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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 year¹. Head and neck cancer (HNC) is the seventh most common cancer diagnosis in men and the ninth in women¹, 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 Europe², including almost 3,200 from the Netherlands¹. 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 consumption³, with almost three quarters of all HNCs being attributable to these environmental risk factors⁴. In addition, infection with the high-risk Human Papillomavirus (HPV) is increasingly being reported as a causative factor for oropharyngeal cancer⁵.

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.

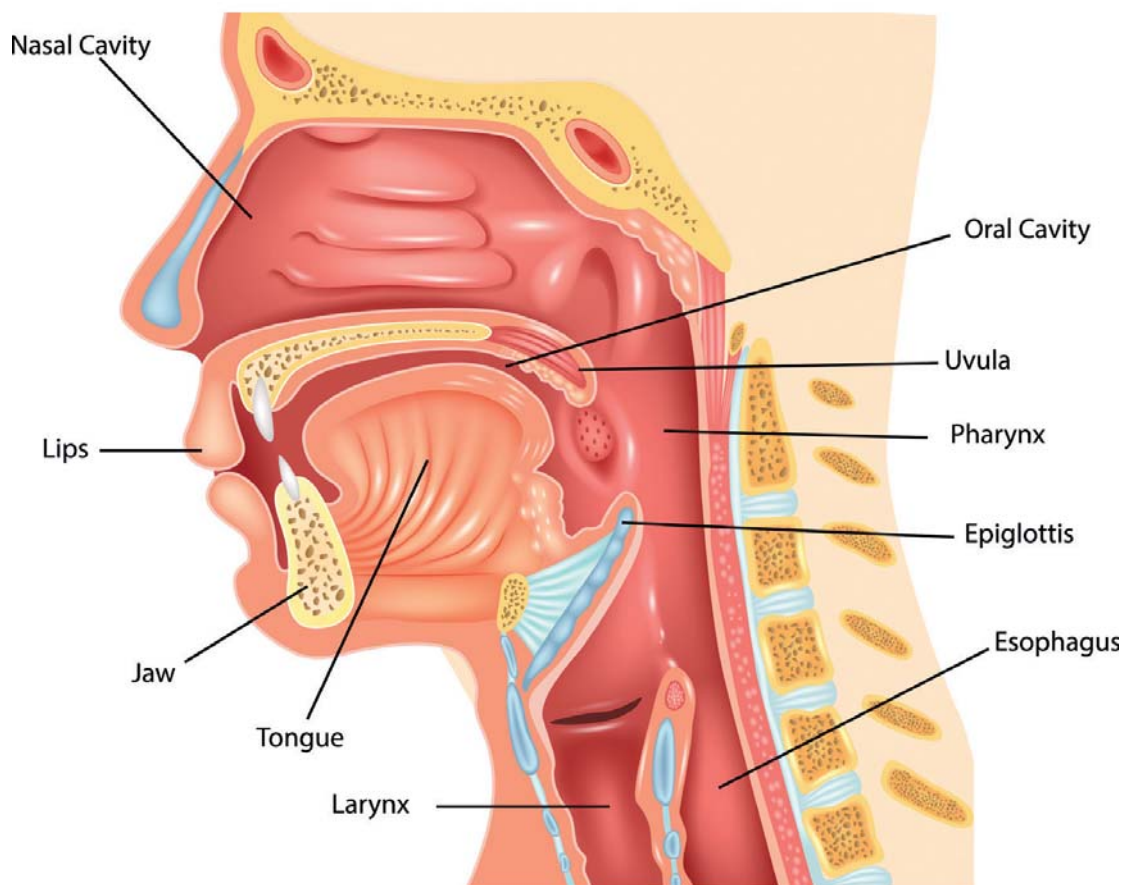


Figure 1. Head and neck region

Total laryngectomy is performed about 150 times a year in the Netherlands¹¹. 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 smell¹²⁻¹⁵.

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 problems¹⁶⁻²⁰. Also, psychological symptoms are often reported, including psychological distress, depression, anxiety, and fear of cancer recurrence²¹⁻²³.

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 functioning²⁴. 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-up²⁷.

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 treatment²⁸, and encompasses, for instance, information and care related to physical functioning, daily living, psychological functioning, sexuality, and lifestyle²⁹⁻³¹. 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 needs³²⁻³⁵. 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 levels³⁹. 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 Questionnaires⁴⁵⁻⁴⁷. 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 practice⁴⁸⁻⁵³. 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 outcomes⁵⁴. Usage of the EORTC QLQ-C30 and QLQ-H&N35 in Dutch clinical care has also been found to be appreciated by HNC patients⁵⁵. 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 sexuality³¹. Translations of the SCNS-SF34 are available in English^{31,64}, French⁶⁵, German⁶⁶, Italian⁶⁷, Mexican⁶⁸, Chinese^{69,70}, and Japanese⁷¹. In addition, several supplementary modules for use in conjunction with the SCNS-SF34, such as a breast cancer module^{72,73} or prostate cancer module⁷⁴, 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 needs⁷⁵⁻⁷⁸. 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 eHealth²⁹.

Several supportive care interventions, including self-management and eHealth interventions, have been developed specifically for HNC patients⁸²⁻⁸⁹. 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 combined⁸². 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 patients⁸²⁻⁸⁹. 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 2015⁹². 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 States⁹³. The total healthcare costs of cancer are estimated to be accountable for on average 4% of the total healthcare expenditures⁹⁴. In the Netherlands, total healthcare costs of cancer are accountable for 5% of the total healthcare expenditures⁹⁵. In comparison, cardiovascular diseases are accountable for 8% and endocrine disorders (e.g., diabetes) for 2% of the total healthcare expenditures⁹⁵. 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 months⁹⁹. 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 high¹⁰⁰. 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 costs⁹⁴.

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 cancer¹⁰²⁻¹⁰⁴. 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 outcomes¹⁰⁴.

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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