592 (patient opportunity costs)) and more effective (incremental QALYs +0.03, sig) than care-as-usual. ICER was $22,200/QALY for the direct costs and $19,733/QALY for the patient opportunity costs.
12-month	QALYs (AQOL-8D)	Healthcare perspective, including intervention costs, direct medical costs and direct non-medical costs (e.g., costs of support services).	Intervention costs were on average $60 (NI) and $181 or $202 (PI) per patient. In patients with low distress (BSI < 63) the psychologist-led intervention was more costly (+$335, NS) and more effective (incremental QALYs +0.016, NS) than the nurse-led intervention. In patients with high levels of distress (BSI > 63) the psychologist-led intervention was less costly (-$332, NS) and more effective (incremental QALYs +0.037, NS) than the nurse led intervention.
48-week	QALYs (EQ-5D)	Healthcare perspective, including intervention costs and direct medical costs.	Intervention costs were on average $935 (£642) per patient. Including only depression-related healthcare costs, DCPC was more costly ($+919 (£631), sig) and more effective (incremental QALYs +0.066, sig) than care-as-usual. ICER was $13,905 (£9,549) per QALY gained.

VAS, Visual Analog Scale; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; CBT, cognitive behavioral therapy; PI, psychologist-led, individual cognitive behavioral intervention; NI, nurse-led, single-session self-management intervention; AQOL-8D, quality of life – eight dimension-; BSI, Brief Symptom Index.

[1] Only those outcomes (i.e., psychosocial outcomes or quality adjusted life years) that were used in this systematic review are presented.

[2] Only results of the cognitive behavioral therapy group are presented (i.e., results regarding the exercise program are not presented).

Studies were heterogeneous regarding the psychosocial care intervention investigated. Four studies investigated a collaborative care intervention[31,34-36], of which three studies investigated the intervention called "Depression Care for People with Cancer", consisting of a nurse-delivered intervention comprising of depression education and its treatment, problem-solving therapy, and communication with each patient's oncologist and general practitioner[34-36]. The other study investigated a centralized telecare management intervention for pain and depression coupled with automated home-based symptom monitoring[31]. Four studies investigated a group intervention: cognitive behavioral group therapy[33,39], supportive-expressive psychosocial group therapy[38], and a mindfulness program in groups[32]. Mandelblatt et al.[37] investigated a psycho-education intervention (an educational video addressing re-entry challenges) or a psycho-education intervention combined with individual psycho-educational counselling. Finally, in Arving et al. and Chatterton et al.[29,30] the cost-utility of individual psychological support incorporating cognitive behavioral therapy was studied.

Most studies compared the intervention group(s) with care-as-usual[29,31-36,38], which comprised of informing the patient's general practitioner on major depressive disorder diagnosis[35,36], identification and treatment of major depressive disorder diagnosis by patient's general practitioner[34], referral to a psychiatrist or social worker when needed[29], provision of educational materials and psychosocial treatment when deemed necessary[38], informing patients on their depressive and pain symptoms and providing screening results to the oncologist[31], or standard post-treatment clinic visits[32]. In one study it was not entirely clear what care-as-usual encompassed[33]. Three studies compared the intervention group(s) with a booklet-control condition[37], supportive-experiential group therapy[39] or a nurse-led self-management intervention[30].

Methods of the cost-effectiveness and cost-utility studies

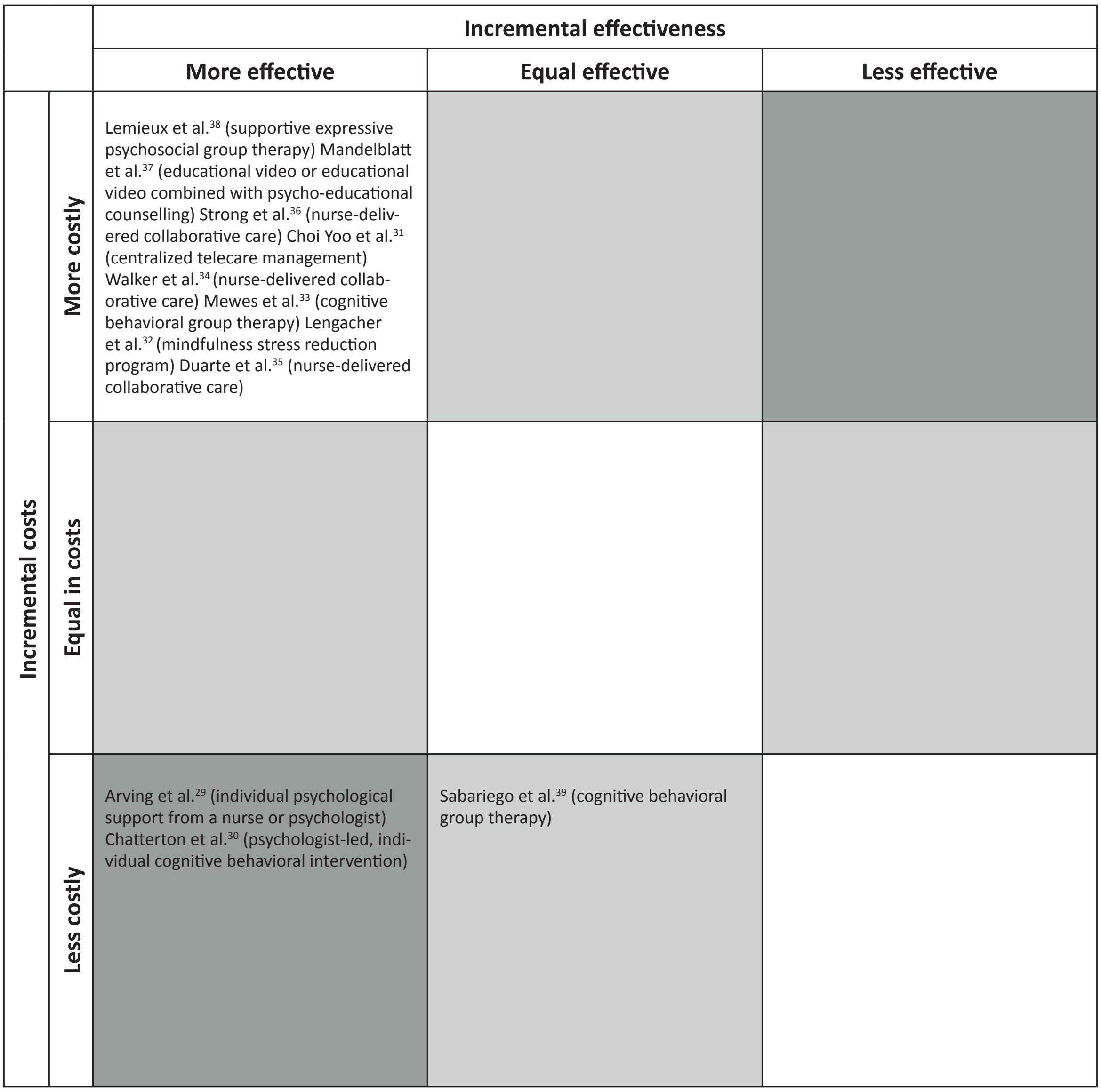
Seven studies performed cost-utility analyses[29,30,32-36] using the EuroQol 5-dimensions (EQ-5D)[35,36], the 12-item Health Survey (SF-12)[32], quality of life - eight dimension - (AQOL-8D)[30], mapping of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) into EQ-5D scores[29,33], or using estimates based on previous studies[34]. Three studies performed cost-effectiveness analyses using Profile of Mood States (mood)[38], Revised Impact of Events Scale (distress)[37], 12-item Health Survey (mental health) or Fear of Progression questionnaire (fear of cancer progression)[39] as outcome measure. One study performed both cost-utility and cost-effectiveness analyses with depression-free days gained (calculated using the 20-item Hopkins Symptoms Checklist) as the outcome in the cost-effectiveness analyses[31].

Follow-up period for measurement of effects and costs was mostly 6 to 12 months after the intervention[30,31,35-39]. One study had a follow-up period of 12 weeks[32], one study of 2 years[29] and the two model studies had a follow-up period of 5 years[33,34].

The majority of studies used the healthcare perspective for measuring costs[29-31,33-36,38], while three studies used a societal perspective[32,37,39], although cost inputs were not always consistent with the perspective taken. In the actual cost-effectiveness analyses, three studies included intervention costs only[31,34,37], five studies included intervention costs and direct medical costs (e.g., hospitalization or visit to the general practitioner)[29,33,35,36,38], and three studies included intervention costs, direct medical costs and direct non-medical costs (e.g., cost for support services)[30,32,39]. One study measured indirect non-medical costs (e.g., productivity losses), however, these costs were not included in the actual analyses[39].

Cost-effectiveness of the included psychosocial care interventions

Information on the cost-effectiveness or cost-utility of the different psychosocial care interventions is presented in Table 2. In Figure 2 these findings are summarized using a permutation matrix. Two studies found evidence that costs were lower, while the intervention was more effective, indicating dominance of psychosocial care[29,30]. Arving et al.[29] found that individual psychological support provided by a nurse or psychologist was significantly less costly ($-8,786 or $-6,630, respectively) and more effective in gaining QALYs (non-significant incremental QALYs of +0.09 and +0.16, respectively) compared to care-as-usual. Chatterton et al.[30] found that in highly-distressed cancer patients treated with cognitive behavioral group therapy, total costs were on average $332 non-significantly lower, while more QALYs were gained (non-significant incremental QALYs of +0.037) compared to a nurse-led self-management intervention. However, in less-distressed patients less strong evidence in favor of cognitive behavioral group therapy compared to the self-management intervention was found (i.e., costs were $335 higher and incremental QALYs were +0.016).



		Incremental effectiveness		
		More effective	**Equal effective**	**Less effective**
Incremental costs	**More costly**	Lemieux et al.[38] (supportive expressive psychosocial group therapy) Mandelblatt et al.[37] (educational video or educational video combined with psycho-educational counselling) Strong et al.[36] (nurse-delivered collaborative care) Choi Yoo et al.[31] (centralized telecare management) Walker et al.[34] (nurse-delivered collaborative care) Mewes et al.[33] (cognitive behavioral group therapy) Lengacher et al.[32] (mindfulness stress reduction program) Duarte et al.[35] (nurse-delivered collaborative care)		
	Equal in costs			
	Less costly	Arving et al.[29] (individual psychological support from a nurse or psychologist) Chatterton et al.[30] (psychologist-led, individual cognitive behavioral intervention)	Sabariego et al.[39] (cognitive behavioral group therapy)	

Figure 2: Permutation matrix

One study showed lower costs in the psychosocial intervention group compared to the control group, while effectiveness was almost equal[39]. This study by Sabariego et al.[39] found on average \$2,889 to \$3,322 non-significantly lower costs in the cognitive behavioral group therapy group compared to the supportive-experiential group therapy. No major difference in effects were found on fear of progression or mental health. The probability that cognitive behavioral therapy was more cost-effective compared to supportive-experiental group therapy without additional costs was 92%, indicating that cognitive behavioral group therapy is likely to be cost-effective.

All of the eight other studies found evidence that psychosocial care is more effective albeit at higher costs[31-38]. Whether the psychosocial care interventions investigated in these studies can be seen as cost-effective depends on the willingness-to-pay for an incremental unit of effect. Of the eight studies, four studies investigated a collaborative care intervention compare to care-as-usual[31,34-36]. These studies found that incremental costs were $144 to $953 higher, while incremental QALYs were 0.009 to 0.088 higher. The corresponding incremental costs for an incremental QALY gained (i.e., ICER) were respectively $9,818/QALY[36], $13,905/QALY[35], $17,132/QALY[34] or ranged from $10,826/QALY to $73,287/QALY, depending on the method used to measure QALYs[31].

Three of the other four studies that found higher effects and higher costs investigated the cost-effectiveness of psychosocial group interventions[32,33,38]. Lemieux et al.[38] found that supportive-expressive psychosocial group therapy was significantly more effective in improving mood than care-as-usual. However, total costs were higher ($+3,526), resulting in incremental costs of $5,550 for an effect size of 0.5 mood. Mewes et al.[33] who investigated the cost-effectiveness of cognitive behavioral group therapy found $239 higher costs and an incremental QALY gain of 0.008 in the intervention group compared to the waiting-list care-as-usual group. The ICER was $29,266/QALY. In addition, Lengacher et al.[32] found that a mindfulness program in groups was more costly ($+666), while significantly more effective in gaining QALYs (incremental QALY gain of +0.03) than a waiting-list care-as-usual group. This resulted in an ICER of $22,200/QALY.

The last study that reported higher effects although at higher costs was a study by Mandelblatt et al.[37]. This study only included intervention costs in the actual cost-effectiveness analyses. They reported that a psycho-education intervention (which consisted of an educational video addressing re-entry challenges) was more costly ($+15), while marginally more effective (non-significant incremental effect in distress of -0.002) compared to a booklet-control condition. A psycho-education intervention combined with individual psycho-educational counseling was not more effective than the booklet-control condition or psycho-education alone, while total costs were higher. Psycho-education combined with individual psycho-educational counseling can therefore be seen as dominated. In additional analyses, direct medical costs between the three groups were compared, which showed no significant differences.

Table 3: Quality assessment of the included studies

	Lemieux (2006)[38]	Mandelblatt (2008)[37]	Strong (2008)[36]
1. Was a well-defined question posed?	No	Yes	No
2. Was a description of the alternatives given? And were all relevant alternatives omitted?	Yes	Partly	Yes
3. Was the effectiveness established?	Partly	Partly	Yes
4. Were all relevant and important costs and consequences identified for each alternative?	No	No	No
5. Were costs and consequences measured accurately in appropriate units?	Partly	No	Partly
6. Costs and consequences valued credibly?	Yes	Yes	Partly
7. Were costs and consequences adjusted for differential timing?	No	NA	NA
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes	Yes
9. Was allowance made for uncertainty for the estimates of costs and consequences?	Yes	Yes	Yes
10. Did the presentation and discussion of study results include all relevant issues?	No	No	Yes
Total	5	6	7

Quality of the included studies

The quality of the included studies was in general moderate; total score ranged from 5 to 9 (Table 3). Lemieux et al.[38] scored lowest, while Arving et al, Walker et al. and Duarte et al.[29,34,35] scored highest. It was remarkable that in four studies the cost-effectiveness or cost-utility of a psychosocial care intervention was investigated, while the effectiveness was not yet properly established[30,32,37,38]. Another major concern was the inclusion of all relevant costs and consequences; three studies only included intervention costs[31,34,37], hampering the measurement of a potential cost offset. In addition, only two studies measured informal care costs[30,39] and only one study measured productivity losses[39]. Another concern was the measurement of costs and consequences; three studies did not provide clear information regarding the source of data[32,36,38], and two studies omitted costs from the actual cost-effectiveness analyses without giving clear arguments[37,39]. Furthermore, four studies did not give sufficient information on the valuation of costs and consequences, lacking for instance information on index year[31-33,36]. A positive point was that the studies, except for one[39], performed sensitivity analyses. In addition, all of the studies provided information on incremental costs and incremental effects.

Sabariego (2010)[39]	Arving (2014)[29]	Choi Yoo (2014)[31]	Walker (2014)[34]	Mewes (2015)[33]	Lengacher (2015)[32]	Chatterton (2015)[30]	Duarte (2015)[35]	% yes or NA
Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	73%
Partly	Yes	Yes	Yes	Yes	Yes	Partly	Yes	73%
Yes	Yes	Yes	Yes	Yes	Unclear	Partly	Yes	64%
Yes	No	No	No	No	No	No	No	9%
No	Yes	Yes	Yes	Yes	Partly	Yes	Yes	55%
Yes	Yes	Partly	Yes	No	Partly	Yes	Yes	64%
NA	NA	NA	Yes	Yes	NA	NA	NA	91%
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	91%
Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	73%
7,5	9	7,5	9	8	6	8	9	

DISCUSSION

In this study we aimed to assess current evidence on the cost-effectiveness and cost-utility of psychosocial care interventions in cancer patients. Eleven studies were included in this review, of which seven in recent years (2014 or 2015). Two of the included studies, both on individual psychological support, found lower costs and higher effects compared to the control group[29,30], while one study on cognitive behavioral group therapy found lower costs and equal effects compared to the control group[39]. These findings support the hypothesis of Carlson and Bultz[11,12] that psychosocial care can improve outcomes, but also lead to cost savings. However, eight other studies on collaborative care, group interventions and psycho-education, found higher effects and higher costs compared to the control group[31-38], indicating that psychosocial care is likely to be effective, although at additional costs.

Whether these additional costs are acceptable, depends on the willingness-to-pay for an incremental unit of effect. Several willingness-to-pay thresholds have been suggested in the literature, with higher thresholds for more serious diseases[40]. An often used threshold is the National Institute for Health and Clinical Excellence (NICE) threshold of about \$28,992 – \$43,488 per QALY (£20,000 - £30,000 per QALY)[41,42]. Based on these thresholds, six of the eight studies in the present study that found higher costs and higher effects are likely to be cost-effective (ICER ranged from \$9,818 to \$29,266 per QALY, with one outlier at \$73,287 per QALY)[31-36]. The other two studies found incremental costs of \$5,550 for an effect size of 0.5 in mood[38] or marginal higher costs (\$+15) for a marginal incremental effect in distress of -0.002[37]. No clear willingness-to-pay thresholds exist for these outcome measures, although the incremental costs for an effect size 0.5 in mood may be judged as acceptable[38].

In summary, findings thus showed that psychosocial care is likely to be cost-effective at potentially acceptable willingness-to-pay thresholds, with three interventions[29,30,39] even cost-effective at a willingness-to-pay threshold of zero. It was remarkable that of these three studies[29,30,39], two studies investigated individual psychological support[29,30]. However, no clear conclusions can be drawn regarding the dominance of individual psychological support compared to other psychosocial care interventions, since there was considerable heterogeneity among studies. Studies differed regarding psychosocial care intervention investigated, care provided in the control group, study population targeted, used outcome measure and included cost categories, which hampers comparability of the results. Further research is therefore called for.

Several recommendations can be formulated for these further studies. At first, more studies should be performed to investigate which psychosocial care interventions are most likely to be cost-effective and for whom these psychosocial care interventions are most likely to be cost-effective. It may be assumed that in line with findings on effectiveness[6], psychosocial care interventions are especially cost-effective in preselected patients who suffer from psychosocial problems. Five of the 11 studies included in this review preselected patients based on psychosocial outcomes. However, no clear conclusion can be drawn as to whether these studies were more cost-effective than studies that did not preselect patients, since studies that did and did not preselect patients differed regarding the type of intervention provided.

In addition, further studies should focus on the cost-effectiveness or cost-utility of psychosocial care from a societal perspective as recommended in several guidelines[22,43,44]. In this review, no study included productivity losses in the actual analyses (although one study measured productivity losses[39]), and only two studies[30,39] measured informal care costs. Productivity losses and informal care costs have been shown to provide an important contribution to the overall economic burden of cancer[25]. Since, it can be hypothesized that the provision of psychosocial care can reduce both productivity losses and costs of providing informal care[11,12,17,18], further studies should take these costs into account, especially when healthcare is being paid for by the society.

Moreover, additional research should be performed using the QALY as outcome measure as also recommended in pertinent guidelines[42,43], which will enhance comparability of results among different psychosocial interventions as well as enhance comparability to cost-effectiveness or cost-utility of other (supportive) care interventions. Although the more recent studies included in this review already used the QALY as outcome measure, the strategies to calculate QALYs widely differed. Different measurement instruments were used to calculate QALYs, such as the EQ-5D, SF-6D and the AQOL-8D. In addition, different strategies were used for mapping outcomes of other instruments, such as the EORTC QLQ-C30 or SF-36, into EQ-5D scores. A more uniform approach is recommended to enhance comparability.

Some limitations of this review are evident. At first, included studies were in general of moderate quality. Several studies lacked sufficient information on the effectiveness of the studied intervention, the source of data, the reasons for data omission, the valuation of costs and consequences, or did not include all relevant costs and consequences, which may limit validity of findings. In addition, studies showed considerable heterogeneity in studied psychosocial care interventions and study methods, hampering the formulation of clear conclusions. Furthermore, most studies were conducted among breast cancer patients and may therefore not be representative for other patient groups. Finally, all studies were conducted in Western countries, hampering generalizability to other non-western countries. A clear strength of this review is that it encompassed an up to date literature search, which included seven studies published in 2014 or 2015, which were not yet included in the most recent review[27]. This reflects the fast growing number of studies that are conducted on the cost-effectiveness or cost-utility of psychosocial care. Also, several protocol papers of currently ongoing studies were identified[45-51], which will provide new evidence on the cost-effectiveness or cost-utility of psychosocial care in the coming years.

In conclusion, results of this review revealed that psychosocial care is likely to be cost-effective at different, potentially acceptable, willingness-to-pay thresholds. Heterogeneity of studies, however, hampered the comparison of findings and consequently the formulation of clear conclusions regarding the most cost-effective psychosocial care interventions. New studies providing insight on which psychosocial care interventions are most likely to be cost-effective and for whom are therefore called for. In these new studies potential important cost drivers from a societal perspective, such as productivity losses or informal care costs, should be taken into account.

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7

Cost-utility of stepped care targeting psychological distress in head and neck cancer and lung cancer patients

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ABSTRACT

Background. A stepped care program in which effective yet least resource-intensive treatment is delivered to patients first, followed by, when necessary, more resource-intensive treatments was found to be effective in improving distress levels of head and neck cancer (HNC) and lung cancer (LC) patients. Information on this program's value for money is now called for.

Purpose. To assess the cost-utility of the stepped care program compared to care-as-usual (CAU) in HNC and LC patients with psychological distress.

Methods. In total 156 patients were randomized to stepped care or CAU. Intervention costs, direct medical costs, direct non-medical costs, productivity losses and health-related quality of life data during the intervention or control period and 12 months follow-up were calculated using TIC-P, PRODISQ and EQ-5D measures and data from the hospital information system. The stepped care program's value for money was investigated by comparing mean cumulative costs and quality-adjusted life years (QALYs).

Results. After imputation of missing data, mean cumulative costs were €-3,950 [95% confidence interval (CI): €-8,158 to €-190] lower and mean number of QALYs were 0.116 [95%CI: 0.005 – 0.227] higher in the intervention compared to the control group. The intervention group had a probability of 96% that cumulative QALYs were higher and cumulative costs were lower than the control group. Four additional analyses which were conducted to assess the robustness of this finding found that the intervention group had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group.

Conclusion. Stepped care is highly likely to be cost-effective; the number of QALYs were higher and cumulative costs were lower compared to CAU.

INTRODUCTION

Recent reviews on the cost-effectiveness and cost-utility of psychosocial care in cancer patients in general found that psychosocial care is likely to be cost-effective at potentially acceptable willingness-to-pay thresholds[1,2]. More research is, however, warranted, since economic evaluations are scarce and heterogeneity among studies hampers comparison of findings. Also no study specifically targeted novel psychosocial care programs as stepped care. To overcome barriers to usage of psychosocial cancer care, a stepped care program targeting psychological distress in cancer patients has been developed consisting of four steps: 1. watchful waiting for two weeks, 2. guided self-help, 3. face-to-face problem-solving therapy, and 4. specialized psychological interventions (e.g., cognitive behavioral therapy) and/or psychotropic medication[3]. Patients proceed to the next step only when symptoms of distress do not resolve.

Recently, this stepped care program was found to have beneficial effects on distress compared to care-as-usual (CAU) in head and neck cancer (HNC) and lung cancer (LC) patients[4]. HNC and LC patients were targeted, since they are seldom involved in randomized controlled trials (RCTs) of psychosocial care, despite a high prevalence of depression[5]. Previous economic evaluation studies of stepped care programs targeting primary care patients[6-9], older patients[10,11], patients with diabetes[12,13], or patients with acute coronary syndrome[14] with psychological distress, have found that, except for one study[10], the stepped care program improved quality-adjusted life years (QALYs) or depression-free days compared to control care, albeit in most studies[6,7,9,11,13] at higher costs. However, no such economic evaluation on stepped care has been performed in cancer patients yet. This study therefore assessed the cost-utility of a stepped care program targeting psychological distress in HNC and LC patients compared to CAU.

METHODS

Study design and population

Detailed information on the study design and population can be found in previous publications[3,4]. In short, this cost-utility analysis was conducted alongside a prospective RCT on the efficacy of a stepped care program for HNC and LC patients with symptoms of psychological distress (Hospital Anxiety and Depression Scale (HADS) distress score > 14 or anxiety or depression score > 7). The study was approved by the Medical Ethics

Committee of VU University Medical Center and conducted according to the principles of the Declaration of Helsinki. The trial has been registered in the Netherlands Trial Register (NTR1868).

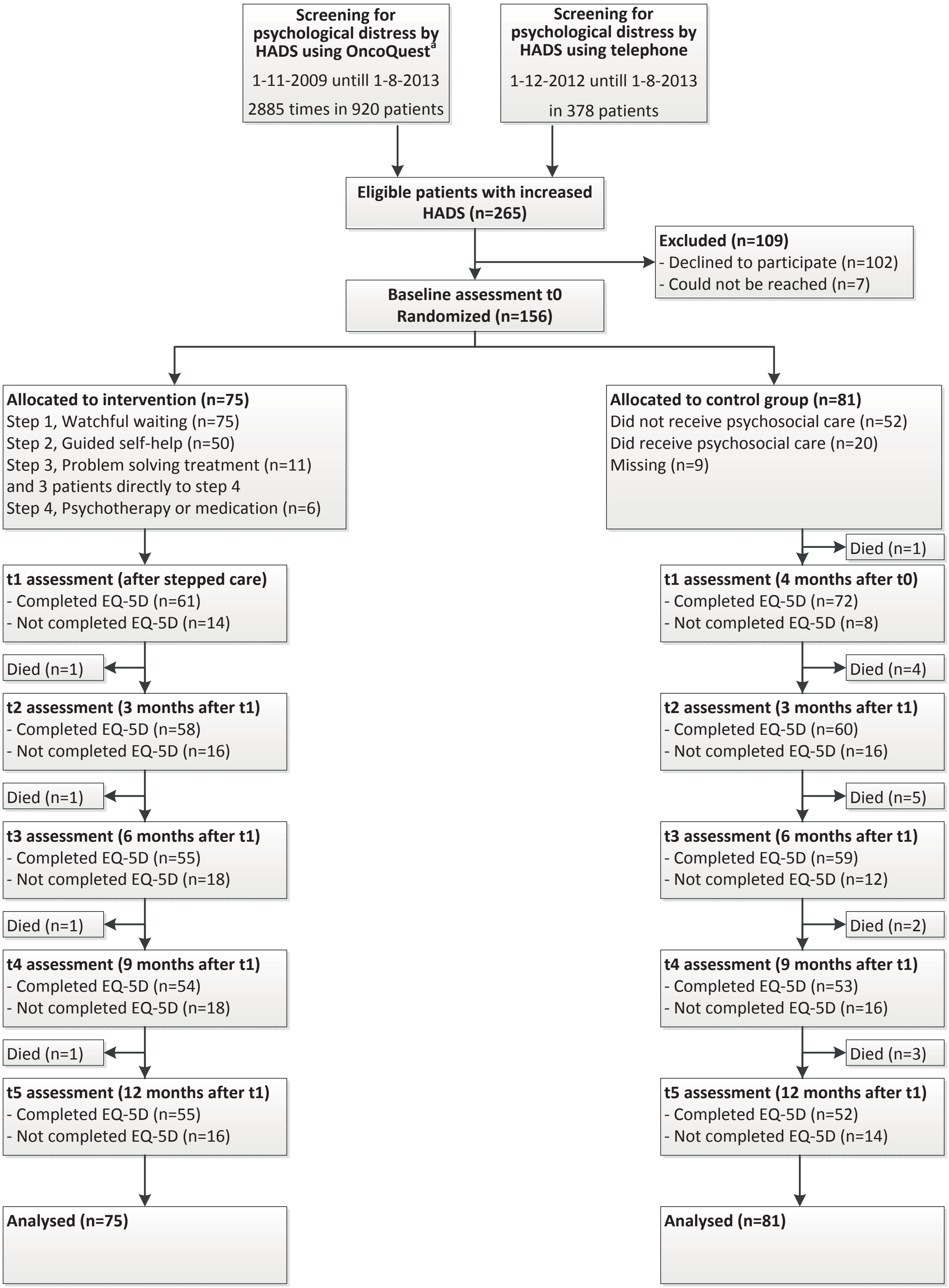
Randomization and treatment allocation

Patients who met the eligibility criteria and signed informed consent were randomized to the intervention group providing stepped care or the control group providing CAU (Figure 1). The stepped care program consisted of four steps: 1. watchful waiting, 2. guided self-help via the internet or booklet, 3. face-to-face problem-solving therapy, and 4. specialized psychological interventions and/or psychotropic medication. Patients who did not recover after a treatment step (HADS anxiety/depression score remained above 7), proceeded to a more intensive step. More information is provided in the protocol[3].

Outcome measures

Cost and clinical endpoint data were collected at baseline (t0), immediately after the intervention or control period indicated as t1, and 3, 6, 9 and 12 months after t1. The economic evaluation was conducted from a societal perspective and included intervention costs, direct medical costs (costs of healthcare utilization and medication), direct non-medical costs (costs of support groups, informal care, travelling to health services and parking), and indirect non-medical costs (productivity losses from paid work). Intervention costs were calculated using a bottom-up approach. Mean costs per patient in the intervention group were €318 (range: €24 to €9,043) (see Table 1).

The Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TIC-P)[15] was used to measure utilization of healthcare facilities (e.g., number of visits to the general practitioner) and other facilities (e.g., time spent in self-help groups or informal care) in the past four weeks and medication used (antidepressants, analgesic, and sedative) in the past two weeks. In addition, healthcare utilization within the hospital (visits to the medical specialist, day treatment, and hospital admission) was collected using the hospital information system. Direct medical and direct non-medical costs of support groups and informal care were calculated by multiplying resource use by the integral cost price[16]. Direct non-medical costs of travelling to health services and parking were calculated by multiplying unit resource use by average distance to the location times the price per km. All prices were adjusted to 2011 prices using the consumer price index. The Productivity and Disease Questionnaire (PRODISQ)[17] was used to measure productivity losses through absence from paid work (absenteeism) or reduced quantity or quality of



[a] At the Department of Otolaryngology - Head and Neck surgery and at the Department of Pulmonary Diseases of the VU University Medical Center in Amsterdam, the Netherlands.

Figure 1: CONSORT flow diagram

performed paid work (presenteeism) in the past four weeks. Losses due to presenteeism were calculated by multiplying the days of less productivity at work by the estimated amount of lost quantity or quality of performed work (ranging from 0 - 10). Indirect non-medical costs from paid work were calculated by multiplying productivity losses by respectively age- and gender-specific costs[16] using the human capital approach.

The EuroQol-5 dimensions (EQ-5D) was used to measure health-related quality of life. The EQ-5D utility score was obtained using the Dutch index tariff[18].

Table 1. Description of healthcare utilization within the stepped care program

Description of healthcare utilization within the stepped care program	**Costs (€)**
Screening	
- Screening for distress	7.97
- Consultation by a nurse for 15 minutes	7.97
Step 1 watchful waiting	
- Monitoring distress by HADS assessment	7.97
Step 2 guided self-help	
- Self-help internet tool or booklet	39.00
- Feedback by e-mail or telephone from a nurse (in total one hour)	31.88
- Monitoring distress by HADS assessment	7.97
Step 3 face-to-face problem-solving therapy	
- Five-sessions of problem-solving therapy by a nurse	151.42
- Monitoring distress by HADS assessment	7.97
Step 4 specialized psychological interventions and/or psychotropic medication	
- Costs were calculated per person individually since type of treatment and number of sessions or duration of treatment differed.	Differed

Abbreviations: HADS, Hospital Anxiety and Depression Scale.

Statistical analyses

All analyses were performed using the IBM Statistical Package for the Social Science (SPSS) version 20 (IBM Corp., Armonk, NY USA) and STATA version 12.1. Descriptive statistics, chi-squared tests and independent t-test were used to describe and compare baseline characteristics between different groups.

To provide information on type of costs included in the analyses and its relative importance (its contribution to the mean total costs per group) at various time points, data of complete cases (patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died) was used. Data of complete cases was also used to provide information on the mean utility scores per group at the different time points.

To assess the value for money of stepped care compared to CAU, at first a base case intention-to-treat cost-utility analysis was performed including all 156 randomized patients and imputing any missing data. Consequently, to assess the robustness of this finding four additional analyses were performed (a) an analysis in which we adjusted the base case analysis using multivariate regression analyses for variables at baseline found to have a major influence (a change of ≥ 20%) on incremental costs (EORTC social functioning and total costs at baseline) and incremental effects (HADS depression at baseline); (b) an analysis excluding patients from the base case analysis who died during the study; (c) an analysis in which data was imputed for patients who died during the study as though they are still alive; and (d) an analysis in which productivity losses were excluded.

All cost-utility analyses were performed in agreement with the intention-to-treat principle. Missing data were imputed as total costs or utility score per time point per treatment arm separately using multiple imputation (predictive mean matching) by chained equations. Data were thus only imputed for those time points that were missing. Linear and logistic regression analyses were performed to investigate which variables (socio-demographic, clinical, HADS-total, HADS-D, HADS-A, and EORTC global quality of life) were associated with missing data, observed costs or EQ-5D utility scores. Variables associated with missing data (gender and HADS-total), observed costs (work situation, EORTC global quality of life, and marital status) or utility scores (HADS-total, EORTC global quality of life score, tumor stage, tumor location, and years of education) and variables which differed at baseline (alcohol dependency, HADS-D, EORTC QLQ-C30 social functioning, and EORTC QLQ-H&N35 social contact and sexuality) were included in the multiple imputation model. Ten imputed data sets were created and analyzed separately. Results of the ten analyses were pooled using Rubin’s (1987) rules.

To perform incremental cost-utility analyses, the cumulative costs and number of QALYs per patient per treatment group were calculated. For patients in the control group cumulative costs as measured using the TIC-P and PRODISQ between t0 and t1 were calculated

Table 2. Baseline characteristics

	Total group	Intervention		
	Total	Total	Complete cases[1]	Non-complete cases[2]
	n = 156	n = 75	n = 47	n = 28
Mean age (SD)	62.0 (9.4)	62.5 (8.7)	62.8 (8.2)	62.1 (9.5)
Gender (%)				
- Male	60.9%	62.7%	53.2%	78.6%
- Female	39.1%	37.3%	46.8%	21.4%
Marital status (%)				
- Married/living with partner	67.9%	72.0%	74.5%	67.9%
- Unmarried/divorced/widowed	32.1%	28.0%	25.5%	32.1%
Work situation (%)				
- Paid job	30.8%	30.7%	34.0%	25.0%
- No paid job/ retired	69.2%	69.3%	66.0%	75.0%
Tumor location (%)				
- Lip/oral cavity/oropharynx	48.7%	40.0%	42.6%	35.7%
- Hypopharynx/larynx	25.6%	28.0%	23.4%	35.7%
- Other head and neck cancers	19.9%	25.3%	25.5%	25.0%
- Lung	5.8%	6.7%	8.5%	3.6%
Tumor stage (%)				
- I	25.0%	22.7%	19.1%	28.6%
- II	16.0%	20.0%	23.4%	14.3%
- III	18.6%	16.0%	19.1%	10.7%
- IV	34.0%	30.7%	25.5%	39.3%
- Unknown	6.4%	10.7%	12.8%	7.1%
Time since treatment (%)				
- < 7 months	35.9%	38.7%	38.3%	39.3%
- 7-12 months	16.7%	13.3%	10.6%	17.9%
- > 12 months	47.4%	48.0%	51.1%	42.9%
Treatment (%)				
- Single treatment	48.7%	52.0%%	42.6%	67.9%
Surgery	22.4%	17.3%	12.8%	25.0%
Radiotherapy	26.3%	34.7%	29.8%	42.9%
- Combination treatment	51.3%	48.0%	57.4%	32.1%

Control			Significance level			
Total n = 81	Complete cases[1] n = 56	Non-complete cases[2] n = 25	Intervention total vs. control total	Intervention complete vs. non- complete cases	Control complete vs. non-complete cases	Intervention complete vs. control complete cases
61.6 (10.0)	63.3 (9.6)	57.7 (10.0)	0.538	0.752	0.019	0.755
			0.663	0.028	0.168	0.254
59.3%	64.3%	48.0%				
40.7%	35.7%	52.0%				
			0.297	0.537	0.599	0.355
64.2%	66.1%	60.0%				
35.8%	33.9%	40.0%				
			0.979	0.411	0.372	0.990
30.9%	33.9%	24.0%				
69.1%	66.1%	76.0%				
			0.176	0.615	0.643	0.189
56.8%	58.9%	52.0%				
23.5%	25.0%	20.0%				
14.8%	12.5%	20.0%				
4.9%	3.6%	8.0%				
			0.146	0.434	0.813	0.069
27.2%	28.6%	24.0%				
12.3%	12.5%	12.0%				
21.0%	17.9%	28.0%				
37.0%	39.3%	32.0%				
2.5%	1.8%	4.0%				
			0.527	0.626	0.445	0.725
33.3%	35.7%	28.0%				
19.8%	16.1%	28.0%				
46.9%	48.2%	44.0%				
			0.430	0.034	0.839	0.694
45.7%	46.4%	44.0%				
27.2%	28.6%	24.0%				
18.5%	17.9%	20.0%				
54.3%	53.6%	56.0%				

Table 2. Baseline characteristics

	Total group	Intervention		
	Total	**Total**	**Complete cases**[1]	**Non-complete cases**[2]
	n = 156	n = 75	n = 47	n = 28
Chemoradiation[3]	17.3%	8.0%	10.6%	3.6%
Surgery and radiotherapy	26.3%	33.3%	36.2%	28.6%
Surgery and chemoradiation[4]	5.1%	5.3%	8.5%	0.0%
Surgery and chemotherapy[5]	2.6%	1.3%	2.1%	0.0%
Anxiety or depressive disorder (%)				
- Yes	22.4%	18.7%	17.0%	21.4%
- No	77.6%	81.3%	83.0%	78.6%
Nicotine dependence (%)				
- Yes	17.3%	16.0%	12.8%	21.4%
- No	82.7%	84.0%	87.2%	78.6%
Alcohol dependence (%)				
- Yes	8.3%	13.3%	6.4%	25.0%
- No	91.7%	86.7%	93.6%	75.0%
Mean HADS anxiety (SD)	9.5 (3.5)	9.3 (3.6)	9.2 (3.6)	9.6 (3.6)
Mean HADS depression (SD)	8.9 (3.8)	8.2 (3.7)	7.9 (3.6)	8.6 (3.7)
Mean HADS total (SD)	18.3 (5.4)	17.5 (5.2)	17.1 (4.9)	18.1 (5.6)
EORTC global quality of life (SD)	58.0 (19.8)	59.2 (20.1)	59.0 (19.0)	59.6 (22.3)
Mean EQ-5D utility score (SD)	0.63 (0.27)	0.66 (0.24)	0.68 (0.22)	0.60 (0.28)
Mean total costs in € (SD)	886 (1614)	790 (1443)	660 (1150)	1046 (1895)

Abbreviations: SD, Standard deviation.

[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died. Non-complete cases are patients who did not complete one or more of the baseline or follow-up measurements.

Control			Significance level			
Total n = 81	Complete cases[1] n = 56	Non-complete cases[2] n = 25	Intervention total vs. control total	Intervention complete vs. non- complete cases	Control complete vs. non-complete cases	Intervention complete vs. control complete cases
25.9%	23.2%	32.0%				
19.8%	21.4%	16.0%				
4.9%	3.6%	8.0%				
3.7%	5.4%	0.0%				
			0.278	0.636	0.053	0.733
25.9%	19.6%	40.0%				
74.1%	80.4%	60.0%				
			0.678	0.322	0.396	0.636
18.5%	16.1%	24.0%				
81.5%	83.9%	76.0%				
			0.030	0.022	0.238	0.825
3.7%	5.4%	0%				
96.3%	94.6%	100%				
9.6 (3.4)	9.3 (3.1)	10.2 (4.0)	0.643	0.676	0.263	0.869
9.5 (3.8)	9.1 (3.6)	10.3 (4.1)	0.029	0.472	0.181	0.103
19.1 (5.6)	18.4 (4.6)	20.6 (7.2)	0.071	0.423	0.185	0.174
56.8 (19.6)	58.3 (21.1)	52.9 (15.2)	0.441	0.915	0.266	0.859
0.60 (0.29)	0.60 (0.30)	0.58 (0.28)	0.179	0.178	0.755	0.115
974 (1762)	1087 (1958)	671 (1060)	0.491	0.290	0.238	0.173

[3] Cisplatin was given in 21 patients, Cetuximab in five patients and in one patient cytostatics was missing. [4] Cisplatin was given in all 8 patients, [5] Cisplatin was given in two patients, Erlotinib was given in one patient and in one patient cytostatics was missing.

Table 3. Mean costs per time point of complete cases[1]

		Intervention group (n = 47)				
	Reference price per unit (€)	Baseline (t0)	t1	t2	t3	t4
Direct medical costs[2]		189 (303)	203 (230)	176 (222)	186 (240)	148 (169)
General practitioner	29	26 (49)	20 (27)	23 (37)	17 (31)	22 (35)
Company doctor	65	11 (34)	11 (25)	12 (29)	7 (24)	3 (13)
Social worker (company)	68	1 (10)	1 (10)	-	-	-
Social worker (general)	68	10 (32)	4 (17)	3 (20)	7 (35)	6 (28)
Physiotherapist	38	65 (193)	58 (100)	46 (99)	52 (117)	31 (72)
Dietitian	28	12 (24)	7 (19)	8 (22)	8 (20)	4 (12)
Psychological help (private practice)	81	-	12 (38)	3 (17)	3 (17)	2 (12)
Psychological help (out-patient)	179	19 (107)	19 (77)	15 (63)	30 (120)	15 (63)
Psychological help (addiction)	179	-	15 (104)	19 (107)	-	-
Psychological help (mental hospital)	181	-	15 (63)	4 (26)	4 (26)	4 (26)
Specialist (general hospital)	67	26 (100)	24 (49)	16 (42)	19 (39)	20 (39)
Priest	122	-	-	3 (18)	3 (18)	3 (18)
House cleaning	25	11 (59)	14 (62)	19 (79)	32 (102)	38 (112)
Personal care	46	-	-	-	-	-
Visiting nurse	68	7 (41)	1 (10)	4 (17)	3 (20)	1 (10)
Other direct medical costs						
Medication[2]	0.19 – 7.58 per DDD	19 (33)	17 (30)	17 (28)	17 (29)	12 (21)
Specialist[3]	130					
Day treatment[3]	252					
Hospitalization[3]	576 or 2184 (IC)					
Direct non-medical costs[2]		80 (177)	34 (83)	79 (230)	60 (158)	49 (146)
Support groups	12.80 – 57.50	34 (138)	4 (14)	18 (54)	37 (150)	16 (55)
Informal care	12.80	41 (123)	24 (80)	57 (223)	19 (59)	30 (137)
Transport and parking costs	0.20 per km / 3.00 parking	4 (8)	6 (7)	4 (6)	4 (6)	3 (4)
Indirect non-medical costs[4]		372 (1127)	264 (914)	205 (582)	172 (747)	124 (422)
Absenteeism paid work	8.97 – 40.32 per h	339 (1128)	149 (482)	169 (503)	145 (593)	96 (405)
Presenteeism paid work	8.97 – 40.32 per h	33 (117)	115 (681)	36 (170)	27 (165)	28 (140)

Abbreviations: DDD, defined daily dose; IC, intensive care; t1: assessment post-intervention (intervention group) or 4 months after baseline (control group); t2: 3 months after t1, t3: 6 months after t1, t4: 9 months after t1; t5: 12 months after t1.

t5	t0 - t5	Control group (n = 56) Baseline (t0)	t1	t2	t3	t4	t5	t0 – t5
116 (170)		315 (581)	260 (479)	280 (518)	226 (414)	199 (459)	190 (747)	
17 (29)		24 (32)	27 (46)	23 (34)	20 (35)	20 (29)	18 (29)	
3 (13)		20 (72)	6 (19)	2 (17)	6 (36)	3 (15)	1 (9)	
-		1 (9)	-	-	-	1 (9)	-	
1 (10)		6 (27)	4 (20)	5 (36)	-	7 (34)	-	
40 (92)		45 (88)	45 (93)	50 (105)	39 (89)	28 (65)	21 (76)	
2 (10)		7 (15)	4 (13)	8 (20)	3 (10)	2 (7)	2 (6)	
12 (38)		-	-	16 (89)	-	4 (32)	4 (24)	
4 (26)		13 (67)	6 (48)	6 (48)	13 (96)	-	-	
-		-	-	-	32 (239)	-	-	
4 (26)		-	13 (97)	-	3 (24)	13 (58)	3 (24)	
16 (40)		37 (66)	36 (96)	18 (45)	29 (67)	20 (56)	42 (6)	
-		13 (69)	4 (23)	2 (16)	-	-	-	
18 (56)		42 (128)	25 (67)	46 (112)	30 (77)	21 (67)	67 (9)	
-		67 (364)	65 (324)	99 (385)	51 (237)	25 (172)	46 (6)	
-		40 (210)	24 (182)	5 (36)	-	55 (366)	727 (97)	
12 (25)		19 (50)	14 (44)	19 (59)	16 (56)	12 (37)	22 (70)	
	1104 (936)							1088 (780)
	27 (94)							27 (115)
	441 (1774)							1882 (5193)
47 (129)		184 (463)	51 (161)	64 (163)	56 (137)	78 (281)	78 (263)	
28 (124)		30 (93)	7 (31)	24 (87)	8 (40)	7 (33)	45 (229)	
16 (47)		149 (459)	40 (159)	43 (127)	43 (127)	68 (280)	31 (107)	
3 (4)		5 (7)	4 (9)	3 (7)	5 (13)	3 (7)	2 (4)	
37 (179)		569 (1530)	305 (1104)	333 (1027)	151 (427)	158 (722)	130 (478)	
16 (93)		509 (1448)	237 (1046)	162 (728)	49 (198)	65 (484)	15 (116)	
21 (92)		61 (214)	68 (335)	170 (500)	103 (365)	94 (275)	115 (461)	

[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died. [2] Measured using the TIC-P over the past four weeks. [3] Measured using the VUmc hospital information system over the entire study period. [4] Measured using the PRODISQ over the past four weeks.

by multiplying the mean costs at time point t1 by the corresponding time period (time between t0 and t1). Unlike patients in the control group, for patients randomized to the intervention group, the costs as measured using the TIC-P and PRODISQ at t1 were not expected to be generalizable to the entire intervention period (a patient was expected to have different costs during step 4 than during step 1). Therefore, cumulative costs between t0 and t1 for intervention patients were calculated by summing costs per step. Mean costs per step per 4 weeks were calculated for all patients who 1) participated in step 4, 2) participated in step 3 but not in step 4, 3) participated in step 2 but not in step 3 or 4, and 4) patients who participated in step 1 but not in step 2, 3 or 4. Subsequently, cumulative costs per patient were calculated by multiplying mean cumulative costs per step per 4 weeks by the time a patient participated in the particular step. Costs between t1 and t5 as measured using the TIC-P and PRODISQ for both groups were calculated using linear interpolation. Total cumulative costs per patient were calculated by summing cumulative costs measured using the TIC-P and PRODISQ with intervention costs and costs measured using the hospital information system. The number of QALYs per patient was calculated by multiplying the EQ-5D utility score by the appropriate time period it accounts for using linear interpolation.

An incremental cost-utility ratio (ICUR) was calculated to obtain the costs per gained QALY by dividing the incremental costs by the incremental effects using the following formula (mean Costs $_{\text{intervention}}$ – mean Costs $_{\text{control}}$) / (mean QALYs $_{\text{intervention}}$ – mean QALYs $_{\text{control}}$). The uncertainty surrounding the ICUR were assessed using bootstrapping with 5,000 replications and projected on a cost-utility plane.

RESULTS

In total, 75 patients were randomized to the intervention group and 81 patients to the control group. Table 2 summarizes the baseline characteristics of both groups and compared patients with complete data with patients without complete data. During the study, 4/75 (5.3%) patients in the intervention group vs. 15/81 (18.5%) patients in the control group died ($p = 0.012$).

Direct and indirect medical costs and productivity costs

The mean costs of patients with complete data (patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died) per time point per group are presented in Table 3. In the four weeks prior to baseline, no statistically significant differences in costs were found between the two groups (p = 0.17), although there were large absolute differences. Mean total costs at baseline in the intervention group were €660 (standard deviation (SD) = 1,150) compared to €1,087 (SD = 1,958) in the control group.

Health-related quality of life

In Table 4 the mean EQ-5D utility score of patients with complete data are presented. At baseline, a non-statistically significant difference in EQ-5D utility score of 0.08 was found in favor of the intervention group (p = 0.12), which exceeded the subjectively appreciable difference of 0.07 reported in Walters et al.[19].

Table 4. Mean EQ-5D utility score per time point of complete cases[1]

Time point	Intervention group (n = 47)	Control group (n = 56)
Baseline	0.68 (0.22)	0.60 (0.30)
t1	0.74 (0.20)	0.65 (0.30)
t2 (3 months after t1)	0.77 (0.19)	0.65 (0.30)
t3 (6 months after t1)	0.75 (0.20)	0.61 (0.32)
t4 (9 months after t1)	0.74 (0.24)	0.61 (0.35)
t5 (12 months after t1)	0.73 (0.22)	0.60 (0.36)

t1: assessment post-intervention (intervention group) or 4 months after baseline (control group)

[1] Complete cases are patients who completed the baseline measurement and all five follow-up measurements, or who completed the baseline measurement and all follow-up measurements until they died.

Cost-utility analyses

Results of the different cost-utility analyses are presented in Table 5 and Figures 2 - 6. In the base case analysis, mean costs in the intervention group were statistically significant lower than mean costs in the control group (incremental costs were €-3,950). Besides, QALYs gained were statistically significantly higher in the intervention group compared to the control group (incremental effects were 0.116). Of the bootstrapped cost-utility pairs, 96% fell into the south-east quadrant, representing the probability that stepped care is more effective and less costly compared to CAU.

To assess the robustness of this finding, four additional analyses were performed as

Table 5. Results of the different cost-utility analyses

	Costs (€) Mean (SEM)	**QALYs** Mean (SEM)	**Incremental costs** € [95% CI]	**Incremental effects** QALYs [95% CI]
Base case analysis			-3,950 [-8,158 to -190]*	0.116 [0.005 to 0.227]*
- Intervention group (n = 75)	9,761 (1,041)	0.884 (0.039)		
- Control group (n = 81)	13,711 (1,828)	0.768 (0.040)		
Analysis adjusted for several variables at baseline			-2,499 [-6,082 to 630]	0.076 [-0.032 to 0.184]
- Intervention group (n = 75)	Not applicable	Not applicable		
- Control group (n = 81)	Not applicable	Not applicable		
Analysis excluding patients who died during the study			-3,939 [-8,722 to 229]	0.052 [-0.053 to 0.156]
- Intervention group (n = 71)	9,934 (1,088)	0.911 (0.037)		
- Control group (n = 66)	13,874 (2,080)	0.859 (0.038)		
Analysis with imputed data for patients who died during the study			-4,692 [-8,898 to -889]*	0.059 [-0.035 to 0.153]
- Intervention group (n = 75)	9,887 (1,035)	0.908 (0.035)		
- Control group (n = 81)	14,579 (1,848)	0.849 (0.033)		
Analysis without productivity losses			-2,888 [-5,630 to -424]*	0.118 [0.009 to 0.227]*
- Intervention group (n = 75)	6,287 (677)	0.885 (0.039)		
- Control group (n = 81)	9,175 (1,161)	0.767 (0.040)		

Abbreviations: QALYs, quality-adjusted life years; CI, confidence interval
*, significant difference between the two groups ($p < 0.05$)

presented in Table 5. In these additional analyses, the intervention group had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group. The analysis that showed the lowest probability of being more effective and less costly was the analysis in which patients who died during the study were excluded (probability of 81%).

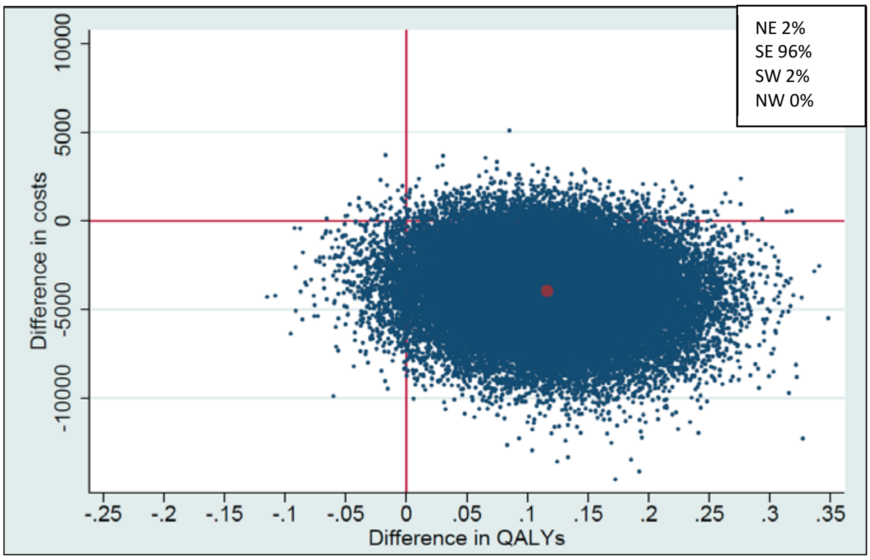


Figure 2. Cost-utility plane of the base case analysis

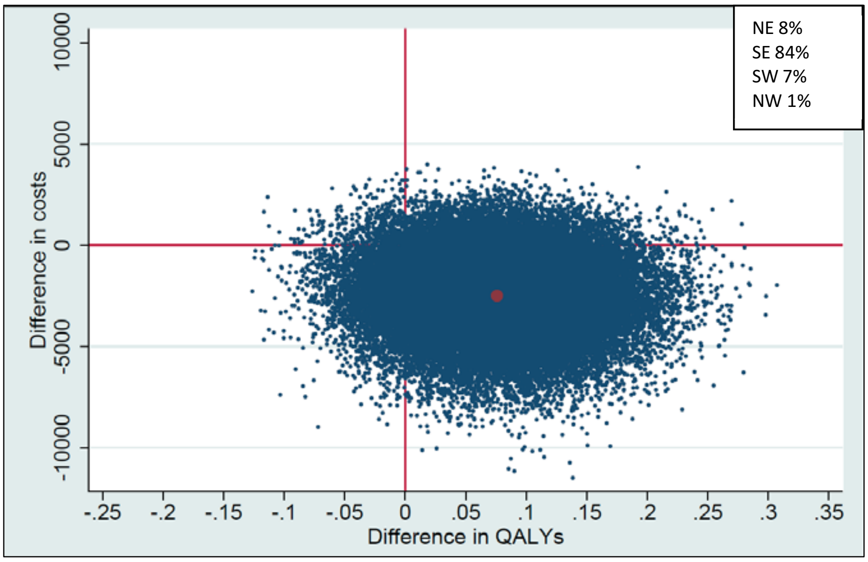


Figure 3. Cost-utility plane of the base case analysis adjusted for social functioning and total costs at baseline (costs) and HADS depression (effects)

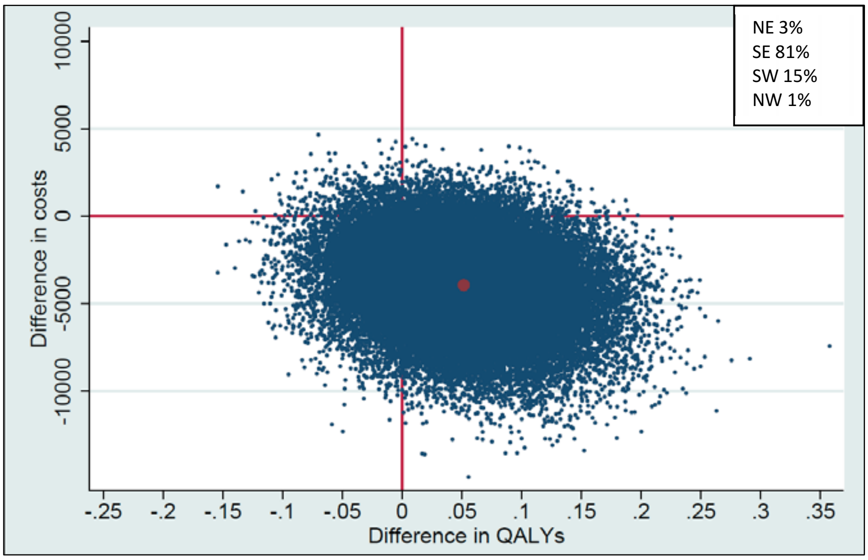


Figure 4. Cost-utility plane of the base case analysis without patients who deceased during the study

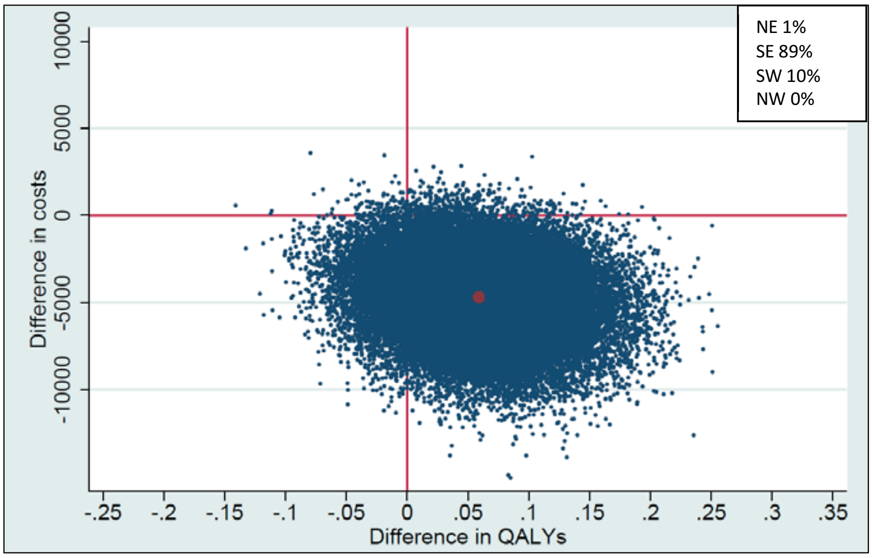


Figure 5. Cost-utility plane of the analysis with imputed data for patients who deceased during the study

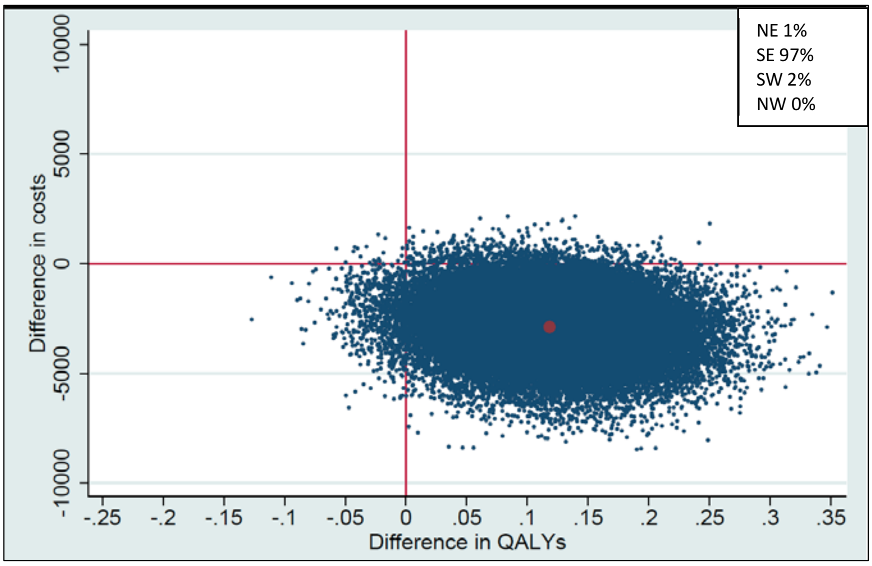


Figure 6. Cost-utility plane of the analysis in which productivity losses are not included

DISCUSSION

This study investigated the cost-utility of a stepped care program targeting psychological distress in HNC and LC patients compared to CAU. In the base case analysis, the number of QALYs were statistically significantly higher and cumulative costs were statistically significantly lower in the intervention group compared to the control group. The probability that cumulative QALYs were higher and costs were lower was 96%, indicating that stepped care is highly likely to be cost-effective compared to CAU.

Several additional analyses were performed to assess the robustness of this finding. In one analysis we adjusted for variables that differed at baseline between the two groups and had a major impact on incremental costs or incremental effects. After correction, incremental costs and QALYs decreased to a non-statistically significant difference, however, the intervention group still had a probability of 93% that cumulative QALYs were higher and a probability of 89% to be less costly than the control group.

In addition, we investigated the influence of the lower mortality rate in the intervention compared to the control group (5.3% vs. 18.5%). A debate is ongoing concerning the influence of psychosocial care on survival in cancer patients, with some authors suggesting that psychosocial care may improve survival[20-22], while others argue against such an effect[23-25]. If we assume that psychosocial care does not improve survival, our cost-utility estimate may be biased, as the higher mortality rate in the control group will have resulted in lower mean QALYs and is expected to influence mean total costs. Therefore, two additional analyses were performed: one analysis in which all died patients were excluded and one analysis in which for all died patients cost and utility data were imputed as though they were still alive. In both analyses incremental costs between the two groups changed somewhat, while the incremental QALYs decreased to a non-statistically significant difference. However, the intervention group still had a probability of 84% - 90% that cumulative QALYs were higher than in the control group and a probability of 96% - 99% that it was less costly. This indicates that when stepped care does not influence survival, it is still likely to be cost-effective.

Our findings are in agreement with one previous study that targeted cancer patients with increased levels of distress[26]. All other previous studies targeting cancer patients with increased levels of distress reported an improvement in QALYs, although, at higher costs[27-29]. This difference in cost benefit may be due to the design of stepped care in which intervention patients are first provided with watchful waiting (recovery rate 28%), followed by guided self-help when not spontaneously recovered after two weeks (recovery rate 34%)[4]. When still not recovered after guided self-help more resource-intensive care was provided, while in the previous studies all intervention patients received relatively more resource-intensive care[26-29]

Another explanation for the difference in cost benefit may be that unlike previous studies[26-29], our study was conducted from a societal perspective, incorporating productivity losses and direct non-medical costs such as informal care costs. Previous studies found that being distressed was associated with unemployment in mixed cancer survivors[30] and that higher levels of depression were associated with unemployment due to loss of job, sick leave or early retirement after cancer treatment for HNC[31]. In another study on employment and return to work among HNC patients, an association between anxiety and return to work was reported, while no such association with distress or depression was found[32]. Our efficacy study showed that stepped care was beneficial in improving level of distress[4], which may have had a beneficial effect on productivity losses in the intervention group compared to the control group. We conducted an additional analysis in which we excluded productivity losses, which showed indeed that the cost difference between the two groups reduced with €1,062. However, even without productivity losses, stepped care had a probability of 97% to be more effective and less costly.

Some potential limitations were evident in this study. A potential limitation is that a number of assumptions were made regarding resource utilization and EQ-5D utility scores for data that were missing. Firstly, missing total costs or utility scores per time point per treatment were imputed using multiple imputation techniques. Secondly, linear interpolation between time points was used. Both assumptions may not necessarily reflect reality, however, since the same assumptions were made for both groups, this was expected not to have influenced our findings. Another potential limitation is that productivity losses were calculated using the human capital approach instead of the recommended friction cost approach[16]. Also, the small sample size of 156 patients is a limitation of this study. Although bootstrapping was performed which supported the finding that stepped care is likely to be more effective and less costly than CAU, it also showed that there is considerable uncertainty. More research is therefore needed on the cost-utility of stepped care in subgroups of the investigated population, such as patients with and without a diagnosis of major depression disorder or anxiety disorder.

In addition, further research should investigate whether findings are replicable in other cancer patient groups. Also, further research should be performed on optimal implementation of stepped care in routine cancer care, which may potentially differ between different health care systems (e.g., the Netherlands compared to The United States). The RE-AIM framework (Reach, Efficacy, Adoption, Implementation, and Maintenance) can be used to evaluate the different steps involved in optimal implementation and maintenance of stepped care[33].

In conclusion, since in the base case analysis the number of QALYs were statistically significantly higher and cumulative costs were statistically significantly lower in the intervention group compared to the control group, supportive care is highly likely to be dominant (more effective and less costly) compared to CAU. After adjustment for differences at baseline, after taking into account differences in mortality rate and after excluding productivity losses, number of QALYs and cumulative costs mostly decreased to a non-statistically significant difference. However, the intervention group still had a probability of 84% - 98% that cumulative QALYs were higher and a probability of 91% - 99% to be less costly than the control group, supporting the finding that stepped care is likely to be cost-effective. In combination with findings on the efficacy of stepped care[4], stepped care is expected to be beneficial in routine HNC and LC care practice. Further research in needed on the optimal implementation of this stepped care program in clinical practice.

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8

General discussion

This thesis focuses on supportive care in head and neck cancer (HNC) patients, especially on patients' need for supportive care and its cost-effectiveness and cost-utility. In this chapter, the main findings of this thesis are discussed in relation to current knowledge and practice of optimal supportive care targeting HNC patients. Both strengths and limitations of this thesis are presented. This chapter finishes with presenting the implications for clinical practice and by providing recommendations for further research.

MAIN FINDINGS OF THIS THESIS

The first part of this thesis is aimed at obtaining insight into HNC patients' supportive care needs using psychometrically assessed patient-reported outcome measures. It was found that the widely-used European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions (EORTC QLQ-C30) and HNC-specific module (EORTC QLQ-H&N35) can be used in clinical practice for identifying patients with a perceived unmet supportive care need. Both sensitive and specific cutoff scores were identified (*chapter 2*). Also, the Supportive Care Needs Survey short-form (SCNS-SF34) and HNC-specific module (SCNS-HNC) were valid and reliable patient-reported outcome measures for measuring supportive care needs in HNC patients (*chapter 3*). Using these SCNS measures among HNC patients treated with total laryngectomy (TL), it was found that many TL patients have supportive care needs, especially regarding HNC-specific functioning (76%), health, system, information & patients support (e.g., written information on aspects of your care) (69%), psychological (66%), and physical and daily living needs (62%) (*chapter 4*). For many of these patients, their need for supportive was satisfactorily fulfilled, as unmet needs were respectively 53%, 35%, 39%, and 37%. Several supportive care interventions have been developed previously to target these unmet supportive care needs.

The second part of this thesis focused on the costs, cost-effectiveness and cost-utility of such interventions. As an increasing number of supportive care interventions encompass a self-management component, in c*hapter 5* the association between patient activation for self-management and total costs was presented. This chapter showed that a better patient activation among TL patients is likely to be associated with lower total costs. In *chapter 6* the literature on the cost-effectiveness or cost-utility of psychosocial supportive care interventions was reviewed. Results showed that psychosocial care in general has the potential to be effective at acceptable costs in cancer patients (mainly breast cancer).

An additional study on a stepped-care program targeting anxiety and depression among HNC and lung cancer patients conducted at the VU University medical center, Amsterdam (published after the conduction of the review), was found to be more effective at lower costs as compared to care-as-usual (*chapter 7*).

OPTIMAL SUPPORTIVE CARE TARGETING HEAD AND NECK CANCER PATIENTS

In the following paragraphs the findings of this thesis are discussed in relation to current knowledge and practice of optimal supportive care targeting HNC patients. To facilitate this discussion the supportive care framework of Fitch[1] (Figure 1) and a cost-effectiveness/cost-utility plane are used (Figure 2).

This thesis addressed three important aspects of optimal supportive care; 1) tailoring supportive care to the needs of the individual patient (patient-centered care), 2) offering effective supportive care (quality care), and 3) offering cost-effective supportive care (affordable care). Tailoring of supportive care should be based on a patient's individual needs and other personal factors (e.g., a patient's goals, skills and preferences). It is represented in Figure 1 by the four different levels of supportive care: 1) screening for supportive care needs and the provision of relevant information; 2) low-intensive supportive care such as additional information, education, self-help or self-management interventions; 3) moderate-intensive supportive care, such as nurse-led specialized interventions or group interventions; and 4) high-intensive supportive care, such as ongoing and complex specialized interventions[1]. It is conceptualized that each increasing level of supportive care is more expensive (i.e., the supportive care intervention itself) and is needed by a decreasing group of patients. In addition, offered care in each level should be effective and preferably also be cost-effective. The concept of cost-effectiveness or cost-utility is visualized in Figure 2. The four main outcomes of cost-effectiveness or cost-utility analyses are visualized by the four different quadrants. In case the supportive care intervention is more effective and more costly (north-east quadrant), the acceptability of the additional costs depends on the willingness-to-pay for an incremental unit of effect. Figure 2 presents two of such potential willingness-to-pay thresholds (i.e., the blue line and the dotted line), of which the dotted line represents the lower willingness-to-pay threshold.

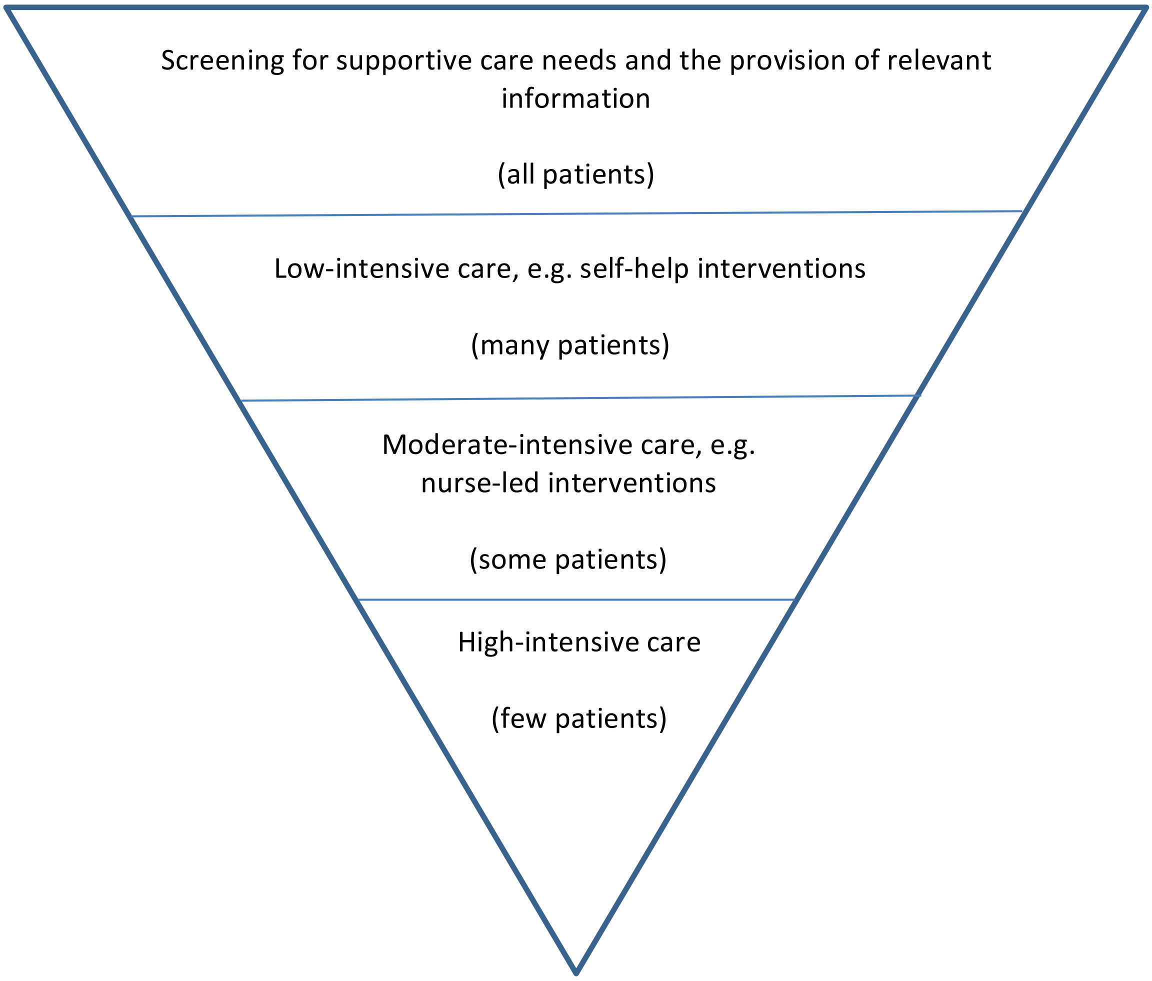

Figure 1. The (slightly-adjusted) supportive care framework of Fitch[1]

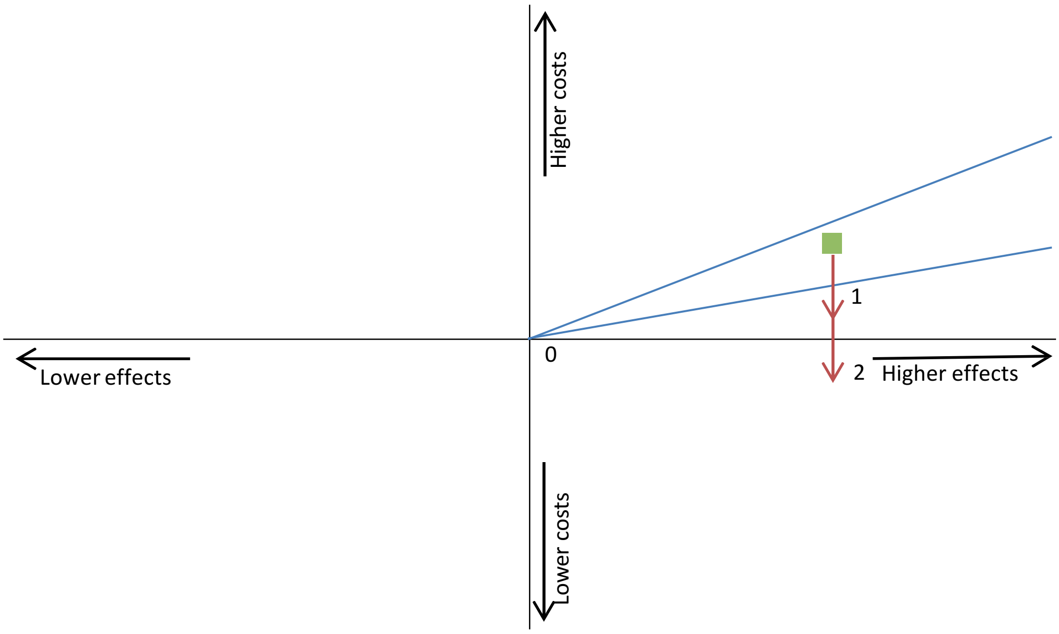

Figure 2. Visualization of a cost-effectiveness or cost-utility plane

In the following section supportive care targeting HNC patients will be discussed following the structure of the supportive care framework[1]. This section ends with a discussion on integrated supportive care approaches, such as stepped care. Also, its potential for improving the cost-effectiveness or cost-utility of supportive care will be discussed. Throughout this section, the added value of the findings presented in this thesis are emphasized.

Level 1: Screening for supportive care needs and the provision of relevant information
The first level of the supportive care framework conceptualizes that all cancer patients should be screened with respect to their need for supportive care and should be provided with relevant information. Screening and monitoring for symptoms and health-related quality of life (HRQOL) has recently also been recommended in the revised guideline on screening for psychosocial care[2]. Screening and monitoring has been found to improve communication between patients and healthcare professionals and to improve patient outcomes[3]. However, some concerns have also been reported[4,5]. One of these concerns is that screening or monitoring by itself does not improve a patient's outcomes[5]. To counteract this concern, screening and monitoring followed by the provision of individual feedback to both the patient and the care professional has been recommended[5,6]. At VU University medical center, Amsterdam, screening and monitoring for symptoms and HRQOL using a touch-screen computer system called OncoQuest in HNC patients is also followed by a consultation with a dedicated nurse[7,8]. As presented by Duman-Lubberding et al.[9], HNC patients value such a nursing consultation. They especially value the time the nurse has to discuss the patient's individual feedback, the personal conversation and advice, and the answers provided on questions about their disease, HRQOL and symptoms.

This thesis adds some information to current knowledge and practice on screening and monitoring in HNC patients by providing cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 for identifying patients with a potential unmet need for supportive care (chapter 2). These cutoff scores might facilitate the nurse or other care professional with cues on the interpretation of a patient's individual outcomes. Some concerns have, however, been reported regarding the use of such cutoff scores, as cases may be missed, and those patients identified with a deviating outcome may not necessarily have a subjective need for supportive care[4,5]. To overcome this last concern, it is recommended that the cutoff scores are used as a signal for further evaluation of a potential problem or symptom (e.g., during a nursing consultation, as is the case in OncoQuest[7,8]), instead of immediate high-intensive follow-up care (e.g., referral to a psychologist).

Level 2: Low-intensive supportive care targeting head and neck cancer patients

The second level of the supportive care framework conceptualizes that many patients identified with a need for additional supportive care may benefit from low-intensive supportive care. Low-intensive supportive care encompasses the provision of information, education, as well as self-help or self-management interventions. In current practice, there has been an increasing focus on self-help and self-management interventions, which are often offered in eHealth formats[10-13]. It is expected that such interventions may influence cancer patients' acquired skills (e.g., self-efficacy, problem-solving skills, and self-monitoring behavior), which in turn may influence patients' confidence in managing their disease. Patients' acquired skills as well as patients' confidence to manage (i.e., patient activation[14]) are hypothesized to influence patient outcomes, such as HRQOL or symptoms, and lower healthcare use and costs[15]. Previous studies have indeed found evidence for a potential effect of such interventions in terms of improved patient outcomes, such as perceived support, knowledge, and information competence[11,16]. This thesis investigated the potential association between patient activation for self-management and total costs (chapter 5). Patients with a better patient activation for self-management were likely to report lower costs than those patients with a lower patient activation. Further studies should be performed on the causality of this finding.

Low-intensive supportive care is also expected to be beneficial for HNC patients, as unmet supportive care needs among HNC patients and TL patients are high, especially regarding HNC-specific functioning (chapter 3 and 4). So far, several low-intensive supportive care interventions have been developed to target these needs[17-20]. An example is the guided self-help program 'In Tune without Cords' for TL patients. In Tune without Cords encompasses information and self-care skills education on stoma care, voice prosthesis care, speech, smelling, nutrition and mobility, and a guided self-help exercise program targeting speech, swallowing and shoulder problems[18,21]. A pilot study showed that this self-help intervention of In Tune without Cords was appreciated by patients[18]. Currently, a randomized controlled trial on the effectiveness and cost-utility of the guided self-help exercise program of In Tune without Cords is being conducted[20].

Level 3: Moderate-intensive supportive care targeting head and neck cancer patients

The third level encompass providing moderate-intensive supportive care, such as nurse-led specialized interventions or group interventions, to those patients for whom low-intensive care is not sufficient. Examples of moderate-intensive interventions developed for HNC patients are a group exercise program targeting physical fitness[22] and a nurse-led intervention for depressive symptoms and HNC-related physical symptoms[23,24]. Beneficial results have been reported regarding feasibility and effectiveness on fitness outcomes, symptom management, HRQOL, and symptoms of depression[22-24]. None of these studies have, however, investigated its cost-effectiveness or cost-utility so far. Previous psychosocial nurse-led interventions or psychosocial group interventions targeting cancer patients (non-HNC) have, however, in general, found that such interventions have the potential to be effective at additional costs (see Arving et al.[25], Lemieux et al.[26], Lengacher et al.[27], Mewes et al.[28] and Sabariego et al.[29] as reviewed in chapter 6). The acceptability of these additional costs depends on the willingness-to-pay for an incremental unit of effect (as visualized in Figure 2). For quality adjusted life years (QALYs), the National Institute of Health and Clinical Excellence has proposed a willingness-to-pay threshold of £20,000 – 30,000 per QALY[30,31]. When using this threshold, several of the psychosocial care interventions are likely to be cost-effective. This may warrant implementation of these interventions in clinical practice. In the Netherlands, however, no such willingness-to-pay threshold exists (although higher thresholds have been proposed for more serious diseases[32]). Therefore, such a willingness-to-pay threshold with respect to supportive care is called for.

Level 4: High-intensive supportive care targeting head and neck cancer patients

Finally, the last level includes high-intensive supportive care targeting a small subgroup of all patients. High-intensive supportive care interventions are, for example, intensive and ongoing consultations with a speech therapist to target speech or swallowing problems or individual psychological interventions (e.g., cognitive behavioral therapy). Previous studies found that such individual psychological interventions are likely to be effective, especially when the study preselects patients regarding their level of symptoms[33]. This is also the idea underlying this supportive care framework (i.e., saving the high-intensive interventions for those patients for whom interventions with lower intensity are not sufficient). So far, two studies evaluated the cost-utility of such high-intensive psychological care in respectively breast cancer and mixed cancer populations (see Arving et al.[25] and Chatterton et al.[26] as reviewed in chapter 6). Both studies reported that the total costs in the intervention group were lower, while the effects were higher (south-east quadrant of Figure 2), implicating dominance of the intervention.

Innovative approaches combining different levels into one intervention

Several supportive care interventions have been developed for HNC patients previously aiming to target patients' unmet supportive care needs. This thesis provided some evidence that such interventions have the potential to be effective at acceptable costs (chapter 5 and 6). However, more innovative approaches are called for[34,35]. Innovative interventions integrating different levels of the supportive care framework into one intervention are expected to improve cost-effectiveness or cost-utility or to be even cost saving (as visualized by respectively arrow 1 and 2 in Figure 2)[36,37].

An example of an integrated approach is the eHealth self-management application OncoKompas[38-40]. Using OncoKompas, cancer patients can monitor their symptoms and HRQOL at home, which is followed by automatically generated tailored information and support to find and obtain the supportive care they need. The advice for supportive care is tailored to a patient's individual needs as well as patient's preferences (e.g., individual or group interventions). Previous studies among HNC patients[39] and breast cancer patients[40] have shown beneficial results regarding feasibility and patient satisfaction and, possibly, also effectiveness in improving patient activation. Until now cost-utility of such an integrated eHealth self-management application targeting (HNC) cancer patients is unclear. Therefore, currently a multicenter randomized controlled trial is conducted coordinated from the Vrije Universiteit, Amsterdam, with the aim to find these answers[38].

Other examples of integrated approaches are collaborative care or stepped care interventions targeting anxiety and depression. Collaborative care is a multidisciplinary care model in which different healthcare providers (e.g., a psychologist or psychiatrist) actively collaborate in the treatment of a patient, assisted by a case manager (e.g., a nurse), and typically combines psychological and pharmacological treatments[41]. Stepped care is an approach in which effective, yet low-intensive treatment is delivered to the patient first (e.g., an intervention of level 2), followed by more intensive treatments if symptoms do not resolve (e.g., an intervention of level 3 or 4). Both collaborative care and stepped care have been found to be effective in improving outcomes (e.g., HRQOL and symptoms of depression) of cancer patients[41,42]. To shed light on the potential of such interventions to improve cost-effectiveness or cost-utility of supportive care, this thesis investigated the cost-utility of a stepped care approach targeting psychological distress in HNC and lung cancer patients. It was found that stepped care was highly-likely to be more effective and less costly compared to care-as-usual (chapter 7). Collaborative care on the other hand has been shown to be effective in cancer patients, however, at additional costs (see Choi Yoo et al.[43], Duarte et al.[44], Strong et al.[45] and Walker et al.[46] reviewed in chapter 6).

One reason why the study on the stepped care intervention found lower total costs, in contrast to previous studies on collaborative care[43-46], may be the societal perspective from which the analyses were performed. This perspective takes into account both healthcare costs and other costs from a societal perspective, such as productivity losses and informal care costs. Usage of a societal perspective is also recommended in current guidelines, including the Dutch guideline of the National Healthcare Institute[31,47-49]. Previous studies on collaborative care, however, were all performed from a healthcare perspective[43-46]. Another reason may be the stepped care design itself. This stepped care program started with two weeks of watchful waiting (step 1), after which 28% recovered from their symptoms (as presented by Krebber et al.[42]). After step 2 (guided self-help), 34% of the participants recovered. When still not recovered, more resource intensive care was offered, namely face-to-face problem-solving therapy (step 3), and specialized psychological interventions and antidepressant medication (step 4). High-intensive, resource-intensive treatments are thus only offered to a small sample of the study population, reducing costs of the supportive care intervention itself.

More research is, however, needed to investigate in more detail the potential of stepped care interventions to be less costly. Other studies in non-cancer populations often found evidence for beneficial effects of stepped care at higher costs[50-58]. Also, more knowledge into the cost-effectiveness of other integrated supportive care interventions is needed. To enhance comparability of findings, it is recommended that in line with the Dutch guideline[47,49], the studies are performed from a societal perspective. In addition, it is recommended that QALYs are used as outcome measure, preferably measured using the EQ-5D, as this increases comparability of outcomes among types of interventions and different diseases. Besides the primary analysis, additional analyses can be conducted using a different outcome measure (e.g., the QLU-C10D based on the EORTC QLQ-C30[59]) or from a different perspective (e.g., a healthcare perspective). Although the societal perspective is the perspective of first choice, it is acknowledged that there is a need to specifically focus on healthcare costs. To bend the cost curve in healthcare, the concept of value based healthcare of Porter and Teisberg (2006) has been introduced in the last years, conceptualizing that shifting current perspective from volume-based to patient-centered care may improve patients' outcomes and lower healthcare costs at the same time[60-62]. Further insight is needed into how this concept may influence current supportive care targeting HNC patients.

STRENGTHS AND LIMITATIONS

A strength of this thesis is the wide range of aspects taken into consideration with regard to optimal supportive care, i.e., from measuring the need for supportive care to the cost-effectiveness or cost-utility of supportive care. Cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 have been identified in this thesis, and a patient-reported outcome measure for measuring unmet supportive care needs has been psychometrically evaluated. This valid and reliable patient-reported outcome measure was used in chapter 4 to measure supportive care needs among TL patients, which is a strength of this thesis. Another strength is the societal perspective used in chapter 5 and 7, which provides a thorough overview of costs that may be influenced by supportive care interventions. The conduction of cost-effectiveness or cost-utility analyses from a societal perspective has also been recommended in several guidelines[31,47,48]. Besides analyses from a societal perspective, additional analyses from a healthcare perspective may be performed. Finally, a strength of this thesis is the up-to-date methodology used to perform the analyses. In chapter 5 and 7, for example, missing data were imputed using multiple imputation. In addition, bootstrapping was performed to provide insight into the uncertainty surrounding the findings.

Some limitations should also be noted. The studies included in this thesis were conducted in relatively small sample sizes ranging from 96 to 288 patients, limiting the statistical power of the analyses. In addition, study participants may not have been representative for the entire group of HNC patients, limiting generalizability of findings to all patients. For example in chapter 2 and 3 only HNC patients were included who completed curative treatment, thereby hampering the generalizability of findings to HNC patients still under treatment or in palliative stage. However, one could also argue that results on the entire group of HNC patients are too broad to interpret in a meaningful way. From both a scientific and clinical point of view therefore a focus on subgroups of HNC patients may be favored.

Furthermore, a potential limitation is the cross-sectional design of some of the studies (e.g., chapter 4 and 5), which hampers the ability to draw conclusions regarding the causality of findings. Finally, a potential limitation of all studies is the missing data. In chapter 5, for instance, missing data on patient activation resulted in the selection of patients that were somewhat younger and that presented within a shorter timespan since TL surgery, hampering generalizability of findings. In chapter 7, patients with missing data were not excluded, however, some assumptions were made regarding the missing data (e.g., multiple imputation and linear interpolation). These assumptions may not necessarily reflect reality.

IMPLICATIONS FOR CLINICAL PRACTICE

An important finding of this thesis for clinical practice is that supportive care has the potential to be effective at acceptable costs. An integrated stepped care intervention may even be effective at lower total costs. These findings lend support for implementation of such supportive care interventions in current clinical practice. An important requirement for offering these types of interventions in clinical practice is, however, the availability of a case manager[63]. A case manager is needed to provide individual feedback to the patient after screening or monitoring for their symptoms and HRQOL (level 1 of the supportive care framework), and to discuss, if necessary, supportive care options with the patient. Also, a case manager is needed to arrange referral to appropriate supportive care tailored to the individual needs and preferences of the patient. In addition, a case manager is necessary to monitor progress of the patient and to refer a patient to a next level of the supportive care framework, in case symptoms do not resolve.

Besides a case manager, an important requirement for implementation is that reimbursement of costs needs to be arranged. Also, all stakeholders (e.g., patient, care provider and insurance companies) need to be informed on the available supportive care options. In addition, a network of care professionals or institutes that can offer the supportive care should be available. Finally, after implementation of supportive care interventions, continued monitoring and evaluation is warranted, for example using the RE-AIM model[64]. This model conceptualizes that attention should be paid to the Reach of the intervention, Efficacy of the intervention in clinical practice, Adoption of the intervention by care providers, Implementation of the intervention in clinical care, and Maintenance of the intervention in long-term clinical practice.

RECOMMENDATIONS FOR FURTHER RESEARCH

Following the chapters of this thesis and the previous paragraphs, several recommendations can be formulated for further research. Firstly, more knowledge is needed on cutoff scores when screening and monitoring for supportive care needs (level 1 of the supportive care framework), and the prevalence of supportive care needs in HNC patients. Previously identified cutoff scores on the EORTC QLQ-C30 and QLQ-H&N35 need to be replicated in other HNC populations. Also, new cutoff scores for those EORTC QLQ-C30 and QLQ-H&N35 domains for which no cutoff scores have been proposed need to be identified. Besides, in the future, cutoff scores on the newly developed QLQ-H&N43 measure may be warranted[65]. In addition, detailed insight into a patient's individual changes in EORTC QLQ-C30 and QLQ-H&N35 scores over time that mandate clinical attention is recommended[66]. Moreover, more research on the course of supportive care needs among (groups of) HNC patients over time is called for. So far, only one study investigated the course of supportive care needs among HNC patients (in this case oral cavity cancer patients)[67]. Insight into the course of supportive care needs among groups of HNC patients over time will provide detailed knowledge on the specific needs patients encounter at specific points in time and may, consequently, facilitate better tailoring of supportive care provision to those specific needs. Currently, a longitudinal cohort study is ongoing in a large group of HNC patients (i.e., up to 739) in which supportive care needs are measured, using the SCNS-SF34 and SCNS-HNC, which is expected to provide valuable information to investigate supportive care needs over time[68].

Secondly, future studies should shed light onto HNC from an economic point of view. Knowledge is needed on medical service utilization, non-medical service utilization and productivity losses among HNC patients at different points in time. This would provide insight in total costs involved in HNC patients as well as excess costs of HNC patients (i.e., how much higher are the costs in HNC patients compared to other comparable non-HNC persons). Also, more information on factors which may influence these costs is needed. Previous studies in cancer patients found that better health outcomes, such as lower levels of psychological distress[69], depression[70-72], and fear of recurrence[73,74] were associated with lower healthcare utilization or healthcare costs in cancer patients. In addition, associations between better health outcomes and other societal cost outcomes, such as between lower levels of anxiety and return to work[75] or lower levels of depression or distress and lower levels of unemployment[76,77], were reported among cancer patients, including HNC patients[75,77]. However, other studies found no such results[78,79]. Further (prospective) studies are needed into the causality of these potential associations. Unravelling these associations may provide knowledge necessary to provide HNC patients with the supportive care they need, while at the same time controlling the total economic burden of cancer.

Thirdly, more research specifically focusing on the cost-effectiveness or cost-utility of certain supportive care interventions is called for. It would be interesting to investigate whether a stepped care program in which effective, low resource-intensive care is offered to patients first, followed by more resource-intensive care in case symptoms do not resolve, will be cost-effective or even cost saving in other cancer populations or for other symptoms than psychological distress (e.g., head, neck and shoulder complaints or sleep problems). Further knowledge is also needed on the optimal order of supportive care interventions in such a stepped care approach, and other opportunities to further match the order of steps to the individual needs and preferences of a patient.

CONCLUSION

This thesis presented evidence that the need for supportive care among HNC patients can potentially be measured using both the EORTC QLQ-C30 and QLQ-H&N35 as well as the SCNS-SF34 and SCNS-HNC. As unmet needs among HNC and TL patients have been reported to be relatively high and varied, tailoring of supportive care to a patient's individual needs is necessary. This thesis found that supportive care aiming to target these unmet needs, might possibly be effective at acceptable costs. An integrated stepped care approach was found to be potentially more effective at lower total costs in HNC and lung cancer patients compared to care-as-usual. More in depth research is, however, needed on the cost-effectiveness and cost-utility of supportive care approaches targeting HNC patients.

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Summary

Chapter 1 provides background information on supportive care targeting head and neck cancer (HNC) patients. Head and neck cancer encompasses cancers originating from the oral cavity, oropharynx, hypopharynx and larynx, and is respectively the seventh and ninth most common cancer diagnosis in men and women. Due to HNC and its treatment, HNC patients often experience general and HNC-specific symptoms (e.g., fatigue, difficulty swallowing, and psychological symptoms), which can have a major influence on a patient's health-related quality of life. Supportive care can be offered in order to prevent and manage these symptoms and its influence on health-related quality of life. It encompasses information and care related to, for example, physical functioning, daily living, psychological functioning, sexuality, and lifestyle. Optimal supportive care is tailored to the needs of the individual patient, is effective, and provides good value for money (i.e., is cost-effective). The aim of this thesis was to obtain insight into supportive care needs in HNC patients using psychometrically tested patient-reported outcome measures, and to provide an economic perspective on supportive care in HNC patients.

MEASURING SUPPORTIVE CARE NEEDS IN HEAD AND NECK CANCER PATIENTS

The first part of this thesis (chapter 2, 3 and 4) focused on measuring the need for supportive care in HNC patients. C*hapter 2* aimed to identify cutoff scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions (EORTC QLQ-C30) and the HNC-specific module (EORTC QLQ-H&N35) that can discriminate between HNC patients with and without perceived unmet supportive care needs. On 12 of the 28 EORTC domains candidate cutoff scores (sensitivity ≥ 0.80 and specificity ≥ 0.60) or borderline candidate cutoff scores (sensitivity ≥ 0.70 and specificity ≥ 0.60 or sensitivity ≥ 0.80 and specificity ≥ 0.50) could be identified. Candidate cutoff scores of 90 were found for the EORTC QLQ-C30 domains physical functioning, role functioning, emotional functioning and social functioning. Cutoffs of 5 or 10 were found for the EORTC QLQ-H&N35 domains on swallowing (5), sexuality (10) and sticky saliva (10). Borderline candidate cutoff scores of 80 were found on global quality of life and of 5 - 30 on fatigue (20), oral pain (10), speech (10, 20, 30) and social eating (5). These cutoff scores may facilitate the interpretation of a patient's individual outcomes on the EORTC QLQ-C30 and QLQ-H&N35 in clinical practice.

C*hapter 3* evaluated the psychometric characteristics of the Dutch translation of the Supportive Care Needs Survey Short-Form 34 (SCNS-SF34) and the newly developed HNC-specific module (SCNS-HNC) for measuring supportive care needs in HNC patients. First, the content validity of the newly developed SCNS-HNC was investigated. The content validity was overall considered to be good, although some frequently discussed HNC topics were missing. Second, the factor structure of both the SCNS-SF34 and SCNS-HNC was investigated. For the SCNS-SF34, four underlying factors with good internal consistency were identified, namely physical and daily living (Cronbach's alpha = 0.89), psychological (Cronbach's alpha = 0.95), sexuality (Cronbach's alpha = 0.79), and health system and information and patient support needs (Cronbach's alpha = 0.95). For the SCNS-HNC two underlying factors were identified: HNC-specific functioning (Cronbach's alpha = 0.89) and lifestyle (Cronbach's alpha = 0.60), and one single item on care of your stoma and/or voice prosthesis. Third, the construct validity was investigated. Construct validity of the SCNS-SF34 and the SCNS-HNC was good; 96% and 89% of the hypothesized correlations with other patient-reported outcome measures were found, and 57% and 67% also showed the hypothesized magnitude of correlation. Regarding expected differences in supportive care needs among groups with different age, sex, treatment procedures, or time since last treatment, three of the ten hypothesis were confirmed. The SCNS-SF34 domains discriminated between treatment procedure (physical and daily living and psychological needs) and time since treatment (health system, information, and patient support needs). Finally, test-retest reliability was studied. Test-retest reliability was in general good (intraclass correlation coefficients (ICC) ranged 0.67 - 0.83), although slightly too low for the domain on lifestyle (ICC = 0.67). Based on the findings of this study it was concluded that the SCNS-SF34 and the SCNS-HNC are valid and reliable instruments to evaluate the need for supportive care among (Dutch) HNC patients.

In *chapter 4*, the SCNS-SF34 and SCNS-HNC were used to measure (unmet) needs for supportive care in a specific group of HNC patients, namely patients treated with total laryngectomy (TL). Results showed that the need for supportive care was highest for HNC-specific functioning needs (76%), followed by health system, information & patient support (69%), psychological (66%), physical and daily living (62%), sexuality (38%) and lifestyle needs (19%). In total 71% reported at least one low, moderate or high unmet need, especially regarding HNC-specific functioning (53%), psychological (39%), physical & daily living (37%), and health system, information & patient support needs (35%). Female gender, living alone, and having a voice prosthesis were significantly positively associated with unmet needs on at least one supportive care domain. A worse health-related quality of life was associated with unmet needs on all domains. As the total explained variance is with 10% – 29% rather low, further research is, however, recommended on explanatory factors in more detail. Also more research is needed on the course of (unmet) supportive care needs over time.

AN ECONOMIC PERSPECTIVE ON SUPPORTIVE CARE IN HEAD AND NECK CANCER PATIENTS

The second part of this thesis (chapter 5, 6 and 7) provided an economic perspective on supportive care. *Chapter 5* provided insight into the association between patient activation for self-management and total costs from a healthcare and societal perspective among TL patients. Patient activation was measured using the patient activation measure. A patient's total score was categorized into one of four levels of patient activation (low to high patient activation). Total costs were measured by patient self-report using the medical consumption and productivity cost questionnaire. Total costs from a healthcare perspective included healthcare costs, such as costs of visiting the medical specialist or costs of admission to the medical center. Total costs from a societal perspective included, besides healthcare costs, also costs relevant from a societal perspective, such as productivity losses and informal care costs. Results of this study showed that the total costs from a healthcare perspective in the three months prior to the study ranged from €1,346 (standard deviation (SD) = 2,597) in the group with the highest (best) patient activation level to €2,282 (SD = 3,798) in the group with the lowest (worst) patient activation level. Total cost from a societal perspective ranged from €1,909 (SD = 3,855) in the group with the highest (best) patient activation level to €2,627 (SD = 4,147) in the group with the lowest (worst) patient activation level. It was found that patients with a better patient activation for self-management are likely to report lower total costs from both a healthcare as a societal perspective, even after adjusting for socio-demographic and clinical characteristics. However, after adjustment for HRQOL, no such association seemed to be present anymore. More research is needed on the causality of the association between patient activation, HRQOL and total costs from both a healthcare and a societal perspective.

Chapter 6 reviewed the literature on the cost-effectiveness and cost-utility of psychosocial supportive care in cancer patients in general. A systematic search in PubMed and Web of Science resulted in 539 unique records, of which 11 studies were included that assessed the cost-effectiveness or cost-utility of psychosocial care in cancer patients. Most studies were recently performed (2014 or 2015) and included breast cancer or mixed cancer populations. The studied interventions included collaborative care interventions (4 studies), group interventions (4 studies), individual psychological support (2 studies) and individual psycho-education (1 study). In general, results indicated that psychosocial care is likely to be cost-effective at different, potentially acceptable willingness-to-pay thresholds.

In *chapter 7* the cost-utility of a stepped-care program targeting anxiety and depression among HNC and lung cancer patients (published after the conduction of the review in chapter 6) was evaluated by means of a randomized controlled trial. This stepped care program consisted of four steps: 1) watchful waiting, 2) guided self-help, 3) face-to-face problem-solving therapy, and 4) specialized psychological interventions and/or medication. Patients stepped-up to the next step only when symptoms of anxiety and/or depression did not resolve. In total 156 patients were randomly assigned to stepped care or care-as-usual. Total costs from a societal perspective were calculated from start of study to 12 months after the end of the stepped care or care-as-usual period. For the total effects quality-adjusted life years were calculated. Total mean cumulative costs were €-3,950 (95% confidence interval (CI) ranged €-8,158 to €-190) lower and mean number of quality-adjusted life years were 0.116 (95%CI ranged 0.005 to 0.227) higher in the stepped care group compared to the care-as-usual group. The probability that quality-adjusted life years were higher and total costs were lower in the stepped care group was 96%. Four additional analyses which were conducted to assess the robustness of this findings showed a probability of 84% - 98% that quality-adjusted life years were higher and a probability of 91% – 99% that total costs were lower. In combination with previous findings on the efficacy of this stepped care program (as published by Krebber et al. (2016)), it was concluded that stepped care is expected to be beneficial in routine HNC and lung cancer practice. Further research is needed on optimal implementation of this stepped care intervention.

DISCUSSION AND CONCLUSION

C*hapter 8* discussed the main findings presented in this thesis. Also, strengths and limitations, implications for clinical practice and recommendations for further research were outlined. To facilitate this discussion the supportive care framework of Fitch (2008) was used. This framework distinguishes among four different levels of supportive care, namely screening and monitoring, low-intensive, moderate-intensive and high-intensive supportive care. The framework conceptualizes that screening and monitoring should be offered to everyone, while each increasing level of supportive care (and often more expensive) is needed by a decreasing group of patients. This thesis specifically focused on supportive care targeting HNC patient. Findings of this thesis showed that the need for supportive care can potentially be screened using the EORTC QLQ-C30 and QLQ-H&N35 (level 1 of the supportive care framework), and that unmet supportive care needs are relatively high and varied among HNC and TL patients. Low, moderate and high-intensive supportive care interventions (level 2, 3 and 4 of the supportive care framework) aiming to target these needs were in this thesis shown to have the potential to be effective at acceptable costs. An integrated stepped care intervention targeting anxiety and depression combining different levels of the supportive care framework into one interventions was even found to be potentially effective at lower total costs. Although this thesis had several strengths, such as its broad focus and the usage of up-to-date methodology and statistical analyses, some potential limitations need to be taken into account. Sample sizes of the studies were relatively small, limiting the statistical power of the analyses. Also, the cross-sectional design of some of the studies, the impaired generalizability, and missing data are potentially important limitations. Despite these potential limitations, this thesis is expected to provide valuable information supporting implementation of supportive care interventions targeting HNC patients in clinical practice. Some specific requirements need, however, to be fulfilled to ensure optimal implementation, for example, the availability of a case manager. Also, continued monitoring and evaluation of implementation is warranted. To further enhance supportive care targeting HNC patients, more research is called for on cutoff scores to identify patients with a perceived unmet need, and the course of supportive care needs among groups of HNC patients over time. Also, more information is needed on healthcare utilization and other important societal costs among HNC patients, and the cost-effectiveness and cost-utility of supportive care approaches targeting HNC patients.

Samenvatting

(Summary in Dutch)

Hoofdstuk 1 geeft achtergrondinformatie over hoofd-halskanker en ondersteunende zorg. Hoofd-halskanker is een verzamelnaam voor kanker van de mondholte, orofarynx, hypofarynx, en larynx (strottenhoofd), en is respectievelijk de zevende en negende meest voorkomende kankerdiagnose in mannen en vrouwen. Als gevolg van (de behandeling van) hoofd-halskanker ervaren hoofd-halskankerpatiënten vaak verschillende algemene en hoofd-halskanker specifieke klachten, zoals vermoeidheid, problemen met slikken en psychologische problemen. Deze klachten beïnvloeden de kwaliteit van leven van de patiënt. Ondersteunende zorg heeft als doel om deze klachten te voorkomen of te behandelen en de kwaliteit van leven te verbeteren en omvat informatieverstrekking en zorg op het gebied van onder andere fysiek functioneren, dagelijks leven, psychologisch functioneren, seksualiteit en leefstijl. Optimale ondersteunende zorg is gericht op de individuele zorgbehoeften van de patiënt, is effectief, en levert waar voor het geld (dat wil zeggen is kosteneffectief). Het doel van deze dissertatie was om inzicht te krijgen in de behoefte aan ondersteunende zorg bij hoofd-halskankerpatiënten gebruikmakend van psychometrisch getoetste vragenlijsten. Daarnaast had deze dissertatie als doel om een economisch perspectief te geven op ondersteunende zorg voor hoofd-halskankerpatiënten.

HET METEN VAN DE BEHOEFTE AAN ONDERSTEUNENDE ZORG BIJ HOOFD-HALSKANKERPATIËNTEN

Het eerste deel van deze dissertatie (hoofdstuk 2, 3 en 4) richtte zich op het meten van de behoefte aan ondersteunende zorg bij hoofd-halskankerpatiënten. *Hoofdstuk 2* had als doel om afkapwaarden te bepalen op de European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30-questions (EORTC QLQ-C30) en de hoofd-halskankerspecifieke module (QLQ-H&N35), die onderscheid maken tussen hoofd-halskankerpatiënten met en zonder onvervulde zorgbehoeften. Op 12 van de 28 EORTC domeinen zijn er kandidaat afkapwaarden (sensitiviteit ≥ 0.60 en specificiteit ≥ 0.60) of borderline kandidaat afkapwaarden (sensitiviteit ≥ 0.70 en specificiteit ≥ 0.60 of sensitiviteit ≥ 0.80 en specificiteit ≥ 0.50) gevonden. Op de EORTC domeinen fysiek functioneren, rol functioneren, emotioneel functioneren en sociaal functioneren zijn kandidaat afkapwaarden van 90 gevonden. Daarnaast zijn er kandidaat afkapwaarden van 5 of 10 gevonden op verschillende EORTC QLQ-H&N35 domeinen: slikken (5), seksualiteit (10) en plakkerig speeksel (10). Ook zijn er borderline kandidaat afkapwaarden gevonden van 80 op het domein globale kwaliteit van leven, en van 5 - 30 op de domeinen vermoeidheid (20), pijn in de mond (10), spraak (10, 20, 30) en eten in gezelschap (5). De verwachting is dat het gebruik van deze afkapwaarden in de klinische praktijk de interpretatie van een patiënt zijn of haar individuele uitkomsten kan faciliteren.

Hoofdstuk 3 onderzocht de psychometrische eigenschappen van de Nederlandse vertaling van de Supportive Care Needs Survey Short-Form 34 (SCNS-SF34) en de nieuw-ontwikkelde hoofd-halskankerspecifieke module (SCNS-HNC) voor het meten van ondersteunende zorgbehoeften bij hoofd-halskankerpatiënten. Allereerst werd voor de nieuw-ontwikkelde hoofd-halskankermodule de inhoudsvaliditeit onderzocht (content validiteit). Over het algemeen was de content validiteit goed, echter sommige veelbesproken onderwerpen bleken nog niet opgenomen te zijn in de vragenlijst. Als tweede is de factorstructuur van de SCNS-SF34 en SCNS-HNC onderzocht. Voor de SCNS-SF34 werden vier onderliggende factoren met een goede interne consistentie gevonden, namelijk zorgbehoeften met betrekking tot fysiek functioneren en dagelijks leven (Cronbach’s alpha = 0.89), psychologisch functioneren (Cronbach’s alpha = 0.95), seksualiteit (Cronbach’s alpha = 0.79) en zorgsysteem, informatie en steun (Cronbach’s alpha = 0.60). Voor de SCNS-HNC werden twee onderliggende factoren geïdentificeerd: hoofd-halskanker specifiek functioneren (Cronbach’s alpha = 0.89) en leefstijl (Cronbach’s alpha = 0.60), alsmede een losse vraag over zorg voor de stoma en/of stemprothese. Als derde is de construct validiteit van de SCNS-SF34 en SCNS-HNC onderzocht. De construct validiteit van zowel de SCNS-SF34 als de SCNS-HNC was goed; 96% en 89% van de veronderstelde associaties werden daadwerkelijk gevonden, waarvan 57% en 67% ook de veronderstelde sterkte had. Met betrekking tot de verwachtte verschillen in ondersteunende zorgbehoeften tussen groepen die verschillen in leeftijd, geslacht, behandeling of tijd sinds laatste behandeling werden drie van de tien hypothesen daadwerkelijk gevonden. Er werden verschillen in SCNS-SF34 domeinscores gevonden tussen patiënten met verschillende behandelingen (fysiek functioneren en dagelijks leven, en psychologisch functioneren) en in tijd sinds laatste behandeling (zorgsysteem, informatie en steun). Tot slot is de test-hertest betrouwbaarheid onderzocht. De test-hertest betrouwbaarheid was in het algemeen goed (intraclass correlatie coëfficiënt (ICC) was 0.67 - 0.83), echter iets te laag voor het leefstijl domein (ICC = 0.67). Naar aanleiding van de resultaten van dit onderzoek kon worden geconcludeerd dat de SCNS-SF34 en de SCNS-HNC valide en betrouwbare vragenlijsten zijn voor het meten van ondersteunende zorgbehoeften bij hoofd-halskankerpatiënten.

In *hoofdstuk 4* zijn de SCNS-SF34 en de SCNS-HNC gebruikt voor het meten van de behoefte aan ondersteunende zorg in een specifieke groep hoofd-halskankerpatiënten, namelijk patiënten behandeld met een totale laryngectomie (TL). Uit dit onderzoek kwam dat de behoefte aan ondersteunende zorg het hoogst is voor hoofd-halskanker specifiek functioneren (76%), gevolgd door zorgsysteem, informatie en steun (69%), psychologisch functioneren (66%), fysiek functioneren en dagelijks leven (62%), seksualiteit (38%) en leefstijl (19%). In totaal rapporteerden 71% van de TL-patiënten ten minste één lage, gemiddelde of hoge onvervulde ondersteunende zorgbehoeften, met name wat betreft hoofd-halskanker specifiek functioneren (53%), psychologisch functioneren (39%), fysiek functioneren en dagelijks leven (37%), en zorgsysteem, informatie en steun (35%). Vrouw zijn, alleenwonend zijn en het dragen van een stemprothese waren significant positief geassocieerd met het hebben van onvervulde zorgbehoeften op ten minste één van de domeinen. Een slechte kwaliteit van leven was daarnaast geassocieerd met onvervulde zorgbehoeften op alle domeinen. De verklaarde variantie was met 10% – 29% echter redelijk laag, meer onderzoek naar verklarende factoren is dan ook gewenst. Ook is er meer onderzoek nodig naar het beloop van ondersteunende zorgbehoeften over de tijd.

EEN ECONOMISCH PERSPECTIEF OP ONDERSTEUNENDE ZORG VOOR HOOFD-HALSKANKERPATIËNTEN

Het tweede deel van deze dissertatie (hoofdstuk 5, 6 en 7) gaf een economisch perspectief op ondersteunende zorg. In *hoofdstuk 5* is de associatie tussen patiënt activatie voor zelfmanagement en de totale kosten vanuit een zorg en een maatschappelijk perspectief bij TL-patiënten onderzocht. Patiënt activatie is gemeten met behulp van de patient activation measure. De totaalscore van een patiënt werd vervolgens gecategoriseerd in één van de vier mogelijke levels (lage tot hoge patiënt activatie). De totale kosten zijn gemeten door zelfrapportage gebruikmakend van de medical consumption and productivity cost questionnaire. Voor de totale kosten vanuit een zorgperspectief werden diverse zorgkosten gemeten, zoals kosten voor een bezoek aan de medisch specialist en ziekenhuisopname. Voor de kosten vanuit een maatschappelijk perspectief zijn naast de zorgkosten ook andere maatschappelijke kosten (bijv. productiviteitsverliezen en kosten voor de belasting van mantelzorgers) in rekening gebracht. De resultaten van dit onderzoek lieten zien dat de totale kosten vanuit een zorgperspectief in de drie maanden voorafgaand aan het onderzoek opliepen van gemiddeld €1.346 (standaarddeviatie (SD) = 2.597) in de groep met de hoogste (beste) patiënt activatie naar €2.282 (SD = 3.798) in de groep met de laagste (slechtste) patiënt activatie. De totale kosten vanuit een maatschappelijk perspectief liepen op van €1.909 (SD = €3.855) in de groep met de hoogste (beste) patiënt activatie naar €2.627 (SD = €4.147) in de groep met de laagste (slechtste) patiënt activatie. De resultaten van het onderzoek toonden aan dat het waarschijnlijk is dat patiënten met een betere patiënt activatie voor zelfmanagement lagere totale kosten hebben vanuit een zorgperspectief en een maatschappelijk perspectief. Ook na correctie voor sociaal-demografische en klinische karakteristieken bleef deze associatie waarschijnlijk bestaan. Echter, na aanvullende correctie voor kwaliteit van leven, werd een dergelijke associatie niet meer gevonden. Meer onderzoek is nodig naar de causaliteit van de associatie tussen patiënt activatie, kwaliteit van leven en totale kosten vanuit een zorg en een maatschappelijk perspectief.

Hoofdstuk 6 presenteert de resultaten van een review naar de kosteneffectiviteit en kostenutiliteit van psychosociale zorg gericht op patiënten met verschillende kankerdiagnosen. De systematische zoekstrategie in PubMed en Web of Science resulteerde in 539 unieke resultaten, waarvan uiteindelijk 11 studies geïncludeerd zijn die de kosteneffectiviteit of kostenutiliteit van psychosociale zorg bij patiënten met kanker hadden onderzocht. Het merendeel van deze studies was recent gepubliceerd (2014 en 2015) en richtte zich op patiënten met borstkanker of een gemengde populatie met kanker. De onderzochte interventies betroffen collaborative care (4 studies), groepsinterventies (4 studies), individuele psychologische interventies (2 studies) en individuele psycho-educatie (1 studie). In het algemeen toonden de resultaten aan dat psychosociale zorg de mogelijkheid heeft om kosteneffectief te zijn tegen verschillende potentieel aanvaardbare kostendrempels.

In *hoofdstuk 7* werd een stapsgewijze zorginterventie gericht op angst en depressie bij hoofd-halskankerpatiënten en longkankerpatiënten middels een gerandomiseerde gecontroleerde studie onderzocht (gepubliceerd na het schrijven van de review in hoofdstuk 6). Deze stapsgewijze zorginterventie bestaat uit vier stappen: 1) waakzaam afwachten, 2) begeleide zelfhulp, 3) face-to-face probleemoplossende therapie, en 4) gespecialiseerde psychologische interventies dan wel medicatie. Patiënten werden doorverwezen naar een volgende stap van het stapsgewijze zorgprogramma indien de symptomen van angst en/of depressie verhoogd bleven. In totaal namen er 156 patiënten deel aan het onderzoek. Zij werden in de stapsgewijze zorggroep dan wel de gebruikelijke zorggroep geloot. De totale kosten werden berekend vanuit een maatschappelijk perspectief van start van de studie tot 12 maanden na einde van de interventie of controleperiode. Voor de effecten werd het aantal voor kwaliteit-gecorrigeerde levensjaren berekend. De gemiddelde totale kosten waren €-3.950 (95% betrouwbaarheidsinterval (BI) €-8.158 tot €-190) lager en het gemiddelde aantal voor kwaliteit-gecorrigeerde levensjaren was 0.116 (95%BI: 0.005 tot 0.227) hoger in de stapsgewijze zorggroep dan in de gebruikelijke zorg groep. De kans dat de voor kwaliteit-gecorrigeerde levensjaren hoger waren en de kosten lager was 96%. Vier aanvullende analysen welke zijn uitgevoerd om de robuustheid van de gevonden resultaten te onderzoeken toonden aan dat de kans dat de voor kwaliteit-gecorrigeerde levensjaren hoger zijn 85% - 98% is en de kans dat de totale kosten lager zijn 91% – 99% is. In combinatie met de eerdere bevindingen naar de effectiviteit van dit stapsgewijze zorgprogramma (gepubliceerd door Krebber e.a. (2016)), wordt verwacht dat dit programma van toegevoegde waarde is in de gebruikelijke zorg voor hoofd-halskankerpatiënten en longkankerpatiënten. Vervolgonderzoek is nodig naar optimale implementatie van dit programma in de klinische praktijk.

DISCUSSIE EN CONCLUSIE

In *hoofdstuk 8* worden de hoofdbevindingen van deze dissertatie bediscussieerd. Daarnaast worden pluspunten en beperkingen, implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek besproken. Om deze discussie te ondersteunen is het ondersteunende zorgmodel van Fitch (2008) gebruikt. Dit model maakt onderscheid tussen vier verschillende niveaus van ondersteunende zorg, namelijk screenen en monitoren, laag-intensieve, gemiddeld-intensieve en hoog-intensieve zorg. Screenen en monitoren moet worden aangeboden aan iedereen, terwijl elk meer intensieve niveau nodig is voor een steeds kleiner wordende groep patiënten. In deze dissertatie is specifiek gekeken naar ondersteunende zorg voor hoofd-halskankerpatiënten. Resultaten van deze dissertatie laten zien dat de behoefte aan ondersteunende zorg kan worden gemeten met de EORTC QLQ-C30 en QLQ-H&N35 (niveau 1 van het ondersteunende zorgmodel) en dat onvervulde zorgbehoeften bij hoofd-halskanker en TL-patiënten relatief hoog en divers zijn. Laag-, gemiddeld- en hoog-intensieve ondersteunende zorginterventies (niveau 2, 3 en 4 van het ondersteunende zorgmodel) voor het voorzien in deze behoeften hebben het potentieel om effectief te zijn tegen potentieel aanvaardbare kostendrempels. Een geïntegreerde stapsgewijze zorginterventie waarin verschillende niveaus van het ondersteunende zorgmodel werden gecombineerd in één interventie is hoogstwaarschijnlijk zelfs effectief tegen lagere totale kosten. Alhoewel deze dissertatie verschillende pluspunten heeft, zoals het brede perspectief en het gebruik van up-to-date methodologie en statistische analyses, zijn er ook een aantal potentiële beperkingen waarmee rekening moet worden gehouden. Zo waren de studiegroottes redelijk klein, wat invloed heeft op de statistische power van de analysen. Daarnaast zijn de cross-sectionele designs van sommige studies, de verminderde generaliseerbaarheid en de missende data mogelijke beperkingen. Desondanks is de verwachting dat deze dissertatie waardevolle informatie geeft ter onderbouwing van de implementatie van ondersteunende zorginterventies in de klinische praktijk. Voor optimale implementatie moet er echter aan bepaalde eisen worden voldaan (bijv. de beschikbaarheid van een case manager). Ook is het van belang dat de implementatie continue gemonitord en geëvalueerd wordt. Voor het verder verbeteren van ondersteunende zorg voor hoofd-halskankerpatiënten is er meer onderzoek nodig naar afkapwaarden voor het identificeren van patiënten met onvervulde zorgbehoeften, alsmede meer onderzoek naar het beloop van ondersteunende zorgbehoeften over de tijd bij hoofd-halskankerpatiënten. Ook is er meer onderzoek nodig naar zorggebruik en andere belangrijke maatschappelijke kosten bij hoofd-halskankerpatiënten en de kosteneffectiviteit en kostenutiliteit van ondersteunende zorginterventies gericht op hoofd-halskankerpatiënten.

Addendum

Dankwoord

About the author

List of publications

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ABOUT THE AUTHOR

Femke Jansen was born in Naarden, the Netherlands, on March 16th, 1989. She graduated from secondary education in 2007 at Goois Lyceum in Bussum, and started studying Health Sciences at Vrije Universiteit Amsterdam. After obtaining her Bachelor’s degree in 2010, she continued her studies with the research Master Lifestyle and Chronic Disorders, also at Vrije Universiteit Amsterdam. She graduated in 2012 as a Health Scientist and obtained her Epidemiologist A registration in 2014. In October 2012, she started working as a research assistant at the department of Otolaryngology – Head and Neck Surgery of VUmc for the research group ‘Living together with cancer’ (chair prof. dr. I.M. Verdonck-de Leeuw). After a year, she started her PhD-project on supportive care in head and neck cancer patients at the same department. During her PhD-project, she visited the University of Bristol for three months to investigate the association between the course of symptoms of depression and survival in head and neck cancer patients, using data of the large prospective Head and Neck 5000 cohort study (PI prof. dr. A.R. Ness). After obtaining her PhD, Femke will continue her research as a postdoc researcher at the department of Clinical, Neuro and Development Psychology, section Clinical Psychology at Vrije Universiteit Amsterdam.

LIST OF PUBLICATIONS

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Jansen F, Eerenstein SEJ, Witte BI, Uden-Kraan CF, Leemans CR, Verdonck-de Leeuw IM. Supportive care needs in patients treated with total laryngectomy and its associated factors. *Submitted.*

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