Move to Eat

Towards personalization of supportive care for patients with head and neck cancer undergoing chemoradiotherapy

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Op weg naar personalisatie van ondersteunende zorg voor patiënten met hoofd-halskanker die behandeld worden met chemoradiotherapie

(met een samenvatting in het Nederlands)

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General introduction

General introduction

Malnutrition and dietary treatment in patients with cancer

Malnutrition has been defined as "a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease".[1] Diagnosing malnutrition requires the assessment of (involuntary) weight loss, body mass index (BMI), muscle mass, food intake or assimilation and the inflammatory condition.[2] Patients with cancer are at high risk for malnutrition because both the disease and its treatment threaten nutritional status. First, due to the tumor-related symptoms, including dysphagia, pain, loss of appetite (anorexia) and nausea, oral nutritional intake might be impaired. Secondly, a systemic inflammation syndrome, the anorexia-cachexia syndrome, is frequently present in cancer patients in varying degrees. This systemic inflammation syndrome causes metabolic derangements of the carbohydrate-, protein and fat metabolism and is associated with fatigue, anorexia and the loss of muscle mass.[3] Side effects of treatment are likely to further deteriorate nutritional intake, increasing the risk for developing malnutrition or enhancing the severity of malnutrition.

In the Netherlands, malnutrition screening in cancer patients is part of usual care. Cancer patients with a high risk of malnutrition are referred to an oncology dietitian. Subsequently, the Dietetic Care Process, a standardized method to provide dietetic care, is started.[4] Assessment for malnutrition diagnosis and grading the severity of malnutrition according to the Global Leadership on Initiative on Malnutrition (GLIM) criteria is performed as part of the Dietetic Care Process.[2] The following dietary treatment is always tailored to the individual. Not only nutritional intake, the disease, treatment and its related nutritional problems are taken into account but also the patients' psychological and social situation, daily activity pattern, eating habits and nutritional knowledge and beliefs. These are important factors which determine the success of dietary treatment and are embedded in the Dietetic Care Process and registered according to the International Classification of Functioning, Disability and Health.[4,5]

Head and neck cancer

Malnutrition

At diagnosis, critical weight loss (weight loss of >5% in 1 month or 10% in 6 months) is prevalent in almost 20% of patients with head and neck cancer (HNC).[6] Due to treatment side effects, the prevalence of critical weight loss increases up to 50% despite nutritional support.[7] Weight loss in patients with cancer and during cancer treatment is characterized by loss of muscle mass. Loss of muscle mass is unwanted, because it is associated with decreased quality of life, physical decline, increased risk of treatment toxicity, higher complication rates and healthcare costs, and lower survival rates in HNC.[8,9] Dietary treatment is embedded in the HNC care pathway and aims to maintain or restore nutritional intake, nutritional status and muscle mass. Dietary treatment is personalized, taking into account the multiple and changing nutritional challenges before, during and after treatment as well as social issues, and personal needs and preferences of patients with HNC.[10] Close collaboration between dietitians, medical specialists and allied health professionals, including physiotherapists, speech pathologists, nurse specialists, social workers and oral hygienists, is necessary to guide patients through the treatment trajectory as well as to assist them in adapting to life after treatment and manage long-term effects of their disease or treatment.[11]

Epidemiology and survival

Head and neck cancer (HNC) encompasses tumors of the upper aerodigestive tract, including the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity, paranasal sinuses and salivary glands. Most head and neck cancers are squamous cell carcinoma. Head and neck cancer is one of the ten most common cancer types in the Netherlands with approximately 3000 new cases yearly.[12] The overall incidence remained more or less stable in the past ten years. When subdividing incidence rates for the different tumor sites, an increase in incidence of tumors in the oral cavity and pharynx (particularly the oropharynx) is seen, whereas the incidence of tumors of the lip and larynx decreases. Survival rates vary per tumor subsite and tend to increase over time for most tumor subtypes. Survival rates for patients with tumors of larynx, oropharynx and oral cavity vary between 50% and 70%.[12] For patients diagnosed with hypopharyngeal cancer the five-year survival remains low with 34%.[13]

Risk factors

Cancer is one of the most prevalent non-communicable disease and the leading cause of death worldwide.[14] It has been estimated that 30% to 50% of cancer cases are preventable. Not smoking or quitting smoking is the most important action to reduce cancer risk. Other means are to adopt a healthy lifestyle which encompasses being physically active and healthy eating and drinking behaviors.[15]

Risk factors for the development of head and neck squamous cell carcinoma are well described. The most important risk factors are smoking and alcohol consumption. The risk of developing HNC due to tobacco smoking is highly dose-dependent.[16] Data from the INHANCE consortium shows that compared to non-smokers, the use of less than 3 cigarettes daily increased the risk of HNC (odds ratio (OR) 1.52; 95% CI: 1.21-1.90), and the use of 5 to 10 cigarettes daily results in an OR of 2.6 (95% CI: 2.00-3.40).[16]

For the consumption of alcoholic drinks, dose-response meta-analysis also showed an increased HNC risk with increasing alcohol consumption (relative risk (RR) 1.04-1.14 per 10 gram of alcohol per day). There is convincing evidence that the combined effect of smoking and alcohol consumption even exceeds multiplicativity of the separate effects.[17]

The prevalence of oropharyngeal tumors is increasing in the higher socioeconomic countries due to Human Papilloma Virus (HPV), a sexually transmitted virus. It is currently the most important risk factor for oropharyngeal tumors, accounting for approximately two thirds of oropharyngeal tumors in developing countries. Patients with HPV positive tumors tend to be younger and are less likely to have a history of smoking and alcohol (ab)use. Patients with HPV-positive oropharyngeal tumors have a better five-year survival as compared to patients with HPV-negative tumors.[18]

Treatment

In the Netherlands, HNC care is centralized in 14 hospitals; eight university medical centers and six affiliated centers.[19] The multidisciplinary team consists of head and neck surgeons, radiation oncologists, medical oncologists, pathologists, radiologists, nuclear physicians, dentists, nurse specialists, speech therapists, dietitians, physiotherapists, oral hygienists and social workers. Medical specialists and allied health professionals are united in two national foundations, the Dutch Head and Neck Society (NWHHT) and the Dutch Allied Health Professionals Society (PWHHT). Both societies aim to increase quality of care for patients with HNC. The Dutch HNC patient advocacy group (PVHH) has an important role in coordinating and offering informal care and education by former HNC patients.

Treatment options for HNC include surgery, radiotherapy, systemic treatment (i.e. chemotherapy or immunotherapy) or a combination of these treatments. Early stage disease is generally treated with surgery or radiotherapy. For patients with locally advanced disease (stage III-IV) current treatment

with curative intent generally consists of a combination of surgery and adjuvant radiotherapy with or without chemotherapy, or radiotherapy combined with chemotherapy (chemoradiotherapy; CRT) or cetuximab (bioradiotherapy; BRT) with salvage surgery in reserve.[20,21] Radiotherapy is applied five times per week for six or seven weeks (30-35 fractions) to a total dose of 66 to 70 Gray. Concurrent chemotherapy (cisplatin or carboplatin) or cetuximab is administered intravenously either weekly or three-weekly. CRT and BRT treatment comes with several acute side-effects, including; mucositis, xerostomia, sensory changes/taste distortion, pain, dysphagia, and nausea and vomiting.[22] The intense treatment schedule with daily visits to the radiation clinic and regular appointments with several health care professionals may coincide with mealtime moments. Besides, fatigue may interfere with meal preparation and purchasing. As a consequence, oral nutritional intake is often impaired, causing involuntary weight loss, a key characteristic of malnutrition.[23]

Dietary treatment

Nutritional interventions for HNC patients have been shown to be beneficial in preventing weight loss and lowering CRT related toxicity and dietary treatment for malnourished HNC patients diminishes health care costs.[24-27] Dietary treatment during CRT is part of usual care and aimed at maintaining or restoring nutritional intake and nutritional status and preventing or reducing muscle mass loss. When oral nutritional intake is impaired due to side effects of treatment, dietary advice is aimed at modifying food texture and increasing the energy and protein content of the diet to meet personal energy and protein requirements. When it remains unable to meeting dietary requirements using solely normal foods, oral dietary supplements or tube feeding is prescribed.[5]

Tube feeding can be administered by a nasogastric tube or a gastrostomy during CRT, with each route having its pros and cons. Placement of a nasogastric tube is easier and cheaper as compared to a gastrostomy but dislodge more often and might be more inconvenient for the patient due to its contact with the inflamed and sore mucous membrane of the pharynx and its visibility.[28] On the other hand, this inconvenience may motivate the patient to increase oral intake as soon as possible after CRT so the tube can be removed. A gastrostomy seems more convenient for patients, although they will experience pain or discomfort for a few days after placement. Gastrostomy placement is not without risk; infection or dislocation are seen in 6% to 16% of patients.[29] Also, the presence of a gastrostomy has been associated with a higher risk of long term dysphagia due to the "use it or loose it" principle of the swallowing musculature.[30]

A gastrostomy can be placed prophylactically (before the onset of symptoms), before or in the early phase of treatment, or reactive (when oral nutritional intake is impaired).

The risk of delaying commencement of tube feeding when deemed necessary is lower in patients who already have a prophylactic gastrostomy. However, careful selection of patients who will benefit from prophylactic gastrostomy is useful to prevent unnecessary placement. A previous study showed that 47% of prophylactic gastrostomies are never used.[31] In the Netherlands it was common practice to place a prophylactic gastrostomy in all HNC patients undergoing CRT until the Dutch national guidelines stated to place a gastrostomy only upon indication thus not in every individual.[32,33] However, indications for gastrostomy placement were not available yet due to a lack of scientific evidence.

Exercise interventions

The term "use it or loose it" also applies for skeletal muscle mass. Besides an adequate nutritional intake, physical exercise is a prerequisite for maintaining or restoring muscle mass.[34] Exercise, especially resistance-type exercise training, stimulates muscle protein synthesis, resulting in an increased muscle mass and strength.[35] Although muscle protein synthesis is impaired in the aging population and in cancer patients, there are no "non-responders" to exercise training.[36] The beneficial effects of exercise interventions in cancer populations are well described.[37,38] Physical

exercise interventions, both endurance as well as resistance-type exercise, during and after cancer treatment positively affects fitness, fatigue, quality of life and treatment completion rates.[39-41] Higher levels of physical activity even seem to be associated with prolonged survival in cancer patients.[42] Most of the evidence is based on studies in patients with breast or colon cancer.

Patients with HNC are not fully comparable to these populations in terms of toxicity of treatment but also in terms of characteristics of the patient population. Patients with HNC are on average older, have a lower social economic status, and have a less healthy lifestyle.[43] Also, only 30.5% of HNC patients meet physical activity public health guidelines before diagnosis and this further decreases to 8.5% after diagnosis.[44]

Although there are no non-responders to exercise, there are certainly non-compliers with exercise training programs during cancer treatment.[45] Physical exercise programs for patients with HNC during treatment are challenging. CRT comes with high toxicity rates which negatively affects physical as well as mental condition and compliance with an exercise program. Compliance might also be negatively affected by the fact that head and neck cancer patients seem to overestimate their actual activity level resulting in a lack of intention to increase physical activity levels and comply with a training program.[20] On the other hand, it has also been shown that patients with HNC are willing to exercise, whilst incorporated in daily life.[20] For increasing physical activity levels throughout the HNC treatment trajectory, it is important to offer exercise interventions tailored to patients' individual capacity and preferences.

Aim and outline of this thesis

The aims of this thesis are trifold: the first aim was to assess variations in current practice with regard to nutritional interventions and dietetic care for HNC patients treated with CRT in the Dutch head and neck centers. Secondly, we aimed to gain insight into predictors for tube feeding use in HNC patients treated with CRT and provide a tool which helps to select patients who could benefit from prophylactic gastrostomy placement. Thirdly, we assessed the feasibility of an exercise intervention during CRT.

In **part I** of this thesis, we describe the current practice in the Netherlands regarding dietary treatment and gastrostomy placement and the development of a tool for selecting HNC patients treated with CRT who would benefit from prophylactic gastrostomy. **Chapter 2** describes the variations in nutritional interventions during CRT among the Dutch head and neck centers. Based on the results of this survey study recommendations are proposed to reduce variation in current dietetic practice.

Part II, **Chapter 3** describes the results of our study in which we determine which factors contribute to tube feeding use and gastrostomy placement in a large cohort of HNC patients at the UMC Utrecht. It was our first attempt to gain insight on potential indicators for the creation of an evidence based gastrostomy placement protocol. In **Chapter 4** we joined forces with the Maastricht University Medical Center and combined retrospective data of a large group of HNC patients treated with CRT or BRT. Based on this data we developed and internally validated a prediction model to identify patients who would use tube feeding for at least four weeks and thus could benefit from prophylactic gastrostomy placement. **Chapter 5** describes the update and external validation of our gastrostomy placement prediction model using data of two other head and neck cancer centers in the Netherlands (Netherlands Cancer Institute and Radboud University Medical Center). The developed model can be used as a tool to support personalized decision making with regard to gastrostomy placement. We also provide a flow chart and recommendation on how to use the model in clinical practice.

In **Part III**, the feasibility of a 10-week exercise intervention for head and neck cancer patients during CRT treatment, the Move Fit study, is described. **Chapter 6** gives an overview of the quantitative results of the exercise intervention with the main focus on feasibility; adherence,

attendance, recruitment and retention rate. Secondary, physical performance, muscle strength, body composition, quality of life and fatigue were assessed. **In Chapter 7**, the qualitative results of the Move Fit study are presented. Data of interviews of participants were analyzed to gain insight into satisfaction with the intervention and barriers and facilitators for participating and completing the intervention according to protocol. The results of this study provide clarity on how to optimize the exercise intervention best suiting patients' preferences and needs.

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Chapter 2

Nutritional interventions in patients with head and neck cancer undergoing chemoradiotherapy: current practice at the Dutch Head and Neck Oncology centers

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Abstract

Objective: To assess variations in nutritional interventions during CRT among the Dutch Head and Neck Oncology Centers (HNOCs).

Methods: An online questionnaire about nutritional interventions and dietetic practices was sent to fourteen oncology dietitians of the HNOCs.

Results: The response rate was 93%. The number of scheduled dietetic consultations varied from two to seven during CRT. Most centers (77%) reported using a gastrostomy for tube feeding in the majority of patients. Gastrostomies were placed prophylactically upon indication (39%) or in all patients (15%), reactive (15%), or both (31%). For calculating energy requirements, 54% of the dietitians used the FAO/WHO/UNU formula and 77% uses 1.2-1.5 gram/kg body weight for calculating protein requirements. Almost half of the centers (46%) reported to remove the gastrostomy between 8 to 12 weeks after CRT. Most centers (92%) reported to end dietary treatment within 6 months after CRT.

Conclusion: This study shows substantial variation in dietetic practice, especially in the use of a gastrostomy for tube feeding, between the HNOCs. There is a need for concise dietetic guidelines.

Introduction

In patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) the standard treatment is primary or adjuvant radiotherapy with concurrent chemotherapy for six to seven weeks.[1] Side effects of this chemoradiotherapy (CRT), e.g., pain, dysphagia, mucositis, taste alterations, xerostomia, sticky saliva and nausea, impair oral nutritional intake.[2,3] As a consequence, these patients are at high risk of malnutrition, which is characterized by unintended weight loss.[4] Weight loss in patients with head and neck cancer (HNC) is associated with an increased rate of treatment interruption[5-7], dose-limiting toxicity[8], more severe radiation-induced toxicity[9], a lower quality of life[10-12] and a lower overall survival.[5,13,14] Intensive nutritional intervention has been shown to be beneficial in preventing weight loss and lowering CRT related toxicity.[15-17] Dietary treatment for malnourished patients also diminishes healthcare costs for HNC patients.[18] Therefore, dietary treatment is usually embedded in the HNC healthcare process from diagnosis until follow-up.
In the Netherlands, head and neck cancer care is centralized in fourteen Head and Neck Oncology Centers (HNOCs); eight university hospitals and six affiliated centers.[19] Medical specialists of these centers involved in HNC care are united in the Dutch Head and Neck Cancer Society (NWHHT).[19] The members of the NWHHT, in consultation with members of the Allied Health Professionals for HNC (PWHHT), have developed the Dutch Head and Neck Cancer guidelines for standardization and increasing quality of HNC care.[20] These guidelines do not provide guidance for the frequency of dietetic consultations during and after CRT. Also, the guidelines provide little information on the nutrition prescription (calculation of energy and protein needs) and nutritional interventions, such as tube feeding use, indications for gastrostomy placement and gastrostomy removal policy.
It is thereby unclear to what extent nutritional interventions vary between the HNOCs in the Netherlands. Therefore, the aim of this survey study is to evaluate current dietetic practice concerning dietary treatment, the dietetic care process, tube feeding and tube placement in patients with LAHNSCC treated with CRT at the HNOCs.

Methods

In January 2019, an email with a link to an online questionnaire was sent to fourteen oncology dietitians of all fourteen HNOCs in the Netherlands.
The questionnaire consisted of eighteen questions concerning nutritional intervention during CRT for LAHNSCC patients (Appendix S1). The following topics were addressed: dietetic consultations during CRT; tube feeding use and route; calculation of energy and protein requirements; tube placement and removal policy and end of dietary treatment.
Respondents were asked to fill out the questionnaire within three weeks. After three weeks a reminder was sent to those who had not filled out the questionnaire. When information was unclear a request for further explanation was sent.
Ethical considerations: no ethical approval was needed for this survey on routine clinical practice and no patients were involved.

Results

Dietetic consultations during treatment

Thirteen of the fourteen (93%) oncology dietitians completed the questionnaire. In all participating thirteen centers, every LAHNSCC patient undergoing CRT was routinely referred to an oncology dietitian. In most centers (69%), dietetic consultations were scheduled weekly for all patients. Two centers (15%) reported scheduling between two and four dietetic consultations during the seven-

week treatment period and the remaining two centers (15%) determined the frequency of dietetic consultations depending on patients' needs and preferences. In all centers, all scheduled dietetic consultations were face-to-face contacts.

Tube feeding and feeding route

When asked what percentage of CRT patients required tube feeding, dietitians provided estimates ranging from 25% to 50% (n=1), 50% to 75% (n=7), and 75% to 100% (n=5). In summary, all but one respondent (92%) estimated that more than half of all CRT patients required tube feeding at some point during CRT treatment. In most centers (77%), a gastrostomy was most frequently used (in 75% to 99% of patients) for the administration of tube feeding during CRT. In the remaining three centers (23%) a nasogastric tube was the preferred route (in 70% to 95% of their CRT patients). Four dietitians reported using a nasoduodenal or nasojejunal tube in a minority of patients (1% to 10%). Five centers (39%) reported placing a gastrostomy only prophylactically upon indication, thus in selected patients. Four centers (31%) reported placing gastrostomies both prophylactically upon indication or reactive. Two centers (15%) reported placing only reactive gastrostomies and two other centers (15%) placed prophylactic gastrostomies in all patients. Six out of the thirteen centers (46%) developed a center-specific protocol with indications for gastrostomy placement. Five other centers (38%) used selection criteria for gastrostomy placement as well, but these were not embedded in a protocol. Reported selection criteria for (prophylactic) gastrostomy placement include, among others: tumor location; tumor size; bilateral neck irradiation; malnutrition risk and pre-treatment dysphagia. Detailed information on gastrostomy placement and selection criteria used can be found in Table 1.

Table 1. Detailed information on gastrostomy placement and the presence of a gastrostomy placement protocol at the thirteen participating Dutch Head and Neck Oncology Centers.

Respondent number	Gastrostomy placement	Selection criteria for gastrostomy placement	Protocol with indications
1	Reactive	Based on weight loss ≥10% and intake <50%	Yes
2	Prophylactic upon indication and reactive	Prophylactic based on criteria: very low BMI, large tumor, dysphagia. Reactive in case of severe complications during treatment and if nasogastric tube is not possible. Reactive often after CRT treatment	No
3	Prophylactic upon indication	If tumor is localized in oropharynx, oral cavity or nasopharynx. If tumor is localized elsewhere, it is based on insufficient intake and weight loss	Yes
4	Reactive	If nasogastric tube is not possible or not tolerated	No

Respondent number	Gastrostomy placement	Selection criteria for gastrostomy placement	Protocol with indications
5	Prophylactic upon indication and reactive	Prophylactic on indication in case of treatment with cisplatin, reactive if enteral nutrition is necessary (but then nasogastric tube is used instead of PEG/PRG)	No
6	Prophylactic upon indication and reactive	-	No
7	Prophylactic upon indication and reactive	No clear indicators, but at least 10% weight loss before treatment and dysphagia at baseline	No
8	Prophylactic (in all patients)	All patients receive a PEG/PRG tube prophylactic, unless it is not possible due to comorbidity. In that case, a nasogastric tube will be placed reactive	Yes
9	Prophylactic upon indication	If nutritional status is insufficient before start of CRT treatment	No
10	Prophylactic upon indication	In case of a primary tumor in oral cavity or oropharynx and/or bilateral neck irradiation	No
11	Prophylactic upon indication	If the physician expects that swallowing problems will be minimal (5% of the cases), a PEG or PRG tube is not placed prophylactic. In other cases, PEG or PRG tubes are placed before the treatment starts	Yes
12	Prophylactic (in all patients)	Prophylactic placement in almost every patient, except if there are contraindications or if the patients does not want a PEG or PRG tube. If the PEG tube is not placed prophylactic and tube feeding is needed in the last weeks of CRT, it will be provided via nasogastric tubes	Yes
13	Prophylactic upon indication	When at least one of the following applies: 1) T3/T4 tumor in oral cavity, oropharynx or hypopharynx; 2) Nasopharyngeal tumor; 3) bilateral neck irradiation; 4) weight loss >5% in one month or >10% in three months; 5) low BMI (<18.5 or <20 when age >65 years); 6) dysphagia with insufficient intake	Yes

Energy and protein requirements

For calculating resting energy expenditure (REE), seven dietitians (54%) reported using the equation of the Food and Agriculture Organization/World Health Organization and United Nations University (FAO/WHO/UNU)[21], four dietitians (31%) reported using the Harris and Benedict equation[22], one respondent (8%) uses a fixed factor (30-35 kcal/kg)[23] and one respondent (8%) uses the mean of

three different equations. None of the respondents measured REE using indirect calorimetry in routine care. In order to calculate total energy expenditure (TEE), all dietitians who use an REE prediction equation instead of a fixed factor, added a percentage between 30% to 50% for physical activity level, illness and thermic effect of food. Most dietitians (77%) reported using 1.2 to 1.5 gram protein/ kilogram body weight to calculate protein requirements during CRT treatment. Only one respondent (8%) uses more than 1.5 gram protein/kilogram body weight and one respondent (8%) uses 1.0 to 1.2 gram protein/kilogram body weight to calculate protein requirements. All but one dietitian (92%), reported using fat free mass or corrected body weight (e.g. body weight corresponding to a Body Mass Index (BMI) of 27) instead of actual body weight for calculating protein requirements in overweight patients. For calculating energy requirements in overweight patients, the actual body weight is used in most institutions (69%).

Gastrostomy removal

Almost half of the centers (46%) reported that a gastrostomy is, on average, removed between 8 to 12 weeks after CRT (Figure 1). At all but two centers (85%), the dietitian and treating physician jointly decided when to remove the gastrostomy. Four dietitians (31%) mentioned that the patient is also involved in this decision making. Three centers (23%) developed a protocol for gastrostomy removal. These centers report that the gastrostomy will be removed when the patient has an adequate oral nutritional intake, a stable weight (or within acceptable range) and their gastrostomy has not been used for 2-6 weeks. One center also added "safe swallowing function/ no aspiration" as a prerequisite for gastrostomy removal.

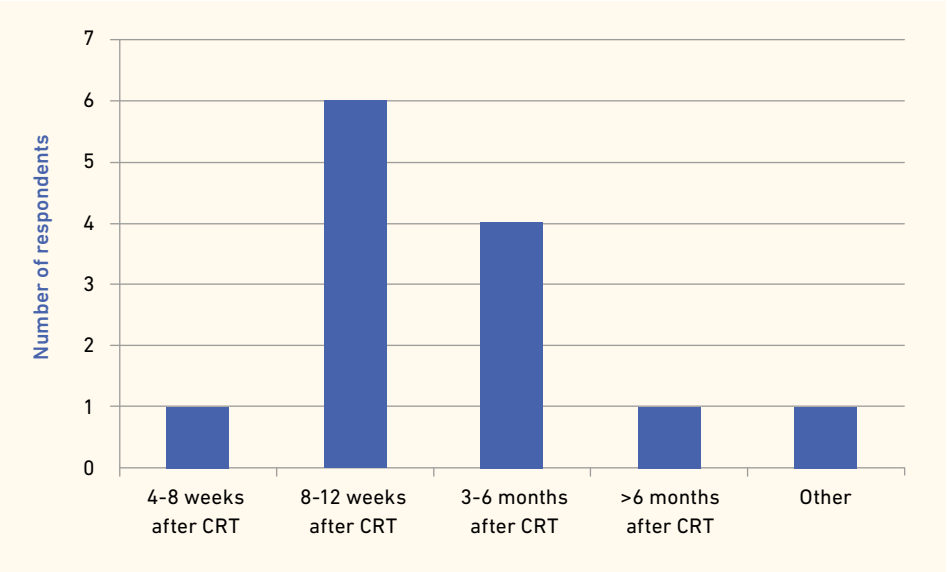

Figure 1. Estimated average time of gastrostomy removal after end of CRT treatment as reported by the thirteen dietitians of the participating centers.

End of dietary treatment

Most dietitians (76%) reported ending dietary treatment on average within 6 months after treatment. Two dietitians (15%) ended dietary treatment between 6 and 9 months and one dietitian (8%) ended dietary treatment, on average, more than nine months after CRT treatment. However, several

respondents denoted that there are considerable differences in the length of dietary treatment between patients, depending on patients' recovery after treatment, needs and nutritional intake. Reasons for ending dietary treatment varied per center and included: an adequate nutritional intake, weight stabilization, reaching dietary treatment goals and removal of the gastrostomy. Two dietitians reported referring to a primary care dietitian if the patient is prolonged tube feeding dependent or if prolonged dietary treatment is indicated.

Discussion

Results of this nationwide survey indicate that there is substantial variation in the number of scheduled dietetic consultations and tube placement (and removal) policy during CRT among the thirteen HNOCs participating in this study. Also, slight variations were reported in the calculation of energy and protein requirements and length of dietary treatment.

In all centers all CRT patients are routinely referred to an oncology dietitian for face-to-face consultations, but the number of these consultations during CRT treatment varied between two and seven. Although the current Dutch Head and Neck cancer guidelines provide no information about the optimal frequency of dietetic consultations during CRT, in most centers (69%) they are scheduled weekly. This is in line with the Dutch Handbook "Nutrition in Cancer" [24] and guidelines from British Association of Head and Neck Oncologists (BAHNO) and Clinical Oncology Society of Australia (COSA).[25,26] Previous studies have shown that intensive, weekly nutritional intervention results in fewer treatment interruptions, less weight loss and milder symptoms of toxicity in head and neck cancer patients.[6,17] These studies do not describe whether patients were compliant with the nutritional intervention. A more recent study showed that compliance with a dietary regimen with weekly nutritional counseling was low: as many as half of the patients missed more than 25% of scheduled appointments.[27] Future research should therefore gain insight into (non-)compliance with weekly consultations and patients' needs and preferences considering the number and type of consultations.

Most dietitians were convinced that tube feeding is required for most patients during CRT treatment. Previous observational studies showed most LAHNSCC patients (68% to 81%) use tube feeding during CRT treatment.[28,29] In this survey, we did not verify the indications used for starting tube feeding. According to the Dutch malnutrition guideline, tube feeding in addition to oral intake is advised when 50% to 75% of calculated nutritional requirements are met, and full tube feeding is advised when less than 50% of requirements are met using only oral intake.[30] Tube feeding is commenced even earlier in this specific patient population in anticipation of side effects of treatment, usually occurring from the second week of treatment onward.[31]

In most of the responding centers (77%), a gastrostomy is the preferred route for the administration of tube feeding, although the optimal route for tube feeding administration has not yet been established. A nasogastric tube has the advantage of its relatively low costs and easy placement procedure in an outpatient setting.[32] However, in contrast to gastrostomies, nasogastric tubes dislodge more often and patients find them more inconvenient.[32] A gastrostomy is preferred when tube feeding is expected to be necessary for at least four weeks.[33,34]

Insertion of a prophylactic gastrostomy in all patients has been subject of debate.[35] In the Netherlands, there is currently a shift from prophylactic gastrostomy in all CRT patients towards prophylactic gastrostomy in selected patients or reactive gastrostomy placement, which is illustrated by the results of this survey: most centers that placed a gastrostomy did so upon indication only. In two centers, however, all patients treated with CRT received a prophylactic gastrostomy. This is in contrast with the Dutch Head and Neck Cancer guideline, that states that a gastrostomy should be placed only upon indication and therefore not in all CRT patients.[14] Although evidence is low, we support the recommendation to place a prophylactic gastrostomy only in

selected patients because 9% to 47% of prophylactic gastrostomies are never used during CRT[29,36], and complication rates are high.[37,38] Moreover, prophylactic gastrostomy insertion in all CRT patients might increase long-term dysphagia and tube feeding dependency due to atrophy of the swallowing muscles in the prolonged absence of oral intake.[39,40]

To better predict which patients would benefit from a prophylactic gastrostomy, we recently developed and internally validated a prediction model for tube feeding dependency for at least four weeks during CRT which can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.[34]

There is no consensus on when to remove a gastrostomy. Most centers reported removing the gastrostomy, on average, between 8 and 12 weeks after CRT. It is essential to stimulate oral intake during and after CRT, to closely monitor tube use and to remove the gastrostomy as soon as possible after CRT treatment to prevent long-term dysphagia.[41,42] Three centers have already formulated indications on when to remove the gastrostomy. Future studies should focus on the optimal timing of gastrostomy removal and criteria for gastrostomy removal, as information in literature is lacking. It should also be noted that in 70% of the centers the patient was not mentioned as being involved in this gastrostomy removal decision making, suggesting that there is ample opportunity to increase the use of shared-decision making.

Several methods were used to calculate energy requirements of patients. This is no surprise, because for calculating a patients' individual energy requirement, various prediction equations for resting energy expenditure (REE) can be used, for example Harris and Benedict, the FAO/WHO/UNU and Schofield formula.[21,22,43,44] The Dutch Head and Neck cancer guidelines provide no information on which formula is best to use in HNC patients. The FAO/WHO/UNU formula seems to perform best in patients with a BMI <30 and the Harris and Benedict in patients with a BMI >30.[24,45] An earlier study showed that the Harris and Benedict underestimates REE in a CRT population with a BMI <25.[46] Therefore, the FAO/WHO/UNU (for BMI<30) or the Harris and Benedict equation (for BMI >30) seem to be the best prediction equations for calculating REE, until a population specific formula for calculating REE in HNC patients has been developed. All respondents reported calculating total energy expenditure by multiplying REE with 1.3-1.5 (physical activity level and illness rate), which is in line with general guidelines for cancer patients.[30,47]

Some variations in calculating protein requirements were observed. Although most dietitians (77%) use 1.2 to 1.5 gram protein/kg bodyweight, which is also used for malnourished patients[48], the optimal protein requirement for cancer patients has not yet been determined.[33] Recommendations vary between 1.0 and 2.0 gram protein/kg bodyweight per day depending on disease stage, type of treatment and complications.[33,49] There is some evidence that protein requirements can be even higher as 1.7 gram /kg bodyweight in patients receiving combination therapy.[50]

Although most dietitians (76%) participating in this survey reported ending dietary treatment shortly (0 to 6 months) after CRT, it is known that late toxicity rates of CRT are considerable. For instance, van den Berg reported that as few as 15.6% of HNC patients were able to eat without restrictions 44 months after treatment and the majority of patients reported to still experiencing a dry mouth and sticky saliva at their late morbidity clinic.[51] Patients with these late toxicities may benefit from long term dietary treatment.

Results of this survey provide a nice overview of dietetic care for HNC in the Netherlands, although it has some limitations. For answering some survey questions, we relied on the judgement of the respondent and we could not verify answers with objective data. Since all are experienced HNC dietitians, we think this would not highly affect our results. However, the number of years of experience in the field of HNC might differ between respondents, but this was not asked in our survey. In the Netherlands, there is no national specialization or training to be a HNC dietitian, which might explain some variation in care between dietitians and centers.

Overall substantial variation was found in nutritional interventions during CRT in the Dutch centers. Previously, Van Overveld et al. assessed variation in quality of head and neck cancer care in the Netherlands.[52] They demonstrated variation was associated with patient characteristics (tumor stage, tumor subsite and performance status) and hospital characteristics (volume of HNC care). Variation in nutritional interventions during CRT is not likely to be influenced by patient characteristics as all CRT patients have advanced disease and a sufficient performance status is usually a prerequisite for CRT treatment. Although we did not assess differences in hospital volume of HNC, this is likely to vary between university hospitals and affiliated centers. This might influence the available dietetic full-time equivalents (FTE's) and thereby the number of scheduled consultations during CRT and length of dietary treatment. Hospital dietetic services in the Netherlands are paid from a fixed hospital budget. This is in contrast to medical specialists who receive budget for every new HNC patient by opening a Diagnose Treatment Combination (DTC).[53] From this case-based budget all hospital services from first consultation until the completion of treatment should be paid, but strangely allied health services do not receive any payment from this DTC. By increasing hospital volume of HNC, the frequency of dietetic contacts and duration of follow up will be lowered as it does not fit available hospital dietetic FTE's. To be able to offer high quality dietetic care in the hospital, payment of hospital dietetic services need to be changed.

For all of the topics assessed in this survey current literature provides some guidance, as discussed above, which can be used in clinical practice. Although available evidence and level of evidence varies, we should be able to develop concise dietetic guidelines for HNC, as has already been done by the British Association of Head and Neck Oncologists (BAHNO) and Clinical Oncology Society of Australia (COSA).[25,26] These guidelines provide guidance on dietetic intervention and frequency of contact and also for prophylactic gastrostomy placement. To create support for and commissioning of these dietetic guidelines in the Netherlands it should be integrated in the Dutch Head and Neck Cancer guidelines which are currently updated. We therefore advise the NWHHT and PWHHT to combine their knowledge and develop multidisciplinary Head and Neck Cancer guidelines, not focusing solely on medical treatment but on multidisciplinary care, including allied health care as has been done by the British Association of Head and Neck Oncologists.

In conclusion, this study shows considerable variation in dietetic practice between the Dutch Head and Neck Oncology Centers. To reduce variation between centers and dietitians, we advise to reconsider the current fixed budget for dietetic services and develop a national training or specialization to become a HNC. Most importantly, we should develop and implement multidisciplinary head and neck cancer guidelines based on the available literature, which provide guidance on dietetic care throughout the whole HNC care process including frequency of contact, nutrition prescription and tube placement.

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Appendix

Supplemental data S1. Questionnaire on dietetic consultations; tube feeding use; tube feeding route; calculation of energy and protein requirements; tube placement and removal policy and end of dietary treatment in patients with LAHNSCC treated with chemoradiotherapy at the Head and Neck Oncology Centers.

<table>
<tr><th colspan="2">Questionnaire</th></tr>
<tr><td>Q.1.</td><td>Are patients with head and neck cancer treated with chemoradiotherapy referred to a dietitian?
a. Yes, they are routinely referred to a dietitian
b. Yes, they are referred upon indication
c. No</td></tr>
<tr><td>Q.2.</td><td>On average, in which frequency are dietetic consultations scheduled for head and neck cancer patients during chemoradiotherapy?
a. Weekly
b. Fortnightly
c. Differs per patient
d. Other, i.e. ....</td></tr>
<tr><td>Q.3.</td><td>How are dietetic consultations mainly scheduled ?
a. By phone
b. Face-to-face
c. Other, i.e.</td></tr>
<tr><td>Q.4.</td><td>What percentage of patients with head and neck cancer uses tube feeding at any moment during chemoradiotherapy treatment at your institution? (please estimate)
a. 0-25%
b. 25-50%
c. 50-75%
d. 75-100%</td></tr>
<tr><td>Q.5.</td><td>Which routes for tube feeding are used in head and neck cancer patients who use tube feeding during chemoradiotherapy at your institution? (please estimate, the sum should be 100%)

<table><tr><th>Route</th><th>Percentage</th></tr><tr><td>Gastrostromy (PEG or PRG)</td><td></td></tr><tr><td>Nasogastric tube</td><td></td></tr><tr><td>Nasoduodenal or nasojejunal tube</td><td></td></tr><tr><td>Sum of total</td><td>100%</td></tr></table></td></tr>
</table>

Q.6.	When a gastrostomy (PEG or PRG) is placed, is this gastrostomy placed prophylactically or reactive? a. Prophylactically in all patients b. Prophylactically upon indication (please clarify indications used) c. Reactive (please clarify indications used) d. Either prophylactically upon indication or reactive (please clarify indications used)
Q.7.	Does your institution have a protocol with indications for gastrostomy placement (either prophylactically or reactive)? a. Yes (please clarify indications used) b. No If yes, could we please receive this protocol?
Q.8.	Which prediction equation in mainly used for calculating energy needs during chemoradiotherapy? a. Harris and Benedict 1918 b. revised Harris and Benedict 1984 c. FAO/WHO/UNU d. Schofield e. 25 kcal/kg/day f. 30 kcal/kg/day g. no prediction equation is used, energy needs are measured indirect calorimetry h. Other, i.e...
Q.9.	What percentage is mainly added to resting energy expenditure for physical activity, stress and thermic effect of food during chemoradiotherapy? a. 30% b. 40% c. 50% d. Other, i.e. ....
Q.10.	Which amount of protein intake is advised during chemoradiotherapy? a. 0.8-1.0 gram/kg bodyweight b. 1.0-1.2 gram/kg bodyweight c. 1.2-1.5 gram/kg bodyweight d. >1.5 gram/kg bodyweight
Q.11.	In case of overweight (BMI >25), which bodyweight is used for calculating the adequate amount of protein intake? a. current bodyweight b. corrected bodyweight (please clarify which weight is used) c. Other, i.e. ....
Q.12.	In case of overweight (BMI >25), which bodyweight is used for calculating energy needs? a. current bodyweight b. corrected bodyweight (please clarify which weight is used) c. Other, i.e. ....

Q.13.	In case of gastrostomy placement, who are involved in gastrostomy removal decision making? (more than one answer allowed) a. dietitian b. oncologist c. radiotherapist d. patient e. Other, i.e. ...
Q.14.	Which indications are used for gastrostomy removal decision making?
Q.15.	Does your institution have a protocol with indications for gastrostomy removal? a. Yes (please clarify indications used) b. No If yes, could we please receive this protocol?
Q.16.	On average, when is the gastrostomy removed ? a. 1 to 4 weeks after finishing chemoradiotherapy treatment b. 4 to 8 weeks after finishing chemoradiotherapy treatment c. 8 to 12 weeks after finishing chemoradiotherapy treatment d. 3 to 6 months after finishing chemoradiotherapy treatment e. >6 months after finishing chemoradiotherapy treatment f. Other, i.e. ...
Q.17.	On average, when is dietary treatment ended? a. At the end of chemoradiotherapy treatment b. Within 3 months after finishing chemoradiotherapy treatment c. 3 to 6 months after finishing chemoradiotherapy treatment d. 6 to 9 months after finishing chemoradiotherapy treatment e. >9 months after finishing chemoradiotherapy treatment f. Other, i.e. ...
Q.18.	What are reasons for ending dietary treatment?

Chapter 3

Indicators for enteral nutrition use and prophylactic percutaneous endoscopic gastrostomy placement in patients with head and neck cancer undergoing chemoradiotherapy

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Abstract

Background: Chemoradiotherapy (CRT) is a major risk factor for malnutrition and dehydration in patients with head and neck cancer. Enteral support is often needed, and a percutaneous endoscopic gastrostomy (PEG) is frequently placed. Specific indicators for PEG placement remain unclear. This study retrospectively determined which factors contributed to enteral nutrition (EN) use and PEG placement in a large patient group to gain insight on potential indicators for PEG placement protocol creation.

Methods: A retrospective chart review of 240 patients with head and neck cancer who underwent CRT in 2012-2015 was conducted. Lifestyle, oncological, treatment and nutritional outcome characteristics were examined and compared between patients who used EN and those who did not, as well as between patients who received a PEG and those who did not.

Results: In total, 195 patients used EN (via PEG or nasogastric tube). Multivariate analysis showed that nodal disease presence (p=.01) and bilateral neck irradiation (p=.01) were significantly related to EN use while increased age (p=.01), nodal disease presence (p=.02), reconstruction extent other than primary closure (p=.02), bilateral neck irradiation (p<.01), and an adapted intake consistency prior to treatment (p=.03) were significantly related to PEG placement.

Conclusion: Important factors for EN usage and PEG placement consideration include nodal disease and planned bilateral neck irradiation. Results from this study in combination with existing literature can be taken into consideration in the design of a PEG placement protocol. A better understanding of predictive indicators to PEG placement should be explored in further prospective studies.

Introduction

Head and neck cancer (HNC) encompasses mainly carcinomas of the oral cavity, oropharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands and are most often of squamous cell origin.[1] In the Netherlands, the incidence of HNC is rising[2], and worldwide, roughly 550,000 new cases are diagnosed each year, making HNC the sixth most common cancer.[1,3,4] HNC is seen more frequently in males, with a male to female ratio ranging from 2:1 to 4:1 depending on tumor location.[1,4,5] Alcohol use, smoking, and human papillomavirus (HPV) are the most important risk factors[1,6], while fruit and vegetable intake has been associated with a reduced risk of HNC.[7] Concurrent chemotherapy and radiotherapy, chemoradiotherapy (CRT), given as primary or adjuvant treatment, is a frequently used treatment regimen in patients with locally advanced squamous cell carcinoma of the head and neck.[8,9]

Common acute side effects of CRT include mucositis, xerostomia, odynophagia, dysphagia, nausea, vomiting, fatigue, and sensory changes. These side effects often reduce nutritional intake, thus inadvertently causing weight loss, dehydration and malnutrition.[10-12] Dysphagia is present in 5%-52% of patients with advanced HNC prior to receiving CRT, depending on tumor location[13] or prior surgery. In addition, patients may already be malnourished when commencing CRT due to tumor-related dysphagia.[14,15] Lean body mass loss in these patients is associated with a decreased functional capacity and a reduced survival rate.[15] Nutritional counseling and intervention are therefore crucial in this patient population, and it has become accepted to use enteral feeding via a percutaneous endoscopic gastrostomy (PEG).[16-18] PEG placement and enteral feeding in patients with advanced stage head and neck cancer receiving CRT is found to be beneficial, safe, and effective in providing nutrition and hydration and allows for minimal interruptions to treatment course.[19,20] Discrepancies remain between studies whether PEG placement increases the risk of long-term dysphagia and feeding tube dependence.[21,22]

Previous studies have identified predictive factors for the necessity of PEG placement following radiation therapy, with or without concurrent chemotherapy, and include male sex, lower body mass index (BMI; <25 kg/m^2), advanced tumor stage, pretreatment swallowing difficulties, increased age (>60 years), concurrent chemotherapy (cisplatin dose ≥200 mg/m^2), and previous surgery.[23-25] To our knowledge, only a few hospitals use decision charts to determine whether a PEG should be placed as indicators for placement remain unclear. Within our institution, physicians decide prior to treatment initiation whether a PEG should be placed based on the condition of the patient and personal experience. This decision is subjective and not yet formalized in a protocol. To see whether more objective indicators could be defined for PEG placement, this study retrospectively determined which factors contributed to PEG placement and enteral nutrition (EN) use in a large patient group. Gaining further insight into these data helps to improve clinical decision making and provides clarity on indicators that could be used in the creation of prophylactic PEG placement protocols for patients with HNC receiving CRT.

Methods

Study design

A retrospective chart review was conducted using electronic patient medical records at the University Medical Center Utrecht (UMCU) in Utrecht, The Netherlands. Ethical approval was obtained and procedures were followed in accordance to national and institutional ethical standards.

Study population

All patients with locally advanced squamous cell carcinoma of the head and neck who commenced primary or adjuvant CRT in 2012-2015 at UMCU were included (n=242). Patients receiving cetuximab

(antibody directed against epidermal growth factor receptor) in combination with radiation instead of standard chemotherapy were not included. Two patients died prior to completion of CRT and were excluded. The total study population consisted of 240 patients. Standard CRT consisted of chemotherapy (cisplatin 100 mg/m^2) administered intravenously on days 1, 22 and 43, and 35 fractions of radiotherapy in 7 weeks, 5 times weekly. Detailed treatment information has been described previously.[26] Cisplatin was initially administered and could be replaced by carboplatin if nephrotoxicity, ototoxicity, or neurotoxicity occurred.

Lifestyle characteristics

Age was determined at the time of CRT initiation. Smoking history was defined as currently smoking or having a history of smoking while alcohol abuse (past or present) was noted when recorded by the physician in the patient's medical chart.

PEG placement and EN

Patients received a prophylactic PEG as deemed necessary. This decision was made by the HNC tumor board. Prophylactic PEG placement is defined as the decision to place the PEG prior to treatment and includes placement of a push PEG, pull PEG, percutaneous radiologic gastrostomy (PRG), or other (surgically placed PEG, percutaneous endoscopic jejunostomy [PEJ]). The actual placement could occur prior to or in the early phases of treatment (during hospitalization for chemotherapy). EN is defined as nutrition support via PEG or nasogastric (NG) tube.

Nutrition status

Patients were counseled weekly by a dietitian during CRT treatment. Percentage of weight loss during treatment was determined using weight at first and last consultation by the dietitian during treatment.

Statistical analysis

Statistical data analysis was carried out using SPSS version 21 (SPSS, Inc, an IBM Company, Chicago, IL) with a significance level of .05. Normality was assessed visually and using the Kolmogorov-Smirnov test. The Student independent sample *t* test was used to analyze continuous variables while Pearson X^2 and Fisher exact tests were used to compare categorical variables. Nonnormally distributed continuous variables were compared using the Mann-Whitney *U* test. Variables that were significant factors to PEG placement and EN use in univariate analysis were then selected for multivariate logistic regression analysis to assess contribution impact on PEG placement. Selected model variables were also tested for multi-collinearity using a variance inflation factor (VIF) > 10.

Results

Patient, oncological, and treatment characteristics

A total of 240 patients were included. Demographic, tumor-related, and treatment characteristics are shown in Table 1. The median (interquartile range [IQR]) population age was 60 (55-65) years, with 158 (65.8%) male patients. Most of the population (184; 83.6%) were current smokers or had a history of smoking, and in 47 (22.8%) patients, an alcohol abuse history (past or present) was noted. Of these patient characteristics, only age was significantly different between the PEG placement groups, as patients with a PEG placed were about 5 years older (p=.02).

Primary tumors of the pharynx (44.6%) and oral cavity (38.8%) were most frequently present. Tumor site significantly differed (p<.01) between both the PEG placement and EN use (via PEG or NG tube) groups. Patients with pharynx or larynx tumors more often received a PEG and/or more often needed EN. Most patients displayed stage T3 and T4 primary tumors, but tumor stage did

not significantly differ between PEG (p=.12) and EN use groups (p=.23). Higher nodal stage was associated with PEG placement (p<.01) and EN use (p<.01).
In total, 108 (45.0%) patients received surgery before CRT, 85 (42.1%) with a PEG in situ and 23 (60.5%) without. Patients with primary closure less often received a PEG (78.3% vs 44.7%), while patients with more extensive reconstruction techniques more frequently received a PEG (Table 1). Most (208; 86.7%) patients completed chemotherapy and received all 3 dosages of either cisplatin or carboplatin. If and when a patient switched to carboplatin during CRT were significantly different (p<.01) between PEG placement groups as more patients switched to carboplatin in the non-PEG placement group. This was also reflected between the EN use groups (p=.01), as less patients switched to carboplatin when EN was used. A total of 205 (85.4%) patients received radiation to the primary tumor or, in the case of adjuvant therapy, to the primary tumor site. This differed significantly (p=.03) between PEG placement groups since in patients in whom a PEG was placed, a larger number of patients receiving radiation to the primary tumor site were seen (87. 6% vs. 73.7%). In addition, significant differences (p<.01) were shown in whether or not the neck nodes received radiation and if this radiation was unilateral or bilateral. Patients in whom a PEG was placed more often received radiation to the neck nodes as well as significantly more (p<.01) bilateral neck node radiations (85.9% vs. 61.1%). Patients who used EN during treatment also received significantly more radiation to the neck nodes (p<.01) and more bilateral neck node radiations (85.6% vs 62.2%).

PEG placement characteristics

In patients in whom a PEG/gastrostomy was placed (n=202), most (148; 76.7%) received a pull PEG. Thirty-six (18.7%) received a push PEG, 6 (3.1%) a PRG, and 3 (1.5%) other. The average (median [IQR]) number of days of PEG in situ was 166 (107-226) with 49 (24.5%) patients who received a PEG prior to initiation of CRT. At the time of data collection, 120 (60.0%) patients had the PEG removed, while 38 (66.7%) of the deceased patients (n=57) died with the PEG in situ. Therefore, in 17% of the patients alive at last follow-up, a PEG-tube was used.

Table 1. Patient, oncological, and treatment characteristics: a comparison between PEG placement and EN use groups.[a]

		PEG placement			EN use		
Parameter	All patients (n = 240)	Placed (n=202)	Not Placed (n=38)	*p*-value	Used (n=195)	Not Used (n=45)	*p*-value
Patient/lifestyle							
Age, median (IQR), y	60 (55-65)	61 (56.5-65.5)	55.5 (48.5-62.5)	**.02**	61 (57-66)	57 (51-64)	.10
Sex, male	158 (65.8)	134 (66.3)	24 (63.2)	.70	126 (64.6)	32 (71.1)	.49
Social status, married/cohabitate	149 (62.1)	125 (61.9)	24 (63.2)	.88	120 (61.5)	29 (64.4)	.87
Smoking history (n=220)	184 (83.6)	156 (83.9)	28 (82.4)	.83	150 (83.8)	34 (83.8)	1.0
Alcohol abuse history (n=206)	47 (22.8)	42 (24.0)	5 (16.1)	.34	43 (25.4)	4 (10.8)	.08
Oncological							
Primary tumor site				**<.01**			**<.01**
Oral cavity	93 (38.8)	76 (37.6)	17 (44.7)		71 (36.4)	22 (48.9)	
Pharynx	107 (44.6)	96 (47.5)	11 (28.9)		92 (47.2)	15 (33.3)	
Nose, inner ear, paranasal sinus	10 (4.2)	4 (2.0)	6 (15.8)		4 (2.1)	6 (13.3)	
Larynx	14 (5.8)	12 (5.9)	2 (5.3)		12 (6.2)	2 (4.4)	
Neck recurrence	4 (1.7)	3 (1.5)	1 (2.6)		4 (2.1)	0 (0.0)	
Unknown primary tumor	12 (5.0)	11 (5.4)	1 (2.6)		12 (6.2)	0 (0.0)	
Synchronous tumors present	10 (4.2)	9 (4.5)	1 (2.6)	1.0	10 (5.1)	0 (0.0)	.22
Tumor stage (n=237)				.12			.23
T0-T2	85 (35.9)	68 (33.8)	17 (47.2)		65 (33.9)	20 (44.4)	
T3-T4	125 (64.1)	133 (66.2)	19 (52.8)		127 (66.1)	25 (55.6)	
Node stage (n=239)				**<.01**			**<.01**
N0	54 (22.6)	34 (16.8)	20 (54.1)		33 (17.0)	21 (46.7)	

	N1	33 (13.8)	31 (15.3)	2 (5.4)		27 (13.9)	6 (13.3)	
	N2	144 (60.3)	130 (64.4)	14 (37.8)		127 (65.5)	17 (37.8)	
	N3	8 (3.3)	7 (3.5)	1 (2.7)		7 (3.6)	1 (2.2)	
	Primary surgery	108 (45.0)	85 (42.1)	23 (60.5)	**.04**	83 (42.6)	25 (55.6)	.13
Reconstruction (n=108)					**.02**			.10
	Primary closure	56 (51.9)	38 (44.7)	18 (78.3)		38 (45.8)	18 (72.0)	
	Predicled flap	6 (5.6)	6 (7.1)	0 (0.00)		6 (7.2)	0 (0.0)	
	Free vascularized transfer	37 (34.3)	34 (40.0)	3 (13.0)		32 (38.6)	5 (20.0)	
	Bone transfer	9 (8.3)	7 (8.2)	2 (8.7)		7 (8.4)	2 (8.0)	
Chemotherapy								
	All (3) dosages received (cisplatin or carboplatin)	208 (86.7)	178 (88.1)	30 (78.9)	.13	166 (85.1)	45 (93.3)	.22
	Switched to carboplatin				**<.01**			**.01**
	Did not switch	174 (72.5)	150 (74.3)	24 (63. 2)		143 (73.3)	31 (68.9)	
	From dosage 1	9 (3.8)	3 (1.5)	6 (15.8)		5 (11.1)	4 (2.1)	
	From dosage 2	29 (12.1)	27 (13.4)	2 (5.3)		27 (13.8)	2 (4.4)	
	Last dosage	28 (11.7)	22 (10.9)	6 (15.8)		21 (10.8)	7 (15.6)	
Radiation								
	Primary tumour (location)	205 (85.4)	177 (87.6)	28 (73.7)	**.03**	171 (87.7)	34 (75.6)	.06
	Neck nodes irradiated (n=195)				**<.01**			**<.01**
	Unilateral	32 (16.4)	25 (14.1)	7 (38.9)		28 (14.4)	17 (37.8)	
	Bilateral	163 (83.6)	152 (85.9)	11 (61.1)		167 (85.6)	28 (62.2)	

EN, enteral nutrition; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy.

[a]Values are presented as number (%) unless otherwise indicated. Statistically significant values ($p<0.05$) are given in bold. N=240, unless otherwise stated.

Nutrition-related characteristics

Weight, EN, and other nutrition-related characteristics are detailed in Table 2. Eighty-seven (43.1%) of the patients with a PEG in situ had used foods and drinks with a consistency that had been adapted to their needs prior to initiation of CRT in comparison to 9 (23.7%) patients without a PEG tube (p=.03). A total of 195 (81.3%) patients needed and used EN during the course of CRT with an average (median[IQR]) of 86 (44-128) days. EN use and average days of EN were significantly different (p<.01 and p=0.01, respectively) between patients who had a PEG placed and those who did not. Nineteen patients (9.4%) who received a PEG did not use EN. A total of 195 (81.3%) patients needed EN either through PEG or via NG tube during treatment. No significant differences were seen between patients who used EN and those who did not. The average percentage weight loss and categorized weight loss prior to and during CRT did not differ between both PEG placement and EN use groups.

Table 2. Nutrition-related characteristics: comparison between PEG placement and EN use groups.[a]

			PEG placement			EN use		
Parameter		All patients (n = 240)	Placed (n=202)	Not placed (n=38)	*p*-value	Used (n=195)	Not Used (n=45)	*p*-value
Adapted intake consistency prior to CRT[b]		96 (40.0)	87 (43.1)	9 (23.7)	**.03**	83 (42.6)	13 (28.9)	.13
EN used during CRT		195 (81.3)	183 (90.6)	12 (31.6)	**<.01**	195 (100.0)	0 (0.0)	-
Days of EN (n=126), median (IQR)		86 (44-130)	90 (46-133)	63 (35-91)	**.01**	86 (44-128)	0 (0.0)	-
Weight loss % prior to CRT (n=235), mean (SD)		5.1 (6.6)	5.3 (6.7)	4.3 (5.9)	.41	5.3 (6.6)	4.4 (6.9)	.46
Weight loss % class prior to CRT (n=199)					.15			.91
	<5%	101 (50.8)	86 (50.9)	15 (50.0)		83 (43.0)	18 (42.9)	
	5%-10%	56 (28.1)	44 (26.0)	12 (40.0)		45 (23.3)	11 (26.2)	
	>10%	42 (21.1)	39 (23.1)	3 (10.0)		36 (18.7)	6 (14.3)	
Weight loss % during CRT, mean (SD)		2.9 (5.7)	2.7 (4.8)	3.1 (4.7)	.62	2.8 (4.7)	2.4 (4.9)	.55
Weight loss % class during to CRT (n=176)					.93			.14
	<5%	107 (60.8)	91 (60.7)	16 (61.5)		87 (58.8)	20 (71.4)	
	5-10%	58 (33.0)	50 (33.3)	8 (30.8)		49 (35.5)	1 (8.3)	
	>10%	11 (6.3)	9 (6.0)	2 (7.7)		8 (5.4)	3 (10.7)	

CRT, chemoradiotherapy; EN, enteral nutrition; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy; -, indicates no *p* value available.

[a]Values are presented as number (%) unless otherwise indicated. Statistically significant values ($p<0.05$) are given in bold. N=240, unless otherwise stated.

[b]Adapted intake consistency prior to treatment includes, ground, minced, liquid or nil per os.

Table 3. Multivariate analysis: baseline, oncological, and nutrition related-characteristics and contribution to PEG placement.[a]

Multivariate Parameter	PEG placement (n = 240, placed = 202)	
	Estimate[b] (95% CI)	*p*-value
Age, y	1.04 (0.99, 1.09)	**.01**
Primary tumor site, pharynx (yes vs no)	1.08 (0.42, 2.77)	.87
Primary tumor site, larynx (yes vs. no)	2.03 (0.32, 12.82)	.45
Node stage (vs N0)	2.94 (1.17, 7.37)	**.02**
Reconstruction (other than primary closure)	2.89 (1.19, 7.01)	**.02**
Bilateral neck node radiation (yes vs no)	5.27 (2.23, 12.43)	**<.01**
Adapted intake consistency prior to CRT[c]	2.72 (1.08, 6.83)	**.03**

CRT, chemoradiotherapy; PEG, percutaneous endoscopic gastrostomy.

[a]Statistically significant values ($p<0.05$) are given in bold. N=240, unless otherwise stated.

[b]Estimate described in terms of odds ratio.

[c]Adapted intake consistency prior to treatment includes, ground, minced, liquid or nil per os.

Multivariate analysis

The PEG placement multivariate analysis (Table 3) showed that increased age, node stage (N1-N3), reconstruction extent other than primary closure, bilateral neck node radiation, and an adapted intake consistency prior to treatment were significantly related to PEG placement. Bilateral neck node radiation increased the odds of PEG tube placement by 5-fold with an odds ratio (OR; 95% confidence interval [CI]) of 5.27 (2.23-12.43; $p<.01$). Multivariate analysis of EN use (Table 4) showed that node stage (N1-N3) and bilateral neck node radiation were significantly related to EN use.

Table 4. Multivariate analysis: baseline, oncological, and nutrition related-characteristics and contribution to EN use.[a]

Multivariate Parameter	EN use (n = 240, used = 195)	
	Estimate[b] (95% CI)	*p*-value
Primary tumor site, pharynx (yes vs no)	1.10 (0.50, 2.44)	.81
Primary tumor site, larynx (yes vs. no)	2.16 (0.40, 11.88)	.45
Node stage (vs N0)	2.83 (1.26, 6.34)	**.01**
Bilateral neck node radiation (yes vs no)	2.61 (1.23, 5.52)	**.01**

EN, enteral nutrition.

[a]Statistically significant values ($p<0.05$) are given in bold. N=240, unless otherwise stated.

[b]Estimate described in terms of odds ratio.

Discussion

To our knowledge, this is the largest retrospective study to date to examine exclusively CRT patients with HNC. This chart review of 240 patients with HNC undergoing CRT showed that patients who had a PEG tube placed were significantly older, more often had pharyngeal or laryngeal tumors, had a higher nodal stage, underwent less primary surgery, had more extensive reconstruction,

less often switched to carboplatin, received radiation to the primary tumor site, and more often received bilateral neck node radiation. Patients who received a PEG also used foods and drinks with a consistency that had been adapted to their needs significantly more often and had a more frequent and longer EN duration. Patients who used EN during treatment more often had pharyngeal or laryngeal tumors, had a higher nodal stage, less often switched to carboplatin, and more often received bilateral neck node radiation.

Univariate analysis results suggest that older age, tumor location (pharyngeal and laryngeal), node stage (N2-3), reconstruction extent, radiation field, and an adapted intake consistency (as an indicator of swallowing or chewing problems upon presentation) may have played a role in the decision making of PEG placement. Tumor location (pharyngeal and laryngeal), node stage, and radiation field may influence need for EN during treatment. Independent variables for PEG placement found through multivariate analysis include a higher age, presence of nodes, extensive reconstruction surgery, bilateral neck node radiation, and an adapted intake consistency prior to treatment.

Interestingly, primary surgery was found significantly more often in patients without PEG placement. Similar results were found in a recent study by Yang et al. in a population of 192 patients with HNC.[25] These results may be influenced by tumor stage, as patients with locally advanced tumors and/or nodal disease are frequently irresectable and therefore receive CRT as the primary treatment.[26]

In line with previous research comparing PEG placement in patients with HNC[25], tumor location (especially pharynx) was shown to be significantly different between the PEG placement groups. This was not reflected in the multivariate analysis. This may be caused by the fact that in patients with oral cancer, surgery is usually the primary treatment while CRT is mainly used as adjuvant treatment through which these patients will frequently have the morbidity of 3 treatment modalities, including previous (extensive) surgery when CRT is indicated. An increased nodal stage was found in patients in whom a PEG was placed and in patients who used EN. An advanced tumor stage has previously been found related to PEG placement and EN need[25], but this was not reflected within the present cohort. This may be because only CRT patients were assessed, who typically have a higher tumor stage or more advanced disease state in comparison to patients with HNC receiving surgery or radiation alone.[26] The variation in tumor stage was in turn smaller than that in comparable studies, potentially leading to the nonsignificant difference found.

To our knowledge, reconstruction after primary surgery and switch of chemotherapy type have not been assessed in previous studies. Results suggest that more invasive reconstruction surgeries (ie, pediculed and free vascularized flaps or bone transfer) contribute to PEG placement when adjuvant CRT is indicated based on adverse outcomes of histopathological examination of the surgical specimen. This may be explained by the fact that more extensive reconstructions have a larger impact on swallowing function and efficacy.[27] This is associated with a higher need for nutrition support due to dysphagia and an increased adapted intake consistency at the start of CRT.[28] Typically, more extensive surgeries require more extensive reconstructions and are associated with a larger tumor size. This is again previously shown to be associated with a higher rate of PEG placement.[25]

Patients with a PEG in situ and patients who used EN seem to switch less often to the chemotherapy carboplatin. This suggests that patients using EN are more likely to complete planned treatment.

It cannot be concluded in the present cohort that patients with a PEG or using EN were better nourished, as a significant difference in weight loss was not observed. Current literature does show this trend and suggests that minimizing weight loss during CRT may improve treatment tolerance and completion rate.[29,30] On the other hand, it can be anticipated that due to feeding via a PEG, patients maintain weight equally well in comparison to patients not anticipated to need EN and therefore not selected for PEG placement. This may suggest that the multidisciplinary team accurately selected patients for PEG placement. Results show that significantly more patients with a PEG in situ had radiation to the primary tumor or original primary tumor site when CRT was used as

adjuvant treatment. Significantly more of these patients also received radiation to the neck nodes, especially bilaterally. A prominent side effect of radiation therapy is dysphagia, as radiation to the neck region causes damage to the soft tissue. This damage is increased if the radiation to the neck nodes occurs bilaterally, therefore putting patients at a higher risk for needing nutrition support or EN.[31] More patients with a PEG in situ had an adapted intake consistency prior to CRT, meaning consumption of a ground or liquid diet upon presentation. This may indicate pretreatment dysphagia or chewing complications due to the nature of disease or prior surgery, which seems to contribute to PEG placement.[25] The significant differences found in EN use during CRT and length of EN use (in patients in whom PEG was placed) can be explained by the fact that the PEG placement group may have had a higher chance of receiving EN due to the PEG in situ. In terms of EN use during CRT, results show discrepancies between physician recommendation regarding placement and actual patient need. Nineteen patients had a PEG placed but did not use EN, while 12 patients who did not have a PEG placed, needed EN.

These results do raise questions regarding the risks and costs of unnecessary PEG placement and reinforces the fact that concrete protocols using indications for PEG placement need to be implemented. Although feeding via a NG or PEG tube has been found equally effective in limiting short-term weight loss[32], each feeding route comes with advantages and disadvantages. Literature shows that patients with HNC with a PEG in place have significantly less weight loss than those without. On the other hand, it has been suggested that PEG tube use increases risk of long-term dysphagia and feeding tube dependence, but discrepancies remain.[21,22] Evidence does show that PEG placement provides a better quality of life to patients, decreases hospital admissions, and minimizes treatment interruptions.[19,20,22,32] Information regarding PEG complications was not collected in the present study, and therefore specific conclusions regarding reasons for unused PEGs cannot be made.

Weight loss, especially lean body mass loss, is very common in patients with HNC undergoing CRT, as previous research has demonstrated that 55% of patients with HNC lose 10% body weight or more.[16,33] Critical weight loss is associated with increased complications, decreased tolerance to surgery and CRT, and a poorer prognosis, clinical outcome and quality of life.[34] Published research typically shows that patients with a PEG in situ have significantly less weight loss during CRT than those without.[30,35] The present analysis did not show a significant difference in weight loss between PEG groups, as mean weight loss during CRT was 2.7% in patients with a PEG in situ and 3.1% in patients without a PEG. On the other hand, this similar weight loss between groups suggests that patients were appropriately selected for PEG placement in our institution. The weight loss shown in this cohort is much smaller than the weight loss during treatment demonstrated in comparable studies for patients with and without PEG placement, as Chen et al. found significant weight losses of 8% and 14%, respectively, and Lewis et al. had figures of 4.3% and 10.5%, respectively.[30,35] The small percentage of weight lost in both groups may also be due to the frequent dietitian counseling that patients received, as significantly less therapy-related weight loss has been shown when dietary counseling is involved.[36-38] Dietitian counseling in comparable studies was not reported. Previous research within our institution examining outcomes and toxicity of CRT did find that starting EN with use of a PEG in the early phases of treatment seemed to lead to significantly less weight loss.[26] From 1998- 2002, the median weight loss during treatment was 8.5% (reactive PEG placement)[26], while 4.3% (prophylactic PEG placement) was reported from 2008-2010.[39] This study found an average weight loss during treatment of 2.9%, which suggests an improvement in practices regarding feeding.

Strengths of this study include the large population size and the fact that radiation to the neck nodes (bilateral vs unilateral) and switch to carboplatin was assessed, which is unique in comparison to similar studies. Limitations include the retrospective design of the study, which can lead to selection bias and inter-healthcare provider recording bias. EN use may also be present bias as patients with

a PEG may have received EN sooner than those without. Information regarding tumor recurrence or previous cancer therapy was not collected, and therefore nutrition intake complications associated with prior tumor or treatment were not taken into consideration and may increase the need for PEG placement. In addition, weight loss post-CRT was not assessed; therefore, long-term weight consequences of PEG placement could not be evaluated.

The aim of this retrospective chart review was to determine which factors contribute to the selection of PEG placement to provide insight and clarity on indicators that could contribute to a PEG placement protocol within our institution. Significant results between PEG placement and EN use groups reflect what was done within the present patient cohort.

The existing Royal Brisbane and Women's Hospital Swallowing and Nutrition Management Guidelines for patients with HNC define a high-risk group for PEG placement and need.[40] The guidelines are based on evidence and expert opinion and experience from the in-hospital head and neck clinic multidisciplinary team.[41] The indicators used to define high-risk patients include oral/oropharyngeal tumors and bilateral CRT, nasopharyngeal/hypopharyngeal/unknown primary tumor and CRT, or severe malnutrition at presentation, defined as weight loss of 10% in 6 months, or a BMI <20 kg/m^2 with unintentional weight loss of 5%-10% in 6 months. Using these validated high-risk indicators on our population sample, 75.8% would require placement of a PEG, which is less than the actual 84.2% who received a PEG. This shows the need for a balance between indicators found in the present study and existing literature.

Based on the contributing factors to EN usage and PEG placement found in this study, in combination with existing literature, it is suggested that the following indicators be taken into consideration in the creation of PEG placement protocols:

- Advanced tumor (T3-T4) and node (N2-N3) stage in combination with expected or planned treatment (CRT and bilateral neck node radiation field),
- Dysphagia or chewing complications (adapted intake consistency) prior to start of CRT,
- Severe pretreatment malnutrition.

Age of patient could also be taken into consideration as older patients (>60 years) may have a higher chance of needing nutrition support during therapy.

As research clearly demonstrates beneficial effects of prophylactic PEG tube placement in selected patients with HNC,[18,30,35,42,43] this study provides insights into protocol development of indicators for prophylactic placement decision making, based on current PEG tube use.

Further research is needed to gain a better understanding of prediction criteria to EN use and PEG placement to validate and support concrete indicator creation, as well as to examine the sensitivity and specificity of proposed indicators. A prospective study within our institute is anticipated.

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Chapter 4

Prediction model for tube feeding dependency during chemoradiotherapy for at least four weeks in head and neck cancer patients: a tool for prophylactic gastrostomy decision making

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Abstract

Background and aims: Chemoradiation and bioradiation (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often comes with high toxicity rates, interfering with oral intake and leading to temporary tube feeding (TF) dependency. High-quality scientific evidence for indicators of prophylactic gastrostomy insertion is not available. The aim of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks.

Methods: Four-hundred-fifty LAHNSCC patients receiving CRT/BRT with curative intent between 2013 and 2016 were included in the study. Primary outcome was TF-dependency for four weeks or longer. Patient, tumor, and treatment characteristics were extracted from the medical records and their effects on the use of TF were analyzed using univariable and multivariable analysis. The prediction model was internally validated using bootstrapping techniques.

Results: Sixty-five percent (294/450 patients) required TF for four weeks or longer. Variables included in the model were: body mass index and adjusted diet at start of CRT/BRT, percentage weight change at baseline, World Health Organization performance status, tumor subsite, TNM-classification, CRT/BRT, mean radiation dose on the contralateral submandibular and parotid gland. The corrected Area Under the Curve after internal validation was 72.3%, indicating good discriminative properties of the prediction model.

Conclusions: We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.

Introduction

The current treatment with curative intent for patients ≤70 years with stage III and IV Locally Advanced Head and Neck Squamous Cell Carcinoma (LAHNSCC) consists of primary or adjuvant radiotherapy (RT) with concurrent radiosensitizing systemic therapy (cisplatin, carboplatin or cetuximab).[1-4] Side effects of this chemo or bioradiation therapy (CRT/BRT) protocol include, among others, mucositis[5], xerostomia, sensory changes/taste distortion, pain, dysphagia, and nausea and vomitus.[6,7] These side effects may contribute to reduced oral intake and consequently weight loss during and after CRT/BRT[5-8], resulting in worse functional and oncological outcomes.[9-12] Maintaining body weight leads to improved therapy tolerance, reduced risk of complications and therapy delay, increased response rate[13], and higher survival rate.[14] When oral intake is insufficient to meet protein and energy requirements, tube feeding (TF) is required.[15,16] TF can be administered by means of a nasogastric tube (NGT) or a percutaneous radiologic or endoscopic gastrostomy (PRG or PEG). Current guidelines recommend gastrostomy insertion, not NGT, when TF is expected to be required for at least four weeks.[13,17,18]

Currently, there is a lack of consentient directives, leading to various policies for tube insertion in CRT/BRT patients in different institutions. Prophylactic gastrostomy insertion has been the subject of debate, because prophylactic TF in all patients might lead to increased long-term dysphagia, considering the "use it or lose it" principle with respect to swallowing structures.[19-21] Moreover, gastrostomy insertion is not a risk-free procedure with complication rates of about 3.3-19%[22,23] and between 9-47% of the prophylactic gastrostomies are never used.[24,25] Therefore, gastrostomies should not be placed prophylactically in every individual, but only upon indication as stated in the Dutch Head and Neck Cancer Society (DHNCS) guidelines.[26] However, this indication has not been described properly due to a lack of scientific evidence.

Previous studies[24,27] identified predictive factors for prophylactic gastrostomy placement and TF during CRT/BRT but failed to develop a strong prediction model. More recently, a prediction model for identifying CRT/BRT patients at risk for long-term (>90 days) tube dependency was presented.[28] By using a model only focusing on long-term TF-dependency, a large proportion of patients requiring TF due to acute toxicities remains unidentified: 68-81% of the patients require TF during CRT/BRT[6,24,28] compared to 20-45% at three months after treatment.[20,24,29]

The purpose of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks.[26]

Patients and methods

Subjects and study design

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. Data were collected in patients with LAHNSCC starting CRT/BRT in Maastricht University Medical Center (MUMC+) and the University Medical Center Utrecht (UMCU) between January 1st 2013 and December 31st 2016. Patients received primary or adjuvant RT combined with either cisplatin, carboplatin or cetuximab with curative intent. Exclusion criteria were histology other than squamous cell carcinoma, esophageal tumors, bilateral resection of the submandibular glands because RT dose on submandibular glands cannot be calculated here, early termination of RT, TF-dependency since surgery, patients refusing TF despite significant malnutrition, and age under 18 years. Part of the UMCU cohort has been described previously.[24] Figure 1 shows the inclusion flowchart.

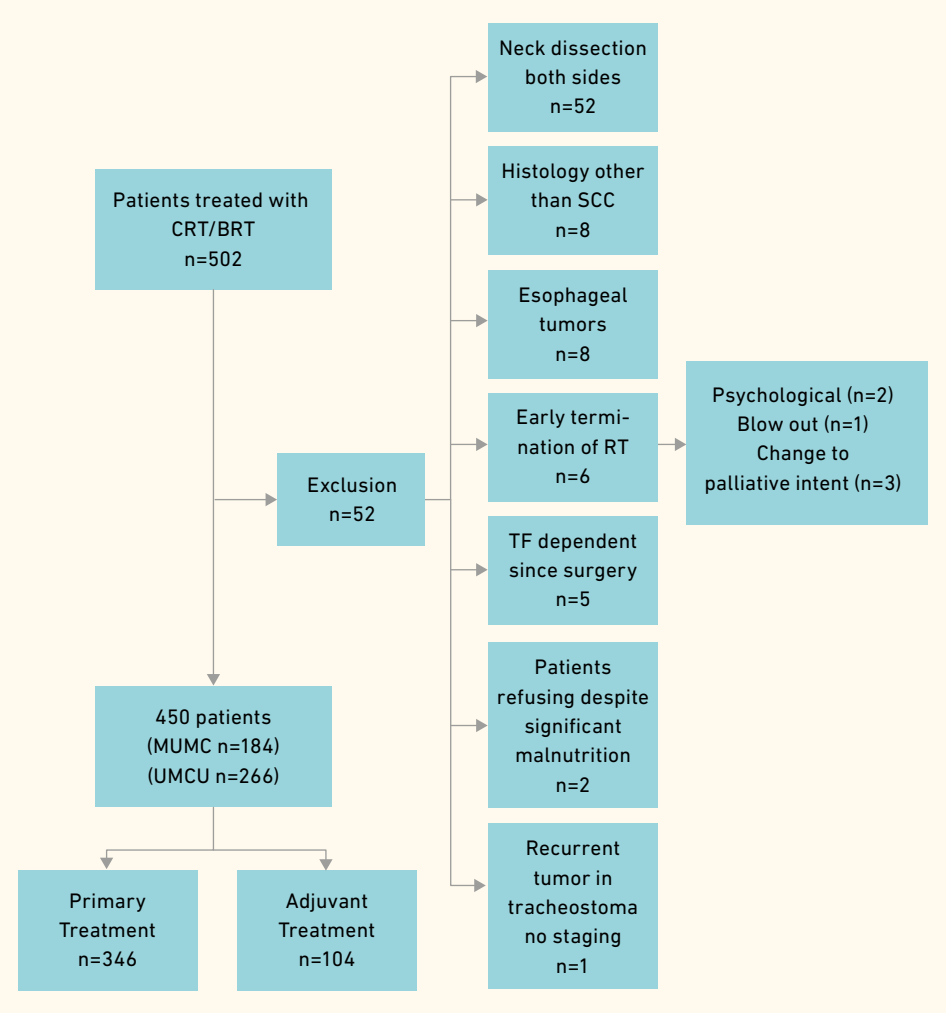

Figure 1. Flowchart of inclusion

Oncological treatment

Cisplatin was administered intravenously on days 1, 22, and 43, in doses of 100 mg/m^2 [3,30] to patients without significant cardiovascular or renal disease, neuropathy or hearing impairment. In case of significant side effects during cisplatin treatment, radiosensitizing systemic therapy was either completely ceased or replaced by carboplatin (dose: area under curve (AUC) 5) for the remaining cycles. Cetuximab was indicated in patients having a contraindication for cisplatin. For cetuximab, a loading dose of 400 mg/m^2 was administered intravenously one week before RT initiation, followed by 250 mg/m2 weekly during RT.[2] RT was administered using intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) and applied five times per week for seven weeks, in 35 daily fractions of 2 Gy to a total dose of 70 Gy. Patients on cetuximab received 30 daily fractions of 2.3 Gy to a total dose of 69 Gy or accelerated fractionated RT twice daily in the final week of IMRT with a total dose of 68 Gy in 34 fractions. Patients undergoing adjuvant CRT received a total dose of 66 Gy in 33 fractions concurrent with cisplatin.

Primary endpoint and tube feeding policy

The primary endpoint of this study was the use of TF for at least four weeks during CRT/BRT or within 30 days after CRT/BRT completion. The four-week cut off point was based on the Dutch national dietary guidelines, recommending gastrostomy insertion as being superior to NGT when TF is required for a period of four weeks or longer.[31,32]

According to the Dutch guideline on malnutrition[32], patients were initially recommended to use oral nutritional supplements or TF in addition to oral intake when 50-75% of the calculated nutritional requirements were met. When oral intake was less than 50% of the calculated nutritional needs, without rapid improvement of oral intake, full TF was indicated, supplemented with any feasible and safe oral intake.[33] Patients were advised to remain on oral intake as much as possible in order to maintain swallowing function.

Potential predictors

Potential predictors were preselected based on clinical reasoning and evidence of previous research. We preselected patient's age[34-38], gender[29,37], tobacco[39], and alcohol use, body mass index (BMI)[40,41], weight loss [42,43], and texture modified diet at baseline (as indicator for dysphagia)[29,37,42], in which baseline is considered right before treatment initiation, World Health Organization performance status (WHO PS)[44-46], tumor subsite[35,37,41,47,48], tumor stage[35-37,40,42,43,47-51], nodal stage[24,36,37,39,41] (TNM-classification[52]), human papilloma virus (HPV) in situ hybridization (ISH) or P16 expression (surrogate biomarker of HPV infection) of the tumor[34], primary or adjuvant setting[41,44,47], type of radiosensitizing systemic therapy (platinum-based chemotherapy or immunotherapy)[35,39,42-44,47], bilateral neck irradiation[24,49,53], mean RT dose on the contralateral submandibular[44] and parotid gland.[43,44]

Sample size

The inclusion of at least ten events per variable is widely accepted as the sample size rule of thumb for multivariable logistic regression analyses.[54] The least frequent outcome, receiving TF less than four weeks (n=156), was defined as an event. Thus, a maximum of fifteen predictors was considered appropriate for developing a model for the cohort in the present study.

Data collection

Patient data were extracted from electronic medical records. Texture modified diet or the use of tube feeding was used as an indicator for dysphagia. Texture modification includes ground, minced or liquid. This information was collected from questionnaires (e.g. functional oral intake scale) if available or patient reported modifications such as eating bread without crust or mashing food.

Missing data

Only for the variables mean contralateral submandibular and parotid gland dose, missing data were imputed through stochastic regression imputation, based on the following covariates: BMI and weight change at baseline, tumor subsite, tumor stage, nodal stage, p16 expression/ HPV ISH in oropharyngeal tumors, primary or adjuvant setting, CRT/BRT, neck irradiation and mean RT dose on the contralateral submandibular and parotid gland. In case of a midline tumor, the contralateral side was considered the side receiving the lowest mean RT dose.

Statistical analysis

Descriptive statistics were reported as mean and standard deviation or absolute numbers and percentages. Baseline differences between those who received TF for at least four weeks and those who did not were tested using the independent samples t-test and the chi–squared test. A p-value <.050 was considered statistically significant.

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p<.300$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. We used stepwise backward elimination to omit all predictors from the model that did not contribute substantially, using a p-value for selection of .100. The resulting prediction model was subsequently internally validated using bootstrapping techniques. The bootstrap validation yields a shrinkage factor between 0 and 1. The regression coefficients were multiplied by this shrinkage factor to penalize the coefficients which counteracts effects of overfitting. Additionally, the bootstrap validation provides estimates of model performance corrected for optimism (i.e., it gives estimates of model performance in future patients compared to the patients used to develop the model).[55,56]

Model performance was quantified as the model's ability to discriminate between those who will and those who will not develop the need for TF for at least four weeks using the area under the receiver operating characteristic curve and measures of calibration. Calibration is the agreement between predicted probabilities and observed probabilities and was tested using the Hosmer and Lemeshow goodness-of-fit test.[57] A significant p-value would denote significant deviation from good model calibration. In addition, we visually inspected a calibration plot. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM, Armonk, NY) and R version 3.5.1 (R Core Team, Vienna, Austria).[58]

Results

Patient sample

Data of both MUMC+ and UMCU yielded 502 patients from which 450 patients met the inclusion criteria. Patient, tumor, and treatment-related characteristics are shown in Table 1. Mean RT dose on contralateral submandibular and parotid gland was missing in 34% (n=151) and 1% (n=6) respectively. These were statistically imputed as described earlier. In 72% of our total population (n=322) a gastrostomy was placed and six percent (n=26) received a NGT. In total 69% (n=311) of all patients used TF during or within 30 days after completion of treatment with a median duration of 107 days (Interquartile range (IQR) 129). Sixty-five percent (n=294) of the patients used TF for four weeks or longer. The median duration of TF use did not significantly differ between subsites oral cavity or oropharynx or hypopharynx on the one hand versus other or remaining subsites on the other hand: 111 (IQR 143) versus 97 (IQR 96) days respectively (p=.086).

Table 1. Frequency distribution of patient, tumor, and treatment characteristics of the studied population.

Variables	Total oral diet or tube feeding <4 weeks n = 156 (35%)	Tube feeding ≥4 weeks n = 294 (65%)	p-value
Patient characteristics			
Mean age	59.7 ± 7.2	58.7 ± 8.0	.223[1]
Male Female	101 (65) 55 (35)	193 (66) 101 (35)	.848[2]
Tobacco use No tobacco use	138 (89) 18 (12)	256 (87) 38 (13)	.671[2]

Alcohol consumption ≥ 1 per day	91 (58)	166 (57)	
Alcohol consumption <1 per day	65 (42)	128 (44)	.703[2]
BMI at baseline (kg/m^2)	25.4 ± 4.9	23.8 ± 4.6	**.001**[1]
Weight change at baseline(%)	-2.7 ± 6.0	-5.0 ± 7.4	**.001**[1]
Diet at baseline			
No texture modified diet	114 (73)	175 (60)	
Texture modified diet*	42 (27)	119 (41)	**.004**[2]
WHO PS			
0	51 (32)	58 (20)	
1	98 (63)	206 (70)	
2	6 (4)	28 (10)	
3	1 (1)	2 (1)	**.007**[2]
Tumor characteristics			
Tumor subsite			
Oral cavity	40 (26)	54 (18)	
Nasopharynx/sinus	6 (4)	25 (8)	
Oropharynx	58 (37)	125 (43)	
Hypopharynx	24 (15)	37 (13)	
Larynx	20 (12)	34 (1)	
Unknown primary	5 (3)	5 (2)	
Synchronous tumors	1 (1)	8 (3)	
Neck recurrence	2 (2)	7 (2)	.151[2]
Tumor classification (TNM)			
Tx	3 (2)	1 (0)	
T0	4 (3)	11 (4)	
T1	20 (13)	23 (8)	
T2	39 (20)	50 (17)	
T3	31 (20)	77 (26)	
T4	59 (38)	132 (45)	**.033**[2]
Nodal classification (TNM)			
N0	40 (26)	48 (16)	
N1	23 (15)	30 (10)	
N2	87 (56)	205 (70)	
N3	6 (4)	11 (4)	**.025**[2]
Tumor stage			
Stage II	7 (5)	6 (2)	
Stage III	26 (17)	29 (10)	
Stage IV	123 (79)	259 (88)	**.030**[2]
P16 expression			
P16+ oropharynx	30 (19)	49 (17)	
Others	126 (81)	245 (83)	.496[2]

Treatment characteristics			
Primary treatment Adjuvant	112 (72) 44 (28)	230 (78) 64 (22)	.128[2]
Radiosensitizing systemic therapy Platinum (carbo-/cis-) Cetuximab	 111 (71) 45 (29)	 230 (78) 64 (22)	 .095[2]
Neck irradiation Unilateral Bilateral No neck RT	 24 (15) 116 (74) 16 (10)	 21 (7) 259 (88) 14 (5)	 **.001**
RT dose on contralateral submandibular gland (Gy)	34.7 ± 17.2	42.3 ± 14.4	**<.001[1]**
RT dose on contralateral parotid salivary gland (Gy)	15.8 ± 8.8	20.4 ± 8.4	**<.001[1]**
Tube type PEG PRG PEJ surgical gastrostomy NGT No feeding tube	 26 (17) 20 (13) 0 (0) 0 (0) 8 (5) 102 (65)	 159 (54) 114 (39) 2 (1) 1 (0) 18 (6) 0 (0)	 **<.001[2]**

Abbreviations: BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray; PRG, percutaneous radiologic gastrostomy; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; NGT, nasogastric tube. Bold values denote statistical significance at the p<0.050 level.

*Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

[1]Independent samples t-test. [2]Pearson's chi-square test.

Univariable regression analysis output (Table 2) yielded a *p*-value <.300 for the following factors: age, BMI, weight change, texture modified, WHO PS, tumor subsite, tumor stage, nodal stage, primary or adjuvant setting, radiosensitizing systemic therapy, neck irradiation and mean RT dose on the contralateral submandibular and parotid gland. In multivariable regression analysis (table 3), age and adjuvant setting did not yield a *p*-value <.100 and were therefore eliminated from the final model. Tumor stage was not statistically significant in multivariable analysis but was considered clinically relevant and proven in previous studies[37,41,47,50] and was therefore nevertheless included in the model. Figure 2 shows the receiver operating characteristic (ROC) curve of the crude prediction model. The AUC was 74.8% (95% CI = 70.1-79.6%), which indicates good discriminative ability.

Table 2. Results of univariable logistic regression analysis of potential predictors presented in odds ratios and *p* values.

	OR	CI-95%		*p*-value
		lower	upper	
Age (years)	0.984	0.959	1.010	.224
Female (ref) Male	0.961	0.640	1.444	.848
No tobacco use (ref) Tobacco use	0.879	0.483	1.598	.672
Alcohol consumption <1 per day (ref) Alcohol consumption ≥ 1 per day	0.926	0.625	1.372	.703
BMI at baseline (kg/m2)	0.932	0.894	0.971	**.001**
Weight change at baseline (%)	0.951	0.921	0.982	**.002**
Diet at baseline No texture modified diet (ref) Texture modified diet*	1.846	1.208	2.819	**.005**
WHO PS 0 (ref) >0	1.976	1.272	3.072	**.002**
P16 expression Others (ref) P16+ oropharynx	0.840	0.508	1.389	.497
Tumor subsite Others (ref) Oral cavity, oro-, and hypopharynx	0.772	0.487	1.222	.270
Tumor classification (TNM) T0, T1, Tx (ref) T2, T3, T4	1.549	0.898	2.670	.115
Nodal classification (TNM) N0, N1 (ref) N2, N3	1.876	1.243	2.831	**.003**
Treatment setting Primary (ref) Adjuvant	0.725	0.462	1.139	.163
Radiosensitizing systemic therapy Platinum (carbo-/cis-) (ref) Cetuximab	0.686	0.441	1.069	.096

No or unilateral neck irradiation (ref) Bilateral neck irradiation	2.552	1.542	4.223	**<.001**
RT dose on contralateral submandibular glands (Gy)	1.032	1.019	1.046	**<.001**
RT dose on contralateral parotid salivary glands (Gy)	1.072	1.044	1.102	**<.001**

Abbreviations: BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray.

Bold values denote statistical significance at the p<0.050 level.

*Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

Table 3. Results of multivariable logistic regression analysis presented in odds ratios and p values. The shrunk regression coefficients represent the regression coefficients after internal validation yielded a shrinkage factor of 0.87.

	Crude OR (CI-95%)	*p*-value	Crude regression coefficient	Shrunk regression coefficients
Model intercept			-0.661	-0.506
BMI at baseline (kg/m^2)	0.953 (0.910-0.999)	**.045**	-0.048	-0.042
Weight change at baseline (%)	0.966 (0.931-1.002)	.066	-0.035	-0.030
Diet at baseline No modified diet (ref) Texture modified diet*	1.682 (1.034-2.737)	**.036**	0.520	0.452
WHO PS 0 (ref) >0	2.012 (1.235-3.279)	**.005**	0.699	0.608
Tumor subsite Others (ref) Oral cavity, oropharynx, and hypopharynx	0.556 (0.329-0.940)	**.028**	-0.586	-0.510
Tumor classification (TNM) T0, T1, Tx (ref) T2, T3, T4	1.430 (0.766-2.670)	.262	0.358	0.311

Nodal classification (TNM) N0, N1 (ref) N2, N3	1.906 (1.186-3.062)	**.008**	0.645	0.561
Radiosensitizing systemic therapy Platinum (carbo-/cis-) (ref) Cetuximab	0.471 (0.283-0.783)	**.004**	0.753	-0.655
Mean RT dose on contralateral submandibular gland (Gy)	1.017 (1.001-1.034)	**.037**	0.017	0.015
Mean RT dose on contralateral parotid gland (Gy)	1.050 (1.017-1.084)	**.003**	0.049	0.042

Abbreviations: OR, Odds ratio; CI, confidence interval; BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray. Bold values denote statistical significance at the $p<0.050$ level.

*Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

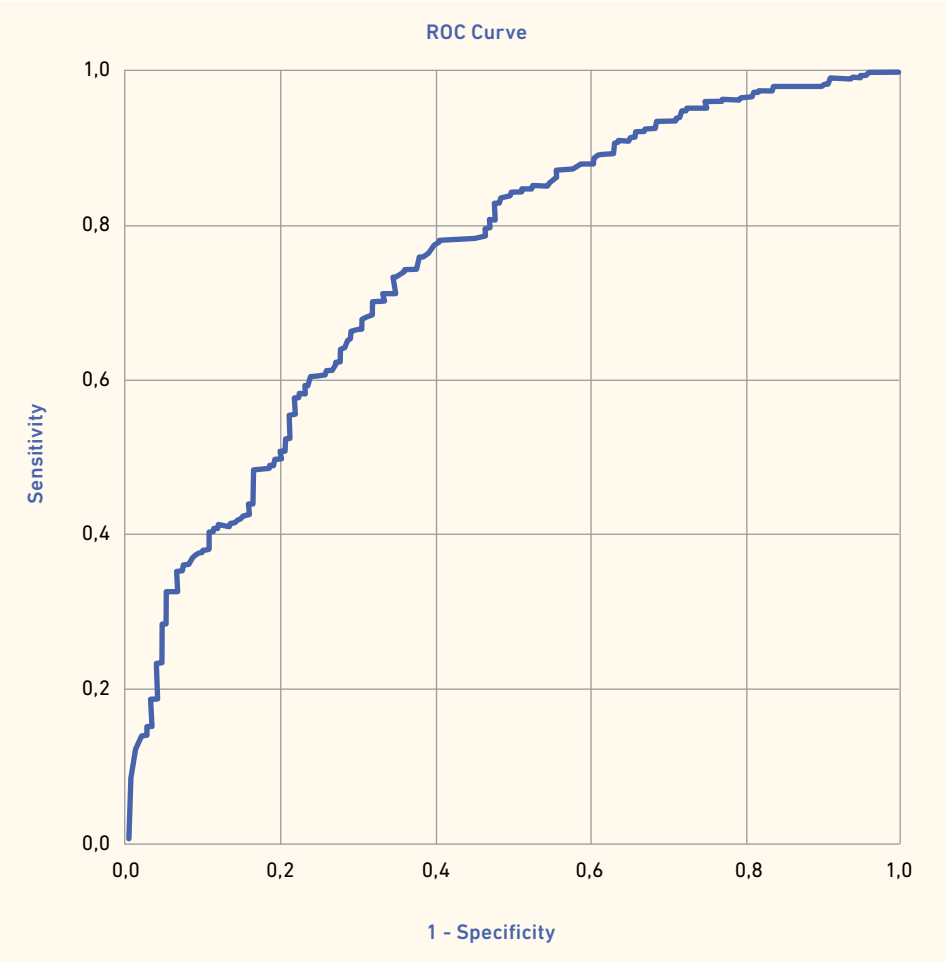

Figure 2. Receiver operating characteristic curve of the prediction model before internal validation (AUC 74,8%; 95% CI 70.1-79.6%), indicating the good discriminative performance of the model.

Internal validation

Internal validation of the model yielded a shrinkage factor of 0.87. The last column of table 3 shows the shrunken regression coefficients and the model intercept.

Furthermore, internal validation gave a degree of optimism of 2.5%, leading to an AUC corrected for optimism of 72.3%. The calibration plot (Figure 3) shows a good agreement between predicted probability of TF for at least four weeks and the observed use of TF. The Hosmer and Lemeshow goodness-of-fit test presented a *p*-value of .844.

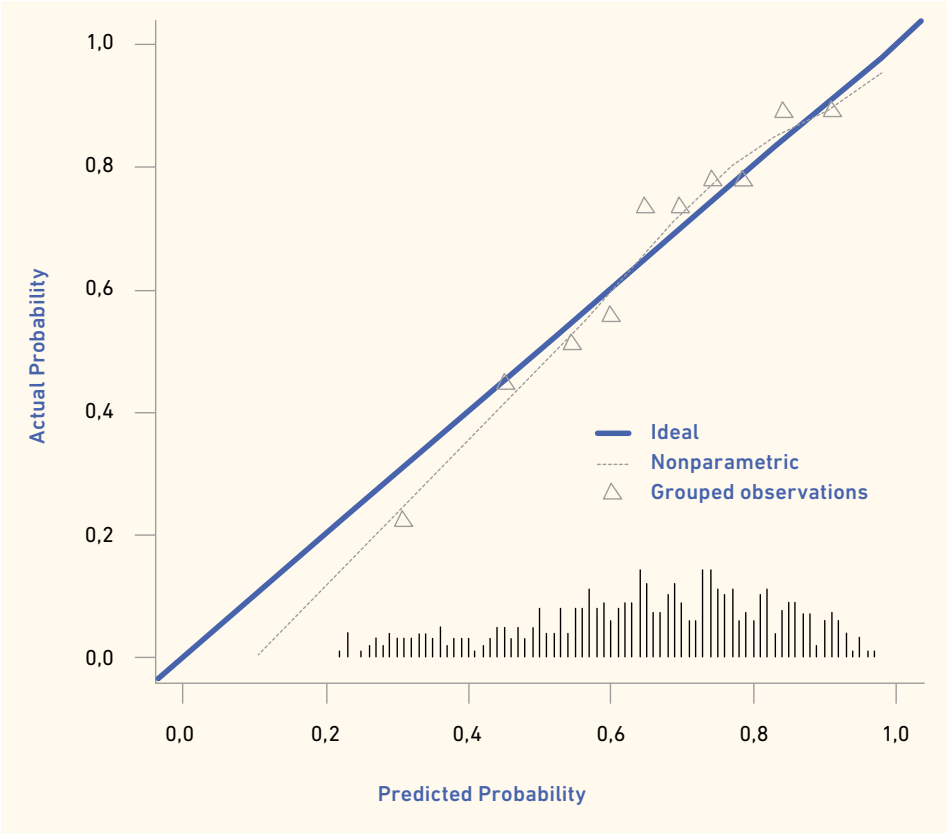

Figure 3. Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.

Formula of the model

The individual probability for TF for at least four weeks can be calculated as:

LP(TF ≥ 4 weeks) = $1/(1 + e^{-LP})$, in which LP is the linear sum of all predictor values multiplied by the regression coefficients, or:

-0.506 -0.042 (BMI) -0.030 (pretreatment weight change) +0.452 (modified diet or TF *[yes = 1]*) +0.608 (WHO PS *[WHO>0 = 1]*) -0.510 (tumor location *[oral cavity, oropharynx and hypopharynx = 1]*) +0.311 (T classification *[T2, T3, or T4 = 1]*) +0.561 (N classification *[N2 or N3 = 1]*) -0.655 (systemic therapy *[Cetuximab = 1]*) +0.015 (mean RT dose on contralateral submandibular gland *[Gy]*) +0.042 (mean RT dose on contralateral parotid salivary gland *[Gy]*).

For example, a patient with a cT3N2bM0 oropharyngeal tumor will receive locoregional RT including bilateral neck irradiation concurrent with cisplatin. She has a BMI of 19.5 kg/m^2, 8% weight loss

at baseline, only eats mashed meals, her WHO PS is 0, and the mean RT dose on the contralateral submandibular and parotid gland will be 36 Gy and 29 Gy respectively.

LP = -0.506 - 0.042 * **19.5** - 0.030 * **-8** + 0.452 * **1** + 0.608 * **0** - 0.510 * **1** + 0.311 * **1** + 0.561 * **1** - 0.655 * **0** + 0.015 * **36** + 0.042 * **29** = 1.487

P(TF ≥ 4 weeks) = 1 / (1+$e^{-1.487}$) = 0.82. This patient has a probability of 82% that she will require TF for a period of four weeks or longer.

Sensitivity and specificity

When choosing 90% as cut off value, the model yields a sensitivity of 9%, specificity of 98%, positive predictive value of 90%, and negative predictive value of 64%. In case of 80% as cut off value, the model yields a sensitivity of 31%, specificity of 93%, positive predictive value of 85%, and negative predictive value of 56%.

Discussion

The purpose of this study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks in LAHNSCC patients treated with CRT/BRT. To our knowledge, this is the first study using TF for four weeks or longer as an outcome measure in a large retrospective cohort (n=450) of LAHNSCC patients receiving CRT/BRT. If the model predicts a high chance of TF for four weeks or longer, prophylactic gastrostomy insertion is advised and preferred over reactive tube insertion, whereby reactive is defined as tube insertion "as required". After internal validation, the model has good accuracy (AUC 72.3%) in discriminating LAHNSCC patients planned for CRT/BRT who will versus will not need TF for at least four weeks and thus would benefit from prophylactic gastrostomy insertion. Our final model includes the following predictors: BMI, weight loss, texture modified diet, WHO PS, tumor subsite, tumor stage, nodal stage, type of radiosensitizing systemic therapy and RT dose on the contralateral submandibular and parotid gland. Previous smaller studies showed largely similar predictors but failed to construct a solid prediction model: BMI <25[40,41], >10% baseline weight loss[42], tumor-related symptoms at diagnosis (e.g. pain and dysphagia)[29,40,42,45,47,59,60], WHO PS[44,46], tumor located in oropharynx[27,41,44,49], tumor stages T3-T4[36,40,42,47-49], nodal stage[24,36,39,41], clinical TNM-stage IV[39,49,61], bilateral neck irradiation[24,49], age>60[61], pack years[39], and surgery prior to CRT/BRT.[41,46] We used texture modified diet as a surrogate marker for dysphagia. Previous studies showed that a higher mean RT dose on the submandibular and parotid glands was associated with dry mouth and sticky saliva, respectively, due to reduced salivary output and a change in salivary composition.[62,63] Remaining salivary production will therefore highly correlate with the RT dose on the spared contralateral salivary glands.[64] To our knowledge, this is the first study including RT dose on the contralateral salivary glands as a possible predictor for TF need combined with other patient and tumor characteristics. Strikingly and unlike other studies, a tumor located in the oral cavity, oropharynx or hypopharynx did not increase the risk of TF for at least four weeks as compared to the remaining tumor subsites in the present patient sample.[35,37,41,47,48] This result might be explained by the chosen cut off point of TF for at least four weeks. The median duration of TF use did not significantly differ between the two subgroups (111 versus 97 days, *p*=.086), but the IQR of TF use was larger in the oral cavity, oropharynx, hypopharynx subgroup (143 vs 96 days) and more outliers towards longer TF duration were seen in these subsite groups. However, long-term TF-dependency was not our primary endpoint and total TF duration could be studied in more detail in future studies. Limitations of our study include its retrospective design, although we do not think this greatly affected our outcomes; the small amount of randomly missing data could be compensated using

statistical imputation. Our cohort was derived from two different university medical centers, both working according to the Dutch Head and Neck Cancer Society guideline, minimizing the possibility of a local therapist effect on group performance or on treatment outcomes. Thereby, this heterogeneity also enables generalization of applicability of the prediction model. Potentially, TF was started earlier in case of early prophylactic insertion, because there were no additional barriers to initiate TF and a better patient compliance was expected compared to reactive feeding tube placement.[65] However, to our experience patients also frequently report barriers initiating TF when the tube was already inserted and ready to use.

Because of a lack of high quality randomized studies, it remains unclear whether prophylactic gastrostomy insertion is superior to reactive insertion. Considering the effect of gastrostomy insertion and TF on weight loss, dehydration, treatment interruptions or change in treatment schedule[24,66], and post treatment health-related quality of life[67,68], prophylactic gastrostomy insertion might be preferred above reactive placement in well selected cases.

Available literature is inconsistent about whether prophylactic gastrostomy insertion increases the risk of long-term dysphagia.[65,67,69-74] The risk of long-term dysphagia can be reduced using a proactive policy of feeding tube removal, guidance by a speech and language pathologist, and swallowing exercise.[75]

The aim of the present prediction model was to support clinicians in obtaining best clinical practice protocols to prevent delayed reactive gastrostomy insertions. Based on the outcome of the prediction model, upfront prediction of TF-dependency can be performed which immediately enables the decision-making on prophylactic tube insertion in patients at risk for TF for four weeks or longer. We are currently working on the external validation of our model, through collaborations with other Dutch head and neck cancer centers. External validation is required to develop and widespread implement this model as a generalizable decision aid for prophylactic feeding tube insertion with consistent cut off values. By combining our data we will preferably develop one tool for the identification of LAHNSCC patients treated with CRT/BRT who need prophylactic gastrostomy placement.

Conclusion

We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.

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Chapter 5

Development and external validation of a prediction model for tube feeding dependency for at least four weeks during chemoradiotherapy for head and neck cancer

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Abstract

Background and aims: Patients who receive chemoradiotherapy (CRT) or bioradiotherapy (BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often experience high toxicity rates interfering with oral intake, causing tube feeding (TF) dependency. International guidelines recommend gastrostomy insertion when the expected use of TF exceeds 4 weeks. We aimed to develop and externally validate a prediction model to identify patients who need TF ≥4 weeks and would benefit from prophylactic gastrostomy insertion.

Methods: A retrospective multicenter cohort study was performed in four tertiary head and neck cancer centers in the Netherlands. The prediction model was developed using data from University Medical Center Utrecht and the Netherlands Cancer Institute and externally validated using data from Maastricht University Medical Center and Radboud University Medical Center. The primary endpoint was TF dependency ≥4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. Potential predictors were extracted from electronic health records and radiotherapy dose-volume parameters were calculated.

Results: The developmental and validation cohort included 409 and 334 patients respectively. Multivariable analysis showed predictive value for pretreatment weight change, texture modified diet at baseline, ECOG performance status, tumor site, N classification, mean radiation dose to the contralateral parotid gland and oral cavity. The area under the receiver operating characteristics curve for this model was 0.73 and after external validation 0.62. Positive and negative predictive value for a risk of 90% or higher for TF dependency ≥4 weeks were 81.8% and 42.3% respectively.

Conclusions: We developed and externally validated a prediction model to estimate TF-dependency ≥4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

Introduction

Side effects of concurrent chemoradiotherapy (CRT) or bioradiotherapy (BRT) often impair oral intake in patients with locally advanced (stage III/IV) head and neck squamous cell carcinoma (LAHNSCC), which may contribute to involuntary weight loss.[1] Weight loss has a detrimental effect on the risk of side effects, therapy tolerance, response rate, and survival.[2-6] In order to maintain sufficient nutritional intake, tube feeding (TF) has to be initiated in 37-74% of LAHNSCC patients undergoing CRT/BRT.[7-9] TF can be administered using a nasogastric tube (NGT) or a percutaneous gastrostomy, either placed radiologically (PRG) or endoscopically (PEG). The advantages of a gastrostomy compared to a NGT are increased physical mobility, less cosmetic disadvantage, and better quality of life. Patients fed via NGT experience more dislodgement and weight loss compared to patients with a gastrostomy tube.[10] Previously, prophylactic gastrostomy insertion (before onset of side effects impairing oral intake) in all LAHNSCC patients undergoing CRT/BRT, used to be common in the majority of the clinical settings.[11-13] However, gastrostomy insertion is not a risk-free procedure; tube-related and infectious complications occur in 6-16%.[14] Therefore, new guidelines recommend that a prophylactic gastrostomy should only be inserted upon indication in LAHNSCC patients treated with CRT/BRT.[15] It is generally agreed that when the expected use of TF exceeds four weeks, gastrostomy insertion should be considered.[16-20] Ideally, patients at risk of TF ≥4 weeks are identified prior to treatment, so they can be provided with a gastrostomy before the onset of side effects potentially complicating insertion, e.g. mucositis (painful insertion), neutropenia (infection risk), and ongoing weight loss (higher complication risk).[21]

Until recently it remained challenging to predict for which patient prophylactic gastrostomy insertion would be appropriate. In a previously published study, we developed and internally validated a prediction model for calculating a patients' individual probability of TF dependency ≥4weeks.[22] New normal tissue complication probability (NTCP) models shed light on the potential additional value of RT doses on the pharyngeal constrictor muscles (PCM) and oral cavity (OC) in predicting swallowing outcomes.[23-25] Therefore, we considered it worth investigating whether these RT parameters could increase the performance of the new model. The present study describes the development and external validation of a prediction model to identify patients at risk for TF dependency ≥4 weeks who would benefit from prophylactic gastrostomy insertion.

Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. We reported this study in accordance with Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[26]

Source of data

The electronic health records of patients treated in four Dutch cancer centers were retrospectively reviewed to compile the development and validation dataset. For every center, data was collected by different independent researchers, in consultation with the executive researchers about the methods of data extraction and any uncertainties about the way of reporting.

Populations

The developmental dataset consisted of LAHNSCC patients treated between 2013 and 2016 in University Medical Center Utrecht (UMCU) and patients treated between 2014 and 2017 in Netherlands Cancer Institute (NCI). The external validation of the model was performed on data

from patients treated between 2013 and 2016 in Maastricht University Medical Center + (MUMC+) and Radboud University Medical Center (RUMC). LAHNSCC patients were included when they were treated with primary or adjuvant concurrent CRT or BRT. Patients were excluded from the study in case of histology other than squamous cell carcinoma, esophageal tumor location, bilateral neck dissection with removal of submandibular glands (RT dose calculation on contralateral gland not possible), refusing TF despite the physician's strong recommendation, premature discontinuation of RT, switch to palliative treatment, or death during oncological treatment. Oncological treatment was previously described in detail.[22,27,28] In brief, patients treated with CRT received cisplatin (100mg/m^2 three weekly or 40mg/m^2 weekly) or carboplatin (1.5 AUC weekly) combined with RT. BRT treatment consisted of a loading dose of cetuximab (400 mg/m^2), followed by a weekly dose of cetuximab (250mg/m^2) combined with RT. RT was given in 33 to 35 daily fractions of 2 Gy (CRT) or 30 to 34 fractions of 2 Gy (BRT). All patients were counseled by a dietitian.

Outcome

The primary endpoint of this study was the use of TF ≥4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. TF was initiated when oral nutritional intake was insufficient in meeting nutritional requirements according to the Dutch guideline on malnutrition[29] as described earlier.[22]

Predictors

The potential predictors of TF dependency we based on the literature and included: age[30], gender[31,32], tobacco use[33], alcohol use, Body Mass Index (BMI) at baseline[34,35], pretreatment weight change[36], texture modified diet at baseline (e.g. ground, minced or liquid)[31], Eastern Cooperative Oncology Group performance status (ECOG PS)[37], tumor site[31,35], T classification[9,31], N classification[31,35] (AJCC 7th edition TNM staging system[38]), disease stage, p16 status[39] (immunohistochemically as a surrogate marker for human papillomavirus (HPV), treatment setting (primary or adjuvant)[35], type of systemic therapy (platinum based or cetuximab)[33] and neck irradiation (non or unilateral versus bilateral).[9] The dosimetric parameters extracted from electronic health records were: mean RT dose (in Gy) to the contralateral submandibular and parotid gland, swallowing muscles (PCM), and oral cavity (OC). The contours for the PCM and the OC were not available in all cases in the radiation treatment planning system and were delineated for the purpose of this study. All organs at risk were contoured according to Brouwer et al.[40] and added to the database.

Sample size

As a rule of thumb, at least ten events should be included for each candidate predictor to minimize the risk of overfitting.[41] The least frequent outcome is defined as an event. In our study, receiving TF <4 weeks was the least frequent outcome and was therefore defined as an event. For the external validation set, at least 100 events and 100 non-events are recommended.[42]

Missing data

Missing data were imputed using stochastic regression imputation with full conditional specification, while considering the following covariates: age, gender, tobacco use, alcohol use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, systemic therapy, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, mean RT dose to the OC, and TF ≥ 4 weeks. Values to be imputed were drawn using predictive mean matching.

Statistical analysis methods

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p<0.30$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. Stepwise backward elimination was used to omit all predictors from the model that did not contribute substantially, using a p-value for selection of 0.10. Model performance was quantified as the model's ability to correctly discriminate between those who will and those who will not develop TF dependency ≥ 4 weeks using the area under the receiver operating characteristic curve (AUC).

For external validation, we applied the model to our validation dataset. For evaluating the performance, the AUC was computed. The Hosmer and Lemeshow goodness-of-fit test was used to assess the agreement between predicted and observed probabilities. A significant p-value would denote significant deviation from a good model.[43] All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, NY).[44]

Results

Patient sample

The development cohort consisted of 409 patients. The validation cohort included 334 patients. Characteristics of both datasets are displayed in Table 1. Of note is the difference between the cancer centers with regard to the tube insertion protocol: In both UMCU and MUMC+ gastrostomies were placed prophylactically in the majority of patients, NCI placed reactive gastrostomies and the RUMC prefers insertion of a NGT, instead of a gastrostomy tube. Details on tube insertion and TF use per cancer center are shown in Supplemental table 1. In the development cohort, 261 out of 409 patients (64%) required TF ≥ 4 weeks, whereas in the validation cohort, 176 out of 334 (53%) required TF ≥ 4 weeks, p=0.003. In the development cohort, 36% (n=148) remained on a total oral diet or used TF < 4 weeks. The risk of overfitting is minimized if no more than fourteen predictors are included in the model. Regarding the 36% without TF or TF <4 weeks, we aimed to compile an external validation set of at least 278 subjects (100/36*100%). With 158 patients (47%) receiving TF < 4 weeks and 176 patients (53%) receiving TF ≥ 4 weeks, our validation dataset meets the criteria of at least 100 events and 100 non-events.

Table 1. Frequency distribution of patient, tumor, and treatment characteristics of the developmental and validation cohort.

	Development cohort UMCU and NCI, n=409[a] (%)	Validation cohort MUMC+ and RUMC, n=334[a] (%)	*p*-value
Patient characteristics			
Age (mean ± SD)	60.2 ± 8.1	58.5 ± 8.1	**0.003**
Male Female	274 (67.0) 135 (33.0)	222 (66.5) 112 (33.5)	0.880
History of tobacco use No history of tobacco use *Missing*	220 (53.8) 39 (9.5) 150 (36.7)	292 (87.4) 42 (12.6) 0 (0.0)	0.383
Alcohol consumption ≥ 1 per day Alcohol consumption <1 per day *Missing*	145 (35.5) 114 (27.9) 150 (36.7)	196 (58.7) 138 (41.3) 0 (0.0)	0.510
BMI at baseline (kg/m^2) (mean±SD)	24.4 ± 4.6	24.9 ± 4.9	0.120
Weight change baseline (%) (mean±SD)	-4.4 ± 7.0	-2.9 ± 5.5	**0.003**
No modified diet at baseline Texture modified diet[b] at baseline	246 (60.1) 163 (39.9)	230 (68.9) 104 (31.1)	**0.014**
ECOG PS 0 ECOG PS 1 ECOG PS 2 ECOG PS 3 *Missing*	142 (34.7) 180 (44.0) 32 (7.8) 2 (0.5) 53 (13.0)	85 (25.4) 224 (67.1) 24 (7.2) 1 (0.3) 0 (0.0)	**<0.001**
Tumor characteristics			
Oral cavity Nasopharynx/sinus Oropharynx Hypopharynx Larynx Unknown primary Synchronous tumors Neck recurrence	85 (20.8) 35 (8.6) 174 (42.5) 56 (13.7) 29 (7.1) 13 (3.2) 9 (2.2) 9 (2.0)	41 (12.3) 29 (8.7) 156 (46.7) 49 (14.7) 54 (16.2) 5 (1.5) 0 (0.0) 0 (0.0)	**<0.001**
Tumor classification (TNM) T0 T1 T2 T3 T4	 20 (4.9) 32 (7.8) 78 (19.1) 101 (24.7) 178 (43.5)	 8 (2.4) 38 (11.4) 64 (19.2) 83 (24.9) 141 (42.2)	0.233

Node classification(TNM) N0 N1 N2 N3	 69 (16.9) 53 (13.0) 269 (65.8) 18 (4.4)	 77 (23.1) 35 (10.5) 213 (63.8) 9 (2.7)	0.106
Disease stage Stage I Stage II Stage III Stage IV	 0 (0.0) 12 (2.9) 47 (11.5) 350 (85.6)	 1 (0.3) 6 (1.8) 49 (14.7) 278 (83.2)	
p16 expression in oropharynx only p16+ p16- *Missing*	 74 (42.5) 92 (52.9) 8 (4.6)	 87 (55.8) 74 (47.4) 5 (3.2)	**0.017**
Treatment characteristics			
Primary treatment Adjuvant	324 (79.2) 85 (20.8)	291 (87.1.) 43 (12.9)	**0.005**
Systemic therapy Platinum-based Cetuximab	 313 (76.5) 96 (23.5)	 264 (79.0) 70 (21.0)	0.413
Neck irradiation Unilateral Bilateral No neck RT	 47 (11.5) 333 (81.4) 29 (7.1)	 22 (6.6) 308 (92.2) 4 (1.2)	**0.040**
Mean RT dose to contralateral submandibular gland (Gy) (mean±SD) *Missing*	44.4 ± 17.4 4 (1.0)	46.6 ± 15.4 0 (0.0)	0.060
Mean RT dose to contralateral parotid salivary gland (Gy) (mean±SD) *Missing*	20.6 ± 9.9 5 (1.2)	21.3 ± 10.7 0 (0.0)	0.279
Mean RT dose to PCM (Gy) (mean±SD) *Missing*	52.6 ± 15.0 7 (1.8)	53.1 ± 11.4 0 (0.0)	0.480
Mean RT dose to OC (Gy) (mean±SD) *Missing*	42.6 ± 16.1 6 (1.5)	39.1 ± 16.3 0 (0.0)	**0.010**
Tube type Gastrostomy Nasogastric tube No feeding tube *Missing*	 256 (62.6) 38 (9.3) 115 (28.1) 0 (0.0)	 132 (39.5) 86 (25.7) 116 (34.7) 0 (0.0)	**<0.001**

Tube feeding use No tube feeding use	274 (67.0) 135 (33.0)	200 (59.9) 134 (40.1)	**0.040**
Tube feeding use ≥ 4 weeks No tube feeding use ≥ 4 weeks	261 (63.8) 148 (36.2)	176 (52.7) 158 (47.3)	**0.003**

Abbreviations: BMI, body mass index; OC, oral cavity; PCM, pharyngeal constrictor muscle; RT, radiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; TNM-classification, tumor, node, metastasis classification according to the 7th edition. Bold values denote statistical significance at the p<0.05 level.

[a]Original data (not imputed) presented as mean (SD) for continuous variables or absolute n (%) for categorical variables.

[b]Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

Model development

Univariable regression analysis revealed $p<0.30$ for the following variables in the development cohort: tobacco use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, and mean RT dose to the OC (Table 2).

Table 2. Results of univariable logistic regression analysis of potential predictors for tube feeding for at least four weeks.

	OR	CI-95%		*p*-value
		lower	upper	
Age (years)	0.988	0.963	1.013	0.341
Male gender	0.947	0.617	1.452	0.801
Tobacco use	1.523	0.751	3.091	0.244
Alcohol consumption one or more per day	0.944	0.554	1.610	0.834
BMI at baseline (kg/m^2)	0.950	0.909	0.993	**0.023**
Baseline weight change (%)	0.943	0.911	0.976	**0.001**
Texture modified diet[a] at baseline	1.981	1.291	3.040	**0.002**
ECOG PS ≥ 1	2.124	1.400	3.223	**<0.001**
Oral cavity, oropharynx, and hypopharynx	0.689	0.419	1.133	0.143
T classification ≥ T2 (TNM)	1.472	0.817	2.652	0.198
N classification ≥ N2 (TNM)	1.984	1.285	3.062	**0.002**
Disease Stage IV	2.205	1.263	3.849	0.005
p16 + oropharynx	0.699	0.424	1.151	0.159
Primary treatment setting	0.765	0.469	1.247	0.283
Cetuximab	0.985	0.612	1.584	0.949
Bilateral neck irradiation	2.315	1.397	3.837	**0.001**
RT dose to contralateral submandibular glands (Gy)	1.022	1.010	1.034	**<0.001**
RT dose to contralateral parotid glands (Gy)	1.046	1.022	1.070	**<0.001**
RT dose to PCM (Gy)	1.027	1.013	1.041	**<0.001**
RT dose to OC (Gy)	1.028	1.015	1.041	**<0.001**

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; OR, Odds ratio; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TNM-classification, tumor, node, metastasis classification according to the 7th edition. Bold values denote statistical significance at the p<0.05 level.

[a]Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

Model specification

In the multivariable regression analysis tobacco use, BMI at baseline, T classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and PCM did not yield a *p*-value <0.10 and were therefore eliminated from the model. Pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, mean RT dose to the contralateral parotid gland and OC were significant predictors of risk of TF use ≥4 weeks. Table 3 shows the regression coefficients for all predictors included in the final multivariable regression model.

Table 3. Regression coefficients in the model for predicting tube feeding use for at least four weeks.

	Regression coefficients	S.E.	*p*-value	OR (95%CI)
Model intercept	-1.419		0.001	
Pretreatment weight change (%)	-0.038	0.020	0.054	0.963 (0.926-1.001)
Texture modified diet[a] at baseline No modified diet (reference) Texture modified diet	0.448	0.247	0.070	1.565 (0.965-2.538)
ECOG PS 0 (reference) >0	0.674	0.232	0.004	1.963 (1.246-3.092)
Tumor site Others (reference) Oral cavity, oropharynx, and hypopharynx	-0.793	0.286	0.006	0.452 (0.258-0.792)
N classification (TNM) N0, N1 (reference) N2, N3	0.646	0.246	0.009	1.908 (1.179-3.088)
Mean RT dose to contralateral parotid gland (Gy)	0.027	0.008	0.038	1.027 (1.001-1.054)
Mean RT dose to the OC (Gy)	0.022	0.013	0.004	1.022 (1.007-1.037)

Abbreviations: BMI, body mass index; CI, confidence interval; ; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; OR, Odds ratio; RT, radiotherapy; S.E., standard error; TNM-classification, tumor, node, metastasis classification according to the 7th edition.[38] Bold values denote statistical significance at the p<0.05 level.

[a]Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

The individual probability for TF ≥4 weeks can be calculated as: P(TF ≥4 weeks) = $1/(1 + e^{-LP})$, in which LP is the linear sum of all predictor values multiplied by the regression coefficients, as shown in Figure 1.
The formula is accessible via the online supplemental material (Supplemental File 1) and invites the reader to use the prediction model in clinical practice, as suggested in Figure 1.

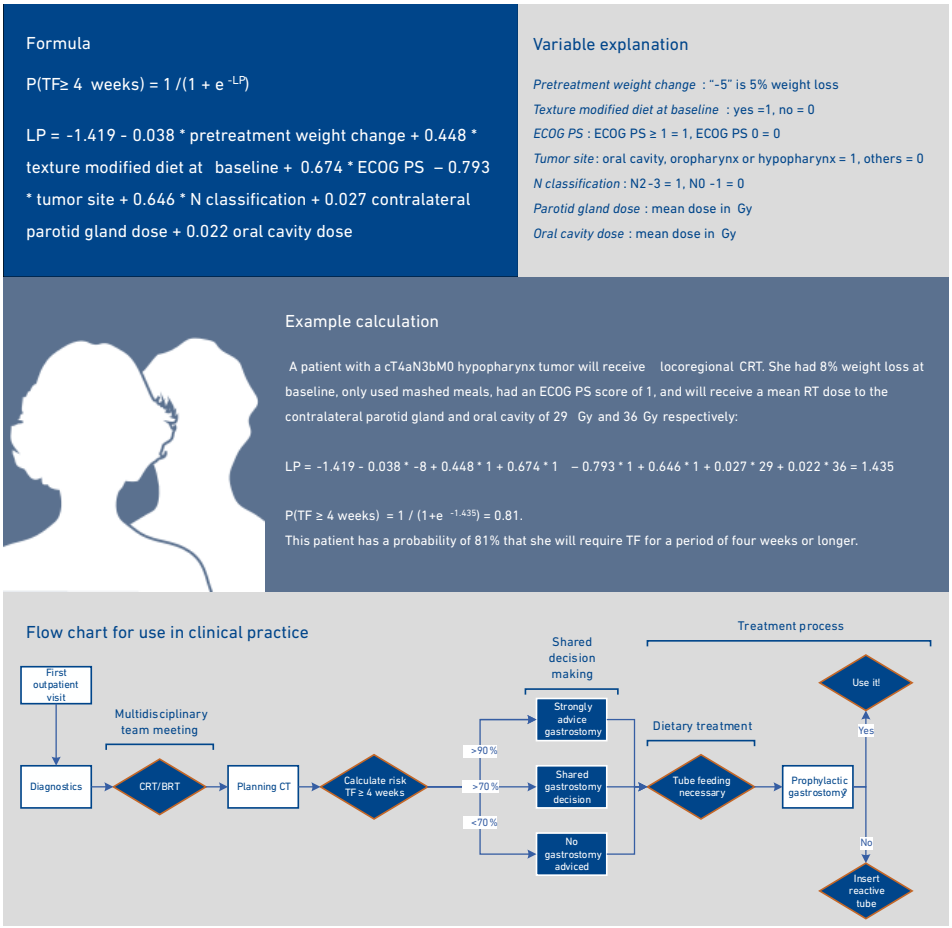

Figure 1. Example calculation and flow chart for the use of the model in clinical practice.

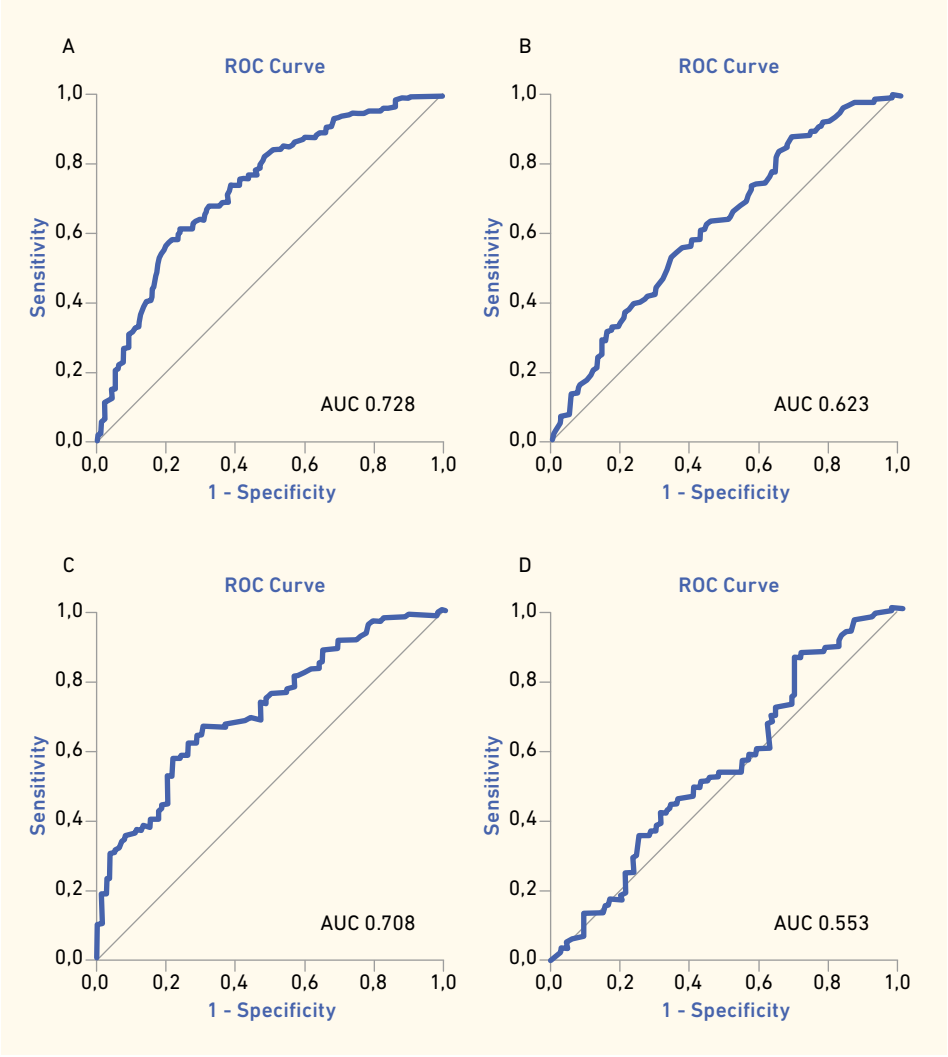

Figure 2. Receiver operating characteristic curve of the prediction model before external validation (A); after external validation in MUMC+ and RUMC combined (B); after external validation in MUMC+ only (C); and after external validation in RUMC only (D).

Model performance

Figure 2a-d and 3 show the performance of the prediction model. The receiver operating characteristic (ROC) curve of the model yielded an AUC of 72.8% before external validation. The Hosmer-Lemeshow test statistics showed a *p*-value of 0.46, indicating a good model calibration. External validation in the combined MUMC+ and RUMC sample showed an AUC of 62.4%. External validation in the MUMC+ sample only showed a considerably higher AUC of 70.8%, whereas external validation in the RUMC sample only showed an AUC of 55.3%. The calibration plot shows a good agreement between predicted probability and the observed use of TF ≥4 weeks.

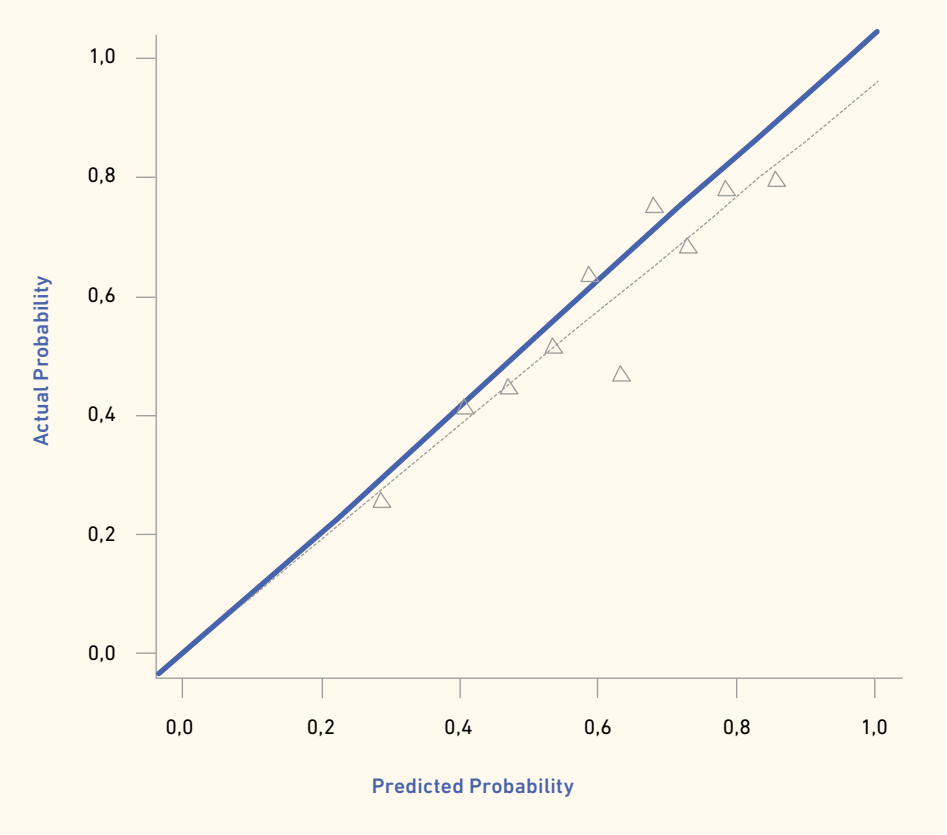

Figure 3. Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.

Sensitivity and specificity

The positive and negative predictive value for a risk of 90% or more of TF dependency ≥4 weeks were 81.8% and 42.3%, respectively. Specifications of sensitivity and specificity at different cut-off values are shown in Supplemental Table A2.

Discussion

In the current study we developed and externally validated a prediction model to identify LAHNSCC patients who are expected to use TF ≥ 4 weeks and thus would benefit from prophylactic gastrostomy insertion. According to our knowledge, this is the first external validation study in a large multicenter retrospective cohort (n=409 and n=334). The model includes the following predictors: pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, and mean RT dose to the contralateral parotid gland and OC.

Remarkably, RT dose to the PCM was not a significant predictor of TF dependency in the model. Previous studies described a significant relationship between increasing RT dose to the PCM and the rising incidence and duration of TF dependency and long-term dysphagia.[24,25,45] An explanation for these different outcomes might be that we used total RT dose to all PCM, while other studies often used RT dose per PCM subtype; superior, middle, and inferior PCM, with dose to the superior

PCM being highly predictive for dysphagia.[25] Although dose to the PCM is not a predictor in our multivariable model, it does not mean that minimizing dose to the PCM in radiotherapy planning is not useful. Indeed our univariable results indicate that dose to the PCM is associated with the risk of TF ≥ 4 weeks. The association between OC dose and TF dependency may be explained by the fact that the OC has an important function in salivation, taste, chewing, and bolus transport. In a recent study by Van de Bosch et al. on the dosimetric effects of organs at risk, the oral cavity was involved in several toxicity-related effects including dysphagia.[46]

Previous studies have also shown that dosimetric variables were statistically dependent, particularly dose to the PCM and OC, the latter being a predictor in our model. Inclusion of such a dependent variable might make the other variable non-significant following correction in the statistical model.[45]

In addition, dysphagia, toxicity-related nausea and severe taste alterations (dysgeusia) causing food aversion can also negatively affect oral intake leading to TF requirement. Up to now, it remains difficult to predict which patients will experience dysgeusia during CRT/BRT.

In contrast to our previously published model, BMI at baseline, disease stage, type of systemic therapy and mean dose to the contralateral submandibular gland were not included into this new model as they did not yield a $p<0.10$ in the multivariable analysis. We included RT dose to the contralateral salivary glands as potential predictors as the remaining saliva production will correlate with the dose on the spared gland.[47] Although one study previously reported mean RT dose to the contralateral submandibular gland to have a predictive value for TF at six months[48], this was not a significant predictor in our model. This could be explained by the different endpoints of both studies: TF initiation during CRT/BRT versus TF dependency at six months. Mean dose to the parotid gland was a significant predictor in accordance with our previously published model. [22]

It should also be noted that potential predictors not included in our final model could still have predictive value. However, the current combination of predictors presented the strongest prediction model.

Performance of the model

The model has good accuracy (AUC on internal validation 0.73 and after external validation 0.62 and 0.71 depending on the composition of the validation cohort), but there was a remarkable difference between the two cancer centers participating in the external validation process. While the AUC did not differ much in the MUMC+ validation cohort, a marked decrease of AUC was seen in the pooled cohort of MUMC+ and RUMC together. Despite adherence to national guidelines on when to initiate TF, individual and institutional preferences in feeding tube insertion policy might have affected the external validity outcome. RUMC had fewer patients receiving TF ≥ 4 weeks compared to the three other centers (43% versus 70%, 61% and 54% for RUMC and UMCU, MUMC+ and NCI respectively). This difference might be explained by the variations in patient characteristics. Also the effect of the cisplatin administration protocol, weekly in RUMC versus three weekly in all other cancer centers, cannot be ruled out as additional explanation for the differences in TF prevalence. High level evidence for best treatment regimen in primary setting in terms of toxicity and survival is lacking.[49,50]

Another remarkable difference that should be highlighted is the significantly lower number of gastrostomy insertions in the validation cohort versus the developmental cohort (39.5% and 62.6%). This is the result of a different policy in the RUMC regarding prophylactic gastrostomy insertion where reactive NGT insertion is preferred with only 5% of the RUMC patient sample receiving a gastrostomy.

To our clinical experience, prophylactic gastrostomy insertion could lower the threshold for TF initiation. Studies have shown that reactive NGT insertion is associated with a shorter duration of TF use.[10,51,52] This was also reflected in our study population, as the median TF duration in RUMC (reactive NGT) was 23 days versus 85 and 82 days in UMCU and MUMC+ respectively (prophylactic

gastrostomy). It has been argued that (prophylactic) gastrostomies might be related to long term swallowing dysfunction based on the 'use-it-or-lose-it' paradigm of dysphagia rehabilitation, but the literature remains controversial on this side effect.[53-56] The present study did not evaluate long-term swallowing function after CRT/BRT with or without gastrostomy insertion. Differences in feeding tube policy between the cancer centers, as shown by our nationwide survey[57] could be considered a limitation of the current study. However, we decided to accept this heterogeneity in patient populations to validate our model, since this reflects real world inter-center heterogeneity. An explanation for the diverse policies is the existence of regional differences in hospital logistics, but also differences in the sociocultural background of patients and health professionals and the lack of high-quality evidence in the literature regarding the indication for prophylactic gastrostomy insertion. These findings emphasize the challenge of standardizing gastrostomy insertion management nationwide. This study was not designed to investigate the best approach for TF initiation and feeding tube insertion. Differences in the effect of reactive versus prophylactic feeding tube insertions on oncological therapy outcome, weight loss and quality of life cannot be evaluated here.

Generalizability of the model (external validity)

We suggest that in case the model estimates a probability >90% for TF dependency, a prophylactic gastrostomy insertion should be recommended. In case of a probability >70%, a prophylactic gastrostomy insertion should be discussed with the patient. For patients' comfort and to reduce the risk of side effects, we recommend prophylactic gastrostomy insertion in high-risk patients before or within the first two weeks of oncological treatment when mucositis and neutropenia have not developed yet.[58,59] This data-driven model indicates that in case of a probability >90%, approximately 18.2% of the patients with a prophylactic gastrostomy insertion will not develop TF dependency ≥4 weeks. However, that does not mean that these 18.2% patients do not benefit from a gastrostomy. They may still need TF but for a period <4 weeks or they may use their gastrostomy for supplemental fluid administration to prevent nephrotoxicity. In 57.7% of the patients with a probability <90%, a reactive feeding tube insertion will be necessary.

Conclusion

We developed and externally validated a prediction model to estimate TF-dependency ≥ 4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

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Appendix

Table A1. Frequency distributions per center.

	UMCU n=259 (%)	NCI n=150 (%)	MUMC+ n=183 (%)	RUMC n=151 (%)	*p*-value
Age (mean ± SD)	59.2 ± 7.8	62.0 ± 8.1	58.9 ± 7.7	58.0 ± 8.5	**<0.001**
Male Female	167 (64) 92 (36)	107 (71) 43 (29)	121 (66) 62 (34)	101 (67) 50 (33)	0.561
History of tobacco use No history of tobacco use *Missing*	220 (85) 39 (15) 0 (0)	 150 (100)	166 (91) 17 (9) 0 (0)	125 (83) 25 (17) 0 (0)	0.107
Alcohol consumption ≥ 1/day No alcohol consumption *Missing*	145 (56) 114 (44) 0 (0)	 150 (100)	109 (60) 74 (40) 0 (0)	87 (58) 64 (42) 0 (0)	0.755
BMI at baseline (kg/m^2) (mean±SD)	24.1 ± 4.6	24.9 ± 4.7	24.8 ± 5.1	25.0 ± 4.6	0.133
Weight change baseline (%) (mean±SD)	-5.1 ± 7.6	-3.1 ± 5.5	-2.8 ± 5.8	-3.2 ± 5.0	**<0.001**
No modified diet at baseline Texture modified diet[a] at baseline	155 (60) 104 (40)	91 (61) 59 (39)	131 (72) 52 (28)	99 (66) 52 (34)	0.060
ECOG PS 0 ECOG PS 1 ECOG PS 2 ECOG PS 3	70 (27) 159 (61) 28 (11) 2 (1)	80 (53) 32 (21) 10 (7) 28 (19)	38 (21) 138 (75) 6 (3) 1 (1)	47 (31) 86 (57) 18 (12) 0 (0)	**<0.001**
Oral cavity Nasopharynx/sinus Oropharynx Hypopharynx Larynx Unknown primary Synchronous tumors Neck recurrence	69 (27) 19 (24) 96 (37) 35 (14) 18 (7) 5 (2) 9 (3) 8 (3)	16 (11) 16 (11) 78 (52) 21 (14) 11 (7) 8 (5) 0 (0) 0 (0)	21 (11) 11 (6) 85 (46) 26 (14) 35 (19) 5 (3) 0 (0) 0 (0)	20 (13) 18 (12) 71 (47) 23 (15) 19 (13) 0 (0) 0 (0) 0 (0)	**<0.001**
T classification (TNM) T0 T1 T2 T3 T4	 12 (5) 21 (8) 50 (19) 61 (24) 115 (44)	 8 (5) 11 (7) 28 (19) 40 (27) 63 (42)	 5 (3) 20 (11) 38 (21) 46 (25) 74 (40)	 3 (2) 18 (12) 26 (17) 37 (25) 67 (44)	0.834
N classification (TNM) N0 N1 N2 N3	 51 (20) 36 (14) 161 (62) 11 (4)	 18 (12) 17 (11) 108 (72) 7 (5)	 37 (20) 15 (8) 125 (68) 6 (3)	 40 (26) 20 (13) 88 (58) 3 (2)	0.065

Disease stage Stage I Stage II Stage III Stage IV	0 (0) 10 (4) 31 (12) 218 (84)	0 (0) 2 (1) 16 (11) 132 (88)	0 (0) 3 (2) 22 (12) 158 (86)	1 (1) 3 (2) 27 (18) 120 (79)	0.216
p16 expression in oropharynx p16+ p16-	35 (36) 61 (64)	44 (56) 34 (44)	46 (54) 39 (46)	44 (62) 27 (38)	**<0.001**
Primary treatment Adjuvant	184 (71) 75 (29)	140 (93) 10 (7)	160 (87) 23 (13)	131 (87) 20 (13)	**<0.001**
Systemic therapy Platinum-based Cetuximab	204 (79) 55 (21)	109 (73) 41 (27)	130 (71) 53 (29)	134 (89) 17 (11)	**0.001**
Neck irradiation Unilateral Bilateral No neck RT	31 (12) 199 (77) 29 (11)	16 (11) 134 (89) 0 (0)	11 (6) 171 (93) 1 (1)	11 (7) 137 (91) 3 (2)	**<0.001**
Mean RT dose to contralateral submandibular gland (Gy) (mean±SD)	18.0 ± 7.5	24.7 ± 12.1	21.2 ± 11.5	21.5 ± 9.6	**<0.001**
Mean RT dose to contralateral parotid salivary gland (Gy) (mean±SD)	18.0 ± 7.5	24.7 ± 12.1	21.2 ± 11.5	21.5 ± 9.6	**<0.001**
Mean RT dose to PCM (Gy) (mean±SD)	51.5 ± 16.6	54.5 ± 11.9	52.1 ± 10.5	54.3 ± 12.3	0.075
Mean RT dose to OC (Gy) (mean±SD)	45.0 ± 16.4	38.3 ± 14.8	36.7 ± 17.0	42.0 ± 14.9	**<0.001**
Tube type Gastrostomy Nasogastric tube No feeding tube	193 (74.5) 15 (5.8) 51 (19.7)	64 (42.7) 23 (15.3) 63 (42.0)	124 (67.7) 10 (5.5) 49 (26.8)	8 (5.3) 76 (50.3) 67 (44.4)	**<0.001**
Tube feeding use Yes No	189 (73.0) 70 (27.0)	86 (57.3) 64 (42.7)	118 (64.5) 65 (35.5)	82 (54.3) 69 (45.7)	**<0.001**
Tube feeding use ≥ 4 weeks Yes No	180 (69.5) 79 (30.5)	81 (54.0) 69 (46.0)	111 (60.7) 72 (39.3)	65 (43.0) 86 (57.0)	**<0.001**
Median TF duration in days (IQR)	85 (176)	49 (144)	82 (137)	23 (51)	0.549

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; OC, oral cavity; PCM, pharyngeal constrictor muscle; RT, radiotherapy; TF, tube feeding; TNM-classification, tumor, node, metastasis classification according to the 7th edition.

Bold values denote statistical significance at the p<0.05 level.

[a]Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

Table A2. Sensitivity, specificity and predictive values of the prediction model at different cut-off values for the chance on tube feeding for at least four weeks.

Cut-off value%	Prevalence of TF ≥4 weeks (n, % of total population n=743)	Sensitivity, %	Specificity, %	PPV %	NPV %
95%	5 (0.1%)	1.4	100.0	100	41.5
90%	27 (3.6%)	6.2	98.0	81.8	42.3
85%	64 (8.6%)	14.6	94.8	80.0	43.7
80%	116 (15.6%)	26.5	90.5	80.0	46.3
75%	165 (22.2%)	37.8	83.0	76.0	48.3
70%	224 (30.1%)	51.3	77.1	76.2	52.6

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Chapter 6

Feasibility of a supervised and home-based tailored exercise intervention in head and neck cancer patients during chemoradiotherapy

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Abstract

Objective: Chemoradiotherapy (CRT) for head and neck cancer (HNC) is associated with high toxicity that adversely affects physical functioning, body composition, fatigue, quality of life and treatment outcomes. Exercise interventions during treatment might counteract these negative effects. We therefore assessed the feasibility of an exercise program for HNC patients during CRT.

Methods: Forty patients were offered a tailored 10-week endurance and resistance training with supervised and home-based sessions. Feasibility endpoints were: (1) adherence (main outcome): ≥ 60% attendance; (2) recruitment: ≥ 30%; (3) retention rate: ≥ 85% and (4) compliance rate: ≥ 60%. Physical performance, muscle strength, body composition, quality of life and fatigue were assessed pre- and post-intervention.

Results: Overall adherence was 54%. The recruitment rate was 36%, and the retention rate was 65%. Compliance to the supervised intervention protocol was 66%. Statistically significant decreases were found in mean grip strength, fat-free mass, and clinically relevant deteriorations on several domains of quality of life and fatigue subscales were found.

Conclusion: We conclude that this exercise program for HNC patients during CRT in its current form is feasible for only a minority of patients. We suggest adaptations to improve adherence and retention rates for a definitive multicenter trial.

Introduction

Radiotherapy combined with concurrent chemotherapy (CRT) for locally advanced head and neck cancer (HNC) is associated with high toxicity with a negative impact on physical functioning, body composition, fatigue and quality of life.[1-4] Treatment toxicity contributes to unintentional weight loss, which is a key characteristic of malnutrition. Already at diagnosis prevalence of critical weight loss is substantial (19%) [5], and may increase up to 50%, despite intensive nutritional support.[6,7] Weight loss during HNC treatment is characterized by loss of lean body mass, including muscle mass.[6,8] Loss of muscle mass is associated with a decreased health-related quality of life (HR-QoL), physical decline, increased risk of treatment toxicity, higher complication rates, and lower survival rates in patients with HNC. [2,3,9-12] To maintain or restore muscle mass during and after treatment, an adequate nutritional intake combined with physical exercise are prerequisites.[13] Physical exercise interventions during and after anti-cancer treatment in cancer populations positively affect fitness, fatigue, HR-QoL, and treatment completion rates.[14-16] Moreover, higher levels of physical activity and fitness are associated with prolonged survival in several cancer populations.[17] Most of this evidence is based on studies in patients with breast or colon cancer. Patients with HNC, however, are generally less active compared to other cancer patients: only 30.5% meet physical activity public health guidelines before diagnosis, which further decreases to 8.5% after diagnosis.[2] This sedentary behavior can exacerbate the loss of muscle mass due to decreased muscle activity. Therefore, interventions aiming at improving physical activity and preserving muscle mass are needed.
On average, compared to other cancer patients, the HNC population is older, less educated and has a less healthy lifestyle, with higher tobacco and alcohol consumption.[18] Moreover, there is an increase in HNC caused by human papillomavirus (HPV), with better prognosis and different patient characteristics leading to a more heterogeneous HNC group.[19] Therefore, effects from exercise interventions in other cancer populations may not be generalizable to the HNC population. Pilot studies investigating physical exercise during (chemo)radiation in HNC are limited, have small sample sizes, and mainly focus on efficacy outcomes (e.g., physical functioning and HR-QoL) instead of feasibility outcomes.[20-22] It therefore remains unclear whether patients with HNC will be able to complete an exercise intervention to a sufficient degree for the intended effects to occur during CRT. In a previous study on exercise preferences, only 50% of the HNC patients indicated that they felt being able to participate in an exercise program.[23] The majority preferred to exercise alone, unsupervised, and with flexible scheduling. We therefore developed an exercise program during CRT adjusted to these preferences, incorporating strength and endurance training at moderate intensity, in a combined supervised and home-based setting. All exercises were suitable for training at home and tailored to patients' individual capacity.
The primary aim of this study was to assess the feasibility of this tailored exercise program for HNC patients during CRT. Our secondary aim was to assess changes from pre- to post-intervention in physical performance, muscle strength, body composition, fatigue and health related quality of life (HR-QoL).

Methods

Participants and design

Consecutive patients with locally advanced HNC were recruited at the University Medical Center Utrecht and the Netherlands Cancer Institute, between January 2018 and January 2020. Study inclusion criteria were (1) scheduled to receive CRT; (2) age ≥ 18 years; (3) sufficient Dutch writing and reading skills; (4) Karnofsky Performance status > 60; (5) able to walk ≥ 60 meters without aid, and (6) no contraindication for physical activity. Demographic and medical data were collected by a study-specific baseline questionnaire and chart review. Weekly dietary consultations were

scheduled as part of usual care. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (17-630) and by the Institutional Review Board of the Netherlands Cancer Institute. Written informed consent was obtained from all participants.

Exercise intervention

The exercise intervention consisted of a 10-week combined endurance and resistance training with supervised sessions as well as home-based sessions. The 10-week intervention started, preferably, the week before the start of the 7-week CRT, continued during treatment, and ended 2 to 5 weeks after CRT completion. Due to the short time frame between treatment decision and the start of treatment, the study protocol was adapted six weeks after start of the study, allowing baseline measurements also in the first or second week of CRT. Patients attended one session per week at the hospital, supervised by a physiotherapist (PT). Patients were instructed to perform home-based endurance exercise for six days a week and resistance training three times a week.

The endurance training consisted of 30 minutes moderate-intensity physical activity; 15 minutes brisk walking and another 15 minutes of physical activity of their own choice. Patients were instructed to use the Borg scale (6-20) to rate perceived exertion (RPE) to guide exercise intensity for the endurance training[24], aiming for an RPE between 12 and 15. An activity tracker, the Fitbit Zip (Fitbit LLC, San Francisco, CA), with daily step count was used to motivate patients and provide them with feedback during home-based activities. Individual targets were based on the distance achieved during the 6-Minute Walk Test (6-MWT).

For the resistance training, patients were instructed to perform six exercises three times a week, targeting major muscle groups (arms, legs, shoulders and core) using body weight and elastic bands for resistance. One of the resistance training sessions per week was performed at the hospital. Exercise type and resistance was adjusted to the participants' capacity based on pragmatic 15-RM testing and RPE range 12 to 15. Exercise intensity was increased in steps of 10% if patients exceeded the prescribed 15 repetitions. Likewise, intensity was decreased if patients were unable to complete 12 repetitions or reported worsening of symptoms due to the exercise.

Primary outcome: Feasibility

The primary outcome of this study was the feasibility of the exercise intervention. Feasibility endpoints and accompanying success criteria were based on previous studies [25]: adherence (main outcome): ≥ 60% attendance to the supervised training sessions; recruitment: ≥ 30% of approached patients participating; retention rate: ≥ 85% completing the intervention, and compliance: ≥ 60% exercising according to the protocol. Adherence to the supervised sessions was defined as the number of attended sessions out of the ten offered sessions and was recorded by the physiotherapist. Adherence, recruitment, and retention rates were obtained by keeping a clinical research file. Compliance with supervised exercise sessions was registered by the physiotherapists, and home-based sessions were recorded by patients in an exercise log.

Secondary outcomes

Secondary outcomes included physical performance, muscle strength, body composition, HR-QoL and fatigue. Physical performance was measured with the 6-MWT.[26] Hand grip strength was assessed using the JAMAR dynamometer (Patterson Medical, Warrenville, IL), upper leg and arm muscle strength was assessed by using the Microfet handheld dynamometer (Hoggan scientific, Salt Lake City, UT) according to standardized procedures using the best of three trials on each side for analysis.[27] Functional lower body strength was measured by the 30-Second Chair Stand Test (30-SCST). [28] Body composition was assessed by Bioelectrical Impedance Analysis (BIA) using the Quadscan 4000 (Bodystat Ltd, Douglas, Isle of Man) according to the standard operating procedures [29] in a fasted state for at least two hours. The Kyle equation was used to calculate fat-free mass

(FFM).[30] Fat-free mass index (FFMI) was derived from FFM (kg) divided by height (m) squared (kg/m^2). Baseline measurements of physical performance, muscle strength, and body composition were performed at the hospital and were re-assessed post-intervention (10 to 12 weeks post-baseline). HR-QoL was measured using the EORTC QLQ-C30 and QLQ-H&N35 questionnaires.[31,32] Fatigue was measured using the Multidimensional Fatigue Inventory (MFI).[33] Clinically important differences were defined as a change in scores of at least ten points on the EORTC subscales and two points on MFI subscales. Questionnaires were administered on paper at baseline, midway (5 weeks post-baseline), and post-intervention (10 to 12 weeks post-baseline). Participants who dropped out were asked to provide the main reason for drop-out and to complete the post-intervention assessments. Consecutive participants and non-participants were approached for an interview (until data-saturation was reached) to gain insight into exercise preferences, barriers and facilitators. These qualitative data will be reported in another paper. Data was captured and stored in Castor (Amsterdam, The Netherlands), an electronic data capture system.

Sample size calculation

The aim for our main outcome, i.e., adherence, was at least 60% with a minimal acceptable adherence of 45%. Therefore, a sample size of 37 patients (power of 80%) was needed. For compliance, the same precision applies. With 37 patients, a precision resulting in a one-sided 95% lower-limit confidence interval (CI) of 17.5% (80% power) was estimated.

Statistical analyses

Analyses were performed using IBM SPSS version 26.0 (IBM Corporation, Armonk, NY). Demographic and clinical data were reported as proportions, mean with standard deviation, or median with interquartile range. Feasibility outcomes were described in counts and frequencies with 95% confidence intervals. Paired t-tests were used to examine within-group changes in physical performance.

Within-group mean changes for patient reported outcomes at baseline, midway and post intervention were evaluated using linear mixed modeling with a random intercept and time as fixed factor, adjusted for center.

Results

In total, 231 patients were screened for inclusion. One hundred and ten patients met the inclusion criteria and were approached for participation in the study. Of those, 40 patients (36%) signed informed consent. Five initially included patients cancelled their participation before the first session of the exercise intervention, due to treatment toxicity and/or emotional distress. Finally, 35 patients (of 110) started the intervention (Figure 1). One participant withdrew consent for using his data, leaving 34 participants for analysis. Due to the COVID-19 pandemic, recruitment had to be terminated after participant 35 started the intervention. Patients' baseline characteristics are listed in Table 1.

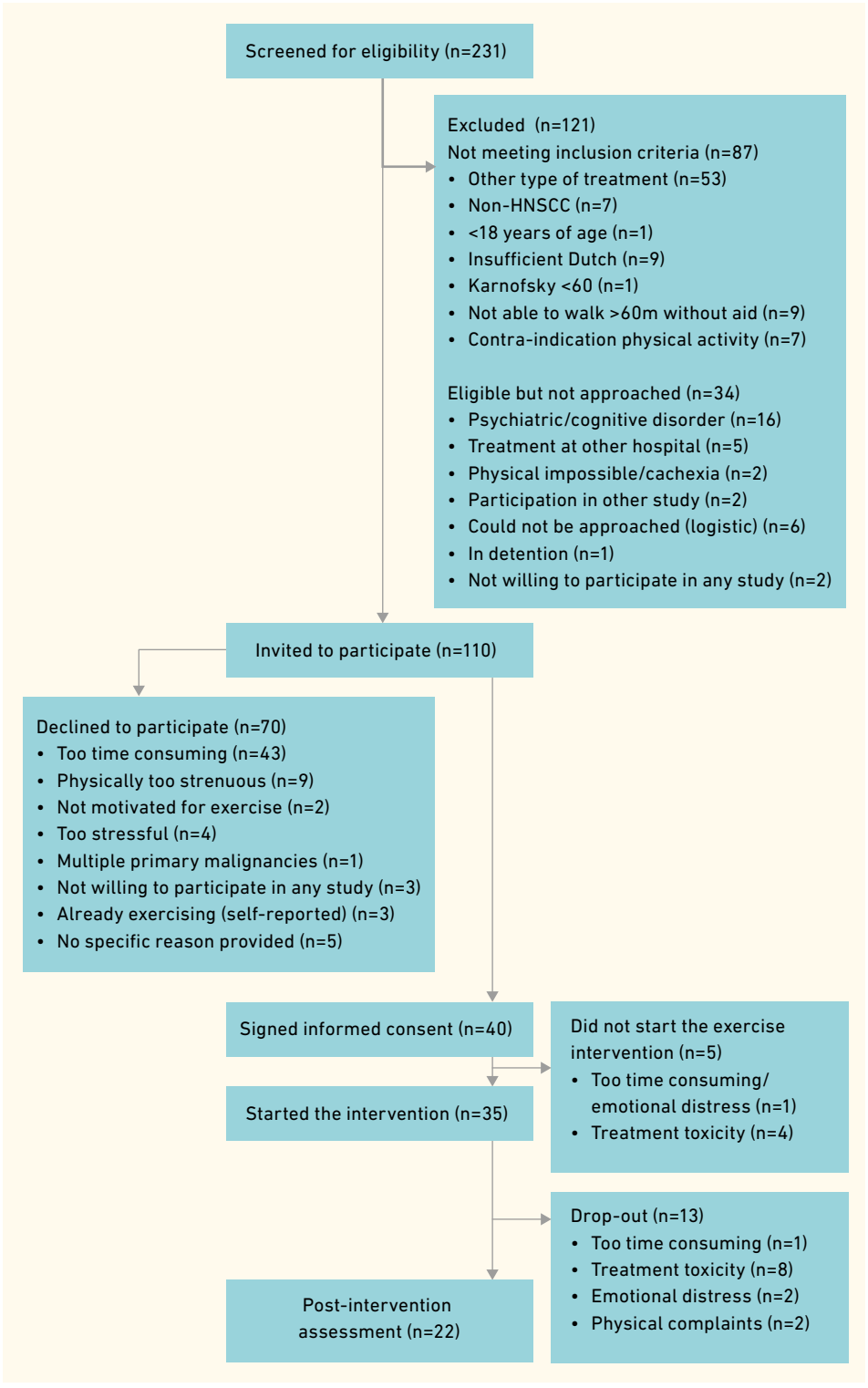

Figure 1. Flow chart participant recruitment and retention

Table 1. Demographic and clinical baseline characteristics of the participants

Variables	Overall study population (n=34)
Sex; n (%)	
Male	27 (79.4)
Female	7 (20.6)
Age (years); median (sd)	58 (35-70)
BMI (kg/m^2); mean (sd)	24.9 (5.4)
Educational level; n (%)	
Low	11 (32.4)
Middle	10 (29.4)
High	10 (29.4)
Missing	3 (8.8)
Marital status; n (%)	
Single/divorced/widowed	11 (32.4)
Married/living together	23 (67.6)
Employment; n (%)	
Paid employed	16 (48.5)
Self-employed	7 (21.2)
Unemployed/household/retired	5 (15.2)
Disabled for work/other	5 (15.2)
Smoking status; n (%)	
Current	2 (5.9)
Past	22 (64.7)
Never	8 (23.5)
Missing	2 (5.9)
Alcohol consumption; n (%)	
Current user	17 (50.0)
Stopped	12 (35.3)
Never	4 (11.8)
Missing	1 (2.9)
Tumor location; n (%)	
Oral cavity	6 (17.6)
Oropharynx	17 (50.0)
Hypopharynx	3 (8.8)
Larynx	2 (5.9)
Nasopharynx	3 (8.8)
Unknown primary tumor	3 (8.8)

TNM stage; n (%)	
stage III	13 (38.2)
stage IV	21 (61.8)
HPV positive; n (%)	15 (44.1)
Type of treatment	
CRT BRT	32 (94.1) 2 (5.9)
Adjuvant CRT	5 (14.7)
Comorbidities; n (%)	11 (32.4)

Abbreviations: BMI, body mass index; BRT, cetuximab-based bioradiotherapy; CRT, cisplatin-based chemoradiotherapy; HPV, human papilloma virus; TNM, tumor, node, metastasis classification according to the 8th edition.

Primary outcome: Feasibility

Adherence

Overall adherence to the supervised sessions for the 34 participants was 182 of 340 sessions (54%). Fifteen of the 34 participants (44%) attended at least 60% of the sessions (Fig. 2). Patients who completed the intervention (n=22; 63%) attended a median number of eight supervised sessions (IQR 4-9), while patients who dropped-out during intervention (n=13; 37%) attended a median number of two supervised sessions (IQR 2-3). Attendance during the sessions planned after completion of cancer treatment was lower as compared to during CRT, respectively 41% versus 58% (Figure 2). Reasons for not attending or cancelling the supervised session are shown in Table 2, in which treatment toxicity was most often mentioned.

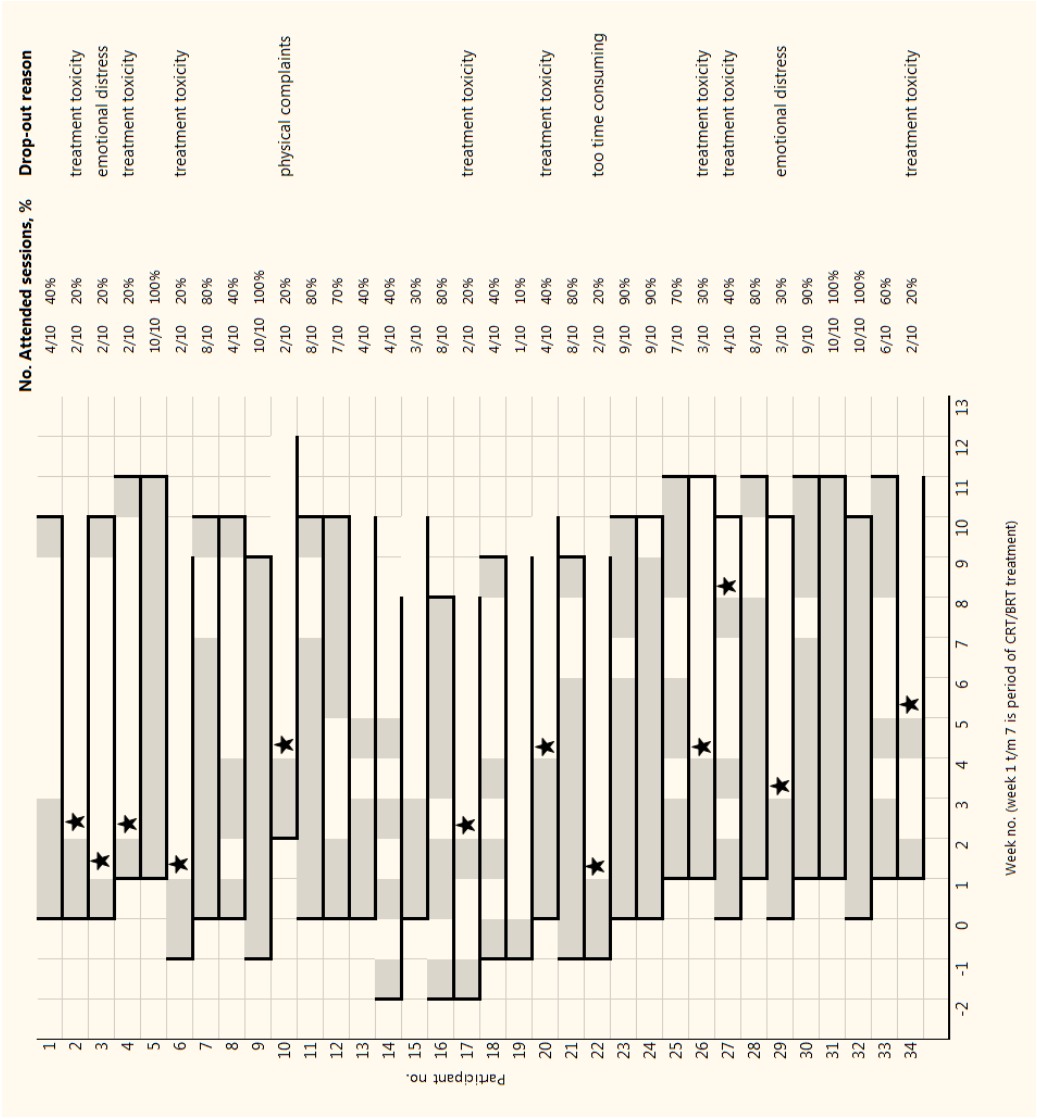

Figure 2. Number of attended training sessions per patient. Each grey box represents an attended session. Each white box represents a not attended session. Horizontal black lines represents the 10-week intervention period. Vertical black lines at the start and end of the intervention period represent the baseline and post-intervention measurements. Star symbols represents the timing of drop-out.

Table 2. Reasons for not attending a training session in the first five weeks and last five weeks of the exercise intervention of the participants who completed the 10-week exercise intervention.

Main reason for absence training session	Missed training sessions week 1-5 (n=24, 100%)	Missed training sessions week 6-10 (n=44, 100%)
Organizational (planning/conflicting appointments)	4 (16.7%)	0 (0.0%)
Patient-related (planning/lack of motivation)	2 (8.3%)	8 (18.2%)
Treatment toxicity	8 (33.3%)	20 (45.5%)
Hospitalization for chemotherapy	2 (8.3%)	3 (6.8%)
Physical complaints (not related to treatment)	3 (12.5%)	0 (0.0%)
Gastrostomy placement	1 (4.2%)	0 (0.0%)
Missing	4 (16.7%)	3 (29.6%)

n = the number of missed training sessions

Recruitment rate

Recruitment rate was 36% (95%CI: 27%-45%) and thus exceeded the feasibility criterion for recruitment (30%). The most common reason for declining participation in the study was the perception that it would be too time consuming (n=43, 61%) (Figure 1). Due to a slow inclusion, the inclusion criteria were broadened in October 2018; from then also patients receiving a combination of cetuximab and radiotherapy were eligible to participate if meeting all other inclusion criteria.

Retention rate

Twenty-two of the 34 (65%) participants completed the 10-week intervention period, resulting in a drop-out rate of 35%. The most important reason for dropping-out was treatment toxicity (n=8, 67%) (Figure 2).

Compliance

Compliance with the home-based program could not be assessed, as only three participants (9%) returned complete exercise logs. Compliance of the supervised strength exercises, defined as an RPE range of 12 to 15 combined with ≥ 15 RM-testing, showed compliance to the protocol in 66% over the sessions attended.

Adverse events

Two serious adverse events occurred. One participant was admitted to the hospital for analysis of loss of arm strength and sensation. These symptoms seemed to be related to previous surgery and were already present prior to study entry, but intensified during the intervention. The participant

was able to continue to participate in the intervention without arm strength exercises. The other participant collapsed during the first training session due to orthostatic hypotension, probably as a result of exercise in combination with chemo-induced dehydration and antihypertensive medication. After stabilization and monitoring in the emergency unit, the participant was dismissed the next day, and discontinued study participation.

Secondary outcomes

Physical performance, muscle strength and body composition

Twenty-four participants completed both the baseline and post-intervention physical performance measurements. No significant differences in physical performance and knee extension strength were found between baseline and post-intervention measurements. Mean hand grip strength and elbow flexion strength significantly decreased during the intervention period (grip strength: -2kg (95% CI:-4; 0); elbow flexion strength: -28N (95%CI:-43; -12). Mean body weight significantly decreased from baseline to post-intervention: -5.7kg (95%CI: -7.5;-3.8) of which 49% was loss of FFM: -2.8kg (95%CI:-4.1; -1.6) (Table 3).

Health related quality of life and fatigue

Results for HR-QoL are shown in Appendix S1 (Table 4). Overall, HR-QoL deteriorated during CRT (week 5 post-baseline). Some domains recovered at 12-week post-baseline, shortly after treatment, whereas scores on most symptom scales were still higher at that time, as compared to baseline. Appendix S1 (Table 5) shows the results for fatigue. At week 5 post-baseline, patients reported clinically relevant increases on all domains, except for mental fatigue. Scores on general fatigue, physical fatigue and reduced motivation in week 12 slightly improved as compared to week 5 post-baseline.

Discussion

The primary aim of our study was to assess the feasibility of a tailored exercise program with combined home-based and supervised endurance and strength sessions, for patients with HNC during CRT. To assess feasibility, we focused on adherence (main outcome), recruitment, retention, and compliance rates. With an overall adherence of 54%, we did not achieve our goal of at least 60%. Recruitment rate was sufficient but the retention rate was lower than expected; 65% instead of 85%. Attendance to the supervised sessions declined after treatment completion, once the participants no longer visited the hospital for radiation treatment. Although the exercise intervention was adjusted to the participants' (changing) capacity during treatment, treatment toxicity was still the most common reason for not attending an exercise session and premature ending study participation. Protocol compliance during the supervised sessions was 66%.

In a recent review on exercise interventions in HNC patients during treatment adherence rates varied between 45% up to 94%.[34] Our adherence rate of 54% was lower than our aim, and in the lower range compared to the other studies. Especially in the period shortly after treatment a high number of sessions were missed, and we hypothesize that on-site training at the hospital does not seem to be feasible after HNC treatment completion. Probably this is due to the highest level of treatment toxicity at the end of CRT and the first weeks afterwards.[7,35] Symptom burden of HNC treatment was also considered as a reason for non-adherence in an exploratory trial.[36] Also, long travelling distance to the hospital and planning difficulties (patients prefer to schedule training sessions combined with medical visits, which are less frequent after treatment) were reported in our study as reasons for not attending the training sessions after treatment.

The recruitment rate of 36% exceeded the 30% we aimed for, and corresponds to previous studies.[25] Yet, the recruitment period was twice as long as expected, even after broadening our eligibility

criteria to include patients receiving cetuximab and radiotherapy due to a lower number of eligible patients. Other studies reported even higher recruitment rates of approximately 60%.[36,37] In accordance with other studies, time constraints often due to travelling time was the main reason for not being willing to participate in our study, even only one session per week was hospital-based.[38] Almost two-thirds of the 34 participants starting with the exercise intervention completed the intervention, resulting in a retention rate of 65%, which was fairly equal to the 60% reported previously.[36] Other studies reported much higher retention rates varying between 83% and 100%.[21,22,39] However, these studies were not completely comparable to ours. Some focused on training during radiotherapy with patients possible experiencing less toxicity as compared to CRT.[22,39] In other studies, interventions were delivered on-site during treatment and post-CRT at home with telephonic support.[21,22] Participants preterm ending their study participation mostly stopped at or before week 5. Treatment toxicity, decreased motivation, and physical inability were the main reasons for drop-out in our study.

While compliance to the home-based intervention could not be assessed, compliance to the protocol of the supervised exercises was 66%. Thus, for those attending the supervised sessions, it seems that the resistance exercises were feasible and sufficiently tailored to their personal capacities. Two serious adverse events were reported resulting in unplanned hospital admissions. We cannot rule out that the exercise intervention contributed to these events, which both occurred during CRT. Careful monitoring of patients before and during the exercise intervention is therefore advised.

The secondary aim of our study was to assess changes in physical performance, muscle strength, body composition, HR-QoL and fatigue. We did not find significant changes in knee extension strength and physical performance. Significant decreases in grip strength and elbow flexion strength were found. Regardless of the exercise intervention and dietary treatment, body weight and FFM significantly declined during CRT. Previous research showed weight loss during CRT for HNC was particularly loss of fat-free mass; i.e., 71% of weight loss was due to loss of FFM.[6,40] In our study, 60% of weight loss could be attributed to a loss in fat mass and only 49% to loss of FFM. Our results suggest that an exercise intervention might help to counteract loss of FFM, but only a large randomized controlled trial would allow definitive conclusions. It is important to prevent FFM loss during CRT as loss of FFM has adverse effect on treatment toxicity, tolerance and survival.[40] Therefore, exercise interventions during treatment should preferably be combined with intensive nutritional support and monitoring.

On average, a relevant decline in HR-QoL during treatment was found, despite the exercise intervention. Fatigue scores increased from baseline to week 5 and remained stable until week 12. A randomized pilot study [39] showed a 9% increase in general fatigue during treatment for the intervention group and a 40% increase for the control group, suggesting a positive effect of exercise on cancer-related fatigue for cachectic patients with HNC during radiotherapy, as was also shown for other cancer types.[41] Due to our small study sample and the lack of a control group, we cannot draw conclusions about whether our exercise intervention led to less deterioration of HR-QoL and less increase in fatigue than would have been the case without the intervention.

Strengths and limitations

With 34 participants at two study sites, this is one of the largest pilot studies assessing the feasibility of a tailored exercise intervention in HNC during CRT with combined supervised and home-based sessions. With this sample size we were able to report feasibility outcomes with sufficient power. However, we also have to consider limitations of our study. Firstly, participants of our study are likely to already be more active than non-participants, which might have resulted in selection bias. This can be inferred from the baseline results of the 6MWT, which show higher scores as compared to comparable HNC populations.[20,21] Also, compared to data from the Dutch Head and Neck audit, participants in our study are younger, and the prevalence of HPV is high (44.1%).[42] Lastly, the lack of

a control group makes it difficult to attribute changes in physical capacity, performance, HR-QoL, and fatigue between baseline and post-intervention to the exercise intervention. However, these preliminary data can be used for sample size calculations for future large-scale interventions.

Recommendations for future exercise trials in HNC

This feasibility study revealed several barriers that could be addressed to increase inclusion and adherence. Lowering the study load for participants (e.g., less travel, improved logistics planning, fewer questionnaires), using activity trackers that automatically record and store data and give immediate feedback might increase adherence, recruitment and completeness of data collection. To offer a more tailored exercise intervention and to improve feasibility understanding of patients' preferences to determine preferable timing, intensity and setting is needed.

Some recommend to engage patients with a training program before treatment but start the actual training program after treatment.[36,43] This might result in higher retention and recruitment rates. We suggest to adapt the training schedule in week 6 to week 10 by replacing on-site supervised training by home-based sessions with remote support, to account for the increasing treatment toxicity.

After treatment, patients with HNC prefer training at a community location.[44] In other cancer patient populations home based training sessions combined with supervised sessions by a physiotherapist resulted in higher adherence rates and showed positive effects on fatigue, cardiorespiratory fitness and muscle strength.[14,45] Training at a community location will be more convenient for our patient population and diminish travel time. The benefits of training in group classes should also be further explored as one study showed that patients with HNC preferred exercise alone prior to participating in an exercise trial, but afterwards preferred group classes which increased motivation for some participants.[44] This also emphasizes the need for tailored exercise interventions: participants should be able to choose between home-based, on-site, alone or group classes. Furthermore, careful focus on the personal goals and capacity of 'hard to engage' patients and addressing knowledge gaps about benefits of physical activity and their perceived barriers might increase recruitment and adherence rate.[46] Analysis of our qualitative data will give insight into exercise preferences, and possible barriers and facilitators from patients' perspective.

Conclusion

We conclude that this intensive exercise training during CRT for patients with HNC is feasible for a minority of patients in its current form. Adherence to the supervised exercise sessions was lower than expected, although the recruitment rate, retention rate and compliance rate during supervised sessions were reasonably good. We suggest adaptations to improve adherence and retention rates. A more personalized approach, including better motivators and immediate feedback by activity trackers, needs further investigation prior to conducting a definitive multicenter trial.

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Appendix

Table A4. Results of functional and symptom scales of the EORTC C30 and EORTC H&N35 quality of life questionnaires at baseline, week 5 (mid-intervention) and week 12 (post-intervention) in means (sd) and mean differences (95% CI).

EORTC subscale	Baseline	5 weeks after baseline	Baseline to 5 weeks differences	p-value	12 weeks after baseline	Baseline to 12 weeks differences	p-value
EORTC-C30							
Global QoL	69.5 (3.7)	50.5 (4.2)*	-19.05 (-18.6; -0.3)	<0.01	60.1 (4.0)*	-9.6 (-19.2; 0.1)	0.04
Physical functioning	94.4 (2.0)	82.7 (2.3)*	-11.7 (-16.9; -6.6)	<0.01	79.8 (2.3)	-14.5 (-19.6;-9.4)	<0.01
Role functioning	84.9 (4.6)	55.1 (5.4)*	-29.8 (-43.7; -15.9)	<0.01	54.3 (5.2)*	-30.6 (-44.3;-16.8)	<0.01
Emotional functioning	79.7 (3.3)	78.7 (3.6)	-1.03 (-8.2; 6.2)	0.77	79.4 (3.6)	-0.3 (-6.6; 7.9)	0.92
Cognitive functioning	85.9 (3.6)	74.4 (4.0)*	-11.5 (-20.8; -2.3)	0.02	80.7 (3.9)	-5.2 (-14.2; 3.8)	0.25
Social functioning	89.4 (3.4)	79.9 (3.8)	-9.5 (-17.6; -1.3)	0.02	77.2 (3.7)	-12.2 (-20.1; -4.3)	<0.01
Fatigue	26.3 (4.0)	53.7 (4.5)*	27.4 (18.0;36.8)	<0.01	44.6 (4.3)*	18.2 (9.1;27.3)	<0.01
Nausea and vomiting	5.5 (4.3)	35.6 (5.0)*	30.1 (41.7;18.5)	<0.01	22.5 (4.8)*	17.0 (5.7; 28.3)	<0.01
Pain	20.1 (4.1)	31.5 (4.7)*	11.4 (0.5; 22.3)	0.04	27.6 (4.5)	7.5 (-3.1; 18.1)	0.16
Dyspnoea	10.4 (3.5)	9.9 (3.8)	-0.5 (-7.6; 6.7)	0.90	11.2 (3.8)	0.9 (-6.2; 7.9)	0.81
Insomnia	23.8 (5.1)	21.8 (5.8)	-2.0 (-14.2;10.2)	0.74	19.4 (5.6)	-4.4 (-16.3; 7.4)	0.46
Appetite loss	19.0 (5.8)	52.1 (6.7)*	33.1 (16.3; 50.0)	<0.01	35.6 (6.4)*	16.6 (0.1; 33.1)	0.05
Constipation	16.9 (5.0)	37.3 (5.7)*	20.4 (6.0; 34.8)	<0.01	23.3 (5.5)	6.4 (-7.7; 20.4)	0.37
Diarrhoea	7.8 (3.7)	22.4 (4.3)*	14.6 (3.9; 25.3)	<0.01	13.5 (4.1)	5.7 (-4.7; 16.0)	0.28
Financial difficulties	10.8 (3.4)	10.3 (3.7)	-0.6 (-8.5; 7.3)	0.88	12.8 (3.9)	2.0 (-5.7; 9.7)	0.61

EORTC-HN35							
Feeling ill	19.5 (5.5)	44.9 (6.3)*	25.4 (9.6; 41.1)	<0.01	37.1 (6.1)*	17.6 (2.0; 33.2)	0.03
Pain	24.6 (4.8)	47.3 (5.3)*	22.7 (10.9; 34.5)	<0.01	29.3 (5.2)	4.7 (-6.7; 16.3)	0.43
Swallowing	25.6 (5.0)	50.2 (5.5)*	24.6 (14.3; 34.8)	<0.01	35.9 (5.5)*	10.3 (0.3; 20.3)	0.28
Senses problems	16.0 (4.8)	56.4 (5.3)*	40.5 (29.4; 51.1)	<0.01	43.7 (5.0)*	27.7 (17.2; 38.3)	<0.01
Speech problems	14.3 (3.5)	22.7 (3.9)	8.4 (-1.3; 18.1)	0.09	15.3 (3.8)	1.0 (-17.4; 2.6)	0.14
Social eating	19.6 (4.4)	42.9 (5.0)*	23.3 (11.9; 34.7)	<0.01	40.0 (4.8)*	20.4 (9.6; 31.2)	<0.01
Social contact	6.4 (2.0)	8.6 (2.2)	2.2 (-3.2; 7.6)	0.42	12.0 (2.2)	5.5 (0.2; 10.8)	0.04
Less sexuality	22.8 (6.3)	48.5 (7.0)*	25.7 (12.3; 39.1)	0.54	44.4 (6.9)*	21.6 (8.5; 34.8)	<0.01
Teeth	10.6 (3.4)	13.9 (3.9)	3.3 (-4.2; 10.7)	0.38	8.7 (3.7)	-1.9 (-9.0; 5.1)	0.58
Opening mouth	20.5 (4.9)	26.2 (5.4)	5.6 (-5.8; 17.1)	0.22	18.8 (5.3)	-1.7 (-13.0; 9.6)	0.77
Dry mouth	23.7 (5.3)	51.3 (5.9)*	27.6 (14.9; 40.3)	<0.01	57.7 (5.8)*	34.0 (21.5; 46.5)	<0.01
Sticky saliva	23.0 (5.4)	60.3 (6.0)*	37.3 (24.2; 50.5)	<0.01	52.1 (5.9)*	29.1 (16.2; 42.0)	<0.01
Coughing	21.5 (4.1)	40.3 (4.7)*	18.8 (6.4; 31.2)	<0.01	28.0 (4.6)	6.5 (-5.8; 18.8)	0.30
Felt ill	19.5 (5.5)	44.9 (6.3)*	25.4 (9.6; 41.2)	<0.01	37.1 (6.1)*	17.6 (2.0; 33.2)	0.03
Pain killers	55.9 (8.2)	78.5 (9.0)*	22.6 (4.7; 40.5)	0.01	74.3 (8.8)*	18.4 (0.7; 36.0)	0.04
Nutritional supplements	31.6 (8.6)	70.0 (9.8)*	38.3 (13.7; 62.9)	<0.01	54.9 (9.6)*	23.3 (-0.9; 47.5)	0.06
Tube feeding	9.5 (7.9)	46.3 (8.6)*	36.9 (18.3; 55.4)	<0.01	64.6 (8.4)*	55.1 (36.9; 73.4)	<0.01
Weight loss	25.8 (8.4)	70.8 (9.6)*	45.0 (19.7; 70.4)	<0.01	60.0 (9.4)*	34.2 (9.1; 59.3)	<0.01
Weight gain	16.7 (6.3)	4.2 (7.1)*	-12.5 (-31.6; 6.6)	0.19	20.0 (6.9)	3.3 (-15.5; 22.2)	0.72

A high score on a functional scale indicates a high level of functioning. A high score on a symptom scale indicates a high level of problems.

* clinically relevant difference (10 points or more)

Table A5. Results of the Multidimensional Fatigue Inventory at baseline, week 5 and week 12 post-intervention in means (sd) and mean differences (95% CI).

MFI Items	Base-line	5 weeks after baseline (mid-intervention)	Baseline to 5 weeks differences	p-value	12 weeks after baseline (post-intervention)	Baseline to 12 weeks Differences	p-value
General fatigue	9.9 (4.3)	13.7 (3.1)	3.5* (1.4 – 5.6)	<0.01	13.2 (4.5)	3.3* (1.9 – 4.7)	<0.01
Physical fatigue	9.5 (4.1)	13.3 (3.7)	3.9* (0.7 – 7.0)	0.20	13.2 (4.1)	3.7* (1.7 – 5.6)	<0.01
Reduced activity	10.5 (4.0)	13.2 (2.3)	2.8* (0.0 – 5.6)	0.05	12.5 (3.7)	2.0* (-0.3 – 4.3)	0.08
Reduced motivation	8.1 (3.5)	11.5 (2.4)	3.0* (0.9 – 5.1)	<0.01	9.8 (3.6)	1.7 (0.8 – 2.5)	<0.01
Mental fatigue	10.6 (3.0)	11.1 (2.3)	0.1 (-1.9 – 2.1)	0.94	11.3 (2.7)	0.7 (-1.2 – 2.5)	0.46

Multidimensional Fatigue Inventory scores range from 4 to 20; high scores indicate more fatigue

* minimal clinically important difference (2 points or more)

Chapter 7

Expectations and experiences of participating in a supervised and home-based physical exercise intervention in patients with head and neck cancer during chemoradiotherapy: a qualitative study

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Abstract

Purpose: Chemoradiotherapy (CRT) for head and neck cancer (HNC) is associated with severe toxicity resulting in fatigue, weight loss, including loss of skeletal muscle mass. Exercise interventions might positively affect physical fitness and quality of life. Sufficient adherence and compliance rates are necessary for optimal effects. This study aimed to gain insight into expectations and experiences and factors influencing adherence, retention and compliance of HNC patients participating in an exercise intervention during CRT.

Methods: This qualitative analysis is part of a study assessing the feasibility of a combined supervised and home-based exercise intervention during CRT. Consecutive participants were invited for semi-structured interviews, conducted pre- and post-intervention. Thematic analysis with a deductive approach was used to identify themes and factors influencing adherence, retention and compliance.

Results: Thematic saturation was reached after interviewing 14 patients pre-intervention. Five themes were identified; planning and time management, treatment toxicity, motivation to exercise, exercise intervention and supervision by a physiotherapist. The intensity of the treatment schedule and treatment toxicity were important barriers. Facilitators mentioned were physical and emotional benefits, social support as well as the simplicity and home-based setting of the intervention.

Conclusion: A personalised approach, considering the individual facilitators and barriers of HNC patients within the themes, is important to increase adherence, retention and compliance to an exercise intervention and to reach optimal effects of the program.

Introduction

Chemoradiotherapy (CRT) for head and neck cancer (HNC) is associated with a high risk for severe toxicity like energy loss, a decreased masticatory functioning, dysphagia, xerostomia, taste alteration and nausea and vomiting. These side effects, but also the cancer itself can complicate physical activity and oral nutritional intake, resulting in fatigue, weight loss, and loss of skeletal muscle mass.[1-3] Loss of muscle mass is associated with a reduced quality of life (QoL), but also a decrease in physical performance and a worse overall prognosis.[4,5] Therefore, interventions aiming at improving physical functioning, body composition, fatigue and QoL are needed. Exercise interventions during cancer treatment have shown to positively affect physical fitness and quality of life and may improve treatment completion rates.[6-8] Supervised exercise interventions appear to be most effective, however, it remains unclear what factors are conclusive regarding, among other things, setting, dose and motivation.[8]

Optimal effects of implementing exercise as part of HNC care can only be achieved when reaching sufficient, adherence, retention and compliance rates. Patients with HNC are generally less physically active, as part of a suboptimal lifestyle, in comparison with other populations with cancer.[5,9] Also, they show a lack of intention to increase exercise levels, probably due to the fact that they perceive their low physical activity level as already being sufficient and experience physical barriers and low self-efficacy.[9] For patients with HNC, achieving sufficient adherence, retention and compliance to exercise interventions during cancer treatment is challenging.[10-13] Specific determinants to improve feasibility and to establish a tailored approach to increase exercising in this population should be further investigated.[14] Previous qualitative studies focused on physical activity and exercise interventions mainly after HNC treatment.[9,14,15] Moreover, these studies did not cover factors influencing feasibility of exercise interventions during HNC treatment.

This study is part of a feasibility study in which adherence, retention and compliance of a combined supervised and home-based exercise intervention during CRT was evaluated. Our quantitative analysis showed that feasibility was influenced by timing, intensity and duration of exercise, as well as travelling time and planning difficulties.[13] In this qualitative part of our study, we aimed to gain insight into preferences and expectations of patients with HNC before participating, as well as, their experiences and satisfaction of this exercise intervention during CRT. Specifically, the objective was to identify factors influencing adherence, retention and compliance from a patients' perspective.

Methods

Ethics

The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht (17-630). All participants signed informed consent prior to the interview. The Consolidated Criteria for Reporting Qualitative (COREQ) Research checklist was used in the preparation of the manuscript.[16] The study was registered at the Dutch National Trial Register (NTR7305).

Setting, eligibility, and recruitment

The study was conducted at the University Medical Center Utrecht (UMCU) and the Netherlands Cancer Institute (NKI), The Netherlands. Patients with HNC scheduled for CRT were consecutively recruited, either face-to-face or by phone, for participation in our exercise intervention study.[13]

For the quantitative part of the feasibility study, 40 patients were included. For the qualitative part of the feasibility study, which is described in this paper, consecutive sampling was used until data saturation was reached.

Exercise intervention

The exercise intervention consisted of a 10-week combined endurance and resistance training during CRT treatment offered by a physiotherapist. Nutritional support was offered by a dietitian as part of usual care in both the UMCU and NKI. The start of the exercise intervention was, preferably, before or in the first week of CRT and ended after 10 weeks (Figure 1). The endurance training consisted of 30 minutes of moderate-intensity physical exercise which included 15 minutes brisk walking, and another 15 minutes of exercise of their own choice. For the resistance training, patients were instructed to perform six exercises three times a week, targeting major muscle groups (arms, legs, shoulders, back, and core) using body weight and elastic bands for resistance. Patients attended one session per week at the hospital, supervised by a physiotherapist. The remaining training sessions were home-based. Further details about the exercise intervention, including adherence, retention, and compliance rate, have been described elsewhere.[13]

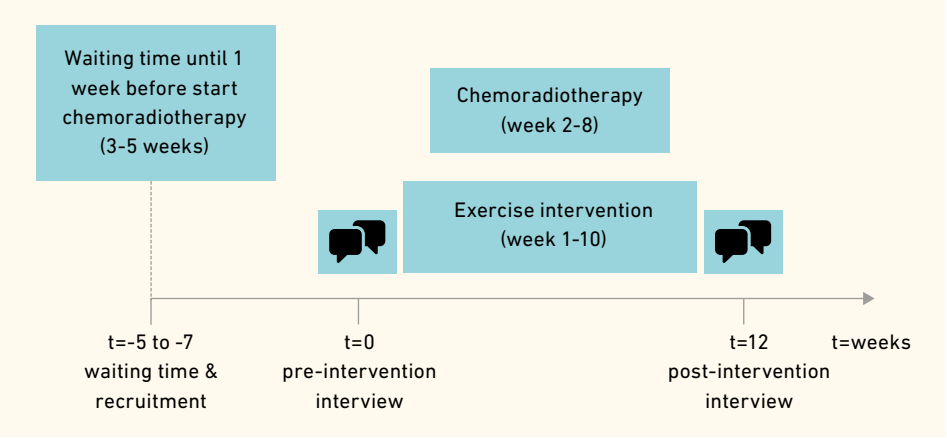

Figure 1. Study flow chart.

Pre- and post-intervention interviews

Semi-structured interviews were conducted from December 2017 through June 2018. Patients were recruited for this qualitative study until data saturation was achieved, which was when no new information could be identified from the last two interviews.[17,18]

Two pre-defined interview guides were used for the pre- and post-intervention interviews, respectively. These guides were developed by the research team in an open discussion, using results from previous studies.[9,15] At baseline, questions focused on patients' expectations regarding their adherence, retention and compliance with the exercise intervention during CRT. The post-intervention interviews focused on their actual adherence, retention and compliance. Questions focused on patients' satisfaction with the intervention (e.g., setting, frequency, intensity, supervision) and on patients' attitude, preferences, motivation, opportunities and barriers towards exercising during CRT, additionally suggestions for improvement were explored. Participants were interviewed at a location of their convenience, either at home or at the hospital. Family members were allowed to be present during the interview, but their perspectives were not collected. Each interview lasted between 30 and 45 minutes and was audio recorded. Field notes were made. The interviews were conducted by EP, who is a nurse specialist and clinical epidemiologist, or by RG, who is a physiotherapist and master's student oncology physiotherapy. Both RG and EP were trained by an experienced researcher (GY) in qualitative methods. No prior relationships existed between the

researchers and participants. After the interviews, the audio recordings were transcribed verbatim. Patient characteristics comprising sociodemographic and medical data were collected from a baseline study-specific questionnaire and from medical files.

Data analysis

We performed a thematic analysis to generate codes from the interview transcripts using a deductive approach in alignment with the interview guides.[19] All interview transcripts were read independently by two researchers (EP and AK), followed by open coding of firstly, the pre-intervention and secondly, the post-intervention interviews. After axial coding, specific codes were identified and labelled and exemplary quotes were selected. Additional codes were generated after reviewing the third and last interview for both the pre- and post-intervention interviews. Codes and categories were established and discussed during meetings with three authors (EP, AK and CMS) subsequently to identify, discuss and clarify overarching themes. To ensure trustworthiness, codes and categories were cross-checked, until no new themes emerged. Any discrepancies in the analysis were discussed until consensus was reached. In addition, agreements between extracted themes from the pre- and post-intervention interviews were investigated. The computer software NVivo version 12 (QSR International LLC, Burlington, MS, USA) was used for coding.

Results

Participants

We reached data saturation after interviewing fourteen participants pre-intervention. None of the participants in this qualitative part of the study experienced adverse events due to the exercise intervention. Two were lost to follow up resulting in 12 interviews after the exercise intervention. During two interviews the partners of the interviewees were present. Mean age of the participants was 57 years (SD: 8.7 years) and 11 of the 14 interviewed participants were male. Five participants in this qualitative study did not complete the exercise intervention. Participants were asked to rate their satisfaction with the exercise intervention on a scale from 0 to 10, 11 interviewees responded with an average of 7.6 (range 5-10). All baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of the fourteen participants.

Participant no.	Age (years)	Gender	Educational level[1]	Disease stage	Tumor location	Number of attended supervised sessions (out of 10)	Completed the intervention	Interview before intervention	Interview after intervention	Rating exercise intervention[2]
1	58	M	Middle	IV	Oropharynx	4	yes	yes	yes	8
2	56	M	High	III	Oropharynx	2	no	yes	yes	missing
3	35	M	Middle	IV	Oral cavity	9	yes	yes	yes	8
4	65	F	Middle	IV	Oropharynx	2	no	yes	yes	8
5	60	M	Middle	V	Oropharynx	9	yes	yes	yes	6
6	47	M	Middle	III	Oropharynx	2	no	yes	yes	8
7	63	M	Middle	IV	Oral cavity	7	yes	yes	yes	8
8	70	M	Low	IV	Hypopharynx	3	no	yes	no	missing
9	59	F	High	IV	Oropharynx	10	yes	yes	yes	8
10	58	M	Middle	III	Oropharynx	8	yes	yes	yes	5
11	53	F	High	III	Oropharynx	4	no	yes	yes	7.5
12	67	M	High	IV	Oral cavity	8	yes	yes	yes	10
13	54	M	Middle	IV	Oral cavity	4	yes	yes	no	missing
14	56	M	High	IV	Oropharynx	10	yes	yes	yes	7.5

[1] Low; primary school or lower general secondary or prevocational secondary education, Middle; upper secondary education or vocational training, High; higher education or university. [2] On a scale between 0 to 10 participants were asked to rate satisfaction with the exercise intervention.

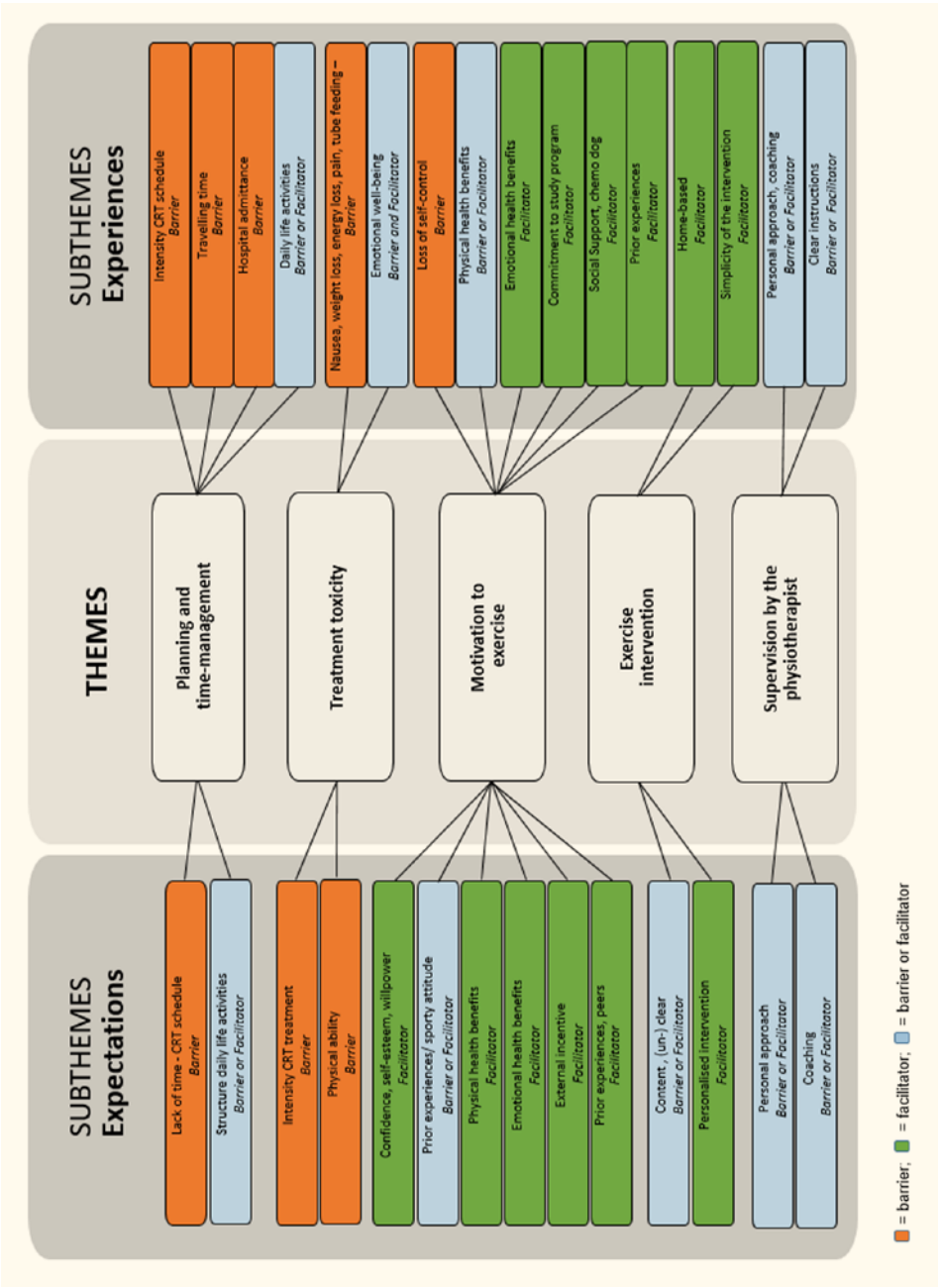

Figure 2. Themes and subthemes extracted from the pre- and post-intervention interviews (representing expectations and experiences, respectively) with head and neck cancer patients participating in an exercise intervention during chemoradiotherapy.

Overview of findings

From the pre-intervention, referred to as *expectations*, and post-interventions interviews, referred to as *experiences*, we extracted five overarching themes: (1) planning and time-management, (2) treatment toxicity, (3) motivation to exercise, (4) exercise intervention, and (5) supervision by the physiotherapist. Figure 1 shows the five themes related to both the *expectation*s and *experiences* of the participants of this study, and the subthemes representing underlying factors. In Table 2, explanatory quotes regarding the (sub)themes are depicted.

Table 2. Quotes illustrating patients' expectations and experiences of an exercise intervention per theme and subthemes.

Themes	Subthemes	Quotes (patient nr, quote nr)
Planning and time management	**Expectations**	
	Lack of time due to chemoradiotherapy schedule	"I hesitated because I already saw my agenda filling up completely with all sorts of different things." (patient nr. 12, quote nr. 1)
	Structure of daily life activities	"My daily routine is completely thrown off, you are not in charge of your own calendar anymore, so it is a bit of a puzzle where to fit this in, but then again this number of exercises should not make this impossible." (patient nr 2, quote nr.2)
	Experiences	
	Intensity of chemoradiotherapy schedule	"You do not know what hits you. You must see the dental hygienist, the dietitian, the speech therapist. ... In the month of May, we had over 50 appointments scheduled at the hospital." (patient nr. 4, quote nr. 3)
	Intensity of chemoradiotherapy schedule, travelling time	"And the reason for dropping out, that had to do with, like, there is so much you have to deal with when starting [therapy], you hardly realize what you agreed to. The intensity of the program and all that comes with it, not just the program, but having to travel more than three hours every day to get to and from the hospital. And then also having to comply to this program, in combination with all kinds of other appointments, that made it too hard." (patient nr. 2, quote nr. 4)

Treatment Toxicity	**Expectations**	
	Intensity of chemoradiotherapy treatment, physical ability	"I can imagine, that when you have just had your chemotherapy treatment, and you are extremely nauseated. Well, then, of course, it becomes difficult to motivate yourself and actually perform the exercises." (patient nr. 10, quote nr. 5)
	Experiences	
	Nausea, weight loss, energy loss, pain, tube feeding	"At one point I could not stop throwing up…in a few days I became scrawny. It terrified me. Then I was admitted to the hospital. So, then you're not like; okay, I should go ahead and do my exercises now." (patient nr. 11, quote nr. 6)
	Emotional well-being	"You are happy after that last radiotherapy treatment; it's over, you could just kiss everyone. But then you fall into a void, and then it is nice that there still is this exercise program, with its weekly appointments with the physiotherapist, so there was at least that, so this was especially helpful mentally. (patient nr.4, quote nr. 7)

Motivation to exercise	Expectations	
	Physical health benefits	"motivation to survive, and also a shorter rehabilitation period, but initially, strive to survive. So, everything I can do to support this treatment I will do. " (patient nr.3, quote nr. 8)
	Will-power	"There is no such thing as "I can't do this anymore", never ever, I can always take it a step further, at least at my level you can always take it a step further. The average top athlete will not be able to run much faster, but in my condition, there is always room for improvement" (patient nr.3, quote nr. 9)
	Confidence	"Self-esteem, increasing confidence. I guess. Feeling less of a pitiful little creature.. feeling better both physically and mentally being more confident. " (patient nr 12, quote nr. 10)
	Sporty attitude	"Anyway, I already had the intention [to exercise] in advance. If you exercise on a regular basis during treatment, that's just better. You pull through easier, you are fitter, you might have less drug side-effects and so on." (patient nr.10, quote nr.11)
	Lack of sporty attitude	"Well, actually, I must confess I am a bit, ehm, this is anonymous right? I am actually very lazy." (patient nr.9, quote nr.12)
	Peers, experiences of peers	"The experiences of someone I know, who has also had cancer, breast cancer, she told me she stayed as active as she could and this helped her a lot. And she is about my age, a few years younger, so I thought: that is a valuable piece of advice. And that's how I selected tips and advice from people around me every now and then." (patient nr.9, quote nr.13)

	Experiences	
	Physical health benefits	"I am convinced that, ehm, that for my recovery and maybe also to prevent deterioration, exercising is simply very beneficial. That is sort of what I think." (patient nr.10, quote nr.14)
	Health beliefs, attitude	"You are also just tired of being ill, so the things that are not absolutely necessary for your health or to survive... well... they can wait until tomorrow." (patient nr.5, quote nr.15)
	Loss of self-control	"at one point I was extremely nauseated, I just did not perform the exercises anymore, I just couldn't. But I did take it up again, one week later. But it did give me a bit of a scare, because I often don't know my own boundaries, so I became scared and then I dropped out". (patient nr.12, quote nr.16)
	Self-control	"And everything I can do to feel less like a patient and to speed up my recovery I will do! So I was quite motivated not to be discouraged and not to become a passive patient, but instead keeping self-control during the treatment trajectory as well as during the rehabilitation phase." (patient nr.14, quote nr.17)
	Physical health benefits	"Sitting is the new smoking", they say, and not without reason, so considering that, and especially in these extreme circumstances, it is just good to do it [exercising]." (patient nr.9, quote nr.18)
	Commitment to the study program	"I already intended to exercise, even if I would not have participated in this study, as I had said before. Anyway, I still would have planned to do something, so that was my motivation. And then it is just discipline, especially when you are not feeling well." (patient nr.10, quote nr.19)
	Chemo dog, social support	"I deliberately borrowed a dog during my treatment, to arrange my physical activity routine." (patient nr.14, quote nr.20)
		"Fortunately, I have little experience with cancer. This is the first time, but you just have no clue... There is so much coming at you, it is very difficult to predict whether it will be feasible [exercising]". (patient nr.2, quote nr.21)

Exercise intervention	**Expectations**	
	Content, unclear expectations	"...I don't know what to expect, so maybe...I don't know what we are going to do yet." (patient nr.6, quote nr.22)
	Personalised intervention	"Yes well, I would assume that, when developing the program, you gave it some consideration that one should be able to keep it up". (patient nr.9, quote nr.23)
	Experiences	
	Simplicity of the intervention, home-based	"the simplicity, that is of course the strength of this program, anyone can do it, you don't have to go to the gym. You can just do it at home whenever you want. It is simple, and that, of course, is the strength of this program. Because, if you're aiming for feasibility you should not add the constraint that one must go to the gym." (patient nr.10, quote nr.24)
	Home-based, social support	"It took me a while to get into it (home-based exercises), because I'm not used to that, but later on I did it together with my wife. She also got one of those (resistance) bands, and then we did it together, she is really good at it". (patient nr.12, quote nr.25)

Supervision physiotherapist	**Expectations**	
	Coaching, motivating	"Well a strong external incentive, I definitely need that, because I think I am rather lazy by nature." (patient nr.9, quote nr.26)
	Coaching, performance	"by correcting me when I didn't perform the exercises properly. You know, of course I did them once and I have seen those pictures, but the correct posture... that is hard. You tend to make it as easy on yourself as possible with those exercises, but you have to adopt the right posture that truly makes you put in the effort." (patient nr.5, quote nr.27)
	Coaching, personal approach	"in any case, it offers me (ehm) a custom-fit solution to stay sportive, or at least physically active". (patient nr.14, quote nr.28)
	Experiences	
	Personal approach, coaching	"that physiotherapist, yeah, I think she put too much pressure on me...to go, (ehm)... to the extreme...for me that works counterproductive". (patient nr.11, quote nr.29)
	Clear instructions	"You can do the exercises in many different ways, and there was actually only one good way. The physiotherapist was always very pleased that I remembered the exercises well and performed them in the correct way."(patient nr.5, quote nr.30)
	Personal approach, coaching	Yes, I found it very stimulating, really empowering, (ehm) the physiotherapist was really driven, and you become aware of what your limits are, and what you can still do...". (patient nr.12, quote nr.31)
		"I think it is truly fantastic! Very well done, inspired, and the physiotherapist is of course a wonderful person, but also the way she presented it and made it attractive by stimulating me, yeah, that is really the way to get someone moving". (patient nr.12, quote nr.32)

Theme (1) Planning and time management

Expectations: Most participants mentioned lack of time, due to the CRT schedule, appointments with health professionals, and travelling, as possible barriers to attend training sessions and to complete the exercise intervention (quote nr. 1). The interaction between time-consuming CRT treatment schedule with a patients' daily life schedule was also mentioned as a barrier for being able to perform the exercises according to the protocol (quote nr. 2). However, one participant expected to have plenty of time because he temporarily paused his (voluntary) work during treatment.
Experiences: Post-intervention, most participants confirmed that the busy treatment schedule including travelling was perceived as an important barrier for participation in the exercise intervention (quote nr. 3) and for some it was the reason for ending their participation in the exercise trial (quote nr. 4). Admittance to the hospital, planned or unplanned, was also a barrier to perform the exercises. Planning the home-based exercises at a fixed time helped some participants to comply with the intervention.

Theme (2) Treatment toxicity

Expectations: Some participants were uncertain whether they would be able to perform the exercises due to expected treatment toxicity, like nausea and loss of energy (quote nr. 5). Some assumed that the CRT treatment schedule and its related toxicity would negatively affect their ability to perform the exercises and/or complete the physiotherapeutic session. The combination of treatment and participating in the exercise intervention was expected as "heavy" and was assumed to require a lot of physical strength.
Experiences: Most participants confirmed that CRT toxicity, including nausea, weight loss, loss of energy, pain, and having a feeding tube, limited their adherence and compliance to the exercise program (quote nr. 6). It was mentioned that participation in the exercise program after treatment positively contributed to emotional and physical well-being (quote nr. 7).

Theme (3) Motivation to exercise

Expectations: The belief that being physically active during treatment could help to stay fit and improve health outcomes or survival, was an important motivational factor for some to participate (quote nr. 8). In addition, some participants mentioned feeling better, enjoying and being active as incentives to exercise. Some participants were self-confident and mentioned that their strong willpower would help them to adhere to and to complete the exercise intervention during treatment (quote nr. 9). Others expected to improve self-esteem and mental wellbeing when participating in the exercise intervention (quote nr. 10). Some mentioned their sporty attitude as a motivating factor (quote nr. 11). On the contrary, for others their lack of a sporty attitude was a reason to participate in this intervention (quote nr. 12). A positive experience with exercising during cancer treatment of peers (quote nr. 13) and having a dog to walk with were also mentioned as a motivating factors. Getting insight into personal physical performance and strength during the intervention was said to be motivating. Some participants deemed the appointment with the physiotherapist necessary to adhere to the exercises, because of a lack of intrinsic motivation.
Experiences: In general, most factors associated with motivation to exercise mentioned at baseline were confirmed post-intervention, including the persuasion of improved health outcomes and participants' motivation not to feel and act like a patient but to "stay in control" (quote nr. 14). One participant regarded exercising as "not being absolutely necessary for his health or survival". Because of this conviction, exercising had low priority for him (quote nr. 15). Some experienced a lack of discipline and loss of self-control (quote nr. 16) due to treatment toxicity and related distress.

Others were able to keep motivated (quote nr. 17) because of their prior exercise behaviour, their attitude (maintaining self-control) or study commitment (quotes nr. 18).
Commitment to the supervised appointments was experienced as motivating to increase adherence as well as having a supportive peer or partner (quote nr. 19).
Having to walk a dog was also mentioned as motivating post-intervention. One participant even borrowed a dog during treatment for that reason (quote nr. 20). Most patients had no previous experience with a cancer diagnosis or treatment and therefore, lacked insight in possible side-effects of CRT, and how these could affect the adherence to the exercise program (quote nr. 21).

Theme (4) Exercise intervention

Expectations: Despite receiving in-depth information about the exercise intervention, for some participants the content and goals of the exercise program were unclear before the start of the intervention (quote nr.22). For others the content was sufficiently clear, in particular for some participants who had previous experiences with supervised exercising. One participant deemed it feasible to perform the exercises according to protocol as he perceived the number of exercises as acceptable. A few participants expected the exercises to be simple to perform. Some participants expected to have sufficient stamina to adhere to the program, provided that it would be adjusted to their (changing) capacity during treatment (quote nr.23)
Experiences: Most participants perceived the simplicity of the exercise program as a facilitator, increasing the feasibility of the exercise program. The home-based setting, not having to go to a fitness centre, lowered the threshold for performing the exercises (quote nr. 24). The home-based setting also enabled social support for one participant, as his partner performed the exercises together with him (quote nr. 25). Yet, some pre-existing physical limitations or physical barriers due to treatment toxicity were also mentioned to negatively influence exercise adherence and compliance.

Theme (5) Supervision by the physiotherapist

Expectations: Participants mentioned various expectations and needs regarding supervision by the physiotherapist. Some had been treated for other indications by a physiotherapist previously and assumed that supervision by a physiotherapist would positively affect adherence and compliance with the exercises (quote nr.26).
Participants thought that a personal approach and coaching style would help to increase adherence to the physical fitness intervention. Also, participants expected the physiotherapist would help them performing the exercises correctly (quote nr.27), thereby increasing the effectiveness of the exercises, and to adjust the exercises to their physical (in)abilities (quote nr.28).
Experiences: Participants reported that guidance by a physiotherapist was important and it was mainly experienced as being very positive and motivating. Some preferred a more directive approach, while others preferred gentle stimulation by the physiotherapist (quote nr. 29).
Clear instructions were perceived as being important for increasing compliance (quote nr. 30).
Physiotherapeutic supervision helped participants to challenge themselves within their personal limits of their ability (quote nr. 31). Motivation by the physiotherapist helped to perform the exercises and facilitated increasing adherence (quote nr. 32)

Suggestions for improvement – comments by participants

One participant suggested developing exercise videos instead of the pictures we used, to increase compliance with the home-based strength program (quote nr.33). Another suggestion mentioned was to enable choosing the training facility (for the supervised sessions) at participants'

convenience, near home or at the hospital (quote nr.34 and 35). Some suggested that exercising in a group with peers might increase adherence (quote nr.36). Others preferred a program which was even more adjusted to one's fluctuating physical capacity during treatment than our current program was (quote nr.37). Some perceived the exercises as being too challenging while others perceived the intensity of the exercises as being too light. Finally, it was suggested to replace the pedometer by a more user-friendly activity tracking application (quote nr.38). Explanatory quotes are shown in Table 3.

Table 3. Quotes illustrating patients' suggestions for improvement of the exercise intervention.

Suggestions for improvement	Exemplary quotes
Exercise video's	"What might be helpful,….you know, I had to do 6 different exercises… and if there were like 6 YouTube videos with exactly those exercises". (patient nr.5, quote nr.33)
Supervised training near home	"I think, yeah, if a physiotherapist had visited me at home, I probably would have done those exercises". (patient nr.6, quote nr.34)
Hospital based training	"during hospital stay, I really liked it, but at home there was so much going on, too many distractions, and all the hassle with medication, tube feeding, that made it impossible to also do it (the exercises) on top of all that". (patient nr.5, quote nr.35)
Exercise in peer group	"I think it is better (to exercise) in a group". (patient nr.4, quote nr.36)
Personalized training program	"Consider each individuals' own personal needs. I had a need for a more intensive program and with that, I would have liked the freedom to adjust the exercises when it's not going well on occasion". (patient nr. 10, quote nr.37)
Health/exercise tracking apps	"to be honest, I didn't find the fitbit very convenient,…I think it would be better to use your smartphone for tracking, because you always have it on you,…you know. I change my trousers before leaving the house and then the fitbit was still attached to the house pair …".(patient nr.5, quote nr.38)

Discussion

This qualitative study was designed to identify factors, influencing adherence, retention and compliance, of patients with HNC regarding a combined supervised and home-based exercise intervention during CRT. Five themes addressing preferences, expectations, experiences and satisfaction regarding the exercise intervention were identified.

Planning and time-management was the first theme identified. Participants perceived the intensive treatment schedule, comprising radiotherapy treatment five times a week combined with three weekly admissions for chemotherapy, and appointments with several health professionals, (unplanned) hospital admissions, and, for some, travelling time as important factors negatively

affecting adherence and compliance. A lack of time has also been mentioned as a barrier for exercising by HNC patients in previous studies.[20,21] To overcome planning and time-management barriers, more flexible (re-)scheduling of supervised sessions as well as training at a location to the patients' convenience might be beneficial.

Our findings are in line with results from other exercise studies in HNC, in which fatigue, nausea and physical weakness were also mentioned as important treatment-related barriers for attending training sessions.[22,23] Treatment toxicity, the second theme in our study, was perceived as main barrier negatively affecting adherence, retention and compliance rate which was also illustrated by our quantitative data.[13] Some adjustments to the exercise program might be helpful to overcome this problem. One option, which might increase adherence, is to start supervised training sessions before treatment and focus on home-based training with remote supervision during and shortly after CRT.[23] We suggest integrating exercise interventions within the oncological care pathway and start exercising as early as possible to achieve relevant effects of the intervention in the short period before the start of treatment. To prevent exercise-induced adverse effects we advise following the guidelines of the National Comprehensive Cancer Network for when medical clearance and/or further medical evaluation by a medical professional is indicated.[8]

The third theme in our analysis identified, is the motivation to exercise. The belief that exercising helps to maintain physical fitness and improves health outcomes, including survival was perceived as a facilitator to adhere to the exercise intervention. Also, mental well-being, like self-esteem and enjoying exercising were mentioned as motivating factors. Loss of self-control due to treatment and related distress were mentioned as factors decreasing motivation to exercise. High levels of distress, anxiety and depression are common in patients with HNC.[24,25] Distress, depression, and anxiety influence physical activity and compliance to exercise.[26] For any intervention to be successful, it seems necessary to adequately address these psychological factors throughout the course of treatment.[14,27] The physiotherapist can have a pivoting role in this.[28] The beneficial effects of exercise on depression, anxiety and distress have been well established[8,29], as some interviewees endorsed; they experienced a positive mental effect of participation in this exercise intervention. Supportive partners or peers positively influenced motivation; which was also reported in previous research.[30]

Theme four describes the exercise intervention. The simplicity of the program, the commitment to the supervised appointments and gaining insight into personal performance increased motivation and adherence. Factors that negatively influenced adherence were unclear expectations regarding the content and lack of goalsetting of the exercise intervention. In patients with HNC, adherence, retention and compliance to exercise interventions can be challenging because they typically have a less active lifestyle compared other populations with cancer and have high symptom burden.[23,31] The exercise intervention was tailored to patients' capacity and preference of endurance training throughout the program. However, physical limitations and perceived insufficient adjustment of the intensity of the program were experienced as barriers. Consequently, adherence, retention and compliance may be increased by more extensive adjustment of the exercise intervention based on physical limitations, and by setting personal goals.[32] More time is therefore needed for supervision and guidance by a physiotherapist during the exercise program. The home-based part of our exercise program was mentioned as a facilitator for high compliance. In addition, group training sessions might increase motivation in patients with HNC, as has been shown in a previous study [22], though this is difficult to achieve in a peripheral setting due to the low prevalence of HNC in the Netherlands.

The last and fifth theme identified was supervision by a physiotherapist. Supervision by a physiotherapist was deemed necessary for proper instructions in performing the exercises correctly and increasing motivation and compliance. As shown in previous studies, the physiotherapist has

an important facilitating role in motivation, mental support and increasing discipline to exercise and supervised exercises programs.[33,34]

The scope of this study was to only include patients who participated in the exercise intervention and only one participant had a low education level, which is not representative for the entire HNC population. We assume the presence of the partner of two interviewees during the interview will not have effected the reliability of our results. To our opinion it might positively affect validation as the interviewee felt more at ease and thus gave more extensive responds. Participants of our study are likely to be more active and might have other beliefs and preferences than non-participants, resulting in selection bias, as has been previously described.[13,35]

Clinical implications and future directions

The current exercise program was adapted to the participants' capacity, however, some expected a more tailored intervention. An optimal personalized intervention with regard to goal-setting, training type, intensity, setting, and timing might further increase feasibility outcomes. A previous study showed to increase physical activity levels in HNC, exercise should preferably be incorporated in daily life activities.[9] As the normal structure of daily life activities is changed due to the intensive treatment schedule, future studies should focus on how to flexible (re-)schedule the supervised training sessions. Exercise programs should preferably be offered as part of usual care with training sessions scheduled around treatment appointments. This would overcome some of the logistic barriers, as well as the low adherence due to treatment toxicity. In a previous qualitative study in HNC survivors, a lack of intention to increase their physical activity level was reported, due to the incorrect assumption that their current physical activity level was already sufficient.[9] The assumption of "already being active" was also an important reason for not willing to participate in this exercise intervention.[13] E-health applications or blended care can be helpful in providing patient-tailored information on activity level, personal goals and monitoring individual progress [36,37], as was also suggested by the interviewees.

Conclusion

In conclusion, five themes, planning and time management, treatment toxicity, motivation to exercise, exercise intervention and supervision by the physiotherapist, were identified. A personalised approach, considering the individual facilitators and barriers within these themes, is important to increase the feasibility of exercise interventions during HNC treatment and to reach optimal physical fitness effects.

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Chapter 8

Summarizing discussion

Summarizing discussion

Malnutrition is common in patients with head and neck cancer (HNC) and is characterized by unintended weight loss.[1,2] In patients with advanced HNC, both the disease itself as well as toxicity of chemoradiotherapy (CRT) treatment negatively affects nutritional intake and status.[3] The resulting weight loss predominantly consists of loss of muscle mass and is associated with lower survival rates, a decreased quality of life (QoL), physical decline, and increased treatment toxicity, complication rates and healthcare costs.[4–6]
Dietary treatment is embedded in the HNC care pathway and aims to prevent or treat malnutrition at an early stage. In malnourished HNC patients dietary treatment has been shown to reduce health care costs. Intensive nutritional intervention, often including the use of tube feeding, has proven to prevent weight loss and beneficially affects CRT related toxicity.[7,8] Besides optimal dietary treatment, exercise training is a prerequisite for maintaining or restoring muscle mass and has been shown to positively affect fitness, fatigue, QoL and treatment completion rates in cancer populations.[9–11] To further optimize supportive care for patients with HNC treated with CRT, we aimed to:

1. gain insight into variations in dietetic practice in the Dutch head and neck cancer centers (***Part I***),
2. identify predictors for tube feeding use and gastrostomy placement and provide a tool to support personalized decision making with regard to prophylactic gastrostomy placement (***Part II***), and
3. assess the feasibility of an exercise intervention for HNC patients during CRT (***Part III***).

In this chapter we will discuss the main findings of our studies and its relevance in improving supportive care for patients with HNC treated with CRT. Secondly, implications for nutritional care and exercise in clinical practice and future directions for scientific research will be discussed.

Main findings

Nutritional intervention and dietary treatment (Part I)

The first aim of this thesis was to assess variations in current practice with regard to nutritional interventions and dietetic care for HNC patients treated with CRT. For this purpose, we performed a survey study (**Chapter 2**) among dietitians of the Dutch head and neck centers and concluded there is substantial variation in dietetic practice within the centers. This is probably due to the absence of national guidelines on how to organize dietetic care for this patient population. Our findings are in line with a previous paper, reporting considerable variation in nutritional support for patients with HNC in Norway.[12] Although all patients receiving CRT are routinely referred to a dietitian in all centers, the number of scheduled consultations and the length of dietary treatment varied. It has been well studied that intensive dietary treatment during CRT reduces weight loss ad toxicity and results in less treatment interruptions.[13,14] However, it has also been demonstrated that the "no-show" rate is high; half of patients missed more than 25% of (weekly) scheduled appointments.[15] This is compliant with our clinical experience. Weekly scheduled appointments are frequently cancelled because patients indicate to have 'no deterioration of nutrition impact symptoms' or 'no request for help'. These findings suggest patients might have different needs and preferences considering the dietary treatment and we might therefore revise our current dietary regimen for patients receiving CRT. Whether this cancelling of appointments affects dietary treatment outcomes would be interesting, however, this has not been studied.
Also, with regard to gastrostomy placement there are different policies within the oncology centers. Some centers place a gastrostomy prophylactically in all patients or upon indication, whereas others prefer to place a tube, either a gastrostomy or a nasogastric tube, only when deemed necessary

(reactive). Half of the centers have developed a center-specific tube placement protocol. This means that, despite having identical tumor size and tumor location, the treatment facility, for example, Groningen or Maastricht, influences whether patients will undergo prophylactic gastrostomy placement.

Indicators for tube feeding use and tube placement (Part II)

As shown in our survey study, there are different policies within the Dutch head and neck centers with regard to gastrostomy placement (**Chapter 2**). It is not a surprise that diverse tube placement policies exist, as the Dutch national guidelines of 2014 stated not to provide all patients treated with CRT with a prophylactic gastrostomy but only upon indication. However, due to a lack of scientific evidence, indications for prophylactic placement were not described. We tried to fill this knowledge gap: the second aim of this thesis was to gain insight into predictors for tube feeding use and prophylactic gastrostomy placement in patients with HNC undergoing CRT (**Chapter 3**) and provide a tool which helps to select patients who could benefit from prophylactic gastrostomy placement (**Chapter 4 and 5**). A retrospective chart review at the University Medical Center Utrecht (UMC Utrecht) was performed for gaining insight into indicators for gastrostomy placement and tube feeding use (**Chapter 3**). Multivariable analysis of our retrospective data showed that increased age, node stage (N1-N3), need for reconstruction, bilateral neck irradiation and the use of a texture modified diet prior to treatment were significantly related to gastrostomy placement. Based on our retrospective data and data from existing literature we advised to take the following indicators into consideration in the development of gastrostomy placement protocols for CRT patients: advanced tumor size (T3-T4) and node stage in combination with bilateral neck irradiation, the use of a texture modified diet prior to treatment and pretreatment malnutrition. To develop and internally validate a prediction model to select patients who would benefit from prophylactic gastrostomy placement, we combined retrospective data of 450 HNC patients treated with CRT at the UMC Utrecht and Maastricht University Medical Center (**Chapter 4**). With the formula of the presented model the individual probability (in percentage) of tube feeding requirement for at least four weeks can be calculated. This calculated probability aids clinicians and patients in deciding whether the patient would benefit from a prophylactic gastrostomy. However, for the widespread use of this clinical model, external validation is required. Therefore, we updated our model and performed an external validation together with colleagues of the Netherlands Cancer Institute and the Radboud University Medical Center (**Chapter 5**), using data of 743 patients with HNC. In this new prediction model radiotherapy dose data was added. This was considered to be useful as previous studies showed radiotherapy dose on the pharyngeal constrictor muscles and oral cavity predicted swallowing outcomes.[16-18] Swallowing difficulties, or dysphagia, is a common side effect of CRT [19] and an important reason for starting tube feeding during CRT. The definitive prediction model includes the following predictors: pretreatment weight change, texture modified diet at baseline, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor site, N classification, and mean radiotherapy dose to the contralateral parotid gland and oral cavity. This model was developed for aiding clinical decision making in prophylactic gastrostomy placement for patients with HNC treated with CRT and is already in use in several Dutch head and neck centers.

Feasibility of an exercise intervention (Part III)

In the Move Fit study, we assessed the feasibility of a combined supervised and home-based exercise program for patients with HNC during CRT (**Chapter 6 & 7**). With an adherence rate of 54%, a retention rate of 65%, a recruitment rate of 36% and a compliance rate of 66%, we conclude that this exercise program in its current form is feasible for a minority of patients. These findings suggest adaptations in this exercise program are necessary to improve adherence and retention rates. Despite exercising, significant decreases in grip strength and fat-free mass and clinically relevant

deteriorations on quality of life (QoL) and fatigue subscales were observed during treatment. The absence of a control group in our study makes it difficult to assess whether exercising alleviates the decline in physical fitness and QoL and decreases fatigue, as has been shown in exercise studies in other cancer populations (**Chapter 6**). Furthermore, the qualitative results of the Move Fit study, including expectations and experiences and factors influencing adherence, retention and compliance of HNC patients participating in the trial were described (**Chapter 7**). We identified five main themes; planning and time management, treatment toxicity, motivation to exercise, exercise intervention and supervision by a physiotherapist. The intensity of the chemoradiotherapy treatment schedule and treatment toxicity were important barriers, negatively affecting adherence, retention and compliance. Facilitators mentioned were physical and emotional benefits, social support as well as the simplicity and home-based setting of the intervention. An even more personalized approach, considering the individual facilitators and barriers of patients with HNC within the described themes, is important to increase adherence, retention and compliance to an exercise intervention and to reach optimal effects of the program.

Implications for clinical care

Dietary treatment and tube placement

The results of our survey (**Chapter 2**) among dietitians in the Dutch head and neck centers showed substantial variation in dietetic care. Reasons for this variation might be the absence of national guidelines, differences in health care logistics between centers, financial structures, and personal preferences and experiences of health care professionals. Whether and how this variation affects dietary treatment outcomes is currently unknown. With the rising number of HNC patients treated with (C)RT, the limited available dietetic full-time equivalents (FTEs) and the high number of "no-shows" with weekly scheduled appointments at our center, we decided to adapt the dietary treatment schedule at UMC Utrecht. Although previous studies showed that intensive, weekly nutritional interventions resulted in less treatment interruptions and less weight loss[13,14], there is also evidence that individualized on-demand nutritional counseling was as efficacious as intensive nutritional counseling.[20] Therefore, we adapted our dietary regimen from weekly to biweekly scheduled dietetic consultations on high risk decision-points during (C)RT, and, subsequently, retrospectively studied the effect of this change in dietary regimen on weight loss. No significant difference was found in weight loss during (C)RT between the patients with biweekly dietetic consultations (n=149) compared to the group with weekly consultations (n=130).[21] This is an example of how dietitians could reorganize dietetic care in line with the Dutch Integral Care Agreement (IZA) principles of appropriate care; proven effective, with less effort and health care costs similar results.[22] This is of importance because of the growing number of patients with chronic conditions in the Netherlands resulting in rising health care costs. At the same time, there is a shortage of healthcare personal. With the IZA, the Dutch healthcare sector, the association of Netherlands Municipalities and the Ministry of Health, Welfare and Sport jointly commit to the importance of keeping good-quality healthcare affordable and accessible, now and in the future, and prevent the situation were not everybody will receive the care they need. As for other health-care professionals, also for dietitians, this means that a shift in our daily dietetic practice is necessary. The Dutch "Zorgmodule Voeding" has been developed in 2012 by the Dutch Dietetic Association on behalf of the Ministry of Health, Welfare and Sport and provides a guideline on how to (re-)organize nutritional care for patients.[23] Four care profiles have been described for offering nutritional care (Table 1). Level 1 consists of self-management without the involvement of healthcare professionals, level 2 consists of individual nutritional advice offered by healthcare professionals, and level 3 and 4 include personalized dietetic care offered by a general, respectively, specialized dietitian. For patients with HNC, although variations exist, dietetic care offered by a specialized oncology dietitian is well-organized at the

head and neck centers and preferred partners. To increase efficiency of specialized dietetic care for patients with HNC we should invest in using and evaluating self-management tools or schedule group consultations instead of one-on-one consultations. In the follow-up phase after treatment we could invest in re-organizing dietetic care by transferring more HNC patients to primary care oncology dietitians (profile 4). As specialized dietitians, we should invest in, jointly, developing transmural dietetic care pathway for all patients with cancer. For HNC survivors, the Zorgmodule Voeding can be used in the follow-up phase after CRT. For those without (severe) nutritional impact symptoms, general nutritional advice can be offered (Profile 1 and 2) aiming at improving lifestyle and preventing or alleviating comorbidities (Table 1). For patients with early-stage HNC the Zorgmodule Voeding can be used as a guide for organizing nutritional care throughout the care pathway.

Table 1. Summary of care profiles based on "Zorgmodule Voeding".

Care profiles "Zorgmodule Voeding"				
	Profile 1 Self-management	**Profile 2** General nutritional advice	**Profile 3** Personalized dietary treatment	**Profile 4** Personalized specialized dietary treatment
Indication	No involvement of healthcare professionals on nutritional advice	Individual care with general nutritional advice by healthcare professionals	Individual care with dietary treatment	Individual care with specialized dietary treatment
Content of the care profile	The patient will take action on lifestyle changes after being directed by the healthcare provider on the importance and necessity of adjusting lifestyle. Relevant information and guidance through online support programs.	The healthcare professional provides general nutritional advice and focuses on raising awareness of existing health risks, establishing the relationship between lifestyle and disease, and creating motivation for lifestyle change, if necessary.	The dietitian provides treatment aimed at preventing, alleviating, reducing, or compensating for nutrition-related or nutrition-influenced disorders, limitations, and participation problems, following available guidelines.	The specialized dietitian provides treatment aimed at preventing, alleviating, reducing, or compensating for nutrition-related or nutrition-influenced disorders, limitations, and participation problems, following available guidelines.

The developed prediction model (**Chapter 4, 5**) fits the IZA principles of appropriate care.[24] Appropriate care has four basic principles; it is value driven, thus effective with a limited use of personnel and resources, it arises together with the patient (shared decision making), it is the right care in the right place and it concerns health rather than illness. With the use of the prediction model we are able to select patients who would benefit from prophylactic gastrostomy placement rather than providing every patient receiving CRT with a gastrostomy. Previous studies showed that between 9% and 47% of prophylactically placed gastrostomies in patients with HNC are never used.[25,26] By carefully selecting patients who would benefit from a prophylactic tube, based on

patient data, less healthcare budget, personnel and resources are needed. The flow chart presented in **Chapter 4** for the use of the prediction model in clinical practice supports shared decision making. Based on the calculated risk for the use of tube feeding for more than four weeks it is up to the health-care professional and patient whether they decide to opt for prophylactic tube placement. It is important that the clinician informs the patient well about the short- and long-term risks and benefits of a prophylactic or reactive gastrostomy and a nasogastric tube. An often mentioned constraint for shared decision making is the clinicians' belief that shared decision making takes more time[27], although a recent systematic review and meta-analysis showed that shared decision-making does not necessary lead to prolonged medical consultation length.[28] However, effective implementation is a prerequisite, and should include the diffusion of tasks in the clinical team, thus dividing the time pressure and the workload.

Also patients hesitate to actively engage in consultations due to concerns about appearing inadequate, bothersome or claiming too much time.[29] Exploring patients' values, including expectations and concerns is important in shared decision making and might eventually increase patient satisfaction as well as compliance.[30] To often we see patients in our consulting room with a prophylactic gastrostomy, "the doctor said I needed this", who are not willing to use the tube and postpone the initiation of tube feeding. Shared decision making includes the perception of a treatment choice, awareness of treatment options and their consequences, and weighing options taking into account personal values.[31] The above case illustrates shared decision-making is not yet fully implemented in the tube decision making process. To save costly consultation time of the medical specialists, other healthcare professionals, for example, specialized nurses or physician assistants, could guide this shared decision-making process for a tube. They are well informed about the tube placement procedure and know the (dis)advantages of the tube types. Because time of all healthcare professionals is becoming more limiting in the near future due to the shortage of healthcare professionals, we should invest in developing interactive, online patient education materials and shared decision making tools. These materials should be developed in collaboration with patients and should also fit the needs for patients with low-(health) literacy. Besides saving valuable time in the consulting room, this may help to put patients in charge of their own health. Face-to-face consultation time can then be efficiently used for establishing an effective healthcare professional-patient relationship, shared decision-making and personalizing (dietary) treatment. There is an important role for dietitians to develop innovative education materials and continuously evaluate and improve the dietary regimen based on objective measurements as well as patient reported outcome measures (PROMs) and patient reported experience measurements (PREMs).

Multidisciplinary pre- and rehabilitation for patients with HNC

As allied health care professionals providing supportive care to patients with HNC, both dietitians and physiotherapists, can contribute to relieving the overloaded health care system. Prehabilitation before colorectal cancer surgery, combining a nutritional intervention and an exercise program, has shown to reduce the number of severe complications and resulted in an enhanced functional recovery after treatment.[32] Despite positive effects in this and other randomized studies, the Dutch National Health Care Institute recently drew the conclusion that it has not been demonstrated that prehabilitation for colorectal cancer patients (the most widely investigated group of oncological patients) is effective.[33] This conclusion is based on the fact that studies on prehabilitation in colon cancer patients included a broad group of patients and did not specifically focus on high-risk patients, who would likely benefit the most from such a program. Due to this lack of evidence for the general colon cancer population, the Dutch National Health Care Institute has decided not to include the multimodal prehabilitation program in the basic health insurance coverage.[33] Recently, a systematic-review and meta-analysis on prehabilitation interventions for HNC patients treated with surgery and/or (chemo)radiotherapy was published.[34] Of the 46 included publications, 23 studies

focused on swallowing exercise interventions, 16 studies described nutrition only interventions, 6 studies were on physical exercise only interventions, and one studied the effect of a psychoeducational program. Although no prehabilitation studies were found combining a nutritional intervention with physical exercise, nutritional interventions and exercise interventions alone resulted both in weight retention, reduced length of stay, less complications, and a reduction in dysphagia.[34]

Exercising during cancer treatment seems to reduce the level of fatigue and to increase QoL and treatment completion rates.[9-11] Exercising during CRT treatment in the understudied HNC population was challenging, especially because treatment toxicity reduced the ability to adhere to the exercise as shown in the Move Fit study (**Chapter 6, 7**). However, patients reported high rates of satisfaction with the exercise intervention. Patients reported that the exercise intervention supported emotional and physical well-being, helped to "feel less like patient", increased confidence and will-power and empowered patients "being able to do something to support the treatment". Despite patients expressed satisfaction with the program, adherence rates should improve to be able to achieve optimal effects of training. Current exercise interventions for cancer patient populations are often designed based on certain patient, disease or treatment characteristics (e.g. age, tumor type and treatment modality).[35,36] However, in line with the results of our qualitative study, further personalization, taking into account patients' motivation, beliefs, health literacy, and contextual factors, including daily life activities, home situation, and social support might further increase the success and efficacy of an exercise intervention.[37]

Both dietitians and physiotherapists use the International Classification of Functioning, Disability and Health (ICF) model as a framework for patient centered care. The use of the model helps to systematically identify above described factors including facilitators and barriers which are necessary for personalizing supportive care and successfully engaging the patient.[38] For some patients, the use of existing digital tools might by helpful to increase motivation, personal goal setting and monitor individual progress. Blended care, the combination of face-to-face consultations and online applications might also help to reach the IZA goals. When considering the appropriate care principle "the right care in the right place", organized close to the patient, we should consider which interventions should be organized at our tertiary center and when to refer to primary health care professionals. For cancer survivors an exercise referral pathway based on literature and adapted to the Dutch Healthcare system has been described.[39] Depending on medical complexity, level of self-efficacy and the level of multidisciplinary required, cancer survivors can be referred to specialized medical rehabilitation, or a supervised exercise program at an oncology physiotherapist, or community based exercise programs (either supervised or unsupervised). During and after HNC cancer treatment, a similar referral strategy can be applied.

HNC survivors might experience long term symptoms impairing QoL, including dry mouth, sticky saliva, dysphagia, trismus, taste dysfunction, and fatigue.[40] It has therefore been advised to assess long-term and late effects of HNC treatment during follow-up visits.[41]

The Utrecht Symptom Diary (USD), a 12-item validated PROM tool, can be used to assess and manage symptoms throughout and after the treatment trajectory.[42,43] Accordingly, the patient can indicate which symptom is most important to him/her, and, if deemed necessary, referred to a dietitian, (orofacial) physiotherapist, speech therapist or a multidisciplinary rehabilitation team. For HNC a disease specific USD has been developed in collaboration with patients.

Future directions for scientific research

With the results of our studies we aim to improve supportive care for patients with HNC receiving CRT. But as in every research, with the results of our studies, new research questions arise. In this paragraph, directions for future research based on the findings of our studies and clinical experience are described.

To optimize tube choice

To improve nutritional care for patients with HNC, the developed prediction model for prophylactic tube placement (**Chapter 5**) can be implemented in usual care. It is recommended to update the tool when new relevant clinical data becomes available. For example, information on the prediction of taste disturbances as a consequence of CRT. Besides dysphagia, taste alterations or loss of taste are important reasons for starting tube feeding, because it severely hampers nutritional intake. Further research to gain insight into causes, consequences and possible preventive measures of taste disturbances in patients with HNC is currently being prepared.

Shared-decision making tools are currently being developed as part of our study funded by the Michel Keijzer Fund in close cooperation with the Dutch HNC patient advocacy group PVHH.[44] With these shared decision making tools, the patient and clinician are able to discuss the pros and cons of the different tube placement options before CRT. Supported by the predicted probability of requiring tube feeding for four weeks or longer using our prediction model, a decision can then be made. Our study was not designed to investigate the best approach for tube feeding initiation and feeding tube insertion, which, of course, would be interesting to study. There is a lack of well-designed clinical trials on optimal tube type and timing of placement. A future multicenter study should study the differences between reactive versus prophylactic (upon indication) tube placement on treatment outcomes, weight loss, PROMs, and PREMs. Besides studying optimal tube type and timing of placement it is also interesting to focus on optimal timing of gastrostomy removement. Our study showed (**Chapter 2**) that there is no consensus in The Netherlands on when to remove the tube. Long-term use of tube feeding, in absence of oral intake, may lead to deconditioning of the swallowing muscles. To prevent this, further research and the development of a guideline on when it is safe and justified to remove the gastrostomy might be helpful.

To optimize adherence to the nutrition prescription

As discussed above, the developed prediction model can be used to optimize nutritional care by identifying patients who would benefit from a prophylactic tube. However, the presence of a prophylactic tube does not inherently guarantee adequate nutritional intake. The advantage of having a prophylactic tube lies in providing a ready-to-use access for tube feeding, minimizing delay in commencing tube feeding when deemed necessary. However, in clinical practice we still observe delays in initiating tube feeding despite having a prophylactic tube. Some patients encounter physiological barriers, for example, "feeling more like an ill person" when starting tube feeding. While others may perceive tube feeding as unnecessary because they are still able to swallow a certain (inadequate) amount of oral nutrition. Additionally, physical barriers, for instance nausea and early satiety, often limit the use of tube feeding according to the prescribed amount. Because of nausea and early satiety, tube feeding is commonly administered continuously using a feeding pump. Some patients experience barriers to using the feeding pump outside their home, due to concerns it makes their disease visible for outsiders and/or logistic difficulties related to the daily travelling to the radiotherapy department. Frequent tube feeding interruptions pose a risk of an inadequate tube feeding intake. A previous study revealed poor adherence to prescribed nutrition intervention in patients with HNC; with only 51% of patients consuming 75% or more of the prescribed tube feeding.[45] To increase adherence to the dietary treatment, including the tube feeding prescriptions, future studies should focus on gaining in depth insight into barriers patients face to adhere to the tube feeding regimen. With this information the multidisciplinary team can proactively address and attempt to overcome these barriers at an early stage.

To optimize dietary treatment and prehabilitation

Besides increasing adherence to the dietary regimen by gaining insight into barriers, there is also a need to gain more insight into changing dietary requirements while exercising during and after

cancer treatment. Energy requirements for cancer patients are assumed to be similar to healthy subjects.[46] Although in some cases energy expenditure might be elevated due to the disease or medical treatment, it is assumed this is compensated by a decrease in physical activity.[47] When increasing physical exercise, it is of the utmost importance to evaluate changes in energy expenditure to prevent weight loss due to inadequate nutritional intake and to reach optimal effects of exercise training. Besides an adequate energy intake, the intake of sufficient protein is necessary to stimulate muscle protein synthesis. A recent study assessed whether patients were able to meet energy and protein requirements during exercise after esophagectomy for esophageal cancer.[48] Results showed that the majority of patients, 77%, did not meet protein requirements, especially when increasing physical activity levels. Moreover, half of the participants did not meet energy requirements, resulting in weight loss, mainly due to loss of fat mass, during the exercise program. These findings underscore the need for future research to gain insights into changing energy and protein requirements of cancer patients and survivors when participating in exercise programs. We are currently studying the effect of the Move Fit exercise program on total energy expenditure, fat-free mass, nutritional status, and muscle strength. Therefore we will compare the results of the Move Fit participants on these measurements with a control group consisting of patients treated with CRT.[49]

Besides assessing the effect of exercise on dietary requirements, also the feasibility and effects of prehabilitation programs, combining exercise and nutritional interventions, for HNC needs further research. As mentioned before, recently the Dutch National Health Care Institute evaluated the prehabilitation program for colon cancer patients and judged it, based on available studies, as not being effective.[33] Coverage from the basic health insurance was thereby ruled out. When offering prehabilitation programs only to selected, high-risk patients, demonstration of efficacy might be better feasible. As shown in the systematic review of Seth[34], until now there are no publications on multimodal prehabilitation programs, including both nutritional and physical exercise interventions, for patients with HNC. We are currently trying to fill this research gap by preparing two prehabilitation feasibility studies, combining an exercise and nutritional intervention, for high-risk HNC patients undergoing surgery.[50,51]

Towards sustainable healthcare and prevention

With a worldwide growing interest and need for sustainability in the healthcare sector and focus on prevention instead of cure, the Dutch government has assigned the Green Deal for Sustainable Healthcare together with more than 300 companies and organizations within and outside the healthcare sector.[52] One of the main themes is to promote healthier, sustainable, and more plant-based nutrition for patients, clients and health workers. Sustainable diets focus on lowering the environmental impact of food production systems and providing healthy diets, sufficient in essential nutrients, for the entire population.[53] For the general, healthy population this includes a transition towards more plant-based nutrition while lowering the intake of animal products. Consuming a mainly plant-based diet, reduces the risk of developing obesity, diabetes, cardiovascular diseases, and some types of cancer.[54] For malnourished cancer patients, a switch towards a more plant-based diet should be guided by a dietitian. Firstly, nutrition impact symptoms related to the disease and cancer treatment, e.g. swallowing disorders, a loss of appetite, poses a threat for an adequate protein intake with protein requirements considered to be 1.5 times higher than for a healthy population.[47] Secondly, plant-based proteins have a lower digestibility and protein quality, a lower content of essential amino acids, as compared to animal proteins.[55] Therefore, it is necessary to combine plant-based protein from different sources for an optimal protein quality and to increase intake to compensate for the lower digestibility. Future research could focus on barriers and facilitators of providing more plant-based protein during cancer treatment in terms of effect on nutritional status and health outcomes as well as palatability and acceptance.

The advantages of a healthy lifestyle, including a more plant-based diet and sufficient physical activity, in cancer prevention have been well studied. It has been calculated that 40% of cancer cases are preventable, if we do not smoke nor drink alcohol, avoid excess sun exposure, consume a healthy diet, maintain a healthy body weight and stay physically active.[54] The World Cancer Research Fund has developed ten recommendations to prevent cancer (Figure 1). Cancer survivors are encouraged to adhere to these recommendations, as far as possible, after treatment, aiming at reducing the risk of cancer recurrence and other non-communicable diseases. For future research it would be valuable to explore the effects of healthy lifestyle interventions in HNC survivors on physical and emotional wellbeing, functional outcomes, cancer recurrence, co-morbidity and mortality. Studying effectiveness, including cost-effectiveness, is necessary to apply for coverage by the basic health insurance. Until now, only a combined lifestyle intervention for overweight people is covered by the basic health insurance in the Netherlands.
To explore adherence of HNC survivors to the Dutch dietary guidelines we are currently studying the prevalence of long-term nutrition impact symptoms and diet quality in HNC survivors treated with CRT.[56]

Figure 1. Cancer prevention recommendations Word Cancer Research Fund International.[54]
This material has been reproduced from the World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

Conclusion

This thesis provides insights in how to further optimize and personalize supportive care for patients with HNC treated with CRT. We have shown that substantial variation exists in dietetic practice for patients with HNC at the Dutch head and neck centers, probably due to a lack of concise guidelines. With regard to gastrostomy placement policy, most centers have developed there own selection criteria for prophylactic gastrostomy placement. We therefore developed and validated a prediction

tool for prophylactic gastrostomy placement. We advice to use the model to identify patients at risk for tube feeding dependency for ≥ four weeks, who could benefit from a prophylactic gastrostomy. Shared decision making tools for tube placement are currently being developed to aid decision making for patients and clinicians. Selecting patients who would benefit from prophylactic tube helps them to maintain adequate nutritional intake which is necessary for preventing or reducing weight loss during treatment. This weight loss mainly consists of loss of fat-free mass, and negatively affects treatment outcomes. Besides adequate dietary intake, exercise is a prerequisite for preserving fat-free mass. With the Move Fit study, we assessed the feasibility of an exercise intervention during CRT. We found that individual adaptations of this exercise program are necessary to increase feasibility, taking into account personal barriers and facilitators with regard to planning and time-management, (dealing with) treatment toxicity, incentive to exercise and the provided supervision. Future studies should asses the added value of combined nutritional and exercise interventions and the feasibility and cost-effectiveness of digital, self-management tools. As well as nutritional care, exercise should become an integral part of care for patients with HNC.

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Nederlandse samenvatting

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Ondervoeding en dieetbehandeling voor mensen met hoofd-halskanker

De diagnose en behandeling van hoofd-halskanker heeft grote impact op het leven van patiënten. Vanwege de tumor en door de bijwerkingen van de behandeling is de orale voedingsinname vaak verminderd. Naast de emotionele gevolgen van het niet kunnen eten, heeft onvoldoende voedingsinname ook invloed op de fysieke conditie. Onbedoeld gewichtsverlies treedt vaak op als gevolg van onvoldoende voedingsinname en is, in combinatie met een lage body mass index en een verminderde spiermassa, een belangrijk criterium voor het stellen van de diagnose ondervoeding. Talrijke studies hebben aangetoond dat ondervoeding een negatief effect heeft op de lichamelijke conditie, toxiciteit van de behandeling, behandelcomplicaties, kwaliteit van leven, zorgkosten en overleving bij hoofd-halskankerpatiënten. Ondervoeding bij patiënten met kanker is multifactorieel. Aan de ene kant leiden symptomen, zoals dysfagie, pijn, anorexia en misselijkheid, veroorzaakt door de tumor of behandeling, tot onvoldoende voedingsinname. Aan de andere kant wordt een systemisch ontstekingssyndroom, het anorexia-cachexiesyndroom, vaak waargenomen bij kankerpatiënten. Het anorexia-cachexiesyndroom omvat metabole afwijkingen, waaronder insulineresistentie, lipolyse en proteolyse, resulterend in vermoeidheid, anorexia en het verlies van skeletspieren.

Dieetbehandeling is ingebed in het zorgpad voor mensen met hoofd-halskanker en heeft tot doel ondervoeding te voorkomen of in een vroeg stadium te behandelen en richt zich op het optimaliseren van de voedingsinname rekening houdend met de persoonlijke behoeften en voorkeuren van patiënten. Wanneer de orale voedingsinname inadequaat blijft, ondanks voedingsadviezen ter verbetering van de orale inname, is sondevoeding vaak onvermijdelijk gedurende de behandeling met chemoradiotherapie. Sondevoeding wordt dan toegediend via een neus-maagsonde of gastrostomie. Naast het optimaliseren van de voedingsinname is inspanningstraining belangrijk om spiermassaverlies te voorkomen of te herstellen. Trainingsprogramma's in andere kankerpatiëntenpopulaties hebben gunstige effecten aangetoond op fysieke fitheid, vermoeidheid, kwaliteit van leven en het voltooien van de medische behandeling.

Bevindingen

In **Hoofdstuk 2** werden variaties in voedingsinterventies en de uitvoering van de dieetbehandeling voor patiënten met hoofd-halskanker tijdens chemoradiotherapie bij de Nederlandse hoofd-halsoncologische centra beschreven. Voor dit onderzoek is een online vragenlijst ontwikkeld en verstuurd naar diëtisten van alle veertien hoofd-halsoncologische centra in Nederland. Dertien oncologiediëtisten vulden de vragenlijst in, zij vertegenwoordigen dertien van de veertien centra. De resultaten van deze studie laten een aanzienlijke variatie in de uitvoering van de dieetbehandeling zien. Het aantal geplande diëtetiek consulten als onderdeel van de gebruikelijke zorg varieerde van twee tot zeven tijdens de 7-weekse behandeling met chemoradiotherapie. Voor het berekenen van de energiebehoefte gebruikt 54% van de diëtisten de FAO/WHO/UNU-formule en de meerderheid (77%) past de eiwitaanbeveling van 1.2-1.5 gram/kg lichaamsgewicht toe. De meeste centra (77%) geven aan dat, wanneer sondevoeding noodzakelijk werd geacht, een gastrostomie werd gebruikt als toedieningsweg bij de meerderheid van de patiënten. In vijf centra (39%) werden gastrostomieën alleen op indicatie profylactisch geplaatst. Twee centra plaatsten profylactische gastrostomieën bij alle hoofd-halskankerpatiënten die behandeld werden met chemoradiotherapie (15%), twee andere centra plaatsten sondes alleen reactief (15%), en vier centra plaatsten sondes zowel profylactisch als reactief (31%). In slechts zes van de dertien centra was een centrum-specifiek protocol aanwezig waarin de indicaties voor het plaatsen van een gastrostomie zijn vastgelegd. Bijna de helft van de centra (46%) meldde dat de gastrostomie tussen 8 en 12 weken na chemoradiotherapie wordt

verwijderd en, in de meeste centra (92%), werd de dieetbehandeling gemiddeld binnen 6 maanden na chemoradiotherapie beëindigd. Om de variatie tussen centra in de inhoud en uitvoering van de dieetbehandeling te verminderen, wordt geadviseerd om multidisciplinaire richtlijnen voor hoofd-halskanker te ontwikkelen en te implementeren op basis van de beschikbare literatuur. Deze richtlijnen bieden handvatten voor het inrichten en uitvoeren van de diëtistische zorg gedurende het hele zorgproces voor patienten met hoofd-halskanker, inclusief frequentie van consulten, inhoud van het voedingsvoorschrift en indicaties en timing van sonde plaatsing.

In **Hoofdstuk 3**, zijn factoren geïdentificeerd die verband houden met het gebruik van enterale voeding (sondevoeding) en gastrostomie plaatsing bij 240 patiënten met hoofd-halskanker die tussen 2012 en 2015 in het Universitair Medisch Centrum Utrecht werden behandeld met chemoradiotherapie. Het doel van dit retrospectieve dossieronderzoek was om potentiële indicatoren voor gastrostomie plaatsing te identificeren om de besluitvorming in de klinische praktijk hieromtrent te ondersteunen. Bij 84% van de patiënten in deze populatie werd een gastrostomie geplaatst en 81% van de patiënten gebruikte sondevoeding tijdens het behandeltraject. Multivariabele analyse toonde aan dat de aanwezigheid van lymfekliermetastasen en bilaterale halsbestraling significant geassocieerd waren met het gebruik van sondevoeding. Een hogere leeftijd, de aanwezigheid van lymfekliermetastasen, een reconstructie anders dan primaire sluiting, bilaterale halsbestraling en het gebruik van voeding met een aangepaste consistentie voorafgaand aan de behandeling, waren significant geassocieerd met de plaatsing van een gastrostomie. De beschreven factoren die geassocieerd zijn met het gebruik van sondevoeding en gastrostomie plaatsing kunnen gebruikt worden in de ontwikkeling van een protocol voor gastrostomie plaatsing. Voor implementatie van een protocol is het echter wenselijk verder onderzoek te doen, bij voorkeur met gebruik van data van meer dan één centrum.

In **Hoofdstuk 4** werd een voorspelmodel ontwikkeld en intern gevalideerd, om patiënten te identificeren die in aanmerking komen voor het plaatsen van een profylactische gastrostomie. Voor deze retrospectieve cohortstudie werden gegevens gebruikt van 450 patiënten met hoofd-halskanker die behandeld waren met chemoradiotherapie of bioradiotherapie in het Universitair Medisch Centrum Utrecht en het Maastricht Universitair Medisch Centrum tussen 2013 en 2016. Het gebruik van sondevoeding gedurende vier weken of langer, werd gedefinieerd als de primaire uitkomstmaat. Dit is in overeenstemming met internationale richtlijnen die aanbevelen om een gastrostomie te plaatsen wanneer sondevoeding naar verwachting gedurende tenminste vier weken nodig is. Patiënt-, tumor- en behandelingskenmerken werden verzameld uit de medische dossiers en de associatie met het gebruik van sondevoeding werd geanalyseerd met behulp van uni- en multivariabele analyse. In totaal hadden 294 van de 450 patiënten (65%) vier weken of langer sondevoeding gebruikt. Body mass index, het gebruik van voeding met een aangepaste consistentie en procentuele gewichtsverandering bij start van de behandeling, Wereld-gezondheidsorganisatie (WHO) performance status, tumorlokatie, TNM-classificatie, chemoradiotherapie, gemiddelde bestralingsdosis op de contralaterale onderkaakspeekselklier en op de contralaterale oorspeekselklier waren significant geassocieerd met het gebruik van sondevoeding en werden in het multivariabele model opgenomen. Na interne validatie vertoonde het voorspelmodel een goed onderscheidend vermogen (Area Under the Curve (AUC) 72,3%). Het model kan worden gebruikt om de gepersonaliseerde besluitvorming over het plaatsen van een profylactische gastrostomie te ondersteunen. Echter, externe validatie is vereist om dit model als beslishulp op grote schaal te implementeren in de klinische praktijk.

Hoofdstuk 5, beschrijft hoe het voorspelmodel geactualiseerd en extern gevalideerd is, om patiënten met hoofd-halskanker die worden behandeld met chemoradiotherapie of bioradiotherapie en baat zouden kunnen hebben bij profylactische gastrostomie plaatsing, te identificeren. Dit geactualiseerde voorspelmodel is ontwikkeld met behulp van retrospectieve gegevens van patiënten met hoofd-halskanker behandeld in het Universitair Medisch Centrum Utrecht en het

Nederlands Kanker Instituut (n=409) en extern gevalideerd met behulp van gegevens van patiënten behandeld in het Maastricht Universitair Medisch Centrum en het Radboud Universitair Medisch Centrum (n=334). Het primaire eindpunt was het gebruik van sondevoeding gedurende ten minste vier weken geïnitieerd tijdens, of binnen 30 dagen na de behandeling met chemoradiotherapie of bioradiotherapie. Naast de potentiële voorspellers verkregen uit de medische dossiers, bevat dit geactualiseerde model ook de bestralingsdosis op de slikspieren en de mondholte, ingetekend voor deze studie. Het definitieve multivariabele regressiemodel bevat de volgende indicatoren; gewichtsverandering en het gebruik van voeding met een aangepaste consistentie vóór de behandeling, Wereldgezondheids-organisatie (WHO) performance status, tumorlokatie, lymfekliermetastasen (N-classificatie), gemiddelde bestralingsdosis op de contralaterale oorspeekselklier en mondholte. Het onderscheidend vermogen van dit geactualiseerde model was goed met een AUC van 73%, en 62% na externe validatie. De positieve en negatieve voorspellende waarde bij een risico van 90% of hoger op sondevoedingsafhankelijkheid ≥ 4 weken waren, respectievelijk, 82% en 42%. Op basis van deze resultaten raden we aan om profylactisch een gastrostomie te plaatsen bij een, volgens het model, voorspeld risico van >90%. Bij een risico van >70%, kan profylactische gastrostomie plaatsing met de patiënt besproken worden. Dit ondersteunt de gepersonaliseerde en gedeelde besluitvorming in de klinische praktijk.

In **Hoofdstuk 6** werd bij veertig patiënten met hoofd-halskanker de haalbaarheid van een beweeginterventie tijdens chemoradiotherapie onderzocht. De 10 weken durende beweeginterventie op maat bestond uit een combinatie van duur- en krachttraining met gesuperviseerde sessies en home-based sessies. De adherence (aanwezigheid bij de gesuperviseerde sessies) was 54%, iets lager dan het nagestreefde doel van 60%, gebaseerd op resultaten van eerdere studies in andere kankerpatiëntenpopulaties. Ook was het retentiepercentage (voltooien van de interventie), met 65%, lager dan het gestelde doel van 85%. Het wervingspercentage en de therapietrouw (naleving van de gesuperviseerde interventie volgens het protocol) waren, respectievelijk 36% en 66%, hoger dan de nagestreefde 30% en 60%. De belangrijkste reden voor het niet bijwonen van de gesuperviseerde trainingsessies en het voortijdig beëindigen van deelname aan de interventie was de toxiciteit van de behandeling. Andere genoemde redenen waren; fysieke en emotionele klachten en organisatorische (plannings)problemen. Statistisch significante afnames in handknijpkracht, vetvrije massa en klinisch relevante verslechteringen op verschillende domeinen van kwaliteit van leven en vermoeidheidssubschalen werden gevonden. Deze haalbaarheidsresultaten suggereren dat dit beweegprogramma voor hoofd-halskankerpatiënten tijdens chemoradiotherapie in zijn huidige vorm slechts voor een minderheid van de patiënten haalbaar is. Naast de kwantitatieve resultaten van de haalbaarheid van de beweeginterventie zoals beschreven in **Hoofdstuk 6**, worden de kwalitatieve resultaten van dit onderzoek beschreven in **Hoofdstuk 7**. In dit kwalitatieve onderzoek werden verwachtingen, ervaringen en factoren beschreven die van invloed zijn op de adherence, retentie en therapietrouw van hoofd-halskankerpatiënten die deelnemen aan de beweeginterventie. Veertien opeenvolgende deelnemers werden uitgenodigd voor semi-gestructureerde interviews, uitgevoerd voor en na de interventie. Met behulp van een thematische analyse met een deductieve benadering werden vijf hoofdthema's geïdentificeerd. Deze thema's waren: planning en time management, behandelingstoxiciteit, motivatie om te oefenen, beweeginterventie en supervisie door de fysiotherapeut. De intensiteit en de toxiciteit van de behandeling waren belangrijke barrières, die de adherence, retentie en therapietrouw negatief beïnvloedden. Facilitators die werden genoemd waren fysieke en emotionele voordelen, sociale steun en de eenvoud en thuisgebaseerde setting van de interventie. Een nog meer gepersonaliseerde aanpak, rekening houdend met de individuele facilitators en barrières van hoofd-halskankerpatiënten binnen de beschreven thema's, is belangrijk om de adherence, retentie en de therapie trouw van een beweeginterventie te vergroten en optimale effecten van het programma te bereiken.

In **Hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift en hun relevantie voor de klinische praktijk en suggesties voor toekomstig onderzoek besproken. We raden diëtisten aan kritisch te kijken naar de organisatie van zorg om deze toegankelijk en betaalbaar te houden. Het gebruik van de Zorgmodule voeding, ontwikkeling van transmurale zorgpaden en innovatieve voorlichtingsmateralen sluiten aan bij de Integraal Zorg Akkoord (IZA) principes en helpt de voedingszorg toegankelijk en betaalbaar te houden. De implementatie van het ontwikkelde PEG beslismodel sluit ook goed aan bij de IZA principes en we stimuleren het samen beslissen bij de keuze voor sonde plaatsing. In een gerandomiseerde studie kan het gebruik van het PEG beslismodel en effect op klinische uitkomsten worden onderzocht.
We stellen voor dat diëtisten en fysiotherapeuten betrokken bij de zorg voor mensen met hoofd-halskanker, de voedings- en beweegzorg nog meer personaliseren en integreren in zorgpaden. Het gebruik van digitale tools kan hierbij ondersteunen en afhankelijk van de complexiteit van de zorg kan verwezen worden naar 1e of 2e lijns zorg. Na de behandeling van hoofd-halskanker is het belangrijk lange-termijn symptomen te monitoren en, zo nodig, tijdig door te verwijzen naar zorgprofessionals. Aandacht voor preventie en een gezonde leefstijl verdient meer aandacht. Het verdient aanbeveling om toekomstig onderzoek te richten op het effect van leefstijlinterventies na hoofd-halskanker op kwaliteit van leven, fysiek functioneren en klinische uitkomsten.

Dankwoord

Dankwoord

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About the author

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Annemieke Kok was born on Whit Monday in Paterswolde, Drenthe, The Netherlands. She completed her secondary pre-university education at Zernike College in Haren (2000), and the bachelor Nutrition and Dietetics at the Hanze University of Applied Sciences in Groningen (2004). During her internship at the University Medical Center Groningen her interest in scientific research and head and neck cancer care was triggered. After receiving her Bachelor's degree in Nutrition and Dietetics, she completed her Master Nutrition and Health at Wageningen University (2006).

She worked as a researcher at the Public Health Service of Amsterdam and as a clinical dietitian at the Flevoziekenhuis in Almere, before starting her work as a dietitian at the department of dietetics at the University Medical Center Utrecht in 2009.

She has a special interest in head and neck cancer care and nutritional assessment. In 2017 she received a grant from the Nationaal Fonds tegen Kanker to explore the effect of exercise training on energy expenditure, fat-free mass, nutritional status and muscle strength (PA-INTENS study). She started her part-time PhD research on April 1st 2019 at the UMC Utrecht Cancer Center. Currently, Annemieke continues her research activities within the PA-INTENS study and other projects focusing on prehabilitation, prevention, and sustainable healthy diets at the department of Dietetics. A grant from the Michel Keijzer foundation (2021) allows her to continue the work on the gastrostomy prediction model with the goal to develop shared-decision making tools.