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The feasibility of physical rehabilitation in patients with head and neck cancer

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Norsk sammendrag / summary in Norwegian

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Abstract

Patients with head and neck cancer (HNC) often experience decreased food-intake and malnutrition due to the cancer disease and treatment related side-effects with subsequent loss of body weight and muscle mass. Muscle wasting has a negative impact on physical function and health-related quality of life (HRQoL). Physical exercise and nutritional support may limit declines in body weight and muscle mass and improve functioning. The aim of this thesis is to evaluate the feasibility of a combined physical exercise and nutrition intervention conducted during or after radiotherapy (+/- chemotherapy) in patients with HNC, assess the impact on muscle mass, body weight and HRQoL and describe how the patients experienced the nutritional situation and perceived nutritional support from diagnosis to the acute post-treatment phase.

The thesis consists of a two-armed randomised pilot study. Patients with head and neck cancer were recruited from St. Olavs hospital, Trondheim University hospital in the period between March 2015 to March 2016. Included patients were randomised to a physical exercise and nutrition intervention during or after radiotherapy, consisting of resistance training and oral nutritional supplements. All patients underwent objective and self-reported measurements before start of radiotherapy, at the end of radiotherapy, two months after radiotherapy and one-year later. Feasibility was measured by recruitment, completion and attrition rates and intervention adherence. Muscle mass was measured by computed tomography scans of the third lumbar vertebrae, body weight by the same scale at each assessment and HRQoL by the European Organisation for Research and Development in Cancer quality of life questionnaire C30 including the head and neck cancer module H&N35. A selection of the patients was invited to complete individual interviews after the end of radiotherapy.

Forty-one out of 50 eligible patients (82 %) were willing to participate in the study. Eighteen of the 20 patients randomised to the intervention during treatment completed the programme. More than 80 % of the exercise-sessions were completed as planned, and 57 % of the nutritional supplements were ingested. The mean loss of muscle mass area was less in the intervention group compared to the "controls" from start to end of radiotherapy, while no differences in mean change of body weight was observed. Clinically relevant differences in

change of global health status/QoL and physical functioning was observed in favour of the intervention group during treatment.

Only 11 of the 21 patients randomised to the intervention after treatment attended and completed the programme. Virtually all the exercise-sessions were completed and 76 % of the nutritional supplements were ingested. An increase in mean muscle mass area was observed in the active intervention after treatment compared to a decrease among the "controls" from week 6 to week 14, and no differences in change of body weight was observed. Clinically relevant differences in global health status/QoL and physical functioning were observed in favour of the intervention group after treatment. The attenders to the intervention after treatment were younger compared to the non-attenders, and more were diagnosed with pharyngeal cancer and scheduled for concurrent chemoradiotherapy. Furthermore, the attenders were characterised by clinically significant worse HRQoL, higher physical activity level and higher functional capacity compared to the non-attenders at baseline.

The interviewed patients described comprehensive nutritional problems from diagnosis to the acute post-treatment phase. Reduced food intake was experienced already prior to the start of radiotherapy. During radiotherapy, the side-effects caused increasing difficulties with eating and drinking, and the participants had to customise their meals to improve the food-intake. Oral nutritional supplements eventually got unbearable to ingest. The participants felt discouraged about the persistent side-effects after the end of radiotherapy, preventing them from eating and drinking as desired. When reflecting on the treatment period, they missed specific information about the expected recovery from side-effects, and the absence of a dietitian as part of the multidisciplinary team was highlighted.

In conclusion, the present thesis demonstrates that a combined physical exercise and nutrition intervention is feasible during radiotherapy in patients with head and neck cancer. The observed mitigation of loss in muscle mass following the intervention during treatment provides support for a full-scale randomised controlled trial (RCT), and the impact on HRQoL is also promising and further supporting a RCT. A post-treatment physical exercise and nutrition intervention seems especially appropriate for patients receiving concurrent chemoradiotherapy. The patients' nutrition-related experiences indicate a need for specialised and individually tailored nutritional support throughout the treatment trajectory.

Acknowledgements

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Errata

Paper I

The following information is missing from the section *EN-DUR intervention* (pages 2-3):

- "All patients allocated for the EN-DUR intervention were scheduled for an initial meeting with the responsible physiotherapist to receive a booklet with nutritional advice specifically designed for patients with HNC, and to taste the various flavours of the provided nutritional drink"
- The description of ONS-intake should also include "in addition to one extra unit after each exercise session"

List of papers

Paper I Sandmæl JA, Bye A, Solheim TS, Stene GB, Thorsen L, Kaasa S, Lund JÅ, Oldervoll LM. *Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial.* Cancer 2017 Nov 15; 123(22):4440-4448. Doi: 10.1002/cncr.30901. Epub 2017 Jul 31.

Paper II Sandmæl JA, Bye A, Solheim TS, Balstad TR, Thorsen L, Skovlund E, Kaasa S, Lund J-Å, Oldervoll L. *Physical rehabilitation in patients with head and neck cancer: Impact on health-related quality of life and suitability of a post-treatment program.* Laryngoscope Investigative Otolaryngology, submitted 27th of August 2019.

Paper III Sandmæl JA, Sand K, Bye A, Solheim TS, Oldervoll L, Helvik A-S. *Nutritional experiences in Head & Neck Cancer (HNC) patients.* European Journal of Cancer Care, accepted for publication 4th of September 2019.

Abbreviations

BIA	Bioelectrical impedance analysis
BMI	Body mass index
CI	Confidence interval
cm^2	Square centimetre
CONSORT	Consolidated standards of reporting trials
CT	Computerised tomography
d	Effect size
DEXA	Dual-energy x-ray absorptiometry
EN-AF	Exercise and nutrition intervention after radiotherapy
EN-DUR	Exercise and nutrition intervention during radiotherapy
ENT-clinic	Clinic of ear-nose-throat, eye and maxillofacial surgery
EORTC QLQ-C30	European organization for research and treatment of cancer quality of life questionnaire-C30
ESPEN	European society for clinical nutrition and metabolism
Gy	Gray
HNC	Head and neck cancer
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HU	Hounsfield units
HUNT 1 PA-Q	The Nord-Trøndelag Health Study 1 Physical Activity Questionnaire
ICF	International classification of functioning
IGF-1	Insulin-like growth factor 1
IMRT	Intensity-modulated radiotherapy
IQR	Inter-quartile range
kcal	Kilocalorie
kg	Kilogram
KPS	Karnofsky performance status
L3	The third lumbar vertebrae
m	Metre
m^2	Square metre
max	Maximum

min	Minimum
MJ	Mega joule
ml	Millilitres
MSWT	Modified shuttle walk test
n	Number
NTNU	Norwegian University of Science and Technology
NV	Nausea and vomiting scale
PEACE	Physical exercise across the cancer experience
PEG	Percutaneous endoscopic gastrostomy
PF	Physical functioning scale
PG-SGA	Patient-generated subjective global assessment
PRT	Progressive resistance training
RCT	Randomised controlled trial
REK	Regional committees for medical and health research ethics
RF	Role functioning scale
RM	Repetition maximum
RPE	Rating of perceived exertion
SD	Standard deviation
30s STS	30 seconds sit to stand test
TNM	Tumour node metastasis staging system

Definitions and clarification of concepts

Physical rehabilitation consists of physical exercise, nutritional support and/or symptom control interventions [1, 2]. The present thesis specifically concerns **physical exercise and nutritional support.**

Feasibility and pilot studies are conducted in preparation for a future definitive randomised controlled trial (RCT). A feasibility study asks whether the future RCT can be done, should be done, and if so, how. **Pilot studies** are a subset of feasibility studies that ask the same questions, in addition to conducting the future RCT, or part of it, on a smaller scale [3, 4].

Physical exercise is planned, structured and repeated physical activity that aims to improve physical capacity, performance or health. Physical activity is any bodily movement produced by skeletal muscles resulting in energy expenditure above resting level [5, 6].

Resistance training is synonymous to strength training and refers to physical exercises specifically aiming for improved muscular strength [7].

Nutritional support is the provision of nutrition or nutrients either orally by regular or therapeutic diet (e.g. fortified food and oral nutritional supplements), or via enteral or parenteral nutrition to prevent or treat malnutrition [8].

Body composition refers to the proportion of bone, fat and muscle mass in addition to body water. **Lean body mass** comprises organs, bones, body water and muscle mass, while **muscle mass** refers to the skeletal muscles [9, 10].

1. Introduction

I was introduced to the field of rehabilitation in 2004, when first employed at a rehabilitation clinic offering services within the specialised healthcare. After working specifically with the orthopaedic, cardiac and return-to-work programmes for a few years, I got the opportunity to take part in establishing the first specialised cancer rehabilitation programme in central Norway. The work was initiated by the Norwegian Cancer Society, and St. Olavs hospital, Trondheim University Hospital, the Norwegian University of Science and Technology (NTNU) and LHL-clinics Røros represented the project's professional partners.

The cancer rehabilitation programme was designed as an open intervention study primarily to examine feasibility-aspects and observe the impact of and changes in objective and self-reported health outcomes. The initial publication from the study showed that the attending patients primarily consisted of highly educated women with breast cancer that reported higher levels and more symptoms and lower functioning, but higher levels of physical activity, compared to the general population [11]. Symptoms and functioning normalised following the programme and were kept stable at six months follow-up.

Taking part in establishing a new rehabilitation programme made me especially interested in the importance of rehabilitation for cancer patients, but also in the field of clinical research. In 2012, I completed my master's degree in health science in which physical activity data from the rehabilitation programme was presented in the final study-assignment. Through the work with the cancer rehabilitation programme, I was introduced to various healthcare and academic professionals that provided me with new insights into the clinical cancer research field.

Patients with head and neck cancer have for a long time been regarded as an understudied patient-group severely troubled by multiple negative consequences from the disease and its treatment. On this background, it was requested from the clinical project partners both to evaluate existing rehabilitation services and test new interventions that could help reduce symptoms and improve functioning. I was invited to take part in the writing of a study protocol that eventually triggered PhD funding in 2014. From March 2015 to March 2016,

patients with head and neck cancer were invited to participate in the present pilot study, and the data-collection was completed in July 2017.

2. Theoretical background

2.1 Head and neck cancer

Head and neck cancer (HNC) is a generic term that refers to malignancies originating from the epithelial lining of the upper aero-digestive tract. HNC can be divided into four subgroups: a) oral cavity cancer, including cancer of the tongue, floor of the mouth, gums, palate and cheek, b) pharyngeal cancer, including cancer of the nasopharynx, oropharynx and hypopharynx, c) laryngeal cancer, and d) other cancers, including nasal cavity, sinuses, salivary glands and lips [12]. Squamous cell carcinomas constitute more than 90 % of all cancers in the head and neck region. Other tumour types include adenocarcinomas, melanomas and sarcomas.

2.1.1 Epidemiology and risk factors

In Norway, almost 800 patients are diagnosed with HNC each year, accounting for 2.4 % of all new cancer cases [13]. The median age at diagnosis is 67 years, and 65 % of the patients are men. The 5-year relative survival rate has increased over the last 10 years and was 67 % for men and 74 % for women from 2012 – 2016 for all stages combined. Worldwide, HNC accounted for an estimated 4.8 % of all new cancers in 2016 [14].

The main risk factors for HNC are tobacco smoking and excessive alcohol consumption, and a combined use increase the risk. Also Epstein-Barr virus and high-risk human papilloma viruses (HPV) have been recognized as etiological agents of nasopharynx and oropharynx carcinomas [15, 16]. It is worth noting that the incidence of HPV-positive oropharyngeal cancer has increased significantly from previous to the present millennium (e.g. 225 % in the U.S.A), while HPV-negative cancer has declined [17-19]. Patients with HPV-positive oropharyngeal cancer are typically middle-aged, non-smoking men of higher socioeconomic status, and thus stand out from the classic HNC patient of at least 70 years old with a history of tobacco and alcohol abuse [20, 21].

2.1.2 Diagnosis and tumour staging

Early recognition of symptoms and signs are vital for prompt diagnosis; however, the symptoms are often vague and similar to that occurring in non-malignant conditions. Common symptoms include hoarse voice, sore throat, swallowing difficulties, ulcers in the

mouth, earache and swollen lymph nodes [22]. Accurate staging is the most important factor for therapeutic decision making and indicates prognosis. HNCs are divided into four stages by the tumour, node, metastasis staging system (TNM) [23]. Stage I and II are considered early stages and comprise T1 and T2 cancers with no nodal or distant metastasis. Stage III and IV are considered late or advanced stages, and comprise T3 and T4 cancers as well as tumours with nodal and/or distant metastasis [24]. About two-thirds of patients with HNC present with advanced stage disease, commonly involving regional lymph nodes [25].

2.1.3 Treatment

Since national guidelines for the management of HNC is currently under preparation in Norway, the present treatment descriptions are based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HNCs (U.S.A), the Multidisciplinary Guidelines for HNC (U.K) and the Danish HNC Group (DAHANCA) Radiotherapy Guidelines [26-30].

Treatment decisions are often complicated in patients with HNC and require a multidisciplinary team primarily consisting of a head and neck surgeon, oncologist, radiologist, pathologist, dentist, nurse specialist and dietitian. Plastic, oral and neurosurgeons are also involved if needed. The treatment options consist of surgery, radiotherapy and chemotherapy, either as single modality or in combination. TNM-stage and primary site determine the choice of therapy, in addition to the patient's health status and preferences [31]. Single-modality treatment with surgery or radiotherapy is the preferred therapy in early stage disease (stage I and II), while advanced stage disease (stage III and IV) entails radiotherapy (+/- chemotherapy) alone or as adjuvant therapy following surgery [25].

Surgery

Surgery is conducted either before radiotherapy (postoperative radiotherapy) or after radiotherapy (preoperative radiotherapy), with postoperative radiotherapy the most common combination [32]. As primary treatment, surgery is reserved for resect able tumours in which clear margins can be achieved and function preserved. Neck dissection could also be carried out when surgery is the primary treatment in order to remove regional lymph nodes with potential metastasis. Depending on the anatomy and tumour characteristics, open surgery or minimally invasive procedures (e.g. trans-oral robotic surgery or laser surgery) can be

employed, which may result in cosmetic deformity and functional impairment although reconstructive surgery has improved significantly in recent years [33].

Radiotherapy

An estimated 75 % of all patients with HNC receive radiotherapy, either as part of their primary treatment or as adjuvant treatment after surgery [32]. Primary radiotherapy has improved loco-regional control markedly, and also cure rates for early stage glottis, base of tongue and tonsillar cancer [30]. The objective of radiotherapy is to deliver a defined radiation dose to a specific volume, with the intent to eliminate tumour cells in this area while minimising radiation of surrounding healthy tissue. The unit of radiation dose is gray (Gy), which is defined as the absorbed dose of radiation by the tissue (1 Gy = 1 joule per kilogram) [34]. The total dose of radiation is divided into fractions, typically given five days a week for a total of 6-7 weeks. Prescribed radiation dose depends on the primary tumour and neck node size, fractionation, and whether to use concurrent chemotherapy. In general, the primary tumour requires a total of 66 to 74 Gy (2.0 Gy per fractionation). Hyper-fractionation includes two or more fractions per day with reduced dose per fraction (usually 1.10-1.25 Gy), often delivered within the same time-period as with standard radiotherapy. Accelerated fractionation is designed to increase radiation dose intensity by delivering fractions of 1.6-1.8 Gy at least once daily, with a reduced treatment period compared to hyper-fractionation [15]. However, no single fractionation schedule has proven to be superior for all head and neck tumours [26].

The major advantage of radiotherapy compared to surgery is the possibility of organ preservation and elimination of any unknown micro-metastases, resulting in better cosmetic and functional outcomes [35, 36]. Conformal radiotherapy refers to modalities in which the radiation beams are shaped to cover the tumour plus surrounding tissue margins, and include three-dimensional conformal radiotherapy, intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy, proton-beam radiotherapy [37]. IMRT is increasingly opted for, and the major advantage is reduced toxicity of salivary glands, temporal lobes, mandible, and auditory and optic structures [38-43].

Chemotherapy

Chemotherapy has become a central component in curative treatment of locally advanced HNC [44, 45]. It is administrated concurrently with radiotherapy (chemoradiotherapy),

typically once a week throughout the radiotherapy period. It improves the treatment efficacy by its radio-sensitising ability and by providing systematic therapy against distant metastatic disease [46, 47]. Various classes of agents such as platinum compounds, antimetabolites, and taxanes are utilised. The platinum compound cisplatin is regarded as the standard agent in combination with radiation or with other agents [48, 49].

2.1.4 Treatment-related side-effects

Despite careful planning and improved techniques, the treatment of HNC does not come without side-effects. Surgery may cause loco-regional pain due to nerve damage or misalignment of remaining structures, and mouth-dryness (xerostomia) due to removal of salivary glands. Nerve damage and removal of tissue as part of the resection may lead to functional impairments, especially chewing and swallowing difficulties [12, 50, 51]. In general, functional impairments increase as the extent of the surgery increase. Facial disfigurement as a result of extensive surgery may negatively affect the patients' self-esteem and body image [52].

Patients with HNC may therefore experience symptoms already before the start of radiotherapy, not only caused by prior treatment, but also by tumour itself. In a prospective study of patient-reported outcomes before, during and after radiotherapy, more than 30 % of the patients reported a high symptom burden prior to radiotherapy [53]. A high symptom burden was correlated with a higher tumour classification, poorer performance status and recent treatment (i.e. surgery and/or chemotherapy). Symptoms of fatigue, sleep disturbance, distress, pain and problems chewing, and eating were most often rated moderate to severe. Similar rating of symptoms prior to treatment start has also been found other studies of symptom burden in patients undergoing radiotherapy or concurrent chemoradiotherapy [54].

Side-effects from radiotherapy with or without chemotherapy are inevitable, although refined modalities such as IMRT are increasingly employed to minimise toxicity [55]. The intensity of the side-effects depends on the radiation modality and dose, treated volume, if combined with chemotherapy or not, and individual factors such as gender, age, smoking habits and nutritional status [56, 57]. Radiotherapy-related side-effects are commonly classified as acute, consequential and late effects. Acute side-effects normally increase in intensity from start to end of radiotherapy and reaches a peak at the end of and immediately after treatment. The side-effects develop during treatment in tissues with rapidly proliferating cells, and include

dermatitis, mucositis, xerostomia, saliva change, taste alterations and swallowing difficulties (dysphagia) [54, 58-60]. [54]. Consequential side-effects consist of acute side-effects that persist beyond tumour directed treatment, while late side-effects develop months to years following treatment completion in tissues with a slower cell-turnover [61, 62]. Late side-effects commonly include spasms of the jaw muscles (trismus), fibrosis, xerostomia, muscle wasting (atrophy), vascular damage and osteoradionecrosis [63, 64]. Fatigue is common both during and after radiotherapy, and has been associated with the inflammatory markers interleukin-6 and C-reactive protein [65-67].

Malnutrition has been found to be present in more than 70 % of patients with HNC at the end of radiotherapy [68, 69]. In clinical settings in general, malnutrition can be caused both by reduced nutritional intake or uptake and can then generally be referred to as simple malnutrition [70]. Cancer-related malnutrition is caused by a combination of reduced food intake and metabolic derangements [71-74]. The metabolic changes include elevated resting metabolic rate, insulin resistance as well as increased lipolysis and proteolysis that may be derived from the host or tumour. Cancer-related malnutrition is in general associated with loss of body weight and muscle mass, impaired physical function, psychosocial stress, lower health-related quality of life (HRQoL), reduced immune function and increased rate of infections, treatment toxicity and increased risk of mortality [69, 75, 76]. The maintenance of an optimal nutritional status is vital for improved health outcomes, treatment tolerance and survival in patients with HNC [77, 78].

During the course of radiotherapy more than 50 % of patients with HNC experience critical weight loss, defined as a weight loss of more than 5 % of the pre-treatment body weight [79, 80]. Critical weight loss has also in patients with HNC been significantly associated with worse disease specific and overall survival rates and deteriorated functional performance and quality of life.[81]. The weight loss experienced by patients with HNC concerns a change in body composition (i.e. fat, bone, water and lean body mass), and more than 70 % of the weight loss is attributed to loss of lean body mass [81, 82]. Loss of lean body mass in cancer is predominantly explained by loss of skeletal muscle mass. Importantly, loss of lean body mass is associated with poorer treatment tolerance and worse cancer outcomes, in addition to numerous negative outcomes such as impaired stress response, frailty, functional impairment, lower quality of life and decreased overall survival in cancer patients [83-85]. The weight loss is more pronounced for patients with oropharyngeal cancer and patients receiving

chemotherapy concurrent with radiotherapy [86-88]. In addition, a high pre-treatment BMI is associated with an increased weight loss during radiotherapy (+/- chemotherapy) [80, 89, 90].

The described side-effects and consequences of tumour growth often result in complex post-treatment impairments for many patients. Compared to patients with other cancer diagnoses, patients with HNC have a high level of unmet needs for rehabilitation, including physical, emotional, family and work-related needs [91]. However, the access to specialised rehabilitation services is often limited, and barriers include lack of awareness among patients and oncology teams about the benefits of rehabilitation services, in addition to challenges related to travel and time away from home for services organised as residential stays at rehabilitation clinics [92, 93].

2.1.5 Patient-experiences of treatment and side-effects

The majority of clinical research involving patients with HNC has focused on the efficacy of various tumour directed treatment modalities and the identification and documentation of side-effects during and after treatment [36, 59]. In addition, several qualitative studies have been conducted to explore the psychological experiences of a HNC diagnosis [94]. Although oral and eating problems have been identified as the most common concerns and unmet needs during the first years following HNC treatment, only a few studies have been conducted to obtain a deeper understanding of the patients' experiences of the own nutritional situation following a HNC diagnosis [95]. However, this perspective is important to consider when planning for nutritional interventions seeking to counteract some of the eating problems experienced by patients with HNC. For example, it is important to gain insight into what type of nutrition-related information the patients need, when and in what way it should be provided and about the patients' own experiences of eating and drinking and the need and timing of nutritional support. These are difficult questions to answer with only quantitative methods.

Former studies have explored different aspects of HNC experiences such as coping strategies related to decreased nutritional intake, the physical, emotional and social losses associated with decreased nutritional intake and experiences from a health behaviour intervention [96-99]. None of the studies has involved experiences from the entire treatment trajectory and they have not addressed the patients' perceptions of the nutritional support delivered as part of the standardised care during treatment. Clinical experience indicates that the patients' nutritional situation is accommodated and managed in different ways within the specialised

health care in Norway, for example illustrated by a somewhat inconsistent involvement of nutrition experts or dietitians across hospitals within this patient-group. Thus, a deeper understanding of HNC patients' nutrition-related experiences is important to be able to gather around a patient-centred nutritional care that meets the individual needs and preferences.

2.2 Cancer rehabilitation

Cancer rehabilitation is a specialty within the rehabilitation discipline that aims to help patients manage cancer-related problems [1]. Numerous attempts have been made to define cancer rehabilitation, with the first definitions arising in the late 1970s [100, 101]. The most recent definition is based on concepts from the International Classification of Function (ICF), and states that "cancer rehabilitation is medical care that should be integrated throughout the oncology care continuum, and delivered by healthcare professionals who have it within their scope of practice to diagnose and treat patients' physical, psychological and cognitive impairments in an effort to maintain or restore function, reduce symptom burden, maximise independence and improve quality of life" [102]. This implies a multidisciplinary integration of skills from various healthcare professionals such as physicians, physiotherapists, nurses and dietitians.

The physical component of cancer rehabilitation includes physical exercise, nutritional support and symptom control interventions [2, 103]. The psychological component usually comprise coping strategies and distress management, while the social component focuses on return to work strategies, personal economy, social security benefits and family functioning [104, 105]. A recently published bibliometric analysis of cancer rehabilitation research from 1992 to 2017 shows that there has been a strong emphasis on studying cognitive, behavioural and psychological interventions, while studies of functional morbidity and physical rehabilitation research are lacking [106]. Three areas of publication deficits were noted from the analysis: research on populations other than breast, prostate and lung cancer (specifically regarding functional screening and assessment), methods for integrating physical rehabilitation services with cancer care, and physical rehabilitation interventions. This thesis is limited to the physical component of cancer rehabilitation, with a specific focus on physical exercise and nutritional support.

2.2.1 Physical exercise

The use of physical exercise within cancer rehabilitation was first acknowledged through the published research by Winningham M. L. and MacVicar M. G. in the late 1980s. They demonstrated improved aerobic capacity and body composition following a 10-week aerobic exercise programme in breast cancer patients receiving adjuvant chemotherapy [107, 108]. However, it was not until a decade later that the international research field on physical exercise in cancer patients really gained momentum. While only 34 scientific papers matched the search terms "neoplasms and exercise/physical fitness" up until 1990 in the medical database MEDLINE (excluding studies primarily related to the prevention of cancer), the number increased to 575 in 2005 and further to 1098 in 2009 [109]. In October 2018, an identical search yielded 4962 hits in MEDLINE.

The physiological changes associated with physical exercise provide a rationale for its use within cancer rehabilitation [110, 111]. These changes include a reduction in chronic inflammatory state associated with a poor prognosis, a reduction in insulin-growth factor and insulin resistance, a reduction in muscle proteolysis and an improvement in muscle synthesis [82]. To date, the prevailing evidence in the field of physical exercise and cancer supports the safety and efficacy of exercise interventions as a method to attenuate many of the side-effects experienced by cancer patients throughout the treatment trajectory [112-118].

Guideline-based exercise-prescriptions for cancer patients typically consist of endurance training performed alone at a moderate intensity (i.e. 50-75 % of age-predicted maximum heart-rate), or in combination with resistance training, two to three sessions per week, 10-60 minutes per session and with a programme-duration of 12-15 weeks [112, 119, 120]. The most essential principles of physical exercise are individualisation, specificity, progressive overload, and rest and recovery. The concept of individualisation comprises customised application of exercise towards the physiological status of the patient [121]. Specificity addresses the notion that the selected exercise must be specific and targeted to the primary underlying system(s) or pathway(s) known or postulated to underpin the primary endpoint of interest [122]. A requirement of effective exercise prescriptions is optimisation and progressive increase in exercise stress to confer continued physiological adaptation, which is about progressive overload [123]. Rest and recovery are often underemphasised when designing exercise prescriptions, but availability of nutrients and rest (or reduced training load) are essential to permit necessary biological re-synthesis to replace the required

constituents of the impacted system(s) [124]. The parameters of frequency (sessions per week), intensity (how hard per session), time (session duration) and type (modality) are most often used to operationalise exercise prescriptions in cancer patients [125].

Effects of physical exercise

Physical exercise interventions have shown to promote significant improvements on clinical and functional outcomes in a variety of cancer diagnoses across the cancer care continuum [126]. An established framework for organising research on physical exercise and cancer control entitled Physical Exercise Across the Cancer Experience (PEACE-model), suggests to divide the cancer experience into two pre-diagnosis periods (i.e. pre-screening and screening/diagnosis) and four post-diagnosis periods: pre-treatment, during treatment, post-treatment and resumption or palliation [127]. Pre-treatment physical exercise interventions, an important component of prehabilitation programmes (in addition to nutrition and psychoeducational components), are mostly tested prior to oncological surgery and have demonstrated improvements in exercise-adherence, tolerance to active cancer treatment and mitigation of functional decline after the initiation of cancer treatment [128-131]. In addition, improvements in endpoints related to post-treatment functional recovery, reductions in length of hospital stay and post-operative complications and return to pre-operative functional status have been reported [132]. These are promising findings within this relatively new field of oncology rehabilitation practice; however, the effects of pre-treatment exercise interventions need to be confirmed in other patients than lung cancer and prior to different treatment modalities such as radiotherapy and chemotherapy.

The more extensive literature on physical exercise interventions during active cancer treatment have demonstrated a positive impact on numerous clinically relevant outcomes, such as aerobic fitness, upper and lower body muscle strength, body weight, physical function, HRQoL, cancer-related fatigue, anxiety and depression, self-esteem and sleep [112, 114, 116, 133-139]. Additionally, the literature has identified support for physical exercise to alleviate impairments of specific body-structures and function in patients with breast, head and neck, gynaecological and prostate cancer [129, 140, 141]. No adverse events associated with blood counts have been noted following physical exercise during active cancer treatment, and several reviews have cited improved immune function and tolerance to chemotherapy in patients exercising during treatment [112, 116, 133, 142].

Post-treatment physical exercise interventions in cancer survivors have demonstrated beneficial effects on aerobic fitness, upper and lower body muscle strength, physical function, HRQoL and cancer-related fatigue, in addition to a positive impact on physical activity level, insulin-like growth factor 1 (IGF-1) and treatment-related side-effects [112, 113, 138, 143-147]. Supervised exercise programmes have shown superior benefits compared to non-supervised programmes in outcomes such as HRQoL, exercise-adherence and other physical and psychological outcomes [103, 137, 148, 149]. The effects of physical exercise in palliative cancer patients (i.e. patients with incurable cancer) is much less investigated, but seems to be feasible and beneficial in improving physical performance and well-being and reducing symptoms of nausea and vomiting [150-152].

The vast majority of the conducted physical exercise trials involve patients with breast, prostate and lung cancer, limiting the generalisability to patients with other cancer diagnoses presenting a different clinical picture throughout the treatment trajectory. In addition, there is limited evidence about the impact of exercise interventions on specific treatment related side-effects such as nausea, dyspnoea and neuropathies [126]. Currently, no interdisciplinary guideline exists to provide insight about the optimal timing, intensity, duration, and frequency of exercise screening and interventions. General exercise guidelines for cancer patients, such as the American College of Sports Medicine (ACSM) Roundtable on Exercise Guidelines for Cancer Survivors and more recently published clinical practice guidelines, do not provide specific context for timing of interventions and the necessary screening for side-effects, toxicities, and functional impairments that define the specialised needs of the cancer population [120, 153]. Thus, more work is needed to refine the general exercise guidelines for cancer patients into specific recommendations that consider the different phases of the cancer care continuum, present and anticipated treatment-related side-effects and the individual's health status.

Resistance training

The first physical exercise intervention studies in cancer patients by Winningham and MacVicar assessed the feasibility and effects of endurance training on aerobic capacity and body composition [107, 108]. More recently, resistance training has been included in physical exercise trials involving various cancer diagnoses, either as a single intervention or combined with endurance training [154]. Although both endurance and resistance training are beneficial

to cancer patients, the specific traits of muscle hypertrophy and muscle strength only change with resistance training.

Resistance training is the most effective approach to rebuild lean body mass in younger and elderly healthy individuals; thus, a potential beneficial role in counteracting cancer related muscle wasting has been proposed [155-158]. Current evidence suggests that resistance training is well-tolerated in cancer patients both during and after treatment and serves as an effective tool to counteract some of the negative treatment-related consequences. More specifically, resistance training have demonstrated beneficial effects on muscle strength and endurance, lean body mass, fat mass in cancer patients [143, 159-161]. However, these results are primarily based on patients with breast cancer and secondly on patients with prostate cancer. In addition, resistance training has often been combined with endurance training in many of the exercise trials, which may interfere with the respective adaptation processes [162]. The documented effects of resistance training interventions are still limited in cancer survivors due to a low number of studies. However, resistance training programmes for cancer patients consistently show significant improvements on muscle strength, which is clinically important due to its documented association with lean body mass and physical function in other populations [163].

2.2.2 Nutritional support

The impact of nutrition on cancer patients during cancer treatment and recovery gained attention from the mid-1970s [164]. In a review from 1978, diet and nutrition were recognised as having important roles during cancer treatment and rehabilitation, and there was a general consensus that patients with adequate nutritional status had an increased chance of successful cancer treatment [165]. Nutritional status can be defined as the state of the body in relation to the consumption and utilisation of nutrients [166]. The first nutritional guideline, however, presenting evidence from which informed decisions could be made regarding dietary choices in the different phases of cancer survival, was not published before the new millennium [167]. The focus of nutritional interventions in cancer patients has been directed at preventing and treating malnutrition. Today, cancer is a disease not only associated with weight loss but also with obesity, and additional weight gain is a frequent complication of treatment especially in patients with breast cancer [168, 169]. However, this thesis is limited to the consequences of inadequate nutritional intake and malnutrition often seen in patients with HNC.

Depending on the type and stage at diagnosis, cancer may cause profound metabolic and physiological alterations that affect the requirements for macro- and micronutrients. In addition, cancer may alter the utilisation of nutrients and not at least reduce the appetite [170]. Common side-effects such as anorexia, early satiety and changes in taste and smell often lead to inadequate nutritional intake and subsequent malnutrition. Substantial weight loss and a poor nutritional status may occur early in the course of some cancer, although the prevalence of malnutrition and weight loss varies widely across cancer types and stages at diagnosis [171].

Nutritional support is the provision of nutrition and nutrients either orally by regular or therapeutic diet (e.g. fortified food and oral nutritional supplements) or via enteral or parenteral nutrition to prevent or treat malnutrition, and also includes nutritional counselling [8]. The aim of nutritional support is to maintain or improve food intake and mitigate metabolic derangements, maintain skeletal muscle mass and physical performance, reduce the risk of interruptions of scheduled anti-cancer treatments, and improve quality of life. Since all the major cancer treatment modalities may affect nutritional needs significantly, regular nutrition risk screening is recommended already from diagnosis to increase awareness and allow early recognition and treatment. Nutrition screening should include assessments of body mass index (BMI), weight loss and food intake [72]. In patients with abnormal screening, it is recommended to quantitatively assess the domains of dietary intake, body composition, physical activity and the predominant metabolic pattern (i.e. the degree of systemic inflammation). The assessments should consider treatment goals (curative, control or palliation) while focusing both on the current nutritional status and anticipated treatment-related side-effects [172, 173].

The content of nutritional support depends on the patient's medical history, appetite, type and stage of cancer and response to treatment if initiated [171]. General nutritional advice is recommended to be provided before any specific nutritional counselling is initiated. Nutritional counselling comprises a dedicated and repeated communication process to provide the patients with a thorough understanding of nutritional topics, as distinct from brief and casual dietary advice [72, 174]. If maintaining or improving the caloric intake is difficult, the use of oral nutritional supplements (ONS) is required in addition to counselling. ONS are commercially available nutrient mixtures for oral consumption, mostly recommended to supplement volitional food intake [175]. They are typically multi-nutrient containing a mix of

macronutrients (protein, carbohydrate and fat) and micronutrients (vitamins, minerals and trace elements). Nutritionally complete supplements are energy dense, mostly containing 1.26 mega joule (MJ), which is about 300 kilocalories (kcal) per serving (125-220 millilitres (ml)), and provide a good source of protein (10-20 grams per 1.26 MJ serving) and a balance of micronutrients [176]. Most oral supplements are ready-made liquids (nutritional drinks) that are easy to administer for most patients. Powder supplements are also available (to be reconstituted with for example whole milk), but are much less in use [177]. If nutritional intake remains inadequate (< 60 % of requirements for more than 1-2 weeks), supplemental or complete nutrition via the enteral or parenteral route may be indicated. Enteral nutrition is delivered either by nasogastric tube or percutaneous endoscopic gastrostomy (PEG). Parenteral infusions (intravenously) may be supplied when enteral nutrition is not sufficient or feasible [178, 179].

In addition to the provision of various nutritional interventions to prevent or treat malnutrition, international guidelines (e.g. the ESPEN guidelines on nutrition in cancer patients) recommend cancer patients to maintain or increase the level of physical activity and avoid inactivity throughout the treatment trajectory [72]. Physical exercise interventions are well tolerated and safe at different stages of cancer, and also patients with advanced stage cancer have reported to be willing and able to engage in exercise programmes [115, 180]. In addition to the beneficial effects on outcomes such as aerobic capacity, muscle strength and muscle mass, physical exercise may stimulate to an improved appetite in patients with cancer [112, 145, 181]. Thus, it is recommended to integrate physical exercise interventions and nutritional support in cancer patients for optimal improvement of clinically relevant outcomes [72].

Effects of nutritional support

Nutrition intervention studies suggest that individualised nutritional counselling and/or ONS improve nutritional intake and body weight in cancer patients who are malnourished or at risk for malnutrition [182, 183]. Interventions combining nutritional counselling and ONS seem to provide superior beneficial effects compared to single interventions. In cancer patients undergoing adjuvant radiotherapy, interventions with nutritional counselling and/or ONS have been found to improve nutritional intake, nutritional status, body weight and certain quality of life domains such as global health status and physical functioning compared to no or standard nutritional advice [184-186]. One prospective follow-up study of a randomised nutrition trial

has indicated positive long-term effects of nutritional counselling on radiation toxicity and survival [187]. Few studies have assessed the effects of nutritional support in cancer patients undergoing chemotherapy alone or concurrently with radiotherapy, but a beneficial effect on body weight has been indicated [188, 189].

2.2.3 Summary of the scientific evidence

Physical exercise and nutritional support have demonstrated beneficial effects in all phases of the cancer treatment trajectory [72, 126]. Several meta-analyses and reviews of physical exercise RCTs have documented effects during and after treatment on several clinically relevant outcomes such as physical performance and function, HRQoL and fatigue [118]. Pre-treatment exercise interventions have shown beneficial effects especially on physical performance; however, the interventions are so far primarily tested in patients with lung cancer scheduled for surgery. Most exercise intervention studies in the various treatment phases include patients with breast, prostate and lung cancer. Thus, most full-scale RCTs providing the highest level of evidence are conducted within these patient groups, limiting the generalisability to patients with other cancer diagnoses. Nutritional support is more scarcely documented compared to physical exercise interventions; however, intervention studies with nutritional counselling and ONS have demonstrated positive effects in malnourished patients or patients undergoing radiotherapy (+/- chemotherapy). Few studies have implemented combined physical exercise and nutrition interventions as part of cancer rehabilitation programmes; thus, more research is needed to assess the feasibility and impact of such interventions in rehabilitation settings.

2.2.4 Methodological aspects

RCTs versus randomised feasibility and pilot studies

The basic intent of an experimental study is to test the impact of a treatment or an intervention on a specific outcome. Double-blinded RCTs are considered the gold standard of experimental designs. By randomly assigning subjects to comparison groups, RCTs can exert control over most factors that may influence the outcome. In this way, evidence supporting a causal relationship can be interpreted with confidence, and a clinical relevant evidence of the intervention's efficacy is provided [190-192]. However, the implementation of a blinded design is considered difficult in rehabilitation trials involving physical exercise interventions.

Experimental studies that include new interventions and/or understudied populations, may need to test certain parameters and practical procedures before initiating a definitive RCT. Both feasibility and pilot studies aim to assess feasibility of conducting the future definitive RCT [4]. *A feasibility study* explicitly asks whether the future RCT can be done, should be done, and if so, how. *Pilot studies* are a subset of feasibility studies asking the same questions about feasibility, in addition to conducting the complete or part of the future RCT on a smaller scale [3]. Thus, pilot studies are not just mini-trials with a smaller sample size as the only difference to the definitive RCT, but in fact represent a distinct study design that plays a vital role for the success of the definitive RCT [193]. Randomised pilot studies differ from RCTs by focusing on the assessment of feasibility rather than effectiveness or efficacy, which implies key differences in the reporting of information such as study objectives, outcomes and interpretation of the results.

Recruitment and retention

Recruitment of patients into clinical trials is challenging, and may be influenced by several factors related to the motivation and attitude of both physicians and patients and the patients' age, gender and performance status [194, 195]. In a cancer setting, the psychological impact of a potential life-threating disease and the significant and often complex symptomatology may cause additional difficulties to the recruitment process [196, 197]. Since participation in physical exercise programmes presupposes personal commitment related to motivation, ability and will, recruiting cancer patients into exercise trials may be even more challenging. Several barriers to engage in physical exercise interventions have been reported in cancer patients, such as fatigue, time restraints, discomfort and lack of exercise experience [198-200].

Patient withdrawal (drop-out) during interventions is also a challenge in experimental research. A high drop-out rate has implications for statistical power and internal and external validity, meaning it reduces the sample's representativeness of the studied population, the strength of the findings, and the ability to generalise from the results [201]. Although strict inclusion criteria may control medically related drop-outs, it also interferes with the generalisability of the study [202]. Low adherence rates are frequently reported in physical exercise interventions with cancer patients both during and after treatment [199, 203].

Physical exercise adherence (tolerability) can be defined as the degree of attendance and completion of a planned prescription of exercise treatment [204, 205]. Access to a nearby training facility, previous experience with physical exercise, high motivation and few exercise limitations have been found to be the most prominent predictors of high exercise adherence during oncological treatment. After treatment, factors such as less extensive surgery, high previous exercise adherence, family support, feedback by training personnel and knowledge and skills of exercise seem to facilitate high exercise adherence [206]. This was considered during the planning of the exercise interventions during and after treatment in the present pilot study, and factors such as nearby training facility during treatment and feedback by training personnel after treatment were implemented to facilitate exercise adherence.

Recruiting patients to exercise trials and achieving acceptable levels of adherence could be extra challenging in patients with HNC considering the high morbidity burden already from diagnosis and the increasing side-effects from start to end of. The few pilot studies that have specifically reported relevant feasibility outcomes from exercise interventions implemented during treatment within this patient-group have demonstrated inclusion rates from 45 % to 63 % and adherence to exercise from 45 % to 93 % [207-210]. Exercise adherence was reported either as the number of completed sessions of the total planned number of sessions or as mean attendance rate to the exercise sessions. These specific findings on recruitment and adherence of exercise trials in patients with HNC were published after the initiation of the present randomised pilot study, except the study by Rogers et al. (2013) [207].

Health-related quality of life (HRQoL)

The term health-related quality of life (HRQoL) is frequently used to distinguish between quality of life (QoL) in its more general sense and the requirements of clinical medicine and clinical trials. HRQoL is patient-reported and subjective and a multi-dimensional concept that consists of an individuals' subjective perspective concerning general health, physical-, emotional, cognitive and social functioning, physical symptoms, well-being, sexual functioning and existential issues. Relevant items and aspects of interest vary form study to study. In the absence of any agreed formal definition, most researchers describe what they mean by quality of life. In this thesis, the term HRQoL is used and include the sub-scales global health status/QoL, physical functioning and symptoms of pain, dry mouth and sticky saliva and assessed by the cancer specific questionnaire EORTC QLQ-C30. In addition, the head and neck cancer module H&N35 is used to assess diagnose specific symptoms [211].

The specific challenges faced by patients with HNC may have a significant impact on functioning and body image that negatively affects HRQoL [52, 212]. Numerous observational studies have reported HRQoL throughout treatment and recovery in patients with HNC, demonstrating that symptoms such as pain, dry mouth and sticky saliva increase steadily during the course of radiotherapy (+/- chemotherapy) while physical functioning and global health status/QoL decrease [213-221]. The patients report maximum symptom burden and minimum functioning at the end of and immediately after radiotherapy [212, 215, 219].

Although generally small in sample sizes and hampered by study design not tailored to study effects several physical exercise intervention studies have indicated a beneficial impact of resistance training on physical functioning, fatigue and global health status/QoL during and immediately after tumour directed treatment [207, 222-224]. The results from nutrition intervention studies are somewhat mixed, but two randomized controlled trials (RCT) have demonstrated less deterioration in physical functioning and global health status/QoL in patients receiving dietary counselling and/or oral nutritional supplements (ONS) during and after treatment [184, 225]. Short- and long-term HRQoL data following an intervention combining physical exercise and nutritional support during or after treatment is missing in patients with HNC; thus, there is a need to explore the development in relevant HRQoL scales.

Validity and trustworthiness

Research findings should be as valid as possible, and every study must be evaluated according to the procedures applied to generate the results. The use of criteria for describing validity in scientific studies differs between the quantitative and the qualitative research traditions. Within the quantitative research tradition, criteria such as internal and external validity are commonly used to judge the quality of experimental studies [192, 226]. Internal validity deals with experimental control and the extent to which correct inferences can be drawn about causal relationships. External validity concerns the generalisability of study-results beyond the internal specifications of the study sample. It is usually strived for the highest possible control in an experimental study; however, this normally weakens the generalisability of the results. In other words, the experimental control is normally far better in a laboratory experiment than in a field experiment, while it is easier to generalise the results from a field experiment beyond the experimental situation.

Trustworthiness is often used for validity in qualitative research, and is about determining whether the findings are trustworthy from the standpoint of the researcher, the participant or the reader [227]. Thus, the researcher should establish accuracy during the research process and give trails to allow the readers to understand how and why decisions were taken [228]. Credibility, dependability and transferability are often used criteria to evaluate the trustworthiness of qualitative studies. Credibility has been identified as an overall goal of qualitative research and refers to the confidence in how well the data and analysis-process address the intended focus (e.g. do the results reflect the experience of participants or the context in a believable way?) [229]. Dependability concerns the degree to which data change over time and alterations made in the researcher's decisions during the analysis-process. Transferability deals with the extent to which the findings can be transferred to other settings or groups outside the study situation [230-232]. Common techniques have been identified to demonstrate or assure criteria of trustworthiness, such as describing data collection decisions, demonstrating saturation, describing data analysis decisions and providing rich descriptions [233, 234].

2.3 Physical exercise and nutrition interventions in patients with HNC

Patients with HNC are faced with specific symptoms and treatment-related side-effects compared to other cancer groups; thus, there is a need to highlight the literature on the feasibility and impact of physical exercise and nutrition interventions separately and in combination specifically within this patient-group.

Physical exercise

The field of physical exercise and HNC is still in its early stages, specifically considering full-body resistance training interventions. Although some intervention studies were published already in 2003 and onwards, the exercise programmes did not involve resistance training: The first identified pilot study by Crevenna et al. consisted of a structured hydrotherapy rehabilitation programme using a special underwater therapy device for laryngectomised patients, while a randomised pilot study by McNeely et al. in 2004 evaluated a specific shoulder resistance training programme to enhance scapular stability and strength of the upper extremity following neck dissection [235, 236]. In 2007, Aghili et al. published a pilot study that assessed the impact of a four-week physical exercise programme during radiotherapy on the incidence and severity of fatigue; however, the programme consisted of only aerobic

training and also involved breast cancer patients in addition to patients with HNC with no separate analyses [237]. Beyond these intervention studies, the initial HNC physical exercise literature mainly consisted of observational studies that reported on physical activity levels, preferences and barriers and associations with biomarkers and survival [238-244].

The first intervention studies involving full-body resistance training in patients with HNC were published in 2013. Since planning of the present randomised pilot study and the process to apply for research funding started already in 2012, one of the key research questions was whether patients with HNC were willing and able to conduct a resistance training programme while undergoing radiotherapy (+/- chemotherapy). At that time in Norway, patients with HNC were not offered any structured physical exercise programme during treatment and referrals to traditional post-treatment rehabilitation programmes were scarce and random.

Eades et al. (2013) evaluated the benefits of a post-treatment rehabilitation programme (mean time since end of treatment > 8 months) consisting of physical exercises, follow-up appointments, individual consultations and information and group discussion sessions in 27 patients with HNC [222]. The programme demonstrated a clinically meaningful reduction in severity of symptoms and distress and improvement in nutritional status, physical function and quality of life. However, the semi-weekly exercise-sessions also involved flexibility-training and exercises to relieve pain, in addition to an exercise programme to improve full-body muscle strength, endurance and post-surgical neck and shoulder stiffness.
Lønbro et al. were among the first that tested a physical exercise programme specifically consisting of resistance training in patients with HNC. In a randomised pilot study published in 2013 ("DAHANCA 25A study"), they investigated the feasibility and changes in relevant physical outcomes following a 12-week resistance training programme with or without dietary supplementation initiated two months after the end of radiotherapy [245]. In total, 70 % of the patients completed the programme and mean adherence to the exercise sessions was 97 % among the completers. In addition, lean body mass, muscle strength and functional performance increased following both interventions (exercise +/- supplements). The effects of the resistance training programme was confirmed in the definitive RCT published in the same year ("DAHANCA 25B study"), demonstrating statistically significant increase in lean body mass and muscle strength irrespectively of early (i.e. 12 weeks post-treatment) or delayed (i.e. 24 weeks post-treatment) start-up of the intervention [224].

The randomised pilot study by Rogers et al. (2013) is to our knowledge the first intervention study that implemented resistance training during radiotherapy in patients with HNC [207]. Fifteen patients were randomised to a 12-week programme consisting of resistance training and nutritional counselling or nutritional counselling only (control group) initiated at start of treatment. The study focused primarily on feasibility outcomes such as recruitment, retention and exercise adherence rates and secondarily on preliminary intervention effects on muscle strength, lean body mass, physical functioning, fatigue and quality of life. Only 45 % of the eligible patients were included in the study and five of seven patients in the exercise group completed week 12 assessment. Seventy of the 84 supervised exercise sessions during treatment were conducted as planned (83 %), while the exercise adherence dropped to 53 % during the last six weeks after the end of treatment. Medium to large effect size differences were noted for fatigue (d=0.64) and quality of life (d=0.52) in favour of the exercise group at the end of radiotherapy, and the authors suggested to include 100 patients per study group allocation to detect statistically significant differences in these outcomes in a definitive RCT. Only a small effect size (d=0.35) in favour of the exercise intervention was noted for lean body mass from start to end of radiotherapy, and the authors explicitly stated that the exercise protocol was conservatively designed to maximise safety and resistance bands instead of weight machines were used to facilitate transition from the clinical to the home-based setting.

Samuel et al. (2013) also implemented resistance training as part of an exercise programme during (chemo)radiotherapy in a power-calculated RCT (n=48) to assess effects on functional capacity measured by the 6 minutes' walk test (6MWT) [223]. The intervention demonstrated statistically significant increase in functional capacity from start to end of treatment compared to a decrease in the control group. However, between-group differences was not reported, no feasibility outcomes such as exercise-adherence were reported, the resistance training exercises for the upper body only involved small muscle groups (i.e. biceps and triceps) and load was conservatively adjusted according to RPE levels (3-5/10) and not according to RM. Zhao et al. compared a functional resistance training and walking programme to a usual care during chemoradiotherapy in a pilot study (n=20), and both groups met with a dietitian before start of treatment [246]. The adherence rate to the exercise programme was 72 %, and the functional exercise tests showed a trend toward less decline in the intervention group compared to the controls at week 7 and a trend towards improvement at week 14. Muscle strength measured by knee extension was maintained for all 14 weeks in the intervention group compared to a decline in the control group.

The first systematic review that summarised the physical exercise literature in patients with HNC was published in 2016 by Capozzi et al. [141]. Due to the early state of the literature, the review included a broad spectre of exercise interventions such as aerobic, resistance or flexibility training alone or in combination and the included studies varied greatly in design, quality and reporting characteristics. Of the 16 eligible studies, only four intervention studies with a randomised design were identified and these were the previously described studies by Lønbro et al. (2013, DAHANCA 25A and B), Rogers et al. (2013) and Samuel et al. (2013). The other identified studies were prospective cohorts, cross-sectional studies, a retrospective cohort and a non-randomised controlled study reporting on different outcomes such as lean body mass, muscle strength, functional performance and HRQoL by various objective tests and self-reported questionnaires.

More recently, Hajdú et al. (2017) published the protocol and preliminary pilot data from an ongoing full-scale RCT investigating the effect of a combined intervention with swallowing and mouth-opening exercises plus progressive resistance training during radiotherapy [209]. Six of nine eligible patients (67 %) were included in the pilot study and adherence to the resistance training programme was 91 %. A small non-randomised pilot study (n=12) also published in 2017 assessed the feasibility of a 12-week resistance training programme initiated at start of concurrent chemoradiotherapy and study logistics in preparation of a definitive RCT [210]. Twelve of 19 eligible patients (63 %) were included in the study, and the mean exercise adherence was 93 % during treatment. A 9.3 % loss of lean body mass was observed from start to end of treatment. And just recently, Samuel et al. (2019) published to our knowledge the largest RCT (n=148) investigating the effectiveness of a physical exercise program in patients with HNC undergoing chemoradiotherapy [247]. They studied the effect of an 11-week program with aerobic and resistance training exercises on quality of life (using the generic Short Form-36), functional capacity and worsening of fatigue. Compared to the control group there was a statistically significant difference in favour of the exercise group on all outcomes from start to end of the intervention. Both the mental and the physical quality of life score was maintained from baseline to immediately after treatment in the exercise group compared to a significant reduction in the control group [247].

Table 1 provides an overview of the *feasibility and pilot studies* that were published while applying for funding of the present pilot study (i.e. 2012-2014), including studies published during implementation (i.e. 2015-2016) and up until publication of paper I in the present

thesis (November 15 2017). As shown in the table, several of the exercise-trials also included a nutritional component.

Table 1. Feasibility and pilot studies testing full-body resistance training programmes (with or without nutrition interventions) during/after radiotherapy in patients with HNC published up until the publication of paper I in the present thesis (November 15, 2017)

Year (m) Author	**Design**	**n**	**Initiation**	**Delivery mode**	**Type, frequency, intensity, length**	**Feasibility outcomes** (+ other outcomes)	**Feasibility results**
2013 (Aug) Lønbro S [245]	Randomised feasibility study (Exercise and dietary supplements)	30	After RT completion (2 months post-treatment)	Mostly unsupervised	Conventional exercises (leg press, knee extension, hamstring curl, chest press, sit-up, back extension, lateral pull-down) 30 sessions (2-3/week) 8-15 RM, 2-3 sets 12 weeks	Inclusion rate, completion rate, adherence to intervention, adverse events (+ LBM, fat mass, muscle strength, functional performance)	Inclusion rate: 28 % Completion rate: 70 % Exercise adherence: 97 % Adverse events: None
2013 (Aug) Rogers LQ [207]	Pilot RCT (Exercise and nutritional counselling)	15	At start of RT	Supervised first 6 weeks, unsupervised last 6 weeks (home-based)	Resistance bands (chest press, leg extension, lateral row, wall push-up, 2-arm front raise, hamstring curl and arm curl) 2 sessions/week Light to heavy bands, up to 10 reps 12 weeks	Eligibility, recruitment and retention rates, adverse events, exercise adherence (+ muscle strength, LBM, physical functioning, fatigue, QoL)	Eligibility rate: 24 % Recruitment rate: 45 % Retention rate: 13 of 15 patients (87 %) completed week 12 assessment Adverse events: n=2 serious, n=1 non-serious Exercise adherence: 83 % first 6 weeks, 62 % last 6 weeks
2015 (Apr) Capozzi LC [248]	Prospective cohort (Exercise)	21	After RT completion (mean time 9.7±10 months post-treatment)	Supervised and unsupervised (home-based)	10 conventional exercises 3 session/week 8-10 reps, 2 sets, moderate intensity 12 weeks	Recruitment, adherence and safety measures (+ fitness outcomes and symptom management)	Recruitment: 66 % Exercise attendance: 66 % Programme completion: 52 % Safety measures: No adverse events
2016 (Apr) Capozzi LC [208]	Exploratory RCT (Exercise and health education)	60	At start of RT (ILI) or 6 weeks after end of RT (DLI)	Supervised and unsupervised (home-based)	10 conventional exercises + health education, behaviour change, social support 4 sessions/week 8-10 RM, 2 sets 12 weeks	Intervention adherence (+ body composition, fitness, QoL, depression, nutrition status)	Program attendance: 45 % ILI, 62 % DLI Recruitment rate (not specified in methods): 56 % Completion rate (not specified in methods): 61 % ILI, 69 % DLI

Table 1 (continued)							
2016 (Apr) Zhao SG [246]	Pilot controlled trial Exercise and nutritional counselling	20	At start of RT	Supervised first 7 weeks, unsupervised last 7 weeks (home-based)	Functional exercises (chest press in squat, wall push-up, military press, side-arm raise, biceps curl, shoulder shrug, calf raise) + home walking programme 3 sessions/week 8-12 reps, 3 sets (RPE 11-13/20) 14 weeks	Enrolment (+ muscle strength, functional mobility, QoL, BMI, LBM, diet, physical activity, concurrent CRT toxicity, barriers to exercise)	Enrolment (not specified in methods): 20 of 27 consenting patients (74 %) underwent baseline assessment Attrition (not specified in methods): 17 of 20 patients (85 %) completed week 14 assessment Attendance rate (not specified in methods): 72 %
2017 (Feb) Hajdú SF [209]	Protocol and pilot data (RCT) (Exercise and swallowing exercise)	6	At start of RT	Supervised	Conventional exercises (leg press, knee extension, chest press, lateral pull down) 2 sessions/week 5–8 reps at 70–85% of 1 RM, 3 sets 10–14 reps, 3 sets (abdominal crunch, back extension) 6 weeks	Inclusion and adherence to program (+ swallowing, fatigue, pain, nausea, xerostomia, QoL, depression, anxiety, nutritional status, tube dependency and intake, length of hospital stay)	Recruitment pilot: 6 of 9 eligible patients (67 %) Interim inclusion RCT: 53 % Adherence to program (pilot): 91 % (resistance training)
2017 (Oct) Lønkvist CK [210]	Pilot study (Exercise and dietary supplements)	12	At start of RT	Supervised	Conventional exercises (abdominal crunch, back extension, chest press, low row, hamstring curl, knee extension, leg press) 3 sessions/week 8-15 RM, 2-3 sets 12 weeks	Participation in training sessions and adverse events (+ functional performance, muscle strength, LBM, fat mass, body weight, muscle biopsies, blood chemistry)	Inclusion (not specified in methods): 63 % Attendance: 77 % overall, 93 % during RT Adverse events: None related to intervention

Apr, April; Aug, August; BMI, body mass index; CRT, chemoradiotherapy; Feb, February; LBM, lean body mass; m, month; Mar, March; n, number; NR, not reported; Oct, October; QoL, quality of life; RCT, randomised controlled trial; reps, repetitions; RM, repetition maximum; RPE, rating of perceived exertion; RT, radiotherapy; w, weeks.

Nutritional support

Nutritional support with high protein and calorie content initiated before or at start of radiotherapy has demonstrated some improvement in nutritional status, HRQoL and treatment tolerance in patients with HNC, but the results are conflicting and based on a few and small studies [186, 249]. Despite limited evidence and requests for more research, international nutrition guidelines recommend the provision of nutritional counselling with or without ONS to patients with HNC receiving radiotherapy (+/- chemotherapy) [72, 178]. Although the use of ONS is known to enhance energy intakes, the benefits in patients with HNC has been somewhat conflicting and compliance to consumption of the prescribed supplements is variable [250, 251]. Clinical experience from patients undergoing radiotherapy also indicates that the consumption of ONS decrease as the intensity of side-effects increase. On this background, we wanted to assess the compliance to a commercially available nutritional drink in the present pilot study.

Already in 1989 Arnold C. and Richter M.P. investigated the effect of ONS (Sustacal™ liquid, 980-1080 kcal/day) in patients with HNC receiving curative radiotherapy lasting from five to eight weeks [252]. Both the intervention group (n=23) and control group (n=27) received nutritional counselling, and the supplements did not demonstrate any additional effect on body weight or treatment tolerance (i.e. side-effects and interruptions) and response (i.e. tumour status). However, none of the patients in the intervention group ingested the prescribed volume of supplement; only seven patients took at least 80 % of the supplement and the mean consumption rate was 62 %. A few years later Nayel et al. (1992) conducted a randomised study in 23 patients with HNC to assess the impact of ONS during radiotherapy, and reported statistically significant improvements in nutritional status and higher treatment tolerance following the provision of high-protein nutritional powder (Ensure, 1500-2000 kcal/day) compared to no supplements [253]. Also in this study, the patients were unable to ingest the prescribed volume of supplement, and the duration of supplementation varied from 10 to 26 days of the 42 days of radiotherapy.

More than a decade later, Ravasco et al. (2005) published a three-armed RCT (n=75) that compared the effect of 1) nutritional counselling (ONS if required) to 2) only ONS or 3) standard nutritional care during radiotherapy [184]. The ONS consisted of a commercially available and ready-to-use high-protein liquid (brand not specified, 400 kcal/day). Calorie and protein intake increased significantly from start to end of radiotherapy in the nutritional

counselling and ONS groups, separately, while maintenance of nutritional intake three months after treatment was only achieved in the counselling group. Although a supplement consumption record was used to ensure compliance, the actual consumption of supplement in the ONS group was unfortunately not reported. A recently published RCT (n=159) by Cereda et al. (2017) evaluated the additional effect of ONS on body weight and other predefined outcomes (e.g. nutritional parameters and treatment tolerance) in patients receiving nutritional counselling as standard care during radiotherapy or chemoradiotherapy [254]. The ONS group were asked to ingest two bottles each day of a ready-to-use high-protein formula (Resource® Support Plus) providing a total of 500 kcal per day, and caregivers and dietitians recorded the number of bottles consumed daily. The mean compliance to ONS was 1.2 (0.6) bottles/day providing and additional mean intake of about 300 kcal/day, resulting in statistically smaller loss of body weight at the end of treatment, higher protein-calorie intake and less need for changes in anti-cancer treatment compared to nutritional counselling alone.

Combined exercise and nutrition interventions

As presented in the previous sections, several single modality intervention studies with physical exercise or nutritional support have been conducted in patients with HNC during the last two decades. The exercise trials mostly consist of feasibility or pilot studies with a small number of patients and recruitment/inclusion rates range from 28 % to 66 % [245, 248]. Adherence to exercise seems to vary across the studies (e.g. 45 % and 97 %) and several of the studies have reported drop-out rates of 30 % or more [208, 245, 248]. The relatively few and some older intervention studies with nutritional support show inconsistent adherence rates to ONS (e.g. 24 % and 62 %) or inadequate reporting [184, 252, 253].

The preliminary effects from the physical exercise and nutrition intervention studies are promising and seem to indicate an impact on several outcomes relevant for patients with HNC such as lean body mass, muscle strength, physical performance, nutritional intake, body weight, fatigue and HRQoL [141, 186]. However, despite the recommended use of a multimodal approach for weight loss management in cancer patients, only a few intervention studies have implemented physical rehabilitation programmes consisting of both physical exercise and nutrition interventions [255]. In Norway, physical exercise and nutritional support have traditionally been offered as part of post-treatment cancer rehabilitation programmes, although other types of programmes have been established more recently (e.g. outpatient services offered during and after treatment). The traditional programmes are mainly

organised as residential stays at rehabilitation clinics due to the scattered settlement and long distances to health-care services. However, there has been an increasing interest among clinicians involved in the treatment and care of patients with HNC to test the feasibility of early initiated physical exercise and nutrition interventions and assess the impact on body weight, physical function, symptom management and HRQoL. This is in line with recently updated international nutrition guidelines for cancer patients recommending a combination of physical exercise and nutritional support to maintain muscle strength, muscle mass and physical function and to support metabolic pattern [72].

The previously described randomised feasibility study by Lønbro et al. ("DAHANCA 25A", 2013), primarily assessing the feasibility of whole body resistance training +/- protein and creatine supplementation two months post-treatment, is to our knowledge the only study comprising both resistance training and ONS in patients with HNC [245]. In addition to 30 exercise-sessions evenly dispersed over the 12-week post-treatment period, the patients were provided with creatine (5 grams) and protein (30 grams) powder supplementation on training days and a creatine maintaining protocol was followed on non-training days. The control group received identical exercises and ingested iso-caloric placebo (maltodextrin) supplementation. Adherence to the supplementation was assessed by self-reported questionnaires administered before and after the intervention. As previously presented, adherence to the exercise programme was excellent (97 %) for the patients completing the intervention; however, a total of nine patients (30 %) dropped out from the study. Sixteen of the 21 completers provided adequate information on adherence to ONS, which showed that 69 % ingested all supplementation, 19 % missed ≤ 3 supplementations and 12 % terminated the supplementation in week 8 due to muscle cramping and increased mucous production. Lean body mass, muscle strength and functional performance increased significantly in both groups (i.e. resistance training +/- supplementation) indicating no additive effect of ONS to resistance training. However, the lack of statistically significant differences between the groups should be interpreted cautiously due to the feasibility nature of the study with a low number of participants (n=30), no power calculation and a high drop-out rate (50 %) for the placebo supplemented group.

The interventions in the feasibility study by Lønbro et al. were initiated two months after the end of radiotherapy, which is a period characterised by gradual recovery and improvement of treatment-related side-effects and functioning [256]. In contrast, the 6-7-week period of

radiotherapy is characterised by gradual worsening of symptoms and decreasing functioning; thus, the feasibility of implementing resistance training and ONS during treatment need specific attention. In 2016, Capozzi et al. published an exploratory randomised exercise trial (n=60, see Table 1) that assessed intervention-adherence and compared body composition, physical performance and patient-reported outcomes between a lifestyle intervention initiated at start of radiotherapy (ILI) versus six weeks after radiotherapy (DLI) [208]. The lifestyle intervention consisted of a 12-week supervised and home-based progressive resistance training programme in addition to nutrition screening, behavioural change support and health education that included relevant themes such as body composition and quality of life, sleep, stress and fatigue and nutrition support. The ILI group attended an average of 45 % (± 39 %) of the physical exercise-sessions during and after treatment, while the patients in the DLI group attended an average of 62 % (±43 %) of the sessions after treatment. Unfortunately, adherence to the nutrition support classes was not reported and any use of ONS was not specified. The ILI intervention did not demonstrate any statistically significant effects compared to usual care; however, small to medium effect sizes were noted in favour of the intervention.

The only intervention study comprising both resistance training and ONS in patients with HNC demonstrated a low inclusion rate (28 %) to the post-treatment programme, a 30 % drop-out rate, excellent exercise adherence (97 %) among the completers and 69 % adherence to ONS with only half of the randomised patients providing information on intake of supplementation [245]. During radiotherapy, an exploratory RCT reported 56 % inclusion rate, 39 % drop-out rate and 45 % exercise adherence to a 12-week resistance training and health education programme initiated at start of treatment [208] As far as we know, only the single-armed pilot study by Lønkvist et al. has tested a combined intervention with resistance training and ONS initiated at start of radiotherapy (+ chemotherapy) in patients with HNC.

3. Aim and research questions

The overall aim of this thesis is to evaluate the feasibility and impact of a physical rehabilitation programme with exercise and nutritional support administered during versus after radiotherapy (+/- chemotherapy) in patients with HNC, and to describe the patients' nutritional situation throughout the treatment trajectory.

The following research questions are specifically addressed:

- Are patients with HNC willing and able to participate in a combined physical exercise and nutrition intervention during or after radiotherapy, and are there any the differences in change of muscle mass and body weight between the interventions?

- What are the short- and long-term differences in HRQoL between a physical rehabilitation programme administered during versus after radiotherapy, and what are the within-group changes in HRQoL in the first year following an HNC diagnosis? And what are the differences in HRQoL and sociodemographic and clinical characteristics between attenders and non-attenders to the programme administrated after treatment?

- How do patients with HNC experience the nutritional situation and perceive nutritional support in the period from diagnosis to the acute post-treatment phase?

4. Material and methods

4.1 Methodological framework

This thesis comprises scientific methods derived from two different philosophical worldviews: post-positivism and constructivism (social constructivism). Since worldviews influence the way research is carried out, it is recommended to make explicit the larger philosophical ideas of the researcher [234]. The term worldview is here related to a basic set of beliefs that guide actions, and is synonym to other terms such as paradigms, epistemologies and ontologies [257-259].

In short, post-positivism represents the thinking after positivism, challenging the traditional positivistic notion of the absolute truth of knowledge [260]. It is based on the assumption that there is only one objective reality and holds a deterministic philosophy in which causes probably determine effects or outcomes. The utilised methods are based on deductive reasoning and focus on experiment, control, objectivity, precise measurement and quantification of data. Thus, quantitative strategies are preferred and accepted within post-positivism, through the utilisation of numerical data to quantify or measure phenomena [261, 262].

Constructivism, on the other hand, is based on the assumption that reality is subjective and changing, and dependent on its context [263]. Reality is not a fixed entity but rather a construction of the individuals. This worldview implies a focus on human experience, and various ways of obtaining knowledge are acknowledged [257]. Rather than starting with a theory as in the post-positivism, the researchers generate or inductively develop a theory or pattern of meaning. Constructivism is typically seen as an approach to qualitative research [264].

Quantitative research methods, such as randomised controlled trials, appear to be the preferred approach within medical and rehabilitation research, mainly through the dominant force of evidence based medicine [265-267]. Although this is an invaluable framework to answer certain questions, it could be argued that very few phenomena within healthcare can be thoroughly understood by using quantitative methods alone [268-270]. Especially when it comes to evaluating rehabilitation programmes consisting of multiple interventions (complex

intervention), often in small and heterogeneous patient samples. Qualitative research methods provide very good ways of studying complex, unstable and non-linear change, and has the potential to improve rehabilitation practice by addressing important concerns such as the lived experience of disability, interactions between persons, environment and disease, and explanatory mechanisms behind benefits/harms of clinical interventions [271, 272]. Since the research questions in the present thesis target assessments of feasibility and preliminary intervention-effects and descriptions of patient-experiences, the use of both quantitative and qualitative methods was considered as the most adequate approach. Collecting and analysing data this way is often referred to as triangulation (i.e. between-method triangulation) [273].

4.2 Study design

The thesis consists of three papers with data from a single centre two-armed randomised pilot study. The design of the interventions was pragmatic and based on a need to test the implementation of especially physical exercise during radiotherapy and to evaluate the use of established post-treatment cancer rehabilitation programmes by patients with HNC. At the time of preparing and planning the study, no standardised physical exercise and nutrition programme was offered to patients with HNC undergoing radiotherapy and referrals to post-treatment programmes were scarce and random within the specialist healthcare. A randomised design was employed to test the integrity of the study protocol for the future RCT, and it was important to explore the acceptability of being randomised to an active intervention during treatment or having to wait for a post-treatment intervention and only receive standard care during treatment. And finally, we wanted to evaluate the speed of recruitment for a longer period in this vulnerable patient-group; thus, a one-year inclusion period was opted for.

Paper I and II are based on quantitative data from the total study sample, and paper III is based on qualitative data (semi-structured interviews) from a sub-sample.

4.3 Study population

The patients were recruited from St. Olavs hospital, Trondheim University Hospital (Clinic of Ear-Nose-Throat, Eye and Maxillofacial Surgery (ENT-clinic)). All residents belonging to the

mid-region of Norway are referred to the ENT-clinic at St. Olavs hospital regarding medical assessment, diagnostics and treatment of HNC.

From 26th of March 2015 to 17th of March 2016, patients were invited to participate in the study if the following inclusion criteria were met: (1) a diagnosis of squamous cell carcinoma in the head and neck (naso-, oro-, or hypo-pharynx, larynx and oral cavity, except stage T1N0M0 laryngeal cancer), (2) referred for curative radiotherapy with or without chemotherapy, (3) possible to complete baseline assessments prior to start of radiotherapy, and (4) 18 - 85 years of age. Patients using walking aids or wheelchair were also screened for eligibility according to the described inclusion criteria. However, patients who had been previously treated with radiotherapy towards the affected area and/or had received systemic anti-cancer treatment the last four weeks prior to study enrolment were excluded, since these patients represent a different population with regard to patient and clinical characteristics. All patients referred to the ENT-clinic in the specified period were screened for eligibility by the responsible physician and nurse specialist.

Brief oral and written study information (Appendix 1) was provided by the responsible nurses during the days of undergoing diagnostic procedures at the hospital (2-3 days before diagnosis). Immediately following the consultation regarding diagnosis and planned treatment, the patients were invited to have a talk with the study coordinator (PhD candidate, JAS) that provided the formal study information including a written informed consent form. The specific study content and implications of participating was reviewed, including information about the purpose of the post-treatment individual interviews. The study information was provided in quiet surroundings and with time for dialogue and questions if needed. After being informed about the study, the patients were asked if they were willing to participate or not. It was up to the patients to give an immediate response to the study request or to use a couple of days to think about it. In the latter case, the study coordinator made an appointment to meet again with the patient at a later visit to the hospital or to give a call. If the patients did not want to participate in the study, they were gently asked to specify reasons for this.

Randomisation

The patients who consented to participate were randomised to a physical exercise and nutrition intervention during radiotherapy (EN-DUR) or after radiotherapy (EN-AF). The

randomisation was carried out by a web-based system developed and administered by Unit of Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim. The system provided an ID-number for each patient, and the reasons for not proceeding to randomisation were documented/registered by the study coordinator. The randomisation was not stratified. The study protocol was registered in the National Clinical Trials Registry (ClinicalTrials.gov, NCT02439892) prior to study start.

The interviewed sub-sample

Towards the end of radiotherapy, a sub-sample of the participants was invited by the PhD candidate to complete individual interviews. The PhD candidate repeated the purpose of the interview and made appointments with the patients regarding time and place of the interview, which was forwarded to the involved research nurse (VV) responsible for conducting the interviews. Those invited were meant to represent the heterogeneity of patients with HNC, including both genders, younger and older and those living in rural and urban areas. A selection was also made based on the availability of the patients regarding conflicting appointments at the hospital. The process of selecting patients to the interviews was continuously discussed and reflected on between the PhD candidate and the research nurse.

A total of 10 participants equally distributed between men and women and with a median age of 59 years (range 49 – 70 years) completed individual interviews from November 2015 to April 2016. Six of the patients received the EN-DUR intervention and four patients the EN-AF intervention. More than half of the participants were employed while others either retired or on disability benefits. The majority had a Karnofsky performance status of 70 % at the end of the tumour directed treatment (scored by a physiotherapist), indicating that they were able to care for themselves but unable to carry out normal activities or do active work [274]. Seven of the participants attended the interview as scheduled between two and three weeks after the end of radiotherapy, while the others were not able to attend the interview before about four weeks after treatment due to severe side-effects. About half of the participants had a feeding tube in place at the time of the interview.

4.4 Interventions

This pilot study had a pragmatic approach with a primary aim to test the feasibility of a new physical rehabilitation programme implemented during tumour directed treatment and an established post-treatment programme. The two interventions therefore differed in setting and duration. The EN-DUR intervention lasted for 6 weeks (i.e. the total radiotherapy period) and was carried out at a training facility within the hospital area, and the EN-AF intervention was conducted as part of a 3-week post-treatment programme at a rehabilitation clinic. Both interventions consisted primarily of resistance training and ONS. The patients allocated to the EN-AF intervention received standard care during treatment and acted as a control group for the EN-DUR intervention.

4.4.1 The EN-DUR intervention

The EN-DUR intervention consisted of a resistance training programme and the provision of ONS. It was initiated in the first week of radiotherapy and lasted until the end of the six-week radiotherapy period and was carried out at an outpatient training facility (Vardesenteret/Pusterommet) located within the hospital area of St. Olavs hospital, Trondheim University Hospital. All patients allocated for the EN-DUR intervention were scheduled for an initial meeting with the responsible physiotherapist to receive a booklet with nutritional advice specifically designed for patients with HNC (Appendix 2), and to taste the various flavours of the provided nutritional drink.

The resistance training programme was carried out two times a week with each session lasting 30 minutes including warm-up, amounting to a maximum of 12 exercise sessions (Appendix 3). The warm-up consisted of 5 minutes of low intensity aerobic exercises (treadmill walking or stationary cycling). The programme was conducted by use of a multi-station weight machine from Technogym® (Plurima Multistation Twin). Upper-body exercises comprised seated chest press and standing row, and lower-body exercises comprised leg extension and seated hamstring curl. The number of repetitions and sets varied according to a fixed programme, ranging from 6 – 12 repetitions maximum (RM) in 3 – 4 sets (Appendix 2). All sessions were supervised by an experienced physiotherapist to ensure individual adjustments and progression. Training days were individually adjusted to fit with the patients' treatment schedule, and it was strived for at least one day of rest between training days. The patients were recommended to continue physical activity after the intervention, in accordance with the

physical activity guidelines for cancer patients (i.e. 150 minutes of moderate intensity exercise per week) [153].

In addition to the resistance training programme, the patients were provided with ONS intended for everyday use. The supplements consisted of energy-dense nutritional drinks (E+® by Tine SA, Norway), with one unit containing 200 ml and providing 15 grams of protein and 350 kcal. The patients were asked to ingest a minimum of one unit per day during weekdays (Monday – Friday), in addition to one extra unit after each exercise session (Appendix 5).

4.4.2 The EN-AF intervention

Patients allocated to the EN-AF intervention were scheduled for a three-week programme, starting two to four weeks after the end of radiotherapy. Before initiating the EN-AF intervention, the patients were recommended to follow the general physical activity guidelines for cancer patients. The intervention consisted of resistance training and provision of ONS, in addition to nutritional counselling and optional low intensity exercises and health education lectures. The intervention took place at a rehabilitation clinic located 150 kilometres away from the hospital, as part of a standardised post-treatment cancer rehabilitation programme within the specialised healthcare service. The patients stayed overnight during weekdays with the weekends off.

The resistance training programme was conducted three times a week (Monday – Wednesday – Friday), with each session lasting 30 – 45 minutes, amounting to a maximum of 9 sessions during the intervention (Appendix 4). The programme was conducted by use of weight-machines from Follo Futura® (Diem MTT), Impulse® (IT 8010 and Leg Extension/Leg Curl) and Plamax® (PL 9021 Multi press). Upper body exercise consisted of chest press, pulldown and seated row, and lower body exercises comprised seated leg press, leg extension and seated hamstring curl. The number of repetitions and sets varied according to a fixed programme, ranging from 6 – 12 repetitions maximum (RM) in 3 – 4 sets (Appendix 5). The programme included a 5 – 10 minutes warm-up of low intensity aerobic exercises (treadmill walking or stationary cycling). All exercise-sessions were supervised by an experienced exercise therapist and a physiotherapist to ensure individual adjustments and progression. In addition to the resistance training program, the patients could participate in two voluntary

sessions a week involving a combination of strength, aerobic and balance exercises performed at a low intensity of 11 on the Borg Rating of Perceived Exertion scale (Borg RPE) [275].

ONS were provided in a similar way as for the EN-DUR intervention, meaning an intake of one unit (200 ml) of the nutritional drink (E+®) on every weekday in addition to one extra unit per exercise session (Appendix 5). Additionally, the patients received nutritional counselling by a dietitian once a week (individually or in small groups), including practical exercises in a kitchen facility. The patients also had the opportunity to participate in lectures and group discussions led by various health professionals that addressed relevant cancer-related topics such as cancer treatment and side-effects, physical activity and mental health.

4.5 Outcome measures

All patients underwent quantitative study assessments before start of radiotherapy (baseline), at the end of radiotherapy (week 6), two months after radiotherapy (week 14) and one-year later (1-year). The 1-year assessment was not originally included in the study. However, the involved researchers and health care professionals found it relevant to include long-term self-reported data to assess administration of questionnaires, response-rates, survival and status in symptoms and functioning in preparation of a definitive RCT.

In addition to the quantitative assessments at baseline, week 6, week 14 and 1-year, qualitative assessments of the patients' experiences were conducted after the end of radiotherapy (week 8). Table 1 presents an overview of the outcome measures, assessment points and use of data in the respective papers.

Table 1. Outcome measures and use of data

	Baseline	**Week 6**	Week 8	**Week 14**	**1 year**	**Use of data**
Feasibility outcomes						
Recruitment, attendance, adherence and attrition	X	X		X		Paper I and II
Objective outcomes						
Muscle mass	X	X		X		Paper I
Body weight	X	X		X		Paper I
Functional capacity	X	X		X		Paper II
Muscle strength	X	X		X		Paper II
Self-reported outcomes						
Nutritional status	X	X		X	X	Paper II
Health-related quality of life	X	X		X	X	Paper II
Physical activity	X	X		X	X	Paper II
Qualitative outcomes						
Patient-experiences			X			Paper III

4.5.1 Quantitative measures

Demographic and clinical characteristics

The patients reported demographic data such as gender, age, marital status, living situation, education, employment and smoking status by a standardised questionnaire at baseline (Appendix 6). Relevant clinical variables such as date, type and stage of diagnosis, treatment modalities, co-morbidity and Karnofsky performance status (KPS) were obtained from the patients' medical journals [274].

Feasibility outcomes

The following feasibility outcomes were tracked by the study coordinator on a weekly basis during the study period: (1) Eligibility and recruitment rates – the number of patients ineligible and declining participation, (2) Attendance, completion and attrition rates – the number of patients attending and completing the interventions, and drop-outs with reasons if

reported, (3) Intervention adherence – the number of completed exercise sessions (by exercise log sheets), and the number of ingested nutritional drinks (by weekly recall questionnaire). For the EN-DUR intervention, exercise-adherence was calculated for the first and the last three weeks separately in addition to the total adherence, given the expected increase in side-effects during the second half of radiotherapy.

Skeletal muscle mass

Skeletal muscle mass was measured by computerised tomography (CT) images of the abdominal region (CT Big Bore, Royal Philips, the Netherlands), with a maximum slice thickness of 5 millimetres. One image at the level of the third lumbar vertebrae (L3) was selected from a series of images by using the software's scrolling function. The first image in which both vertebral transverse processes of L3 were clearly visible was selected for analysis. A commercially available medical imaging software programme (Slice O' Matic v 4.3 by Tomovision®, Canada) was used to quantify the cross-sectional area of skeletal muscles. All visible muscles (i.e. musculi erector spinae, psoas major and minor, obliquus internus and externus abdominis, transversus abdominis and rectus abdominis) were identified and quantified by use of Hounsfield Units (HU) thresholds (-29 to +150 HU) [276, 277]. The cross-sectional muscle area was expressed in square centimetres (cm^2) and normalised for stature (metres, m^2) when presenting the results (cm^2/m^2).

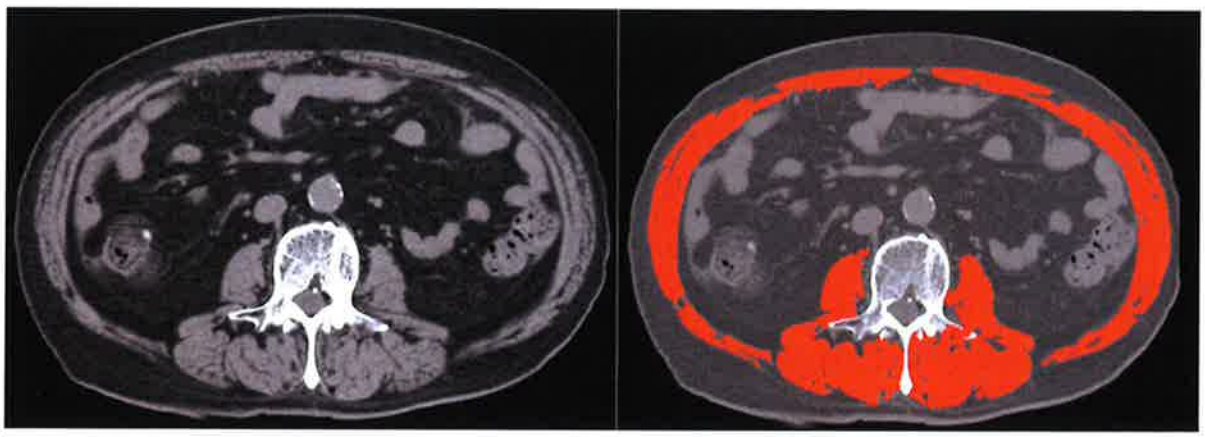

Figure 1. One CT-image at L3 before (left) and after (right) marking the muscles by the Slice O' Matic software.

Body weight

Body weight was measured with the patients wearing light clothes and no shoes, and with the identical scale for each assessment point (Seca® 876, Seca corp, Hanover, MD, USA). The weight was recorded in the nearest 0.1 kilogram (kg).

Functional capacity

Functional capacity was measured by the field exercise test Modified Incremental Shuttle Walk Test (MSWT). The 15-level MSWT required the patients to walk or run at increasing speeds (by audio signals) back and forth on a 10-metres course. Patients were accompanied by an operator during the first minute of the test to help them pace themselves with the audio signal. At the end of each level, the patients were offered a standardised verbal encouragement ("good", "keep going" or "you are doing well"). The patient was also told to go a little faster and reminded that they were permitted to run at any time during the test. Patients continued with the test until they were unable to do so or failed to maintain the set pace. A practice test was unfortunately not completed due to patient time restraints. The total distance covered was recorded and calculated from the number of completed levels and shuttles. MSWT performance has demonstrated to be a valid indicator of cardiorespiratory fitness (VO_{2peak}) in patients with cystic fibrosis, chronic obstructive pulmonary disease (COPD), sarcoidosis and primary hypertension, with a high test-retest reliability [278-282]. A difference of 70 metres is considered clinically relevant following cardiac rehabilitation [283].

Muscle strength

Muscle strength was measured by the 30 seconds sit to stand test (30s STS). From sitting in a chair of 43-45 cm height and with the hands placed on the opposite shoulder (crossed at the wrists), the patients were asked to stand and sit as many times as possible for 30 seconds. The number of times coming to a full standing was recorded. The patients were given oral instructions about the test and up to five repetitions were demonstrated by the operator. The 30s STS has shown to be a reliable and valid indicator of lower body muscle strength in generally active older adults (mean age 71 years) and patients with COPD [284-286]. A difference of three repetitions is considered clinically relevant in patients with hip osteoarthritis [287].

Nutritional status

Nutritional status was measured by the Patient-Generated Subjective Global Assessment Short Form (PG-SGA© SF), which is a commonly used instrument to measure nutritional status in cancer patients (Appendix 6). The patients answered four questions regarding weight history, food intake, symptoms adversely affecting intake and functional status [288, 289]. A total score was summarised ranging from 0 (no problem) to 36 (severe problems), and further categorised based on the recommended use of the instrument: score 0 to 1 – no particular problems/no need for interventions, score 2 to 8 – increasing nutritional problems/might benefit but not in critical need of interventions, score ≥ 9 – a critical need for improved symptom management and/or nutrition-intervention options) [290-292].

Health-related quality of life

HRQoL was measured by the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30, version 3.0, Appendix 6) and the head and neck cancer module EORTC QLQ-H&N35 [293, 294]. The EORTC QLQ C-30 is a cancer-specific questionnaire that include a total of 30 items, comprising five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting and pain), a global health status/overall HRQoL scale and six single symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-H&N35 consists of seven multi-item symptom scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality and six single-item symptom scales assessing side-effects related to problems with teeth, opening mouth, dry mouth, sticky saliva and coughing and the feeling of being ill. In addition, the questionnaire consists of five optional single-item scales assessing the use of pain killers, nutritional supplements and feeding tube and weight loss and gain. A high score for a functional scale or global health status/QoL represents high functioning or high global health, whereas a high score for a symptom scale represents a high level of symptoms. Raw scores were linearly transformed to 0 – 100 scales according to the recommendations in the EORTC QLQ-C30 scoring manual [295]. We chose to report specifically on global health status/QoL, physical functioning and symptoms of pain, dry mouth and sticky saliva since these are clinically relevant outcomes for patients with HNC undergoing radiotherapy (+/- chemotherapy).

Physical activity

Self-reported physical activity was measured by the Nord-Trøndelag Health Study 1 Physical Activity Questionnaire (HUNT 1 PA-Q), which is a short questionnaire capturing leisure time physical exercise (Appendix 6). It comprises one item each on frequency, duration and intensity of physical exercise during the last seven days. Physical exercise was addressed as "going for walks, skiing, swimming or training/doing sports" [11, 296, 297]. A total score was calculated based on the product of frequency (0.0-5.0 points), duration (0.10-1.00 points) and intensity (1-3 points), ranging from 0 (no physical activity) to 15 (vigorous physical activity for more than 1 hour almost every day) [297].

4.5.2 Qualitative measures

Individual interviews were conducted to capture patient experiences from the HNC pathway. The interviews were carried out at a meeting place and retreat for cancer patients and their families close by the hospital (Vardesenteret, St. Olavs hospital), unless the participants preferred another localisation. One participant chose to complete the interview in her home on another day than the scheduled post-treatment consultation. Three participants were accompanied by their partners, who did not have an active role during the interview.

The interviews lasted from 30 to 98 minutes (48 minutes on average) and were carried out by a research nurse (VV) involved in the present pilot study. The interviewer was at the time working in the Cancer Clinic's Research Department of the involved hospital and did not take part in the oncologic treatment of the participants. The interviewer was experienced within the clinical HNC field and had previously been involved in several clinical cancer trials utilising both quantitative and qualitative methods.

A semi-structured interview guide (Appendix 7) was used to ensure guidance to the aim of describing the participants' nutritional experiences before, during and immediately after treatment. The interview guide was developed by the PhD candidate (JAS) and the research nurse, with input from the PhD candidate's main supervisor. The interviewer strived to use broad open-ended questions, made reflections of content and feelings to encourage the patients to elaborate and lowered the voice and allowed pauses to facilitate sharing of information. Topics illuminating the phases of the HNC pathway were pursued by follow-up questions such as "can you please tell me more about that", "I am not sure I understand, what do you mean by that" and "how did you cope with that". The consequences of the disease and

side-effects that negatively affect the nutritional situation were addressed early during the interviews by most participants, and thus represented a main topic throughout the interviews. The PhD candidate and the research nurse met both before and after the interviews, and continuously reflected on the information provided by the participants and the discussed the focus of the interview-guide. The interviews were audio-recorded and transcribed verbatim after all interviews were completed. The texts were managed and systematised by Microsoft Word® and by working manually with printouts and pen and paper. Quotations from the texts were translated from Norwegian to English by the present PhD candidate.

4.6 Ethics

The pilot study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 2013/2098). All eligible patients were provided with a flyer containing brief information about the study (Appendix 1), in addition to the more detailed and standardised study information sheet. A written informed consent was obtained from each patient prior to study enrolment, in which the patients also accepted to be contacted about participation in the interview-study. The patients were informed orally and in writing that they could withdraw from the study at any time, with no consequences for the care during and after treatment.

4.7 Analyses

Descriptive and inferential statistics were used to organise, summarise and analyse quantitative data from the physical measures and tests and self-reported questionnaires. A narrative strategy was utilised for the data collection, analysis and writing of the qualitative data. The following sections elaborate in detail on the quantitative and qualitative strategies for analysis.

4.7.1 Quantitative analysis

A formal sample size calculation was not performed due to the feasibility design of the study. Determining initial data for the primary outcome measure is a major reason for conducting a pilot study, and 30 patients or greater has been suggested as a general rule of thumb to estimate a parameter in order to perform a sample-size calculation for a definitive RCT [298]. Based on a review of clinical treatment-data from previous years at the involved hospital, about 50 patients were expected to be diagnosed with HNC and referred for curative treatment

in the upcoming year of study inclusion. A high level of attrition was expected in this vulnerable patient-group due to the poor health and nutritional status often seen at diagnosis and the increasing side-effects during radiotherapy or chemoradiotherapy. In addition, the number of patients referred to the hospital varied significantly from month to month, meaning that recruitment for a short period of time would not inform the future RCT adequately. Therefore, it was important to determine consent and attrition rates over a one-year period, as this has a direct impact on how long it will take to recruit patients into the definitive RCT.

Distributions of the included variables were checked for normality by inspection of histograms, Q-Q-plots and tests of normality, and presented as mean with standard deviation (SD) if approximately normally distributed or median with inter quartile range (IQR) if skewed. Descriptive statistics were reported by distribution in numbers (n) and percentages for categorical variables, and by means (SD) for normally distributed continuous variables. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using the IBM SPSS® Statistics 22.0 software (IBM Corporation, Armonk, NY).

In paper I, independent samples t-tests were used to assess between group differences on muscle mass and body weight from baseline to week 6, from week 6 to week 14 and from baseline to week 14. Paired samples t-tests were used for within-group change between the identical assessment points. Intervention effect size (d) was calculated by using the mean and SD of the between group differences, and defined as small ($d = 0.2$), moderate ($d = 0.5$) and large ($d = 0.8$) according to Cohen's criteria [299]. Only data from patients that completed the intervention and presented valid measurements at all assessment points were analysed (per-protocol analyses).

In paper II, descriptive statistics was the focus of the analyses, due to the pilot design of the study. Differences between the groups in global health status/QoL and physical functioning and symptoms of pain, dry mouth and sticky saliva were assessed by analysis of covariance (ANCOVA) at week 6, week 14 and 1-year with the respective baseline-scores as covariate. Within-group changes were assessed by paired sample t-tests from baseline to week 6, week 6 to week 14 and baseline to 1-year and presented with 95 % confidence intervals (95 % CI). A difference in HRQoL scores of 10 points or more was considered clinically relevant [300]. Background characteristics of the attenders and non-attenders to the EN-AF intervention were compared by distribution in numbers for categorical variables and median (IQR) and mean

(SD) for continuous variables. Difference in mean scores of HRQoL, nutrition status, physical activity level and physical tests was presented with 95% CI.

4.7.2 Qualitative analysis

The individual interviews were analysed by qualitative content analysis, which is a method to analyse qualitative data. The first descriptions of content analysis were initially developed exclusively for a quantitative approach; however, later descriptions indicate it has moved towards a more interpretative approach within the qualitative paradigm [301-304]. Today, qualitative content analysis is suggested to be positioned hovering between a descriptive and interpretative paradigm.

Qualitative content analysis focuses on subject and context and emphasises variation, such as similarities within and differences between parts of the text. The method offers the opportunity to analyse manifest and descriptive content (i.e. close to the text) as well as latent and interpretative content (i.e. distant from the text) [305]. Although both manifest and latent content require interpretation, this may vary in depth and level of abstraction. Manifest content can be seen as a phenomenological description, while latent content can be seen as a hermeneutic interpretation. The process of analysis often starts by sorting the coded manifest content into categories and continues to search for the latent content formulated as themes on various levels. Thus, depending on the aim of the study, the researcher may take various scientific positions during analysis [306].

The methodological approach to qualitative content analysis may be inductive, deductive or abductive [307]. Since an inductive approach is characterised by a search for patterns (i.e. similarities and differences in data) described in categories and/or themes on various levels of abstraction and interpretation, this was found appropriate for the qualitative work in the present thesis. Based on the aim of paper III, we chose to focus on the visible and clear components from the interviews, in a bid to shed light on the participants' experiences from the various phases of the HNC pathway. This implied that the headings of the preliminary categories describe the content on a manifest level with a low degree of interpretation and a low level of abstraction. Later in the analysis and right up to submission of the manuscript, the degree of abstraction varied, still with a low degree of interpretation. Based on the study aim and the content of the data, we chose to end the analysis on a descriptive level as presented in the results-section of the manuscript.

Initially, all the interviews were read and reread by the core analysing team (JAS, ASH, and KS) to get a general overview and a sense of topics. The topics were discussed, leading to a consensus among all the authors regarding the focus of the analysis. Next, all relevant meaning units were extracted (i.e. the constellation of words or statements that relate to the same central meaning) and meaning units that deviated from the focus of the study were excluded. The meaning units were then sorted into the preliminary categories 'before treatment', 'symptoms/side-effects', 'consequences', 'supportive actions', and 'after treatment'. Based on these preliminary categories, codes were created to label all meaning units (e.g. 'nutritional preparations', 'mucous, nausea and vomiting', 'swallowing difficulties', 'coping strategies', 'hospital-admission and tube-feeding', 'hope and expectations' and 'thoughts and reflections').

Sub-categories were then abstracted, combining one or more of the codes within the preliminary categories to cover the entire treatment trajectory. Finally, new category-names were created, and narrative descriptions were written. The phases of developing codes, sub-categories and categories were continuously reflected on and discussed between the core analysing team throughout the process. The core analysing team continuously returned to the original text to ensure that that the core meaning was preserved, and this process was maintained throughout the entire analysis.

5. Summary of results

A total of 41 out of 50 eligible patients were included from March 2015 to March 2016 in the randomised pilot study, resulting in a recruitment rate of 82 %. The data-collection was completed in July 2017, including the one-year follow-up data. Figure 2 presents information of the patient-flow through each phase of the trial, as recommended by the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement: extension to randomised pilot and feasibility trials [4, 308].

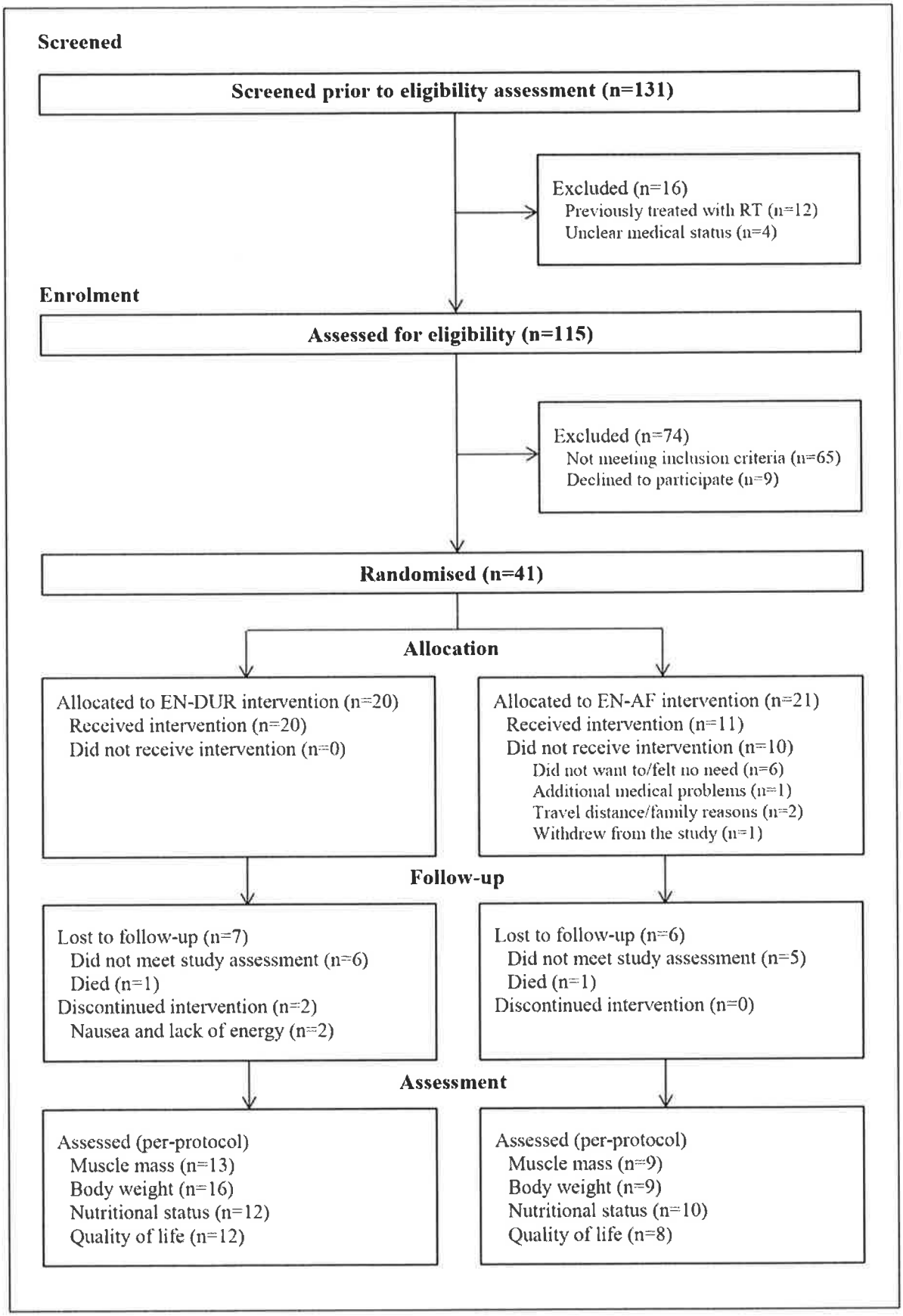

Figure 2. Flow diagram of the randomised pilot study.

Abbreviations: RT; Radiotherapy, EN-DUR; Exercise and nutrition during radiotherapy, EN-AF; Exercise and nutrition after radiotherapy.

Patient characteristics

The total study sample consisted of 25 men and 16 women with an average age of 63 years (min-max: 42 – 82 years). Median time from diagnosis to the baseline assessments was 14 days (IQR 11 days). Twenty-eight patients (68 %) reported secondary school or college/university as the highest educational level, and 20 patients (49 %) were employed with 10 patients currently working. Six patients (15 %) were current smokers and 24 patients (59 %) past smokers. A selection of the patients was invited to conduct individual interviews after the end of radiotherapy. Table 2 presents the detailed baseline characteristics of the total study sample (n=41) and the interviewed sub-sample (n=10).

Table 2. Baseline characteristics of the study sample (n=41) and the interviewed sub-sample (n=10)

	Study sample n=41		**Interviewed sample n=10**	
Age; years (mean, min–max)	63	42–82	60	49–70
Gender				
Men	25		5	
Women	16		5	
Tumour site				
Pharynx	20		7	
Salivary glands	8		2	
Oral cavity	5		0	
Larynx	4		0	
Pharynx/larynx	1		0	
Nasal cavity	1		0	
Unknown origin	2		1	
Planned treatment				
Radiotherapy	24		4	
Concurrent chemoradiotherapy	17		6	
KPS				
Score ≥ 90	33		6	
Score = 80	6		3	
Score = 70	1		1	
Score = 60	1		0	
Weight; kg (mean, SD)	81.5	18.5	77.7	18.0
BMI; kg/m^2 (mean, SD)	26.7	6.0	25.2	4.5

Abbreviations: n – number, min – minimum, max – maximum, KPS – Karnofsky Performance Status, kg – kilograms, BMI – Body Mass Index, kg/m^2 – kilograms per square metre

5.1 Paper I

Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with HNC – A pilot randomized trial

Paper I addresses the feasibility and preliminary effects of a new physical exercise and nutrition intervention during radiotherapy (EN-DUR), compared to an established intervention after radiotherapy (EN-AF). Forty-one of 50 eligible patients (82 %) agreed to participate in the study. Five patients declined to participate with no specific reason, two patients due to travel distance and two patients due to other medical problems. Twenty patients were randomised to the EN-DUR intervention and 21 patients to the EN-AF interventions. Baseline characteristics of the included patients are presented in Table 2.

Eighteen of 20 patients (90 %) completed the EN-DUR intervention, and two patients dropped out in the second week due to side-effects. Adherence to the supervised exercise-sessions was 81 %, and the main reasons for missed sessions were lack of energy, medical illness and patient refusal. Adherence to the ONS was 57 %, and 10 patients had to quit ingesting the nutritional drinks in week 3-4 due to side-effects. Eleven of 21 patients (52 %) attended the EN-AF intervention. The 10 patients that did not attend the intervention expressed a lack of need (n=6), medical problems and/or travel distance/family reasons (n=3), and one patient withdrew from the study. Adherence to the supervised exercise-sessions was 94 % for the attending patients. Adherence to the ONS was 76 %, and eight of the 11 patients ingested all nutritional drinks as prescribed.

From baseline to week 6, the EN-DUR group experienced a reduction in muscle mass of –1.7 cm^2/m^2 compared to a reduction of –4.0 cm^2/m^2 in the EN-AF group. A medium effect size (d=0.79) was noted in favour of the EN-DUR intervention. From week 6 to week 14, the EN-DUR group experienced a reduction in muscle mass of –0.8 cm^2/m^2, compared to an increase of +0.9 cm^2/m^2 in the EN-AF group. A medium effect size (d=0.75) was noted in favour of the EN-AF intervention. No difference in muscle mass was observed between the groups from baseline to week 14 (–0.3 kg^2/m^2). Both intervention-groups experienced loss of body weight during and after treatment, with no differences between the groups from baseline to week 6 (0.9 kg), from week 6 to week 14 (0.1 kg) or from baseline to week 14 (0.7 kg).

5.2 Paper II

Physical rehabilitation in patients with head and neck cancer: Impact on health-related quality of life and suitability of a post-treatment program

Paper II addresses differences and changes in relevant HRQoL domains from baseline to 1-year follow-up in the exercise and nutrition interventions during (EN-DUR) versus after (EN-AF) radiotherapy. Since only half of the patients in the EN-AF group attended the programme, baseline HRQoL scores and sociodemographic and clinical characteristics were explored between the attenders and non-attenders.

The analysis did not demonstrate any statistically significant differences between the EN-DUR and EN-AF groups in global health status/QoL, physical functioning or symptoms of pain, dry mouth and sticky saliva. However, clinically relevant changes in global health status/QoL and physical functioning were observed from start to end of the study within the EN-DUR and EN-AF groups as well as clinically relevant differences in change.

From baseline to week 6, global health status/QoL decreased 9 points (95 % CI -20.6, -3.1) in the EN-DUR group compared to 23 points (-34.0, -12.5) in the EN-AF group, and physical functioning decreased 13 points (-22.3, -3.0) compared to 21 points (-33.7, -9.0). From week 6 to week 14, global health status/QoL increased 14 points (0.9, 27.6) in the EN-DUR group compared to 26 points (7.4, 43.6) in the EN-AF group, while physical functioning did not change in the EN-DUR group (0 points, -6.8, 7.4) compared to an increase of 16 points (4.8, 26.6) in the EN-AF group.

From baseline to 1-year follow-up, global health status/QoL increased 11 points (0.8, 21.4) in the EN-DUR group compared to reaching baseline level in the EN-AF group (-11.9, 11.9) and physical functioning reached baseline level in the EN-DUR group (-11.9, 11.9) compared to a decrease of 7 points (-13.9, -0.7) in the EN-AF group.

The attenders to the EN-AF intervention reported lower global health status/QoL (62 vs. 73 points) and more pain (30 vs. 16 points) compared to the non-attenders at baseline. Furthermore, the attenders were younger than the non-attenders (61 vs. 67.5 years) and more of the attenders were diagnosed with pharyngeal cancer (n=9 vs. n=1) and scheduled for chemotherapy in addition to radiotherapy (n=8 versus n=2).

5.3 Paper III

Nutritional experiences in Head & Neck Cancer (HNC) patients

Paper III addresses the nutritional situation from diagnosis to the acute post-treatment phase, including perceptions of nutritional support. The participants' experiences and needs for nutritional support evolved within the four categories *'Waiting to get started'*, *'Undergoing daily radiotherapy turns everyday life upside down'*, *'Finally done but still troubling'* and *'Reflecting on the treatment trajectory'*.

The category *'Waiting to get started'* refers to the experiences in the time-period from diagnosis to the start of radiotherapy and consists of the sub-categories *'Preparing for radiotherapy'* and *'Receiving information'*. Living as normal as possible and maintaining the usual dietary pattern was the way to cope with this time-period. However, the participants who underwent surgery described eating and drinking difficulties afterwards, and the situation was experienced as a negative nutritional starting-point for the up-coming radiotherapy. The participants received both oral and written information about the expected consequences of radiotherapy, but preferred different delivery methods of the information: "I'm a craftsman and a man, and you have to tell these things to idiots like me and not just deliver a stack of papers", while another really appreciated the written information and "read it all".

The second category *'Undergoing daily radiotherapy turns everyday life upside down'* comprises various nutrition-related experiences from the radiotherapy-period arranged in the sub-categories *'Increasing side-effects and diminishing food intake'*, *'Coping with increasing nutritional problems'*, *'Using ONS as nutritional first aid'* and *'Deciding hospitalisation and starting tube-feeding'*. The participants experienced a decreasing food-intake as the side-effects increased in intensity. It was indicated that especially the combination of mouth-soreness, pain and increased mucous production represented the main cause of the swallowing difficulties, and loss of appetite was evident. Thus, the participants had to customise their meals to improve the food-intake, such as "I squeezed the potatoes in the sauce, I even used a knife and fork to cut the crust from a slice of bread". ONS were recommended for all, but eventually got unbearable to ingest due to the increasing swallowing difficulties. About halfway through radiotherapy, virtually no food intake was experienced, and hospital-admissions and initiations of tube-feeding occurred in this period. The hospitalisation was regarded as a necessary way out of an unbearable nutritional situation.

In the third category *'Finally done but still troubling'*, the sub-categories were *'Persisting side-effects and altered senses'* and *'Moving towards the usual life'*. Side-effects like pain, nausea, altered taste and increased mucous production were still troubling the participants after radiotherapy to such an extent that they were not able to eat or drink nowhere near a normal intake. Food they normally enjoyed now tasted awful, and the participants felt discouraged about the situation. However, different strategies to cope with the deteriorated nutritional situation were indicated, mainly focusing on maximising the food-intake either through the tube, orally or a combination of both. To optimise oral intake, the participants referred to strategies such as utilising the best times during the day for eating and adjusting the consistency of the food. The participants hoped for a gradual increase of their food-intake, but it was recognised that the recovery would take some time.

The fourth and final category *'Reflecting on the treatment trajectory'* comprises reflections about the nutritional situation from diagnosis to the post-treatment phase and consists of the sub-category *'Highlighting tailored information and specialised nutritional support'*. When looking back at the entire period from diagnosis to the current situation, the participants questioned their ability to absorb the provided information prior to start of radiotherapy. Furthermore, they requested more information about what is normal and not regarding recovery from the side-effects, and it was stated "it's still unclear when I can expect to start eating again" and "nobody has told me when it is expected that the mucous and saliva production will normalise". It was suggested to introduce peer-support in the period before radiotherapy to make the information more valid and enhance absorption. The absence of a dietitian as part of the multidisciplinary team was particularly noted.

6. Discussion

The aim of the present thesis was to evaluate the feasibility and impact of a combined physical exercise and nutrition intervention during and after radiotherapy in patients with HNC, and to describe how the patients experienced the nutritional situation and perceived nutritional support in the period from diagnosis to the acute post-treatment phase. The following sections present methodological issues related to the study design, validity of the findings and assessment of outcome measures, a discussion of the main findings and clinical implications. Finally, conclusions of the thesis are presented before future research within the field is proposed.

6.1 Methodological considerations

All three papers in the present thesis are based on data from one pilot study with an experimental and pragmatic randomised design. In addition to the quantitative measurements that usually come with a randomised design, qualitative methods were also utilised in a selection of the sample to describe patient-experiences. This between-method triangulation was considered an appropriate approach to get a comprehensive understanding of physical exercise and nutrition interventions in patients with HNC in a first-step pilot study.

6.1.1 Study design

Despite the inherent advantage of blinding both study personnel and participants within a randomised study design, this was not possible in the present pilot study considering the interventions of resistance training and ONS [309]. Nevertheless, all baseline measurements were completed before randomisation, which is vital to avoid that assessments are biased in any way by the assigned groups. A total blinding of all involved assessors could have been implemented in the present study but was considered inexpedient considering the use of resources and personnel in a pilot study primarily addressing feasibility aspects of recruitment, measurements and interventions. The healthcare professionals (i.e. radiation-therapists) who performed the follow-up CT-scans were not informed about the assigned group of the patients, which could be considered blinding on a group level during the phases of analysis and assessment of changes in muscle mass. Unfortunately, the assessor conducting the follow-up measurements of physical performance and self-reported outcomes was not

blinded due to restraints in study personnel. This was far from optimal since masking of the assessor is especially important if a baseline measure of the endpoint is to be used in the evaluation of intervention-effects.

Since only a few studies have tested a combined physical exercise and nutrition intervention during radiotherapy in patients with HNC, we found it necessary to evaluate key feasibility aspects such as willingness to participate, adherence to interventions, drop-out rates and outcome measures before taking on a full-scale RCT. The choice of also including an intervention-group after treatment was based on a need to evaluate the use of traditional post-treatment rehabilitation programmes which was the standard service offered to patients with HNC in Norway at the time of study-planning. Thus, the design of the present randomised pilot study (i.e. during vs. after treatment) provided an opportunity to evaluate the feasibility of a new physical exercise and nutrition intervention during radiotherapy, and to make comparisons of early versus delayed interventions.

The present pilot study employed broad inclusion criteria (i.e. HNC diagnosis, referred for curative radiotherapy/chemoradiotherapy and age 18 – 85 years), in an attempt to include as many patients as possible representing the population of newly diagnosed HNCs. In addition, the broad inclusion criteria were used to be able to complete the present pilot study within a reasonable amount of time, considering the small number of patients diagnosed with HNC each year at the involved hospital (i.e. estimated 50 patients). Stratification according to human papillomavirus (HPV) status was not considered appropriate due to the feasibility nature of the study. However, since HPV positive patients are markedly younger than HPV negative patients, they potentially hold superior physical attributes and thus constitute a different HNC population compared to HPV negative patients [21]. Therefore, a stratification according to HPV status needs to be performed in a future full-scale RCT assessing intervention-effects of a physical exercise and nutrition intervention.

6.1.2 Validity

Internal validity

The use of random assignment and a control group in the present pilot study reduces many of the threats to internal validity, such as the occurrence of specific events (history), changes in the participants' behaviour or abilities (maturation), regression toward the mean, selection of participants and familiarisation of outcome measures (testing) [234]. However, these issues

are only partially cancelled out, since a total equalisation is dependent on a larger number of patients that are equally likely to be affected by events during the study-period [192].

Attrition is a well-known challenge in experimental studies posing a threat to the internal (and external) validity. In paper I of this thesis, about half of the patients allocated to the EN-AF intervention dropped out prior to the start of the intervention mainly due to a self-perceived lack of need. The characteristics of these patients versus those who received the intervention as allocated were specifically addressed in paper II. Interestingly, the analyses showed clinically relevant in demographic and clinical characteristics and self-reported outcomes between the attenders and non-attenders to the EN-AF intervention. Thus, the attrition in the EN-AF group causes a bias to the reported findings of muscle mass and body weight presented in paper I of the present thesis. This limits the strength of the findings and the ability to generalise from the study. Thus, precautions must be made when comparing the observed changes between the EN-DUR and EN-AF from before to after the respective interventions.

There are also some social threats to the internal validity in the present pilot study, since several patients got to know each other and were aware of each other's assigned groups. Hence, the patients randomised to the EN-AF intervention (i.e. standard care during radiotherapy) may have attempted to change their physical activity and nutritional habits similar to the patients participating in the EN-DUR intervention during radiotherapy. A change in behaviour may also have occurred due to the simple fact that they received study information and wanted to participate in the study. Furthermore, receiving physical exercise and nutritional support may be considered as a desirable service during treatment, and there is also a risk that the healthcare providers involved in the treatment and care of the patients provided compensatory services to the patients in the EN-AF group during radiotherapy. Both the imitation of intervention and compensatory equalisation of intervention may have interfered with the findings reported in paper I of this thesis. Unfortunately, we did not include specific physical exercise or dietary logs for the patients in the EN-AF group during radiotherapy. The utilisation of logs and registrations of appointments with physiotherapists, dietitians and other relevant healthcare professionals will be considered in a future full-scale RCT. Indeed, a thorough discussion of the matter is vital before deciding to implement such measures, since an increased surveillance of a control group may lead to an increased risk of change in behaviour.

Confounding factors from the environment or personal characteristics may also affect the dependent variable(s) in a study, and thus pose a threat to the internal validity. Although random assignment is the preferred method for equalising groups (i.e. in a theoretical infinitely large sample) and control confounders, it does not guarantee equivalence in clinical samples often limited in size [310]. The random assignment in the present study resulted in disparate groups most notably on gender (n=15 vs. n=10 males). A post-hoc sensitivity analysis could have been applied to adjust for this potential confounder especially on muscle mass and body weight; however, it was not considered appropriate in a small pilot study primarily focusing on feasibility outcomes. In addition, the number of included variables is limited in an analysis of 41 patients.

External validity

Threats to the external validity are primarily related to the selection of patients and the specific setting in which the study was carried out [234]. Since the patients were eligible for the present study according to relatively broad inclusion criteria, these criteria define the target population to which the results can be generalised. The patients included in the present study were recruited from a public hospital in which all residents belonging to the mid-region of Norway are referred for assessments, diagnostics and treatment of HNC, and the treatment procedures are intended to be carried out according to national and international guidelines. All patients referred to the hospital with a suspicion of HNC were screened for eligibility from March 2015 to March 2016. Nine out of the 50 eligible patients (18 %) declined to participate in the study and specified no specific reason/"I do not want to" (n=5), travel distance (n=2) and additional medical problems (n=2) for not participating. Since almost one in five declined participation and unfortunately no demographic or medical information was obtained from these patients, there is some uncertainty related to the representativeness of the present study sample to Norwegian patients with HNC receiving curative treatment. The findings from the present study are not necessarily generalisable to other settings outside Norway since HNC populations in other countries may differ in for example proportions of HPV-positive patients and physical activity and nutritional habits [14].

The settings in the present study consisted of an outpatient training facility within the hospital-area (EN-DUR intervention) and a rehabilitation clinic located 150 kilometres from the hospital (EN-AF intervention). The outpatient training facility was included to involve a clinically relevant setting for patients undergoing radiotherapy, and to utilise the existing

facilities for patients with cancer at the hospital. This ensured a high degree of applicability of the programme beyond the specific study setting. The main reason to include the setting of a rehabilitation clinic outside the hospital was due to the established healthcare system in Norway that includes rehabilitation services offered as residential stays to patients with cancer and other diagnoses. The rehabilitation programmes are carried out at rehabilitation clinics as part of the specialised healthcare service, they usually consist of multi-disciplinary interventions and implies that the patients stay overnight in weekdays. To our knowledge, the Norwegian residential rehabilitation model with public funding is not directly comparable to rehabilitation models in other western countries, except for similar models in Germany although financed with health-insurances. Thus, the implementation of a residential rehabilitation setting in the present study reduces the applicability to rehabilitation settings in other comparable Nordic and European countries, and to other rehabilitation settings within the specialist healthcare in Norway.

Trustworthiness of the qualitative study

The focus of the qualitative study (paper III) in the present thesis was to obtain patient-experiences specifically related to nutritional issues from diagnosis to the acute post-treatment phase. In order to facilitate meaningful critique of the presented findings and thus judgement of the quality of the study, the critical issues of credibility, dependability and transferability will be discussed [233]. Even though different aspects of trustworthiness are separated here, they should be viewed as intertwined and interrelated.

To achieve credibility, it is crucial to include participants who have experiences of the phenomenon under study and who can tell about it [306]. The participants in the qualitative study were invited from an ongoing randomised pilot study that involved the majority of all patients with HNC scheduled for curative treatment within the health region of central Norway over a one-year period. The invitation to the interview was based on an intent to include the heterogeneity of patients with HNC, such as both genders, younger and older and living in rural and urban areas. Inviting patients with various experiences increases the possibility of including a variety of aspects regarding related to the research question [311]. In addition, the invitation was based on the availability of the participants regarding conflicting appointments at the hospital or other personal appointments. Thus, the participants possessed relevant and recent experiences from the HNC pathway, and the participants were prepared to share their experiences as part of the pilot study. Another crucial aspect to achieve credibility

concerns the number of participants. Although it is not possible to suggest a specific number of participants in a qualitative study utilising qualitative content analysis, there must be enough data to cover significant variations since the method emphasises variation in content and multiplicity [312]. When approaching 10 interviews in the present study, the provided information was redundant regarding variations in experiences from the HNC pathway; thus, inclusion was ended [313]. During analysis, categories were established based on converging information from several patients representing the diversity of the patient-group, and different patient-perspectives and detailed descriptions of the patients' situation were presented to show the diversity in nutritional experiences and needs for nutritional support.

To enhance dependability, the steps of analysis were followed as closely as possible [305]. The research team strived for clarity throughout the research process to make the decision trial visible, by for example using quotations [314]. To address the challenge of deciding which codes and supporting quotes from the text to be included in a category, it was strived for clear rules for differentiating between categories. The research team met on a regular basis to continuously share the analyses and made sure they had a common understanding of the process and findings at the start and end of every meeting. The analysing team continuously returned to the original text to assure that that the core meaning was preserved. Another challenge concerning dependability is the view that interviews are co-created between the researcher and the interviewee, and between the text and the researcher during analysis [315]. This was addressed by awareness of the interviewer's (VV) pre-understanding of the population under study, the treatment trajectory and common side-effects, and by awareness of the PhD candidate and the rest of the research team regarding interpretation of the narratives. Within the analysing team, the senior researcher possessed extensive experience from the clinical field of HNC, while the PhD candidate gradually obtained relevant experience from the field by running the present pilot study including tasks related to patient-recruitment, study-assessments and the physical exercise programme during treatment. Including more than one researcher has been suggested to enhance dependability as co-researchers can contribute to alternative interpretations [306].

Several strategies have been suggested to determine if the method used is consistent in qualitative studies, such as checking manuscripts for obvious mistakes made during transcription, constantly comparing data with the codes including memos about the codes and co-ordinate communication between coders by regular documented meetings and by sharing

analyses [316, 317]. About half of the audio-recorded interviews in paper III were transcribed by a student from outside the project. These transcripts were reviewed by the present PhD candidate, resulting in corrections regarding missing words or wrong use of terms and phrases due to difficulties in understanding the patients' dialects, unclear pronunciations and unknown medical terms used by the patients. The other half of the interviews was transcribed by the PhD candidate, who also reviewed these transcripts afterwards. Since the interviews were carried out over a 6 months period (i.e. November 2015 to April 2016), there was a risk of inconsistency during data collection. On one hand, the interviewer and the PhD candidate agreed it was important to follow the interview guide and question the same pre-defined areas for all participants. On the other hand, interviewing is an evolving process that continuously leads to new insights that may influence follow-up questions or narrow the focus [227]. Thus, an open dialogue within the research team was employed to address whether judgement about similarities and differences were consistent over time.

The aforementioned strategies for credibility also enhance transferability of the present study, since transferability has been suggested to depend on the credibility of a study to a large extent [230]. Furthermore, transferability was ensured by the fact that all participants experienced treatment related side-effects with subsequent nutritional problems, and that they showed a positive attitude towards the interview and the purpose of the pilot study. The sampling method aimed to capture the heterogeneity of patients with HNC, resulting in participants of various age and gender considered representative for the HNC population. It was also strived to give a clear description of context, selection and characteristics of participants, data collection and analysis process, in addition to a rich presentation of the findings including appropriate quotations, in order to enable readers to evaluate to what degree the findings can be transferred to other settings or groups.

Most of the participants (7 out of 10) were diagnosed with pharyngeal cancer in the present sample, and patients with oral cavity and laryngeal cancer were not represented. While the treatment modalities of oral and laryngeal cancer are similar to that of pharyngeal cancer (i.e. radiotherapy +/- chemotherapy), patients with laryngeal cancer often experience less side-effects compared to oral and pharyngeal cancer due to much smaller irradiated areas, depending on stage [318]. Since more than half of the participants (6 out of 10) participated in the EN-DUR intervention (i.e. during radiotherapy), while the other participants received standard care in the same period, the intervention may have influenced the perceptions of

supportive care and the provision of nutritional drinks. However, the interviewer experienced that the participants did not distinguish between the study-specific support and standard care.

Unfortunately, taking the final analyses back to the patients to check whether they felt that the descriptions were accurate (i.e. member-checking) was not carried out. Furthermore, the aspects of bias that the PhD candidate brought to the study was not clarified, meaning that information about how the interpretation was shaped by the background of the researcher is missing. Since the interviews were conducted about two weeks after the end of radiotherapy, and even about four weeks after treatment for three participants, oversights and recall biases of relevant events cannot be ruled out. Repeating the interviews during the different treatment phases would result in more accurate snapshots of the patients' experiences and will be conducted in a planned follow-up study within this patient-group.

6.1.3 Outcome measures

Choosing outcome measures in experimental studies should be undertaken with consideration to the outcome(s) of interest, as defined by the specific study objectives and/or research questions. Furthermore, the measures should be able to capture the factors most likely to be influenced by the intervention [192]. The objective and self-reported measures included in the present pilot study were intended to assess the feasibility of a combined physical exercise and nutrition intervention during and after tumour directed treatment, and to capture possible changes following the interventions. The individual interviews were utilised to describe the patients' subjective experiences of the nutritional situation within the different treatment-phases.

Although p-values of ≤ 0.1 were examined for trends in paper I of this thesis for between-group differences in muscle mass, these should be interpreted with caution since the results from small and under-powered pilot studies can only be used to estimate the sample-size for a definitive RCT [319]. Even if statistical significance is found in a pilot study, only a full-scale RCT could generate reliable results. Furthermore, it has been recommended to put more emphasis on confidence interval estimation rather than hypothesis testing in pilot studies, since this will provide a clearer picture of the imprecision of the estimates [298]. In paper II of this thesis, confidence intervals were presented to assess differences in HRQoL between the attenders and non-attenders to the EN-AF intervention, and formally statistical differences were not reported.

Feasibility

The objectives in a pilot study should differ from those in a definite RCT, by stipulating the issues of uncertainty to be addressed in the future trial [193]. The primary objective in paper I of this thesis was to evaluate feasibility of the interventions, specifically by tracking recruitment, attendance, adherence and attrition rates. Each of the feasibility outcomes were specified within a separate section of the paper, to inform a future definitive RCT. These outcomes are in line with previously published work that has recommended several key objectives of pilot or feasibility studies, such as to test data collection questionnaires and randomisation procedures, estimate rates of recruitment and consent, determine the acceptability of the intervention and select the most appropriate primary outcomes measure(s) [298].

Skeletal muscle mass

The secondary objective of paper I was to assess changes in muscle mass (and body weight) from start to end of the interventions. Magnetic resonance imaging (MRI) and CT are considered gold standard methods to assess whole-body and regional skeletal muscle mass, subcutaneous adipose tissue and visceral adipose tissue [10]. Other methods often used to determine body composition include dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA), in addition to BMI to estimate body fat. The application of MRI is often restricted because of limited availability of devices and high costs, while CT is readily available in clinical settings since cancer patients frequently undergo routine CT-scans for diagnosis and monitoring of treatment-progression.

Abdominal CT imaging at the level of L3 is frequently used to assess muscle mass in cancer patients. The method is based on MRI-studies demonstrating that cross-sectional muscle area (cm^2) from a single slice in the lumbar area is strongly correlated with total skeletal muscle volume measured by whole-body MRI [320-322]. CT-measured cross-sectional L3 muscle area is commonly normalised for stature (m^2), providing a skeletal muscle index (cm^2/m^2) used as a measure of relative muscle mass. Thresholds for classifying sarcopenia (i.e. depletion of skeletal muscle) in cancer patients have been proposed based on the skeletal muscle index, and sex specific percentiles in a healthy population have also been provided to help interpret and compare index-scores [323, 324]. It is important to notice that a single slice image has limited applicability for estimating total body muscle mass in individuals; however,

group comparison in studies of muscle mass volumes may advantageously utilise the muscle areas estimated from single slices [320].

CT-image analysis of muscle mass has demonstrated a measurement error of only 1.5 – 2 %, with a minimum detectable change of about 2 % [276, 325]. Thus, the method was considered appropriate in the present study to detect the expected small changes in muscle mass from start to end of interventions with a short duration (i.e. six and three weeks, respectively). To minimise the risk of systematic errors when analysing the images, a trained researcher with experience of the method and the specific software was responsible for the analysis.

Recent development within the area of CT and muscle mass assessment in patients with HNC suggests that CT-images from the neck (C3) may replace the standardised abdominal imaging (L3). Cross-sectional muscle area estimated at C3 has demonstrated a strong correlation with L3 muscle area (r=0.785), and C3-imaging has shown robustness regarding vertebrae and slice selection and an excellent interobserver agreement [326, 327]. These are exciting findings considering the feasibility, costs and patient-burden of additional abdominal imaging, since CT-scans of the neck are part of the standardised diagnostic work-up in patients with HNC. This new method allows for an easy access to study the predictive and prognostic value of low muscle mass at diagnosis in patients with HNC, and not at least to assess changes in muscle mass following appropriate physical exercise and nutrition interventions.

HRQoL

Although a variety of outcome measures are available to capture HRQoL in cancer patients, two cancer-specific questionnaires are often used in clinical trials: the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy-General (FACT-G) [328]. The EORTC QLQ-C30 was opted for in the present pilot study, since it seems to be a preferred instrument in Europe and especially within the Nordic countries.

Changes in HRQoL-scores over time may be more difficult to interpret than differences in absolute scores at one assessment point, which was also evident in the HRQoL scores from baseline to one-year follow-up in the present study. In addition, statistically significant changes do not necessarily reflect clinically relevant changes. Different approaches have been used to define the minimal clinically important difference in change of HRQoL, with the work of Osoba and colleagues as one of the most used definitions involving the EORTC QLQ-C30

[329]. Their work demonstrated that subjectively perceived "little change" corresponded to a change of 5-10 points on the QLQ-C30, "moderate change" to a change of 10-20 points and "very much change" to a change greater than 20 points in patients receiving chemotherapy for either breast cancer or small-cell lung cancer [330]. These proposed cut-offs in scores were used to interpret clinically relevant changes in HRQoL in paper II of the present pilot study, since clinical features of receiving chemotherapy for either breast or lung cancer were considered adequately similar to that of patients with HNC.

Patient-experiences

A qualitative study with individual interviews was employed in paper III of this thesis to describe how the patients experienced their situation from diagnosis to the acute post-treatment phase. Qualitative research is a broad field comprising interpretative activities of a variety of empirical data (e.g. personal experience, life-story, interview, artefacts and texts), and no single strategy of inquiry is considered superior to another [316]. The various strategies, also called approaches to enquiry or research methodologies, provide specific direction for procedures in a research design [234]. Interviewing is considered a basic method of collecting empirical data both by quantitative and qualitative researchers, with the most common form involving individual, face-to-face verbal interchange [331]. Since clinical experience from the field of HNC suggested a large variety in intensity of side-effects and management of these, we decided to make use of semi-structured interviewing in paper III of this thesis. Using open-ended questions gave us a great opportunity to receive both breadth and depth of the information compared to structured interviewing. Relevant topics that emerged were pursued by follow-up questions, and the interview guide ensured information from all phases of the HNC pathway.

The interviews were only conducted at one point of time (i.e. after treatment), mainly due to restraints in study-personnel in this first-step pilot study. Conducting several interviews at various time-points may have provided richer descriptions and other reflections. Thus, the use of repeated interviews will be planned and implemented in a future study. However, it is important to recognize that being exposed to several interviews is more demanding for the patients. In addition, several methodological challenges arise since the study-personnel and healthcare providers responsible for the treatment of the patients should not be involved in the interviews to avoid a linkage between the patient and the interviewer.

6.2 Main findings

The present randomised pilot study demonstrated that more than three quarters of the eligible patients were willing to participate in an intervention study involving physical exercise and nutritional support during or after radiotherapy. The majority of the patients randomised to the EN-DUR intervention completed the physical exercise programme, and the intervention indicated less muscle wasting and reduction in HRQoL compared to standard care. Only half of the patients randomised to the EN-AF intervention attended the programme, but all attending patients completed the programme. The attenders to the EN-AF intervention were younger and more were diagnosed with pharyngeal cancer and received concurrent chemoradiotherapy compared to the non-attenders. In addition, the attenders reported worse HRQoL and higher physical activity level compared to the non-attenders before treatment start and had a higher functional capacity. The interviewed patients' experiences emphasised the negative nutritional consequences from diagnosis to the acute post-treatment phase and highlighted the need for specialised and individually tailored nutritional support throughout the HNC pathway. These main findings will be discussed in detail in the following sections.

6.2.1 Feasibility of the interventions

Although physical exercise and nutritional support may help patients with HNC to manage treatment-related side-effects and preserve physical function, rehabilitation programmes have traditionally been offered after the completion of treatment [141, 186]. This may be explained by an established conception about rehabilitation primarily as a post-treatment health-service, and on a clinical notion that active interventions during treatment are too strenuous and thus inappropriate for patients with HNC. Due to the lack of clinical experience in Norway regarding early interventions with physical exercise in patients with HNC, it was important to test if the present combined physical exercise and nutrition intervention was applicable in the clinical hospital setting, and if the patients were able to complete the intervention while undergoing radiotherapy. In the planning and execution of the study, efforts were made to make the intervention fit with the six-weeks radiotherapy schedule (and chemotherapy schedule, if relevant), utilise the existing training facility located at the hospital and include few and simple resistance training exercises while still aiming for optimal increase in muscle mass and strength. We considered these efforts as key elements to facilitate the implementation of a similar intervention within the treatment trajectory of patients with HNC.

The recruitment rate of 82 % in the present pilot study can be considered high in an intervention study involving physical exercises in patients with HNC. In comparison, the recruitment rates from similar physical exercise trials in patients with HNC range from 55 to 63 % [207, 208, 210]. It is worth mentioning that the initiation of the present pilot study was appreciated among the clinical staff working at the involved hospital, since standardised rehabilitation interventions were not part of the HNC pathway at that time. Thus, study participation was recommended especially by several of the nurses during the days of the medical examinations prior to diagnosis. The patients received oral study information and a brief study flyer (Appendix 1) already at the start of the medical examinations, and we believe this facilitated a gradual absorption of study information. The study-coordinator conducted the formal study request immediately following diagnosis, and the patients were given time to ask questions and a couple of days to think about participation if needed. Based on the experiences from the present pilot study, it seems appropriate to include the clinical staff in the study-planning and preparation of a common information-strategy to ensure optimal recruitment within this patient group.

The EN-DUR intervention

The adherence to the physical exercises in the EN-DUR intervention was considered high, with more than 80 % of the physical exercise-sessions completed as planned. Adherence-rates from similar HNC studies involving physical exercise interventions during radiotherapy range from 45 % to 83 % [207, 208, 210, 246]. Although the adherence dropped markedly from the first three weeks to the last three weeks of radiotherapy, still almost three quarters of the exercise-sessions were completed during the last three weeks. The decline in adherence to the physical exercises was expected due to the well-known increase in side-effects especially from midway through radiotherapy [54]. These findings indicate a need to employ easily accessible areas to facilitate completion of physical exercises in the final weeks of radiotherapy, and to adjust the type of exercises accordingly in a future trial. Simple home-based exercises would be a sensible addition to the standard programme, allowing the patients to do some of the exercises in the hospital ward or at home if prevented from attending the scheduled sessions. A decline in adherence was also evident for the provided ONS, with more than half of the patients quitting the nutritional drinks between the third and fourth week of radiotherapy due to swallowing difficulties. Thus, ONS and other relevant nutritional support (e.g. dietary advice) should be provided and monitored thoroughly by healthcare professionals with nutritional expertise.

The timing of the exercise-sessions in the present study were adjusted according to changes in the treatment schedule, but still within pre-defined fixed days (i.e. Monday/Tuesday and Thursday) allowing for adequate physical restitution. To facilitate a social arena outside the clinical setting and exploit the potential added value of peer-support, the exercise-sessions were if possible, conducted in small groups of two to three patients. Such an approach is supported by an explorative study of group cohesion in cancer patients participating in a physical exercise intervention during treatment, revealing that the exercise programme made purposeful togetherness possible while allowing to let the illness fade into the background [332]. In addition, the explorative study showed that the patients experienced group cohesion as an interim goal aimed to maximise their peak performance potential. All exercise-sessions in the present study were supervised by a physiotherapist to ensure safety and provide corrections and optimal progression. Supervised physical exercise programmes have demonstrated improved adherence compared to non-supervised programmes in various cancer patients, in addition to superior benefits on HRQoL and other physical and psychological outcomes [103, 137, 148, 149].

The EN-AF intervention

Only eleven of the 21 patients randomised to the EN-AF intervention attended the programme. However, as much as 94 % of the physical exercise sessions were completed and 76 % of the provided ONS were ingested among the attending patients. Especially the adherence to the supplements was markedly higher in the EN-AF intervention compared to the EN-DUR intervention (76 % versus 51 %) and indicates that this type of nutritional support may be easier to implement and thus is more appropriate in the post-treatment phase. The only study to our knowledge that has specifically investigated the feasibility of providing dietary supplementation, in combination with resistance training, after radiotherapy in patients with HNC, showed that 69 % of the patients ingested all supplements as prescribed [245].

Since only half of the patients received the EN-AF intervention as allocated, a thorough sub-group analysis of the attenders and non-attenders was conducted in paper II of this thesis. It is worth noting that the EN-AF intervention was conducted at a rehabilitation clinic located 150 kilometres from the hospital, as part of the cancer rehabilitation programmes offered within the specialist healthcare service in Norway. The sub-group analysis showed that the attenders differed to the non-attenders in demographic, clinical and patient-reported outcomes and in physical performance before the start of treatment. The finding of younger age among the

attenders compared to the non-attenders is in line with other studies reporting that younger cancer patients express an increased need for rehabilitation compared to older patients [91, 333]. Thus, the utilisation of cancer rehabilitation services is significantly higher in younger age groups, presumably due to a greater self-perceived loss of functioning [334]. The latter and the aspect of still being within working age may have influenced the choice to attend the EN-AF intervention in the present study, possibly as a means to regain physical and work-related functioning.

A clear difference in clinical characteristics was that as much as eight of the 11 attenders were scheduled for concurrent chemoradiotherapy compared to only two of the 10 non-attenders. Receiving chemotherapy concurrently with radiotherapy is associated with increased symptoms of mucositis, nausea, vomiting and fatigue compared with receiving only radiotherapy [15]. Thus, a clinically significant increase in symptoms could be expected especially among the attenders before start of the EN-AF intervention. The attenders' symptom-scores were similar to previously published data from the EORTC QLQ-C30 in patients with HNC receiving concurrent chemoradiotherapy [214, 216, 218, 219, 221]. A Norwegian cross-sectional study that evaluated the needs for rehabilitation in patients with various cancer diagnoses, found that patients who received concurrent chemoradiotherapy were more likely to report need for two or more rehabilitation services (e.g. physical exercise, psychological counselling and supportive group sessions) compared to those not receiving chemotherapy [335]. Also, a Danish nationwide study demonstrated that chemotherapy was one of the factors predicting patient-perceived unmet needs of rehabilitation [336]. The findings in paper II indicate that patients with HNC scheduled for concurrent chemoradiotherapy should be prioritised when selecting and referring patients to post-treatment rehabilitation services, and also when planning recruitment to a definitive RCT investigating the effects of physical rehabilitation interventions.

Since the EN-AF intervention was carried out as a traditional residential stay at a rurally located rehabilitation clinic, this may have influenced the choice not to attend the programme in addition to the mentioned factors of age and lack of rehabilitation needs. Although only specifically stated by one of the non-attenders, the travel distance to the clinic (i.e. at least two hours for most patients), and the prospect of being away from home for three weeks immediately following a six-week treatment period at the hospital, may presumably represent reasons for not utilising the service offered. Thus, there is a need to map out existing out-

patient and community-based rehabilitation services in preparation for a definitive RCT and consider the need to implement programmes closer to where the patients live.

6.2.2 Changes in muscle mass and body weight

The CT-analyses presented in paper I revealed a loss of muscle mass in both the EN-DUR and EN-AF group from start to end of radiotherapy. However, the observed loss of muscle mass was less in the EN-DUR group compared to the EN-AF group (–3.2 % vs. –7.9 %), and a moderate effect size was detected in favour of the EN-DUR intervention (d=0.79). Although these are promising findings, they still need to be confirmed in a full-scale RCT.

To our knowledge, no other randomised trial has specifically investigated changes in muscle mass following a combined intervention with resistance training and ONS during radiotherapy in patients with HNC. The few experimental studies that have assessed changes in muscle mass from interventions with only physical exercise show inconsistent findings compared to the present findings. A randomised pilot study similar to the present study that examined the preliminary effects of twice weekly resistance training during radiotherapy (+/- chemotherapy), reported a mitigating effect on lean body mass compared to standard care from start to end of treatment (–0.3 % vs. –4.0 %, d=0.35) [207]. Lean body mass was also unchanged (i.e. 0.2 % change) following a resistance and walking exercise intervention during concurrent chemoradiotherapy in a non-randomised pilot study, however the lean body mass in fact increased some in the control group (i.e. 1.0 % change) [246]. And in a recently published pilot study without control group in 12 patients scheduled for concurrent chemoradiotherapy, the loss of lean body mass was 9.3 % at the end of treatment despite the implementation of resistance training three times a week during the treatment period [210]. Other methods than CT-scans were used to measure lean body mass in these pilot studies, more specifically BIA and DEXA, which may explain some of the differences in findings [10]. Although BIA is a widely available and easy method to measure body composition, it has a lower accuracy for muscle mass compared to CT and DEXA measurements [337]. Thus, full-scale RCTs are needed to investigate the effects of physical exercise and nutrition interventions on muscle mass in patients with HNC undergoing radiotherapy (+/- chemotherapy), preferably by utilising gold standard methods.

As described in paper I of the present thesis, no difference in change of weight loss was observed between the EN-DUR and EN-AF groups from start to end of radiotherapy (–3.4 kg

vs. –4.3 kg). Also the resistance and walking exercise intervention in a non-randomised trial by Zhao et al. demonstrated declines in BMI while lean body mass was preserved at the end of radiotherapy [246]. A similar result was also reported in the randomised exercise-trial by Rogers et al., who specifically noted that the positive effect size observed for lean body mass was noteworthy considering the decline in body weight [207]. Overall, the results from these small pilot studies indicate that although the patients experience weight loss from start to end of the interventions, muscle mass seems to be preserved. Interestingly, the non-randomised pilot study by Lønkvist et al. that tested a progressive resistance training programme during and after concurrent chemoradiotherapy, showed both a loss of body weight (–9 %) and lean body mass (–9.3 %) from start to end of treatment [210]. However, the study consisted of only patients with HPV positive oropharyngeal cancer, and thus represents a younger HNC population than the present study and the study by Rogers et al.

While the mean weight loss in the EN-DUR group represented a 3.9 % reduction of the baseline weight at the end of radiotherapy, the weight loss in the EN-AF group represented a 5.5 % reduction. Reporting weight loss in proportions of initial body weight instead of absolute changes in kilograms is highly relevant in the present study, since the EN-DUR group consisted of more men than the EN-AF group (15 vs. 10 men) and thus had a clinically significant higher body weight at baseline (84.5 kg vs. 78.2 kg). A retrospective study that investigated changes in body weight in 476 patients with HNC, reported a mean weight loss of 6.7 % (±5.7 %) from start to end of radiotherapy [80]. This is more than the 5 % cut-off often used to categorise a significant weight loss with increased risk of underweight among patients with HNC [90]. Even though no statistically significant differences in weight loss was detected between the EN-DUR and EN-AF from start to end of radiotherapy in the present pilot study, it is worth noting that the mean weight loss in the EN-DUR group is not considered a significant weight loss. Thus, the present physical exercise and nutrition intervention may contribute to the preservation of body weight compared to standard care during radiotherapy, but needs to be investigated more thoroughly by detailed assessments of changes in body composition in a definitive RCT.

6.2.3 Impact on HRQoL

Paper II assessed differences and changes in HRQoL from baseline to 1-year follow-up in the EN-DUR and EN-AF groups. Not unexpectedly in a small underpowered pilot study, no statistically significant differences were demonstrated. However, clinically relevant changes

in global health status/QoL and physical functioning were observed in both groups, with differences in change in favour of the active interventions during and after treatment respectively.

The findings in paper II confirm earlier findings from numerous observational studies that global health status/QoL and physical functioning decrease during radiotherapy or chemoradiotherapy while symptoms increase steadily [213-221]. The post-treatment period is normally characterised by gradual recovery and improvement in HRQoL and less symptoms. However, an interesting and novel finding in our study is that the patients that receiving the active intervention during treatment (EN-DUR) experienced clinically relevant improved global health status/QoL and physical functioning compared to the patients that received standard care during treatment. A similar trend was observed in the active intervention after treatment (EN-AF), with clinically larger improvements in global health status/QoL and physical functioning compared to the "controls" in the EN-DUR group. This indicates that a physical rehabilitation programme with physical exercise and nutritional support initiated at start or after radiotherapy may have positive impact on self-reported health status and physical functioning. This justifies a full scale RCT being conducted to investigate whether exercise and nutrition interventions lead to statistically significant improvements.

A future RCT may preferably investigate the effects of a physical exercise and nutrition intervention and could be initiated before start of tumour directed treatment with continuation during treatment and into the post-treatment recovery phase compared to a usual care group. To our knowledge, the largest RCT that has investigated the effectiveness of a physical exercise program in patients with HNC undergoing chemoradiotherapy was recently published by Samuel and colleagues (2019), concluding that physical exercise during treatment has the potential to enhance HRQoL [247]. The effect of an 11-week programme with aerobic and resistance training exercises was assessed on quality of life (using the generic Short Form-36), functional capacity and worsening of fatigue. Compared with the control group there was a statistically significant difference in favour of the exercise group on all outcomes from start to end of the intervention. Both the mental and the physical quality of life score was maintained from baseline to immediately after treatment in the exercise group compared to a significant reduction in the control group [247]. These are exciting results from a full-scale trial supporting the findings in the present paper, although not directly comparable due to differences especially in content of interventions and measurement instruments.

6.2.4 Nutritional experiences

The qualitative interview-data in paper III emphasises the comprehensive nutritional problems that patients with HNC experience during the different phases of treatment and indicates a need for specialised and individually tailored nutritional support.

The period following surgery (and biopsies) was characterised by pain, swallowing difficulties, appetite loss, reduced food intake and fatigue, and the situation was experienced as a poor starting-point for the up-coming six-weeks of radiotherapy. Since patients with HNC are at a high risk of malnutrition already from diagnosis, early nutritional strategies are required in order to minimise the negative consequences of the involved treatment modalities [69, 338, 339]. The time period from diagnosis to start of radiotherapy, at least two weeks in general, may easily be utilised for initiation of nutritional support. Clinical experience suggests that patients with HNC are eager to try themselves to be best prepared for radiotherapy, and most patients have time to spare in this waiting period.

Specialised nutrition competencies and skills are needed to make early detections of needs for nutritional support, and to initiate relevant nutritional interventions if needed. Updated international clinical guidelines on nutritional support in cancer patients recommend that dietitians or nutrition experts play a central role in the multidisciplinary team responsible for the supportive care of patients with HNC [72, 340]. Not only may a dietitian improve the nutritional support through working with the patients, but also through increasing the nutritional expertise in the multidisciplinary team involved in the patientcare of patients with HNC.

The patients experienced a lack of information about the expected nutritional consequences of treatment, and it was specifically asked for an estimated timeline regarding when to resume eating and drinking like normal again. Most written information to this patient-group typically consists of generic themes intended to apply for all patients. In general, it could be argued that a generic provision of information is not sensitive enough to capture the variation that exists between patients in their desire for and understanding of information [341-343]. Since there are great individual differences in the severity of side-effects throughout the treatment trajectory in patients with HNC, information provided on a group level may not fit with the progress of the individual recovery. Providing individually tailored information and involvement of patients with HNC in the decision-making by requesting values and food-

preferences, has been found to result in higher levels of knowledge and satisfaction with information and lower levels of anxiety compared to providing generic information [344, 345]. Thus, individual assessments of the patients' needs and preferences should be considered before providing information to these patients. Such a patient-centred approach may not fit the current streamlined cancer treatment trajectories in Norway; therefore, we suggest implementing individually tailored nutritional support as a part of the cancer pathway for HNC.

6.3 Clinical implications of the findings

The multiple side-effects of HNC treatment are well-documented, often leading to malnutrition and loss of body weight and muscle mass with subsequent deterioration in physical function and HRQoL. Interventions consisting of physical exercise and nutritional support hold the potential to mitigate some of the side-effects and improve functioning. However, few combined exercise and nutrition interventions have been tested within the pathway for patients with HNC, and there is still a need to explore the optimal timing, type of interventions, factors optimising adherence and relevant outcome measures and determine intervention-effects.

The findings from the present qualitative interviews stress the importance of specialised nutritional support throughout the treatment trajectory in patients with HNC. Addressing nutritional issues immediately following diagnosis enables appropriate interventions on time. Nutritional screening is recommended for all patients with HNC, followed by a full assessment if nutritional risk is present. General nutritional advice should be provided to all patients, before specific nutritional counselling is initiated by a dietitian if relevant. Nutritional counselling comprises a dedicated and repeated communication process to provide the patients with a thorough understanding of nutritional topics. Since radiotherapy and chemotherapy are carried out on an out-patient basis in patients with HNC, nutritional interventions need to be adjusted to the patient's treatment schedule and hospital visits.

The high recruitment-rate in the present pilot study and the high exercise-adherence during radiotherapy, indicate that healthcare providers at the hospitals should be aware of gatekeeping potentially preventing patients with HNC from exercising while undergoing treatment. The present study confirms that supervised resistance training is safe during

radiotherapy. We believe that especially the tailoring of exercise-sessions according to the treatment schedule, utilisation of existing facilities within the hospital-area and providing a supervised programme constitute the main reasons for the high exercise-adherence. In addition, it is vital that participation in physical exercise is supported within the clinic. Since the use of ONS not unexpectedly dropped markedly about halfway through radiotherapy, the energy-sources (i.e. oral and/or enteral nutrition) and the specific amount of daily energy-intake need to be continuously monitored and adjusted right up until the end of treatment, preferably by healthcare providers with nutrition expertise. The present physical exercise and nutrition intervention indicated a mitigating effect on muscle wasting compared to standard care during radiotherapy. This is a promising finding considering the potential preservation of physical function and the increased ability to tolerate and complete planned treatment. However, the findings from this under-powered pilot study need to be confirmed in a large-scale RCT.

A traditional post-treatment residential rehabilitation programme does not seem to be an appropriate service for all patients with HNC shortly after the end of radiotherapy. In the present pilot study, more of the patients who attended the EN-AF intervention had received chemotherapy in addition to radiotherapy compared to the non-attenders. The attenders were younger, reported increased symptoms, worse global health status/QoL and higher physical activity level and had higher functional capacity than the non-attenders before treatment start. This indicates that patients receiving concurrent chemoradiotherapy have an increased need for post-treatment rehabilitation services. Screening of rehabilitation needs among patients with HNC could easily be implemented already from diagnosis, followed by monitoring of patient-reported symptoms and functioning throughout treatment. The information from the present pilot study regarding attenders and non-attenders to the EN-AF intervention could already be used by doctors responsible for referring patients with HNC to the existing post-treatment rehabilitation programmes.

Clinical experience from the rehabilitation field and the present study indicates that many patients with HNC find it too strenuous to make a travel to a rurally located rehabilitation clinic and stay away from home for several weeks shortly after having completed treatment. Allowing for adequate treatment recovery by postponing the start of the post-treatment programme may have resulted in a higher attendance, and potentially improved intervention response. Thus, individually tailored timing of post-treatment rehabilitation interventions

should be utilised in patients with HNC. Considering the beneficial effects of physical exercise programmes after treatment, more locally-based rehabilitation services within the specialised healthcare seems appropriate [224].

7. Conclusions

The conclusions of the present thesis are summarised as follows:

- Most patients with HNC seem willing to participate in a physical rehabilitation programme initiated at start or after tumour directed treatment. Resistance training with conventional exercises is feasible during treatment, and supervision of sessions and utilisation of training-facilities within the hospital area may help to facilitate exercise-adherence. The use of ONS to increase calorie and protein intake needs close monitoring and individual adjustments for optimal adherence, especially in the second half of the radiotherapy period. The combination of resistance training and ONS may mitigate loss of muscle mass compared to standard care during treatment; however, a full-scale RCT is needed to confirm intervention effects.

- Physical rehabilitation programmes with resistance training and nutritional support may have a positive impact on relevant HRQoL domains such as global health status/QoL and physical functioning during tumour directed treatment and enhance recovery after treatment in patients with HNC. A residential post-treatment rehabilitation programme seems appropriate for patients undergoing concurrent chemoradiotherapy.

- The comprehensive and increasing nutritional problems that patients with HNC experience from diagnosis to the acute recovery phase after treatment highlight the need for specialised and individually tailored nutritional support within this patient-group. This implies early nutritional assessments conducted by nutrition-experts immediately following diagnosis, with continuous re-assessments of the changing needs beyond treatment completion.

8. Future research

The research field of physical exercise and nutritional support in patients with HNC is still in its early stages, and several areas need to be further investigated. The present pilot study was conducted in preparation for a full-scale RCT, and thus primarily contributes with increased knowledge about patient-recruitment and timing and content of interventions with physical exercise and nutritional support. In addition, the study provides insight into the patients' own experiences related to the nutritional situation and perceptions of nutritional support from diagnosis to the acute post-treatment phase.

The findings in paper II of this thesis demonstrated that the post-treatment intervention was almost entirely utilised by patients with pharyngeal cancer who had received concurrent chemoradiotherapy. This may indicate an increased need for supportive measures and a positive attitude towards physical exercise within this HNC population, and it may be appropriate to specifically focus on these patients in future intervention-studies. Multisite trials are required due to the low prevalence of patients with HNC, and international studies with collaboration between researchers from different countries are warranted.

Clinical experiences from the present study and from another exploratory trial suggest that patients with HNC are motivated to engage in lifestyle interventions already before treatment start [208]. Capitalising on the "teachable moment" by implementing interventions shortly after diagnosis may enhance adoption and adherence [346]. Thus, there is a need to test physical exercise and nutrition interventions initiated shortly after diagnosis. Considering the verified feasibility from the present and other similar pilot studies of conducting physical exercise interventions during radiotherapy, early imitated interventions should extend into the treatment phase [207, 210, 246, 347]. The interventions should also include the post-treatment phase but allowing for adequate treatment-recovery. In short, future research should investigate the feasibility and effects of physical exercise and nutrition interventions extending throughout the HNC pathway compared to standard care. Settings and timing of interventions in the post-treatment phase should be based on the patients' recovery-time, preferences and geographical residence.

Since the physical exercise programme during treatment was conservatively designed and well-tolerated in the present study, future research needs to examine the effects of resistance training with increased intensity and complexity. When planning the content of nutritional support in future trials, relevant interventions should be based on the patients' individual and changing needs throughout the treatment trajectory and involve healthcare professionals with nutritional expertise to ensure adequate nutritional intake.

Full-scale RCTs are needed to determine the effects of physical exercise and nutrition interventions in patients with HNC. Although muscle mass is an important endpoint considering its potential positive impact on weight loss and functional performance, HRQoL, morbidity and mortality, the use of only this endpoint cannot be considered clinically relevant. Therefore, endpoints in future large-scale RCTs should include a combination of objectively measured outcomes (e.g. muscle mass and/or physical performance) and self-reported HRQoL (e.g. global health status and/or physical functioning).

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Paper I-III

Original Article

Feasibility and Preliminary Effects of Resistance Training and Nutritional Supplements During Versus After Radiotherapy in Patients With Head and Neck Cancer: A Pilot Randomized Trial

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BACKGROUND: Patients with head and neck cancer (HNC) experience involuntary weight loss that has a negative impact on physical function, morbidity, and survival. The objective of the current study was to evaluate the feasibility of an exercise and nutrition intervention during radiotherapy (RT) compared with after RT, and to examine preliminary effects on skeletal muscle mass. **METHODS:** Patients with HNC were randomized to an exercise and nutrition intervention during RT (EN-DUR) or after RT (EN-AF). The EN-DUR intervention was conducted at a hospital and the EN-AF intervention took place at a rehabilitation center. The interventions consisted of progressive resistance training (PRT) and oral nutritional supplements (ONS). Feasibility outcomes were tracked weekly and muscle mass was measured by computed tomography scans before and after RT and at 2 months follow-up. **RESULTS:** Of the 50 eligible patients, 41 (82%) agreed to participate. 90% of patients completed the EN-DUR intervention and the adherence to PRT and ONS was 81% and 57%, respectively. 52% of patients attended the EN-AF intervention and adherence to PRT and ONS was 94% and 76%, respectively. The EN-DUR demonstrated a trend toward mitigating loss of muscle mass during RT and the EN-AF demonstrated a similar trend after RT. No difference in muscle mass was detected between the groups from baseline to week 14. **CONCLUSIONS:** An exercise and nutrition intervention is feasible for patients with HNC during RT, and the intervention is potentially effective in mitigating loss of muscle mass both during and after RT. Future trials should assess the feasibility and effects of extended interventions during and after treatment. ***Cancer* 2017;000:000-000.** © *2017 American Cancer Society.*

KEYWORDS: body weight changes, dietary supplements, head and neck cancer, muscular atrophy, radiotherapy, resistance training.

INTRODUCTION

Radiotherapy (RT) is a mainstay of treatment for patients with head and neck cancer (HNC) and is offered to nearly 75% of all patients.[1] Although modern RT regimens have improved survival markedly, a large percentage of patients with HNC are severely troubled by side effects such as mucositis, dry mouth, loss of taste, locoregional pain, and skin damage both during and after treatment.[2] Mucositis and mouth dryness especially impair swallowing function, leading to decreased food intake, malnutrition, and ultimately weight loss.[3]

Malnutrition accompanied by a critical weight loss of >5% has a negative impact on physical function, morbidity, and overall and disease-specific survival in patients with HNC.[4-6] A weight loss of 8% to 10% is common after RT, and it has been reported that >70% of the weight loss is attributed to muscle wasting associated with decreased muscle strength and reduced physical function.[7,8] Interventions that can limit declines in body weight and muscle mass are important not only for the preservation of physical function but also to enhance the patient's ability to tolerate and complete the treatment as planned.[1]

Resistance training and nutritional supplements may counteract weight loss and muscle wasting as well as improve quality of life in patients with HNC.[9,10] Current exercise and nutrition interventions are offered primarily after the completion of treatment, based on a clinical notion that active interventions during treatment are too strenuous and not appropriate for patients with HNC. However, nearly two-thirds of patients report decreased energy intake already at the time of

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diagnosis, and therefore it is reasonable to assume that interventions initiated before or during treatment could be preferable to posttreatment interventions for the preservation of body weight.[11,12]

Physical exercise interventions have been shown to mitigate functional declines and improve recovery in patients with breast, colorectal, and prostate cancer.[13,14] However, patients with HNC are faced with unique and different side effects from treatment compared with patients with other tumors, which reduces the generalizability of exercise intervention results to patients with HNC. To our knowledge to date, the majority of HNC trials have examined the impact of single interventions consisting of either physical exercise or nutritional supplements with or without nutritional counseling.

In a recent systematic review that summarized the literature on HNC and physical exercise, only 4 of the 16 included studies were randomized controlled trials (RCT), with only 1 of these 4 studies found to be a full-scale RCT primarily assessing the effects of resistance training on lean body mass.[15] The latter study demonstrated a significant increase in lean body mass and muscle strength after RT compared with controls.[16] Nutritional interventions with supplements and dietary counseling have shown beneficial short-term effects on energy intake during RT in patients with HNC; however, these data were based on only 1 study of a recent date.[17,18] To our knowledge, the only randomized intervention study that has addressed the potential benefits of combining resistance training and nutritional supplements in patients with HNC reported no differences in lean body mass or muscle strength between exercise and nutritional supplements versus exercise and placebo supplements.[19] However, the effects of interventions should be interpreted cautiously due to the feasibility nature of the study, and it is worth noting that the interventions were performed after treatment.

Before the performance of full-scale trials to determine the effects of exercise and nutrition interventions during RT in patients with HNC, issues of recruitment and retention need to be properly addressed due to the increase in morbidity burden in the second half of the treatment period. Therefore, the primary objective of the current study was to evaluate the feasibility of an exercise and nutrition intervention during compared with after RT by tracking recruitment, attendance, adherence, and attrition rates. The secondary aim was to compare the preliminary effects of the intervention during versus after RT on skeletal muscle mass and body weight.

MATERIALS AND METHODS

The study was designed as a single-center, 2-arm, randomized controlled pilot trial. Patients were recruited from the Ear-Nose-Throat, Eye and Maxillofacial Surgery clinic at Trondheim University Hospital in Norway. The eligibility criteria were: 1) a diagnosis of squamous cell carcinoma originating in the head and neck (nasopharynx, oropharynx, or hypo pharynx; larynx; and oral cavity, except T1N0M0 laryngeal cancer); 2) referral for curative RT with or without chemotherapy; 3) potential to complete baseline assessments before the initiation of treatment; 4) aged 18 to 85 years; and 5) willingness to comply with study procedures. All patients with HNC who were referred to the Ear-Nose-Throat, Eye and Maxillofacial Surgery clinic were screened for eligibility. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 2013/2098), and registered with the National Clinical Trials Registry as NCT02439892 before the start of the study. Written informed consent was obtained from each study participant.

Included patients were randomized to an exercise and nutrition intervention during RT (EN-DUR) or an exercise and nutrition intervention after RT (EN-AF). Randomization was performed using a Web-based system developed and administered by the Unit of Applied Clinical Research in the Department of Cancer Research and Molecular Medicine at the Norwegian University of Science and Technology in Trondheim. The system provided an identification number for each patient and any reasons for not proceeding to randomization were documented by the study coordinator.

Interventions

EN-DUR Intervention

EN-DUR was initiated during the first week of RT and conducted during the 6-week treatment period. The intervention was performed at an outpatient training facility located within the hospital area (Pusterommet, St. Olavs Hospital, Trondheim, Norway), and consisted of progressive resistance training (PRT) and oral nutritional supplements (ONS). All patients were scheduled for an initial consultation to receive treatment-specific nutritional advice, including a booklet specifically designed for patients with HNC, and to taste various flavors of the nutritional drink.

Physical exercise was conducted with 2 PRT sessions per week of 30 minutes each (total of 12 sessions), including a 5-minute warmup of low-intensity aerobic exercises (treadmill walking or stationary cycling). The PRT

sessions involved 2 lower body exercises (leg extension and seated hamstring curl) and 2 upper body exercises (chest press and standing row). The number of sets and repetitions varied according to a planned program and ranged from 3 to 4 sets at 6 to 12 repetitions maximum. All sessions were supervised by an experienced physiotherapist to ensure individual adjustments and progression. The patients were asked to ingest a minimum of 1 nutritional drink (E+; Tine SA, Oslo, Norway) each weekday (Monday-Friday), containing 2 deciliters and 350 kilocalories. The patients were recommended to continue physical activity in accordance with the physical activity guidelines for patients with cancer (150 minutes of moderate-intensity exercise per week) after completing the intervention.[14]

EN-AF Intervention

Patients randomized to EN-AF were scheduled for a 3-week intervention 2 to 4 weeks after the end of RT. Before the initiation of RT, the patients were recommended to follow the physical activity guidelines for patients with cancer during the treatment period. EN-AF was conducted at a rehabilitation center (LHL Clinics, Roros, Norway) located 150 kilometers from the hospital, and the patients took part in an established rehabilitation program for patients with various cancer diagnoses. All patients attending the program stayed overnight during the week with the weekends off. The intervention consisted of PRT, ONS, and nutritional counseling.

PRT was conducted with 3 sessions per week for 45 minutes each session (a total of 9 sessions) and involved 3 lower body exercises (seated leg press, leg extension, and seated hamstring curl) and 3 upper body exercises (chest press, pulldown, and seated row). The number of sets and repetitions varied according to a planned program and ranged from 3 to 4 sets at 6 to 12 repetitions maximum. All sessions were supervised by experienced physiotherapists and an exercise therapist to ensure individual adjustments and progression. In addition to PRT, the patients could participate in 2 voluntary sessions each week involving a combination of strength, aerobic, and balance exercises performed at a low intensity of 11 on the Borg Rating of Perceived Exertion Scale.[20]

The patients were asked to ingest a minimum of 1 nutritional drink (E+; Tine SA) each weekday (Monday-Friday), containing 2 deciliters and 350 kilocalories. In addition, nutritional counseling was conducted individually or in small groups by a dietitian once a week, including practical exercises in a kitchen facility. The patients also had the opportunity to participate in lectures and group discussions led by various health professionals addressing various cancer-related topics such as cancer treatment and side effects, physical activity, and mental health.

Assessments

Demographic variables were collected by a self-report questionnaire. Medical data regarding diagnosis and time of diagnosis, specific tumor treatment, previous cancer treatment, comorbidities, height, body weight, and Karnofsky performance status were drawn from medical records by the attending physician.[21] Physical activity was assessed by the Nord-Trondelag Health Study Physical Activity Questionnaire (HUNT PA-Q) that comprises 1 item each regarding the frequency, duration, and intensity of physical activity.[22,23] An index score was calculated based on the product of the items ranging from 0 (no physical activity) to 15 (high-intensity activity for >1 hour nearly every day), with a score of 7.5 regarded as meeting the recommended physical activity guidelines for patients with cancer.[14]

Feasibility Outcomes

The following feasibility outcomes were tracked weekly: 1) eligibility and recruitment rates (the number of patients ineligible and declining participation); 2) attendance, completion, and attrition (the number of patients attending and completing the intervention and dropouts); and 3) adherence to the interventions (the number of completed exercise sessions [exercise log sheets] and the number of ingested nutritional drinks [weekly recall questionnaire]). For the EN-DUR group, exercise adherence was calculated for the first and the last 3 weeks separately in addition to the total adherence, given the expected increase in side effects during the second half of RT.

Efficacy Outcomes

Preliminary efficacy outcomes were measured before start of RT (week -4 to 0), at the end of RT (week 6), and at 2 months of follow-up (week 14). All assessments were completed at the RT area or at the hospital ward for optimal patient convenience and to ensure optimal data collection. Skeletal muscle mass was measured by cross-sectional computed tomography images at the third lumbar vertebra (CT Big Bore; Royal Philips Electronics, Eindhoven, the Netherlands). Cross-sectional images at the third lumbar region provide precise estimates of body composition, including regional abdominal adipose tissue, skeletal muscle mass, and waist circumference.[24] The SliceOmatic (v 4.3; TomoVision, Magog, Quebec,

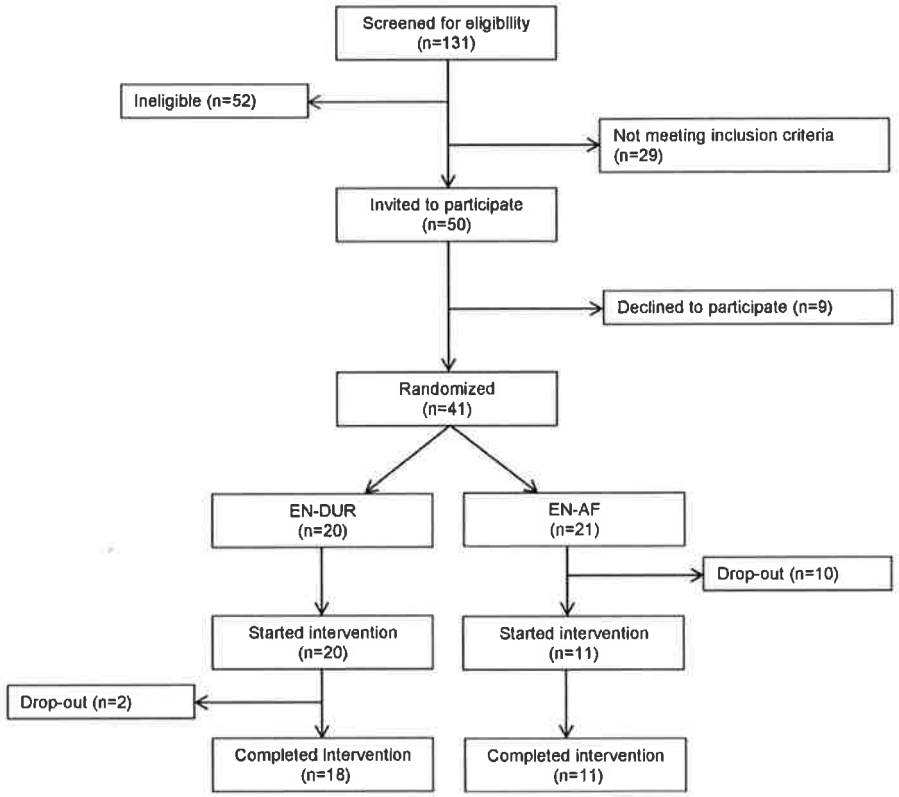

Figure 1. Patient recruitment, allocation, and dropouts by study group. EN-AF indicates exercise and nutrition intervention after radiotherapy; EN-DUR, exercise and nutrition intervention during radiotherapy.

Canada) was used for image analyses. One image (maximum slice thickness of 5 mm) at the third lumbar region with both vertebral transverse processes clearly visible was selected for each measurement. Radiodensity of the skeletal muscle was calculated by use of Hounsfield units, with thresholds from -29 to +150.[25] The results were expressed as cm^2/m^2. Body weight was measured to the nearest 0.1 kg with the patient wearing light clothes and no shoes and using the same scale at each visit (Seca 876 scale; Seca Corporation, Hanover, Maryland).

Statistical Analysis

Due to the feasibility nature of the study and the need to determine effect sizes for a larger trial, 40 patients were considered sufficient for the current pilot study. All relevant variables were tested for normal distribution by histograms, Q-Q plots, and tests of normality. Descriptive statistics were reported by distribution in percentages for categorical variables and by average and standard deviations (SDs) for normally distributed continuous variables. Student *t* tests for paired data and Student independent-sample *t* tests were used to assess within-group changes and between-group differences on muscle mass and body weight from baseline to week 6, from week 6 to week 14, and from baseline to week 14. Intervention effect sizes (d) were calculated by using the mean and SD of the between-group differences, and defined as small ($d = 0.2$), moderate ($d = 0.5$), and large ($d = 0.8$) according to Cohen criteria.[26] Only data from patients who completed the intervention and with valid measurements were analyzed (as per protocol analyses). All statistical analyses were performed using the IBM SPSS Statistics 22.0 software (IBM Corporation, Armonk, New York). A P value $<.05$ was used to define statistically significant effects and P values ≤ 0.10 were examined for trends.

RESULTS

Figure 1 presents the patient flow from March 2015 to March 2016. A total of 131 patients were screened at tumor board sessions and 52 patients were ineligible due to receiving treatment other than RT (38 patients), a non-cancer diagnosis (10 patients), and unclear medical status

TABLE 1. Baseline Demographic and Medical Characteristics for the 2 Intervention Groups

	EN-DUR N = 20	EN-AF N = 21	*P*
Mean age (SD), y	62.1 (2.2)	64.3 (2.0)	.451
Sex			.072
Men	15 (75%)	10 (48%)	
Women	5 (25%)	11 (52%)	
Mean weight (SD), kg	84.5 (3.9)	78.2 (4.5)	.325
Mean BMI (SD)	26.9 (1.1)	26.8 (1.6)	.933
KPS			.687
100	1 (5%)	1 (5%)	
90	14 (70%)	17 (81%)	
80	3 (15%)	3 (14%)	
70	1 (5%)	0	
60	1 (5%)	0	
PA level, mean (SD)	2.0 (2.7)	2.3 (2.3)	.656
Marital status			.294
Married/cohabitant	17 (85%)	15 (71%)	
Single/widow(er)	3 (15%)	6 (29%)	
Education			.240
Primary/secondary school	18 (90%)	16 (76%)	
College/university	2 (10%)	5 (24%)	
Employment			.502
Employed	11 (55%)	9 (43%)	
Retired	6 (30%)	10 (47%)	
Disability benefits	3 (15%)	2 (10%)	
Smoking status			.114
Current smoker	5 (25%)	1 (5%)	
Past smoker	11 (55%)	13 (62%)	
Never smoked	3 (15%)	7 (33%)	
Missing data	1 (5%)	0	
Tumor site			.448
Oral cavity	1 (5%)	4 (19%)	
Pharynx	10 (50%)	10 (47%)	
Larynx	2 (10%)	2 (10%)	
Pharynx and larynx	1 (5%)	0	
Salivary glands	4 (20%)	4 (19%)	
Nasal cavity	0	1 (5%)	
Unknown origin	2 (10%)	0 (0%)	
Planned treatment			.412
RT only	13 (65%)	11 (52%)	
CRT	7 (35%)	10 (48%)	

Abbreviations: BMI, body mass index; CRT, chemoradiotherapy; EN-AF, exercise and nutrition intervention after radiotherapy; EN-DUR, exercise and nutrition intervention during radiotherapy; KPS, Karnofsky performance status; PA, physical activity; RT, radiotherapy; SD, standard deviation.

(4 patients). Of the 79 eligible patients, 29 did not meet the inclusion criteria due to being aged >85 years (15 patients), having received previous RT within the current localization (12 patients), and the use of walking aids (2 patients). A total of 50 patients met the inclusion criteria and were invited to participate. Five patients declined participation with no specific reason ("did not want to"), 2 patients declined due to travel distance, and 2 patients declined due to additional medical problems, leaving 41 patients randomized to either EN-DUR or EN-AF.

The study sample of 41 patients consisted of 25 men and 16 women, with an average age of 63.2 years (SD, 9.3 years). The median time from diagnosis to baseline assessments was 14 days (interquartile range, 11 days), 33 patients (80%) had a Karnofsky performance status score of ≥90 at baseline, and all patients completed the planned RT. Ten patients reported no physical activity at baseline and 3 patients reported meeting the physical activity recommendations. Table 1 presents the detailed baseline demographic and medical characteristics separately for the EN-DUR and EN-AF groups, with no statistically significant differences noted between the groups.

EN-DUR Intervention

All 20 patients met for the start of EN-DUR, but 2 patients discontinued during week 2 due to nausea and lack of energy, leaving 18 patients (90%) who completed the intervention (Fig. 1). Overall adherence to the supervised exercise sessions was 81% (174 of 216 sessions) for the patients completing the intervention. The exercise adherence dropped from 88% in the first 3 weeks to 73% in the last 3 weeks. Sixteen patients (89%) completed >50% of the exercise sessions (7 of 12 sessions) and were able to follow the planned upper and lower body exercises with progression in load from week to week. Two patients (11%) completed 6 of 12 sessions, but were unable to follow all the planned exercises and progression. The main reasons for missed exercise sessions were lack of energy, medical illness with hospitalization, and patient refusal. The overall exercise adherence for all patients randomized to EN-DUR was 74% (177 of 240 sessions).

Adherence to ONS was 57% (309 of 540 nutritional drinks) for the patients completing EN-DUR. Seven patients (39%) ingested ONS every weekday and 10 patients (56%) discontinued the use of ONS between week 3 and week 4 due to swallowing difficulties and/or because the texture of the drink was too thick. A total of 9 patients (45%) initiated nasogastric tube feeding (NGT) during the intervention, compared with 10 patients (48%) in the EN-AF group ($P = .867$). One patient used a NGT before the start of the program and never started ONS. The overall adherence to ONS for all patients randomized to EN-DUR was 52% (309 of 600 nutritional drinks).

EN-AF Intervention

Eleven patients (52%) met and completed the EN-AF intervention (Fig. 1), including 2 patients who had to delay the start by 8 weeks and 12 weeks, respectively, due to severe side effects from treatment (mucositis and difficulties in swallowing). Ten patients (48%) did not meet for the intervention due to the following reasons: did not want to/felt no need (6 patients), additional medical

TABLE 2. Preliminary Intervention Effects on Skeletal Muscle Mass and Body Weight

				Week 0 to 6			Week 6 to 14		
	Week 0 Mean (SD)	Week 6 Mean (SD)	Week 14 Mean (SD)	Mean change (SD)	Group difference (SD)	*d*	Mean change[a] (SD)	Group difference[a] (SD)	*d*
Muscle mass, cm^2/m^2									
EN-DUR	53.9 (9.6)	52.2 (9.6)	51.4 (9.9)	−1.7[b] (2.6)			−0.8 (2.2)		
EN-AF	50.7 (7.9)	46.7 (7.0)	48.5 (8.7)	−4.0[b] (3.0)	2.3[c] (1.1)	0.79	0.9 (2.4)	−1.7[c] (1.0)	−0.75
Body weight, kg									
EN-DUR	86.0 (17.5)	82.6 (16.7)	80.1 (16.1)	−3.4[b] (2.8)			−2.5[b] (2.6)		
EN-AF	78.3 (20.1)	73.9 (19.6)	72.1 (16.0)	−4.3[b] (2.8)	0.9 (1.1)	0.33	−2.6 (5.9)	0.1 (2.1)	0.03

Abbreviations: *d*, effect size; EN-AF, exercise and nutrition intervention after radiotherapy; EN-DUR, exercise and nutrition intervention during radiotherapy; SD, standard deviation.
[a] Change scores may vary from the presented group means due to missing values.
[b] $P \leq .05$.
[c] $P \leq .10$ (trend only).

problems (1 patient), travel distance (1 patient), family reasons (1 patient), and withdrawal from the study (1 patient). Adherence to the supervised exercise sessions was 94% (93 of 99 sessions) for the patients who met for the intervention. Ten patients (91%) completed at least 8 of 9 exercise sessions, with 1 patient completing 7 of 9 sessions. All 11 patients were able to perform the planned lower and upper body exercises with progression in load from week to week. The reasons for missed exercise sessions were illness and conflicting consultations. The overall exercise adherence rate for all patients randomized to EN-AF was 49% (93 of 189 sessions).

Adherence to ONS was 76% (126 of 165 nutritional drinks) for the patients who met for EN-AF. Eight patients (73%) ingested ONS every weekday during the 3-week intervention, and 3 patients (27%) never started ONS due to NGT feeding (1 patient), having been assessed as having no need for supplements by the dietitian (1 patient), and inability to swallow because of the texture (1 patient). The overall adherence to ingestion of ONS for all patients randomized to EN-AF was 40% (126 of 315 nutritional drinks).

Efficacy Outcomes

Skeletal muscle mass

From baseline to week 6, the difference in changes in muscle mass was 2.3 cm^2/m^2 ($P = .063$) between the groups, with a medium effect size ($d = 0.79$) in favor of EN-DUR (Table 2). The within-group difference in muscle mass was -1.7 cm^2/m^2 (SD, 2.59; $P = .032$) for the EN-DUR group and -4.0 cm^2/m^2 (SD, 3.03; $P = .001$) for the EN-AF group (Table 2). From week 6 to week 14, the difference in the change in muscle mass was -1.7 cm^2/m^2 ($P = .095$) between the groups, with a medium effect size ($d = 0.75$) in favor of EN-AF. The within-group difference in muscle mass was -0.8 cm^2/m^2 (SD, 2.20; $P = .208$) for the EN-DUR group and 0.9 cm^2/m^2 (SD, 2.45; $P = .284$) for the EN-AF group. No difference in change in muscle mass was noted between the groups from baseline to week 14 (-0.3 cm^2/m^2; $P = .821$), with a total muscle mass reduction of -2.6 cm^2/m^2 (SD, 2.26; $P = .002$) for the EN-DUR group and -2.3 cm^2/m^2 (SD, 3.16; $P = .062$) for the EN-AF group.

Body weight

From baseline to week 6, no difference in change in body weight was noted between the groups (0.9 kg; $P = .403$) (Table 2). The within-group difference in body weight was -3.4 kg (SD, 2.78; $P<.001$) for the EN-DUR group and -4.3 kg (SD, 2.81; $P<.001$) for the EN-AF group (Table 2). From week 6 to week 14, no difference in change in body weight was noted between the groups (0.1 kg; $P = .955$). The within-group difference in body weight was -2.5 kg (SD, 2.63; $P = .002$) for the EN-DUR group and -2.6 kg (SD, 5.89; $P = .224$) for the EN-AF group. No difference in change in body weight was noted between the groups from baseline to week 14 (0.7 kg; $P = .818$), with a total weight loss of -5.9 kg (SD, 4.38; $P<.001$) for the EN-DUR group and -6.6 kg (SD, 8.03; $P = .040$) for the EN-AF group. The change in body weight during RT represented a weight loss of 3.9% ($P<.001$) for the EN-DUR group and a weight loss of 5.5% ($P<.001$) for the EN-AF group, whereas the change in body weight from week 6 to week 14 represented a weight loss of 2.7% ($P = .002$) for the EN-DUR group and 2.1% ($P = .449$) for the EN-AF group.

DISCUSSION

A high percentage of patients with HNC who were scheduled for RT were willing to participate in a structured exercise and nutrition intervention when asked before the initiation of treatment. The majority of the patients randomized to the intervention during RT (EN-DUR) were able to perform at least 50% of the scheduled exercise sessions, but less than one-half of the patients ingested ONS daily. Only one-half of the patients met for the intervention after RT (EN-AF); however, the vast majority of the attending patients were able to perform resistance training 3 times a week and nearly 75% of patients ingested ONS daily. Both the EN-DUR and EN-AF interventions demonstrated a trend toward reducing loss of muscle mass compared with controls during and after RT, although no difference was noted between the interventions from baseline to the final assessment.

The recruitment rate of 82% in the current study is high compared with what to our knowledge are the few exercise trials among patients with HNC conducted during treatment. Two previous randomized trials that evaluated the feasibility and efficacy of resistance training during RT both reported a recruitment rate of 55%.[27,28] The main reasons for declining participation in these 2 studies were "too time-consuming" and "feeling overwhelmed or emotional distress." Also in the current study, we noted that although many patients appeared to be overwhelmed by the medical situation at the point of study request, few declined to participate in the study. All eligible patients received oral and written study information a few days before the study request, and the patients expressed that they perceived the study as part of the standard medical assessment and treatment procedures. The request was conducted in quiet surroundings with enough time for study-specific questions but also for questions regarding their medical situation and upcoming treatment if needed. It is reasonable to assume that more patients would decline participation if the study information was given "on the run," with minimal time for questions and discussion. Considerations regarding the most appropriate ways to provide study information and the use of time are of particular importance when recruiting vulnerable patients, such as individuals with HNC, into clinical trials.

Because the majority of the patients in the current study were able to complete the EN-DUR, an exercise and nutrition intervention appears feasible for patients with HNC who are undergoing RT. As many as 90% of the patients were able to attend at least one-half of the prescribed exercise sessions during the 6-week treatment period; however, only a little more than one-third of the patients were able to adhere to the daily prescription of ONS as expected due to side effects from RT. The majority of the patients not adhering to ONS reported swallowing difficulties to such an extent that they were scheduled for NGT halfway through the treatment period in accordance with the clinical practice at the hospital. The percentage of patients receiving NGT during RT in the current study (nearly 50% in both groups) was in keeping with that reported in a prospective randomized trial regarding nutritional support in patients with HNC.[29] In a future RCT, the sources of energy intake (oral, enteral, and parenteral) and the specific amount of daily energy intake in kilocalories need to be closely monitored to increase knowledge regarding optimal nutrition interventions for patients with HNC who are undergoing RT. Unfortunately, we were not able to obtain such data in the current pilot study.

The attendance rate for the EN-AF intervention was low (52%) compared with other posttreatment HNC exercise trials that have reported attendance rates of 80%.[16,19] However, the interventions in the 2 latter studies were initiated at a later stage after RT (8 weeks) compared with the current study (2-4 weeks), and the patients were not recruited before the 2-month follow-up. Thus, it appears easier and more appropriate for patients with HNC to attend a posttreatment intervention when allowed to have enough recovery time after RT. Another explanation for the low attendance rate after RT in the current study could be that the patients had to travel for at least 2 hours to the rehabilitation center and stay overnight during the weekdays. "Inpatient" rehabilitation programs are part of the standardized rehabilitation services that are offered to patients with cancer and other patient groups in Norway. Even though only 1 patient specifically reported travel distance as the main reason for not attending, it could be reasonable to assume that some patients find it difficult to be away from home for 3 weeks with regard to their family and work situation. Future studies should include community-based interventions that allow the patients to stay at home during the intervention period.

Only a small reduction in muscle mass was noted for patients on the EN-DUR intervention from baseline to week 6 compared with those on the EN-AF intervention (-1.7 cm^2/m^2 vs -4.0 cm^2/m^2), with a medium effect size in favor of EN-DUR. The results indicate that an exercise and nutrition intervention initiated at the start of treatment is potentially efficacious for minimizing muscle wasting in patients with HNC who are undergoing RT,

and is worthy of further investigation. It is interesting to note that the patients in the EN-DUR group managed to limit muscle wasting despite a significant loss of body weight from baseline to week 6, and similar results have been reported in another HNC exercise trial during RT.[27] However, from week 6 to week 14, a nonsignificant reduction in muscle mass was noted for the EN-DUR intervention, whereas a nonsignificant increase in muscle mass was noted for the EN-AF intervention (-0.8 cm^2/m^2 vs 0.9 cm^2/m^2). In other words, the muscle wasting appeared to continue for the EN-DUR group after RT, whereas a process of rebuilding muscle mass appeared to start for the EN-AF group. Unfortunately, we did not obtain information regarding to what extent the patients in the EN-DUR group continued to exercise after the RT period. The preliminary effects on muscle mass observed in the current study suggest that in the planning of future exercise and nutrition interventions, both the 6-week RT period and the posttreatment period should be used for the optimal preservation of muscle mass in patients with HNC. Although no difference in weight loss was detected between the groups during RT, the mean weight loss in the EN-DUR group represented less (-3.9%) than the 5% cutoff used for screening potentially underweight patients with HNC.[30] The weight loss for the EN-AF group during RT represented a percentage (-5.5%) similar to that reported in a retrospective cohort study tracking weight change in 476 patients with HNC during RT.[31]

Strengths and Limitations

The current study was performed in a public hospital (St. Olavs Hospital, Trondheim, Norway) to which all residents residing in the mid-region of Norway are referred to for medical assessment, diagnostics, and the treatment of HNC. The patients participating in the current study were treated according to national and international guidelines and could be considered as a representative cohort.

Because the current study was performed as a pilot trial in preparation for a larger multicenter trial, there are several limitations that should be considered. The study design was based primarily on the current standards of posttreatment cancer rehabilitation services in Norway and the need for evaluating a new exercise and nutrition intervention during treatment for patients with HNC. Consequently, the differences in the content, duration, and localization of the 2 interventions did not allow for direct comparisons. Furthermore, the study did not include a control arm throughout the study period, which was a pragmatic choice based on the small population and the feasibility nature of the study. Stratification according to human papillomavirus status was deemed unnecessary in a first-step feasibility trial, but should be considered in a larger trial because it represents 2 different patient populations, especially with regard to age and physical function. Although the recruitment rate was higher than expected in this vulnerable patient population, 1 in 5 patients nevertheless declined participation and unfortunately no demographic or medical information was obtained from these patients.

Conclusions

Resistance training appears to be a feasible and acceptable intervention for patients with HNC during RT. The timing and setting of posttreatment exercise and nutrition interventions need to be individually tailored for optimal attendance. Interventions both during and after RT appear to mitigate muscle wasting compared with standard care, calling for future trials to assess the feasibility and effects of extended interventions conducted throughout the treatment trajectory.

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CONFLICT OF INTEREST DISCLOSURES

Stein Kaasa is a stakeholder in Eir Solutions.

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Physical rehabilitation in patients with head and neck cancer: Impact on health-related quality of life and suitability of a post-treatment program

Running title: Quality of life in head and neck cancer

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ABSTRACT

Objective:

Physical rehabilitation programs hold the potential to mitigate deterioration in health-related quality of life (HRQoL) in patients with head and neck cancer (HNC). The objective was to assess development in relevant domains of HRQoL following a physical exercise and nutrition intervention administrated during or after treatment.

Methods:

In a pilot study, 41 patients were randomized to resistance training and oral nutritional supplements during (EN-DUR, n=20) or after (EN-AF, n=21) radiotherapy. Global health status/QoL (GHS) and physical functioning (PF) was measured by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire at baseline, week 6 and week 14. Differences between the groups were assessed by analysis of covariance. A difference of ≥10 points in GHS and PF was interpreted as clinically relevant.

Results:

No statistically significant differences were detected between the groups; however, clinically relevant changes and differences in GHS and PF were observed. From baseline to week 6, GHS decreased 9 points in the EN-DUR group and 23 points in the EN-AF group and PF decreased 13 points and 21 points respectively. From week 6 to week 14, GHS increased 14 points in the EN-DUR group and 26 points EN-AF group and PF did not change (0 points) in the EN-DUR group and increased 16 points in the EN-AF group.

Conclusion:

The findings from the present pilot study are promising and indicate that a physical rehabilitation program may have a positive impact on HRQoL during treatment and enhance recovery after treatment. A definitive randomized trial is warranted.

Key words:

Head and neck cancer; physical rehabilitation; resistance training; nutritional support; health-related quality of life.

Level of evidence:

1b – Individual randomized controlled trial

INTRODUCTION

Patients with head and neck cancer (HNC) are faced with specific challenges and needs due to the complex treatment involving changes to critical structures for speaking, eating and breathing in addition to facial and neck disfigurement.[1,2] This may have a significant impact on function and body image that negatively affects health-related quality of life (HRQoL) and survivorship.[3,4]

Numerous observational studies have reported HRQoL throughout treatment and recovery in patients with HNC, demonstrating that symptoms such as pain, dry mouth and sticky saliva increase steadily during the course of radiotherapy (+/- chemotherapy) while physical functioning and global health status/QoL decrease.[5-13] The patients report maximum symptom burden and minimum functioning at the end of and immediately after radiotherapy.[4,7,11] The post-treatment period is normally characterized by gradual recovery and improvement; however, only global health status/QoL seems to reach pre-treatment levels within one year after treatment completion.[11,13,14] Thus, the following year(s) of HNC survivorship is characterized by persistent treatment-related side-effects accompanied by deteriorated functional status.[15]

Rehabilitation programs that include physical exercise and/or nutrition interventions hold the potential to mitigate some of the side-effects and counteract the reduced functioning experienced by patients with HNC.[16,17] Although generally small in sample sizes and hampered by study design not tailored to study, several physical exercise intervention studies have indicated a beneficial impact of resistance training on physical functioning, fatigue and global health status/QoL during and immediately after tumor directed treatment.[18-21] The results from nutrition intervention studies are somewhat mixed, but two randomized controlled trials (RCT) have demonstrated less deterioration in physical functioning and global health status/QoL in patients receiving dietary counseling and/or oral nutritional supplements (ONS) during and after treatment.[22,23] However, to the best of our knowledge no study has reported short and long-term HRQoL following an intervention combining physical exercise and nutritional support in patients with HNC.[24]

On this background, we conducted a randomized pilot study in 2015-2016 to examine the feasibility and impact of a rehabilitation program consisting of resistance training and ONS during (EN-DUR) versus after (EN-AF) radiotherapy in patients with HNC. Previously we have reported data on feasibility and short-term effects on lean–body mass and body weight.[25] The EN-DUR intervention demonstrated high exercise-adherence (81 %)

and moderate ONS-adherence (57 %), and a beneficial impact on lean body mass was indicated. The adherence-rates for the patients attending the EN-AF intervention was even higher (94 % and 76 %, respectively); however, only half of the randomized patients met for the scheduled post-treatment program. This raises several questions related to patient needs as well as timing and setting of rehabilitation services. Sub-group analyses of attenders and non-attenders may therefore provide valuable information regarding possible factors associated with needs and utilization of rehabilitation services in patients with HNC.

The objective of the present study was to assess short and long-term differences in HRQoL between the physical rehabilitation program administrated during versus after tumor directed treatment and describe within-group changes in HRQoL during the first year after diagnosis of HNC. Due to the low attendance-rate to the program after treatment, differences in HRQoL and sociodemographic and clinical characteristics between the attenders and non-attenders were explored.

MATERIALS AND METHODS

Patients and study design

Patients were recruited in the period between March 2015 and March 2016 from the Clinic of Ear-Nose-Throat, Eye and Maxillofacial Surgery (ENT-clinic) at St. Olavs hospital, Trondheim University Hospital in Norway. The patients were eligible if the following inclusion criteria were met: 1) a diagnosis of squamous cell carcinoma (SCC) originated in the head and neck (naso, oro, or hypo pharynx, larynx and oral cavity, except from stage T1N0M0 laryngeal cancer), 2) referred for curative radiotherapy with or without chemotherapy, 3) 18 – 85 years of age and 4) able to complete baseline assessments prior to start of radiotherapy.

The study was designed as a randomized pilot study and the patients were allocated to an exercise and nutrition intervention during radiotherapy (EN-DUR) or after radiotherapy (EN-AF). The EN-DUR intervention was conducted from start to end of radiotherapy (6 weeks) at an outpatient training facility within the hospital area and consisted of 12 resistance training sessions (maximum 30 minutes per session). In addition, all patients received a booklet with nutritional advice specifically designed for patients with HNC and were provided with minimum one unit (200 ml) of ONS on weekdays (E+® by Tine SA, Norway, 350 kcal and 15 g protein per unit). On training days, the patients were asked to take one extra unit after the session. The EN-AF intervention started 2-4 weeks after the end of radiotherapy and was conducted at a rehabilitation clinic as part of an

established 3-week cancer program. The program consisted of nine resistance training sessions (maximum 40 minutes per session), daily intake of ONS similar to the EN-DUR intervention and dietary counseling once a week provided by a dietitian. A detailed description of the interventions has been published previously [25].

Background variables

Sociodemographic data (age, sex, marital status, living situation, education, employment and smoking status), nutritional status and self-reported physical activity was obtained by a questionnaire prior to start of radiotherapy (baseline), and clinical data (diagnosis date, type and stage, recurrence, type of treatment and co-morbidities) was obtained from the patients' medical journals. Karnofsky performance status (KPS) was scored by the involved physiotherapist (JAS).[26]

Nutritional status was measured by the short form of the Patient-Generated Subjective Global Assessment (PG-SGA), and a total score was summarized ranging from 0 (no problem) to 36 (severe problems) based on the recommended use of the instrument.[27-31] Self-reported physical activity level was measured by the Nord-Trøndelag Health Study Physical Activity Questionnaire (HUNT PA-Q) with a total score calculated based on the product of frequency, duration and intensity, ranging from 0 (no physical activity) to 15 (vigorous physical activity for more than 1 hour almost every day).[32-34] Functional exercise capacity was measured by the field exercise test Modified Shuttle Walk Test (MSWT), and functional muscle strength was measured by the 30 seconds sit to stand test (30s STS).[35-37]

Outcome variables

The patients completed HRQoL questionnaires at baseline, at the end of radiotherapy (week 6), at two months follow-up (week 14) and one year later (1-year). HRQoL was measured by the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30, version 3.0) and the head and neck cancer module EORTC QLQ-H&N35. [38,39] The EORTC QLQ-C30 consists of five functional scales, three symptom scales, a global health status/QoL scale and six single items. Global health status and physical functioning was considered relevant C30 scales in the present study. The EORTC QLQ-H&N35 consists of seven multi-item symptom scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality and six single-item symptom scales assessing side-effects related to problems with teeth, opening mouth, dry mouth, sticky saliva and coughing and the feeling of being ill. In addition, the

questionnaire consists of five optional single-item scales (i.e. question 31-35) assessing the use of pain killers, nutritional supplements and feeding tube and weight loss and gain. Pain, dry mouth and sticky saliva were considered relevant H&N35 scales. Scoring for the C30 and H&N35 questionnaires was conducted according to the EORTC QLQ-C30 scoring manual recommendations and range from 0 to 100.[40] A high score for global health status/QoL and physical functioning represents high HRQoL/high functioning and a high score for a symptom scale represents a high level of symptoms/problems.

Statistical analyses

Descriptive statistics with confidence intervals (95 % CI) was the focus of the analyses due to the pilot design of the study. Distributions of the included variables were checked for normality by inspection of histograms, Q-Q-plots and tests of normality, and presented as mean with standard deviation (SD) if approximately normally distributed or median with inter quartile range (IQR) if skewed. Differences between the groups were assessed by analysis of covariance (ANCOVA) at week 6, week 14 and 1-year with the respective baseline-scores as covariate. Within-group changes were assessed by paired sample t-tests. A difference in HRQoL scores of 10 points or more was considered clinically relevant.[41] All statistical analyses were performed using the IBM SPSS® Statistics 22.0 software (IBM Corporation, Armonk, NY). P-values < 0.05 were considered statistically significant.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK midt 2013/2098), and the study was registered at ClinicalTrials.gov prior to study start (Identifier: NCT02439892). All patients provided written, informed consent before entering the study.

RESULTS

The study sample consisted of 41 patients (25 male) with an average age of 63.2 years (SD 9.3 years). Median time from diagnosis to baseline assessment was 14 days (IQR 11 days) and 80 % had a KPS score of ≥ 90 at baseline. Twenty patients were randomized to the EN-DUR intervention and 21 patients to the EN-AF intervention. Characteristics of the randomized groups and attendance, attrition and adherence rates have been presented previously.[25] The number of complete EORTC QLQ-C30 and H&N35 forms in the EN-DUR and EN-AF groups is presented in Table 1. From baseline to 1-year follow-up respectively 4 patients died in the EN-DUR group and 2 in the EN-AF-group

Table 1. The number of completed EORTC QLQ-C30 and H&N35 forms at each assessment point.

	Baseline	Week 6	Week 14	1-year
EN-DUR group (n=20)	20	19	18	15
EN-AF group (n=21)	21	19	18	18

Changes in HRQoL

The ANCOVA-analysis did not demonstrate any statistically significant differences between the EN-DUR and EN-AF groups in global health status/QoL, physical functioning or symptoms of pain, dry mouth and sticky saliva. Figure 1 presents the mean scores in global health status/QoL and physical functioning in the two groups at baseline, week 6, week 14 and 1-year, based on the number of complete questionnaires as presented in Table 1.

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However, clinically relevant changes in HRQoL from start to end of the study were observed within the EN-DUR and EN-AF groups as well as clinically relevant differences in change between the groups. From baseline to week 6, global health status/QoL decreased 9 points (95 % CI -20.6, -3.1) in the EN-DUR group compared to 23 points (-34.0, -12.5) in the EN-AF group, and physical functioning decreased 13 points (-22.3, -3.0) compared to 21 points (-33.7, -9.0). From week 6 to week 14, global health status/QoL increased 14 points (0.9, 27.6) in the EN-DUR group compared to 26 points (7.4, 43.6) in the EN-AF group, while physical functioning did not change in the EN-DUR group (0 points, -6.8, 7.4) compared to an increase of 16 points (4.8, 26.6) in the EN-AF group. Symptoms of pain, dry mouth and sticky saliva increased in both groups from baseline to week 6 and decreased in both groups from week 6 to week 14 (see Table 2 for the respective scores).

Table 2. Changes in mean symptom scores from baseline to week 6 and from week 6 to week 14 in the EN-DUR and EN-AF group.

	Baseline – week 6				Week 6 – week 14			
	EN-DUR	Diff. (CI)	**EN-AF**	Diff. (CI)	**EN-DUR**	Diff. (CI)	**EN-AF**	Diff. (CI)
Pain	**30–53**	23 (11.6, 34.9)	**24–52**	28 (17.1, 39.7)	**52–34**	-18 (-27.8, -7.5)	**53–22**	-31 (-40.6, -21.9)
Dry mouth	**24–77**	53 (33.1, 72.2)	**19–77**	58 (42.9, 72.9)	**76–74**	-2 (-13.2, 9.3)	**79–61**	-18 (-33.8, -1.5)
Sticky saliva	**39–84**	45 (23.4, 67.8)	**21–84**	63 (46.3, 80.0)	**82 – 61**	-21 (-41.6, -1.5)	**86–55**	-31 (-44.2, -18.6)

CI; 95 % confidence interval, Diff.; difference of mean scores.

From baseline to 1-year follow-up, global health status/QoL increased 11 points (0.8, 21.4) in the EN-DUR group compared to reaching baseline level in the EN-AF group (0 points, -11.9, 11.9) and physical functioning reached baseline values in the the EN-DUR group (0 points, -11.9, 11.9) compared to a decrease of 7 points (-13.9, -0.7) in the EN-AF group. Symptoms of pain decreased 13 points (-27.7, 1.0) in the EN-DUR group compared to an increase of 1 point (-12.7, 14.6) in the EN-AF group. Dry mouth and sticky saliva increased 36 points (22.6, 48.5) and 9 points (-16.7, 34.5) in the EN-DUR group compared to 46 points (26.5, 66.1) and 20 points (-1.0, 41.7) in the EN-AF group.

Attenders versus non-attenders to the EN-AF intervention

Only 11 of the 21 patients (52%) randomized to the EN-AF intervention attended the program. Table 3 presents the background characteristics of the attenders and non-attenders to the EN-AF intervention before the start of treatment (baseline). The median age of the attenders to the EN-AF intervention was 61 years (IQR 11 years) compared to 67.5 years (IQR 15 years) among the non-attenders, and body mass index (BMI) of the attenders was 25.7 kg/m^2 (SD 5.0) compared to 27.8 kg/m^2 (SD 9.0) among the non-attenders. More of the attenders were diagnosed with pharyngeal cancer compared to the non-attenders (n=9 versus n=1), and more of the attenders were scheduled for chemotherapy in addition to radiotherapy (n=8 versus n=2).

The attenders reported clinically relevant lower global health status/QoL compared to the non-attenders (62 vs. 73 points) and more symptoms of pain (30 vs. 16 points). Furthermore, the attenders reported a clinically relevant higher level of physical activity (2.7 vs. 1.8 points) and had a higher functional capacity compared to the non-attenders (683 vs. 504 meters). No clinically relevant differences in physical functioning, dry mouth, sticky saliva, nutritional status or muscle strength were detected between the attenders and non-attenders.

Table 3. Baseline characteristics of the attenders and non-attenders to the EN-AF intervention.

	Attenders n=11	**Non-attenders** n=10	
Age; years (median, IQR)	61 (11)	67.5 (15)	
Sex			
Women	5	6	
BMI; kg/m² (mean, SD)	25.7 (5.0)	27.8 (9.0)	
Marital status			
Married/cohabitant	8	7	
Single/widow	3	3	
Education			
Primary or secondary school	9	7	
College/university	2	3	
Employment			
Employed	6	3	
Retired	3	7	
Disability benefits	2	0	
Smoking status			
Current smoker	0	1	
Past smoker	7	6	
Never smoked	4	3	
Karnofsky performance status			
Score ≥ 90	9	9	
Tumor site			
Pharynx	9	1	
Larynx	0	2	
Oral cavity	2	2	
Salivary gland/nasal cavity	0	5	
Planned treatment			
Concurrent chemoradiotherapy	8	2	
Radiotherapy	3	8	
	Mean (SD)	**Mean (SD)**	**Diff.**[†] (95 % CI)
HRQoL			
Global health status/QoL	62.1 (22.8)	72.5 (21.9)	10.4 (-30.8, 10.1)
Physical functioning	89.1 (20.7)	92.5 (16.8)	3.4 (-20.7, 13.9)
Pain	29.5 (25.4)	15.8 (24.7)	13.7 (-9.2, 36.6)
Dry mouth	18.2 (17.4)	20.0 (23.3)	-1.8 (-20.5, 16.9)
Sticky saliva	21.2 (34.2)	20.0 (23.3)	1.2 (-25.8, 28.2)
Nutritional status	2.4 (3.4)	3.5 (5.6)	1.1 (-5.3, 3.1)
Physical activity level	2.7 (2.7)	1.8 (1.7)	0.9 (-1.2, 3.0)
Functional capacity (m)	683 (228)	504 (154)	179 (-5, 362)
Muscle strength (reps)	15 (4)	14 (3)	1 (-2, 4)

[†]Difference in mean scores.

BMI; body mass index, CI; confidence interval, Diff.; difference in mean scores, HRQoL; health-related quality of life, IQR; inter quartile range, kg; kilogram, m; meters, m^2; square meters, n; number, reps; repetitions, SD; standard deviation.

DISCUSSION

The overall aim of the present pilot study was to assess differences and describe within-group changes in HRQoL following two physical rehabilitation programs administered during or after radiotherapy (+/- chemotherapy). Due to the pilot design of the study (n=41) with the inherent lack of power to detect statistically significant differences between groups, the main focus was to perform descriptive analyses to explore changes in HRQoL over time. Clinically relevant changes in global health status/QoL and physical functioning were observed in both groups, with differences in change in favour of the active interventions both during and after treatment. Only half of the patients attended the intervention after treatment. Analysis of the attenders and non-attenders indicate that the two sub-groups represent different populations. The attenders to the program administered after treatment reported clinically relevant lower global health status/QoL and more pain compared with the non-attenders. In addition, the attenders were younger, and more were diagnosed with pharyngeal cancer and scheduled for concurrent chemoradiotherapy than the non-attenders.

To our knowledge, this is the first intervention study that explores the development in HRQoL following a rehabilitation program administered during or after radiotherapy (+/- chemotherapy) consisting of a combination of resistance training and ONS in patients with HNC. Rogers and colleagues (2013) conducted a randomized pilot study (n=15) to assess the feasibility and preliminary effects of a 12-week resistance training program initiated at start of radiotherapy in patietns with HNC, and reported similar findings as in the present study with less decline in overall well-being (FACT-General) and HNC specific well-being (FACT H&N) compared to standard care from baseline to week 6.[19] However contrary to our findings, the intervention group reported less increase in overall and HNC specific well-being compared to the control group from week 6 to week 12. Capozzi and colleagues published an exploratory RCT (n=60) in 2016 that evaluated the timing and effects of a 12-week lifestyle intervention with resistance training and health education initiated during versus after radiotherapy.[42] HRQoL was included as a secondary outcome, with a total symptom score and overall HRQoL measured before and after the interventions. In line with our results, no statistically significant differences were detected between the interventions in total symptom score or overall HRQoL, probably due to lack of power. However, contrary to our findings, no clinically relevant differences in mean scores were observed between the groups from start to end of the intervention initiated at start of treatment.[42] Another single-armed (n=12) exercise trial by Lønkvist and colleagues (2017) showed deterioration in most functional scales in EORTC QLQC-30 during treatment, but only minor deterioration was reported in physical functioning.[43]

The findings in the present study confirm earlier findings from numerous observational studies that global health status/QoL and physical functioning decrease during radiotherapy (+/- chemotherapy) while symptoms of pain, dry mouth and sticky saliva increase steadily, and that the post-treatment period normally is characterized by gradual recovery and improvement in HRQoL and less reported symptoms. [5-13] However, an interesting and novel finding in our study is that the patients receiving the active intervention during treatment (EN-DUR) experience clinically relevant better global health status/QoL and physical functioning compared with the patients receiving standard care. A similar trend was observed in the active intervention after treatment (EN-AF), with clinically larger improvements in global health status/QoL and physical functioning compared to the "controls" (EN-DUR). The results indicate that an intervention with resistance training and ONS either during or after radiotherapy may have positive impact on self-reported health status and physical functioning. This justifies a full scale RCT being conducted to investigate whether exercise and nutrition interventions lead to statistically significant improvements.

The future RCT should probably include a combination of physical exercise and nutritional support initiated before start of tumor directed treatment with continuation during treatment and into the post-treatment recovery phase compared to a usual care group. To our knowledge, the largest RCT that has investigated the effectiveness of a physical exercise program in patients with HNC undergoing chemoradiotherapy was recently published by Samuel and colleagues (2019), and conclude that physical exercise during treatment has the potential to enhance HRQoL.[44] They studied the effect of an 11-week program with aerobic and resistance training exercises on quality of life (using the generic Short Form-36), functional capacity and worsening of fatigue. Compared with the control group there was a statistically significant difference in favor of the exercise group on all outcomes from start to end of the intervention. Both the mental and the physical quality of life score was maintained from baseline to immediately after treatment in the exercise group compared to a significant reduction in the control group.[44] These are exciting results from a full-scale trial supporting the findings in the present paper, although not directly comparable due to differences especially in content of interventions and measurement instruments.

In order to gain more insight into possible factors associated with the utilization and needs of rehabilitation within this population, background characteristics were compared between the attenders and non-attenders to the program administrated after treatment. A clear difference at baseline was that most of the attenders (8 of 11 patients) were scheduled for concurrent chemoradiotherapy compared with only two of the 10 non-attenders.

Receiving chemotherapy concurrently with radiotherapy is associated with increased symptoms of mucositis, nausea, vomiting and fatigue compared with only radiotherapy.[45] Thus, an increase in symptoms could be expected among the attenders at the end of treatment. The younger age among the attenders may explain the higher level of self-reported physical activity and the superior functional capacity compared to the non-attenders before treatment start. However, younger cancer patients often express an increased need for rehabilitation compared to older patients, and the utilization of cancer rehabilitation services has been found to be significantly higher in younger age groups.[46-48] One of the reasons for this is suggested to be related to a greater self-perceived loss of functioning among younger patients. The latter and the aspect of still being within working age may have influenced the choice to attend the post-treatment program in the present study, possibly to regain physical and work-related functioning. In addition, the setting of the program (i.e. a rehabilitation clinic located 150 kilometers from the hospital) may have affected the decision to decline participation, and the need for more local services needs to be addressed. As a further preparation for the definitive RCT, we will map-out any existing outpatient and community-based rehabilitation services within the current geographical area and, based on the findings, consider the need to design and implement new locally based interventions.

Strengths and limitations

The present data was obtained from a relatively small single-center pilot study (n=41) with no predefined clinically relevant difference or power and sample size calculations. Statistically significant differences between the interventions (EN-DUR and EN-AF) were neither the aim nor expected in this feasibility study; thus, we chose to explore and compare absolute mean scores even in the absence of formal statistical significance. The two interventions administrated during and after tumor directed treatment respectively were not directly comparable due to differences in content, duration and setting, and the reason for designing two different interventions was based on the current standards of post-treatment rehabilitation programs in Norway and the need for testing new interventions during treatment. The utilised data in the analysis of the attenders and non-attenders was obtained from only one of the two intervention arms in the pilot trial (i.e. the post-treatment intervention), which implies a small number of patients (n=21) split into smaller sub-groups of attenders (n=11) and non-attenders (n=10).

Conclusion

No statistically significant differences in HRQoL between the physical rehabilitation programs were demonstrated, but interesting findings of importance for designing a full-scale RCT were observed. The findings indicate that a physical rehabilitation program may have a positive impact on relevant HRQoL domains during treatment and enhance recovery after treatment in patients with HNC. In addition, the present findings also indicate an increased need for post-treatment rehabilitation among patients receiving concurrent chemoradiotherapy.

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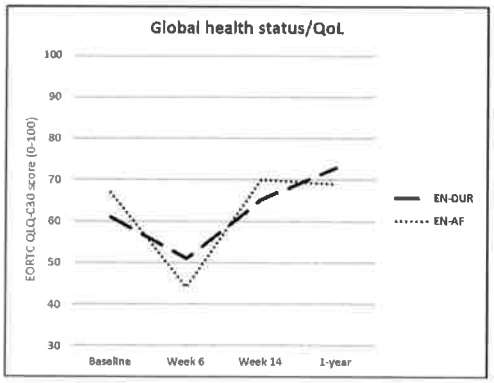
List of figure legends/titles

Figure 1. Mean scores in global health status/QoL and physical functioning in the EN-DUR and EN-AF groups at baseline, week 6, week 14 and 1-year.



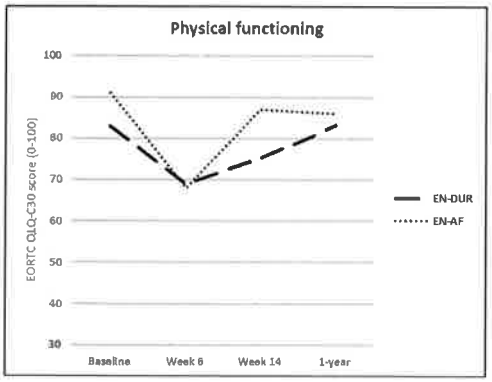


Figure 1. Mean scores in global health status/QoL and physical functioning in the EN-DUR and EN-AF groups at baseline, week 6, week 14 and 1-year.

Nutritional experiences in Head & Neck Cancer (HNC) patients

Running title: Nutritional experiences head and neck cancer

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Conflict of interest statement:

The authors declare that they have no competing interests.

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Nutritional experiences in Head & Neck Cancer (HNC) patients

Abstract

Objective:

Extensive research has documented the negative nutritional impact of head neck cancer (HNC) treatment, but few studies have addressed the patients' experiences. The purpose of this study was to describe how patients with HNC experience the nutritional situation and perceive nutritional support from diagnosis to the post-treatment phase.

Methods:

Patients with HNC were recruited from a randomised pilot study. Individual interviews were conducted after radiotherapy with 10 participants aged 49 – 70 years, and analysed by qualitative content analysis.

Results:

Undergoing surgery was experienced as a poor nutritional starting point for the up-coming radiotherapy. During radiotherapy, increasing side-effects made the participants customise their meals to improve food-intake. About halfway through radiotherapy, virtually no food intake was experienced and hospital-admissions and initiations of tube-feeding occurred in this period. Oral nutritional supplements were recommended for all, but eventually became unbearable to ingest. When radiotherapy was finally completed, the participants felt discouraged about the persistent side-effects preventing them from resume eating. The participants missed tailored information about development of side-effects and involvement of a dietitian when reflecting on the treatment-period.

Conclusion:

The comprehensive nutritional problems experienced by patients with HNC require early nutritional assessments and improved individually tailored nutritional support.

Key words (MeSH):

Head and Neck Cancer; Adverse effects; Diet, Food, and Nutrition; Qualitative Research.

Trial registration:

ClinicalTrials.gov, NCT02439892. Registered 30 April 2015, https://clinicaltrials.gov/ct2/show/NCT02439892.

INTRODUCTION

Patients with head and neck cancer (HNC) may already experience reduced food-intake before the start of radiotherapy, due to consequences of the diagnostic procedures, the psychological stress of a cancer diagnosis and location of the tumour (Chencharick & Mossman, 1983; Cunningham & Bell, 2000; Harrison, Sessions, & Kies, 2013). After the start of radiotherapy, increasing side-effects such as mucositis, pain and swallowing difficulties further aggravate the food-intake (De Sanctis et al., 2016; Schindler et al., 2015; van der Laan et al., 2015). Malnutrition is common (> 70 %), often leading to severe weight loss, impaired immune function, interrupted or incomplete treatment and decreased quality of life (Hebuterne et al., 2014; Jellema, Slotman, Doornaert, Leemans, & Langendijk, 2007; Kruizenga et al., 2003; Unsal et al., 2006). Thus, the maintenance of an optimal nutritional status is vital for improved patient outcomes, treatment tolerance and survival for patients receiving tumour-directed treatment (Odelli et al., 2005; Paccagnella et al., 2010; Pressoir et al., 2010).

To date, most clinical research in patients with HNC has focused on the efficacy of anti-cancer treatments and identification and documentation of side-effects during and after treatment (Gregoire, Langendijk, & Nuyts, 2015; Schindler et al., 2015). Various nutritional interventions have been tested, and individualised nutritional counselling has shown particular beneficial effects on nutritional status during radiotherapy (Langius et al., 2013). In addition, numerous qualitative studies have been conducted to explore the psychological experiences of a HNC diagnosis (Lang, France, Williams, Humphris, & Wells, 2013). However, although oral and eating problems have been identified as the most common concerns and unmet needs during the first five years following HNC treatment, only a few studies have been conducted

to obtain a deeper understanding of the patients' nutritional experiences following a HNC diagnosis (Wells et al., 2015).

Two older qualitative studies have specifically addressed how patients with HNC cope with the decreased nutritional intake, which were found to cause a number of severe negative consequences in daily life (Larsson, Hedelin, & Athlin, 2003; Wilson, Herman, & Chubon, 1991). A later published study has highlighted the physical, emotional and social losses associated with decreased nutritional intake in patients with HNC (McQuestion, Fitch, & Howell, 2011). A recently published study explored the experiences from participating in a dietitian-delivered health behaviour intervention during radiotherapy, by focusing on the patient's working relationship with the dietitian, specific components of the intervention and suggestions for improving the intervention (McCarter et al., 2018).

However, none of the previous qualitative studies have involved experiences from the entire clinical pathway of HNC (i.e. from diagnosis to the acute post-treatment phase), and neither of the studies have specifically addressed the patients' perceptions of nutritional support delivered as part of the standardised care. Clinical experience indicates that nutritional support for patients with HNC shows considerable variation within the specialised health care in Norway. As an example, the involvement of nutrition experts or dietitians seems to be somewhat inconsistent across hospitals, although international clinical nutritional guidelines recommend that oncology dietitians play a central role in the supportive care within this patient group (Arends, Baracos, et al., 2017). A more thorough understanding of the patients' subjective experiences of the nutritional situation is vital to ensure a more patient-centred nutritional care that meets the patients' individual needs and preferences.

Therefore, the aim of this study was to describe how patients with HNC experience the nutritional situation and perceive nutritional support in the period from diagnosis to the acute post-treatment phase.

METHODS

A qualitative study with individual interviews was conducted to describe the patients' experiences and perceptions. The interviews were planned to be completed after the end of radiotherapy, if possible on the same day as the standard physician consultation about two weeks post-treatment.

Recruitment and participants

Patients with HNC were recruited from a randomised pilot study (n=41) that investigated the feasibility of a rehabilitation intervention during versus after radiotherapy consisting of physical exercise and nutritional support. Enrolment in the pilot study was carried out at St. Olavs hospital, Trondheim University Hospital (Norway) from April 2015 to April 2016. Only patients with HNC who were scheduled for radiotherapy towards the affected area for the first time were included in the pilot study. The oncologic treatment was intended to be provided according to national and international guidelines. The need for nutritional support (e.g. oral nutritional supplements and nasogastric tube-feeding) was continuously monitored by the responsible multidisciplinary team.

The intervention during treatment was carried out at a meeting place and retreat for cancer patients and their families close by the hospital, where the patients conducted resistance training twice a week and were provided with daily oral nutritional supplements ("E+" by

Tine SA, Norway) during the six weeks radiotherapy period. The patients randomised to the post-treatment intervention received standard care during radiotherapy, and were scheduled for a three-week stay at a rehabilitation clinic two to four weeks after the end of radiotherapy.

The patients had received both oral and written information about the qualitative study prior to start of treatment, and agreed to be contacted about participation in the study. Towards the end of treatment, some of the patients were invited either face-to-face or by phone/SMS to complete an interview. Efforts were made to ensure participants were representative of the HNC population, including both genders, younger and older, and those living in rural and urban areas. A selection was also made based on the availability of the patients with regard to conflicting appointments at the hospital.

A total of 10 participants equally distributed between men and women and with a median age of 59 years (range 49 – 70 years) participated in the present study (see Table 1). Six patients participated in the rehabilitation intervention during treatment and four patients in the intervention after treatment (controls during treatment). More than half of the participants were employed while others either retired or on disability benefits. The majority had a Karnofsky performance status of 70 % at the end of treatment (scored by a physiotherapist), indicating that they were able to care for themselves but unable to carry out normal activities or do active work (Yates, Chalmer, & McKegney, 1980). Seven of the participants attended the interview as scheduled, while the others were unable to attend the interview until 4 weeks after treatment due to severe side-effects. About half of the participants had a feeding tube in place at the time of the interview.

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"Table 1. Characteristics of the participants"

Interviews and interview guide

Individual interviews were completed from November 2015 to April 2016. The interviews were carried out at a meeting place and retreat for cancer patients and their families near the hospital, unless the participants preferred another localisation. One participant chose to complete the interview in her home on another day than the post-treatment consultation. The interviews lasted from 30 to 98 minutes (48 minutes on average), and were carried out by a research nurse (VV) with experience from the clinical HNC field who did not take part in the treatment of the participants. The research nurse was at the time working in the research department of the involved hospital's cancer clinic, and had experience from conducting clinical trials in cancer patients utilising both quantitative and qualitative methods. Three participants were accompanied by their partners, who did not have an active role in the interview.

A semi-structured interview guide (Appendix 1) was used to ensure open-ended questions about the participants' nutrition-related experiences and needs for nutritional support from diagnosis to the current situation after treatment. The interviewer used broad questions and made reflections of content and feelings to encourage the patients to elaborate, and relevant topics that emerged were pursued by follow-up questions. The interviews were audio-recorded and transcribed verbatim after all interviews were completed. The texts were managed and systematised by Microsoft Word® and by working manually with printouts and pen and paper. Quotations from the texts were translated from Norwegian to English by the first author of the present paper (JAS).

Ethical considerations

The present qualitative study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK midt 2013/2098) as a sub-study of the previously described pilot study. The written study information and informed consent included both the pilot study and the qualitative sub-study. All participants that were invited for the qualitative study after treatment renewed their consent before the interview. The interviewer strived to create trust with the participants, by recognising their situation and the experiences from the treatment-period. All participants were offered to read the transcribed interviews and to know more about the analysis-process, but none of them expressed any interest.

Analysis

The transcribed interviews were analysed by qualitative content analysis. This is a method mainly focusing on the subject and context, emphasising differences and similarities within codes and categories (Graneheim & Lundman, 2004). The manifest content analysis, rather than latent content analysis, was chosen to describe visible and clear components from the interviews (Downe-Wamboldt, 1992; Kondracki, Wellman, & Amundson, 2002).

Initially, all the interviews were read and reread by the core analysing team (JAS, ASH, and KS) to get a general overview and a sense of topics. The topics were discussed, leading to a consensus among all of the authors regarding the focus of the analysis. Next, all relevant meaning units (i.e. the constellation of words or statements that relate to the same central meaning) were extracted, and meaning units that deviated from the focus of the study were excluded (Graneheim & Lundman, 2004). The meaning units were then sorted into the preliminary categories 'before treatment', 'symptoms/side-effects', 'consequences', 'supportive

actions', and 'after treatment'. Based on these preliminary categories, codes were created to label all meaning units (e.g. 'nutritional preparations', 'mucous, nausea and vomiting', 'swallowing difficulties', 'coping strategies', 'hospital-admission and tube-feeding', 'hope and expectations' and 'thoughts and reflections'). Sub-categories were then abstracted, combining one or more of the codes within the preliminary categories to cover the time periods from diagnosis to the acute recovery phase after treatment. Finally, new category-names were created and narrative descriptions were written. The phases of developing codes, sub-categories and categories were continuously reflected on and discussed between the core analysing team throughout the process. The core analysing team continuously returned to the original text to ensure that that the core meaning was preserved, and this process was maintained throughout the entire analysis.

RESULTS

The patients' nutritional experiences and needs for nutritional support evolved within the four categories *Waiting to get started*, *Undergoing daily radiotherapy turns everyday life upside down* , *Finally done but still troubling* and *Reflecting on the treatment trajectory.*

Waiting to get started

Preparing for radiotherapy

Except from following generalised advice to increase the caloric-intake and acquire nutritional drinks, the participants did not highlight any specific nutritional preparations before starting radiotherapy. Living as normal as possible and maintaining everyday routines, including their dietary pattern, was the way they coped with the situation. However, the participants who underwent surgery prior to radiotherapy described commonly soreness, pain and swallowing difficulties. It was experienced as difficult to eat and drink as normal, and initial weight loss started. Also fatigue and appetite loss was mentioned, and the situation was described as not the most ideal for the up-coming radiotherapy:

> *My starting point for radiotherapy was really bad. I had gone through surgery with removal of the tumour and tonsils, and then biopsies from different locations in my throat 14 days after that. I felt exhausted already at the first day, and I think that was the reason I got so sick and dehydrated during the initial days of radiotherapy.*
>
> Participant 4

Receiving information

The participants received both oral and written information about the expected nutrition-related consequences of treatment, but preferred different delivery methods. One participant

stated "I'm a craftsman and a man, and you have to tell these things to idiots like me and not just deliver a stack of papers", while another found the written information really relevant and "read it all". The participants appreciated to have someone among the treatment staff to ask questions as they appeared.

Undergoing daily radiotherapy turns everyday life upside down

Increasing side-effects and diminishing food intake

The participants described that side-effects started slowly in the first week of radiotherapy and "just increased as the weeks went by", and included soreness, pain, nausea, increased mucous production, alterations of taste and smell, swallowing difficulties and mouth dryness:

> *But in the second week, the side-effects became more evident, and in the third week they really struck [...]. It was just painful to swallow, pain and soreness [...]. The taste disappeared completely, and everything tasted crap, metal, like in a weird way [...]. And then the increased mucous production on top of that, which was the worst part.* Participant 5

It was indicated that a combination of soreness, pain and increased mucous production represented the main cause of the swallowing difficulties, and most participants suffered from a decreased nutritional intake. "The feeling of being really sick" was also highlighted, and loss of appetite was evident. Some participants gave detailed descriptions of their weight-development, while others made rough estimates.

Coping with increasing nutritional problems

The participants expressed different strategies to manage their increasing nutritional problems during radiotherapy. "To live like normal at home" and "avoid losing too much weight" was highlighted as a motivation for keeping up the nutritional intake, and actions were taken like "I squeezed the potatoes in the sauce, I even used a knife and fork to cut the crust from a slice of bread". One participant stated "I just forced myself to eat because I knew I needed food", and made several active efforts to make this possible:

> *The next week I brought a blender back to the outpatient accommodation and mashed all the food in my room, and then I was able to ingest some [...]. During the weekends at home, I made it a bit more advanced by blending for example broth, meat and vegetables into a drinkable soup, which I brought back to the outpatient accommodation.* Participant 3

Using oral nutritional supplements as nutritional first aid

All participants were introduced to oral nutritional supplements prior to or during radiotherapy. Those tasting the nutritional drinks from the start of radiotherapy, found them "really good when testing the different flavours". All participants expressed that it became gradually more difficult to ingest the drinks as the intensity of the side-effects increased, and most participants had to quit the drinks about halfway through radiotherapy:

> *I tried to continue with the nutritional drinks, but it was becoming increasingly unbearable. The taste of it just got more nasty, it became more and more difficult to swallow and I got really nauseous [...]. It tasted of metal and cardboard, I don't know how else to put it.* Participant 1

Deciding hospitalisation and starting tube-feeding

Hospital-admissions occurred in the third or fourth week of radiotherapy. It was expressed that the side-effects affected the nutritional intake to such an extent that "I just wasn't able to swallow anymore". Although the participants highlighted that it was the treatment staff's suggestion and decision to admit them to the hospital, the participants regarded hospitalisation as a necessary way out of an unbearable nutritional situation.

Tube-feeding was started in virtually all participants just after hospitalisation, and was described as "I felt much better already the day after I started the tube-feeding" and "my body weight was stabilised after I got the tube". However, the tube was tolerated differently among the participants. One expressed "I barely managed the tube in my throat because I easily throw up", while another, that had to change the tube several times, stated "it was not a problem because they do it in a really smooth and quick way".

Most of the participants that did not start tube-feeding were not hospitalised, and were able to ingest food although "smaller and smaller portions of dinner" and despite that "it was very painful to eat and everything tasted the same". One participant really wanted to avoid the tube, even if it was recommended by the treatment staff:

> *But I really didn't want to install a tube, because from that moment on you really mark the transition from a person to a patient.* Participant 4

Finally done but still troubling

Persisting side-effects and altered senses

After treatment, side-effects like pain, nausea, altered or loss of taste and increased mucous production were still troubling the participants. Decreased saliva secretion was also addressed,

and it was stated that "some of the saliva secretion has returned, but it's not like it used to be, it's stickier". Most participants expressed they were still unable to achieve a normal intake, and it was stated that "the food still needs to have a smooth texture and definitely not any sharp edges to slide down". Pain and sticky saliva were highlighted as the main causes for the swallowing difficulties. Food they normally enjoyed now tasted awful, or the taste was totally or partly missing:

> *Now I can feel a hint of flavour when I start to eat some food like soft-boiled eggs and maybe tomato sauce. But the flavour is gone already after a couple of spoons. So it doesn't matter what I eat, it all tastes the same.* Participant 3

The three participants who completed the interviews about four weeks after treatment expressed improvements of the side-effects but still troubled to eat adequately: "The soreness in my throat has improved some, and I try to ingest some porridge, soup and half a slice of bread". It was also described eating problems despite being able to swallow:

> *Now I'm able to swallow, but the thing is that nothing tastes anything and I get nauseous from it [...]. It's such a pity because I really want to eat, but it's so disgusting in a way.* Participant 10

Moving towards the usual life

The participants expressed different strategies to cope with their deteriorated nutritional situation after radiotherapy, mainly by focusing on maximising the food-intake either through the tube, orally or a combination of both. With regard to the tube-feeding, the participants expressed concern regarding their ability to get enough calories and about "getting nauseous

again if I take too much at once". To optimise oral intake, patients referred to strategies such as finding the best time during the day for eating and adjusting the consistency of the food. Patients tried to use nutritional drinks "as a snack meal in between the tube-feeding", and tried to take these drinks on a regular basis. The importance of living as normal as possible was also expressed as a way of maintaining the food-intake:

> *I have tried to live as normal as possible from diagnosis and until now, also when it comes to nutrition and food. So, now I blend the ingredients separately, not making one soup out of it, and serve it separately on the plate like a normal dinner.*
>
> Participant 3

The participants hoped for a gradual increase of their food-intake in the upcoming period. One explicitly stated "that's what I'm hoping for now, to be able to eat, you know, and get rid of the tube", while it was recognised that "the recovery will take some time" and "I guess it's different from person to person how long time it takes to be able to eat again". It was pointed out some specific expectations related to the type of food, like "I expect to be able to ingest some soup or porridge from now on".

Reflecting on the treatment trajectory

Highlighting tailored information and specialised nutritional support

When looking back at the entire treatment trajectory, the participants questioned their ability to absorb the provided information prior to start of radiotherapy:

I'm not sure I was able to absorb the information at that time. It's something completely different when you actually experience the side-effects compared to hearing or reading about them. Participant 5

The participants requested more information about "what is normal and not" regarding the time-aspect of the side-effects, and stated "it's still unclear when I can expect to start eating again" and "nobody has told me when it is expected that the mucous and saliva production will normalise". It was suggested that "the treatment staff could have informed a little bit more in detail about when it is expected to start chewing and eating again" and it was also suggested to introduce peer-support in the period before radiotherapy. The absence of nutritional support from a dietitian was specifically addressed:

A doctor, nurse and dental hygienist were all present at the weekly status meetings. But a dietitian was never present, and I was never offered a referral for dietary counselling. Participant 4

DISCUSSION

While waiting to get started with radiotherapy, the reduced food intake after surgery was experienced as a poor starting point. When undergoing daily radiotherapy, the side-effects caused increasing difficulties with eating and drinking, and loss of appetite was evident. The participants had to customise their meals to improve the food-intake. Using oral nutritional supplements as nutritional first aid only made sense during the initial weeks of radiotherapy, since it eventually got unbearable to ingest them. Hospital-admissions occurred about halfway through radiotherapy, and tube-feeding was initiated just after being hospitalised. Although finally done with radiotherapy, the participants felt discouraged about the persistent side-effects, preventing them from eating and drinking as desired. When reflecting on the course of treatment, the participants questioned their ability to absorb the pre-treatment information about nutritional side-effects. They missed specific information regarding the expected recovery from side-effects and when to resume eating, and the absence of a dietitian as part of the multidisciplinary team was highlighted.

Being exposed to the side-effects of radiotherapy was experienced as quite different from just hearing and reading about them in the present study. Even though the participants received standard information before the treatment started, it is a well-known challenge for patients to realise the practical implications of medical information, and in particular for patients with HNC that are exposed to extensive information from various health-care professionals (Diefenbach et al., 2009; Ishikawa, Hashimoto, & Kiuchi, 2013; Ziegler, Newell, Stafford, & Lewin, 2004). This could be caused by the lack of time to assimilate the information, and the fact that traumatic experiences are indescribable until they have been experienced (Llewellyn, McGurk, & Weinman, 2005). Also, the shock of diagnosis in conjunction with the tumour morbidity may reduce the patients' ability to absorb the information adequately despite

careful explanations. The latter is in line with research documenting that many patients with HNC suffer from psychological distress already from diagnosis, which may interfere with the patients' ability to absorb and process relevant information (Chen et al., 2009; Williams, 2017). Ensuring that key messages are repeated continuously, and preferably coupled with written materials, may facilitate for an improved understanding of the information. In addition, as highlighted in the present study, utilising former patients with similar experiences to provide relevant information may improve the credibility and thus the absorption of the information.

The participants called for more specific information about the nutritional consequences of the side-effects, and stressed the need to provide an approximate time-line of recovery in the post-treatment phase. This is in line with the findings from a survey of information needs and preferences in patients with HNC, which showed that information about treatment and recovery time-frames was considered most important, in addition to signs and symptoms of recurrence, cure rates, post-treatment rehabilitation and financial support (Saroa et al., 2018). Medical information provided to patients with HNC is typically generic, and intended to apply for all patients. However, the duration of recovery vary greatly between patients with HNC, and information provided on a group level may not fit with the progress of the individual patient's recovery. Several studies have shown that a generic provision of information is not sensitive enough to capture the variation that exists between patients in their desire for and understanding of information (Fujimori & Uchitomi, 2009; Kreuter, Strecher, & Glassman, 1999; Rodin et al., 2009). In addition, a recently published qualitative study that described HNC patients' perceptions of information delivery indicates that comprehensive verbal information and audio-visuals may prepare the patients in a better way compared to providing only verbal information in an ad-hoc manner (D'Souza et al., 2018).

Providing individually tailored information, and involving the patients in the decision-making by requesting values and preferences with regard to food, has been found to result in higher levels of cancer knowledge and satisfaction with information, and lower levels of anxiety, compared to providing generic information (D'Souza, Blouin, Zeitouni, Muller, & Allison, 2013a, 2013b). This indicates that an assessment of HNC patient's needs for information is vital before deciding information strategies, although the findings need to be confirmed with a randomised approach. However, such a patient-centred approach of providing information and nutritional interventions may not fit the current streamlined cancer pathways in Norway, and we therefore suggest that individually tailored nutritional support forms a part of the clinical pathway of HNC treatment. Clinical nurse specialists are recommended to act as gate keepers to the patients' cancer pathway to provide a seamless journey; they therefore form a vital part of the multidisciplinary team to support implementation of more patient-centred nutritional support in all phases of the treatment trajectory (Dempsey, Orr, Lane, & Scott, 2016).

The absence of a dietitian as part of the multidisciplinary team was highlighted. Both after surgery and during the initial weeks of radiotherapy, the participants had to customise their meals to the best of their ability. Nutritional drinks were recommended for all on a general basis. The majority of the participants were hospitalised about halfway through radiotherapy, and tube-feeding was then initiated. Since patients with HNC are at a high risk of malnutrition already from diagnosis, specific nutritional strategies are required to minimise the negative consequences of surgery, radiotherapy and chemotherapy (Hebuterne et al., 2014; Silva, de Oliveira, Souza, Figueroa, & Santos, 2015; Weimann et al., 2017). Specialised nutrition competencies and skills are needed to make early detections of patients in need of nutritional support, and to assess and initiate relevant nutritional support. Hospital stays are longer and

costs per hospitalisation are higher in malnourished cancer patients, thus actions that may delay or prevent hospital admissions during treatment are desired (Maasberg et al., 2017; Planas et al., 2016; Pressoir et al., 2010). Updated international clinical guidelines on nutritional support in cancer patients recommend that dietitians play a central role in the multidisciplinary team responsible for the supportive care of HNC patients (Arends, Bachmann, et al., 2017; Thompson et al., 2017). The reasons for the inconsistent provision of dietitian-delivered nutritional support to Norwegian HNC patients need to be clarified in order to improve the quality of patient care. Not only may a dietitian improve the nutritional support through direct contact with HNC patients, but also through increasing the nutritional expertise of the involved health care professionals.

Strengths, limitations and trustworthiness

Qualitative methods may contribute with a deeper understanding of the nutritional impact of a HNC diagnosis and treatment, and is an excellent fit to quantitative data documenting the occurrence of side-effects and effective nutritional interventions. The use of a semi-structured interview-guide allowed for unexpected aspects and themes to arise. All interviews were carried out by a research nurse with experiences clinical trials utilising both quantitative and qualitative methods, and with clinical experience from the field of HNC.

The included participants were invited from a randomised rehabilitation study that involved the majority of all HNC patients scheduled for curative treatment within the health region of central Norway (2015-2016). The participants represent the heterogeneity of HNC patients, including both genders, younger and older than 60 years and living in rural and urban areas. Most of the participants (7 out of 10) were diagnosed with pharyngeal cancer in the present sample, and patients with oral cavity and laryngeal cancer were not represented. While the

treatment modalities of oral and laryngeal cancer are similar to that of pharyngeal cancer (i.e. radiotherapy +/- chemotherapy), patients with laryngeal cancer often experience less side-effects compared to oral and pharyngeal cancer due to much smaller irradiated areas, depending on stage (Evensen, 2015). Since more than half of the participants (6 out of 10) participated in the rehabilitation intervention during radiotherapy, while the other participants received standard care in the same period, the intervention may have influenced the perceptions of supportive care and the provision of nutritional drinks. However, the interviewer experienced that the participants did not distinguish between the study-specific and standard care, since nutritional drinks also were recommended as part of the standard care.

Since the interviews were conducted about two weeks after the end of radiotherapy, and even about four weeks after treatment for three participants, oversights and recall biases of relevant events cannot be ruled out. Repeating the interviews during the different treatment phases would result in more accurate snapshots of the patients' experiences, and will be conducted in a planned follow-up study within this patient-group.

Clinical implications

The findings from the present study stress the importance of dietitian led nutritional care during all phases of the clinical pathway in patients with HNC. Addressing nutritional issues immediately following diagnosis enables appropriate interventions on time (Larsson, Hedelin, Johansson, & Athlin, 2005; Sanson-Fisher et al., 2000). A nutritional screening is recommended for all patients with HNC, followed by a full assessment if nutritional risk is present (Arends, Baracos, et al., 2017). Subsequent nutritional support should be initiated before treatment start, since nutritional interventions are most successful if initiated early

(Capra, Ferguson, & Ried, 2001; Langius et al., 2013; Ottery, 1995; Piquet et al., 2002). Nutritional counselling is recommended as the first line of nutritional support, and should consist of a patient-centred and repeated communication process to provide the patients with a thorough understanding of nutritional topics, as distinct from brief and casual dietary advice (Arends, Bachmann, et al., 2017). Such counselling will ensure that relevant nutrition-related information is provided. Since radiotherapy and chemotherapy are intended to be carried out on an out-patient basis in patients with HNC, it is necessary to co-ordinate and adjust nutritional interventions to the patients' hospital visits. Finally, the interventions should meet the patients' changing needs in order to enhance coping and self-care in the home situation (Wells, 1998).

In addition to the importance of early detection and initiation of nutritional support, the present study also revealed the need for individual strategies for providing medical information during the different treatment phases. Continuous assessments of health-status and side-effects are essential to be able to provide meaningful information to each patient, which may enhance self-care (Larsson et al., 2003).

Conclusion

The comprehensive nutritional problems that patients with HNC experience from diagnosis to the recovery phase after treatment indicate a need for dietitian led individually tailored nutritional care to improve patient outcomes. This implies early individual assessments of needs for information and nutritional support for all patients, including continuous reassessments of the changing needs. In this way, individualised nutritional care may become an integrated part of the clinical HNC pathway.

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Table 1. Characteristics of the participants

	Number of participants		Number of participants
Gender		**Tumour site**	
Males	5	Oropharynx	7
Females	5	Salivary glands	2
Age distribution		Unknown origin	1
40-49	1	**Tumour stage**	
50-59	4	Stage I-II	2
60-69	4	Stage III	2
70-79	1	Stage IVA	5
Civil status		Not assessed	1
Married/cohabiting	7	**Treatment modality**	
Single	3	Surgery + chemoradiotherapy	4
Education		Surgery + radiotherapy	3
Primary/secondary school	7	Chemoradiotherapy	2
College/university	3	Radiotherapy	1
Employment status		**Hospital admissions**	**7**
Employed	6	**No hospital admission**	**3**
Disability benefits	2	Staying at home	2
Retired	2	Staying at outpatient accommodation	1
		Nasogastric tube	**6**
		Still in place at the time of the interview	5
Karnofsky performance status (0-100) †			
Score=80 %	3		
Score=70 %	7		
Symptoms (0-100) ‡			
Fatigue-score ≥ 50	7		
Nausea/vomiting-score ≥ 50	5		
Pain-score ≥ 50	9		
Nutritional status (0-36) §			
Score ≥ 9	9		
Score 2 – 8	1		

†Scored by a physiotherapist at the end of radiotherapy, 0=dead and 100=normal no complaints (80 %: able to do normal activity/work with some effort, some signs or symptoms, 70 %: cares for self, but unable to carry on normal activity or to do active work (Yates et al., 1980).
‡Self-reported by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at the end of radiotherapy, 0=no symptoms and 100=maximal symptoms (Aaronson et al., 1993).
§Self-reported by the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form at the end of radiotherapy, 0=no problems and 36=severe problems (0-1: no interventions needed, 2-8: require nutritional interventions, ≥ 9: critical need for improved symptom-management and/or nutrient intervention options) (Detsky et al., 1987; Gabrielson et al., 2013).

Appendices

Appendix 1. Study flyer

- Mange pasienter som får kreft i munn og svelg opplever problemer med å spise og får mindre matlyst. Dette kan føre til vekttap og utfordringer med å klare dagliglivets gjøremål.
- Fysisk aktivitet, riktig kosthold og ernæring kan forebygge vekttap under og etter behandling, og dermed bidra til at du opprettholder din fysiske funksjon i hverdagen.
- Dersom du ønsker å delta i forskningsprosjektet, vil du få ekstra oppfølging på trening og ernæring under eller etter strålebehandling.
- Snakk gjerne med en sykepleier på avdelingen om eventuell deltakelse i prosjektet.

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Appendix 2. Booklet with nutrition advice (table of content)

Kostråd til deg som får strålebehandling mot hode-, hals- og brystregionen

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

Oslo universitetssykehus

Innhold

Appendix 3: Exercise programme during treatment

Navn:

Uke 1 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	12	3				8	4		
Knefleksjon	12	3				8	4		
Brystpress	12	2				8	3		
Stående roing	12	2				8	3		

Uke 2 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	12	3				8	4		
Knefleksjon	12	3				8	4		
Brystpress	12	2				8	3		
Stående roing	12	2				8	3		

Uke 3 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	12	3				8	4		
Knefleksjon	12	3				8	4		
Brystpress	12	2				8	3		
Stående roing	12	2				8	3		

Uke 4 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	10	4				6	4		
Knefleksjon	10	4				6	4		
Brystpress	10	3				8	3		
Stående roing	10	3				8	3		

Uke 5 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	10	4				6	4		
Knefleksjon	10	4				6	4		
Brystpress	10	3				8	3		
Stående roing	10	3				8	3		

Uke 6 (Husk vekt, ESAS og recall)

Økt 1	Reps	Serier	Kg	Tilpasning/kommentar	**Økt 2**	Reps	Serier	Kg	Tilpasning/kommentar
Kneekstensjon	10	4				6	4		
Knefleksjon	10	4				6	4		
Brystpress	10	3				8	3		
Stående roing	10	3				8	3		

Appendix 4. Exercise programme after treatment

Treningsintervensjon etter strålebehandling

3-ukers program for styrke og muskelvekst

LHL-klinikkene Røros

Øvelser bein	**Øvelser overkropp**
Beinpress	Brystpress
Kneekstensjon	Nedtrekk
Knefleksjon	Sittende roing

Uke 1

Økt 1 onsdag	Økt 3 fredag
Repetisjoner x serier	Repetisjoner x serier
Tilvenning pretest: 10x1, 5x1, 3x1, 1x1	1 RM pretest benpress
Overkropp: 15x2	12 RM x2

Uke 2

Økt 1 mandag	Økt 2 onsdag	Økt 3 fredag
Repetisjoner x serier	Repetisjoner x serier	Repetisjoner x serier
Underkropp: 12 RM x3	80 % av økt 1:10 x3	6 RM x4
Overkropp: 12 RM x2	80 % av økt 1:10 x3	8 RM x3

Uke 3

Økt 1 mandag	Økt 2 onsdag	Økt 3 fredag
Repetisjoner x serier	Repetisjoner x serier	Repetisjoner x serier
Underkropp: 12 RM x3	80 % av økt 1:10 x 3	6 RM x4
Overkropp: 12 RM x2	80 % av økt 1:10 x 3	8 RM x3

Uke 4

Økt 1 mandag
Repetisjoner x serier
Underkropp: 1RM posttest benpress
Overkropp: 8 RM x 3

Ankomst: tirsdag uke 1

Avreise: tirsdag uke 4

Appendix 5. Log nutritional supplements during and after treatment

Registrering inntak av næringsdrikke (E+)

Navn:

Har du tatt 1-2 næringsdrikker (á 2 dl) hver dag siste uke?

Dato	Dato	Dato	Dato	Dato	Dato
JA:	JA:	JA:	JA:	JA:	JA:
NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:

Dato	Dato	Dato	Dato	Dato	Dato
JA:	JA:	JA:	JA:	JA:	JA:
NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:

Dato	Dato	Dato	Dato	Dato	Dato
JA:	JA:	JA:	JA:	JA:	JA:
NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:	NEI: - Antall:

Appendix 6. Self-reported questionnaires

Reported only at baseline:

Pasientnummer: ☐☐☐

Kjønn ☐ Mann ☐ Kvinne

Sivil status ☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

Bosituasjon
- ☐ Alene
- ☐ Sammen med ektefelle/partner
- ☐ Sammen med ektefelle/partner og barn
- ☐ Sammen med barn
- ☐ Sammen med andre voksne
- ☐ Annet

Høyeste fullførte utdanning
- ☐ Grunnskole
- ☐ Videregående skole
- ☐ Høyskole eller universitet

Arbeid- og trygdestatus
- ☐ Yrkesaktiv ☐☐☐ % stilling
- ☐ Selvstendig næringsdrivende
- ☐ Student
- ☐ Jobbsøker/arbeidsledig/permittert
- ☐ Sykmeldt ☐☐☐ % sykemeldt
- ☐ Arbeidsavklaringspenger (AAP)
- ☐ Uføretrygd
- ☐ Alderspensjon

Røyk
- ☐ Aldri
- ☐ Tidligere, år røykeslutt: ☐☐☐☐
- ☐ Røyker for tiden

8366

Reported at week 6, week 14 and 1-year:

Pasientnummer: ☐☐☐

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

1. Vekt

a. Jeg veier ca. ☐☐☐.☐ (kg)

b. Jeg er ca. ☐☐☐.☐ (cm)

c. For en mnd siden veide jeg ca. ☐☐☐.☐ (kg)

d. For 6 måneder siden veide jeg ca. ☐☐☐.☐ (kg)

e. De siste 2 ukene har vekten min: (velg en)

☐ minsket ☐ vært uforandret ☐ økt

2. Matinntak

Sammenliknet med mitt normale, har matinntaket mitt siste måneden vært: (velg et alternativ)

☐ uendret

☐ mer enn vanlig

☐ mindre enn vanlig

Hvis mindre enn vanlig: (velg ett alternativ)

☐ Vanlig mat, men mindre mengde enn vanlig

☐ litt fast føde

☐ kun flytende

☐ kun næringsdrikker

☐ veldig lite av alt

☐ kun sondeernæring eller intravenøs ernæring

Pasientnummer: ☐☐☐

3. Symptomer

De siste to ukene har jeg hatt følgende problem som har hindret meg fra å spise tilstrekkelig (angi ett eller flere alternativer)

- ☐ ingen problem
- ☐ ingen appetitt, ikke lyst til å spise
- ☐ kvalme
- ☐ oppkast
- ☐ forstoppelse
- ☐ diaré
- ☐ sår i munnen
- ☐ munntørrhet
- ☐ maten smaker annerledes eller ingenting
- ☐ plaget av lukter
- ☐ problemer med å svelge maten
- ☐ blir fort mett
- ☐ smerter, i så fall hvor? Vennligst spesifiser _____
- ☐ Annet: Vennligst spesifiser _____

4. Fysisk aktivitet

Den siste måneden vil jeg beskrive aktiviteten min som: (velg ett alternativ)

- ☐ normal, med ingen begrensninger
- ☐ ikke normal, men er oppe og er i noe aktivitet
- ☐ ikke vært i form, vært i seng eller i en stol mindre enn halve dagen
- ☐ vært i litt aktivitet, tilbringer det meste av dagen i sengen eller i stol
- ☐ ligget for det meste i sengen

Pasientnummer: ☐☐☐

MOSJON/FYSISK AKTIVITET

1. Med mosjon mener vi at du for eksempel går tur, går på ski, svømmer eller driver trening/idrett.
   Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*
   - ☐ Aldri
   - ☐ Sjeldnere enn en gang i uka
   - ☐ En gang i uka
   - ☐ 2-3 ganger i uka
   - ☐ Omtrent hver dag

2. Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? *(Ta et gjennomsnitt)*
   - ☐ Tar det rolig uten å bli andpusten eller svett
   - ☐ Tar det så hardt at jeg blir andpusten og svett
   - ☐ Tar meg nesten helt ut

3. Hvor lenge holder du på hver gang? *(Ta et gjennomsnitt)*
   - ☐ Mindre enn 15 minutter
   - ☐ 15 – 29 minutes
   - ☐ 30 minutter til en time
   - ☐ Mer enn en time

Pasientnummer: ☐☐☐

Fatigue Severity Scale (FSS)

Siste uke har jeg følt at : *(Kryss av for det som passer for deg).*	Uenig 1	2	3	4	5	6	Enig 7
1. Mitt pågangsmot blir dårligere når jeg er utmattet	☐	☐	☐	☐	☐	☐	☐
2. Jeg blir fort utmattet ved anstrengelser	☐	☐	☐	☐	☐	☐	☐
3. Jeg har lett for å bli utmattet	☐	☐	☐	☐	☐	☐	☐
4. Utmattelse nedsetter min fysiske funksjonsevne	☐	☐	☐	☐	☐	☐	☐
5. Utmattelse skaper ofte problemer for meg	☐	☐	☐	☐	☐	☐	☐
6. Utmattelse fører til at jeg har dårlig fysisk utholdenhet over lengre tid	☐	☐	☐	☐	☐	☐	☐
7. Utmattelse virker negativt inn på mine gjøremål og forpliktelser	☐	☐	☐	☐	☐	☐	☐
8. Utmattelse er ett av mine tre mest plagsomme symptomer	☐	☐	☐	☐	☐	☐	☐
9. Utmattelse virker negativt inn på mitt arbeid, min familie og mitt øvrige sosiale liv	☐	☐	☐	☐	☐	☐	☐

Pasientnummer: ☐☐☐

EORTC QLQ-C30

(Versjon 3.0)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

Pasientnummer: ☐☐☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

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Pasientnummer: ☐☐☐

EORTC QLQ - H&N35

Endel pasienter opplever av og til at de har noen av følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka. Sett ett kryss under det svaret som best beskriver din tilstand.

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
31. Har du hatt smerter i munnen?	☐	☐	☐	☐
32. Har du hatt smerter i kjeven?	☐	☐	☐	☐
33. Har du vært sår i munnen?	☐	☐	☐	☐
34. Har du hatt smerter i halsen?	☐	☐	☐	☐
35. Har du hatt problemer med å svelge flytende?	☐	☐	☐	☐
36. Har du hatt problemer med å svelge moset mat?	☐	☐	☐	☐
37. Har du hatt problemer med å svelge fast føde?	☐	☐	☐	☐
38. Har du satt noe i vrangstrupen når du har svelget?	☐	☐	☐	☐
39. Har du hatt problemer med tennene?	☐	☐	☐	☐
40. Har du hatt problemer med å gape høyt?	☐	☐	☐	☐
41. Har du vært tørr i munnen?	☐	☐	☐	☐
42. Har du hatt seigt spytt?	☐	☐	☐	☐
43. Har du hatt problemer med luktesansen?	☐	☐	☐	☐
44. Har du hatt problemer med smakssansen?	☐	☐	☐	☐
45. Har du hostet?	☐	☐	☐	☐
46. Har du vært hes?	☐	☐	☐	☐
47. Har du følt deg syk?	☐	☐	☐	☐
48. Har ditt utseende plaget deg?	☐	☐	☐	☐

Pasientnummer: ☐☐☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
49. Har du hatt vanskeligheter med å spise?	☐	☐	☐	☐
50. Har du hatt vanskeligheter med å spise i familiens påsyn?	☐	☐	☐	☐
51. Har du hatt vanskeligheter med å spise i andre menneskers påsyn?	☐	☐	☐	☐
52. Har du vanskeligheter med å nyte måltidene?	☐	☐	☐	☐
53. Har du hatt vanskeligheter med å snakke med andre mennesker?	☐	☐	☐	☐
54. Har du hatt vanskeligheter med å snakke i telefonen?	☐	☐	☐	☐
55. Har du hatt vanskeligheter med å ha sosial omgang med familien?	☐	☐	☐	☐
56. Har du hatt vanskeligheter med å ha sosial omgang med venner?	☐	☐	☐	☐
57. Har du hatt vanskeligheter med å være ute på offentlige steder?	☐	☐	☐	☐
58. Har du hatt vanskeligheter med å ha fysisk kontakt med familie eller venner?	☐	☐	☐	☐
59. Har du vært mindre seksuelt interessert?	☐	☐	☐	☐
60. Har du hatt mindre seksuell glede?	☐	☐	☐	☐

I løpet av den siste uka:	Nei	Ja
61. Har du brukt smertestillende?	☐	☐
62. Har du tatt ernæringstilskudd (bortsett fra vitaminer)?	☐	☐
63. Har du brukt ernæringssonde?	☐	☐
64. Har du gått ned i vekt?	☐	☐
65. Har du gått opp i vekt?	☐	☐

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Appendix 7. Interview-guide

- How did you experience the time from diagnosis to the start of treatment?
    - Tags: Hospital-reception, appointments/logistics, information about up-coming treatment, support/care, personal preparations (physical, mental, social, other?)

- How did you experience conducting daily radiotherapy for six weeks?
    - Tags: Appointments/logistics, side-effects (information, development, support/care, personal management/coping strategies)
    - Did you miss any kind of follow-up? Nutritional support (diet, oral nutritional supplements, tube-feeding), physical, mental, other?

- How do you experience the situation now after treatment completion?
    - Tags: Side-effects (intensity, management, support/care, information), nutrition/diet, other?

- Finally, is there anything you find relevant to talk about that we didn't address?