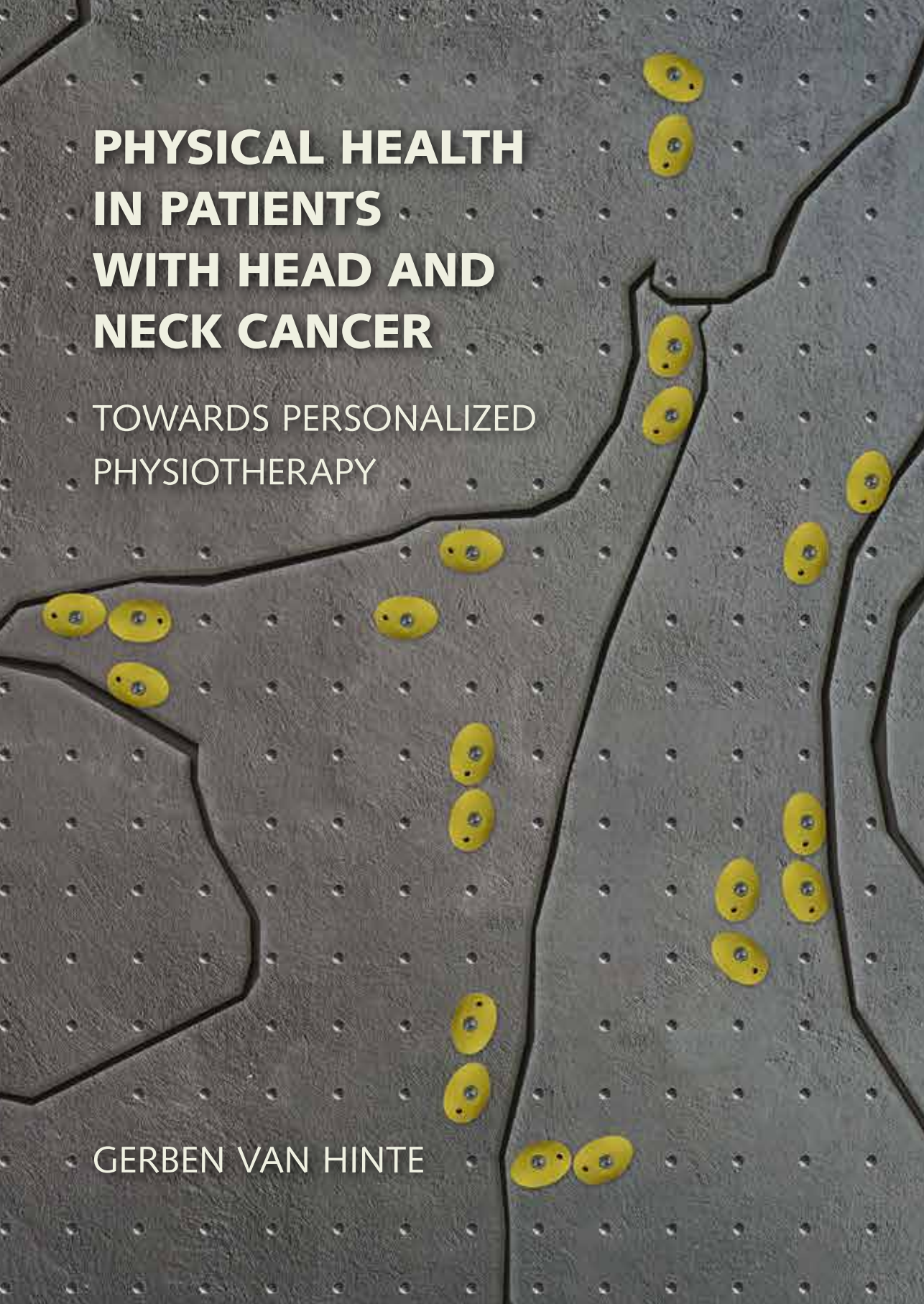

# PHYSICAL HEALTH IN PATIENTS WITH HEAD AND NECK CANCER

## TOWARDS PERSONALIZED PHYSIOTHERAPY

GERBEN VAN HINTE

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# Physical health in patients with head and neck cancer

## Towards personalized physiotherapy

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op
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om 14:30 uur precies

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**Gerben Jan van Hinte**

geboren op 10 januari 1980
te Nijmegen

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from Radboud University Nijmegen
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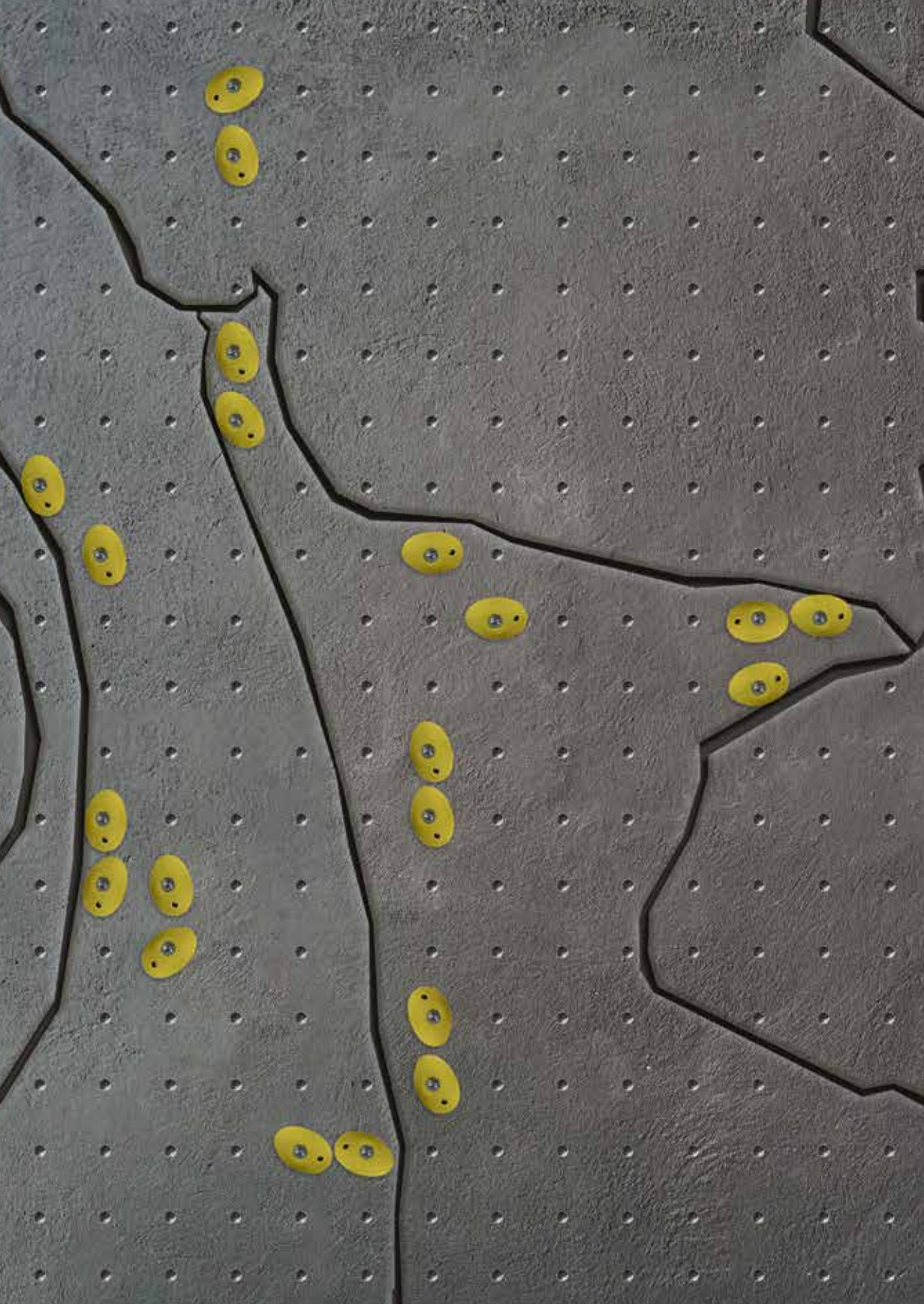

Chapter 1

# General introduction

When a patient is diagnosed with cancer, the primary focus of the medical treatment is on patient survival and the prevention of cancer recurrence. The secondary aim is to reduce treatment-related morbidity and optimize post-intervention health-related quality of life (HR-QoL). With the introduction of new diagnostic tools, new treatment modalities and advancements of existing treatments, a gradual change from cancer generic treatment into more personalized medicine is gaining speed. Personalized medicine is expected to increase survival, prevent overtreatment and reduce treatment-related morbidity. These extensive and sophisticated treatments will lead to a higher number of cancer survivors, experiencing treatment-related morbidity in physical, social, emotional, and psychological health.[1] This will lead to a higher demand on medical and supportive healthcare professionals.

In accordance with this, the importance of maintaining good physical health before, during, and after medical treatment is widely recognized as an integrated part of improving outcome and HR-QoL in cancer care.[2,3] An important role can be played by specialized physiotherapy that can prevent, identify and treat morbidity in physical health. However, with exponentially rising costs it is essential to provide personalized and cost-effective physiotherapy. It is therefore important to gain insight into patient, clinical, and intervention characteristics that increase the risk of developing treatment-related morbidity in physical health. As research shows that a blanket approach of providing physiotherapy care is likely to be less effective than a patient and cancer-specific model in which physiotherapy is employed on a patients needs basis rather than at set time points. This will likely lead to greater patient satisfaction and efficiency savings.[4]

## My personal experience

*In the past 20 years, I myself have experienced how my role as a physiotherapist, working in one of the Head and Neck Cancer (HNC) oncological centers has changed. My work as a young physiotherapist for example started with instructing all post neck dissection HNC patients in a protocolized generic exercise program for shoulders and neck mobility. Physiotherapy was regarded by other treatment professionals as a "visiting" profession. My role has since then progressed into providing physiotherapy examination and treatment that is tailored to their personals needs and problems. Physiotherapy care has thereby also been made available as a consulting professional during all phases of follow-up. Hospitals based physiotherapy is now coordinated with primary care physiotherapy and the other members of the medical and supportive care treatment team. My role*

*has changed from a "one stop" visitor into being a part of the extended treatment team. To accelerate this development, additional knowledge on reliable measurements on physical function and the identification of HNC patients at risk of developing problems in physical health is essential. With this knowledge, healthcare resources can then be focused and timed to provide effective physiotherapy care in HNC patients.*

Baring in mind, that the intensive multimodal medical intervention is aimed at an area that is very important for functioning in daily life. Patients diagnosed with HNC can experience specific treatment-related morbidity in physical health, in for example oral function (eating, talking, opening of the mouth), neck and shoulder function, or a decreased walking ability due to a decrease in general fitness. Further knowledge regarding risk profiles could improve the integration of physiotherapy services in the cancer care continuum and ultimately improve functional outcomes and quality of life for HNC survivors. Physiotherapy, however is currently only involved as a member of the extended treatment team in the Netherlands, Canada, and New Zealand.[5]

The purpose of this thesis is to specifically improve physiotherapy care by optimizing the identification of patient, clinical and intervention characteristics of patients with HNC at risk of developing limitations in physical functioning after medical intervention. This introduction starts with the epidemiology of HNC and the medical treatment modalities, followed by HNC-specific limitations in physical functioning. Then the role of the physiotherapist and current evidence on physiotherapy interventions is described. Followed by the research goals that illustrate the gap of knowledge regarding measurements in physical function and the identification of patient, clinical, and intervention characteristics that increase the risk of developing treatment-related physical morbidity in physical function. The introduction ends with the research aims and describing the research questions for each chapter of this thesis.

## Head and neck cancer

Head and neck cancer has a worldwide incidence of more than 650.000 and mortality of over 330.000 persons per year.[6] HNC is the 6th most common type of cancer in the world and ranks in the top 10 of most common cancer types in the Netherlands. [6, 7] Every year approximately 3100 people in the Netherlands are diagnosed with HNC, which includes tumors that originate

from the oral cavity, pharynx, larynx, nasal cavity, paranasal sinus, and salivary glands (www.cijfersoverkanker.nl). The survival rate is 60% after five years.[7] The most common location in the Netherlands for HNC is the oral cavity with 971 new cases in 2021 in the Netherlands (www.cijfersoverkanker.nl) and a worldwide incidence of more than 350.000.[6] The oral cavity includes the tongue, the floor of the mouth, the gingivae, the alveolar ridge, the buccal mucosa, the hard and soft palate, the uvula, and the inner part of the lips. The five-year survival rate for cancer of the oral cavity is around 60% in the Netherlands.[8] Risk factors for developing HNC are predominantly to be found in patient's lifestyle. The most important risk factors are smoking and alcohol consumption that synergistically increase the risk of HNC.[9-11] The third major risk factor is the presence of the Human Papilloma Virus (HPV) infection.[12]

## Medical intervention

The multimodal treatment of Head and Neck Cancer (HNC) can consist of surgery, radiotherapy, and/or chemotherapy. The choice and extent of treatment are influenced by patient characteristics and tumor location, tumor size, and locoregional and/or distal metastasis expressed in Tumor Node Metastasis (TNM)-status.[13] Surgical intervention can consist of removal of the primary tumor, with or without reconstructive surgery, and curative or elective lymph node dissection of the neck. Neck dissection (ND) involves the resection of cervical lymph nodes to remove regional spread or prevent recurrence due to occult metastasis. Instead of elective neck dissection, a recent development for patients with oral squamous cell carcinoma (OSCC) and no clinically detected lymph node involvement ($cT_{1\text{-}2}N_0$) is the less invasive Sentinel Lymph Node Biopsy (SLNB).[14] SLNB can assess the individual drainage pattern of lymph nodes and, using step serial sectioning and immunohistochemistry, enable the accurate detection of micro metastases and isolated tumor cells. In the case of no detected lymph node metastases, no complementing ND treatment is necessary, while a positive lymph node is followed in most cases by ND or radiotherapy.[14] In patients with $cT_{1\text{-}2}N_0$ OSCC, the choice between the two strategies Elective Neck Dissection and SLNB, is still up for debate.[15,16]

Radiotherapy as a primary treatment is used frequently in early-stage oropharyngeal, laryngeal and hypopharyngeal carcinomas.[17] Adjuvant radiotherapy and adjuvant chemo-radiotherapy can be used in HNC patients with locoregional positive lymph nodes complementary to

surgical intervention and in patient with inadequate primary tumor resection margins. Chemotherapy as a primary treatment, and in some cases immunotherapy is the choice of treatment for patients with incurable recurrent or metastatic HNSCC. The focus is then on palliation and prolonging survival.[18]

## Head and neck cancer and limitations in physical functioning

Treatment-related morbidity in physical health as experienced by HNC patients can be divided into local, regional en generic morbidity. Local morbidity can be related to alterations in the functional anatomy and physiology of the head and neck. The effect of tumor location and size often deteriorates mastication[19], swallowing (dysphagia)[20,21], and opening of the mouth (trismus).[22] These deficits may be caused by the tumor itself, but also by surgery due to resection, reconstruction, neck dissection (ND), by radiotherapy causing pain, fibrosis, skin problems, mucositis, or by systemic responses of chemotherapy.[23] Regional morbidity can be found in decreased active range of motion (AROM) of shoulders and neck, as well as a decrease in upper body strength.[24-26] The etiology is multifactorial and lies in a combination of nerve and soft tissue damage and a change in movement patterns due to pain and shoulder disuse mostly related to surgery and radiotherapy.[24, 26] An important part of shoulder morbidity can be related to loss of function of the accessory nerve (n.XI).[26-28] The 11$^{th}$ cranial accessory nerve innervates the upper trapezius and the sternocleidomastoid muscle. The loss of trapezius muscle function can limit shoulder movements that require scapular rotation and stabilization. Patients can experience limitations and pain in activities that require more than 90 degrees shoulder abduction and forward flexion. Secondary shoulder pain and limitations in function can develop due to altered shoulder kinematics and compensation strategies that cause a local overload of shoulder cuff muscles and joint capsule.[27-29] Neck and shoulder problems in HNC have a high incidence and can pose severe problems during activities in daily life and participation.[24] Generic morbidity can concern cancer-related fatigue[30], a lower level of physical mobility, decreased walking ability, and generic skeletal muscle mass depletion (sarcopenia), which limits return to work and daily activities.[31,32] Local, regional and generic morbidity leads to a decrease in functional status in HNC resulting in limitations in daily activities and difficulty returning to work, which subsequently negatively influences HR-QoL.[33,34]

# Physiotherapy

Physiotherapy aims to provide Evidence Based Practice (EBP) that relates a patient's unmet needs and beliefs to the current scientific body of knowledge. In the past two decades physiotherapy education has evolved from experience-based generic care into EBP providing specialized care. This is illustrated by master-level physiotherapy education programs leading to highly trained specialized physiotherapists. In the past decade, the oncologic and orofacial physiotherapy master's degrees were introduced. Both these physiotherapy specialists use EBP in their clinical reasoning to deduct a physiotherapy diagnosis and compose a treatment aimed at recovery, optimization, and maintenance of physical function. The orofacial physiotherapist focusses on patients with complaints in the head and neck area. The oncology physiotherapist is an expert in the treatment of patients with limitations in physical health in relation to cancer. Both specialists have overlapping fields of expertise and knowledge regarding the current body of knowledge concerning physiotherapy in HNC patients.

## Measurements

For a physiotherapist to be able to correctly assess patients with head and neck cancer on treatment-related morbidity in physical health, it is important to have adequate measurements to discriminate between the level of functioning of patients and evaluate performance. Knowledge of HNC-specific psychometric properties on measurements that assess local, regional and generic treatment-related morbidity in physical health is currently lacking. Due to the HNC-specific treatment-related morbidity and pathophysiological etiology of the limitations it is important to assess these psychometric properties specifically for HNC patients. To assist physical measurements, Patient Reported Outcome Measurements (PROMs) can be used to assess patient's perspective on disease symptoms, treatment side effects, functional status, well-being, unmet needs, and HR-QoL. PROMS can also be used for clinical research, to evaluate treatment, and to identify patients with unmet needs or limitations in physical health.

## Local morbidity

Current evidence for physiotherapy interventions for oral function is only available for limitations in the maximum mouth opening (MMO), also known as trismus.[35] Two systematic reviews describe that the included studies were very heterogenous and that the reported changes

in mouth opening ranged considerably. They concluded that treatment had no effect on the prevention of trismus but exercise therapy does have a positive effect on improving MMO in patients with trismus.[36,37] Previous research has identified that HNC patients with trismus before the medical intervention, receiving radiotherapy, or having a tumor located near the temporomandibular joint or chewing muscles leads to a higher risk of developing trismus.[22]

## Regional morbidity

Current evidence on physiotherapy interventions on neck and shoulder shows that progressive resistance training is effective for improving shoulder pain and dysfunction in patients with HNC.[38, 39] More patient-specific shoulder rehabilitation treatments that focus are currently being researched.[40] Research has identified undergoing ND as a risk factor for developing myofascial pains syndrome.[41] Neck dissection, tumor site, and extensive reconstruction are related to the deterioration of shoulder function shortly after medical intervention. [24, 42] It remains unclear if other patient, clinical or intervention characteristics influence shoulder and neck morbidity.[41]

## Generic morbidity

Post-intervention physical exercise interventions demonstrated improvements in physical function, muscular endurance, overall quality of life, and showed reduction of fatigue in HNC patients.[39]

Local, regional and generic morbidity are not self-contained manifestations in HNC patients and frequently present simultaneously. For example, a HNC patient with a limitation in MMO, causing malnutrition that is strongly associated with loss of physical functioning.[43]

# Aims and outline of the thesis

The overall aim of this thesis was to improve the identification of patients with head and neck cancer who could benefit from physiotherapy. For an adequate identification the following factors form the foundation:

1. Reliable measurement tools that can discriminate and evaluate problems in physical health in HNC survivors (Chapter 2).
2. Knowledge of limitations in physical health, as obtained with a core set of physical measurements on cancer generic and HNC-specific outcomes in HNC survivors (Chapter 3).
3. Knowledge of unmet needs for supportive care in physical health as reported by HNC survivors with cancer generic and HNC specific PROMs (Chapter 3).
4. Insight into how these limitations in physical health are associated with reported unmet needs in physical health (Chapter 3).
5. Insight into the course of shoulder and neck morbidity over a longer period of follow-up and the identification of patient, clinical and intervention characteristics that influence it (Chapter 4).
6. Insight in the different influence of the END and SLNB treatment strategies on shoulder and neck morbidity for the patient with $cT_{1\text{-}2}N_0$ cancer located in the oral cavity (Chapter 5 and 6).
7. Reflection on the results and the implications for future clinical practice, education and research (Chapter 7).

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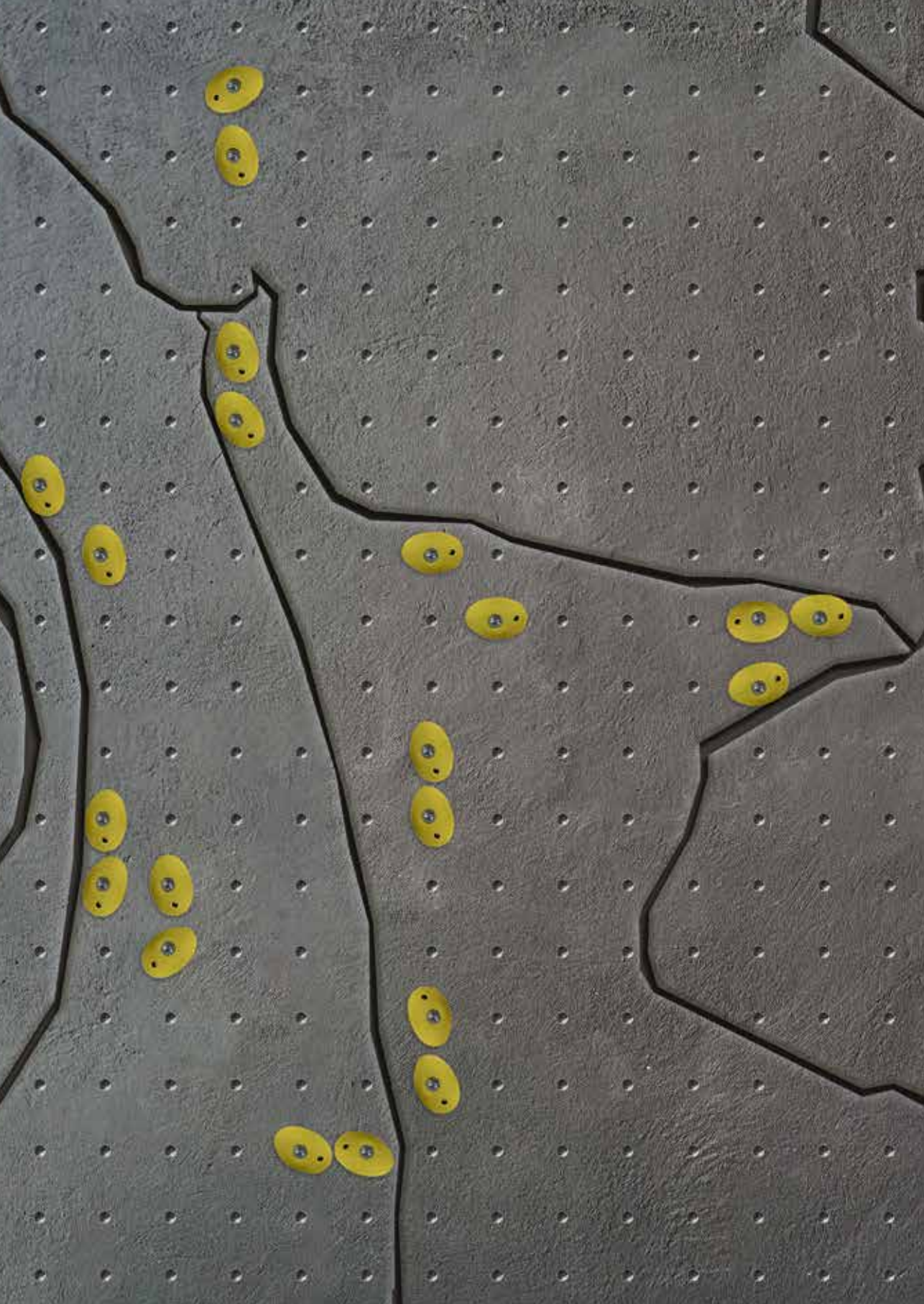

Chapter 2

# Reproducibility of measurements on physical performance in head and neck cancer survivors; measurements on maximum mouth opening, shoulder and neck function, upper and lower body strength, level of physical mobility, and walking ability

Gerben van Hinte, Ruud A. Leijendekkers, Bram te Molder, Lizzy Jansen, Corinda Bol, Matthias A.W. Merkx, Robert Takes, Maria W.G. Nijhuis-van der Sanden, Caroline M. Speksnijder

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## Abstract

**Background:** Survivors of Head and Neck Cancer experience specific problems in functional performance. The aim of this study was to obtain the test-retest reliability of measurements on Maximal Mouth Opening (MMO), shoulder and neck function, lower and upper body strength, level of mobility and walking ability.

**Materials and methods:** Test-retest study design. Measurements on MMO (intra- and extra orally), Active range of motion of shoulders and neck, 30 Seconds Chair Stand Test, Grip Strength, Timed Up and Go test, and Six Minute Walk test.

**Results:** In total 50 participants were included. The mean age was 68.6. ± 9.9 years and median time since end of treatment was 3.0 years (Q1–Q3: 1.0–5.25 years). We found good to excellent test-retest reliability on the core set of measurements (Intraclass Correlation Coefficient (ICC) 0.77 to 0.98). Measurement of MMO with cardboard card, forward flexion shoulder and Six Minute Walk test had a relatively small measurement error (Smallest Detectable Change (SDC) % 5.4% - 15.1%). Measurement of MMO with a caliper, shoulder abduction, shoulder external rotation, later flexion and rotation of the neck, grip strength, 30 Seconds Chair Stand Test, and Timed up and Go test had a relatively large measurement error (SDC% 19.8% - 44.7%).

**Conclusion:** This core set of measurements on physical performance is found reliable and therefore able to differentiate in physical performance. The reported measurement errors should be taken into consideration when interpreting the results of repeated measurements.

**Implications for Cancer Survivors:** A core set of physical measurements can be used to measure physical performance in survivors of Head and Neck Cancer.

# Introduction

Curative treatment of Head and Neck Cancer (HNC) may consist of surgery, radiotherapy, chemotherapy, or a combination of these treatments. The choice and extent of treatment is influenced by tumor size and cervical lymph node involvement expressed in TNM-status.[1] Survivors of HNC (sHNC) commonly experience treatment-related morbidity that impairs their physical, social, emotional, and psychological performance.[2, 3]

Local morbidity can be related to alterations in the functional anatomy and physiology of the head and neck. Local limitations can occur in the Maximum Mouth Opening (MMO) and other oral functions (speech, swallowing) [4-7]. Consequently, a decrease in oral function is associated with malnutrition, which is an important outcome factor for recovery and survival rate.[8-10] Regional morbidity can be found in decreased active range of motion (AROM) of shoulders and neck, as well as a decrease in upper body strength.[11-13] The etiology of limitations in neck and shoulder function is multifactorial and lies in a combination of nerve and soft tissue damage and a change in movement patterns due to pain and shoulder disuse mostly related to surgery and radiotherapy.[11, 13] Neck and shoulder problems in sHNC have a high incidence and can pose severe problems during activities in daily life and participation.[11]

General morbidity can concern cancer-related fatigue [14], a lower level of physical mobility, and decreased walking ability which limits return to work and daily activities.[15] Treatment related morbidity may be caused by surgery due to resection, reconstruction, neck dissection (ND), by radiotherapy causing fibrosis, skin problems, mucositis, or by systemic responses of chemotherapy.[16] Local, regional and general morbidity lead to a decrease in functional performance in sHNC resulting in limitations in daily activities and difficulty returning to work, which subsequently negatively influences Health-Related Quality of Life (HRQoL).[17, 18] These findings, together with an increasing number of sHNC, reveal a clear need for rehabilitation interventions focusing on problems in the physical domain. In contrast to this, research shows that sHNC are mostly sedentary (> 50%) and very few participate in moderate or vigorous exercise.[15] However, during treatment 73% of the patients indicated the need for physiotherapy. After 8-11 years, 23% still indicate a need.[19]

Several measurements provide insight into the limitations within the physical performance, such as MMO, shoulder and neck mobility, upper and lower body muscle strength, level of mobility, and walking ability. Measurement methods on MMO vary and are performed both

intra- and extra-orally.[7, 20] In cancer rehabilitation, a frequently used core set of measurements to objectify physical performance, consists of the measurement of AROM with gonio- or digital inclinometers, grip strength (GS) as proxy for upper body strength, the 30-second chair-to-stand test (30SCTS) for lower body strength, the Timed Up and Go test (TUG) for level of mobility, and the 6-Minute Walk Test (6MWT) for walking ability. This core set of physical performance measurements can be used in addition to Patient Reported Outcome Measurements (PROM's) on physical status. Insight in test-retest reproducibility of these instruments is important as it illustrates if measurements have the capacity to differentiate between sHNC when measured twice under the same conditions.[21] Insight into agreement parameters is important because it provides information on the Standard Error of Measurement (SEM) and the Smallest Detectable Change (SDC) which are essential for clinical interpretation of the (re)assessment of sHNC. Up to now, this core set of measurements was primarily studied on reliability in other patient populations or included in a case mix of sHNC and HNC patients still undergoing treatment.[22-25] Therefore, this study aims to examine the reliability, by investigating test-retest reproducibility, SEM, and SDC, of a core set of measurements on physical performance in sHNC.

# Methods

## Study setting and participants

Two subgroups participated in this cross-sectional study. Between January and June 2018, the first group of sHNC was recruited by convenience sampling from three regional patient support groups of the Dutch Head and Neck Oncology patient federation (regional support groups: Nijmegen, West-Brabant and Centre of Holland). Between March and June 2019, the second group was recruited from sHNC scheduled for usual care follow-up appointments at the Radboud university medical center. Inclusion criteria were: sHNC, completed medical treatment, 18 years or older and able to walk unaided.

sHNC that were not able to speak or understand Dutch, patients receiving palliative care, and patients at risk when performing physical measurements were excluded. The safety and possible risk when performing physical measurements was assessed before inclusion, using a modified Physical Activity Readiness Questionnaire (PARQ), leading to the exclusion of willing

participants who answered both yes to one or more out of seven questions and were judged on these items by their general practitioner to be unfit or unsafe for exercise.[26, 27]

## Sample size calculation

An a-priori sample size calculation was conducted following the recommendations of Donner & Eliasziw.[28] With a more than acceptable intraclass correlation coefficient (ICC) of 0.80, an level of significance of 0.05, and power of 0.8 ($\beta$=0.2) it was established that 45 participants were required in the final analysis. It was anticipated that approximately 10% would drop out for motivational or practical reasons. Thus, the goal became including at least 50 patients in total. This number is sufficient to achieve a score of good on adequate sample size conform the COSMIN checklist.[29] The COSMIN checklist can be used to evaluate the methodological quality of studies on measurement properties of health status measurement instruments.

## Study procedure

Members of the Dutch Head and Neck Oncology patient federation attended a presentation about the research project during a regular federation meeting. If interested, they received the patient information brochure. Before their follow-up appointment, the usual care follow-up group was contacted by telephone to inform about the study and send the patient information brochure. The week following the presentation or phone call, both groups were contacted by telephone to determine if there were any questions and acquire verbal informed consent. Participants then received the PARQ digital questionnaire using Castor (Ciwit BV, Amsterdam, The Netherlands) electronic data capture (EDC) program (http://www.castoredc.com). The measurements took place at the physical therapy department of the Radboud university medical center. Prior to the physical measurements written consent was obtained. The study was conducted according to the principles of the Declaration of Helsinki (64$^{th}$ version, October 19$^{th}$, 2013). The protocol (NL2017-3508) was approved by the Ethics Committee of the Radboud university medical center. This study followed the COSMIN checklist to ensure methodological and statistical quality and reduce bias.[29]

## Measurements

The patient's demographic and clinical data including age, sex, body weight, body height, smoking status (yes/ no/ history of smoking, packyears), alcohol usage (yes/no, number of units

daily), level of education (lower, middle, higher), social status (living alone, living with partner), years since completion of medical intervention, tumor location (oral cavity, nasopharynx, oropharynx, larynx, other), treatment modality (surgery, radiotherapy, chemotherapy, or combinations of these), and neck dissection status (yes, unilateral/bilateral, no) were obtained using a custom patient reported questionnaire send by the electronic data capture software program Castor (see also Table 1). Measurements were performed in a standardized order and according to a standardized measurement protocol. The MMO was measured using two methods. Method one measured intra-orally with a cardboard ruler (TheraBite© Range of Motion Scale, Atos Medical Inc., New Berlin, Wisconsin, United States). Method two measured MMO extra-orally with a calibrated caliper (Electronic Digital Caliper 150 mm/6", Somultishop, Echt, Holland) following a previously described protocol.[7] Shoulder abduction and forward flexion were measured with a digital inclinometer (Baseline© Digital Inclinometer, Fabrication Enterprises Inc., White Plains, New York, USA).[30] External rotation of the shoulder was measured with a goniometer (Universal goniometer, Mathys Synthes, Bettlach, Switzerland). The CROM (Cervical Range of Motion Instrument, Performance Attainment Associates, Lindstrom, Minnesota, USA) was used to measure the lateral flexion and rotation of the neck.[31] Grip strength was measured with a hand-held dynamometer (JAMAR©, Sammons Preston Rolyan, Warrenville, Illinois, USA).[32] The 30SCTS was used to examine lower body strength.[33] The level of mobility was measured with the TUG.[24] Walking ability was evaluated using a self-paced 6MWT on a 20-meter circuit.[24]

Measurements were performed by physical therapy students who received intensive training. Measurements were supervised by an experienced physical therapist. The time interval between the test and retest measurement was at least one hour and maximal two hours. Test and retest were performed by the same physical therapy student. After the first test session, the data collection form was collected by the researcher to limit bias. In accordance with guidelines, during both the test- and retest session the 30SCTS and 6MWT were measured once, MMO and neck and shoulder function were measured twice, and GS and TUG were measured three times. For both test and retest measurement, the best score of each participant was used.

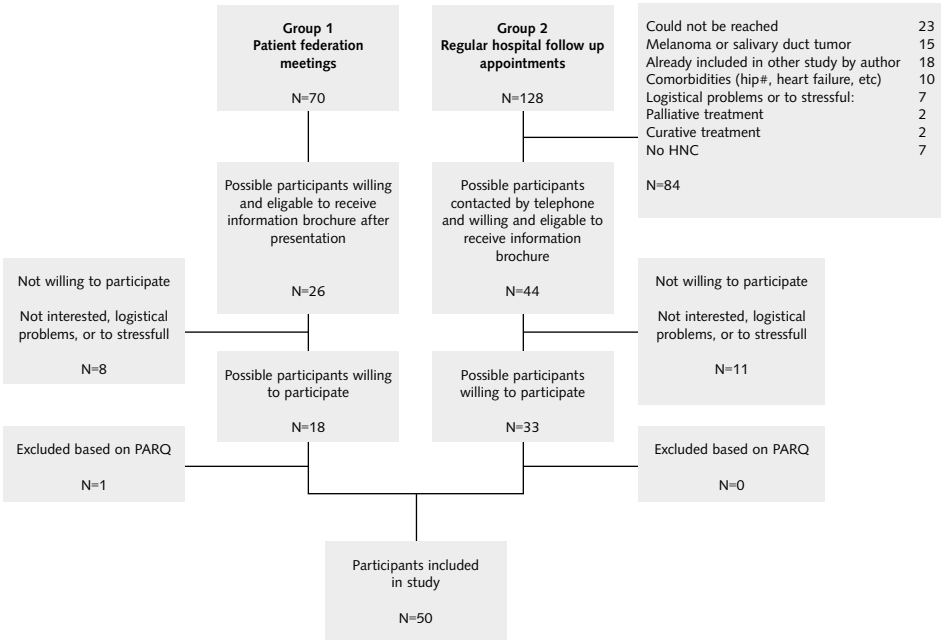
## Statistical analysis

The demographic, personal, and treatment characteristics of the participants were described. Categorical data were presented as exact numbers and percentages were calculated. For the continuous data, means and standard deviations (SD) were calculated. Differences in MMO between the two measurement methods were tested with paired samples t-test in case of normally distributed data or Wilcoxon signed rank test for not normally distributed data. Reliability was divided into test-retest reproducibility and agreement parameters.[34] Test-retest reproducibility was tested using the intraclass correlation coefficient (ICC). ICC's were calculated using a two-way mixed effect model ($ICC3.1_{agreement}$) with absolute agreement and 95% confidence intervals (CI). Cut-off points for the ICC were chosen as poor (0.01–0.20), slight (0.21–0.51), fair (0.41–0.60), good (0.61–0.80), very good (0.81–0.92), and excellent (0.93–1.00).[35] Both were expressed in the unit of measurement. SEM was calculated as $SEM_{agreement} = \sqrt{\sigma 2error} = \sqrt{(\sigma 2o + \sigma 2residual)}$.[36] The variance due to systematic differences between measurements ($\sigma 2o$) and the residual variance ($\sigma 2residual$) was obtained from the varcomp analysis.[36] The $SEM_{agreement}$ was used to calculate the $SDC_{agreement} = 1.96 * \sqrt{n} * SEM$. In this formula, 'n' refers to the number of measurements, which was two in this study. Additionally, the SDC% was calculated as agreement outcome independent of the unit of measurement. The SDC% was calculated by dividing the SDC by the mean of the summed test and retest score, then multiplied by 100. For SDC% a 20% difference was set as cut off value for measurement error being relatively small (<20%) or large (>20%). Bland-Altman plots visualize the relationship between the measurement error and the observed value including the presence of systematic bias and bias related to the magnitude of the test outcome.[37] These plots show the test-retest difference (y-axis) against the mean of the first and second test outcomes (x-axis). Mean differences between the test and retest measurements were calculated with their standard deviations to calculate the 95% limits of agreement (95% LoA). In the plot, 95% LoA are shown (mean difference ± 1.96 * SD of the difference). All analyses were performed using IBM SPSS Statistics v25 (SPSS, Inc., Chicago, Illinois, United States). In all cases, two-sided p-values smaller than 0.05 were considered to be statistically significant.

# Results

In total 50 sHNC participated in the study, of which 29 were male and 21 were female. Fig 1 shows the flowchart of the recruitment and enrollment of participants.

**FIGURE 1:** *Recruitment and enrollment participants*




HNC: Head and Neck Cancer, PARQ: Physical Activity Readiness Questionnaire

The mean age of participants was 69 years, with a standard deviation of 9.9. The median time of cancer survivorship was 3 years. All demographic, participant, and treatment characteristics are presented in Table 1.

**TABLE 1.** *Demographic, participant, and treatment characteristics*

| Characteristic | Total (n=50) | SD | PCTL 25th centile; 75th centile | % |
|---|---|---|---|---|
| Sex | | | | |
| Male, n | 28 | | | 56 |
| Female, n | 22 | | | 44 |
| Age (years), mean | 68.6 | 9.9 | | |
| Body Mass index, median | 25.0 | | 23.5 - 26.7 | |
| Smoking | | | | |
| Yes, n | 4 | | | 8 |
| Pack-years, median | 19 | | 4.0 - 34.0 | |
| No, but used to, n | 39 | | | 78 |
| Pack-years in history, median | 20 | | 9.0 - 31.0 | |
| Never, n | 7 | | | 14 |
| Alcohol usage (>1 daily) | | | | |
| Yes, n | 22 | | | 44 |
| Glasses per day, median | 2 | | 0.5 - 3.5 | |
| No, n | 28 | | | 56 |
| Level of education | | | | |
| Lower, n (%) | 20 | | | 40 |
| Middle, n (%) | 17 | | | 34 |
| Higher, n (%) | 13 | | | 26 |
| Social status | | | | |
| Living alone, n (%) | 16 | | | 32 |
| Living with a partner, n (%) | 34 | | | 68 |
| Years since cancer treatment, median | 3.0 | | 1.0 - 5.25 | |
| Tumor location | | | | |
| Oral cavity, n (%) | 28 | | | 56 |
| Nasopharynx, n (%) | 1 | | | 2 |
| Oropharynx, n (%) | 2 | | | 4 |
| Larynx, n (%) | 12 | | | 24 |
| Other, n (%) | 7 | | | 14 |
| Oncology treatment | | | | |
| Surgery, n (%) | 19 | | | 38 |
| Surgery and radiotherapy, n (%) | 18 | | | 36 |
| Radiotherapy, n (%) | 4 | | | 8 |
| Surgery, radiotherapy and chemotherapy, n (%) | 7 | | | 14 |
| Radiotherapy + chemotherapy, n (%) | 2 | | | 4 |
| Neck dissection | | | | |
| Unilateral, n (%) | 22 | | | 44 |
| Bilateral, n (%) | 6 | | | 12 |
| No, n (%) | 22 | | | 44 |

SD: standard deviation; PCTL: Percentile

**TABLE 2.***Reliability of measurements on physical performance in sHNC*

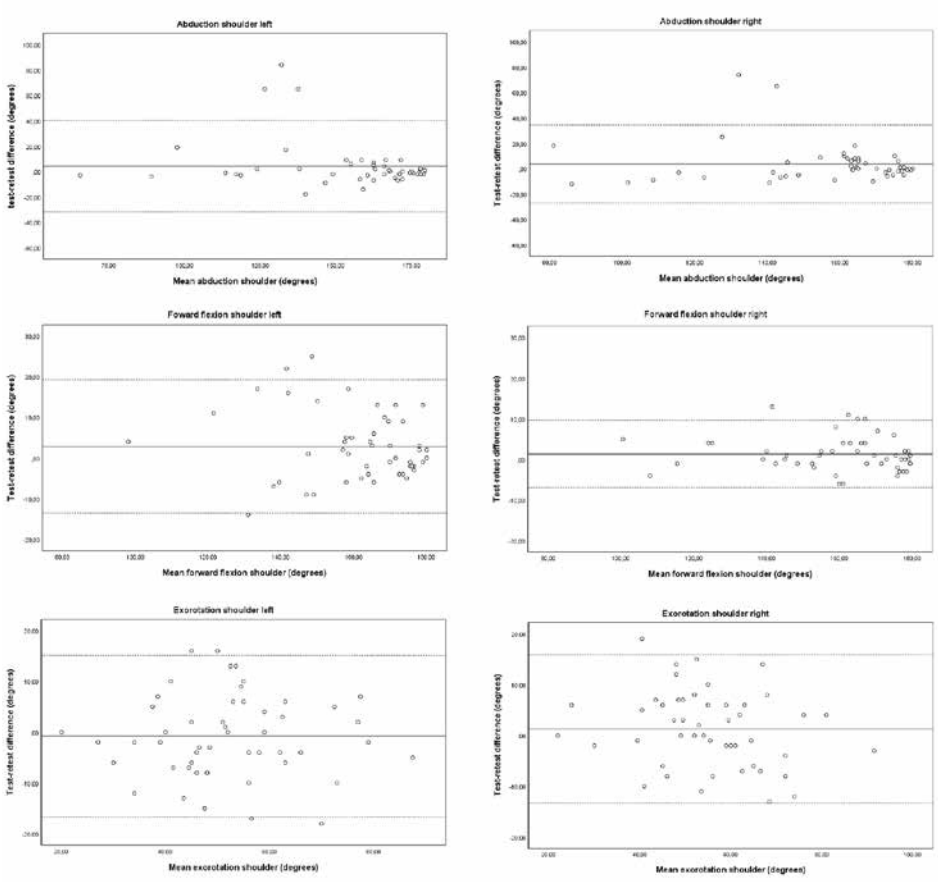
| | Test | Retest | Diff test-retest | 95% LoA | ICC3.1 (95% CI) | $SEM_{agreement}$ ** | $SDC_{agreement}$ ** | SDC % |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | | | | | |
| MMO (millimeter) | | | | | | | | |
| Card | 43.16 (10.57) | 43.98 (10.51) | -0.82 (3.30) | -7.29; 5.65 | 0.95 (0.91-0.97)* | 2.38 | 6.60 | 15.1% |
| Caliper | 44.78 (11.90) | 48.42 (11.07) | -3.63 (4.03) | -11.53; 4.27 | 0.90 (0.54-0.96)* | 3.81 | 10.57 | 22.7% |
| AROM shoulder forward flexion (degrees) | | | | | | | | |
| Left | 162.14 (17.41) | 160.16 (17.31) | 2.86 (8.38) | -13.56; 19.28 | 0.95 (0.89-0.97)* | 4,08 | 11.30 | 7.0% |
| Right | 160.64 (19.48) | 159.28 (19.86) | 1.36 (4.20) | -6.87; 9.59 | 0.95 (0.96-0.99)* | 3.09 | 8.57 | 5.4% |
| AROM shoulder abduction (degrees) | | | | | | | | |
| Left | 156.90 (25.19) | 152.62 (29.32) | 4.28 (18.40) | -31.79; 40.35 | 0.77 (0.62-0.86)* | 13.23 | 36.68 | 23.7% |
| Right | 158.36 (24.97) | 154.68 (26.48) | 3.68 (15.68) | -27.06; 34.42 | 0.81 (0.69-0.89)* | 11.28 | 31.27 | 20.0% |
| AROM shoulder external rotation (degrees) | | | | | | | | |
| Left | 51.88 (14.46) | 52.66 (14.48) | -0.78 (8.10) | -16.67; 15.11 | 0.85 (0.74-0.91)* | 5.70 | 15.80 | 30.2% |
| Right | 55.82 (13.07) | 54.52 (14.83) | 1.30 (7.45) | -13.27; 15.87 | 0.86 (0.76-0.92)* | 5.28 | 14.65 | 26.6% |
| AROM neck lateral flexion (degrees) | | | | | | | | |
| Left | 31.68 (10.47) | 31.50 (10.93) | 0.18 (5.48) | -10.56; 10.92 | 0.87 (0.78-0.93)* | 3.84 | 10.64 | 33.7% |
| Right | 32.76 (8.41) | 32.20 (8.92) | 0.56 (5.63) | -10.46; 11.58 | 0.79 (0.66-0.88)* | 3.96 | 10.97 | 33.8% |
| AROM neck rotation (degrees) | | | | | | | | |
| Left | 63.86 (11.89) | 62.66 (14.48) | -1.52 (7.18) | -15.60; 12.56 | 0.80 (0.67-0.88)* | 5.14 | 14.25 | 22.1% |
| Right | 64.26 (12.05) | 64.52 (14.83) | -0.66 (7.93) | -16.20; 14.88 | 0.79 (0.65-0.87)* | 5.57 | 15.44 | 23.9% |
| GS (kilogram) | | | | | | | | |
| Left | 29.08 (12.73) | 28.86 (14.60) | 0.22 (6.67) | -12.86; 13.30 | 0.88 (0.80-0.93)* | 4.67 | 12.96 | 44.7% |
| Right | 30.20 (14.67) | 29.68 (15.42) | 0.52 (4.23) | -7.76; 8.80 | 0.96 (0.93-0.98)* | 2.98 | 8.26 | 27.6% |
| 30SCST (number of times) | 10.56 (3.55) | 11.04 (3.90) | -0.48 (1.47) | -3.31; 2.35 | 0.92 (0.85-0.95)* | 1.07 | 2.96 | 27.4% |
| TUG (second) | 7.79 (3.69) | 7.73 (3.56) | 0.05 (0.79) | -1.50; 1.60 | 0.98 (0.96-0.99)* | 0.55 | 1.54 | 19.8% |
| 6MWT (meters) | 447.18 (117.04) | 456.68 (120.12) | -9.50 (27.59) | -63.57; 44.57 | 0.97 (0.95-0.98)* | 20.45 | 56.67 | 12,5% |

*: p<0.001; **: expressed in unit of measurement; AROM: Active range of motion; CI: confidence interval; ICC: intraclass correlation coefficient; GS: grip strength; LoA: limits of agreement; MMO: maximal mouth opening; SDC: smallest detectable change; SD: standard deviation; SEM: standard error of measurement; TUG: timed up and go; 6MWT: 6-minute walking test; 30SCTS: 30-second chair-to-stand test.

MMO showed no significant difference between the cardboard ruler and the digital caliper at the test measurement (p=0.08), but MMO measured using the digital caliper was significantly larger (10.1%) at the retest measurement compared to the card ruler (p<0.001).
The calculated ICC values ranged from 0.77 to 0.98 (see Table 2).

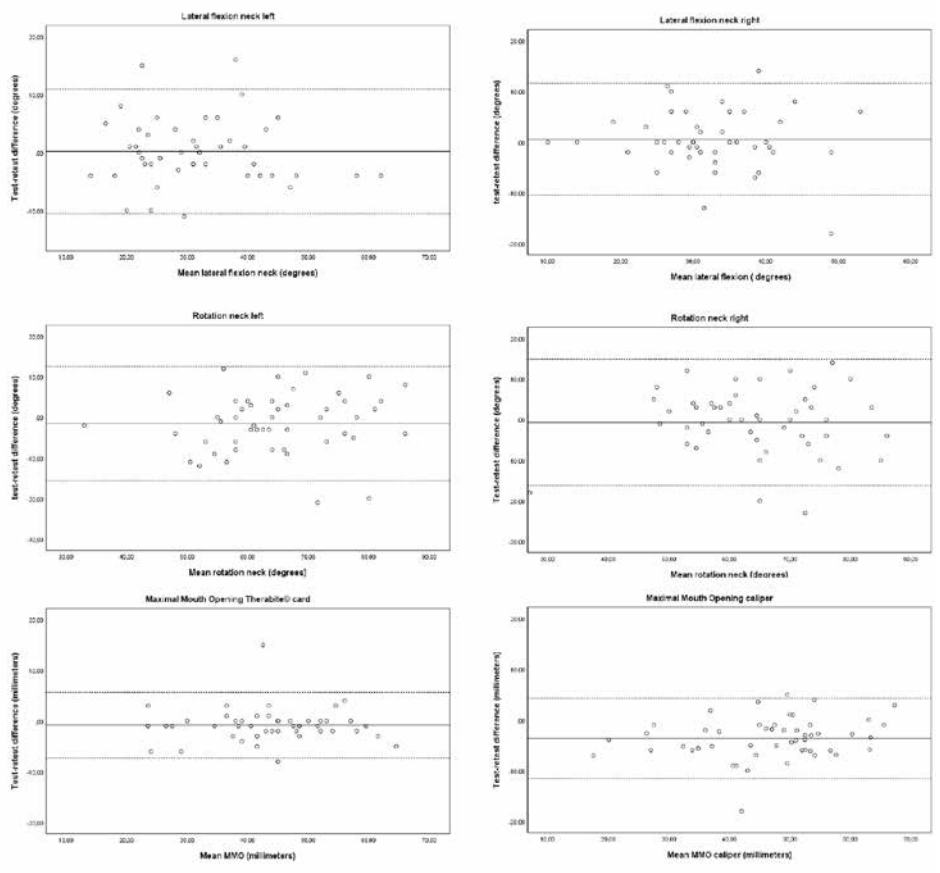
These values indicate good to excellent test-retest reproducibility.[35] Agreement expressed in SDC% ranged between 5.4% and 44.7% for the whole core set of physical measurements. MMO measured with cardboard card, forward flexion shoulder and 6MWT had an acceptable measurement error (SDC%: 5.4% - 15.1%) compared to caliper measured MMO, shoulder abduction, shoulder external rotation, later flexion and rotation of the neck, grip strength, 30SCST, and TUG (SDC%: 19.8% - 44.7%). The Limits of Agreement for all measurements are visualized in Figs 2, 3 and 4.

**FIGURE 2:** *Bland–Altman plots for test-retest reproducibility of maximal mouth opening, shoulder abduction, forward flexion of the shoulder, external rotation of the shoulder.*



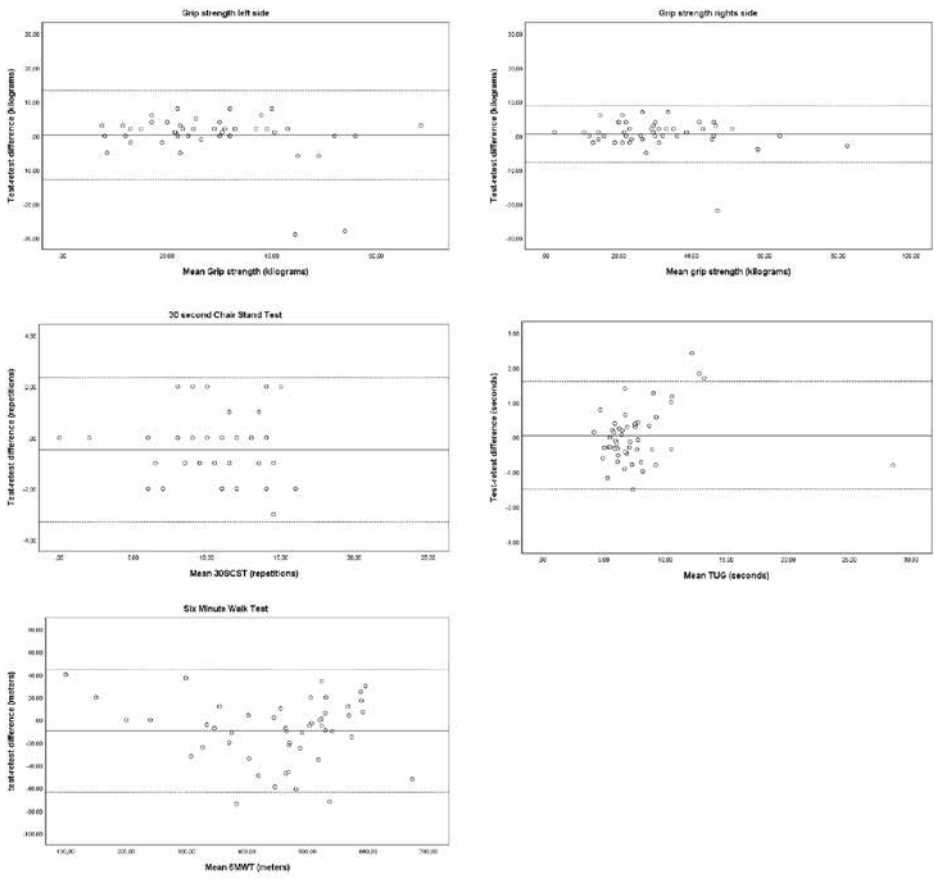

The solid line represents the mean difference (systematic bias) and the dashed lines illustrate the 95% limits of agreement (mean difference ± 1.96 SD of the difference).

**FIGURE 3:** *Bland–Altman plots for test-retest reproducibility of lateral flexion of the neck, rotation of the neck, maximal mouth opening.*




The solid line represents the mean difference (systematic bias) and the dashed lines illustrate the 95% limits of agreement (mean difference ± 1.96 SD of the difference).

**FIGURE 4:** *Bland–Altman plots for test-retest reproducibility of grip strength, 30 Second Chair Stand Test, Six Minute Walk Test, and Timed Up and Go test.*




The solid line represents the mean difference (systematic bias) and the dashed lines illustrate the 95% limits of agreement (mean difference ± 1.96 SD of the difference).

## Discussion

This study establishes good to excellent test-retest reliability of a core set of measurements on physical performance for sHNC in two frequently used measurements on MMO (Therabite© cardboard card (intra orally) and a digital caliper (extra orally)), shoulder and neck AROM, upper body strength (GS), lower body strength (30SCTS), level of mobility (TUG), and walking ability (6MWT). It also provides clinically usable information on measurement error to interpret and evaluate physical performance in sHNC. The measurement error reported in caliper measured MMO, shoulder abduction, shoulder external rotation, lateral flexion of the neck, rotation of the neck, GS, 30SCST and TUG is large in relation to the mean scores of the test and retest measurements. This leads to the question if this variance is related to the testers, the measurement procedure, or the participants. Although measurements were performed by physical therapy students, they received extensive training and supervision during measurements by experienced physical therapists. The measurement protocol was based on guidelines and training sessions were performed to solve possible uncertainties. This advocates that measurement error caused by variance in testers, or the measurement procedure should be limited. Possible variance between measurements caused by participants will be discussed per measurement.

MMO measured with the Therabite© cardboard ruler (ICC 0.95) and the digital caliper (ICC 0.90) showed ICC's that are slightly lower in comparison with measurement of MMO using a normal ruler intra-orally (ICC 0.99).[20] This however still indicates a good ability to differentiate in MMO between sHNC.[20] Digital caliper scores are systematically higher for the retest measurement compared to the cardboard ruler, indicating more variation in MMO with the digital caliper (Fig 3). One hypothesis for the higher MMO is related to observations made by the students performing the measurements. They observed sHNC experiencing fear of the digital caliper being directly in their field of view during the first test measurement. The participants might have experienced discomfort related to possible contact between the nose or chin and the metal digital caliper. This fear was less present during the retest measurement possibly resulting in a larger MMO. This variation is also illustrated by a higher SEM (3.81 to 2.38), SDC (10.57 to 6.60), and SDC% (22.7% to 15.1%) compared to the Therabite© cardboard ruler. The SEM and the SDC of the Therabite© cardboard are comparable to

measurements performed in a population with temporomandibular joint problems (SEM 2.9 and SDC 8.1 mm), providing evaluative values for clinical use. Based on these findings we would favor the use of the Therabite© cardboard ruler in sHNC.

The ICC's on shoulder abduction, forward flexion and external rotation (ICC 0.77 to 0.95) found in our study are slightly lower than ICC's measured in healthy subjects (ICC 0.95 to 0.99) With specific problems in shoulder problems to be expected in sHNC, these ICC's still demonstrate a good ability to differentiate in shoulder function between sHNC.[30] A remarkable finding is the high SDC and SDC% for shoulder abduction and external rotation. Shoulder abduction is an important indicator of accessory nerve damage, associated with a high risk of shoulder pain and limitations in activities in daily life.[38, 39] The high shoulder abduction SDC illustrates a large measurement error between test and retest scores. This measurement error is especially observed in scores on shoulder abduction smaller than 150 degrees (Fig 2). Pain, proprioceptive dysfunction, or decreased upper body strength may have contributed to the use of compensation strategies which could have resulted in confounded measurement results, increasing the measurement error. However, even with extensive training of the testers and the use of a strict measurement protocol, these compensation strategies could not be prevented. This supports clinical examination of the shoulder function by a physical therapist. Future research should take this into account when standardizing measurement protocols.

The ICC's on neck function measured with CROM device are slightly lower, and the SEM's are higher compared to literature investigating healthy subjects.[31] This could advert to the CROM device being able to differentiate between sHNC. However, the measurement error is slightly higher compared to healthy subjects when it is used in an evaluative setting. The high SDC% values confirm poor evaluative measurement properties. Variation in measurement outcomes could be related to sHNC undergoing ND surgery and radiotherapy, leading to local alterations in anatomy and physiology causing different compensation strategies.[12, 40]

GS ICC scores of 0.96 for the right side and 0.88 for the left side are in line with community-dwelling elderly (right ICC 0.95 and left ICC 0.91), which demonstrates a good ability to differentiate in upper body strength between sHNC.[41] When compared to literature, the SEM for GS was higher (SEM left 4.67, right 2.98) in sHNC compared to healthy individuals (SEM scores for men 2.77, women 1.66). The high SDC% values (45% for the left side, 28% for the right side) illustrate that the measurement error for the GS is too large to be used in a clinical setting which limits evaluative usability.[42]

The ICC found for the 30SCST (ICC 0.92) is in line with previous research investigating HNC patients (ICC 0.95)[25] and a study investigating community-dwelling adults (ICC 0.84 men, ICC 0.92 women)[33]. This indicates that the 30SCST can differentiate in functional lower body strength between sHNC. With a mean test-retest score of 11 repetitions and an SDC being nearly 3 repetitions, a sHNC must show an improvement of at least 3 repetitions (SDC% 27%) to be above the measurement error, which limits clinical evaluative usability.

The 6MWT demonstrated an ICC value of 0.97, which is in line with a study that included sHNC and patients with HNC receiving treatment (ICC 0.97). This indicates excellent capability to differentiate in walking ability between sHNC. The SEM of 20.5 meters is lower compared to patients undergoing hemodialysis (SEM 28.4) and comparable to patients with Alzheimer's, SEM 20.28. The SDC and SDC% indicate that in relation to mean 6MWT test- and retest scores a 13% change is above the measurement error.

Level of mobility was assessed by the TUG which showed a comparable ICC (ICC 0.98) to test-retest studies in people with chronic conditions as Parkinson or stroke.[43, 44] The Bland Altman plot showed homogenous scores for the TUG in our sample (Fig. 4). This disputes whether the TUG should be a standard test to differentiate in the level of mobility in sHNC. The SDC score (1.54 sec.) seems relatively small but in percentage (SDC%: 20%) to the average scores (7.73 to 7.79 sec) it is quite large regarding evaluative purposes.

## Strengths and limitations of this study

This study followed the COSMIN checklist to ensure methodological and statistical quality and reduce bias. Similar to other studies, the participants in this study represent a heterogeneous group of sHNC, displaying different characteristics.[45-49] Although specific subgroups in sHNC (for example, patients after laryngectomy) are known to have specific problems in physical performance.[50] The heterogeneity in this sample is likely to provide an adequate representation of the total group of sHNC as found in daily practice. Therefore, this study provides clinically useful information on reliability of a core set of measurements on physical performance.

The selection of participants came from two different groups resulting in a heterogeneous sample of sHNC that improves generalizability. The sHNC contacted through the patient federation had no treatment relationship with the researcher. For this reason, they were asked to report on treatment and tumor characteristics. This allows for mistakes and misinterpretations

by the sHNC. The time interval between the test and retest measurement was at least one hour and maximal two hours. Even though intervals of one or two weeks are typically recommended by experts to allow recovery and limit recall bias.[51] The time between the test and retest measurement was chosen because of logistical reasons and was estimated to be long enough to recover from fatigue; the data showed no signs of fatigue. Higher retest measurements were found for both measurements on MMO and 6MWT. This indicates a possible learning effect for these outcomes. This initial learning effect has not been found in previous literature for measurements on MMO and is in line with literature for 6MWT.[52] For all three measurements it does not influence reliability. Another limitation is the absence of measurements on inter-rater reliability. An additional measurement to determine inter-rater reliability was deemed to be too exhausting and time consuming for participants.

### Clinical relevance

More than half of sHNC are sedentary and experience specific problems in physical performance due to treatment of the head and neck area.[15] Insight into reliability of a core set of measurements on physical performance in sHNC is essential to improve supportive care and research on the physical performance of sHNC. To gain full insight into sHNC physical status these measurements can be used in addition to Patient Reported Outcome Measurements (PROMs) that measure patients' perceptions and views on physical status and performance.

## Conclusion

This study demonstrated good to excellent test- retest reliability of a core set of measurements on physical performance which illustrates that this coreset can be used to differentiate in physical performance between sHNC. The reported measurement errors should be taken into consideration when interpreting the results of repeated measurements.

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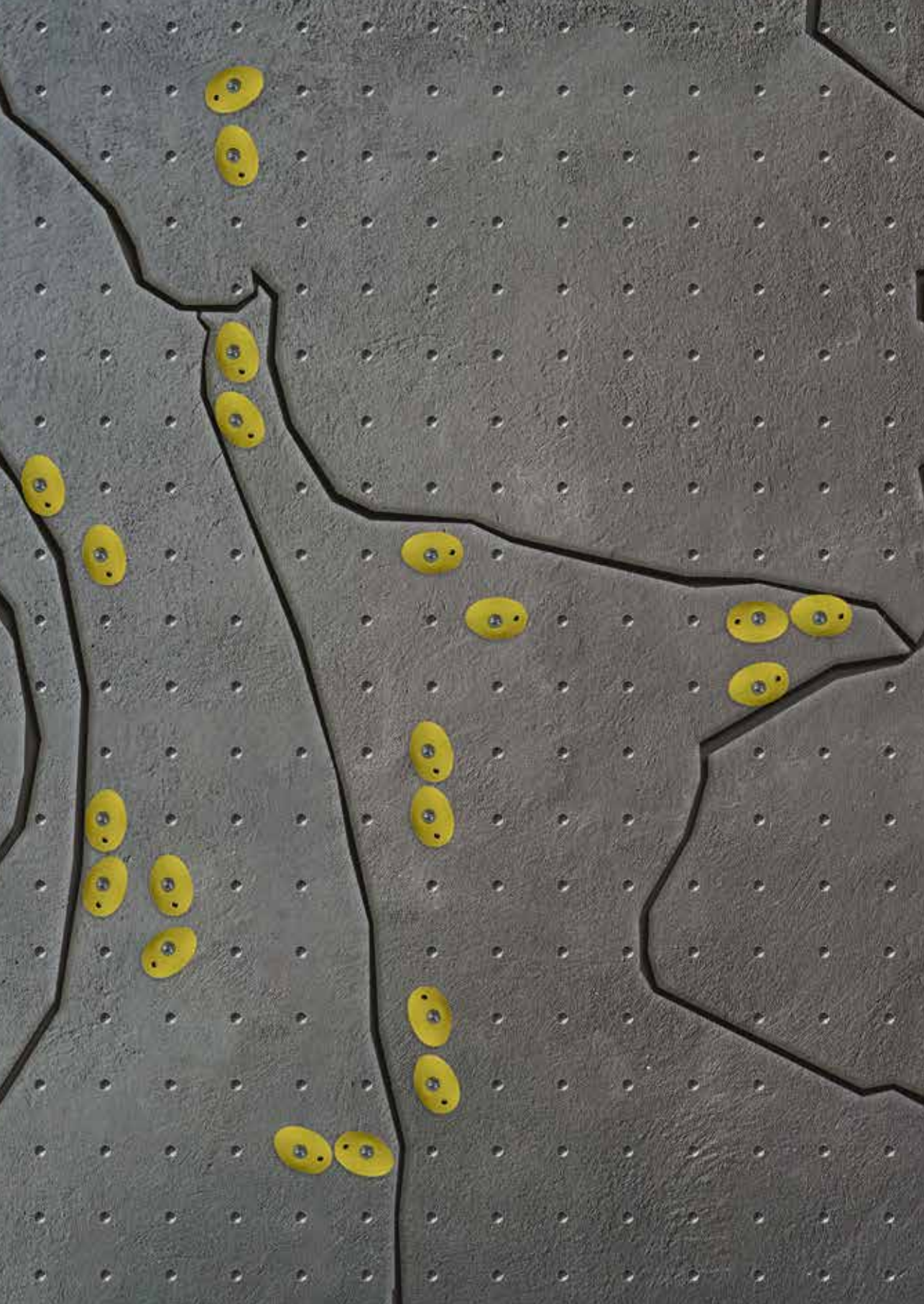

Chapter 3

# Identifying unmet needs and limitations in physical health in survivors of Head and Neck Cancer

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## Abstract

**Objective:** To gain insight into the level of unmet needs and limitations in physical health experienced by survivors of head and neck cancer, and to evaluate if unmet needs in physical health and limitations in physical performance are associated.

**Materials and methods:** In this cross-sectional study unmet needs were measured with Supportive Care Needs Surveys (SCNS-SF34, SCNS-HNC). Limitations in physical health were measured for maximal mouth opening, neck and shoulder function, hand grip strength and lower body strength, level of mobility, and walking ability.

**Results:** The SCNSs showed that 48% had a cancer generic unmet need and 46% had at least one HNC specific unmet need. In total 76% of sHNC had a cancer generic limitation in physical health and that 58% had an HNC specific limitation in the mobility of neck and shoulders or maximum mouth opening. The domain of physical and daily living needs showed a weak association with lateral flexion of the neck to the left (R = -0.319; $P = 0.024$).

**Conclusion:** Survivors of HNC might benefit from the use of both SCNSs and physical performance measurements during usual care follow up for early and optimal identification of unmet needs and limitations in physical health.

# Introduction

Head and neck cancer (HNC) is a major healthcare issue, reflected by a worldwide incidence of more than 650.000 and mortality of over 330.000 persons per year.[1] Advancements in medical treatment and diagnosis have led to an increase in the number of survivors of Head and Neck Cancer (sHNC). In contrast, a high number of sHNC experience treatment-related morbidity causing deficits in physical, social, emotional, and psychological health. These deficits influence the Health-Related Quality of Life (HR-QoL) negatively.[2-4] Physiotherapy, as part of the interdisciplinary treatment team, focuses on the treatment of limitations in physical health. Treatment indications are limitations in Maximum Mouth Opening (MMO), neck and shoulders function, hand grip strength (HGS) and lower body strength, level of mobility, and/or walking ability.[5-11] The reported incidence of these physical limitations is high but varies considerably due to heterogeneous study populations, treatment modalities, and different methods of measurement.[5-11] However, an important prerequisite for initiating physiotherapy intervention is adequate identification of sHNC with unmet needs or limitations in physical health. The identification of sHNC with unmet needs or limitations in physical health can be based on Patient Identified Problems (PIPs), and Non-Patient Identified Problems (NPIPs), as described by Rothstein et al.[12] The PIPs are defined as unmet needs or limitations expressed by sHNC during for example follow-up consultations. Identification of possible unmet needs or limitations requiring physiotherapy is thereby dependent on the ability of sHNC to express and recognize their limitations in physical health. This can result in an inconsistent referral and fragmented care.[13] The identification of NPIPs concerns the unmet needs and limitations that remain unrecognized or unexpressed by sHNC. The NPIPs can be identified by the treatment team during follow-up based on clinical reasoning, physical performance measurements, and Patient Reported Outcome Measurements (PROMs). For example, a sHNC who is satisfied with being on a liquid diet and doesn't express any limitations during follow-up could still be identified with trismus through a simple measurement of MMO. This patient can consequently be made aware of the problem and its consequences, and possibly start treatment. The identification of NPIPs is important because when left untreated, limitations in physical health can negatively influence treatment-related morbidity and HR-QoL.[2, 4, 14]

The identification of unmet needs and limitations in physical health can therefore possibly be optimized by routinely using Supportive Care Needs Surveys (SCNSs) and Physical

Performance Measurements during follow-ups.[15, 16] SCNSs offer valid and reliable PROMs that give insight into the level and area of the experienced unmet needs in physical health but the use of SCNSs shows great variation across HNC treatment centers.[17] Physical performance measurements alternatively offer objective outcomes on limitations in physical health. Limitations in physical health can be objectified for each sHNC with the use of age and sex-stratified reference values. Physical performance measurements are currently no routine part of clinical follow-up and are mainly performed for research purposes.[18]

This study, therefore, aims to get insight into the level of unmet needs and limitations in physical health as measured with SCNSs and physical performance measurements for sHNC. The secondary aim of this study was to assess if unmet needs in physical health as identified by SCNSs, and limitations in physical health as identified with physical performance measurements measure the same construct within physical health. If they measure the same construct, there would be no need for implementing both methods during clinical follow-up consultations. It was hypothesized that worse performance on physical performance measurements would be associated with more unmet needs measuring the most similar construct in physical health. The findings of this study could help to optimize the identification of sHNC with limitations in physical health.

# Methods

## Study setting and participants

Participants for this cross-sectional study were recruited between January 2018 and June 2019. Two convenience samples were used. The first group was approached during patient support group meetings of the Dutch Head and Neck Oncology patient federation. The second group consisted of sHNC scheduled for usual care follow-up appointments at Radboud university medical center (Radboudumc, Nijmegen, The Netherlands). Measurements took place at the physiotherapy department of the Radboudumc in Nijmegen, the Netherlands. SHNC were included in this study when they completed medical treatment and were 18 years or older. SHNC were excluded from this study when they were not able to speak or understand Dutch, were receiving palliative care, or were at risk when performing physical measurements. Safety and possible risks during physical measurements were assessed before inclusion, using the modified Physical Activity Readiness Questionnaire (PARQ). Participants were also excluded

if they answered both yes to one or more out of seven questions of the PARQ and were judged to be unsafe to participate in exercise after patients contacted their general practitioner.[19, 20] Prior to the physical measurements written consent was obtained. This study was conducted according to the principles of the Declaration of Helsinki (64th version, October 19th, 2013). The protocol (NL2017-3508) was approved by the Ethics Committee of the Radboudumc. The electronic data capture (EDC) program of Castor (Ciwit BV, Amsterdam, The Netherlands; http://www.castoredc.com) was used for filling out the questionnaires by the participating sHNC in this study and for storing all physical performance measurement data.

## Measurements

Cancer generic unmet needs were measured with the Supportive Care Needs Survey Short-Form 34 (SCNS-SF34). Head and neck cancer specific unmet needs were identified with the Supportive Care Needs Survey Head and Neck Cancer (SCNS-HNC).[21]

Cancer generic limitations in physical health were identified with physical performance measurements on HGS and lower body strength, the level of mobility, and walking ability. SHNC specific limitations in physical health were measured for MMO, and neck and shoulder function.[18] Limitations in physical health were defined as participants scoring 80% or lower on the physical performance measurement in relation to validated age and sex reference values. The cut-off value of 80% was based on the author's expert opinion and considers the previously published measurement errors.[22]

## Supportive Care Needs Surveys

The SCNS-SF34 was used to measure generic cancer-related unmet needs as experienced in the last month. It consists of 4 underlying domains using 34 items: physical and daily living needs (5 items), psychological needs (10 items), sexuality needs (3 items), health system need (1 item), and information and patient support needs (15 items).[17, 21] Each item can be scored on a 5-point scale. Each scale can be divided into a "no need" category (1 = not applicable, for issues that were no problem to the patient; 2 = satisfied, for issues on which a patient needed support but the support was satisfactory) and a 'need' category that has three subcategories (3 = low need, 4 = moderate need, and 5 = high need) indicating the level of need for additional care. To interpret this, scores of 2 or lower indicate no unmet need, and scores higher than 2 indicate some level of unmet need. A standardized Likert summated for unmet needs per domain can be calculated and converted to a standardized 0 to 100 score, with a higher score

indicating a higher level of need. For this study only the physical and daily living needs domains were used.

The SCNS-HNC measured HNC-specific unmet needs for supportive care in the last month. It measures the need for supportive care for 11 HNC-specific issues using the same scaling (1 to 5 Likert scale) as the SCNS-SF34 added by one single free-text item in which patients could report any additional needs.[17] For this study, next to the total score, we selected the questions with relevant outcomes in physical health. These were question 1: "Do you have an unmet need for help with problems with chewing and/or swallowing?", and question 9: "Do you have an unmet need or problem in the mobility of neck and shoulders?".

Both the SCNS-SF34 and SCNS-HNC were found to be reliable and valid in Dutch.[17] The test-retest reliability of SCNS-SF34 and SCNS-HNC domains shows Intraclass Correlation Coefficients (ICC's) of 0.74 to 0.83.[17]

## Physical performance measurements

### Maximum mouth opening

The MMO was measured intra-orally with a cardboard ruler (TheraBite© Range of Motion Scale, Atos Medical Inc., New Berlin, Wisconsin, United States). The measurement of MMO with a cardboard ruler is found test-retest reliable (ICC of 0.95), with a Smallest Detectable Change (SDC) of 6.6mm.[22] To determine if limitations were present reference values corrected for age and sex were used as published by Gallagher et al.[23]

### Neck function

The CROM© (Cervical Range of Motion Instrument; Performance Attainment Associates, Lindstrom, Minnesota, USA) was used to measure the lateral flexion and rotation of the neck.[24] These measurements have been demonstrated to be reliable with an ICC between 0.79 and 0.87 and SDCs between 10.64 and 15.44 degrees.[22] Reference values corrected for age and sex as described by Youdas et al. for the cervical range of movement were used.[25]

### Shoulder function

Shoulder abduction of the left and right side was measured with a digital inclinometer (Baseline© Digital Inclinometer, Fabrication Enterprises Inc., White Plains, New York, USA), which has an ICC of 0.77 and 0.81 for test-retest reliability and an SDC of 36.68 and 31.27

degrees respectively. Reference values corrected for age and sex for the abduction of the shoulder as reported by Stathoskas et al. were used.[26] For participants younger than 55 years of age reference values were not reported and a reference for 55-year-old persons (142°) was used.[26]

### Hand Grip strength

Hand grip strength was measured for the left and right hand by the JAMAR© hand-held dynamometer (Sammons Preston Rolyan, Warrenville, Illinois, USA) with an ICC of 0.88 and 0.96 for test-retest reliability, and SDC of 12.96 and 8.26 kilograms respectively.[22] Reference values corrected for age and sex were used as described by Dodds et al.[27]

### Lower body strength

Lower body strength was measured with the Thirty Seconds Chair To Stand test (30-SCTS).[28] The 30-SCST has been found test-retest reliable with an ICC of 0.92 and SDC of 2.96 repetitions.[22] Reference values corrected for age and sex for community-dwelling elderly as described by Jones and Rikli were used.[28]

### Timed up and go test

The level of mobility was measured with the Timed Up and Go test (TUG). The measurement of the level of mobility measured with TUG has been found test-retest reliable with an ICC 0.98 and an SDC of 1.54 seconds.[22] Reference values for designated age groups were used (60 to 69, 8.1 seconds; 70 to 79, 9.2 seconds; 80 to 99, 11.3 seconds.[29] In the case of age below 60, the lowest value was used (8.1 seconds).[29]

### Six minute walking test

Walking ability was evaluated using a self-paced six minute walking test (6MWT) on a 20-meter circuit.[29] The measurement of walking ability with the 6MWT has been found test-retest reliable with an ICC of 0.97 and an SDC of 56.67 meters.[22] For reference values, we used the age and sex-stratified regression formula as described by Gibbons et al. [30]

## Statistical analysis

The demographic, personal, and clinical characteristics of sHNC were described. Categorical data were presented as exact numbers and percentages. For normal distributed continuous data, means, and standard deviations (SD) were calculated. For ordinal and non-normal distributed

continuous data medians and interquartile ranges (IQR; the difference between the 25th and 75th percentile) were calculated. Differences between the two included groups of sHNC (patient federation group versus the Radboudumc routine follow up group) were analyzed with independent samples T-tests for normally distributed data and the Mann-Whitney U test for not normally distributed data. Chi-square tests were used for nominal and ordinal data. Unmet needs as identified with SCNS-SF34 and SCNS-HNC were presented for the physical and daily living needs domain score and single-item scores. Limitations in physical health as identified with physical performance measurements were presented as a percentage of the age and sex corrected reference values. In all analyses, two-sided p-values <0.05 were considered to be statistically significant. All analyses were performed using SPSS version 25 (SPSS Inc, Chicago, Illinois, USA).

**TABLE 1.** *Associations between unmet needs identified with Supportive Care needs Surveys and limitations in physical health as measured with physical performance tests*

| Unmet needs identified with SCNS domain/item | Limitations in physical health identified with physical performance measurements | Association R | *p*-value | OR | 95% CI |
|---|---|---|---|---|---|
| | **Hypothesized strong relationship** | | | | |
| SCNS-SF34 Physical & Daily Living Needs Domain | Upper body strength | 0.251 | 0.079 | | |
| | Lower body strength | 0.160 | 0.268 | | |
| | Level of mobility | -0.153 | 0.287 | | |
| | Walking ability | -0.023 | 0.876 | | |
| SCNS-HNC, Question 1: problems with chewing and/or swallowing | Maximum Mouth Opening | | | 0.286 | 0.031 - 2.556 |
| SCNS-HNC, Question 9: problems with mobility of neck and shoulders | Shoulder abduction left | | | n/a | n/a |
| | Shoulder abduction right | | | n/a | n/a |
| | Lateral flexion neck left | | | 2.488 | 0.741 - 8.350 |
| | Lateral flexion neck right | | | 1.200 | 0.250 - 5.760 |
| | **Hypothesized moderate relationship** | | | | |
| SCNS-SF34 Physical & Daily Living Needs Domain | Shoulder abduction left | -0.195 | 0.175 | | |
| | Shoulder abduction right | -0.121 | 0.402 | | |
| | Lateral flexion neck left | -0.319 | 0.024* | | |
| | Lateral flexion neck right | -0.021 | 0.885 | | |

*: $p < 0.05$
SCNS-SF34: Supportive Care Needs Survey Short-Form 34; SCNS-HNC: Supportive Care Needs Survey Head and Neck Cancer module; OR: Odds Ratio; N/A: not applicable (to small number of sHNC with limitations); * ($P$<0.05)

## Bivariable analyses

To determine the strength of the association between unmet needs as measured with SCNSs and limitations in physical health we formulated hypotheses (see also Table 1).

Cancer generic unmet needs as measured by the SCNS-SF34 physical and daily living needs domain score were hypothesized to be associated with limitations in physical health as measured with cancer generic physical performance measurements. HNC specific unmet physical needs (SCNS-HNC) were hypothesized to be associated with physical performance measurement which measured a similar HNC specific construct (questions 1 and 9). For example, question 9 of the SCNS-HNC: "Do you have an unmet need in the mobility of neck and shoulders?" was expected to show association with limitations in shoulder abduction. An association smaller than 0.50 was defined as weak, 0.50 to 0.75 as moderate, and greater than 0.75 as strong.[31]
Association analyses were performed using Pearson correlation coefficients for normally distributed data and Spearman's Rho for non-normally distributed data. A Chi-square analysis was performed to test the association between unmet needs (yes/no) for questions 1 and 9 of the SCNS-HNC, and limitations in physical performance dichotomized (yes/no). An OR below or above 1 was regarded as an indication of association, while a proxy for statistical significance was considered if the Confidence interval of the OR did not include a value of 1.[32]

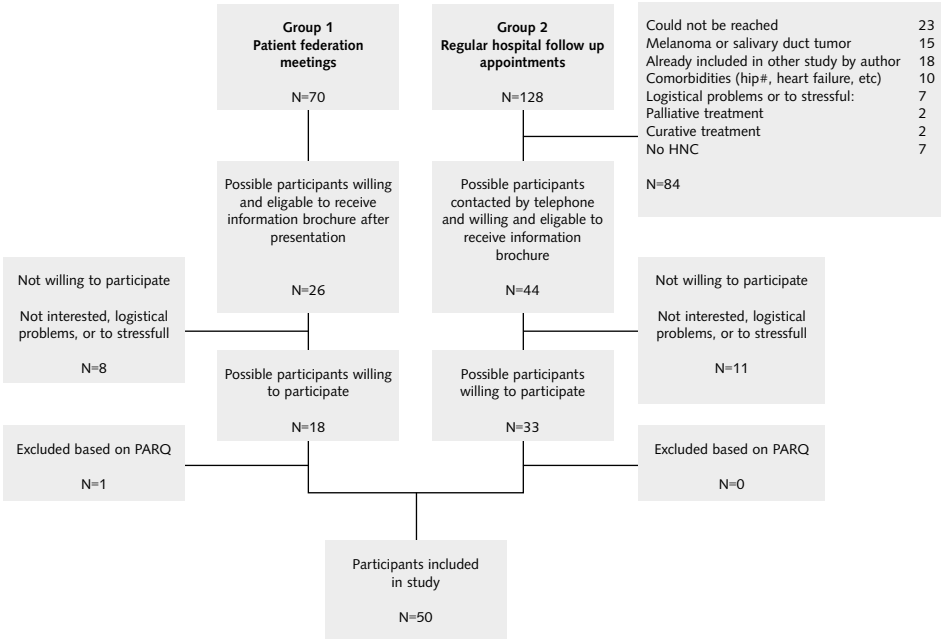
## Multivariable analysis

The hypothesized associations were checked for the influence of confounding variables as known in literature (age, sex, years of HNC survivorship, number of physiotherapy treatments)[18] and the included group (patient federation or usual care follow-up). The magnitude of associations was verified through binary logistic and linear regression model analysis. To determine the maximum number of variables to be included in the regression model, we used the rule of thumb of 10 patients per determinant. Consequently, our sample of 50 patient allowed to include a maximum of 5 variables into the regression model. No multicollinearity ($rp > 0.60$) was found.

## Results

In total 50 sHNC participated in this study, of which 29 were male and 21 were female. The mean age of all participants was 69 years (SD 9.9). The median time of cancer survivorship was 3 years (IQR 1.0 – 5.25). In the patient federation 18 out of 70 asked patients agreed to participate. In the usual care follow up group 33 out of 128 patients agreed to participate. The flowchart of the recruitment and enrollment of participants is depicted in Fig. 1.

**FIGURE 1:** *Recruitment and enrollment participants HNC, head and neck cancer; PARQ, Physical Activity Readiness Questionnaire*




Demographic, participant, and treatment characteristics for the two included groups of participants are depicted in Table 2.

**TABLE 2.** *Demographic, participant and treatment characteristics*

| Characteristic | Patient federation Group N = 17 | SD IQR Percentage | Usual care follow-up Group N = 33 | SD IQR Percentage | *P* |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male (%) | 13 | 76.5% | 15 | 45.5% | 0.04* |
| Female (%) | 4 | 23.5% | 18 | 54.5% | |
| Age (years) (mean, SD) | 68.3 | 8.0 | 68.7 | 10.9 | 0.46 |
| Body Mass index (median, IQR) | 25.3 | 23.3 - 27.5 | 25.4 | 23.9 - 26.2 | 0.90 |
| Smoking | | | | | |
| Yes (%) | 0 | - | 4 | 12.1% | |
| No, but used to (%) | 16 | 94.1% | 23 | 69.7% | 0.13 |
| No (%) | 1 | 5.9% | 6 | 18.2% | |
| Pack-years in history (median, IQR) | 26.3 | 12.5 - 45 | 15 | 1.9 - 23.0 | 0.15 |
| Alcohol usage (>1 daily) | | | | | |
| Yes (%) | 9 | 52.9% | 13 | 39.4% | 0.32 |
| No (%) | 8 | 47.1% | 20 | 60.6% | |
| Glasses per day (median, IQR) | 1 | 0.0 - 3.0 | 0 | 0.0 - 1.5 | 0.28 |
| Level of education | | | | | |
| Lower (%) | 7 | 41.2% | 14 | 42.4% | |
| Middle (%) | 8 | 47.1% | 9 | 27.3% | 0.33 |
| Higher (%) | 2 | 11.8% | 10 | 30.3% | |
| Social status | | | | | |
| Living alone (%) | 5 | 29.4% | 11 | 33.3% | 0.78 |
| Living with a partner (%) | 12 | 70.6% | 22 | 66.7% | |
| Years since cancer treatment (median, IQR) | 4.0 | 2.0 - 10.5 | 2 | 1.0 - 4.5 | 0.02* |
| Tumor location | | | | | |
| Oral cavity (%) | 1 | 5.9% | 27 | 81.8% | |
| Nasopharynx (%) | 0 | 0.0% | 1 | 3.0% | |
| Oropharynx (%) | 1 | 5.9% | 1 | 3.0% | 0.00* |
| Larynx (%) | 12 | 70.6% | 0 | - | |
| Other (%) | 3 | 17.6% | 4 | 12.1% | |
| Oncology treatment | | | | | |
| Surgery (%) | 3 | 17.6% | 16 | 48.5% | |
| Surgery and radiotherapy (%) | 9 | 52.9% | 9 | 27.3% | |
| Radiotherapy (%) | 1 | 5.9% | 3 | 9.1% | 0.24 |
| Surgery, radiotherapy and chemotherapy (%) | 3 | 17.6% | 4 | 12.1% | |
| Radiotherapy + chemotherapy (%) | 1 | 5.9% | 1 | 3.0% | |
| Neck dissection | | | | | |
| Unilateral (%) | 3 | 17.6% | 19 | 57.6% | |
| Bilateral (%) | 2 | 11.8% | 4 | 12.1% | 0.17 |
| No (%) | 12 | 70.6% | 10 | 30.3% | |

IQR: Inter Quartile range; SD: Standard deviation; * $P < 0.05$

The usual care follow-up group consisted of more females ($P = 0.04$), showed fewer years of cancer survivorship ($P = 0.02$) and the tumor location was different compared to the patient federation group ($P = 0.00$).

In the SCNS-SF34 physical and daily living needs domain, 48% of the sHNC reported one or more cancer generic unmet needs. In total 46% of sHNC reported at least one HNC specific unmet need (SCNS-HNC) as measured with question 1 and 9. An oversight of unmet needs identified with SCNSs is depicted in Table 3.



**TABLE 3.** *Generic and head and neck cancer specific unmet physical needs for supportive care*

| | Number of items | Number of patients with a need | Percentage of patients with at least 1 unmet need | Mean total domain score (SD) | Median total domain score (IQR) |
|---|---|---|---|---|---|
| **SCNS-SF34** | 34 | 35 | 70% | - | - |
| **Physical & daily living domain** | 5 | 24 | 48% | 18.5 (20.1) | 15 (0 - 25) |
| Question 1: Pain | 1 | 13 | 26% | - | - |
| Question 2: Lack of energy/ tiredness | 1 | 18 | 36% | - | - |
| Question 3: Feeling unwell a lot of the time | 1 | 5 | 10% | - | - |
| Question 4: Work around the home | 1 | 11 | 22% | - | - |
| Question 5: Not being able to do things you used to do | 1 | 10 | 20% | - | - |
| **SCNS-HNC** | 11 | 42 | 84% | - | - |
| **Head and neck cancer-specific functioning total domain score** | 9 | 37 | 74% | 26.5 (20.1) | 23.3 (12.5 - 40.6) |
| Question 1: Problems with chewing and/or swallowing | 1 | 15 | 30% | | |
| Question 9: Problems with mobility of neck and/or shoulders | 1 | 17 | 34% | | |
| Question 1 & 9: total number of participants reporting HNC specific unmet needs. | 2 | 23 | 46% | | |

SCNS-SF34: Supportive Care Needs Survey 34-item short-form survey; SCNS-HNC: Supportive Care Needs Survey Head and Neck Cancer Module; SD: standard deviation; IQR: inter Quartile range.

Identifying limitations in physical health with the use of physical performance measurements demonstrated that 76% of the sHNC had at least 1 cancer generic limitation. Cancer generic limitations in physical health in sHNC were measured for HGS and lower body strength (both 30%) and walking ability (70%). HNC specific limitations in physical health were measured in 16% of the sHNC for MMO and 6% and 8% shoulder abduction for the left and right shoulder respectively. In total 58% of sHNC demonstrated at least one HNC specific limitation in physical health. Specified information on limitations in physical health as identified with physical performance tests are presented in Table 4.

## Bivariable association analyses

Unmet needs identified in the physical and daily living needs domain score (SCNS-SF34) showed no association with limitations in physical health as identified with the measurements on physical performance except for a weak association between the domain score of physical health and lateral flexion of the neck to the left (R = -0.319; $P$ = 0.024) ( Table 1). Unmet needs identified with the SCNS-HNC question 1: "Do you experience problems with chewing and/or swallowing?" showed no significant association with the measurements on MMO (OR 0.286; CI 0.031 – 2.556). Unmet needs identified with the SCNS-HNC for question 9: "Do you experience problems with mobility of neck and shoulders?" showed a non significant association with the left lateral flexion of the neck (OR 2.488; CI 0.741 – 8.350).

## Multivariable analysis

The corrected models revealed no significant effect of the possible confounders on the associations as hypothesized in this study or demonstrated in the bivariable analysis.

**TABLE 4.** *Cancer generic and head and neck cancer specific physical limitations*

| Physical outcome | Test | Mean (SD) | Median (IQR) | Number of patients ≥20 % under reference value of 100% | Number of patients ≥40 % under reference value of 100% |
|---|---|---|---|---|---|
| Maximum opening of the mouth | Therabite cardboard ruler | 106% (25%) | 108% (78%-138%) | 8* (16%) | 3 (6%) |
| Shoulder abduction left | Digital inclinometer | 114% (18%) | 119% (106%-132%) | 3 (6%) | 1 (2%) |
| Shoulder abduction right | Digital inclinometer | 115% (18%) | 115% (98%-132%) | 4 (8%) | 0 (0%) |
| Lateral flexion neck left | CROM | 108% (34%) | 105% (54%-156%) | 13 (26%) | 1 (2%) |
| Lateral flexion neck right | CROM | 112% (35%) | 107% (70%-144%) | 7 (14%) | 2 (4%) |
| Rotation neck left | CROM | 118% (25%) | 118% (84%-152%) | 1 (2%) | 0 (0%) |
| Rotation neck right | CROM | 116% (24%) | 114% (83%-145%) | 3 (6%) | 1 (2%) |
| Lower body strength | 30SCST | 92% (31%) | 93% (59%-127%) | 15 (30%) | 8 (16%) |
| Grip strength | Grip Strength | 99% (36%) | 97% (43%-151%) | 15 (30%) | 7 (14%) |
| Level of mobility | TUG | 127% (35%) | 130% (80%-180%) | 6 (12%) | 2 (4%) |
| Walking ability | 6MWT | 71% (19%) | 73% (59%-97%) | 35 (70%) | 11 (22%) |
| HNC specific limitations | Therabite cardboard ruler, digital inclinometer, CROM | n/a | n/a | 29 (58%) | 4 (8%) |
| Cancer generic limitations | 30SCST, Grip Strength, TUG, 6MWT | n/a | n/a | 38 (76%) | 17 (34%) |

CROM= Cervical Range Of Motion, IQR Inter Quartile Range, N/A: Not Applicable, SD = Standard Deviation, TUG = Timed up and Go Test, 6MWT = Six Minute Walk Test, 30SCST = 30 seconds Chair to Stand Test

## Discussion

The primary aim of this study was to gain insight into the level of unmet needs and limitations in physical health experienced by sHNC, and to research if unmet needs in physical health and limitations in physical health showed an association. This insight could improve the referral to physiotherapists and thereby optimize patient care and HR-QoL. It was shown that a high number of sHNC experience cancer generic, and HNC specific unmet needs and limitations in physical health as measured with SCNSs and physical performance measurements. More specifically, a higher percentage of sHNC showed generic limitations (76%) compared to generic unmet needs (48%). For HNC specific limitations (58%) and unmet needs (46%), this difference was in the same direction, but smaller. This could indicate that generic and HNC specific measurements in part overlap but also measure different constructs. This was confirmed when we only found two limited associations based on our predefined hypotheses. The association found between the domain of physical health and lateral flexion of the neck was weak. This could be explained by the limited rationale for an association between a generic domain score and a specific range of motion measurement. The association found between the HNC specific question about neck and shoulder mobility and lateral flexion of the neck to the left does have a clear rationale but is not significant. The confidence interval of the Odds Ratio (OR 2.488; CI 0.741 – 8.350) is wide and contains the value of 1 which limits the strength of the association. No other associations between unmet needs in physical health and limitations in physical performance measurements were found. This indicates that unmet needs as identified by SCNSs and physical measurements focus on different constructs, which is in line with the findings of other authors.[33-35] The high level of cancer generic limitations found with physical performance measurements that did not associate with unmet needs could indicate that sHNC do not report problems concerning strength or walking distance. These NPIPs can severely impact HR-QoL and are therefore important to identify.[11] The measurement of unmet needs based on these SCNSs is therefore unlikely to provide complete and optimal identification of PIPs and NPIPs in physical health for sHNC. Therefore, these SCNSs could be combined with objective measured physical performance measurements.[34, 35]

## Unmet needs identified with Supportive Care Needs Surveys

In our study, the number of sHNC reporting generic unmet needs measured with the SCNS-SF34 (48%) is in line with previous research on sHNC with a total laryngectomy (37%).[36] Wells et al. describe that most unmet needs are in the physical and daily living needs domain, however, there is a lack of specified data to compare our findings.[37] The study of Giuliani et al. only reports single items in the domain of physical health (f.e. "unmet needs in comprehensive personal recovery and rehabilitation assessment/clinic" (23.2%)), and these numbers are comparable to SCNS-SF34 single items in our study regarding "not being able to do the things you used to do" and "work around the house".[38] The number of generic unmet needs in our study is slightly lower in comparison to the general cancer survivor population of which 66% reported unmet needs in physical health.[39] This could be due to the specific socio-economic distribution of sHNC which can lead to avoidance of care and an underreport of unmet needs.[40]

We used the SCNS-SF34 and SCNS-HNC to identify unmet needs because they are used most frequently in HNC research, and have both been validated in Dutch for HNC patients.[17] We dichotomized the 5-point SCNS scales into yes/no unmet needs which limits the ability to differentiate between patients. Patients that reported no needs or have unmet needs that were met were both scored as no need. The level of unmet needs (low, moderate and high) was also lost in the dichotomization. It would be of interest to investigate specific subgroups of patients and for example the patients who report that their needs were met and explore possible association with limitations in physical health or reported use of physiotherapy. Other PROMs that can be used as for example the distress thermometer have limitations. The distress thermometer is not a cancer-specific instrument, and it measures the presence of problems, not unmet needs or physical limitations. Considering the widespread use of the distress thermometer, it would be of interest to include the distress thermometer in future studies to evaluate its association with the other two methods of identifying unmet needs. Unmet needs can also be identified through the widely used EORTC-QLQ-C30 and EORTC-QLQ-HN35. However, the studies that provided the cut-off values used the SCNS-SF34 as a criterium. This indicates that SCNS-SF34 can be regarded as the primary and most optimal measurement for the identification of unmet needs. But we acknowledge that the widespread use of the EORTC questionnaires would advocate future research into association between unmet needs as identified by the EORTC questionnaires and limitations in physical health as identified by physical performance tests.[41-43]

The use of PROMs, like SCNSs, to identify problems and/or unmet needs during follow-up consultations in cancer care is a point of debate. PROMs offer a time-efficient and practical method of gaining insight into for example distress, unmet needs, health problems, and HR-QoL.[34] However, efficacy can be limited by patient adherence, interpretation, and response handling by treating physicians.[34, 44] In HNC care, an eHealth application like Oncokompas that uses PROMs to support self-management of symptoms/needs and HR-QoL provides tailored advice to sHNC on allied healthcare. Research has shown it to be feasible, equally effective on utilities, and not more expensive than usual care.[45-47]

However, our study has shown that a large part of the limitations in physical health is likely to remain unreported or unidentified with the use of PROMs as a single method of identification. Survivors of HNC could therefore benefit from the identification and objectification of limitations in physical health with the use of a core set of physical performance measurements. The challenge thereby lies in providing patient-tailored, effective, and practical methods of identifying limitations in physical performance for supportive care without overdemanding sHNC. This is confirmed by research that states that sHNC feel that allied health professional care is not needed or beneficial due to a blanket approach, and more targeted allied health professional care would be beneficial.[48]

## Unmet needs identified with physical performance measurements

Physical measurements are currently no routine part of sHNC follow-up consultations and are mainly used for research purposes or during physiotherapy care.[18]

Our study is unique in the fact that it relates sHNC physical performance measurement outcomes to sHNC to age and sex-stratified reference values. To determine if a survivor has limitations in physical health, the age and sex-stratified reference values were chosen based on expert opinion and guideline recommendations, but are known to vary among populations and measurement protocol used.[27, 49] The reference values used have not been validated for use with sHNC, which may have led to over- or underestimation of performance. The use of the 80% cutoff value to identify problems in physical health with the use of physical performance measurements is arbitrary. A possible benefit of the use of physical performance measurements is the ability to objectify both patient-reported problems in physical health as non-patient identified problems.[12] The 80% percent was chosen to take into account measurement error as we previously published for the physical performance measurements used.[22] The reference

values give insight into sHNC performance in comparison to age and gender stratified healthy peers, but it is unclear if recovery up to the level of healthy peers can be expected in the sHNC population.



## Physical performance related to age and sex-stratified reference values

The number of sHNC that showed limitations in MMO is nearly the same compared to when the criteria for trismus (MMO ≤35mm) would have been used (16% versus 18%). These numbers are lower than trismus incidence for sHNC reported in the literature[50]. However, this could be explained by the shorter moment of survivorship during measurement in these studies (<1 year).[51]

A remarkable finding was that measured AROM for shoulder in sHNC was predominantly as good or better than the reference values. Research confirms that shoulder function significantly deteriorates after the medical intervention to restore up to normal after 1 year of follow-up with except for sHNC with a high-risk profile.[7, 8, 52, 53] This study also showed that a high percentage of sHNC had reduced HGS (30%) and lower body strength (30%) and walking ability (70%). This indicates that sHNC are weaker and less mobile compared to healthy peers. This is in line with research that indicates that sHNC are more sedentary and less physical active, which results in less strength and endurance which is related to a lower HR-QoL.[10, 11, 54]

## Strengths and limitations

The cross-sectional design, patient-reported treatment-related variables, and a relatively long median survivorship time of 3 years gives insight into the physical health status of the population of sHNC. The cross-sectional design prevents insight into causal relationships or different phases during the course of reported unmet needs and limitations in physical performance during cancer survivorship. The participation rate for the two groups in this study was low; patient federation group (24%), hospital follow-up group (26%).[22] The participants possibly represented a "relatively active" selection of sHNC because they all were living independently, were mobile without walking aid, and didn't have comorbidities that prevented them from safely performing the physical measurements. These two factors could indicate a possible participation bias, with only the actively persons engaged. The relatively high percentage of females in this study is not in line with other studies researching sHNC possibly caused by volunteer bias. The study included 50 sHNC where other publications on unmet needs in

sHNC included larger populations.[35-37] We transformed the outcomes of the SCNSs into a binary outcome (yes/no needs) which removed the level need (low, moderate, high) from the analysis.

The primary strength is that this study combines PROMs and objective physical measurements to identify sHNC with unmet needs in physical health. Another strength of this study is the two groups of participants that more accurately reflect all types of sHNC and the use of an electronic data capture system that ensured completion of all questionnaires without missing data. The physical performance measurements also had no missing data.

### Future research

Future research could be focused on the longitudinal course of unmet needs and limitations in physical performance in physical health for sHNC. Secondary, research into the most optimal SCNSs and physical performance measurements could optimize the identification of sHNC with reported and unreported limitations in physical health. The SCNSs used in this study are not physiotherapy specific, and an interdisciplinary diagnostic analysis with the use of shared decision-making should take place to find an optimal and adequate healthcare plan. This future research could improve the referral of sHNC with unmet needs or limitations in physical health to allied healthcare professionals as physiotherapists and improve research into patient tailored interventions in physical health.

## Conclusion

This study showed that sHNC experience both a high level of unmet needs and limitations in physical health. The domain of physical and daily living needs showed a weak and less clinically relevant association with lateral flexion of the neck to the left ($R = -0.319$; $P = 0.024$). Unmet needs in physical health as identified with SCNS-SF-34 and SCNS-HNC do not associate with limitations in physical health as identified with physical performance measurements, indicating that they measure a different construct. Identification of sHNC with unmet needs or limitations in physical health might benefit from the addition of physical performance measurements during follow-up. This could lead to better patient awareness regarding physical health, and optimization of referral of sHNC to specialized physiotherapy.

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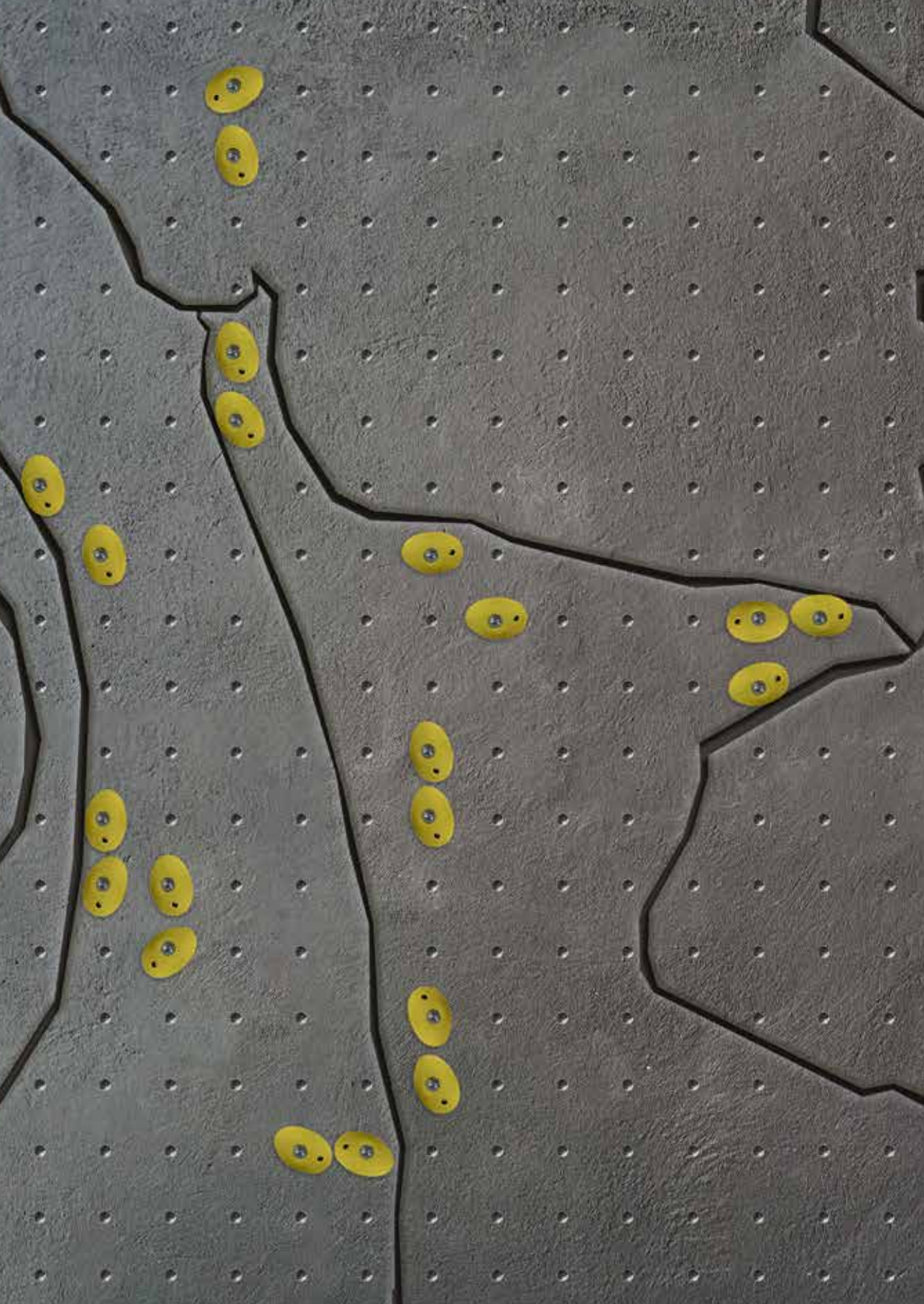

Chapter 4

# Factors influencing neck and shoulder function after oral oncology treatment: A five-year prospective cohort study in 113 patients

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## Abstract

**Background:** The aim of this study was to identify factors influencing shoulder and/or neck function in patients up to five years after treatment.

**Materials and methods:** Lateral flexion of the neck, ipsilateral forward flexion, and abduction of the shoulder were measured. Potential factors were entered into a linear mixed model analysis to create a multivariate model for describing the results.

**Results:** Predicted neck and shoulder function were negatively influenced by higher age before intervention. Contralateral flexion of the neck was lower for patients undergoing surgery and radiotherapy compared to surgery. Ipsilateral flexion of the neck is influenced by a higher age at baseline. Ipsilateral shoulder abduction is lower for female gender, bone graft/flap reconstruction and more extensive neck dissection. Ipsilateral forward flexion of the shoulder is lower for bone graft/flap reconstruction and better for patients with a T2 tumor in comparison to T3 and T4 tumors, as predicted.

**Conclusion:** By our five-year follow-up outcomes of this study neck and/or shoulder impairments can be found for high-risk patients by physiotherapists.

# Introduction

The curative treatment of oral cancer has become less invasive and more targeted in order to minimize negative side effects and improve functional and cosmetic results.[1] Survivors of oral cancer commonly experience treatment-related morbidity that impairs oral functions[2-5] and general physical condition in addition to causing limitations in daily activities involving neck and shoulder function.[6] A decrease in neck and shoulder function is negatively correlated with the extent of neck dissection (ND), and it can lead to functional limitations that hamper activities of daily life (ADL) and decrease Quality of Life (QoL).[6-8]

Lateral flexion of the neck is affected on both the side of the ND surgery and the contralateral side[6,8], although patients experience the greatest impairment in shoulder abduction on the side of the ND and/or radiotherapy.[6,8] Reports on prevalence of shoulder dysfunction exhibit wide variation in how the limitations in function progress over time, and they are often limited to one-year follow-up or a single moment of measurement.[9] One cross-sectional study measuring shoulder range of motion at five-year follow up reports slightly lower scores for shoulder function, as compared to studies reporting one-year measurements.[10] There is thus no definitive prognostic information that can be provided to patients during rehabilitation. During treatment, 73% of all patients report the need for physical therapy, and 23% report such needs after 8-11 years.[11] Patients and clinicians also tend to under-appreciate the late effects of oral oncology treatment. Insight into late effects is nevertheless critical for maximizing function and minimizing symptom burden in long-term survivors. Rehabilitation intervention studies aimed at minimizing neck and shoulder complaints are scarce.[12,13] In our opinion, one limitation of the existing intervention studies is their lack of attention to customized care for patients who are at risk for neck and/or shoulder complaints. Interventions should be made more patient-centered through the application of risk-stratified rehabilitation programs. Studies identifying these clinical factors and patient characteristics for the purpose of informing patients and clinicians and developing optimally timed patient-centered risk-stratified rehabilitation programs are lacking.

The purpose of this study was to identify clinical factors and patient characteristics that influence a patient's neck and shoulder function during the five-year period following curative oral cancer treatment.

# Methods

## Study setting and participants

Patients were recruited between January 2007 and August 2009 in the University Medical Center Utrecht (UMC Utrecht) and the Radboud university medical center (Radboudumc) in Nijmegen. The study was conducted according to the principles of the Declaration of Helsinki (59th version, 21-10-2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The research protocol was approved by the respective Ethics Committees of the University Medical Center Utrecht and Radboud University Nijmegen Medical Center. Patients received oral information about the study. Inclusion criteria were having primary oral cavity cancer and undergoing curative cancer treatment (i.e. surgery only or both surgery and radiotherapy). To be included, patients were required to be 18 years or older and to provide informed consent. Patients with bilateral neck dissection (BND), previous or synchronous malignancies, pectoral flap reconstruction, cognitive impairment, or the inability to speak Dutch were excluded. Post-operative radiotherapy was given by indication within six weeks after surgery, in accordance with the guidelines of the Dutch Head and Neck Society. The total radiotherapy dosage (primary or adjuvant) was 54-70 Gy. Age, gender, tobacco use, and alcohol consumption were recorded at the pre-treatment session. Details on tumor location (maxilla, mandible, tongue/floor of mouth [TFM]), tumor size [T of TNM], lymph nodes involved [N of TNM])[14], treatment modality (surgery [S], surgery-radiotherapy [SR] , surgical reconstruction of the oral cavity (no reconstruction, local flap, free or myocutaneous flap, bone graft/flap), and type of ND (no neck dissection [No ND], selective neck dissection [SND], modified radical neck dissection [MRND], radical neck dissection [RND][15]) were obtained from medical records. A distinction was made between patients who smoked daily and those who either did not smoke or who smoked infrequently. With respect to alcohol consumption, a distinction was made between patients who consumed an average of more than one alcoholic beverage per day and those who consumed one alcoholic beverage per day or less. In this study, tumor locations included the mandible, maxilla (with or without ingrowth in the maxillary antrum), and tongue/floor of mouth.

## Study procedure

The measurement moments were 4-6 weeks before intervention ($T_0$), 4-6 weeks after surgery ($T_{1a}$), and/or 4-6 weeks after radiotherapy ($T_{1b}$), and 6 ($T_2$), 12 ($T_3$), and 60 ($T_4$) months after intervention.

## Measurements

Patients were measured according to a standardized measurement protocol. The active range of motion (AROM) for the neck and shoulders was determined using the MicroFET 6 electronic inclinometer (Hoggan Health Industries; West Jordan, UT). Digital inclinometry has demonstrated good intraclass correlation (ICC) scores of 0.93 for patients with neck pain[16] and 0.83 for shoulder abduction in patients with shoulder pain.[17] The following AROM variables were determined: active maximal lateral flexion of the neck to the left and right side in a sitting position; active maximal abduction; and forward flexion of the shoulder on the side of the ND in a standing position. The endpoint in AROM measurements was determined by musculoskeletal restrictions or pain. The mean of two sequential measurements was used for further analysis.

In this discussion, the side with ND is referred to as the ipsilateral side, with the opposite side referred to as the contralateral side. For patients with ND, we only used the outcomes of the affected (ipsilateral) side for shoulder abduction and forward flexion, given the relationship of limitations in shoulder function and pain to ND surgery.[8,18]

## Statistical analysis

Descriptive statistics were calculated for patients without ND, selective neck dissection (SND), modified radical neck dissection (MRND) and radical neck dissection (RND). Categorical variables are presented as numbers and percentages, and continuous variables are presented as means and standard deviations in the case of normally distributed variables. The Fisher's exact test was used to analyze any differences in patient characteristics with respect to neck dissection; one-way analysis of variance (ANOVA) was used to examine age differences among the groups.

Patients who were treated with surgery and radiotherapy were measured shortly after surgery and shortly after radiotherapy ($T_{1a}$ & $T_{1b}$). Results from a paired t-test nevertheless revealed no statistical differences ($P > 0.05$) between these measurement moments. We therefore used the

AROM scores obtained shortly after the total oral oncology treatment (i.e., shortly after both surgery and radiotherapy; $T_1$) were used.

Linear mixed-effects models were constructed for all measurement moments up to five-year follow up, in order to explore the effect of patient and clinical variables on the maximum AROM of the ipsilateral and contralateral flexion of the neck, ipsilateral abduction, and ipsilateral forward flexion of the shoulder. Age at baseline, gender, tobacco use at baseline, alcohol consumption at baseline, tumor location, tumor size (T of TNM), lymph nodes involved (N of TNM), treatment modality, resection site, surgical reconstruction, type of neck dissection, and the measurement moment were added as fixed effects, as were the interaction of clinical factors and patient characteristics with the measurement moment. A random patient factor was added, in order to account for within-patient correlations. The fixed effects that were not significant at a 0.05 level were removed in a backward process, beginning with the interactions, in order to build a parsimonious model with a sufficiently good fit and maintaining a hierarchical structure. In this context, a hierarchical structure means that, if an interaction with the measurement moment was included in the model, the main effect was also included in the final model. For the significant variables, the main effects on ipsilateral and contralateral flexion of the neck, ipsilateral shoulder abduction, and ipsilateral forward flexion were calculated. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

## Results

In all, 113 patients were included in this study. The baseline characteristics are depicted in Table 1.

**TABLE 1.** *Characteristics of groups related to (no) neck dissections at baseline.*

| | No ND (n=42) | SND (n= 55) | MRND (n=14) | RND (n=2) | *P* value |
|---|---|---|---|---|---|
| Age (average, SD) | 66.6 (14.4 | 65.3 (12.9) | 62.3 (13.2) | 67.5 (11.3) | 0.775 |
| Sex | | | | | |
| Female | 22 | 22 | 7 | 1 | 0.672 |
| Male | 20 | 33 | 7 | 1 | |
| Smoking | | | | | |
| Yes | 32 | 34 | 10 | 1 | 0.397 |
| No | 10 | 21 | 4 | 1 | |
| Alcohol | | | | | |
| Yes | 31 | 36 | 10 | 1 | 0.700 |
| No | 11 | 19 | 4 | 1 | |
| Tumor location | | | | | |
| Mandible | 8 | 28 | 7 | 2 | 0.000* |
| Maxilla | 25 | 2 | 2 | 0 | |
| Tongue/Floor of mouth | 9 | 25 | 5 | 0 | |
| T of TNM14 | | | | | |
| T1 | 20 | 18 | 1 | 0 | 0.084 |
| T2 | 10 | 17 | 6 | 2 | |
| T3 | 1 | 5 | 2 | 0 | |
| T4 | 11 | 15 | 5 | 0 | |
| N of TNM14 | | | | | |
| N0 | 40 | 39 | 0 | 0 | 0.000* |
| N1 | 0 | 5 | 6 | 1 | |
| N2 | 2 | 11 | 8 | 1 | |
| N3 | 0 | 0 | 0 | 0 | |
| Oncology treatment | | | | | |
| Surgery | 26 | 27 | 3 | 0 | 0.023** |
| Surgery and Radiotherapy | 16 | 28 | 11 | 2 | |
| Oral reconstruction | | | | | |
| Primary closure | 27 | 20 | 6 | 1 | 0.122* |
| Local flap | 1 | 2 | 0 | 0 | |
| Myocutaneous/free flap | 12 | 20 | 6 | 1 | |
| Bone graft/flap | 2 | 13 | 2 | 0 | |

*: $P < 0.001$, **: $P < 0.05$
Differences in patients sorted by type of ND were tested by Fisher's exact tests and one-way ANOVA for age.
ND: neck dissection; SND: selective neck dissection; MRND: modified radical neck dissection; RND: radical neck dissection.

Of these patients, 56 patients had been treated with primary surgery, 57 had been treated with surgery followed by radiotherapy. Further details concerning the patient characteristics have been previously described.[2] At one-year follow-up, 79 patients were measured. Between the baseline measurement and one year, 11 patients died, 19 stopped participating, and 4 were excluded due to recurrence of the tumor. The patients who were measured at one year consisted of 42 patients in the surgery group and 37 patients in the surgery-radiotherapy group. In all, 66 patients were measured at five-year follow-up. Between one-year and five-year follow-up, 12 patients died, 2 stopped participating, and 1 patient re-entered after missing a measurement at one-year follow-up.



## Contralateral flexion of the neck

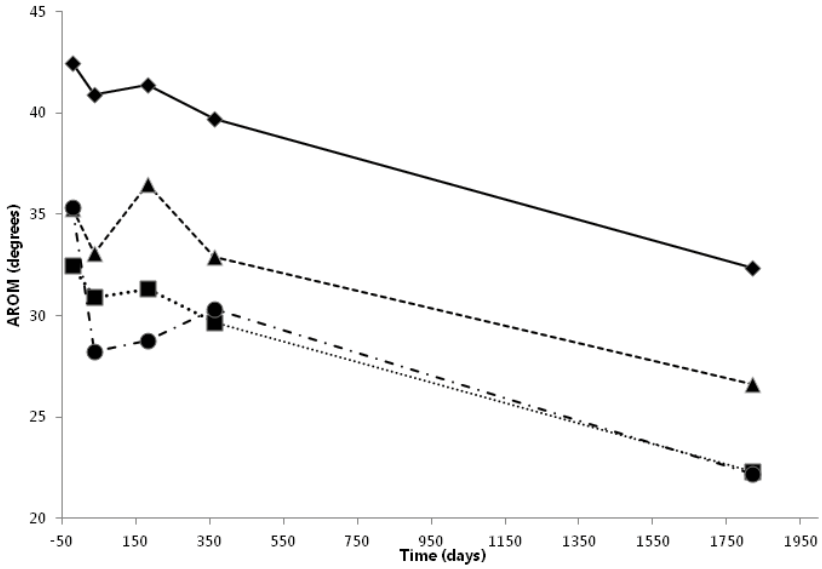
Results of the mixed model analysis indicate that contralateral flexion showed significant lower scores at the 6-week post intervention ($P < 0.05$) and 1 year moment of measurement ($P < 0.01$). Higher age at baseline negatively influenced AROM by 0.31 degrees per year of life ($P < 0.001$; e.g., the AROM of a 65-year-old patient was 3.1 degrees lower at every measurement, as compared to the scores of a 55-year-old patient).

The moment of measurement interacted significantly with the type of treatment ($P < 0.05$) and type of ND ($P < 0.05$). In this model, this means that undergoing both surgery and radiotherapy compared to only a surgery intervention leads to a lower AROM at the one- and 5-year moments of measurement. The influence of type of ND varies per moment of measurement. The course of contralateral flexion of the neck is visualized in Figure 1 for contrasting patients. The model for baseline, one-year, and five-year follow-up is presented in Appendix A.

## Ipsilateral flexion of the neck

The mixed model analysis indicates that ipsilateral flexion of the neck was significantly lower at all the follow up measurement moments, as compared to baseline ($P < 0.001$). Higher age at baseline negatively influenced AROM by 0.33 degrees per year ($P < 0.001$; e.g., the AROM of a 65-year-old patient was 3.3 degrees lower at every measurement, as compared to the scores of a 55-year-old patient). The course of ipsilateral flexion of the neck is visualized in Figure 1 for contrasting patients. The model for baseline, one-year, and five-year follow-up is presented in Appendix B.

**FIGURE 1:** *Ipsilateral and contralateral flexion of the neck, example patients.*




▲ = Contralateral flexion of the neck, 70-year-old patient, surgery, SND ● = Contralateral flexion of the neck, 70-year-old patient, surgery and radiotherapy, MRND ♦ = Ipsilateral flexion of the neck, 50-year-old patient. ■ = Ipsilateral flexion of the neck, 70-year-old patient
SND = Selective Neck Dissection. MRND = Modified Radical Neck Dissection AROM = active range of motion
of motion.

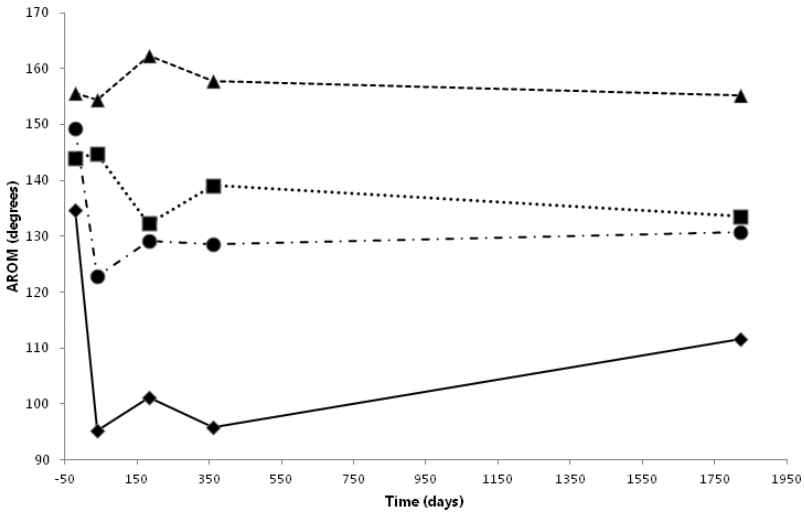
## Ipsilateral abduction of the shoulder

Ipsilateral abduction of the shoulder showed significant lower scores at follow up compared to baseline ($P < 0.01$). Higher age at baseline negatively influenced AROM by 0.90 degrees per year ($P < 0.001$; e.g., the AROM of a 60-year-old patient was 9.0 degrees lower at every measurement, as compared to the scores of a 50-year-old patient).

Female patients had lower predicted AROM scores over the five-year course. For example, at the one-year moment of measurement, the predicted AROM of female patients was 8.7 degrees lower than that of male patients ($P < 0.01$). The course of ipsilateral shoulder abduction was also significantly influenced by type of reconstruction ($P < 0.001$), with lower predicted scores for bone graft/flap reconstruction ($P < 0.05$) and a more extensive ND ($P < 0.01$). The course of ipsilateral abduction is visualized in Figure 2 for two patients with contrasting characteristics. The model for baseline, one-year, and five-year follow-up is presented in Appendix C.



**FIGURE 2:** *Ipsilateral shoulder abduction and forward flexion, example patients*




■ = ipsilateral abduction, 60 year old male, primary closure, No ND, ; ♦ = ipsilateral abduction, 60 year old female, bone graft/flap reconstruction, SND; ▲ = ipsilateral forward flexion, 60 year old patient, myocutaneous or free fllap reconstruction, T2 tumor, SND, TFM. ● = Ipsilateral forward flexion, 60 year old patient, bone graft/flap reconstruction, T4 tumor, SND, mandibula.
SND= Selective Neck Dissection. TFM = tumor located in the tongue or floor of mouth, AROM = active range of motion of motion.

### Ipsilateral forward flexion of the shoulder

Ipsilateral forward flexion of the shoulder was none significantly progressively lower at all post-intervention measurements with all being significantly lower than baseline ($P < 0.05$). Higher age at baseline negatively influenced AROM by 0.70 degrees per year ($P < 0.001$). Type of reconstruction, type of ND, tumor location and T in TNM significantly interacted with the moment of measurement. This means in this model that patients with bone graft/flap reconstruction perform worse. Tumor location maxilla performed worse at the 6-week post intervention and 6-month moment of measurement. The influence of type of ND shows a non-significant trend for worse AROM with more extensive ND. T in TNM status shows better scores for patients with a $T_2$ tumor [$P< 0.05$]) compared to T3 and T4 tumors. The course of ipsilateral forward flexion is visualized in Figure 2 for two patients with contrasting characteristics. The model for baseline, one-year and five-year follow-up is presented in Appendix D.

## Discussion

Neck and shoulder function were significantly lower over the 5-year course of follow up when compared to baseline. When exploring risk factors, higher age was shown to be the common factor negatively influencing active range of motion outcomes of the neck and shoulders. Contralateral flexion of the neck was predicted lower for patients treated with both surgery and radiotherapy compared to only a surgery intervention. Ipsilateral shoulder abduction was lower for females compared to male patients. Ipsilateral shoulder abduction and forward flexion were lower for patients undergoing bone graft/flap reconstruction. Ipsilateral forward flexion was also predicted by the type of ND, location and T in TNM state with different influences at the moments of measurement.

The models could be used to target patients who are at risk for developing lower neck and shoulder function in future intervention studies.

### The five-year course of neck and shoulder function

Only one other cross-sectional study has described shoulder function at five-year follow-up. It describes ipsilateral forward flexion and abduction as being persistently lower at five years, as compared to the normative AROM value of 150 degrees.[10] Mean scores of all the predicted

values in our models were lower than 150 degrees, which is in line with these findings and indicating shoulder limitation. Visual analysis of the course of neck and shoulder function for patients with different characteristics (Figure 1 and 2) showed a decline in neck and shoulder function after intervention with partial recovery of function up the 1 year moment of measurement [6,8] The description of the five-year course of neck and shoulder function in our study confirms findings of other authors that neck and shoulder function deteriorate after medical intervention and partly recover during follow up. This could mean that physical therapy interventions can be started as soon as possible, and when patients didn't receive post intervention physical therapy it can also be indicated at longer follow-up.[6,13,19]



## Factors influencing neck function

This is the first study to identify higher age at baseline as a risk factor for developing limitation in neck function. According to the results of the mixed model analysis, age was responsible for a decline of 0.31 degrees per year for contralateral flexion of the neck and a decline of 0.33 degrees per year for ipsilateral flexion of the neck. Normative data show that AROM of the neck during adulthood decreases with age at a rate of 5 degrees per decade.[20] This natural decline in range of motion could thus offer an explanation for the decrease in neck function with higher age. Contralateral flexion of the neck was worse for patients undergoing surgery and radiotherapy in comparison to only surgery. The negative effect of adjuvant radiotherapy on AROM is in contrast with previous research.[6,8] Although pain and radiation fibrosis offer plausible explanations for limitations in contralateral flexion of the neck. Studies on chewing ability and trismus also show a negative effect of radiotherapy.[2,5]

## Factors influencing shoulder function

The effect of age in the model for ipsilateral abduction (-0.90 degrees) per year and for forward flexion (-0.70 degrees) per year can be explained only partially by normative data, which indicate a natural decline of 0.33 degrees per year between 40 and 70 years of age for forward flexion and abduction of the shoulder.[21] Higher age might be related to higher vulnerability, and it might therefore have a higher impact of the oncology treatment. In this study, ipsilateral shoulder abduction was lower for female patients than it was for male patients. This result is in contrast to results reported in studies on healthy subjects, in which females exhibited better AROM.[22] The model for ipsilateral abduction also included characteristics that are likely to be strongly correlated with each other (T in TNM, tumor location, type of reconstruction,

and type of ND). The negative effect of the extent of neck dissection surgery on shoulder abduction and forward flexion has been described before, and it is partly related to accessory nerve damage.[6,23,24] The only previous cross-sectional study to describe shoulder function at five-year follow-up also reported a negative effect for the extent of ND surgery.[10] The negative effect of bone graft/flap reconstruction is in line with previous studies, which have reported negative effects for extensive reconstructive surgery.[6,25]

## Limitations of this study

The models should be interpreted with care, as the predicted AROM of patients with clinically more common characteristics are likely to be more valid. Information on the accessory nerve status of patients in this cohort is lacking. Accessory nerve status can explain about 50% of the limitations in shoulder function[26], in addition to providing prognostic information to patients and physical therapists. Accessory nerve status could be examined by electromyography (EMG), by screening the operative report for accessory nerve status, or by examining active trapezius muscle function. Due to time constraints no measurement of external rotation of the shoulder was performed. A decrease in external rotation could be an indication for secondary shoulder complaints, like adhesive capsulitis.[8,27] The patients receiving neck dissection surgery in this study were treated by different head and neck oncology surgeons. This could have influenced the outcomes of function related to the (years of) experience of these surgeons. However, until now, there is no evidence to underpin this. This study could have been biased by the rate of loss to follow-up due to death and withdrawal, with patients in better condition being more likely to survive and less likely to withdraw from the study. In all, 28% of the patients in this sample died between baseline and five-year follow up. These patients probably had worse characteristics, but the use of mixed model analysis corrects for this possibility. The design of this study was explorative design, and it did not present a prediction model, due to the absence of a clinical cut-off point for identifying patients at risk. This limits the clinical usability of the results.

All patients undergoing ND had received instructions from a physical therapist regarding basic neck and shoulder mobility exercises before discharge from the hospital. Although outpatient physical therapy was registered, the content and frequency of the treatments were unclear. The level of daily activity or exercise performed by the patients included in this study was not registered at baseline or during follow up. It could be hypothesized that the more active and sportive patients recover better. Future research should include measurements on the level of daily activity and exercise.

## Future perspectives

This study provides clinicians with insight into factors that influence the course of lateral flexion of the neck, ipsilateral abduction, and forward flexion of the shoulder for patients with oral cancer.[12,28] Patients with characteristics that predict worse AROM recovery over five years, as compared to baseline, could be the focus for future physical therapy interventions. The interventions can be aimed at patients that have a high-risk profile for developing limitations in neck and shoulder function. The results could be used to inform patients and customize exercise interventions. Patients who are expected to regain neck and shoulder function comparable to baseline could be helped with a basic exercise instruction. Patients who are expected to develop limitations in neck and shoulder function could possibly benefit more from patient-tailored program. The specific exercises must be determined in future research as underlying mechanisms for developing neck and shoulder complaints can be different. The effects and optimal exercise strategies of such programs should be studied. This would be in line with the current public demand for cost-effective and risk-stratified care. In conclusion, this study identified high-risk patients for neck and/or shoulder impairments over a five-year follow-up.

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**APPENDIX A.** *Active range of motion of the contralateral flexion of the neck, estimated values in degrees*

| Type of Intervention | Type of ND | Baseline Mean (95% CI) | 1 year follow-up Mean (95% CI) | 5-year follow-up Mean (95% CI) |
|---|---|---|---|---|
| Surgery | No ND | 37.1 (34.4 – 39.7) | 37.7 (34.7 – 40.7) | 30.5 (27.4 – 33.7) |
| | SND | 38.4 (35.8 – 41.0) | 36.0 (33.2 – 38.8) | 29.7 (26.8 – 32.6) |
| | MRND | 36.3 (31.7 – 41.0) | 34.7 (29.3 – 40.0) | 27.5 (22.1 – 32.9) |
| | RND | - | - | - |
| Surgery & Radiotherapy | No ND | 39.2 ( 36.2 – 42.2) | 36.4 (32.7 – 40.2) | 28.3 (24.5 – 21.1) |
| | SND | 40.5 (38.0 – 43.1) | 34.7 (31.9 – 37.5) | 27.5 (24.4 – 30.5) |
| | MRND | 38.4 (34.4 – 42.5) | 33.3 (28.7 - 38.1) | 25.3 (20.3 – 30.2) |
| | RND | 47.3 (36.6 – 58.0) | 29.8 (19.1 – 40.5) | - |

ND: neck dissection; SND: selective neck dissection; MRND: modified radical neck dissection; RND: radical neck dissection. All patients presented are 60 years old.

**APPENDIX B.** *Ipsilateral flexion of the neck, estimated values in degrees.*

| Age | Baseline Mean (95% CI) | 1 year follow-up Mean (95% CI) | 5 year follow-up Mean (95% CI) |
|---|---|---|---|
| 50 | 42.5 (40.6 – 44.4) | 39.7 (37.7 – 41.8) | 34.2 (30.2 – 34.5) |
| 60 | 39.2 (37.7 – 40.7) | 36.4 (34.7 – 38.0) | 29.0 (27.3 – 30.8) |
| 70 | 35.8 (34.3 – 37.3) | 33.0 (31.4 – 34.7) | 25.7 (23.9 – 27.5) |
| 80 | 32.5 (30.6 – 34.4) | 29.7 (27.6 – 31.8) | 22.3 (20.2 – 24.5) |

**APPENDIX C.** *Ipsilateral abduction of the shoulder, estimated values in degrees from mixed model analysis*

| Gender | Type of reconstruction | Type of ND | Baseline Mean (95% CI) | One-year follow-up Mean (95% CI) | Five-year follow-up Mean (95% CI) |
|---|---|---|---|---|---|
| Female | Primary Closure | No ND | 134.4 (124.4 – 144.5) | 126.0 (114.2 – 137.7) | 137.0 (124.8 – 149.1) |
| | | SND | 130.9 (119.3 – 142.5) | 113.6 (100.4 – 126.7) | 147.2 (133.8 – 160.7) |
| | | MRND | 132.7 (116.6 – 148.9) | 103.2 (85.0 – 121.5) | 130.7 (116.6 – 149.8) |
| | Local flap | No ND | 137.5 (105.5 – 169,4) | 139.8 (107.6 – 172.0) | 136.2 (100.6 – 171.8) |
| | Myocutaneous/ free flap | No ND | 144.8 (132.4 – 157.1) | 137.6 (123.5 – 151.6) | 141.2 (126.4 – 155.9) |
| | | SND | 141.3 (129.4 – 153.1) | 125.2 (111.6 – 138.7) | 151.4 ( 137.4 – 165.4) |
| | | MRND | 143.1 (126.9 – 159.4) | 114.8 (96.9 – 132.7) | 134.9 (115.3 – 154.4) |
| | | RND | 149.9 (112.0 – 187.8) | 114.2 (76.1 – 152.3) | |
| | Bone graft/flap | No ND | 133.8 (117.6 – 150.0) | 103.7 (84.2 – 123.2) | 96.8 (75.9 – 117.7) |
| | | SND | 130.3 (116.5 – 144.0) | 91.3 (74.5 – 108.1) | 107.1 (88.1 – 126.0) |
| Male | Primary closure | No ND | 139.4 (129.0 – 149.8) | 134.6 (122.3 – 146.9) | 129.0 (115.9 – 142.1) |
| | | SND | 135.9 (125.5 – 146.3) | 122.2 (111.1 – 133.3) | 139.3 (127.6 -151.1) |
| | | MRND | 137.8 (121.7 – 153.8) | 111.9 (92.9 – 130.8) | 122.7 (103.6 – 141.9) |
| | | RND | 144.6 (106.6 – 182.5) | 111.3 (73.1 – 149.4) | |
| | Local flap | SND | 139.0 (108.2 – 169.8) | 136.1 (105.2 – 167.0) | 138.6 ( 103.5 – 173.6) |
| | Myocutaneous/ free flap | No ND | 149.8 (137.5 – 162.1) | 146.2 (131.8 – 160.6) | 133.2 (118.1 – 148.4) |
| | | SND | 146.3 (135.9 – 156.7) | 133.8 (122.5 – 145.1) | 143.5 (131.6 - 155.4) |
| | | MRND | 148.2 (132.2 – 164.2) | 123.5 (104.9 – 142.0) | 126.9 (107.7 – 146.2) |
| | Bone graft/flap | SND | 135.3 (121.2 – 149.5) | 100.0 (82.9 – 117.0) | 99.1 (80.8 – 117.4) |
| | | MRND | 137.2 (117.3 – 157.0) | | 82.6 (58.1 – 107.0) |

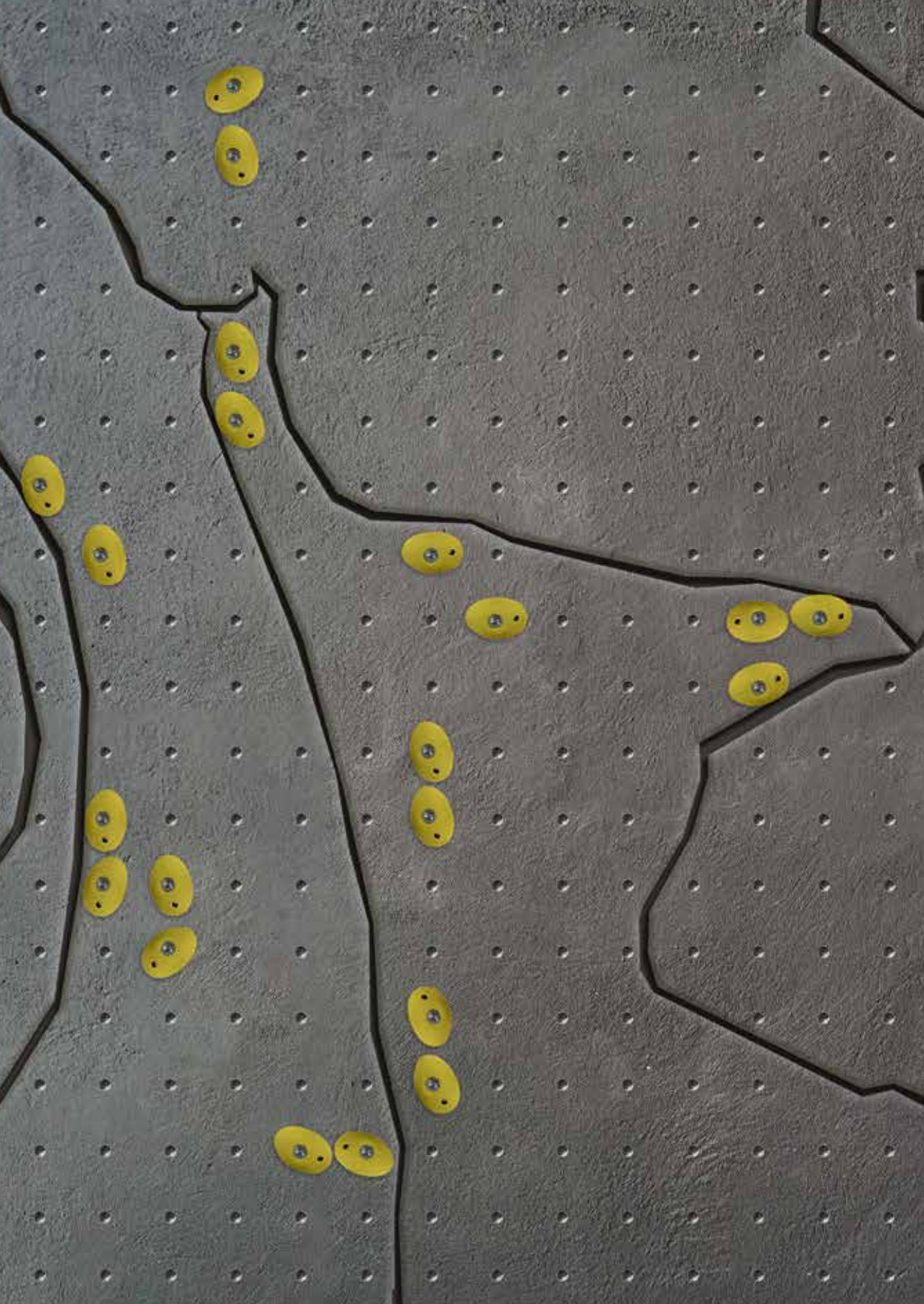
ND: neck dissection, SND: selective neck dissection, MRND: modified radical neck dissection, RND: radical neck dissection. Numbers are presented in mean values and 95% confidence intervals. All patients represented in this table were 65 years of age. Combinations of clinical factors that could not be predicted are not presented in this table.

**APPENDIX D.** *Ipsilateral forward flexion of the shoulder, estimated values in degrees from mixed model analysis.*

| Type of reconstruction | T in TNM | Type of ND | Location | Baseline Mean (95% CI) | One-year follow-up Mean (95% CI) | Five-year follow-up Mean (95% CI) |
|---|---|---|---|---|---|---|
| Primary closure | T1 | No ND | Maxilla | 146.0 (135.1 – 156.9) | 142.4 (130.4 – 154.3) | 147.4 (134.5 – 160.3) |
| | | | Mandibula | 149.8 (138.6 – 160.9) | 133.7 (120.8 – 146.6) | 137.7 (124.4 – 151.0) |
| | | | TFM | 148.9 (138.7 – 159.1) | 138.2 (126.1 – 150.3) | 134.4 (122.0 – 146.7) |
| | | SND | Maxilla | 138.7 (121.8 – 155.6) | 136.7 (117.6 – 155.7) | 156.0 (135.7 - 176.3) |
| | | | Mandibula | 142.5 (131.4 – 153.6) | 128.1 (116.0 – 140.2) | 146.2 (133.4 – 159.1) |
| | | | TFM | 141.6 (132.1 – 151.2) | 132.5 (122.2 – 142.8) | 143.0 (132.3 – 153.6) |
| | | MRND | TFM | 149.8 (135.3 – 164.2) | 130.0 (113.5 – 146.5) | 137.8 (120.4 – 155.1) |
| | T2 | No ND | Maxilla | 149.4 (138.9 – 159.9) | 153.4 (141.2 – 165.6) | 162.7 (149.2 – 176.2) |
| | | SND | Maxilla | 142.1 ( 128.0 – 156.3) | | |
| | | | Mandibula | 145.9 (134.5 – 157.3) | 139.1 (126.1 – 152.2) | 161.5 (147.5 – 175.4) |
| | | | TFM | 145.0 (134.5 – 155.6) | 143.6 ( 132.4 – 154.7) | 158.2 (146.5 – 169.9) |
| | | MRND | Mandibula | 154.0 (140.3 – 167.8) | 136.6 (120.5 – 152.8) | 156.3 (140.1 – 172.5) |
| | | | TFM | 153.2 (139.2 – 167.1) | 141.1 (125.2 – 157.0) | 153.0 (136.7 – 169.3) |
| | | RND | Mandibula | 155.2 (126.4 – 184.0) | 124.3 (95.5 – 153.2) | |
| | T3 | SND | TFM | 139.7 (122.6 – 156.9) | 119.0 (101.1 – 136.8) | 135.2 (116.5 – 153.9) |
| | T4 | No ND | Maxilla | 145.1 (134.0 – 156.3) | 141.5 (126.4 – 156.6) | 144.6 (128.4 – 160.8) |
| | | MRND | Maxilla | 146.0 (129.4 – 162.4) | | |
| | | | Mandibula | 149.8 (134.3 – 165.3) | 124.7 (106.9 – 142.5) | 138.2 (119.1 – 157.3) |
| Local flap | T1 | No ND | Maxilla | 143.8 (118.5 – 169.0) | 152.7 (127.0 – 178.4) | 135.8 (107.1 – 164.6) |
| | | SND | Mandibula | 140.3 (116.5 – 164.1) | 138.4 (114.3 – 162.5) | |
| | T4 | SND | Mandibula | 139.4 (113.8 – 165.0) | 137.5 (111.3 – 163.6) | 131.8 (102.8 – 160.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Myocutaneous/ free flap | T1 | No ND | TFM | 156.0 (143.2 -168.7) | | |
| | | SND | Mandibula | 149.6 (137.2 – 161.9) | 138.9 (125.4 – 152.4) | 139.8 (125.4 – 154.2) |
| | | | TFM | 148.7 (137.5 – 159.9) | 143.3 (130.8 – 155.9) | 136.5 (123.1 – 149.9) |
| | T2 | No ND | Maxilla | 156.4 (145.2 – 167.7) | 164.2 (151.9 – 176.6) | 156.2 (143.0 – 169.5) |
| | | SND | Mandibula | 152.9 (142.1 – 163.8) | 149.9 (137.6 – 162.3) | 155.0 (142.2 – 167.80 |
| | | | TFM | 152.1 (141.8 - 162.4) | 154.4 (143.3 – 165.5) | 151.7 (140.3 – 163.2) |
| | | MRND | Mandibula | 161.1 (147.2 – 175.0) | 147.4 (131.5 – 163.4) | 149.8 (133.6 – 166.0) |
| | | RND | Mandibula | 162.3 (133.5 – 191.0) | 135.1 (106.3 – 164.0) | |
| | T3 | No ND | Maxilla | 151.1 (134.2 – 168.0) | 139.6 (121.7 – 157.6) | 133.2 (114.4 – 152.1) |
| | | SND | Mandibula | 147.6 (130.6 – 164.7) | 125.3 (107.4 -143.3) | 132.0 (113.2 – 150.9) |
| | | | TFM | 146.8 (131.2 – 162.4) | 129.8 (113.7 – 145.8) | 128.8 (11.8 – 145.7) |
| | | MRND | TFM | 154.9 (137.3 – 172.5) | 127.3 (107.9 – 146.7) | |
| | T4 | No ND | Maxilla | 152.2 (141.1 – 163.3) | 152.3 (137.6 – 166.9) | 138.1 (122.2 – 154.0) |
| | | SND | Mandibula | 148.7 (135.6 – 161.8) | 138.0 (122.1 – 153.9) | |
| | | | TFM | 147.8 (135.3 – 160.4) | | |
| | | MRND | Maxilla | 153.0 (136.7 – 169.4) | 144.1 (124.8 – 163.4) | |
| | | | TFM | 155.9 (140.6 – 171.3) | 140.0 (122.1 – 157.8) | 128.4 (108.4 – 148.5) |
| Bone Graft/flap | T1 | No ND | Mandibula | 153.9 (138.2 – 169.6) | 131.7 (113.0 – 150.4) | 121.6 (102.3 – 140.9) |
| | | SND | Mandibula | 146.6 (131.8 – 161.5) | 126.0 (109.0 – 143.0) | 130.2 (112.5 – 148.0) |
| | T3 | SND | Mandibula | 144.7 (127.3 – 162.2) | 112.5 992.8 – 132.2) | |
| | | MRND | Mandibula | 152.8 (132.9 – 172.8) | | 117.3 (93.3 – 141.3) |
| | T4 | No ND | Mandibula | 153.0 (138.8 – 167.30 | | |
| | | SND | Mandibula | 145.8 (135.4 – 156.2) | 125.1 (112.2 – 138.1) | 127.4 (112.5 – 142.2) |
| | | MRND | TFM | 153.0 (134.9 – 171.1) | | |

ND: neck dissection, SND: selective neck dissection, MRND: modified radical neck dissection, RND: radical neck dissection. Numbers are presented in mean values and 95% confidence intervals. All patients represented in this table were 65 years of age. Combinations of clinical factors that could not be predicted are not presented in this table.



Chapter 5

# Effect of elective neck dissection versus sentinel lymph node biopsy on shoulder morbidity and health-related quality of life in patients with oral cavity cancer: A longitudinal comparative cohort study

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## Abstract

**Objective:** To research the difference in shoulder morbidity and health-related quality of life between patients with $cT_{1\text{-}2}N0$ oral cavity squamous cell carcinoma that undergo either elective neck dissection (END) or a sentinel lymph node biopsy (SLNB) based approach of the neck.

**Materials and methods:** A longitudinal study with measurements before surgery, 6 weeks, 6 months, and 12 months after surgery. Shoulder morbidity was determined with measurements of active range of motion of the shoulder and patient-reported outcomes for shoulder morbidity (SDQ, SPADI) and health-related quality of life (HR-QoL) (EQ5D, EORTC-QLQ-HN35). Linear mixed model analyses were used to analyze differences over time between patients that had END, SLNB or SLNB followed by complementing neck dissection.

**Results:** We included 69 patients. Thirty-three patients were treated with END. Twenty-seven patients had SLNB without complementing neck dissection (SLNB), and nine were diagnosed lymph node positive followed by completion neck dissection (SLNB+ND). Ipsilateral shoulder abduction ($P$=.031) and forward flexion ($P$=.039) were significantly better for the SLNB group at 6 weeks post-intervention compared to the END and SLNB+ND group. No significant differences for shoulder morbidity, or health-related quality of life were found at 6 weeks, 6 months, and 12 months between the three groups.

**Conclusion:** With oncologic equivalence for the END and SLNB as strategies for the $cN_0$ neck already demonstrated, and the SLNB being more cost-effective, our demonstrated benefit in short-term shoulder function strengthens the choice for the SLNB as a preferred treatment strategy.

# Introduction

Oral cavity squamous cell carcinoma (OCSCC) is the most common type of oral cavity neoplasm with a worldwide approximate incidence of 354,864 patients in 2018.[1] Early-stage $T_{1-2}$ tumors account for almost half of this population.[2] The surgical removal of the primary tumor is complemented by a (therapeutic) neck dissection (ND) when regional lymph node metastases are detected pre-operatively ($cN_+$). When no local lymph node metastases are detected with the pre-operative diagnostic procedures, this is classified as $cN_0$. However, patients with a $cN_0$ neck are still at risk of regional recurrence because occult undetected lymph node metastases are present in 20-30% of these patients.[3] The three most frequently used strategies to manage regional disease recurrence in patients with a $cN_0$ neck are elective neck dissection (END), sentinel lymph node biopsy (SLNB), and a "wait and see" strategy with patient observation (PO).[4] Patients diagnosed as lymph node positive with SLNB are treated with ND, a procedure comparable to that of the END strategy.

The question of which strategy for the treatment of $cN_0$ neck is most optimal is currently one of the most heavily debated subjects in head and neck oncology. A systematic review published in 2020 showed significantly better results for recurrence rate, disease-specific and overall survival for END compared to PO.[5] Both a systematic review and a randomized clinical trial (RCT) published in 2020 showed that END and SLNB are comparable on recurrence rate, disease-specific and overall survival, favoring these over PO.[6, 7] However, with occult lymph node metastasis present in only 20-30% of the patients, END causes overtreatment of 70-80% of the $cT_{1-2}N_0$ OCSCC patients in comparison to completion neck dissection after a positive SLNB only.[8] In addition, the SLNB is a less invasive and more cost-effective procedure compared to END.[9] With PO performing worse, and oncologic equivalence for the END and SLNB, the optimal strategy for the $cN_0$ neck is, however, still open for debate. Differences in treatment-related morbidity and health-related quality of life (HR-QoL) between $cN_0$ locoregional management strategies are therefore important outcomes to determine the preferred choice. An important part of treatment-related morbidity of surgical procedures in the neck is experienced by patients in limitations and pain in shoulder function.[10, 11] A recent systematic review including five observational studies showed less shoulder morbidity for the SLNB strategy compared to the END strategy.[6] A more recent RCT showed that this benefit for SLNB was only present at 6 months follow-up and not at longer follow-up.[7] Although closely related to

treatment-related morbidity, up till now research found no significant differences in HR-QoL between the END and SLNB strategies.[6, 7, 12] High-quality longitudinal research on shoulder morbidity and HR-QoL that compares both strategies with the inclusion of SLNB, diagnosed lymph node positive, followed by complementing neck dissection (SLNB+ND) patients is scarce. Moreover, adequate physical performance measurements on shoulder AROM are missing. Further research is needed to determine which locoregional management strategy is more beneficial for patients, using models corrected for covariates that are known to influence shoulder morbidity and HR-QoL as for example age, sex, and the extent of the ND.[11, 13, 14] Therefore, our aim is to study the difference in shoulder morbidity and HR-QoL between patients with $cT_{1\text{-}2}N_0$ oral squamous cell carcinoma that undergo END, SLNB, or SLNB+ND. We expect patients in the SLNB group to experience less shoulder morbidity and better HR-QoL in comparison to patients undergoing END and patients in the SLNB+ND group.



# Materials and methods

## Study setting and patients

A prospective longitudinal comparative study was conducted between January 2014 and June 2020 at the Radboud university medical center. The locoregional management strategy for patients with $cN_0$ transitioned from END to the SLNB strategy during the end of 2015 and the start of 2016 providing the opportunity for a natural comparative study. We identified three separate groups, including the Elective Neck Dissection (END) group, SLNB (SLNB) group, and SLNB with complementing neck dissection (SLNB+ND) group. Patients treated with the END were included between January 2014 and 2016. Patients treated with the SLNB (SLNB and SLNB+ND) were included between 2015 and 2019. Both SLNB groups underwent SLNB where dual -labelled (tc99m-ICG) nanocolloid was injected peri-tumoral. Lymphoscintigraphy and SPECT-CT were used to detect the sentinel lymph node on imaging. During surgery, the ICG near-infrared signal and radioactivity were respectively detected by a near-infrared camera system and gamma detection probe. The sentinel lymph node was surgically removed and histopathologically examined using stepped serial sectioning and immunohistochemistry. In the case of a negative lymph node, no complementing neck dissection treatment is necessary (SLNB group while a positive lymph node is followed in most cases by ND (SLNB+ND). In some cases of SLNB, diagnosed lymph node positive, patients

could be treated with radiotherapy. These patients were analyzed in the SLNB group because no complementing neck dissection was performed.

Inclusion criteria were: 1) a clinically confirmed early-stage OCSCC ($cT_{1-2}$) with a clinically negative neck ($cN_0$) and 2) 18 years or older. Exclusion criteria were: 1) inability to read Dutch, 2) cognitive impairments, 3) prior history of oral oncology treatment, and 4) prior history of shoulder trauma or shoulder surgery. The study was conducted according to the principles of the Declaration of Helsinki (64th version, October 19th, 2013). The research protocol was approved by the Ethical Commission of Radboud university medical center (NL2014-2019). All patients signed informed consent forms before measurements. This study followed guidelines provided by the Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) statement and checklist.[15]

## Study procedure

Patients were measured at baseline before surgery (M0), 6 weeks (M1), 6 months (M2), and at 12 months (M3) after surgery. The outcomes of this study were shoulder morbidity and HR-QoL. Active Range of Motion (AROM) measurements of the shoulder were performed in a standardized order and according to a standardized measurement protocol by a senior physiotherapist. Shoulder AROM was expressed as the ipsi- or contralateral side of neck intervention.

## Patient characteristics, demographic and clinical data

The demographic and clinical data were obtained from the patient during the baseline measurement and/or from medical records. These data included treatment modality (END, SLNB, SLNB+ND), age, sex, body mass index (BMI), smoking status (non-smoker, former smoker, current smoker), pack-years, alcohol usage (no alcohol use, one or more units daily), ASA score, tumor location (lip, tongue, gingiva, floor of the mouth, cheek, retromolar trigonium, palatum durum), clinical T-stage score, pathologic T- and N-stage score, number of lymph nodes resected, if level 2b was resected (yes/no), surgical reconstruction of the oral cavity (no reconstruction, local flap, free skin or myocutaneous revascularized flap), postoperative radiotherapy (yes/no), local recurrence during the first 12-months post-intervention (yes/no), survival during first 12 month post-intervention (yes/no), and number of physical therapy sessions.

## Shoulder morbidity

Shoulder morbidity was defined as shoulder AROM and patient-reported shoulder pain and limitations in daily life. We obtained the AROM of abduction, forward flexion, and external rotation of the shoulder. Shoulder abduction and forward flexion was measured with a digital inclinometer (Baseline© Digital Inclinometer, Fabrication Enterprises Inc., White Plains, New York, USA).[16] External rotation of the shoulder was measured with a goniometer (Universal goniometer, Mathys Synthes, Bettlach, Switzerland).[16]

Shoulder pain and limitations were measured with the Shoulder Disability Questionnaire (SDQ) and Shoulder Pain and Disability Index (SPADI). The SDQ contains 16 questions regarding physical activities in the last 24 hours that could provoke possible shoulder complaints. This questionnaire addresses physical, emotional, and social impairment due to shoulder complaints or incapability of performing an activity by the usage of a 3-point scale (1: Yes, I experience complaints, 2: No, I do not experience complaints, 3: The question does not apply to me). An overall score was calculated by dividing the number of given answers as "Yes" by the total amount of answers without the "does not apply to me" answers. The test-retest reliability of the SDQ was good in head and neck cancer (HNC) patients (ICC=0.84).[17] The SPADI is a validated 13-item questionnaire with two main categories regarding pain (5 items) and impairment in daily activities (8 items) based on an 11-point scale (0-10) for each item. A higher score indicates more pain or impairment due to the treatment of the shoulder.[17] An overall score for each category and a total score was calculated. The test-retest reliability showed excellent reliability (ICC=0.91) in HNC patients.[17]

## Health-related quality of life

The EQ-5D-3L is a validated HR-QoL questionnaire that explores 5 items of health status regarding mobility, self-care, daily usual activities, pain/discomfort, and anxiety/depression. The questionnaire also includes a Visual Analogue Scale (VAS) from 0 to 100 mm to get an impression about the current health status, which we used as an outcome measurement for general HR-QoL for this study. Higher scores on the VAS indicate a better HR-QoL.[18] The EQ-5D-3L showed good psychometric properties.[19]

The European Organization for Research and Treatment for Cancer Quality of Life Questionnaire – Head and Neck 35 questions (EORTC-QLQ-HN35) is an HNC-specific Quality of Life Questionnaire. This questionnaire contains 35 items that can be transformed into a score from 0 to 100. For the function scales, a score of 100 means the perfect quality of

life, whereas for the symptom scales it indicates a heavy burden.[20] The EORTC-QLQ-HN35 showed good psychometric properties.[20]

### Statistical analysis

Categorical patient characteristics are presented as numbers and percentages, while continuous characteristics are presented as means and standard deviations (SDs). In the case of non-normally distributed variables, outcomes are presented as medians and 25$^{th}$ and 75$^{th}$ percentiles. Differences between baseline characteristics of patients in the 3 groups were analyzed with a Chi-square test for nominal and ordinal data, one-way ANOVA for normally distributed continuous data, and a Kruskal-Wallis test for non-normal distributed continuous data. Longitudinal data regarding shoulder AROM and overall scores of the questionnaires were analyzed using linear mixed models analysis. For this analysis, a random intercept for the subject was used. For fixed factors, the time of measurement (M0-M3), treatment group (END, SLNB, SLNB+ND), and their interaction were used. The additional fixed factors or covariate factors included in the model were based on known effects on shoulder morbidity or HR-QoL reported in research: age, sex, postoperative radiotherapy, TNM-classification, BMI, dissection of cervical level IIb, the amount of dissected cervical levels, and smoking status (in pack-years).[11, 13, 14, 21] Differences between the three groups were tested by the likelihood ratio test. Furthermore, time effects within groups were analyzed using the linear mixed model. The individual ordinal sub-items of the questionnaires were analyzed with Generalized Linear Models analysis with the same random and fixed factors. The individual ordinal sub-items of the questionnaires were analyzed with Generalized Linear Models analysis for the same random and fixed factors. Data analysis was performed using IBM SPSS Software Version 26.0 (SPSS, Inc., Chicago, Illinois, United States).

## Results

In total, the data of 69 patients was used in this study (Figure.1) of which 33 belonged to the END group, 27 to the SLNB group, and 9 to the SLNB+ND group.

Proportionally there were fewer T2-stage patients in the SLNB group compared to both the END and SLNB+ND groups (*P*=.001) (Table 1).

**FIGURE 1:** *Participant recruitment and follow-up.*

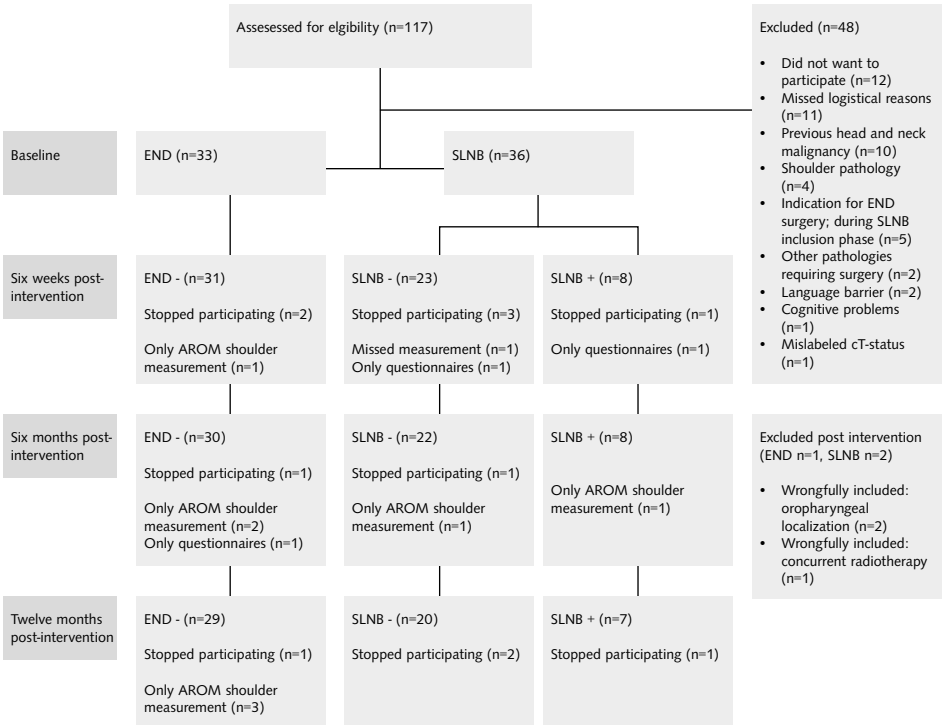



**TABLE 1.** *Demographic and clinical characteristics*

| Patient characteristics, n (%) | END (N = 33) | SLNB (N = 27) | SLNB-ND (N = 9) | *P*-value |
|---|---|---|---|---|
| Sex | | | | |
| Female | 19 (57.6) | 12 (44.4) | 5 (55.6) | 0.584† |
| Male | 14 (42.4) | 15 (55.6) | 4 (44.4) | |
| Age (years), mean (SD) | 64.5 (10.2) | 64.5 (11.0) | 66.3 (11.3) | 0.893¥ |
| BMI; mean (SD) | 25.0 (5.5) | 26.5 (4.9) | 25.0 3.6) | 0.513¥ |
| Smoking (daily) | | | | |
| Non-smoker | 17 (51.5) | 11 (40.7) | 2 (22.3) | |
| Former smoker | 7 (21.2) | 8 (29.6) | 3 (33.3) | 0.596† |
| Current smoker | 9 (27.3) | 8 (29.6) | 4 (44.4) | |
| Pack years, median ($25^{th}$- $75^{th}$ PCTL) | 0 (0-41) | 5 (0-45) | 30 (1-43.5) | 0.713 |

| | | | | |
|---|---|---|---|---|
| Alcohol use (daily) | | | | |
| No alcohol use | 15 (45.5) | 11 (40.7) | 6 (66.7) | 0.596† |
| One or more unit(s) daily | 18 (54.5) | 16 (59.3) | 3 (33.3) | |
| ASA classification | | | | |
| ASA I | 8 (24.2) | 5 (18.5) | 0 (0) | 0.097† |
| ASA II | 22 (66.7) | 13 (48,1) | 7 (77.8) | |
| ASA III | 3 (9.1) | 9 (33.3) | 2 (22.2) | |
| Location tumor | | | | |
| Tongue | 18 (54.5) | 16 (59.3) | 4 (44.4) | 0.195† |
| Floor of the mouth | 7 (21.2) | 5 (18.5) | 4 (44.4) | |
| Cheek | 6 (18.2) | 1 (3.7) | 1 (11.1) | |
| Trigonum retromolare | 0 (0.0) | 3 (11.1) | 0 (0.0) | |
| Lip | 0 (0.0) | 1 (3.7) | 0 (0.0) | |
| Gingiva | 2 (6.1) | 1 (3.7) | 0 (0.0) | |
| Palatum durum | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| cT | | | | |
| $cT_1$ | 7 (21.2) | 18 (66.7) | 2 (22.2) | 0.001*† |
| $cT_2$ | 26 (78.8) | 9 (33.3) | 7 (77.8) | |
| pTN | | | | |
| $pT_1$ | 13 (39.4) | 20 (74.1) | 3 (33.3) | 0.054† |
| $pT_2$ | 18 (54.5) | 5 (18.5) | 6 (66.7) | |
| $pT_3$ | 2 (6.1) | 1 (3.7) | 0 (0.0) | |
| $pT_4$ | 0 (0.0) | 1 (3.7) | 0 (0.0) | |
| pN0 | 26 (78.8) | 23 (85.2) | 0 (0.0 | 0.000† |
| $pN_1$ | 3 (9.1) | 2 (7.4) Ω | 8 (88.9)ϖ | |
| $pN_2$ | 4 (12.1) | 2 (7.4)Ω | 1 (11.1) | |
| Number of nodes resected, median ($25^{th}$- $75^{th}$ PCTL) | 5 (5-5) | 2 (1-3) | 6 (5-10) | 0.000*‡ |
| Level 2B resected (yes) | 33 (100.0) | 22 (81.5) | 9 (100.0) | 0.065† |
| Reconstruction | | | | |
| Primary Closure | 18 (54.5) | 9 (70.4) | 4 (44.4) | 0.525† |
| Local Flap/Thiersch | 11 (33.3) | 7 (25.9) | 4 (44.4) | |
| Bone graft/Free vascularized flap | 4 (12.1) | 1 (3.7) | 1 (11.1) | |
| Radiotherapy post-intervention | 22 (66.7) | 24 (88.9) | 7 (77.8) | 0.127† |
| Mortality | 0 (0.0) | 1 (3.7) | 0 (0.0) | NA |
| Local Recurrence | 1 (3) | 0 (0.0) | 4 (44.4) | NA |
| Number of PT treatments, median ($25^{th}$- $75^{th}$ PCTL) | 0 (0-0)# | 0 (0-5)# | 0 (0-0) | 0.516‡ |

*$p$: < 0.001; †: Chi-Square; ¥: ANOVA; U; ‡: Kruskal-Wallis.

#: Four END patients received more than 20 treatments, 1 SLNB patient received more than 20 treatments

∏: Five out of 8 patients labeled as pN1 had a positive lymph node in the SLNB but did not have any positive lymph nodes in the complementing neck dissection.

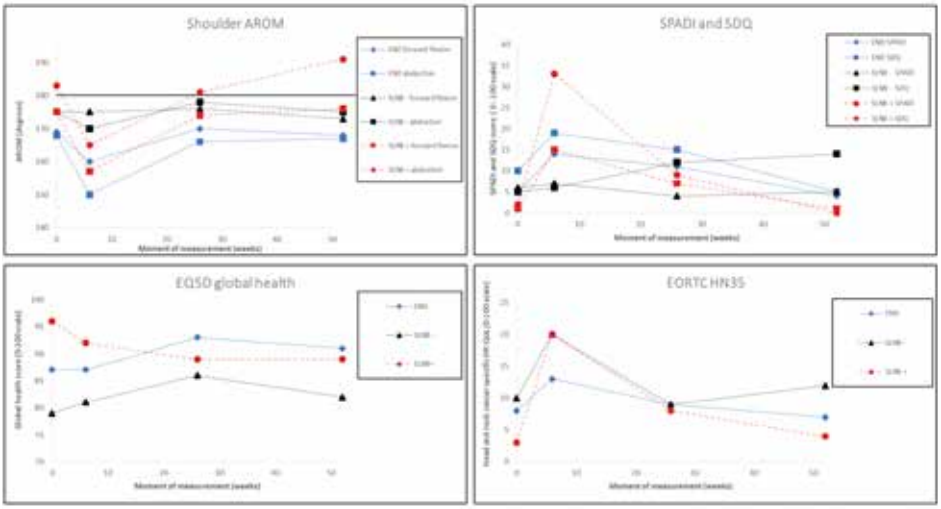
Ω Patients diagnosed lymph node positive but treated with radiation therapy and therefore analyzed in the SLNB without complementing neck dissection group (SLNB).

ASA-score: American society of anesthesiologists physical status classification system, BMI: body mass index, cT: clinical tumor stage, END: elective neck dissection, IQR: interquartile range, NA: not applicable, pTN: pathologic tumor node stage; PT: physical therapy; SD: standard deviation; SLNB: sentinel lymph node biopsy.

## Shoulder morbidity

Within groups analyses for shoulder AROM are depicted in Table 2, showing that ipsilateral forward flexion was lower at 6 weeks post-intervention for the END group and SLNB+ND group compared to baseline (*P*=.002).

**FIGURE 2:** *Visualization of the within differences for shoulder patient-reported morbidity and Health-related Quality of life.*




Ipsilateral forward flexion recovered between 6 weeks and 6 months after treatment for the END and SLNB+ND group (*P*=.003). Ipsilateral shoulder abduction deteriorated at 6 weeks (*P*=.000) and recovered at 6 months (*P*=.002) for the END group. External rotation of the shoulder deteriorated between 6 and 12 months for the END group (*P*=.003). Visualization of the within differences for shoulder AROM is depicted in Fig 2.

Within groups analyses for patient-reported shoulder morbidity are presented in Table 3. Shoulder morbidity was higher compared to baseline at 6 weeks in the END group for SPADI (*P*=.001) and SDQ (*P*=.029), and for the SDQ (*P*=.024) in the SLNB+ND group. Between the 6- and 12-months measurements, the END group showed recovery of the SPADI (*P*=.006) and SDQ (*P*=.025).

**TABLE 2**. *Shoulder range of motion: between and within differences for three intervention groups analyzed with mixed model analysis*

| | M0 | M1 | M2 | M3 | Mixed model Within groups *P*-value | Mixed model Within groups *P*-value | Mixed model Within groups *P*-value | Mixed model Between groups *P*-value |
|---|---|---|---|---|---|---|---|---|
| Active Range of Motion Shoulder (degrees, SD) | | END (n =33) | | | M0-M1 | M1-M2 | M2-M3 | |
| Forward flexion | 169 (18) | 160 (17) | 170 (20) | 168 (21) | 0.002** | 0.003** | 0.833 | 0.039* |
| Abduction | 168 (26) | 150 (32) | 166 (32) | 167 (27) | 0.000*** | 0.002** | 0.468 | 0.031* |
| External rotation | 56 (21) | 52 (19) | 60 (23) | 52 (23) | 0.201 | 0.092 | 0.033* | 0.836 |
| | | SLNB - (n = 27) | | | | | | |
| Forward flexion | 175,0 (13) | 175 (12) | 176 (12) | 173 (17) | 0.868 | 0.662 | 0.351 | 0.039* |
| Abduction | 175 (25) | 170 (14) | 178 (30) | 175 (18) | 0.302 | 0.081 | 0.466 | 0.031* |
| External rotation | 56 (16) | 60 (17) | 55 (17) | 54 (18) | 0.438 | 0.387 | 0.986 | 0.836 |
| | | SLNB + (n = 9) | | | | | | |
| Forward flexion | 175 (20) | 157 (26) | 174 (14) | 176 (17) | 0.017* | 0.016* | 0.963 | 0.039* |
| Abduction | 183 (25) | 165 (26) | 181 (21) | 191 (22) | 0.079 | 0.114 | 0.477 | 0.031* |
| External rotation | 51 (19) | 59 (16) | 60 (11) | 53 (10) | 0.506 | 0.689 | 0.427 | 0.836 |

* $P < 0.05$; **$p < 0.01$; ***$p < 0.001$
END: elective neck dissection, SD: standard deviation, SLNB: sentinel lymph node biopsy

**TABLE 3.** *Patient reported outcome measurements on health-related quality of life and shoulder morbidity: between and within differences for three intervention groups analyzed with mixed model analysis*

| | M0 | M1 | M2 | M3 | Mixed model Within groups *P*-value | Mixed model Within groups *P*-value | Mixed model Within groups *P*-value | Mixed model between groups *P*-value |
|---|---|---|---|---|---|---|---|---|
| Questionnaire | | END (n =33) | | | M0-M1 | M1-M2 | M2-M3 | |
| EORTC-QLQ HN-35 | 8 (8) | 13 (10) | 9 (10) | 7 (9) | 0.034* | 0.092 | 0.654 | 0.693 |
| EQ5D | 87 (16) | 87 (19) | 93 (18) | 91 (15) | 0.942 | 0.015* | 0.509 | 0.930 |
| SPADI | 5 (12) | 14 (22) | 11 (19) | 4 (8) | 0.001** | 0.537 | 0.006** | 0.568 |
| SDQ | 10 (28) | 19 (27) | 15 (23) | 5 (12) | 0.029* | 0.318 | 0.025* | 0.246 |
| | | SLNB- (n = 27) | | | | | | |
| EORTC-QLQ HN-35 | 10 (12) | 20 (19) | 9 (8) | 12 (16) | 0.000*** | 0.000*** | 0.218 | 0.693 |
| EQ5D | 79 (23) | 81 (21) | 86 (24) | 82 (23) | 0.916 | 0.424 | 0.860 | 0.930 |
| SPADI | 6 (14) | 7 (18) | 4 (10) | 5 (10) | 0.770 | 0.542 | 0.947 | 0.568 |
| SDQ | 5 (20) | 6 (18) | 12 (24) | 14 (30) | 0.684 | 0.433 | 0.664 | 0.246 |
| | | SLNB+ (n = 9) | | | | | | |
| EORTC-QLQ HN-35 | 3 (8) | 20 (16) | 8 (7) | 4 (8) | 0.002** | 0.045* | 0.816 | 0.693 |
| EQ5D | 96 (8) | 92 (15) | 89 (15) | 89 (13) | 0.727 | 0.677 | 0.613 | 0.930 |
| SPADI | 1 (12) | 15 (21) | 7 (17) | 1 (14) | 0.095 | 0.220 | 0.312 | 0.568 |
| SDQ | 2 (5) | 33 (33) | 9 (18) | 0 (35) | 0.024* | 0.067 | 0.780 | 0.246 |

* $P < 0.05$; **$p < 0.01$; ***$p < 0.001$

END: elective neck dissection, EORTC-QLQ-HN35: european organization for research and treatment of cancer quality of life questionnaire head & neck module, EQ-5D: euroqoL five-dimensional instrument, SLNB: sentinel lymph node biopsy, SDQ: shoulder disability questionnaire, SNLB: sentinel lymph node biopsy, SPADI: shoulder pain and disability index.

A visualization of the within differences for patient-reported shoulder morbidity is depicted in Fig 2. Between groups analysis of the AROM scores showed that ipsilateral forward flexion (*P*=.039), and ipsilateral shoulder abduction (*P*=.031) were lower for the END group and SLNB+ND group compared to the SLNB group at 6 weeks post-intervention (Table 2). No significant differences between groups in external rotation of the shoulder (AROM) and morbidity (SPADI and SDQ) were found (Table 3).

### Health-related quality of life

The within groups analyses (Table 3) showed lower head and neck-specific HR-QoL at 6 weeks post-intervention compared to baseline for all three groups: the END group (*P*=.034), the SLNB group (*P*<.001), and the SLNB+ND group (*P*=.002). The SLNB group (*P*<.001) and SLNB+ND group (*P*=.045) recovered between the 6 weeks and 6 months measurements (Table 3). The HR-QoL (EQ-5D) improved significantly between the 6 and 12 months in the END group to an above baseline measurement score (*P*=0.015). Visualization of the within differences for shoulder patient-reported morbidity and HR-QoL is depicted in Figure 2. No between group differences were found for HR-QoL between the three groups (Table 3).

## Discussion

This study found that shoulder AROM expressed in ipsilateral forward flexion and abduction is better for patients in the SLNB group at 6 weeks post-intervention compared to both patients undergoing END and patients diagnosed SLNB positive followed by complementing neck dissection (SLNB+ND). No differences in patient-reported shoulder morbidity (SDQ and SPADI), HNC specific HR-QoL (EORTC-QLQ-HN35), and cancer generic HR-QoL (EQ-5D) were found between the 3 groups. This confirms our hypothesis that patients without pre-operatively detected regional lymph node metastasis ($cN_0$) can benefit from the SLNB strategy due to less short-term shoulder morbidity. With 70 to 80% of $T_{1-2}$ clinically negative OCSCC expected to be diagnosed lymph node negative with SLNB, this short-term benefit in shoulder AROM could strengthen the choice for SLNB as a preferred treatment strategy. The SLNB+ND group, although small (n=9), was included because this gives the most optimal representation of patient trajectories in both the END and SLNB strategies. Other studies chose to include the SLNB+ND as a representative for END patients[12] or to exclude

them [22, 23] which limits a true representation of the strategies. Only one other randomized study described the three different groups, but chose not to correct for possible confounding variables in the analysis, lacked a baseline measurement, and dichotomized shoulder AROM measurements.[7] Our longitudinal study thereby used a complete set of physical and patient-reported measurements.[16, 17] These findings provide new insights into treatment-related shoulder morbidity and HR-QoL that can be used to substantiate the choice between END and SLNB as strategies for patients with $CN_0$) OCSCC.

## Shoulder morbidity



A better ipsilateral forward flexion and abduction of the shoulder at 6 weeks for SLNB group patients is in line with the hypothesis that the less invasive procedure causes less shoulder morbidity. It also confirms the hypothesis that these benefits are to be expected in the first year after medical intervention as demonstrated by Garrel et al.[7] This latter study also found better outcomes for shoulder morbidity at 4, 6, and 12 months after intervention which we didn't find but the differences are possibly related to the larger group sizes in that study. This is also confirmed by our previous cross-sectional study in which no significant differences were demonstrated between the END and SLNB strategies after more than 1-year of follow-up.[24] Other long-term cross-sectional studies found better results for SLNB compared to END at long-term follow-up, but the differences were small and limited in clinical relevance.[12, 22, 23, 25] The within groups analysis showed a significant decline in shoulder range of motion and an increase in shoulder morbidity at the 6-week measurement for the END group. This progressively recovered up to baseline values at 6 and 12 months after oral oncological treatment. This initial deterioration in shoulder morbidity is comparable to previous research in patients undergoing ND.[10, 11, 26] Remarkably, the modelled shoulder AROMs for all strategies are above age and gender stratified reference values, indicating no limitations in shoulder and neck AROM for the 3 groups.[16] This could possibly be related to overcorrecting the modeled scores. This was confirmed when we analyzed the raw data on mean shoulder range of motion. Mean range of motion scores for forward flexion and abduction of the shoulder were approximately 5-10 degrees lower than the modelled scores. In contrast to this, four END patients received more than 20 physiotherapy sessions for problems regarding neck and shoulder function in comparison to one patient in the SLNB group. The relatively high variance in the modeled outcomes also indicates that possible outliers in shoulder morbidity could be present in both the END and SLNB groups. The higher variance could also be explained by the relatively high

measurement error in measurements on shoulder range of motion in patients with head and neck cancer. [16] This means that adequate identification of patients at risk is still of importance.

## Health-related quality of life.

We found no differences in cancer generic or HNC specific HR-QoL between the three groups. This is in contrast with the previous research that found better health utility scores (EQ-5D) for SNLB compared to END representing HR-QoL.[23] The results we found are in line with the study by Flach et al. who described no significant difference between END and SLNB.[12] Within group analyses showed a significant deterioration in HNC-specific HR-QoL at the 6 week measurement for all three strategies that improved up to baseline values at 6 months. This means that no specific effect of neck dissection (groups 1 and group 2B) on HNC-specific HR-QoL was found. The decrease in HNC specific HR-QoL experienced by all patients could therefore be related to reduced oral function caused by the surgical removal of the primary tumor.

## Strengths and limitations of the study

Our study is the first to compare the END and SLNB locoregional management strategies in a longitudinal design, with a combination of objective shoulder AROM measurements and patient-reported outcomes. The use of mixed model analysis strengthens the validity of the outcomes taking into account the effect of the repeated measurements, the influence of patient and treatment characteristics, and its ability to correct for missing data strengthens the outcomes. No formal power analysis or simulation was performed because the study was a natural comparative study dependent on the change of treatment strategy. However, the modelled outcomes and the reported variance allow for adequate interpretation, except for the third small group. Information on the accessory nerve status objectified with electromyography (EMG) of patients in this study is lacking. Accessory nerve status can explain about 50% of the limitations in shoulder function, in addition to providing prognostic information to patients and physical therapists.[26, 27] Information on the type of physiotherapy treatment and the level of experience of the physiotherapist is missing which could have given more insight into the problems as experienced by patients.

## Conclusion

SLNB patients treated without complementing neck dissection (SLNB) have better postoperative shoulder AROM at 6 weeks after the intervention compared to patients undergoing the END strategy or diagnosed lymph node positive SLNB+ND followed by completion neck dissection (SLNB+ND). Shoulder morbidity as measured with patient-reported outcomes and quality of life is comparable for the END, SLNB and SLNB+ND groups. With oncologic equivalence for the END and SLNB as strategies for the $cN_0$ neck already demonstrated, and the SLNB being more cost-effective, our demonstrated benefit in short-term shoulder morbidity strengthens the choice for the SLNB as a preferred treatment strategy.

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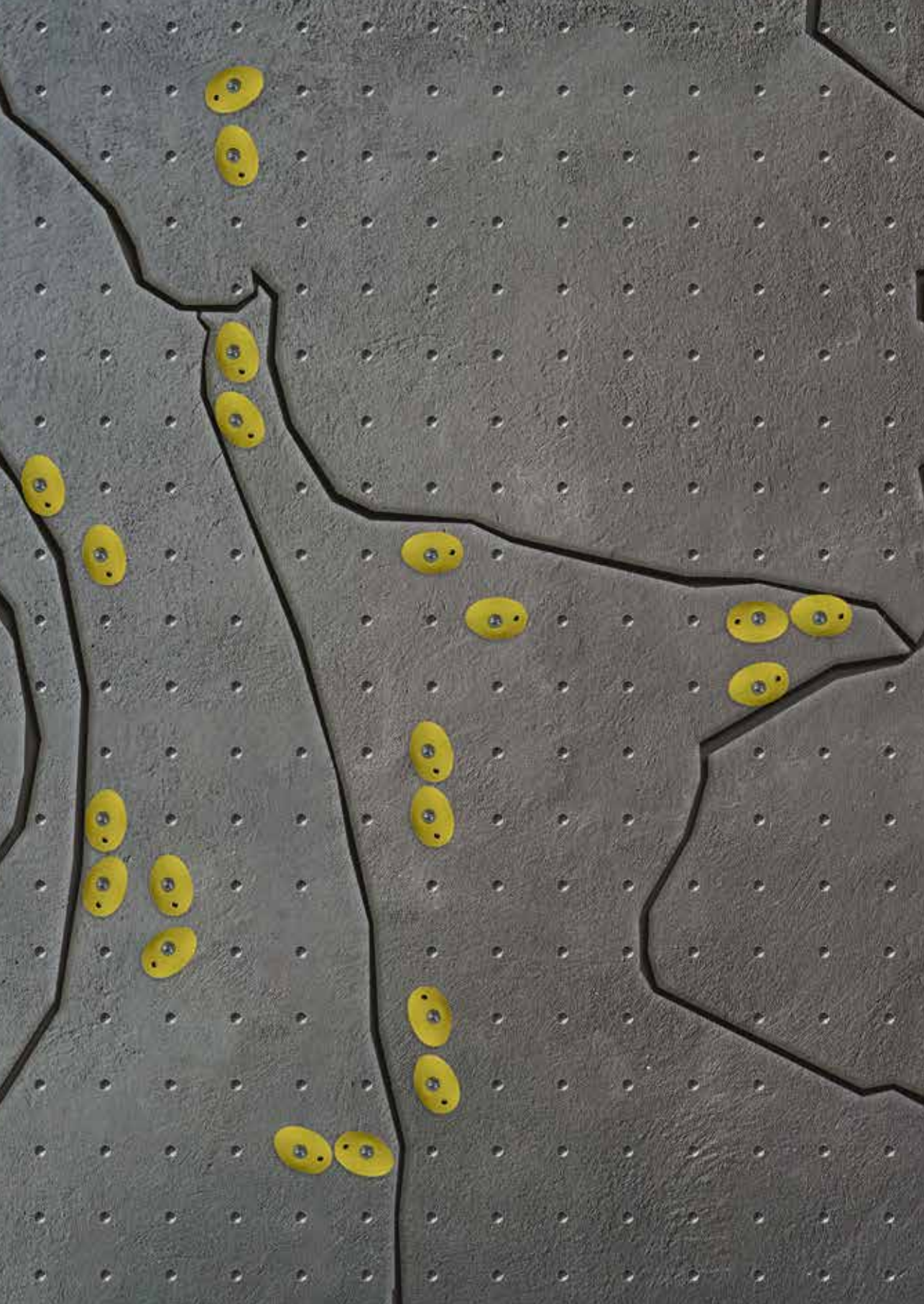

Chapter 6

# Neck and shoulder morbidity in patients with oral cancer and clinically negative node neck status: a comparison between the elective neck dissection and sentinel lymph node biopsy treatment strategies

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## Abstract

The choice for the most optimal strategy for patients with a $cT_{1-2}N_0$ carcinoma of the oral cavity, sentinel lymph node biopsy (SLNB) or elective neck dissection (END), is still open for debate in many head and neck cancer (HNC) treatment centers. One of the possible benefits of the less invasive SLNB could be reduced neck and shoulder morbidity. Recent studies have shown a benefit in favor of SLNB the first year after intervention, but the long-term consequences and differences in neck morbidity remain unclear. This cross-sectional study aimed to research differences in neck and shoulder morbidity and Health-Related Quality of Life (HR-QoL) in patients with a $cT_{1-2}N_0$ carcinoma of the oral cavity, treated with either END or SLNB. Neck and shoulder morbidity and HR-QOL were measured with patient-reported questionnaires (SDQ, SPADI, NDI, NDII, EORTC-QLQ-C30, EORTC-QLQ-HN35) and active range of motion (AROM) measurements. In total 18 patients with END and 20 patients with SLNB were included. We found no differences between END and SLNB for long-term neck morbidity, shoulder morbidity, and HR-QOL. The significant differences found in the rotation of the neck are small and not clinically relevant.

# Introduction

Head and neck squamous cell carcinomas arise in the mucosal linings of the upper respiratory digestive tracts and are considered an important part of the global burden of cancer [1]. The most frequent anatomical site for head and neck squamous cell carcinomas is the oral cavity. Approximately half of the patients are diagnosed with early stage $cT_{1\text{-}2}$ (<4 cm without cancer cells present in nearby structures, lymph nodes or distant sites) oral cavity squamous cell carcinoma (OCSCC) [2]. Advancements in medical treatment have improved survival, but a high number of patients experience treatment-related morbidity regarding physical, social, emotional, and psychological health [3,4]. Patients can experience limitations in functions of the head and neck, activities of daily living, and oral functioning [5–9]. Limitations in physical health can remain present in the long term and are strongly correlated with a lower health-related quality of life (HR-QoL) [3,10]. Limitations in active range of motion (AROM) of neck and shoulder are highly prevalent in patients with OCSCC [5,11].

The $cT_{1\text{-}2}$ OCSCC patient is labeled as a clinically negative neck ($cN_0$) when during the pretreatment phase no regional lymph nodes metastases are detected by palpation, fine needle aspiration cytology, and/or imaging techniques. The $cN_0$ patients are, however, still at risk of occult lymph node metastases that are present in 20 to 30% of $cN_0$ OSCC patients [12]. The two most used management strategies to improve locoregional recurrence-free survival as compared to observation are the elective neck dissection (END) and the sentinel lymph node biopsy (SLNB). The END usually consists of the removal of all lymph nodes at risk located at levels I, II, III, and sometimes level IV [13]. The SLNB consist of a surgical procedure in which the first draining lymph node(s), called sentinel lymph nodes (SLNs), are identified, removed, and examined by a pathologist to determine whether cancer cells are present. Only if positive nodes are present, a neck dissection is subsequently performed. Thereby, SLNB limits possible surgical overtreatment of the neck up to 80% compared to a strategy in which all $cN_0$ patients undergo END. Recent research has shown that the END and SLNB strategies have comparable outcomes on neck node recurrence-free survival at 2 years follow up (89.6% for END and 90.7% for SLNB) [14]. With the SLNB being considered a less invasive strategy compared to END it is expected to cause less local morbidity and better HR-QoL in comparison to END and therefore less need for physical therapy intervention or screening [15,16]. However, the choice for the most optimal strategy for the $cN_0$ patients is still open for debate in many head and neck

cancer (HNC) treatment centers. It is also unclear if a patient undergoing SLNB should also be screened for neck and shoulder limitations by a physical therapist as is advised for patient undergoing END in treatment guidelines in the Netherlands [17]. It is therefore important to research differences in neck and shoulder morbidity and health-related quality of life (HR-QoL). Previous research reported lower postoperative shoulder morbidity for SLNB compared to END [14,18–20]. A patient's perspective study showed that patients undergoing SLNB preferred this strategy over END [20]. However, in two studies the END group received END after SLNB [18,20] and four studies lack objective measurements on neck and shoulder morbidity [14,18,19,21]. Our previous longitudinal comparative study showed less shoulder morbidity at 6 weeks post intervention for SLNB but lacks information on neck morbidity and long-term follow-up (>1 year). Although less invasive, a recent systematic review showed that the difference in HR-QoL between END and SLNB remains unclear [22]. Therefore, more insight is needed into the difference between END and SLNB regarding long-term neck and shoulder morbidity and HR-QoL. This study aimed to compare shoulder and neck morbidity and HR-QoL between $cT_{1\text{-}2}N_0$ OCSCC patients with $cN_0$ undergoing END or SLNB. For OCSCC patients with a clinically negative neck, we hypothesized less neck and shoulder morbidity and better HR-QoL after SLNB as compared to the END strategy.



# Materials and Methods

## Study Setting and Participants

This cross-sectional study included patients who were treated for $cT_{1\text{-}2}N_0$ OCSCC between 2012 and 2019 at the UMC Utrecht, The Netherlands. The study was conducted according to the principles of the Declaration of Helsinki 2013 and in accordance with the Medical Research Involving Humans Subjects Act (WMO). The research protocol was approved by the Ethics Committees of UMC Utrecht (NL68148.041.18). Informed consent was obtained from all participating patients.

Patients were included if they: (1) had $cT_{1\text{-}2}N_0$ OCSCC, (2) underwent END or SLNB, and (3) were at least 18 years old. Patients were excluded when they: (1) received postoperative radiotherapy, (2) had recurrent OCSCC, (3) were unable to read Dutch and/or complete the questionnaires, (4) had a history of neck or shoulder surgery, (5) underwent END after positive SLNB, and (6) were treated with a bilateral neck dissection. This study followed guidelines

provided by the Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) statement [23].

## Study Procedure

Patients scheduled for usual care follow-up appointments at the UMC Utrecht were informed and asked to participate in the study. Informed consent was obtained before the measurements. Demographic, participant, and treatment characteristics were collected from the electronic hospital treatment and registration system: age, gender, END or SLNB strategy, tumor location (maxilla, mandibular, floor/mouth, cheek), treated side (left/right), time since treatment and cTNM-stage ($cT_{1\text{-}2}$). During the research appointment additional patient characteristics were collected for height (meters) weight (kilograms), alcohol consumption after treatment (units of alcohol per day), tobacco use (pack-years), use of physiotherapy (yes/no), number of physiotherapy treatments in the past years and if they received physiotherapy for head and neck related problems (yes/no). Data was collected between February–December 2019.

### Shoulder Morbidity

The Shoulder Disability Questionnaire (SDQ) is a valid and reliable pain-related disability questionnaire, which contains 16 items describing common situations that may induce symptoms in patients with shoulder disorders and was the primary outcome of this study [24]. All items refer to the preceding 24 h.

The Shoulder Pain and Disability Index (SPADI) is a valid and reliable self-report questionnaire that measures shoulder pain and disability experienced during the last week [25].

### Neck Morbidity

The Neck Disability Index (NDI) is a valid and reliable self-assessment questionnaire that measures neck disability such as pain and headache experienced by patients during the last four weeks [26].

### Shoulder and Neck Morbidity

The Neck Dissection Impairment Index (NDII) is a valid and reliable self-rated questionnaire that assesses both neck and shoulder morbidity in patients with a neck dissection [27,28].

### Shoulder and Neck Active Range of Motion

The AROM for the shoulder was measured for external rotation, abduction, and forward flexion. The AROM of the neck was measured for rotation, flexion, extension, and lateral flexion. Objective measurements on active range of motion (AROM) of the neck was performed with the participant in a sitting position and in a standing position for shoulder AROM according to a predefined measurement protocol For both shoulder and neck AROM, the side of treatment was considered the ipsilateral AROM and the opposite side the contralateral AROM [29]. AROM was measured using the MicroFET 6 electronic inclinometer (Hoggan Health Industries; West Jordan, UT, USA)®. For AROM in the transverse plane (external rotation of the shoulder) the universal goniometer was used [30].



### Quality of Life

The European Organization for Research and Treatment for Cancer—Quality of Life Questionnaire—Core 30 questions (EORTC-QLQ-C30) is a valid and reliable self-report questionnaire that assesses the multiple dimensions of Quality of Life among cancer patients [31].

The European Organization for Research and Treatment for Cancer-Quality of Life Questionnaire—Head and Neck 35 questions (EORTC-QLQ-HN35) is an HNC-specific Quality of Life Questionnaire [32].

## Sample Size

We used an convenience sample for this comparative study. This limits the power to detect true differences between groups giving the study are more explorative design.

## Statistical Analysis

Descriptive statistics were used to describe patient characteristics. Categorical outcomes are presented as numbers and percentages. Normal distributed continuous outcomes are presented as mean and standard deviation and skewed continuous outcomes, ordinal outcomes as median and interquartile range. Normal distribution was tested with the Shapiro–Wilk Test of Normality and equality of variances with Levene's test. Normally distributed continuous data were analyzed by the independent t-test. The Mann–Whitney U test was used for both ordinal and skewed continuous data and the Chi-Square test for categorical data. Means and standard deviations and medians and interquartile ranges were presented for all outcome

measurements. Possible confounders were selected based on known effects on shoulder morbidity, neck morbidity, and HR-QoL (age, time since treatment) [5]. The influence of the confounders on the outcome measurement was tested through association analysis using the Pearson's (continuous data) and Spearman's rank correlation coefficients (ordinal and non-normal distributed continuous data). The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS IBM version 25.0 (IBM Corporation, Armonk, NY, USA).

## Results

In total, 38 patients agreed to participate in this study, after informed consent all patients completed the measurements. Demographic and clinical characteristics are described in Table 1. Of all included patients, eighteen patients underwent END (47.4%) and twenty patients SLNB (52.6%). The participants in the END group were older ($P = 0.001$), were measured at a longer time since treatment ($P < 0.000$), varied more in tumor location ($P = 0.032$), and more frequently consulted a physical therapist ($P = 0.024$), also indicated by a higher number of physical therapy treatments received ($P = 0.022$). The six END patients that were treated by a physical therapist received between two and more than a hundred treatment sessions in comparison to one SLNB patient that had six physiotherapy treatment sessions. Shoulder and neck related problems were the indication for physical therapy treatment of all patients (100%).

The outcomes of questionnaires on neck and shoulder morbidity, HR-QoL showed no significant differences between the End and the SLNB group (Table 2). For AROM measurements there were significantly better scores for ipsilateral ($P = 0.008$) and contralateral rotation ($P = 0.029$) of the neck for the SLNB strategy compared to END. No association was demonstrated between the possible confounding variables age and time since treatment and the outcome measurements. Because time since treatment was significantly different between END and SLNB at baseline, we chose to visually represent the relationship between time since treatment and the nine clinically most relevant outcome measurements in Figures 1–9.

**TABLE 1.** *Demographic and clinical characteristics.*

| | END (N = 18) | SLNB (N = 20) | *p*-Value |
|---|---|---|---|
| Sex (n, %) | | | 0.299 ¥ |
| Male | 12 (66.7) | 10 (50.0) | |
| Female | 6 (33.3) | 10 (50.0) | |
| Age in years (median, IQR) | 72.0 (11.0) | 63.5 (16.5) | 0.001 †** |
| BMI (median, IQR) | 24.8 (6.4) | 26.4 (8.0) | 0.907 ° |
| Time since treatment in months (median, IQR) | 60.0 (49.3) | 13.0 (29.8) | 0.000 †*** |
| Treated side (n, %) | | | 0.107 ¥ |
| Left | 11 (61.1) | 7 (35.0) | |
| Right | 7 (38.9) | 13 (65.0) | |
| TNM-stage (n, %) | | | 0.552 ¥ |
| cT1 | 10 (55.6) | 13 (65.0) | |
| cT2 | 8 (44.4) | 7 (35.0) | |
| Tumor location (n, %) | | | 0.032 ¥* |
| Mandible | 4 (22.0) | 2 (10.0) | |
| Tongue/flour of mouth | 10 (55.6) | 18 (90.0) | |
| Buccal mucosa | 4 (22.0) | 0 (0.0) | |
| Pack years (median, IQR) | 6.7 (38.8) | 1.1 (37.5) | 0.613 † |
| Alcohol use in units daily (median, IQR) | 1.0 (1.6) | 0.0 (1.6) | 0.346 † |
| Post-operative physiotherapy (n, %) | | | 0.024 ¥* |
| Yes | 6 (33.3) | 1 (5.0) | |
| No | 12 (66.7) | 19 (95.0) | |
| Numbers of physiotherapy treatment (median, IQR) | 0.0 (27.5) | 0.0 (0.0) | 0.022 †* |

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ¥: chi-square test; †: Mann–Whitney U test; °: independent t-test; BMI: body mass index; END: elective neck dissection; IQR: interquartile range; SLNB: sentinel lymph node biopsy.

**TABLE 2.** *Morbidity and active range of motion of neck and shoulder and health related quality of life.*

| | END (N = 18) | SLNB (N = 20) | | | |
|---|---|---|---|---|---|
| | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) | *p*-Value |
| SDQ | 11.9 (26.3) | 0.0 (3.25) | 8.0 (20.4) | 0.0 (4.75) | 0.828 † |
| SPADI | 9.6 (18.9) | 0.0 (11.2) | 8.0 (17.4) | 1.2 (10.0) | 0.635 † |
| NDI | 9.9 (12.9) | 5.0 (15.5) | 8.5 (7.8) | 6.0 (13.5) | 0.825 † |
| NDII | 7.9 (13.2) | 0.0 (13.1) | 7.9 (11.1) | 5.0 (11.9) | 0.442 † |
| AROM shoulder | | | | | |
| External rotation ipsi | 62.1 (14.8) | 64.0 (19.8) | 63.5 (15.6) | 63.5 (19.5) | 0.788 ° |
| Abduction ipsi | 158.1 (36.0) | 171.5 (16.5) | 167.5 (18.9) | 174.5 (13.5) | 0.237 † |
| Forward flexion ipsi | 168.3 (17.4) | 174.0 (11.7) | 174.6 (7.1) | 175.0 (7.5) | 0.176 † |
| AROM neck | | | | | |
| Rotation ipsi | 53.7 (12.0) | 53.0 (14.0) | 63.0 (7.9) | 63.5 (16.3) | 0.008 °** |
| Rotation contra | 55.8 (11.0) | 59.0 (11.7) | 62.5 (6.7) | 62.0 (7.5) | 0.029 °* |
| Flexion | 49.7 (12.0) | 50.0 (14.5) | 56.5 (11.6) | 52.5 (15.0) | 0.086 ° |
| Extension | 53.1 (10.4) | 52.0 (18.6) | 56.8 (14.1) | 59.0 (24.7) | 0.362 ° |
| Lateral flexion ipsi | 36.0 (12.7) | 33.5 (13.5) | 36.8 (6.6) | 36.5 (7.3) | 0.349 † |
| Lateral flexion contra | 36.0 (13.5) | 35.5 (12.5) | 38.4 (5.5) | 38.0 (6.7) | 0.468 ° |
| EORTC-QLQ-C30 ¥ | | | | | |
| Global Quality of Life | 79.4 (14.5) | 83.3 (20.8) | 82.1 (13.0) | 83.3 (22.9) | 0.729 † |
| Physical functioning | 88.2 (14.2) | 93.3 (23.3) | 88.0 (16.4) | 93.3 (13.3) | 0.964 † |
| Role functioning | 81.4 (28.2) | 100.0 (33.3) | 85.8 (26.6) | 100.0 (29.2) | 0.598 † |
| Emotional functioning | 84.3 (20.8) | 91.7 (29.2) | 82.5 (19.5) | 87.5 (31.3) | 0.707 † |
| Cognitive functioning | 83.3 (25.0) | 100.0 (16.7) | 89.2 (9.8) | 83.3 (16.7) | 0.845 † |
| Social functioning | 89.2 (17.7) | 100.0 (16.7) | 89.2 (17.3) | 100.0 (16.7) | 0.916 † |
| EORTC-QLQ-HN35 | | | | | |
| Oral Pain | 15.7 (21.6) | 0.0 (29.2) | 15.0 (17.0) | 8.3 (25.0) | 0.675 † |
| Swallowing problems | 12.0 (22.0) | 0.0 (16.7) | 8.7 (12.5) | 0.0 (20.8) | 0.988 † |
| Senses problems | 10.2 (19.1) | 0.0 (8.3) | 11.7 (14.4) | 8.3 (16.7) | 0.426 † |
| Speech problems | 14.2 (23.7) | 0.0 (33.3) | 13.9 (13.4) | 11.1 (22.2) | 0.317 † |
| Trouble with social eating | 19.4 (30.4) | 0.0 (25.0) | 9.2 (11.8) | 0.0 (22.9) | 0.534 † |
| Trouble with social contact | 6.3 (9.8) | 0.0 (13.3) | 3.3 (8.2) | 0.0 (0.0) | 0.313 † |
| Less sexuality | 8.3 (20.0) | 0.0 (0.0) | 15.8 (22.6) | 0.0 (33.3) | 0.276 † |
| Teeth problems | 19.3 (15.4) | 0.0 (33.3) | 11.7 (24.8) | 0.0 (25.0) | 0.942 † |
| Trouble with opening mouth | 14.8 (23.5) | 0.0 (33.3) | 13.3 (27.4) | 0.0 (25.0) | 0.718 † |
| Dry mouth | 33.3 (32.3) | 33.3 (66.7) | 23.3 (24.4) | 33.3 (33.0) | 0.409 † |
| Sticky saliva | 12.3 (23.3) | 0.0 (33.3) | 10.0 (15.7) | 0.0 (33.3) | 0.965 † |
| Coughing | 16.7 (23.6) | 0.0 (33.3) | 20.0 (29.4) | 0.0 (33.0) | 0.874 † |
| Feeling ill | 5.6 (12.8) | 0.0 (0.0) | 15.0 (22.9) | 0.0 (33.0) | 0.303 † |

¥ The EORTC-QLQ-C30 scores had 1 patient in the END group with missing data. *: $p < 0.05$; **: $p < 0.01$; †: Mann–Whitney U test; °: independent t-test. AROM: Active Range Of Motion; END: Elective Neck Dissection; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-H-N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head & Neck; IQR: interquartile range; NDI: Neck Disability Index; NDII: Neck Dissection Impairment Index; SDQ: Shoulder Disability Questionnaire; SNLB: sentinel lymph node biopsy; SPADI: Shoulder Pain And Disability Index.

**FIGURE 1:** *Shoulder disability questionnaire (SDQ) in relation to time since treatment.*

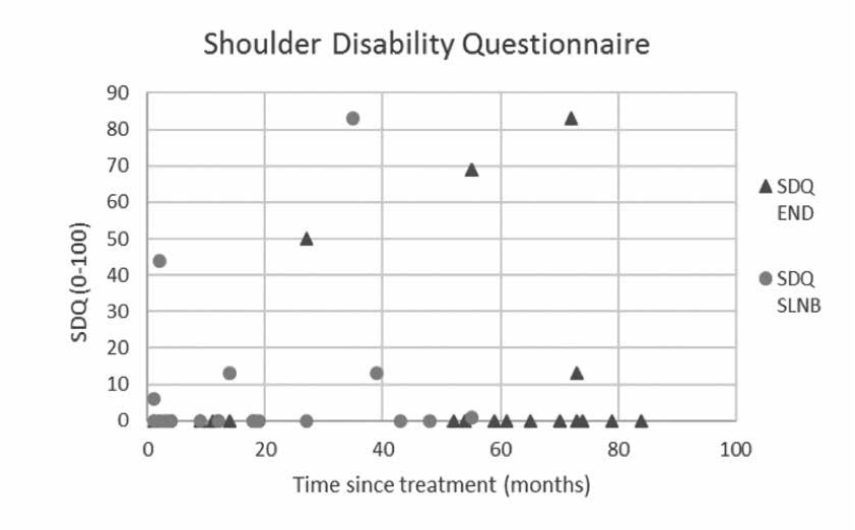



**FIGURE 2:** *Shoulder pain and disability index (SPADI) in relation to time since treatment.*

**FIGURE 3:** *Neck disability index (NDI) in relation to time since treatment.*

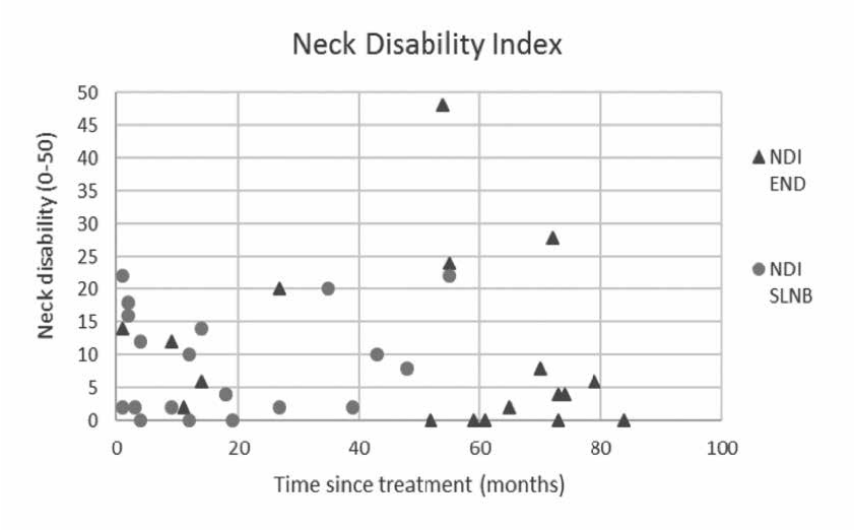



**FIGURE 4:** *Neck dissection impairment index (NDII) in relation to time since treatment.*

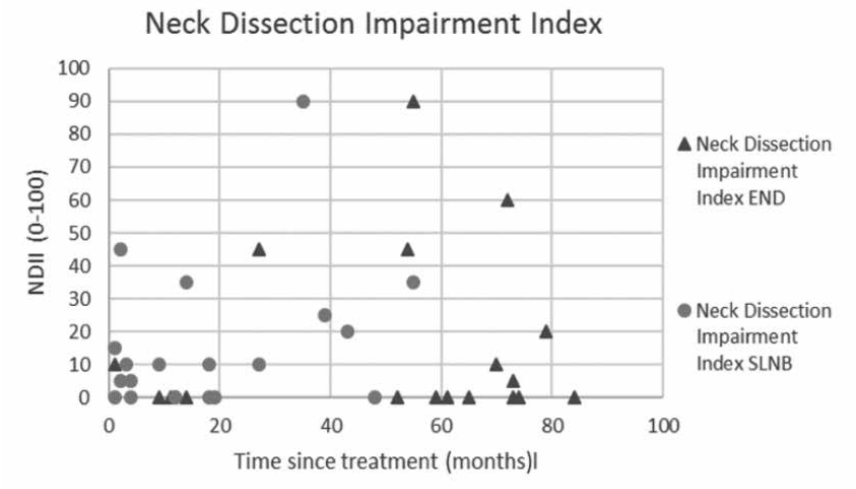


**FIGURE 5:** *EORTC HR-QoL C30 in relation to time since treatment.*

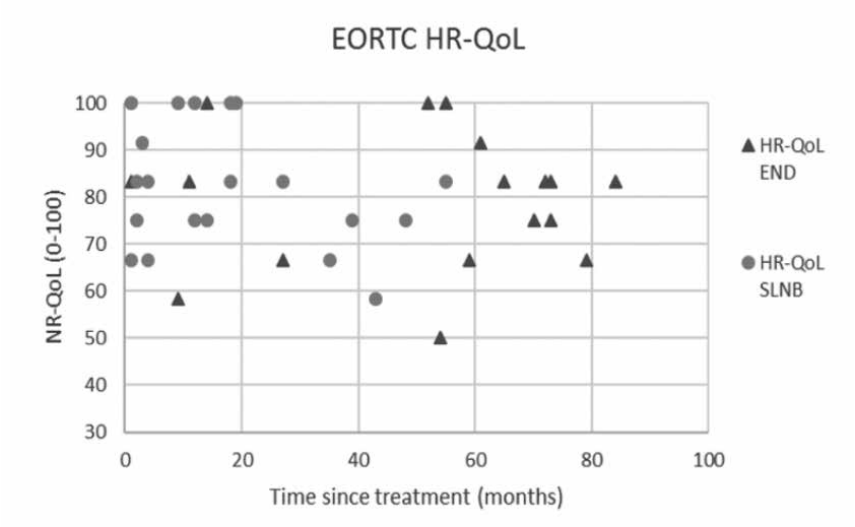



**FIGURE 6:** *EORTC HR-QoL C30 Physical function subscale in relation to time since treatment.*

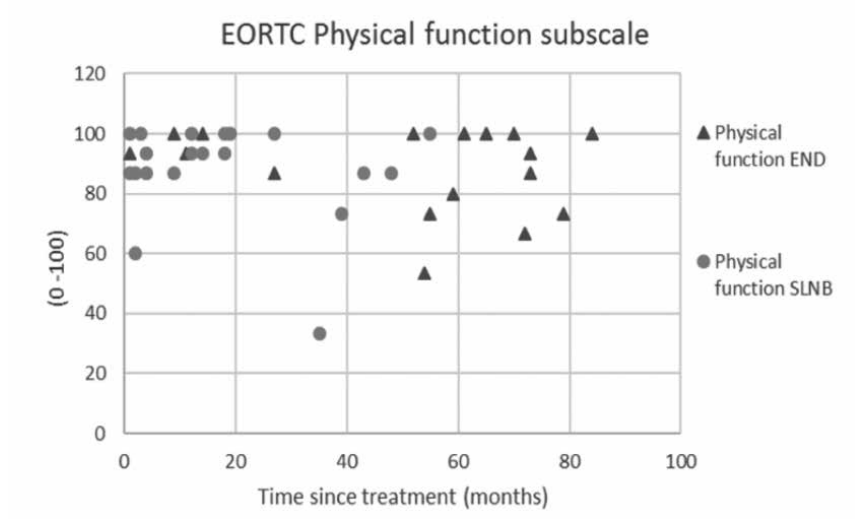


**FIGURE 7:** *Shoulder ipsilateral abduction in relation to time since treatment.*

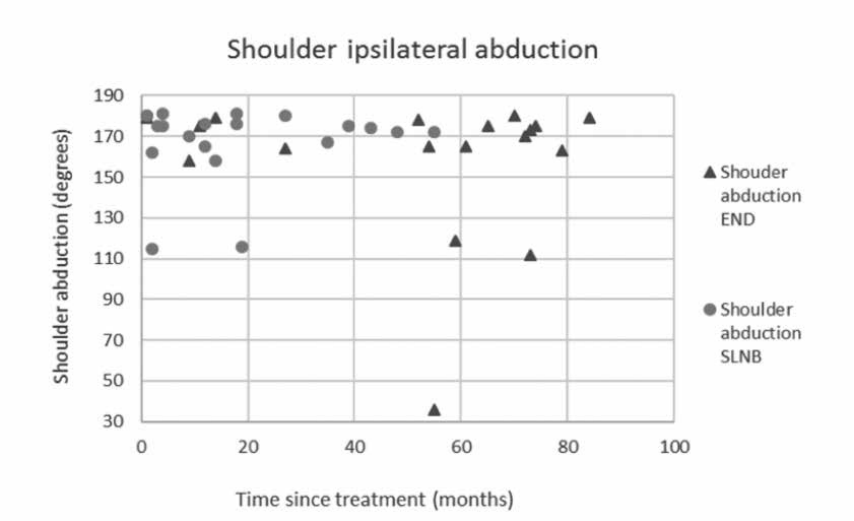



**FIGURE 8:** *Neck ipsilateral rotation in relation to time since treatment.*

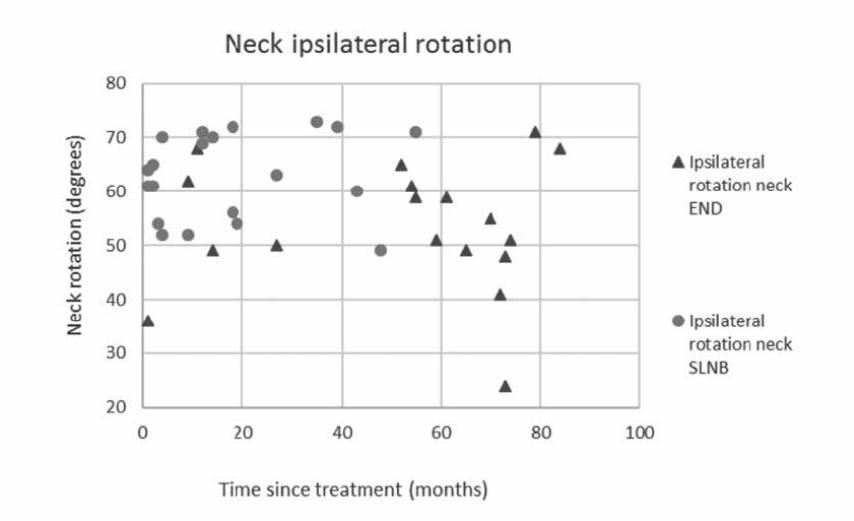
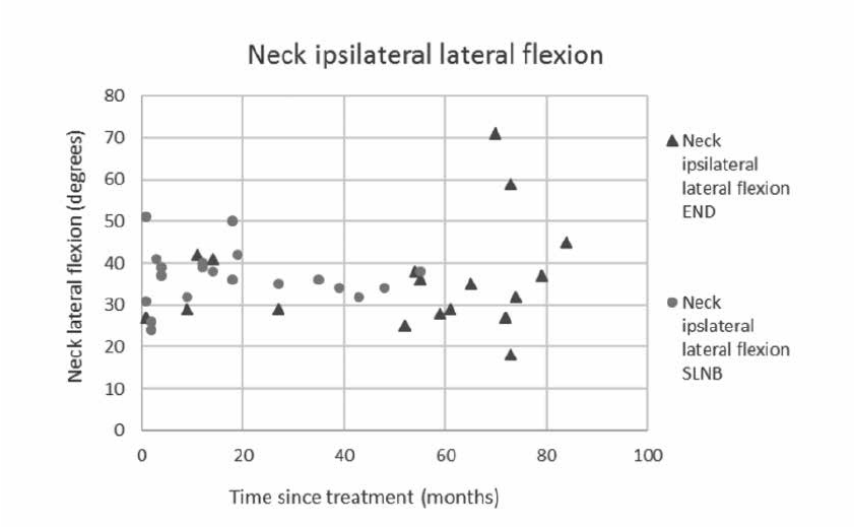


**FIGURE 9:** *Neck ipsilateral lateral flexion in relation to time since treatment.*






## Discussion

This study found no differences in shoulder morbidity, neck morbidity, and health-related quality of life between the END and the SNLB treatment strategy for patients with clinically negative neck T1/T2 carcinoma of the oral cavity. The differences found between strategies for ipsilateral and contralateral rotation of the neck are significant but small, and within known measurement errors limiting the clinical relevance [33]. In addition, the median AROMs for shoulder and neck, for both strategies are above age and gender stratified reference values, indicating no limitations in shoulder and neck function for both strategies [33]. The absence of differences between strategies is not in line with our hypothesis that patients undergoing the SLNB strategy would experience less treatment-related morbidity due to the less invasive procedure. END patients reported more frequently that they had consulted a physical therapist for shoulder and neck-related problems. END patients also reported slightly higher levels of shoulder and neck morbidity. This higher consumption of outpatient physical therapy could

be related to the standard clinical physical therapy consultation of END patients in our clinic. Because it was thought that SLNB patients do not generally experience substantial shoulder and neck problems, consultation and information by a physiotherapist were not routinely provided to SLNB patients. This has led to more outpatient physical therapy referrals of END patients in comparison to SLNB patients. Although not statistically significant, the END patients showed higher shoulder- and neck morbidity (SDQ, SPADI, NDII). The visual inspection of Figure 1 shows that 2 participants in the SLNB group and 3 patients in the END group have a shoulder function of below 120 degrees or shoulder abduction. A decrease in shoulder abduction is one of the clinical indicating accessory nerve palsy [34]. This finding supports the importance of awareness and screening both END and SLNB patients on shoulder morbidity during regular follow-up consultations. Two other cross-sectional studies have researched the difference in shoulder morbidity at equally long moments of follow-up (1.9 to 6.0 years) and both studies showed better outcomes for SLNB compared to END [18,19]. The study by Govers et al. had a larger sample size (n = 181) which makes it more sensitive to detect differences between groups [19]. The other study by Murer et al. [18] measured very low incidence scores in neck and shoulder morbidity compared to other studies, possibly limiting the clinical relevance of the reported differences. A third study that longitudinally researched shoulder morbidity found worse scores for shoulder morbidity at 6 months for patients undergoing END (within-group comparison with baseline), but no differences were found when comparing both strategies over time [21]. A randomized prospective study by Garrel et al. demonstrated that with the use of a self-reported questionnaire, shoulder morbidity was significantly lower at 2, 4, 6, and 12 months in favor of the SLNB strategy, but not at month 24 [14]. Although this study is lacking a baseline measurement and specific AROM measurements, it confirms our findings that treatment-related morbidity at longer follow-up (>12 months) is less prevalent and outcomes in shoulder morbidity are comparable between the two strategies at long-term follow-up. We found no differences in cancer generic or head and neck-specific HR-QoL. This is in contrast with the previous research that found better health utility scores (EQ-5D-3L) for SNLB compared to END representing HR-QoL. The study by Flach et al. also compared HR-QoL (EORTC-QLQ-C30, EORTC-QLQ-H-N35) and also found no significant difference between the two strategies [21]. In our study, 33% of the END patient received post-operative outpatient physiotherapy in comparison to only 5% of SLNB patients. In total five out of six END patients received more than 35 physiotherapy treatments, indicating persistent shoulder- and neck morbidity. This finding is in line with the findings of the study by Garrel et al. where

significantly more physical therapy treatment was reported by the END patients. It is unclear if this could also be related to standardized clinical physiotherapy consultations and referral [14]. Referral to a physical therapist has to be considered when pain or limitations in the shoulder or neck AROM are present.

Our study was the first to measure differences in shoulder and neck morbidity, and HRQoL between the END and SLNB strategy, with a set of validated patient-reported questionnaires and physical range of motion measurements. The patients included in our END strategy group are not derived indirectly from the SLNB group (after a positive lymph node) as in other studies, and therefore give a more valid representation [21]. Important factors to take into account when evaluating our findings are the cross-sectional design, the small sample size, and a median moment of measurement of 60 months for the END group and 13 months for the SLNB. The END and SLNB groups both had a median time since treatment that can be labeled as a long term moment of follow-up, where contrast is expected to be smaller due to natural recovery over time. The small sample sizes limit the power to identify true differences in neck and shoulder morbidity. With low incidence of neck and shoulder morbidity and relatively large standard deviations for the SDQ questionnaire, this would require larger groups (>100 participants). This limits the generalizability of our results and gives the findings a more explorative character. Future research could be focused on the longitudinal course of shoulder and neck morbidity and HR-QoL for both the END and SLNB treatment strategies. It would be specifically of interest to have multiple measurements during the initial post-intervention phase because it is expected that possible benefits from the less invasive SLNB strategy are to be found in the first 6 months. When further research would confirm that patients undergoing SLNB can also experience shoulder and neck morbidity, treatment guidelines and information that is given to patients who have undergone an SLNB should be updated.



## Conclusions

We found no differences between the END and SLNB treatment strategies regarding shoulder morbidity, neck morbidity, and HR-QOL as measured with patient-reported questionnaires after long-term follow-up. The significant differences between strategies found in forward flexion of the shoulder and lateral flexion of the neck are small and not clinically relevant.

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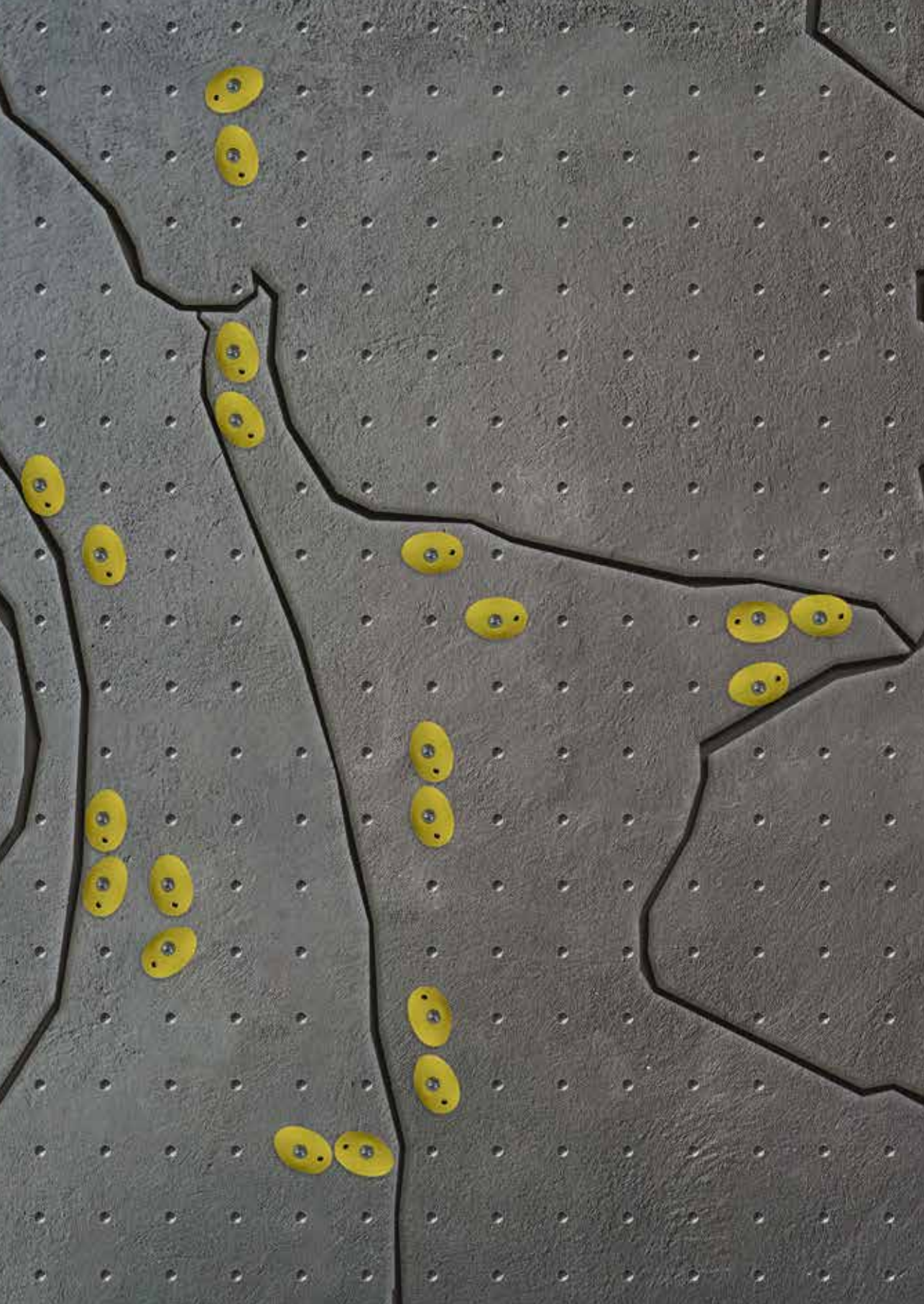

Chapter 7

# General discussion

The overall aim of this thesis is to improve the identification of patients with head and neck cancer (HNC) who can benefit from physiotherapy. Identification of patients that may benefit from physiotherapy is dependent on: 1) reliable physical measurements to identify and monitor limitations in the domain of physical health, 2) insight into patient, clinical, and intervention characteristics that increase the risk of limitations in physical health from the moment of diagnosis up to the phase of cancer survivorship, and 3) insight into differences in shoulder and neck morbidity between the Elective Neck Dissection (END) and Sentinel Lymph Node Biopsy (SLNB) strategy in patients with ($T_{1\text{-}2}$ $N_0$) oral cavity squamous cell carcinoma (OCSCC).

In this final chapter we provide an overview of how and to what extent the studies performed help to improve the identification of patients with head and neck cancer that could benefit from physiotherapy. This is weighed against their methodological shortcomings and the existing body of knowledge. Additionally, we discuss the implications of this thesis for future clinical practice and future eduction and research purposes.



In the first part of this thesis (Chapter 2), we showed that in HNC survivors a core set of physical measurements, consisting of four cancer generic (hand grip strength, lower body strength, the level of mobility, and walking ability) and two HNC specific measurements (maximum mouth opening, and neck and shoulder function) had a good test-retest reliability. This core set can therefore be used to discriminate in performance on these outcomes between HNC survivors. Based on these outcomes health care providers and especially physiotherapists have competences to assess and interpret the results regarding physical health of HNC survivors. Physiotherapeutic interventions can consequently be composed in cooperation with the HNC survivors. Thereby, measurement outcomes can be used to motivate patients and to stimulate self-management during a physiotherapeutic intervention.[1] Our clinometric study also provided clinically usable information on agreement parameters that can help to interpret evaluative measurements in physical health during follow-up or after physiotherapy treatment.[2] This can be important to assess physical functioning in future physiotherapy research studies. The cross-sectional study on HNC survivors (Chapter 3) highlighted that approximately half of the HNC survivors have limitations in physical health when measured with the core set of physical measurements, and half of the participants report unmet needs in physical health as measured with patient-reported outcome measurements (PROMs). Remarkably, HNC survivors that were identified as having limitations in physical health were not the same HNC survivors that reported unmet needs in physical health, as no association was demonstrated.[3]

This advocates the importance of the use of physical measurements in addition to PROMs during follow-up care. The optimization of the identification of reported and unreported limitations in physical health in HNC survivors by physiotherapists could reduce treatment-related morbidity and improve health-related quality of life (HR-QoL).[4-7] Physical measurements also facilitate the identification of unreported non-Patient Identified Problems (nPIPs). NPIPs concern the unmet needs and limitations that remain unrecognized or unexpressed by HNC survivors.[8] These nPIPs can be identified by clinical reasoning, physical performance measurements, PROMs, and physical examination.[8] The HNC survivors can consequently be made aware of the potential problem and its consequences, and when needed physiotherapeutic treatment can be started. To optimize the identification of nPIPs an increased physiotherapy involvement during HNC follow-up might be beneficial. Physiotherapy as a member of the treatment team could therefore be considered, comparable to the role of a speech therapist in HNC care in the Netherlands.[9] However, additional consultations could lead to an increase in costs of healthcare services. Patient self-measurement of physical health with the use of e-health applications, or wearable (smartphone-bases) technologies, logistically facilitated by web-based platforms could provide a cost-effective and valid alternative.[10-14]

The second part of this thesis consists of three studies (Chapters 4, 5, and 6), specifically focused on HNC patients with OCSCC. OCSCC make up for 90% of the cases of oral cavity cancer and 25% of all patients with HNC.[15, 16] We performed a five-year longitudinal follow-up study that provided insight into patient, clinical, and intervention characteristics that help to identify patients with OCSCC at risk of shoulder and neck morbidity. Based on our research, patients with oral cancer undergoing more extensive neck dissection and reconstructive surgery should be regarded as having a high-risk profile for developing shoulder limitations (Chapter 4). Patients undergoing both surgery and radiotherapy showed more limitations in contralateral lateral flexion of the neck. Patients with a high-risk profile could possibly benefit from early physiotherapy consultation and treatment. Both shoulder abduction and lateral flexion of the neck are essential in the execution of activities in daily life, for example putting on a sweater in the morning, or for looking over your shoulder during a bike ride. Early physiotherapy consultation is therefore advised for patients with a risk profile before discharge from the hospital.[17] The next step in the improvement of physiotherapy care could be pre-operative physiotherapy instruction in HNC care paths for patients with an increased risk profile.[18, 19] Pre-operative physiotherapy instructions and information are hypothesized to improve patient awareness and their ability to self-manage problems in physical health during the post-intervention

phase.[18, 20] A positive effect of pre-intervention exercise instructions and information on functional outcomes, as demonstrated in patients with breast cancer, has not been demonstrated yet in HNC patients.[18, 21, 22] Currently, a prehabilitation strength and cardio-respiratory program for HNC patients is being researched in the Radboud university medical center (Fit for Surgery-study). Additional information and instructions on shoulder and neck function could be practically added to this consult when a positive effect of prehabilitation is demonstrated.

Approximately half of the OCSCC patients present with an $T_{1\text{-}2}$ $N_0$.[16] The two most optimal diagnostic strategies in these patients are Elective Neck Dissection (END) and Sentinel Lymph Node Biopsy (SLNB).[23-25] With the most optimal diagnostic strategy up for debate [23-26], and comparable diagnostic efficacy demonstrated, a difference in treatment-related morbidity could strengthen the choice for the less invasive SLNB. [27] In Chapter 5 and 6 we describe the results of one longitudinal and one cross-sectional study that specifically focused on the difference in treatment-related shoulder and neck morbidity and HR-QoL between the END and SLNB strategies. In the longitudinal study a short-term (6 weeks after intervention) benefit in lower levels of shoulder morbidity was found in favor of the SLNB strategy.[28] The cross-sectional study demonstrated that this difference was no longer present at longer follow-up.[29] This knowledge supports the choice for the less invasive SLNB as the most optimal diagnostic strategy and is confirmed in other recent publications.[24, 30] However, physiotherapy consultation should still be considered in both END and SLNB patients when pain and/or limitations in shoulder and neck function are reported.[17] The etiology of shoulder and neck morbidity is multifactorial and not exclusively related to the (extend of) surgical intervention.[18, 31, 32] With a better range of motion after intervention SLNB patients are, however, expected to require less physiotherapy care. Both studies (Chapter 5 and 6) showed that a small number of patients undergoing SLNB had limited shoulder abduction function (<90 degrees) both in the short and long term indicative of shoulder morbidity.[17] In summary the results from these studies provide additional knowledge to optimize the identification and timing of physiotherapy care for HNC patients in general and OCSCC patients in specific.

## Patient-specific treatment

In the Introduction (Chapter 1) we described the ongoing change in medical care that is aimed at transitioning from cancer generic into personalized medical care. Physiotherapy and other supportive-care professionals have stated in accordance with the medical professions that patient-specific care is essential in providing high-quality comprehensive interdisciplinary care.[13, 19, 33, 34] The essence is that patients must be recognized as a unique combination of health conditions, environmental factors, and personal factors expressed in a unique demand for supportive care. This requires the involvement of patients in decision-making, based on information collected in cooperation with patients, as illustrated in the research we performed.[35]

We are proud that one of our studies was planned and executed in cooperation with the Dutch HNC patient federation (Patiënten vereniging Hoofdhals) and its members (Chapter 2 and 3). The patient federation also funded the study as it empowered their goal of improving patient-specific care for HNC survivors patients. Members of the patient federation participated in the study as well. Patient-expert involvement is regarded as an important focus of future medical research and the transition of translating research findings into patient-specific clinical care.[36]

Providing insight and managing expectations in physical health is an important factor in patient-specific care. The research on modeled shoulder and neck function (Chapter 4) provided insight into the course and factors influencing the 5-year course. The models offer the possibility of identifying "patients like me" to provide insight and information to future HNC patients on expected function based on their characteristics.[35] The optimal use of "patients like me" models is however dependent on continuous improvement of the model through data collection as part of usual care.[37] With increasing numbers of participants with different characteristics improving the accuracy and validity of the modeled outcomes.[37] This also substantiates an increased physiotherapy involvement in HNC care. Physiotherapy can facilitate continuous and structured physical health data collection to provide "patients like me" models that can inform patients and support shared decision-making.[37]

The observational studies (Chapters 2 and 6) represent samples of patients in real-world conditions ensuring optimal external validity.[38] The studies that researched the difference between END and SLNB (chapters 5 and 6) were performed in two university medical hospital centers that changed their diagnostic strategy from END to SLNB, allowing for a

natural comparative study. This provided the option for a natural comparative research design that optimally reflects clinical care of patients with $T_{1\text{-}2}$ $N_0$ OCSCC. In contrast to this, many HNC treatment centers around the world still use the END, stating that the SLNB is a logistically and practically challenging procedure resulting in little benefit for the patient.[24, 39, 40] These old-school versus new-school, or advanced technology versus conservative treatment dilemmas are also seen in other fields of oncological surgery. The initial discussion between the benefits of minimally invasive endoscopic procedures versus open laparotomy in different types of cancer located in the bowel [41, 42], and conflicting opinions on the possible benefits of robot-assisted over surgeon-based surgery in different types of cancer surgery offer comparable examples.[43, 44] The modern and less invasive techniques aiming for less treatment-related morbidity and better HR-QoL require evidence, time, and an innovative environment to be adapted. The steep learning curve, the lack of incentives or encouragement from the hospitals, and the high costs are described as barriers to implement technically advanced techniques that aim to advance patient-centered care.[45]

In conclusion, the results of this thesis all reflect outcomes based on participants reflecting on daily clinical practice and are presented in a way that should promote cooperative treatment decisions in physiotherapy care.



## My personal experience

*The goal for me was to improve physiotherapy care for HNC patients. The research presented in this study was based on clinical studies that were collected by me during my work as an embedded scientist-physiotherapist in the Radboud university medical center.[46] Being part of the extended HNC treatment team facilitated me in the direct implementation of the research outcomes. It consequently made the research outcomes relevant in improving daily physiotherapy care. To illustrate this, direct translation of the research results into follow-up care was also made possible with the installment of a multidisciplinary supportive care rehabilitation treatment team in the Radboud university medical center. The team provided patients with HNC the possibility of a 1-day "check-up" involving consultations with a rehabilitation physician, speech therapist, dietician, physiotherapist, and if needed an occupational therapist to treat limitations and unmet needs in physical health (chapter 3). For me as a physiotherapist, this allowed me to use the core set of measurements to gain insight into the level of cancer generic and HNC specific limitations*

*in physical health (chapters 2 and 3). The outcomes of the measurements provided an increased awareness of possible nPIPs. This facilitated me during the process of clinical reasoning and identification of unmet needs and limitations in physical health.*

*The results from our 5-year follow-up study on shoulder and neck function confirmed the need for post-operative physiotherapy consultation for patients undergoing more extensive ND (chapter 4). The physiotherapy consultation of patients undergoing ND was therefore made mandatory by the medical staff and was labeled as a treatment quality indicator for HNC care in the Netherlands.[47] The choice was made not to differentiate in which patients should undergo physiotherapy consultation based on the extent of ND or levels resected. No clear cut-off points to the extent of ND or number of levels of resected was established based on our research. Therefore, a standardized clinical physiotherapy assessment of all patients undergoing ND as an indicator is in line with providing high-quality patient-centered care. This indicator will also be used in all the other HNC treatment centers in the Netherlands as it was endorsed by both the Dutch supportive care professionals and medical health care professionals in HNC care associations (NWHHT, PWHHT). A postoperative consultation for patients undergoing extensive reconstructive surgery was also instated as shoulder function is often affected [48, 49]. With all $cT_{1\text{-}2}N_0$ patients in our hospital undergoing the SLNB strategy, the number of patients undergoing neck dissection (ND) was reduced. With the etiology of limitations in shoulder and neck problems being complex, the importance of raising awareness that limitations and pain in the shoulders and neck can still be present in SLNB is therefore important.[28, 32]*

*To implement the research findings of this thesis in HNC patient care an important role is to inform and educate physiotherapists involved. Therefore, next to my work in the Radboud university medical center I worked as a teacher for several master-level physiotherapy programs (AVANS+; master oncology physiotherapy, SOMT; master orofacial physiotherapy, HAN; master orofacial physiotherapy, NPI; masterclasses orofacial physiotherapy). This provided me with the chance to "spread the word" and implement the results of the research performed. Knowledge of the core set of measurement instruments, the high incidence of limitations and unmet needs in physical health in HNC survivors, and characteristics that help identify HNC patients at risk of developing limitations in physical health were structurally nested into these educational programs. Next to this, the results were also presented at national, and international congresses to reach physiotherapy colleagues working with HNC patients. In summary, the findings of the research performed were implemented in clinical, outpatient, educational, scientific, and at patient federation level. I believe my research has made a structural and continuous impact in improving quality of physiotherapy care as provided to HNC patients.*

## Local morbidity: implications for physiotherapy interventions focusing on trismus

The research performed regarding trismus provided additional insight into reproducibility parameters for two frequently used measurements of maximum mouth opening. The current evidence from RCT's revealed that exercise therapy can lead to improvement of cancer treatment-induced trismus, but does not prevent trismus in patients being treated for HNC.[50] The clinical exercise programs used in the studies were heterogeneous; therefore, additional high-quality RCT's are required. Based on our research the Therabite© cardboard ruler can be used to assess maximum mouth opening (chapter 2).

## Regional morbidity: implications for physiotherapy interventions focusing on shoulder and neck

The research we performed did not include a physiotherapy intervention study focusing on shoulder or neck morbidity. The research outcomes we found can however help to target and time future intervention studies at the HNC patients expected to benefit the most. High-quality evidence regarding physiotherapy interventions is scarce. Two reviews have been published that show moderate evidence for physiotherapy interventions in HNC patients following ND.[51, 52] The number of controlled studies is, however, limited and the number of participants is low. In addition, it is also questionable if the classic RCT design is suitable for physiotherapy intervention research in patients with HNC. The design of a randomized clinical trial in physiotherapy research in most cases requires a standardized exercise intervention and control group. Patient-specific problems in physical health are lost in generic exercise prescription for heterogeneous groups of participants. To illustrate this, the much-cited research performed by McNeely et al. demonstrated a positive effect of Progressive Resistance Exercise Training (PRET) on shoulder pain and disability in patients after ND.[53] The underlying construct for this intervention was to improve scapular posture and stability through a standardized exercise program focusing on the scapular muscles, improving function, and reducing pain. Participants varied in time after intervention ranging from months to years after medical intervention and the McNeely exercise intervention was not personally adapted. In our opinion, this "one size fits all" intervention does not tailor to a patient's needs and was not applied as early as possible. We hypothesize that outcomes of studies can be improved by adapting the intervention to patients needs or problems. As previously stated, shoulder and neck problems are multifactorial.

In our opinion, patients treated with HNC form a very heterogeneous group that shows a wide variation in patient, clinical, and intervention characteristics resulting in different care demands/unmet needs requiring personalized physiotherapy intervention. Another limitation of current research is that most of the RCT's report a possible selection bias with only low percentages of the total number of patients agreeing to participate or fulfilling the inclusion criteria. A possible solution is to compare standardized versus personalized physiotherapy intervention. The personalized intervention can be developed through a systematic problem analysis. This design is well suited to heterogenous and complex patient groups in which a personalized intervention is expected to be more effective. [54-56] Early intervention is also complicated due to the debilitating effects of post-surgical radiation therapy and lower levels of pre-operative physical activity that limit the motivation to participate in exercise/training interventions.[5, 57] Based on our results, patients with HNC and limitations or unmet needs in shoulder- or neck function should be offered an early and patient-specific physiotherapy treatment related to a patients individual unmet needs. The contents of personalized physiotherapy treatments should be the focus of future research.[57, 58] Improving awareness and self-management through early or pre-intervention physiotherapy consultation and adapting the intervention to a patient's individual unmet need might improve participation, adherence, and compliance. The development of a personalized physiotherapy treatment strategy could be based on a systematic problem analysis.[59] Future research can consequently compare personalized physiotherapy intervention with a standardized physiotherapy intervention.

### Generic morbidity: implications for physiotherapy interventions focusing on physical activity, grip strength and lower body strength

Previous research showed that pre-treatment levels of physical activity, cardiorespiratory fitness and lower body muscle function are low in patients with HNC.[5] After intervention more than half of HNC survivors are sedentary and experience specific problems in physical performance due to treatment of the head and neck area as measured with PROMs.[6] Our research confirmed that walking ability, grip strength and lower body strength were severely lower in up to half of the HNC survivors when compared to age and sex-stratified reference values. There is early evidence that supports the benefit of physical activity interventions for patients with head and neck cancer, both during and following treatment.[4] The benefit of an early intervention has yet to be demonstrated. Research on prehabilitation in HNC care is limited. Prehabilitation interventions in colorectal cancer patients have been shown to improve functional capacity and shorter hospital stays.[60] Complication rates and the number of emergency department visits postoperatively also diminished due to the prehabilitation program, while the number of re-admissions were unexpectedly higher in the prehabilitation group. [60] The target HNC population that may benefit from prehabilitation possibly differs from colorectal cancer patients. HNC patients show limited willingness to participate, low levels of pre-intervention physical activity, and experience high time pressure during medical treatment.[61] These factors limit exercise participation, adherence, and compliance in patients with HNC.[61] Physiotherapy interventions before, during, or after treatment have to take these factors into account.

## Methodological considerations

### Participants

This dissertation is the result of 2 cross-sectional and 2 longitudinal studies. The efforts of the four groups of participants (chapter 2 and 3: n = 50, chapter 4: n = 114, chapter 4: n = 69, chapter 5: n = 38) facilitated the research performed. The observational research performed is based on patients in their clinical or daily life settings which improves the generalizability of the presented results.[62] The participants included in our studies may have been influenced by a self-selection bias as in any study where participating is voluntary. It is plausible that the

highest functioning patients were more willing and able to participate in research leading to an overestimation of the physical health of the total population.[62] This effect could have been plausible in our test-retest study as half of the participants were approached at a patient federation meeting and had to be able to walk without aid and were all living independently. The opposite effect that functionally disabled patients may have been extra interested in participating in a study about neck and shoulder dysfunction seems less plausible. Other indications that any of the two effects were present were not found. Participants in the studies (except from chapters 3 and 6) were from one geographical region of the Netherlands (east- southeast) and most of the patients in these cohorts were Caucasian, elderly, and predominantly male. Extrapolating data to other subsets of patients (young, non-Caucasian, women) may not be advisable. A general limitation across all the studies performed was a lack of information on physiotherapy received by the participants. And if such information was collected it was patient-reported, based on recollection, allowing for over- or underestimation. Additional knowledge on the number, the timing, and the type of physiotherapy is important as it could have influenced the outcomes. Information on the level of experience of the physiotherapist and if he or she received specialized education would be of interest for future studies as well.

## Study design

The clinometric study (Chapter 2) included only HNC survivors. The results can therefore not be generalized to patients with HNC during treatment. Underlying factors influencing variability between repeated measurements may be completely different for both groups as the level of limitations in physical health and unmet needs is known to vary during follow-up.[6, 7, 48, 63] The variability in measurements is expected to be higher in the initial post-intervention phase as reported HNC specific and cancer generic morbidity is at the highest during this period. The large measurement error demonstrated is related to the variation between the execution of two consecutive measurements. This can possibly be explained by the multifactorial etiology of limitations in physical health in patients with HNC influencing the execution of the measurement.[32] All studies performed were observational studies providing descriptive outcomes but preventing conclusions on causal relationships. We did not use the Randomized Clinical Trial (RCT) design, regarded as the gold standard in Evidence Based research (EBP). The RCT could have been used to research the difference between END and SLNB as performed in a recent study by Garrel et al.[30] Garrel et al. confirmed the short-term benefit in shoulder morbidity for the SLNB strategy over the END strategy. The

RCT is resource intensive and mostly focuses on the short-term effects of an intervention among a small and selective population. The results derived from a RCT show good internal validity but limited generalizability because of their strict inclusion and exclusion criteria that usually under-represent vulnerable patient groups and only provide results of average patients.[62] No qualitative research was performed in this thesis that could have given more insight and understanding of unmet needs and limitations as experienced by patients with HNC. Qualitative research is a particularly useful methodological approach when exploring the psychosocial and contextual aspects of illnesses such as cancer, as it allows for a rich exploration of participants' lived experiences and captures the complexities and context of their experiences.[64] Qualitative research could also help to understand the barriers and facilitators for HNC patients in participating in physiotherapy treatments.[64]

## Statistical analysis

In Chapter 4 and 5 we made use of mixed-model analysis. In Chapter 4 we used mixed-model analysis to explore which characteristics influence neck and shoulder function. This resulted in a model and a supplementary file that provided the equations that can be used to model shoulder and neck function over a 5-year follow-up. The benefit is that mixed model analysis allows for more power and the inclusion of more confounding characteristics/variables in the explorative model.[65] The limitation is that less represented characteristics can be over-modeled.[65] Another difficulty is that the influence of characteristics can vary per moment of measurement making it difficult to label one characteristic as a generic negative or positive overall. The interpretation is more complicated in comparison to presenting averaged outcomes and comparing them between moments of measurement with paired and unpaired student T-tests. The mixed-model design was explorative, and it did not present a prediction model, due to the absence of a clinical cut-off point for identifying patients at risk. This limits the clinical usability of the results. A clinical cut-off point is in our view contradictory to patient-specific care. A previously described cut-off point of <90 degrees shoulder abduction indicating shoulder morbidity would provide false-positives and negatives as patients can experience limitations at 110 degrees as well.[17]

In Chapter 5 we used mixed-model analysis to compare shoulder- and neck function between END and SLNB taking into account the effect of known confounding variables and the dependency of repeated measurements. Correcting for factors that influence shoulder and

neck function improves the internal validity of the results.[65] Our study was the first to combine a longitudinal design (including a pre-intervention assessment), objective functional measurements, and PROMs to research the difference in shoulder- and neck morbidity between END and SLNB. Future studies could increase model validity by continuous data collection possibly as part of routine care, offering information for HNC patients and healthcare professionals.

## Directions for future research

With our studies we added to the body of knowledge on 1) reliable measurements to identify and monitor limitations in the domain of physical health 2) insight into patient, clinical, and intervention characteristics that increase the risk of limitations in physical health from the moment of diagnosis up to the phase of cancer survivorship (3) insight into differences in shoulder and neck morbidity between END and SLNB. But still, several questions remain unanswered. In this paragraph, we describe recommendations for future research based on our experiences and study findings.

## Reliable and responsive measurements

Reproducibility of the core set of measurements on physical function for HNC was researched in sHNC. Future research should investigate if reliability and agreement parameters are different for measurements of physical function in patients with HNC during or just after treatment. The reduction of measurement errors improves the identification of problems in physical health.

- Future research is needed on choosing the most optimal measurement instrument for the different complex problems physical health as experienced by HNC patients.
- Future research could assess if patient self-measurement of physical function offers a valid and cost-effective alternative in comparison to measurements performed by a trained healthcare professional as for example a physiotherapist.
- Research on measurement instruments that measure HNC-specific morbidity in physical health related to reconstructive surgery is currently lacking. Reconstructive surgery techniques influencing for example wrist function after radial free forearm flap reconstruction or ankle stability in free fibular graft reconstructions could be researched.
- Precision medicine and targeted therapies could have an impact on different anatomical/

physiological structures that could cause cancer generic limitations in physical health. This may require additional measurements that assist in the identification of these specific limitations in physical health. Insight into levels of unmet needs and limitations in physical health in patients undergoing targeted therapies or immunotherapy can then be researched.

### Patient, clinical, and intervention characteristics that increase the risk of limitations in physical health

Future research could be focused on the first phase after intervention for shoulder and neck morbidity. It would be specifically of interest to have multiple measurements during the initial post-intervention phase as our research has shown that shoulder and neck morbidity deteriorates the most at the six-weeks post-intervention moment of measurement (chapters 4 and 5). This could help to gain more understanding of the course of shoulder and neck morbidity, and this could benefit the timing of early physiotherapy interventions.



- Our research showed that extensive reconstructive surgery, used to preserve form and function of large head and neck defect (e.g. free vascularized tissue transfers or pedicled flaps), influences shoulder function. We hypothesize that extensive reconstructive surgery must be strongly associated with more extensive ND, and extensive surgery in general (chapter 4). It remains unclear to what extend reconstructive surgery influences shoulder and neck function. Future research into the influence of frequently used reconstructive surgery techniques that are expected to influence shoulder and/or neck function as for example the pectoral myocutaneous flap is deemed relevant.
- Research on the effectiveness of a possible framework for patient-specific physiotherapy interventions in HNC specific and cancer generic morbidity, based on risk profiles, patient preferences, and the existing body of knowledge would be of interest.
- It would be interesting to research if prehabilitation or early physiotherapy patient-specific intervention could reduce cancer generic and HNC-specific limitations in physical health.
- Prospective structural multi-disciplinary clinical data collection on physical health to get insight into "patients like me" data for both clinicians and patients with HNC.

### Research the difference in shoulder and neck morbidity between the END and SLNB diagnostic strategies

- With the SLNB strategy expected to be the dominant strategy, it would be interesting to research SLNB patients who experience pain or limitations in function in the shoulder or neck and the characteristics that influence it. Although the number of patients with morbidity is expected to be small, we think it is important to gain more understanding of the etiology and construct of shoulder and neck morbidity in SLNB patients to benefit to develop guidelines on physiotherapy in SLNB.

## Directions for future physiotherapy care and education

- The aim should be to provide personalized, well timed, stratified physiotherapy care. Physiotherapy care with a central role for a hospital-based physiotherapist embedded in a multidisciplinary HNC treatment team. This hospital-based physiotherapist can educate, inform and connect with primary physiotherapy care before, during and after intervention to provide a continuum of care in physical health.
- Physiotherapy care for HNC patients is benefited by specialized, evidence-based physiotherapy care that is delivered in cooperation with the other healthcare professionals involved. The education of physiotherapists working in primary, secondary and tertiary care, specialized in orofacial and oncology problems in physical health is therefore of the essence. In accordance with clinical practice this education should ideally be provided in a multidisciplinary team-based setting.

# General conclusion

HNC cancer treatment can have a debilitating impact on various aspects of physical health. A core set of cancer generic and HNC measurements can be used to discriminate between HNC patients performing good or bad (Chapter 2). Survivors of HNC report a high incidence of unmet needs and limitations in physical health (Chapter 3). Patients with a more extensive neck dissection (ND) and reconstructive surgery have an increased risk of developing shoulder limitations (Chapter 4). Patients undergoing post-surgery radiotherapy have an increased risk of limitations in neck function (Chapter 4). A short-term (6 weeks after intervention) benefit in shoulder morbidity was found in favor of the SLNB diagnostic strategy over the END strategy in patients (Chapter 5 and 6).

Patient-specific (p)rehabilitation by physiotherapeutic interventions based on risk profiles and patient preferences can be the focus of future research. Patient self-measurement and the use of "patient like me" models that could benefit patient awareness and their ability to self-manage problems in physical health should be considered.

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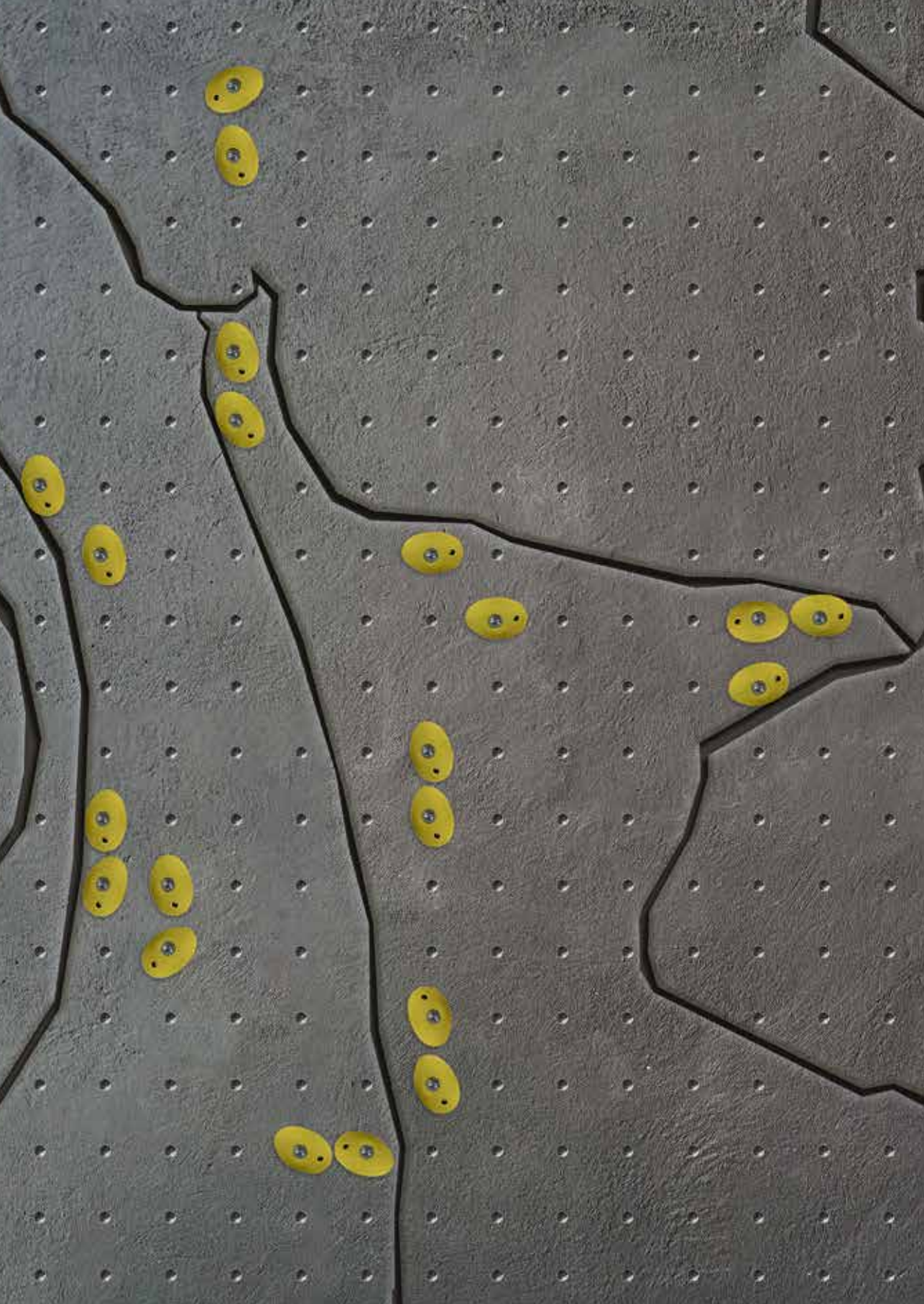


# Summary
# Samenvatting

# Summary

## Physical health in patients with head and neck cancer Towards personalized physiotherapy

A number of patients with head and neck cancer (HNC) experience physical problems before, during, and after their medical treatment. Surgical and radiotherapy interventions specifically target the head and neck area, potentially limiting oral function and movements of neck and shoulders. Patients consequently report problems in activities in daily life as for example opening your mouth to eat a sandwich or looking over your shoulder when riding a bike. Chemo- and radiotherapy can cause more generic problems as for example fatigue or the inability to walk your normal 5 k distance with the dog. These interventions can also limit normal eating of a sandwich due to inflammation of the soft tissue of the mouth (mucositis). The physiotherapist as part of the extended treatment team can help to prevent, treat or manage problems in physical health. To optimize physiotherapy care in patients with head and neck cancer the aim of this dissertation was to gain insight into: 1) reliability and agreement of a core set of physical measurements relevant for HNC patients; 2) physical performance status as measured with objective measurements in relation to age and sex-stratified reference values, and reported unmet needs for supportive care in physical health; 3) insight into the 5-year course of shoulder and neck morbidity and the patient characteristics (for example male/female), clinical characteristics (for example location of the tumor) and intervention characteristics (for example radiotherapy yes/no) that influence it; and 4) the difference in shoulder and neck morbidity between the elective neck dissection and sentinel lymph node biopsy strategies for patients with clinically negative $T_{1-2}$ tumors of the oral cavity. This knowledge can be put into daily clinical use in personalized physiotherapy care that is delivered at the right moment for patients with HNC.

**Chapter 1.** Patients with HNC can experience specific treatment-related morbidity and limitations in physical health. This physical health might benefit from physiotherapy treatment. The identification and timing of physiotherapy treatment requires reliable measurements on physical function and insight into patient, clinical, and intervention characteristics that increase the risk of developing problems in physical health. To outline the research problem

epidemiology, etiology, medical treatment and the specific treatment-related morbidity in physical health in patients with HNC are described.

**Chapter 2.** The aim of this cross-sectional study was to assess the test-retest reliability of measurements on maximum mouth opening (intra and extra orally), active range of motion of shoulders and neck, lower body strength (30 seconds chair stand test), grip strength, level of mobility (timed up-and-go test) and walking ability (six-minute walking test). In total 50 participants were included from both patient federation meetings and regular follow-appointments. This core set of measurements that can be used to assess local, and generic morbidity in physical health demonstrated all at least a good test-retest reliability. The measurements are therefore able to differentiate in physical performance between HNC survivors. The reported measurement errors should be taken into consideration when interpreting the results when for example evaluating physiotherapy treatment.

**Chapter 3.** The aim of this cross-sectional study was to gain insight into the level of unmet needs for supportive care and limitations in physical health as experienced by survivors of head and neck cancer (sHNC). Unmet needs were measured with two patient Supportive Care Needs Surveys (SCNS-SF34, SCNS-HNC) for cancer generic and head and neck cancer-specific unmet needs in physical health. Limitations in physical health were measured with a core set of physical measurements and related to age and sex-stratified reference values. A secondary aim was to evaluate if unmet needs in physical health and limitations in physical performance were associated. The SCNSs showed that 48% of survivors of head and neck cancer had a cancer generic unmet need and 46% had at least one HNC specific unmet need. In total 76% of sHNC had a cancer generic limitation in physical health and 58% had an HNC specific limitation. This shows that even at the stage of cancer survivorship a large percentage of sHNC report unmet needs in physical health and limitations in physical performance. No association between unmet needs and physical limitations was demonstrated. This could indicate that both methods measure different constructs and should be used in conjunction when identifying HNC patients that could benefit from physiotherapy.

**Chapter 4.** This longitudinal study reports shoulder and neck function over a five-year follow-up of 113 patients with cancer in the oral cavity. Measurements of forward flexion and abduction of the shoulder and lateral flexion of the neck were collected at baseline, 6 weeks, 6

months, 12 months, and 60 months. The aim of this study was to identify factors influencing shoulder and/or neck function in patients up to five years after treatment. We found that shoulder and neck function decreases the most at the 6-week post-intervention moment of measurement. A bigger decrease and worse recovery are predicted for older age at baseline. Additional radiotherapy treatment negatively influenced contralateral flexion of the neck. A more extensive neck dissection and the use of a bone graft/flap reconstruction negatively influenced shoulder function. Patients with characteristics that predict worse recovery over five years could be the focus for future physiotherapy interventions.

**Chapter 5.** This longitudinal study researched the difference in shoulder morbidity and health-related quality of life (HR-QoL) between the elective neck dissection (END) and the sentinel lymph node biopsy (SLNB) strategies for patients with clinically lymph node negative $T_{1-2}$ cancer of the oral cavity. Shoulder function, patient-reported shoulder morbidity, and HR-QoL were measured at baseline, 6 weeks, 6 months, and 12 months after intervention. Patients undergoing SLNB without complementing neck dissection showed better short-term shoulder function at 6 weeks post-intervention. No significant other differences were demonstrated. The short-term benefit in shoulder function strengthens the choice for the SLNB as the preferred medical strategy.

**Chapter 6.** This cross-sectional study also researched the differences in shoulder- and neck morbidity, and HR-QoL between END and SLNB strategies. It provided additional knowledge to the results as found in chapter 5 as it included participants at a later moment of follow-up (median time since treatment >12 months) and also provided insight on neck morbidity. This study showed no differences in shoulder and neck morbidity between the END and SLNB treatments strategies.

**Chapter 7**. The general discussion reviews the most important findings of this dissertation. It takes into account the available body of knowledge, methodological considerations, and clinical implications. The optimization of care in physical health for patients with HNC requires cooperation between all the health-professionals involved. This thesis underlines the importance of recognizing that patients represent an unique combination of health conditions, environmental factors, and personal factors expressed in a unique demand for supportive care. Patient-specific (p)rehabilitation by physiotherapeutic interventions based on risk profiles and

patient preferences can be the focus of future research. Patient self-measurement and the use of "patient like me" models that could benefit patient awareness and their ability to self-manage problems in physical health should be considered.

# Samenvatting

## De fysieke gezondheid van patiënten met hoofd-halskanker
## Het pad naar gepersonaliseerde fysiotherapeutische zorg

Patiënten met hoofd-halskanker (HHK) kunnen voor, tijdens en na de medische behandeling fysieke problemen hebben. De chirurgische en radiotherapeutische behandeling richten zich specifiek op het hoofd-halsgebied. Dit kan zorgen voor beperkingen in orale functies en het bewegen van nek en schouders. Als gevolg hiervan kunnen patiënten beperkingen hebben bij activiteiten in het dagelijks leven, zoals bijvoorbeeld bij het openen van je mond wanneer je een boterham eet, of het over je schouder kijken wanneer je fietst. Chemo- en radiotherapie kunnen voor meer algemene klachten zorgen zoals een verminderde algehele conditie, waardoor het bijvoorbeeld niet meer lukt om 5 km met de hond te wandelen. Lokaal kan chemo- en radiotherapie zorgen voor bijvoorbeeld een ontsteking van de slijmvliezen in de mond (mucositis) wat het eten van een broodje moeilijk maakt. Bij het voorkomen en behandelen van deze problemen in fysieke gezondheid kan de fysiotherapeut een rol spelen. Om de fysiotherapeutische zorg van patiënten met HHK te verbeteren zijn voor dit proefschrift de volgende doelen opgesteld: 1) inzicht in de betrouwbaarheid van meetinstrumenten die fysieke gezondheid meten specifiek bij HHK patiënten; 2) inzicht in fysieke gezondheid gemeten met objectieve meetinstrumenten afgezet tegen voor leeftijd en geslacht gecorrigeerde referentiewaarden, en de mate van behoefte aan ondersteunende zorg binnen het domein van fysieke gezondheid; 3) inzicht in het 5-jaars beloop van schouder- en nekfunctie, en of dit beloop beïnvloed wordt door patiënt eigenschappen zoals leeftijd en geslacht, klinische karakteristieken zoals de locatie van de tumor, en welke behandeling gegeven is; en 4) inzicht in het verschil in schouder- en nekmorbiditeit tussen de electieve nek dissectie (END) en de schildwachtklierprocedure (SNLB) bij patiënten met een klinisch negatieve $T_{1-2}$ tumor in de mondholte, op zowel de korte als lange termijn. De overkoepelende doelstelling van deze thesis was tweeledig: het verbeteren van de identificatie van patiënten met HHK met een verhoogd risico op klachten binnen de fysieke gezondheid, en het vergelijken van de END en SLNB diagnostische strategieën bij patiënten met een klinisch negatieve $T_{1-2}$ tumor in de mondholte op schouder- en nekmorbiditeit en gezondheidsgerelateerde kwaliteit van leven. Deze kennis

kan gebruikt worden om op het juiste moment gepersonaliseerde fysiotherapie aan de patiënt met HHK te bieden

**Hoofdstuk 1.** Patiënten met HHK kunnen specifieke problemen in fysieke gezondheid ervaren. Deze patiënten zouden baat kunnen hebben bij fysiotherapie. Het identificeren en optimaal timen van fysiotherapeutische zorg vraagt om betrouwbare meetinstrumenten en kennis over welke patiënt-, klinische en interventie karakteristieken een verhoogd risico geven op het ontstaan van fysieke gezondheidsproblemen. Om de problematiek van het onderzoek te kaderen worden epidemiologie, etiologie, medische behandeling en veel voorkomend problemen in het fysiek functioneren bij HHK beschreven.

**Hoofdstuk 2.** Het doel van deze cross-sectionele studie was het beoordelen van de test-hertest betrouwbaarheid van een set meetinstrumenten die de maximale mondopening (intra- en extra-oraal), schouder- en nekfunctie, kracht van de onderste extremiteit (30 seconden zitten-staan test), knijpkracht, niveau van mobiliteit (timed up-and-go test) en het loopvermogen (6 minuten wandeltest) meten. In totaal werden 50 patiënten geïncludeerd tijdens bijeenkomsten van de patiëntenvereniging Hoofd-hals en vanuit patiënten die kwamen voor reguliere controleafspraken in het ziekenhuis. Deze meetinstrumenten, die kunnen worden gebruikt om lokale, en generieke beperkingen in fysieke gezondheid te meten, lieten een goede test-hertest betrouwbaarheid zien. Dit betekent dat ieder meetinstrumenten goed in staat is om onderscheid te maken tussen een goede en een slechte fysieke gezondheid bij patiënten die behandeld werden voor HHK. De meetfout voor een aantal meetinstrumenten was relatief groot. Het is belangrijk hier rekening mee te houden als de meetinstrumenten evaluatief worden gebruikt. Deze informatie over de betrouwbaarheid en meetfout geeft de fysiotherapeut praktische handvatten bij de diagnostiek en evaluatie van de behandeling van HHK-patiënten.

**Hoofdstuk 3.** Het doel van deze cross-sectionele studie was om inzicht te krijgen in de mate van zorgbehoefte en beperkingen in fysieke gezondheid bij patiënten die behandeld zijn voor HHK. Zorgbehoefte werd gemeten met één kanker generieke vragenlijst en één HHK specifieke vragenlijst (Supportive Care Needs Surveys: SCNS-SF34, SCNS-HNC). Uit deze vragenlijsten kon het aantal zorgbehoeften in het fysieke domein in het algemeen, en specifiek bij HHK bepaald worden. Beperkingen in fysieke gezondheid werden gemeten met de set meetinstrumenten die de maximale mondopening (intra- en extra-oraal), schouder- en

nekfunctie, kracht van de onderste extremiteit (30 seconden zitten-staan test), knijpkracht, niveau van mobiliteit (timed up-and-go test) en het loopvermogen (6 minuten wandeltest) meten. De uitkomsten van deze fysieke metingen werden vergeleken met leeftijd- en geslacht gecorrigeerde referentiewaarden. Een uitkomst op een fysieke test van 80% of lager dan de referentiewaarde werd als beperking beschouwd. Een tweede doel was om te bepalen of zorgbehoeften en fysieke beperkingen een verband met elkaar hadden. Zijn de patiënten met HHK die een zorgbehoefte hebben in fysieke gezondheid ook de patiënten die slechter scoren op de fysieke testen. We vonden dat 48% van de deelnemers een kanker generieke en 46% een HHK specifieke onvervulde zorgbehoefte hadden in fysieke gezondheid. Kanker generieke fysieke beperkingen werden bij 76% en HHK specifieke bij 58% van de deelnemers aangetoond. Deze resultaten laten zien dat op de lange termijn nog een hoog percentage van de patiënten die zijn behandeld voor HHK, een onvervulde zorgbehoefte of beperking in fysieke gezondheid heeft. Er werd geen verband aangetoond tussen zorgbehoeften, gemeten met vragenlijsten en fysieke beperkingen, gemeten met fysieke testen bij deze patiënten. Dit zou erop kunnen duiden dat beide instrumenten een ander construct meten en dat ze gezamenlijk gebruikt dienen te worden om HHK-patiënten die profijt zouden kunnen hebben van fysiotherapie te identificeren.

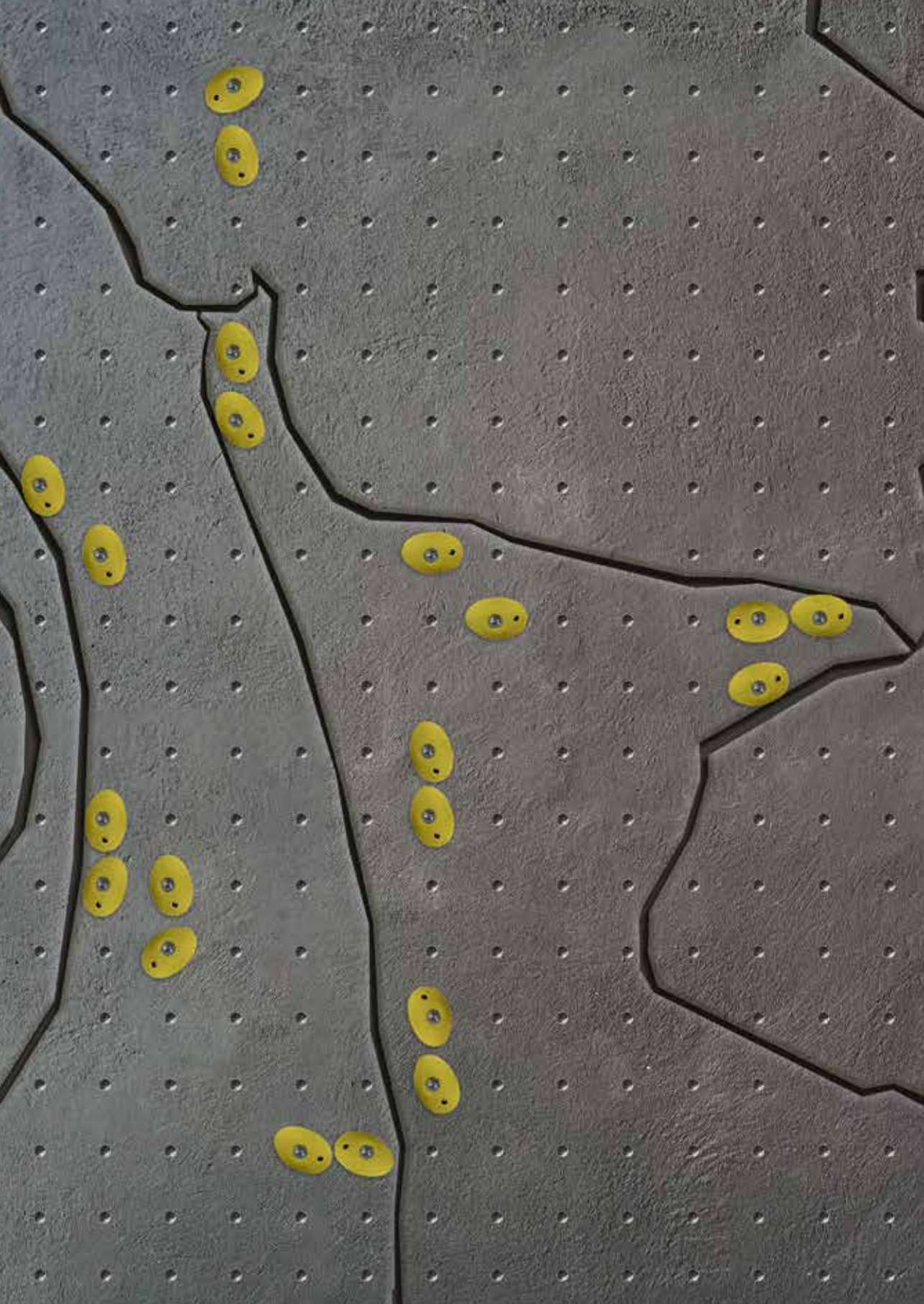
**Hoofdstuk 4.** Deze longitudinale studie beschrijft de schouder- en nekfunctie van 113 patiënten met kanker in de mondholte over een follow-up periode van 5 jaar. Anteflexie en abductie van de schouder en latero-flexie van de nek werden gemeten op baseline, 6 weken, 6 maanden, 12 maanden en 60 maanden na de behandeling van HHK. Het doel van de studie was om inzicht te krijgen in het beloop en de factoren die van invloed waren op het beloop van schouder- en nekfunctie. Schouder- en nekfunctie lieten 6 weken na de HHK-behandeling de scherpste daling zien. De oudere patiënt liet een sterkere achteruitgang zien na de behandeling en een slechter herstel. Radiotherapie had een negatieve invloed op contralaterale latero-flexie van de nek. Na een meer uitgebreide halsklierdissectie en een grote reconstructie met een bottransplantaat was de schouderfunctie slechter. Patiënten met eigenschappen die een slechter herstel van schouder- en nekfunctie voorspellen, zouden mogelijk baat hebben om in een vroeg stadium door een fysiotherapeut gezien te worden.

**Hoofdstuk 5.** Deze longitudinale studie met 1 jaar follow-up onderzocht het verschil in schouderfunctie, patiënt gerapporteerde schoudermorbiditeit en kwaliteit van leven tussen de

electieve nek dissectie en de schildwachtklierprocedure bij patiënten met een $T_{1-2}$ tumor in de mondholte zonder bij klinisch onderzoek gevonden positieve lymfeklieren. Dit werd gemeten voor de operatie, 6 weken, 6 maanden en 12 maanden. Patiënten die behandeld werden met een schildwachtklierprocedure zonder aanvullende halsklierdissectie lieten 6 weken na de behandeling van HHK een betere schouderfunctie zien. Er werden echter geen andere significante verschillen tussen de twee strategieën gevonden. De schildwachtklier-procedure leidt bij de patiënten in dit onderzoek tot minder schoudermorbiditeit op de korte termijn. Dit versterkt de onderbouwing voor de schildwachtklierprocedure als voorkeurs strategie voor patiënten met HHK en $T_{1-2}$ tumoren van de mondholte.

**Hoofdstuk 6.** In deze cross-sectionele studie werd onderzoek gedaan naar de verschillen in schouder- en nekmorbiditeit en kwaliteit van leven tussen de electieve nek dissectie en schildwachtklierprocedure bij patiënten met een $T_{1-2}$ tumor in de mondholte. Deze studie gaf aanvullende informatie ten opzichte de studie van hoofdstuk 5 omdat het inzicht gaf in schoudermorbiditeit op de lange termijn (moment van follow-up: mediaan >12 maanden sinds interventie) en ook de nek morbiditeit werd gemeten. Deze studie vond op dit latere moment van follow-up geen verschillen tussen de twee strategieën.

**Hoofdstuk 7.** De overkoepelende discussie beschouwt de belangrijkste bevindingen van dit proefschrift. Het plaatst de bevindingen in de context van de al bekende wetenschappelijke kennis en geeft weer wat dit onderzoek toevoegt. De discussie bespreekt ook de methodologische beperkingen van het uitgevoerde onderzoek en de vertaling van de bevindingen naar de dagelijkse fysiotherapie praktijk. De zorg voor de fysieke gezondheid vraagt een goede samenwerking tussen betrokken behandelaars en patiënten met HHK. Het onderzoek in dit proefschrift onderbouwt dat gepersonaliseerde zorg die gebaseerd is op informatie die samen met de patiënt is verzameld de basis moet zijn voor optimale zorg. Iedere patiënt moet daarbij worden gezien als een unieke combinatie van gezondheids-, omgevings-, en persoonlijke factoren die leiden tot een unieke zorgvraag voor fysiotherapeuten en de andere leden van het behandelteam. Toekomstig onderzoek zou zich kunnen richten op de effectiviteit van patiënt-specifieke fysiotherapie aangepast op risicoprofielen en de voorkeuren van de patiënt met HHK. Het meten van fysieke gezondheid door de patiënt met HHK zelf, en het gebruik van "patiënten zoals ik" modellen die patiënt betrokkenheid en bewustzijn faciliteren, zou daarbij overwogen kunnen worden.



# About the author

Gerben van Hinte was born in Nijmegen, the Netherlands on the 10th of January 1980. He grew up with his parents Rob and Marja, younger sister Suzanne and younger brother Vincent. After primary school (de Weteringshof) he completed his secondary school (atheneum) at the Elshof college in Nijmegen (1998). After this he studied physical therapy at the HAN University of Applied Sciences in Nijmegen (BSc. 2003) and started working as a physiotherapist at the Radboud University Medical Center. In 2012 he received his master's degree from Utrecht University in Clinical Health Sciences, direction Physiotherapy Sciences.

He worked as physiotherapist at different departments in the hospital, eventually specializing into the field of oncology. For ten years he was part of the Radboud amputee rehabilitation team that pioneered the click-prosthesis. His colleague, dr. Carien Beurskens introduced him into the field of orofacial physiotherapy. He was inspired, and he focussed on treating patients with problems in the head and neck area. During his master thesis he was supervised by dr. Caroline Speksnijder who encouraged him to continue his research on functional limitations in patients with head and neck cancer in a PhD project. Next to treating patients, he enjoys teaching and started working as a teacher at several master level physiotherapy programs (Avans+, SOMT, HAN, NPI).

After completing his PhD, Gerben will continue to work as a physiotherapist and will combine this with teaching and research projects. Next to this, he will start as program manager for the center of brain and senses in the Radboud University Medical Center.

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# List of publications

## In this thesis:

1. **van Hinte G**, Leijendekkers RA, Te Molder B, Jansen L, Bol C, Merkx MAW, Takes R, Nijhuis-van der Sanden MWG, Speksnijder CM. Reproducibility of measurements on physical performance in head and neck cancer survivors; measurements on maximum mouth opening, shoulder and neck function, upper and lower body strength, level of physical mobility, and walking ability. PLoS One. 2020 Sep 3;15(9):e0233271. doi: 10.1371/journal.pone.0233271. PMID: 32881858; PMCID: PMC7470389.

2. **van Hinte G**, Leijendekkers RA, Merkx MAW, Takes RP, Nijhuis-van der Sanden MWG, Speksnijder CM. Identifying unmet needs and limitations in physical health in survivors of Head and Neck Cancer. Eur J Cancer Care (Engl). 2021 Sep;30(5):e13434. doi: 10.1111/ecc.13434. Epub 2021 Mar 11. PMID: 33709466; PMCID: PMC8519003.

3. **van Hinte G**, Wetzels JGH, Merkx MAW, de Haan AFJ, Koole R, Speksnijder CM. Factors influencing neck and shoulder function after oral oncology treatment: a five-year prospective cohort study in 113 patients. Support Care Cancer. 2019 Jul;27(7):2553-2560. doi: 10.1007/s00520-018-4534-1. Epub 2018 Nov 14. PMID: 30430300; PMCID: PMC6541579.

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6. Prins MC, **van Hinte G**, Koenders N, Rondel AL, Blijlevens NMA, van den Berg MGA. The effect of exercise and nutrition interventions on physical functioning in patients undergoing haematopoietic stem cell transplantation: a systematic review and meta-analysis. Support Care Cancer. 2021 Nov;29(11):7111-7126. doi: 10.1007/s00520-021-06334-2. Epub 2021 Jun 16. PMID: 34131848; PMCID: PMC8464580.

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10. Leijendekkers RA, **van Hinte G**, Frölke JP, van de Meent H, Atsma F, Nijhuis- van der Sanden MW, Hoogeboom TJ. Functional performance and safety of bone-anchored prostheses in persons with a transfemoral or transtibial amputation: a prospective one-year follow-up cohort study. Clin Rehabil. 2019 Mar;33(3):450-464. doi: 10.1177/0269215518815215. Epub 2018 Dec 12. PMID: 30537856; PMCID: PMC6416705.

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## National Publications

15. Aandachtspunten na een beenamputatie, dhr. G. van Hinte van, Dr. C. Beurskens, Nurse Academy Sept 2009.

16. Fysiotherapie bij mondkanker. Dr. Speksnijder C.S.M, G. van Hinte, Physios. Sept. 2013.

17. Fantoompijn na een beenamputatie. Nurse Academy. 2017 juni: volume 2 Charlotte Bockting, Gerben van Hinte, Shanna Bloemen, Ruud Leijendekkers

18. Hoofd-hals-oncologie: Aandachtspunten vanuit de fysiotherapie. G. van Hinte, Dr. C. Beurskens, Dr. C. Speksnijder. Hoofd-Hals Magazine 2017.

19. Fantoompijn na beenamputatie. Fysiopraxis. 2018 mei: pp 30-32 Charlotte Bockting, Gerben van Hinte, Shanna Bloemen, Ruud A. Leijendekkers.

20. Stamceltransplantatie bij hematologisch oncologische maligniteit. Medische en fysiotherapeutische behandeling. G. van Hinte, B. van den Buijs, Dr. C. Speksnijder Fysiopraxis 2018.

21. Een dynamische reconstructie bij een aangezichtsverlamming. G. van Hinte, C. Beurskens, K. Ingels. Themanummer orofaciale fysiotherapie Fysiopraxis 2019.

22. Hoofd-halsoncologie en orofaciale fysiotherapie. Gerben van Hinte. Themanummer orofaciale fysiotherapie Fysiopraxis 2019.

23. Fysiotherapie bij Mondkanker. Gerben van Hinte; Caroline Speksnijder. O2 magazine 2020.

## Grants

Michel Keijzer Fonds 25.000 euro. "Fysieke klachten bij hoofd-halskanker survivors. Het Beweeg-APK onderzoek"

# PhD portfolio of Gerben van Hinte

| | |
|---|---|
| Department: | Department of Rehabilitation |
| PhD period: | 01/01/2018 – 01/03/2023 |
| PhD Supervisor(s): | Prof. dr. Maria W.G. Nijhuis - van der Sanden, Prof. dr. Thijs A.W. Merkx, Prof. dr. Robert P. Takes |
| PhD Co-supervisor(s): | Dr. Caroline M. Speksnijder |

| **Training activities** | Hours |
|---|---|
| **Courses** | |
| 2019 Scientific Integrity course | 20 |
| 2019 RIHS – Introduction course for PhD candidates | 15 |
| 2019 eBROK course | 42 |
| 2019 PhD retreat | 28 |
| 2020 PhD retreat | 28 |
| 2022 Multilevel statistics IQ- Healthcare workshop | 16 |
| **Seminars** | |
| 2019 Oral presentation + Poster presentation . NWHHT Jonge onderzoekers dag | 28 |
| 2020 Oral presentation at patient federation meeting | 28 |
| **Conferences** | |
| 2018 Poster presentation at: Dag van de fysiotherapie KNGF Annual Congress. | 28 |
| 2019 Poster presentation at: Dag van de fysiotherapie KNGF Annual Congress | 28 |
| 2019 Oral presentation PhD retreat | 28 |
| 2021 Oral presentation IPT-HOPE | 28 |
| **Other** | |
| n/a | |

| Teaching activities | |
|---|---|
| **Lecturing** | |
| 2018, 2019 teaching oncology course and basic research skills: AVANS+, master oncology physical therapy | 112 |
| 2018-2022 Facial paralysis course | 248 |
| 2018-2022 Physical therapy in head and neck oncology for dentists | 32 |
| 2019-2022 Physical therapy in head and neck oncology masterclass for PT's | 24 |
| 2020-2022 Physical therapy in head and neck oncology for nurses | 8 |
| 2018-2022 Physical therapy in head and neck oncology for PT's HAN | 112 |
| **Supervision of internships / other** | |
| 2018,2019 Supervision HAN students (bachelor thesis Physical therapy) | 112 |
| 2019 Supervision student AVANS+ (master thesis, Oncology Physical therapy) | 112 |
| 2020 Supervision medical student Radboudumc (2X) (master thesis) | 224 |
| **Total** | 1301 |

# Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. The studies described in chapter 2, 3, 4, 6 were subject to the Medical Research Involving Human Subjects Act (WMO) and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical ethical review committee 'METC Oost-Nederland' has given approval to conduct these studies (file number: NL63632.091.17, NL1200604106). Informed consent was obtained from research participants. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage). The Medical Ethics committee for Research Involving Human Subjects Region Arnhem and Nijmegen, Nijmegen, the Netherlands has given approval to conduct the study in chapter 5 (2014/129). The research protocol for the study in chapter 6 was approved by the Ethics Committees of the UMC Utrecht (NL68148.041.18) .

Informed consent was obtained from research participants. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage).

Data for chapter 2, 3, 5 and 6 were collected through electronic Case Report Forms (eCRF) using CASTOR EDC. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA). Pseudonymized data were stored on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc. Paper (hardcopy) data is stored in cabinets on the department.

## Availability of data

The data will be archived for 15 years after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

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