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NUTRITIONAL FOLLOW-UP OF PATIENTS WITH HEAD AND NECK CANCER

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ABSTRACT

Head and neck (H&N) cancer constitutes approximately 5.1% of all cancers worldwide and 2.2% in Sweden. It is a heterogeneous group of malignant tumours with differences in natural history and prognosis. The treatment is often multiple, where the main treatment modalities are external beam radiotherapy (RT) and surgery. For many patients with H&N cancer, nutritional problems are an immense and complex range of challenges. If the patient cannot swallow and the gastrointestinal tract is functioning normally, nutritional support is mainly given with enteral nutrition. The most common way to administer enteral feeding is via a polyurethane nasogastric feeding tube (NGT) or via a percutaneous endoscopic gastrostomy (PEG) tube. In this thesis different cohorts of patients with H&N cancer have been studied with the ultimate goal to identify patients in need of nutritional support and to improve nutritional surveillance.

Study I The predictive value of systematic inflammatory and metabolic markers was prospectively studied in 27 patients with H&N cancer undergoing RT. All patients lost body weight with the greatest loss at the end of RT. Highly sensitive C-reactive protein (hsCRP) increased during RT. None of the systemic inflammatory and metabolic markers was significantly associated with body weight loss.

Study II A retrospective study of consecutive patients who received a PEG tube is presented. Of the 171 patients planned for PEG, 156 were successfully carried out, while the attempt failed in 15 patients**.** The duration of PEG tube usage varied considerably. Complications were seen in 42% (n=65) of the patients. Seven patients (5%) had fatal complications related directly or indirectly to the PEG tube placement, 33 patients (21%) had severe complications and 25 patients (16%) had minor complications.

Study III Consecutive patients (n=157) with H&N cancer who were seen for nutritional control at a nurse-led outpatient clinic were evaluated for factors known to contribute to body weight loss. Nadir of body weight was observed at 6 months after RT. In total, 92 patients (59%) with no evidence of residual tumour after treatment received enteral nutrition. Patients that maintained oral feeding did not lose as much body weight as patients who received enteral nutrition. Tumour stage was the only independent predictive factor of maximum body weight loss. Body weight loss was not found to be associated with post-operative infections or mortality.

Study IV Using a descriptive, prospective design, semi-structured interviews about what in life is influenced by disease and feeding (oral feeding, NGT or PEG) were conducted in 41 patients with H&N cancer. More than 50% of the patients manifested eating-related problems. No significant differences in life areas (e.g., fatigue, pain, nutrition and social and family life) influenced by disease were observed over time between oral feeding and enteral nutrition. Furthermore, no differences were noted between patients having NGT or PEG, except that patients with NGT expressed negative views regarding social limitations and patients with PEG felt confined by the tube.

The conclusions of this thesis are that body weight and CRP are valuable variables to follow-up. The risk for complications because of PEG ought to be considered when deciding on an enteral nutrition method of feeding. NGT should be regarded as the first choice of enteral nutrition in patients with an expected limited time of tube feeding, whereas in patients in which prolonged treatment is needed PEG could be the choice for most patients. The extended body weight loss after treatment indicates that a nutritional surveillance programme (e.g. managed by a nurse-led outpatient clinic) is important before, during but not in the least after treatment.

Key worlds: Head and neck cancer, Radiotherapy, Body weight loss, Nutrition, Enteral nutrition, Percutaneous endoscopic gastrostomy (PEG), Nasogastric feeding tube (NGT), SEIQoL, Quality of Life.

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LIST OF PUBLICATIONS

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Percutaneous endoscopic gastrostomy (PEG) – a long-term follow-up study in head and neck cancer patients.
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CONTENTS

LIST OF ABBREVIATIONS

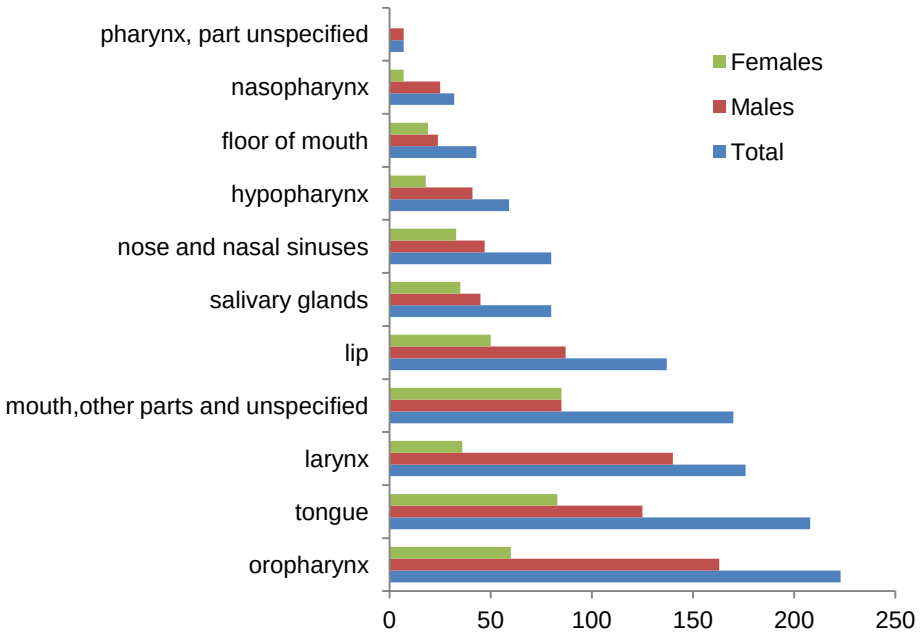
BMI	body mass index
CT	computed tomography
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire-Cancer
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire-Head and Neck
FACT-G	Functional Assessment of Cancer Therapy-General Scale
FACT-H&N	Functional Assessment of Cancer Therapy-Head and Neck Scale
Gy	Grey
H&N	head and neck
HPV	human papilloma virus
HRQoL	Health-Related Quality of Life
hsCRP	highly sensitive C-reactive protein
IGF-1	insulin-like growth factor 1
IGFBP-1	insulin-like growth factor binding protein 1
IGFSD	insulin-like growth factor 1, standard deviation score
MNA	Mini Nutritional Assessment
MUST	Malnutrition Universal Screening Tool
NGT	polyurethane nasogastric feeding tube
PEG	percutaneous endoscopic gastrostomy
PRO	patient-reported outcome
PROM	patient-reported outcome measures
PSS-HN	Performance Status Scale for Head and Neck
QoL	Quality of Life
RT	external beam radiotherapy
SEIQoL	Schedule for the Evaluation of Individual Quality of Life
SEIQoL-DR	Schedule for the Evaluation of Individual Quality of Life-Disease-Related
SEIQoL-DW	Schedule for the Evaluation of Individual Quality of Life-Direct Weighting
SEIQoL-EN	Schedule for the Evaluation of Individual Quality of Life-Enteral Nutrition
SEIQoL-G	Schedule for the Evaluation of Individual Quality of Life-Generic
SGA	Subjective Global Assessment
UICC	Union Internationale Contre le Cancer
UW-QoL	University of Washington Quality of Life Questionnaire
WHO	World Health Organisation

1 INTRODUCTION

1.1 HEAD AND NECK CANCER

Head and neck (H&N) cancer constitutes approximately 5.1% of all cancers worldwide[1] and 2.2% in Sweden[2]. H&N cancer comprises malignant tumours located in the lip, oral cavity, nose, sinuses, nasopharynx, oropharynx, hypopharynx, larynx, salivary glands and ear. Worldwide, 633,000 new cases per year are estimated[1] and in Sweden about1,200 cases are reported annually[3]. In 2009, 1,215 H&N cancer cases were reported in Sweden and of these 789 were males and 426 females. Figure 1 shows the incidence at different anatomical sites[2]. Squamous cell carcinoma is the most common histological type (90%). Other histological types are salivary gland tumours, such as adenocarcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, as well as different types of sarcoma[4,5].

Figure 1. Cancer incidence in 2009 at different anatomical sites in patients with H&N cancer in Sweden[2].



The most commonly known aetiological factors for H&N cancer are cigarette smoking and extensive consumption of alcohol, specially a combination of both[4,5]. Men are affected more often than women, although there is an increasing incidence of women, which is possibly caused by an increase in tobacco and alcohol use. Human papilloma virus (HPV) has also been associated with cancers of the oropharynx and oral cavity[4,6-8], with an increasing trend for HPV-positive oropharyngeal cancer. Bad oral health, diet with a low intake of fruits and vegetables, betel chewing and exposure to high levels of wood dust or chemicals are other risk factors[4].

The prognosis depends on the location of the tumour, tumour extension and spread, as well as several individual factors. Patients with co-morbidity have been shown to have poorer overall survival[9,10]. The primary cancer can spread to surrounding tissues and

often metastasize to cervical lymph nodes[5]. The presence of cervical lymph node metastases represents a prognostic factor that influences outcome[11,12]. Distant metastases are unusual at the time of diagnosis[5]. The TNM staging system, according to the Union Internationale Contre le Cancer (UICC), is used in Europe for classification of tumour and treatment decisions but also to predict prognosis. T describes the size of the primary tumour (range T0-T4), N describes regional lymph node involvement (range N0-N3) and M describes distant metastases (range 0=no metastasis to 1=metastasis). X is used when classification cannot be resolved. Subsequent to the TNM classification system the stage of the cancer disease ranged from 0 to IV.

H&N cancer is a heterogeneous group of malignant tumours with differences in natural history and prognosis. The prognosis for survival has not changed in the past decades as patients still often have loco-regional recurrences, distant metastases and second primary tumours[7] . Early disease stage often presents vague symptoms and minimal physical findings[4] and is presented in proximately one third of all patients with H&N cancer[7,13]. Subsequently, two thirds of all patients presented with H&N cancer have advanced disease (stage III and IV)[13]. In general, the 5-year survival rate is about 60%[13,14], although it differs markedly depending on diagnose and not least stage. The 5-year survival rate in patients with oropharynx cancer and early stage is 80-85% (advanced stage is 30-60%), patients with hypopharynx and early stage 70-90% (advanced stage 15-30%) and patients with nasopharynx early stage 80% (advanced stage 20-60%)[4].

1.1.1 Treatment

Treatment can have either curative or palliative intention[15]. Treatment is based on type and location of the tumour, but the patients' general health condition has to be considered as well[10,13]. Treatment is often multiple but the main treatment modalities are external beam radiotherapy (RT) and surgery, although there is an increasing role for chemotherapy[4] and pharmacological treatment with cetuximab[13,16,17]. Brachytherapy is used in a small scale[5,13]. Patients with early stage oral cancer are usually treated with surgical resection to avoid toxic effects of RT. Patients with laryngeal cancer are treated with either surgery or RT, or a combination of both. Because it has the best cure rate, the first choice of treatment for patients with oropharyngeal and hypopharyngeal cancer is RT[13]. The treatment regimen of locally advanced disease (stage III and IV) is mainly the combination of RT and surgery. In clinical practice a multidisciplinary approach is preferable[5,13,18] because the treatment is complex, time consuming and requires accurate planning and coordination[19]. In most parts of Sweden treatment modalities are presented to the patient and, if possible, with relatives present at a weekly multidisciplinary team conference[3,18]. The team generally includes oncologists, H&N surgeons, a pathologist, a dentist and a coordination nurse; however, at some H&N cancer centres a radiologist, oral surgeon, plastic surgeon, speech therapist, dietician and almoner are also present[18].

1.1.1.1 External beam radiotherapy

RT can be used as single modality treatment or given pre- or postoperatively. The question of whether to use pre- or postoperative RT has been debated for years. The argument for preoperative RT is that the risk for recurrence may decrease and the

argument for postoperative RT is that it can be negative for surgery, particularly if surgical reconstruction is used and if surgery is delayed longer than 6 weeks from the termination of RT[20]. When comparing pre- and postoperative RT, postoperative RT has shown better loco-regional control but with an increased risk for distant metastases[21]. In Sweden, RT is mainly used as a single modality treatment or given preoperatively. Plan for target volumes and dosages are performed on a three-dimensional treatment planning system. The treatment is given using an isocentric technique with 4–6 MV photon beams from linear accelerators. The RT is either conventional with five daily fractions per week and 1.7–2.5 Grey (Gy) per fraction (total dose 50–68 Gy) or accelerated twice daily with a fraction size of 1.1 and 2 Gy (total tumour dose 68 Gy)[22].

1.1.1.2 Surgery

Surgery can be used alone in early-stage cancer or in combination with other treatment modalities. Surgery with radical tumour extirpation is performed with the intent to cure the patient. The primary neoplasm is removed with a marginal of surrounding tissue, sometimes with the expense of functions, even though the surgeons strive to minimise morbidity and disfiguration to the patient[5,13,18]. Surgical reconstruction is used when required, with the attempt to improve cosmetic deformity and to restore functions (e.g., oestecutaneos flap for reconstruction of the mandible and radical forearm flap for reconstruction of the floor of the mouth and hypopharynx)[23]. Cervical lymph node metastasis can be treated with neck dissection (radical, modified radical and selective procedures). It has been shown that patients who have remaining viable tumour cells in the neck after RT have poorer prognosis[11]. In the literature there is a consensus that N-positive neck should be treated with neck dissection, whereas treatment of N-negative neck in oral cancer is under debate. An argument for neck dissection despite a negative N is the risk for micrometastases. Ebrahimi et al.[24] argue that even if N is negative, neck dissection should be performed to improve regional control and overall survival in patients with T1 or T2 oral cancer.

1.1.1.3 Brachytherapy

Brachytherapy, which is used on a small scale and mainly after RT, can only be used on accessible tumours. It can be used on patients with early disease (e.g., lip carcinoma) with good cosmetic and functional results[25], as well as on advanced inoperable recurrent disease in palliation and tumour control[26]. In brachytherapy a catheter implantation in the tumour is performed in the operation theatre under local anaesthesia. A catheter containing radioactive wires is inserted under the skin or mucosal surface sometimes with the help of interactive computed tomography (CT) scanning. A high dose of radiation is given directly to the tumour without passing through normal tissue. Treatment schedules and dose are individually determined depending on earlier dose volumes and tumour location[25,26].

1.1.1.4 Chemotherapy and pharmacological treatment

Chemotherapy is used in palliative care for patients with metastatic disease in that it may temporarily reduce tumour burden[13]. Chemotherapy is also used in combination with RT (especially in locally advanced disease) and can be given as induction/neoadjuvant therapy or concomitant/concurrent/ with RT or adjuvant after

surgery[13,27]. Induction chemotherapy may improve loco-regional control and especially distant control of metastases[27]. Concomitant chemotherapy is used together with RT. RT has a local antitumour activity that may be improved by chemotherapy. Furthermore, chemotherapy may eradicate micrometastasis outside the radiation field[27]. Induction chemotherapy followed by concomitant chemotherapy and RT has been shown to improve complete response in locally advanced unresectable disease[28]. Examples of drugs used in the treatment of H&N cancer are docetaxel, cisplatin and 5-fluorouracil, often administered as two-drug or three-drug combinations[4]. In a randomised study on patients with advanced H&N cancer by Bonner et al.[16] cetuximab, a monoclonal antibody against the extracellular domain of the epidermal growth factor receptor, was explored concurrent with RT and compared with RT alone. The result showed a significant improvement in survival with the additional cetuximab regimen. Since then, concurrent treatment with RT and cetuximab is increasing in the treatment of H&N cancer. Even clinical studies are increasing on which patients respond best to these types of drug. A recent study has shown that 5-year overall survival increases in patients with loco-regional advanced oropharynx, hypopharynx and larynx with the use of cetuximab in combination with RT (45.6% in the cetuximab and RT group compared with 36.4% in the RT alone group)[17]. The benefits with chemotherapy and pharmacological treatment for the patient should always be evaluated against the increased risk for toxic side effects[29,30]. The patients included in this thesis were not given pharmacological treatment with cetuximab.

1.1.2 Sequelae in general

The tumour itself and side effects induced by the treatments of H&N cancer can have a profound impact on the patients' daily life[31-33]. It should be kept in mind that combination treatment with chemotherapy and pharmacological treatment is associated with increased toxicity, which leads to increased sequel. Many of the most basic aspects of daily life (such as eating, respiration, speech and even appearance) are disturbed in many patients with H&N cancer, resulting in considerable challenges for the patients and their families[34-36]. The burden after treatment can affect the patients' daily life, including their relationship with family members and friends, social functions and work ability[34]. Furthermore, many patients may struggle with psychological problems such as depression, anxiety, insecurity and hopelessness[37].

Changes in appearances that are caused by the tumour and surgery may cause embarrassment and changes in self-awareness, self-esteem and self-confidence, largely because for many people the face represents who we are. This situation may lead to isolation, which in turn would affect relationships with family and friends and work ability[34,35]. Breathing difficulties and speech and voice problems can lead to distress, communication problems and difficulties to socialise in a group[34,38]. Shoulder dysfunction that is caused by radical neck dissection surgery may lead to disability[39], causing pain and problems when returning to work[34]. In a study conducted by Buckwalter et al.[40] 91 of 239 (31%) employed patients with H&N cancer had to discontinue work after cancer treatment. Significantly more patients with severe stage and multiple modality treatment did not return to work[40]. Nutritional problems affect many patients with H&N cancer, problems that can lead to body weight loss and undernutrition that are caused by several dysfunctions (e.g., xerostomia, chewing and

swallowing disturbances)[41,42]. Eating problems may lead to increased eating time and altered pleasure of eating[34]. Patients with dysphagia often avoid eating with others and many feel embarrassed at meal times[43]. Problems with eating may not only lead to the loss of eating food but also to the loss of eating with others, i.e. the social aspect of eating[44]. The positive meaning of food intake is changed for patients with H&N cancer treated with RT because they often experience physical problems with eating (e.g., chewing, opening of the mouth, loss of taste and experiencing pain). Physical problems may lead to emotional distress related to changes in appearance because of body weight and muscle loss and dentures not fitting[45]. In a follow-up of 105 patients with H&N cancer 1 year after treatment improvements were seen in variables related to eating in public, normalisation of diet and speech, although the changes were not statistically significant and dysfunctions were still noted. Other areas that are negatively affected by disease and treatment are marital and sexual function, as well as increased alcohol use[46].

Rehabilitation of H&N cancer patients is not common and few randomised trials have been performed to test the efficacy of rehabilitation measures. Rehabilitation can be described in terms of preventative, compensatory and therapeutic exercises and manoeuvres. Optimal rehabilitation planning includes detailed pre-treatment assessment of deglutition. For example, after adequate healing in the post-operative phase, exercises such as the Mendelsohn manoeuvre can be introduced after assessment. In one study by van der Molen et al.[47] patients with different H&N cancer diagnosis (stage III-IV) were randomised into a standard logopedic strengthening exercise programme (n=25) versus an experimental rehabilitation programme using a TheraBite (handheld portable medical device to treat trismus and mandibular hypomobility) (n=24). Although the patients in the experimental group practiced significantly fewer days per week, there results were comparable to the standard group. The methods used on mouth opening and swallowing were feasible and acceptable to the patients. However, patients' mouth opening, oral intake and body weight decreased significantly 10 weeks after chemo-RT despite preventive rehabilitation[47]. In a study of self-management Ahlberg et al.[48] found that a preventive rehabilitation programme did not improve body weight loss and functional impairment despite training instructions on swallowing, mouth opening and neck stiffness.

1.1.3 Nutrition

1.1.3.1 Malnutrition and cancer cachexia

Malnutrition is usually defined as "a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome"[49]. The term malnutrition typically includes undernutrition, overnutrition and nutritional deficiencies. In this thesis, however, malnutrition refers only to undernutrition, which is characterised by changes in body composition and weight, depending mainly on protein and energy loss[50].

Cancer cachexia is caused by reduced oral intake and by catabolic factors secreted by the tumour leading to involuntary body weight loss[51]. Cancer cachexia is clinically characterised by an emaciated face and pale and atrophic skin, substantial loss of subcutaneous fat and skeletal muscle wasting. Sometimes the patients may also have

oedema[52]. The complex interaction between tumour-related factors, inflammation, hypermetabolism, neuro-hormonal changes and proteolytic and lipolytic factors can lead to cancer cachexia[53]. Furthermore, treatment can cause cachexia because of impaired oral intake, which is caused by mucositis, taste alterations, nausea, pain, dysphagia, depression and fatigue[53]. About 70% of all cancer patients in general have cancer cachexia during the terminal phase of the illness[52].

1.1.3.2 Nutritional deterioration in head and neck cancer patients

For many patients with H&N cancer, nutritional problems are overwhelming and complex. Nutritional deterioration is often multifactorial. Loss of body weight is mainly attributed to reduced dietary intake and increased energy expenditure[54]. Biological influences of the tumour, tumour location, surgical defects and side effects of treatment modalities (such as anticipated acute toxicities that are caused by RT and pharmacological treatment) can cause this loss of body weight (as well as dehydration), which can result in malnutrition[54-56]. Other individual factors that can lead to malnutrition include unhealthy feeding habits, excessive alcohol consumption and heavy tobacco use[57].

Prior to treatment, many patients with H&N cancer already have started to lose body weight. The tumour itself can affect the oral function, causing problems of chewing and forming a food bolus and finally swallowing the food[58]. Furthermore, the tumour can cause pain while eating and be aggravated by poorly fitted dentures[42,59].

During treatment, numerous side effects occur, but how frequently they affect the patients depends mainly on treatment modality. During treatment with RT (acute phase), patients can suffer from oral, pharyngeal and oesophageal mucositis, all of which can lead to serious eating problems[60-62]. Oral mucositis usually starts by the end of the first week of RT treatment in the movable mucosa. At this time, erythema is visible and patients have diffuse food burn. At the end of the second week, the symptoms increase. At about 30 Gy, diffuse mucosal ulcerations are common. Continued problems may exist with ulcerative lesions, erythema and pseudomembranes (made of dead cells and fibrinous exudates), which are painful for the patient. Eating orally is usually not possible. The ulcerative lesions resolve spontaneously after 2-4 weeks after the termination of RT[63]. Trotti et al.[62] analysed 33 studies (n=6181) and the mean overall incidence of mucositis was 80%. The side effect of RT can also cause alterations in smell or taste, loss of appetite[42,61] and function loss of the salivary glands, leading to xerostomia and thick saliva. Some of the symptoms may increase by chemotherapy. Chemotherapy and RT can cause nausea, vomiting and diarrhoea [58,61]. During treatment, patients may suffer from constipation that is usually due to, e.g., opioid-based pain medications[61]. Nourissat at al.[64] found that problems with increased constipation at the end of RT lead to a significant lower dietary intake. Late side effects of RT can be that the xerostomia can cause tooth decay and oral infections[5]. Another late side effect can be fibrosis of soft tissues and oesophageal strictures, found in 3.3%, i.e. 59/1805 patients after treatment with RT[65].

Side effects that are caused by radical surgery (e.g., tongue mobility, jaw defects and sensation loss) can result in drooling, difficulties in transporting food to the mouth and

chewing problems. In addition, dysphagia may also occur after radical surgery, which is due to interference in swallowing[5,42,43,58,61]. Late side effects with dysphagia have been seen in half of the patients with H&N cancer after treatment with surgery in conjunction with RT or chemo-RT[43]. In another study all patients with H&N cancer suffered from severe mucositis and dysphagia after concomitant chemo-RT[60].

Loss of body weight can lead to undernutrition, muscle loss and eventually cachexia. This severe condition can lead to interruption in treatment, which may have a negative effect on the treatment outcome[60,66]. Loss of body weight may also affect the patient's well-being, leading to depression, anxiety and fatigue[42,67-70]. Severe body weight loss with undernutrition has been reported to be related to increased mortality in patients with cancer[60,71]. Capuano et al.[60] studied 40 patients with H&N cancer. Six of 17 patients that had a body weight reduction of >20% and one of 23 patients that had a body weight reduction of <20% died within 30 days after the termination of concomitant chemo-RT. The authors found that >20% body weight reduction was significantly correlated with early mortality. In contrast, Rabinovitch et al.[72] demonstrated a poorer 5-year control and survival rate in H&N cancer patients (n=1073) receiving nutritional support during treatment compared with patients who did not receive such support.

1.1.3.3 Nutrition screening and assessment

Nutritional screening is done to identify patients at risk for undernutrition. Patients who are at risk based on the screening should have a nutritional plan in place. Nutritional assessment is carried out when nutritional standard plans are insufficient to prevent metabolic or functional problems[73]. Nutritional screening includes anthropometric measurements, such as body weight and height, arm anthropometry measurements and calculation of body mass index (BMI): weight (kg)/height (m^2). BMI can be classified into the following four categories: BMI 1 = underweight <20 if < 70 years old and <22 if > 70 years old; BMI 2 = normal weight >20-24.9 if < 70 years old and >22-24.9 if > 70 years old; BMI 3 = overweight 25.0- 29.9; and BMI 4 = obese, 30.0 and above for sick adults[74]. Moreover, percentage body weight loss is a sensitive and specific tool to identify undernutrition[54]. Body weight loss of >10% in the past 6 months, body weight loss of >5% in the past 1 month or >1-2% per week are regarded as reliable indicators of malnourishment[75]. Screening tools in general include questions about loss of body weight, ability to eat and the effect of the disease on nutritional deterioration, as well as whether the condition will become worse because of treatment[73]. There are several nutritional screening tools developed to use in hospital and community settings. One example is the Malnutrition Universal Screening Tool (MUST) for adults used to detect undernutrition by looking at BMI, body weight loss in the last 3-6 months and acute disease effects[73,76]. The Mini Nutritional Assessment (MNA) is another tool to detect the presence and the risks of undernutrition in such groups as the elderly and patients with chronic obstructive pulmonary disease by looking at food intake, body weight loss, mobility, physical stress or acute disease, neuropsychological problems and BMI[77-79]. Subjective Global Assessment (SGA) is an instrument that includes questions about body weight changes, changes in dietary intake, gastrointestinal symptoms, functional capacity, disease and physical changes (about loss of fat and muscles and oedema)[80]. Nutritional assessment includes a more detailed examination of metabolic,

nutritional or functional variables. It is a longer process with the goal to make an appropriate care plan by doing a full history, carrying out an examination and taking appropriate laboratory tests[73].

The cancer disease itself has an immune suppressive capacity[81] and in malnourished patients with H&N cancer, the immune system is frequently affected[82]. There are several gastrointestinal hormones that affect the arcuate nucleus of the hypothalamus that may regulate changes in food intake and energy balance[83].

The recommendation of daily calorie intake differs between 25-35 kcal/kg/day[61,71]. The recommendation in Stockholm, Sweden for patients with H&N is 30-35 kcal/kg/day[18]. A more definitive way to estimate calorie needs for each patient is by indirect calorimetry in which a specific device is used to calculate energy expenditure by measuring respiratory gases. This procedure, however, is expensive and time-consuming and therefore it is mainly used only in intensive care units[61]. Protein need is estimated to 1.0 to 1.5 g/kg body weight/day[61].

1.1.3.4 Nutritional management

Initial nutritional treatment often involves food enrichment and oral supplements[50,61]. If the patient cannot swallow but the gastrointestinal tract is functioning, enteral nutrition is the preferred route for nutritional support[84]. There is still lack of a definitive consensus regarding when to initiate enteral nutrition. Clavel et al.[85], for instance, suggest a "wait and see" approach, which means to start enteral nutrition when oral eating is not sufficient, where manifest nutritional deficit occurs or if there is a risk of aspiration. In a study by Corry et al.[86] the indication for enteral nutrition was oral intake of <50% of the calculated daily nutritional requirements or >5 kg loss of body weight. Piquet et al.[87] recommend enteral nutrition before RT in patients with body weight loss of >10% or BMI <20 kg/m² or age >70 years. With a "wait and see" approach, the decision to start enteral nutrition is left to clinical judgment and the patient's preferences[61]. Others advocate that enteral nutrition should begin before treatment ("prophylactic placement"), especially in patients with advanced disease (stage III and IV), as an attempt to reduce body weight loss and minimise hospital stay during RT treatment[88-90]. By using enteral nutrition instead of parenteral nutrition, the integrity of the gut mucosa is maintained and by that atrophy is prevented[42,84]. The most common way to administer enteral nutrition is via a polyurethane nasogastric feeding tube (NGT) or via percutaneous endoscopic gastrostomy (PEG)[42]. To maintain body weight in patients with H&N cancer the two methods have been known to be equally effective[91,92]. Different feeding tubes have been used since the 16th century, but it was after the 1960s that the NGT with a guide wire was developed[93], which is generally inserted transnasally into the stomach. PEG, which was introduced in 1980 by Gauderer, Ponsky and Izant, is an artificial tract placed endoscopically between the stomach and the abdominal surface[94].

NGT is mainly used for short-term use[91,95]. Known complications are pharyngeal ulceration, altered body shape, tube blocking and tube dislodgements, which require replacement and risk for aspiration[42,86,91,95]. On the other hand, it is a comparably easy procedure to replace a NGT and is rather inexpensive[86]. The advantage with PEG is

that it can lead to cosmetic improvements and increased mobility[42,95]. Moreover, it reduces the risk for displacement or blockage and allows bolus feeding. PEG is also associated with risk for complications, such as pain (especially in the first days/weeks after placement), wound infections, bleedings, leakage, gastric/oesophageal perforation, pneumoperitioneum and peritonitis[42,86,95] and tumour implantation in the stoma site[96,97].

Administration of enteral nutrition can be given in different ways. One way is by bolus/syringe feeding in which a formula is slowly injected using a plastic syringe. Another way is by gravity feeding in which a formula from a bag or bottle is gradually infused for approximately 30-60 minutes. A third way is by continuous feeding, which requires a feeding pump to infuse the formula from a bag or bottle[61].

1.1.3.5 Nutritional outcome measurements

Outcome from nutritional care and treatment should be monitored. For this purpose, there are several measurements and observations to use. Examples are to record dietary intake by registering what the patients consume in total energy, other nutrients and fluid, as well as regular measurements of body weight and detection of possible side effects[73]. Another outcome measurement could be maximum body weight loss in which the lowest registered body weight is compared with the first registered pre-treatment body weight expressed in per cent[54]. Maximum body weight loss can also be used when comparing number of complications, mortality and costs.

1.1.4 Nurse-led outpatient clinics

Studies have shown that nurse-led clinics are an important part of care before, during and after treatment because they can provide medical and psychosocial support for the patients and can serve as a component of a clinical quality improvement process in H&N cancer centres[98-100]. Additional important aims are education about different side effects and providing care related to emotional issues[98,100]. The nutritional management of patients with H&N cancer is complex, partly because H&N cancer consists of a number of subgroups. Early identification and treatment of nutritional problems might be of benefit for patients with cancer[101,102]. Furthermore, studies have shown that nutritional management with regular nutritional counselling and oral nutritional supplements can improve the patients' dietary intake of protein and energy[103,104]. For these reasons, nurse-led outpatient clinics are of importance in the management of the patients' nutritional situation.

1.1.5 Quality of Life, Health-Related Quality of Life and Patient Reported Outcome Measures

The concept Quality of Life (QoL) is multidimensional and subjective, with different meanings for different people. QoL often refers to general well-being, including physical, psychological/emotional and social functioning, disease- and treatment-related symptoms and perceived health status[105]. The World Health Organisation (WHO) have provided a definition of QoL as "the individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[106]. Among clinicians and clinical researchers, the concept Health-Related QoL (HRQoL) is often used because

the definition is not as broad as QoL and focuses on health status and disease-related issues. HRQoL is a multi-dimensional concept that includes domains related to physical, psychological, emotional and social well-being and the overall satisfaction of life[107,108]. Today, the concept patient-reported outcome (PRO) is often used instead of QoL. PRO is a measure of any aspect of a patient's health status, where the patients' responses come directly from the patient without interpretation of caregivers or anyone else[109]. The responses can include QoL aspects, symptoms, function and treatment satisfaction. By using patient-reported outcome measures (PROM), the patient's perspective can be conveyed[109]. PROM includes subjective observations of symptoms, functions and HRQoL. It is an essential tool in the overall assessment of chronic illness, including cancer and related treatment[110].

Many different outcomes can be used in QoL studies[105]. The instruments measuring QoL, HRQoL and PROM are mainly generic or condition/disease-specific[105] and they are used together to capture both generic and condition/disease-specific issues. The measurements used are either quantitative or qualitative. Methods are questionnaires, semi-structured interviews and open interviews. Questionnaires have different individual strengths and unique characteristics. A weakness in general with standardised questionnaires is that they focus on problems rather than on the individual perspective. In addition, the patients might be forced to answer questions that are not a problem for the patients and thus many (important) aspects of QoL might be overlooked. The advantages with questionnaires are that they are often easy to administer and self-administered by the patient. Further, all patients are asked the same questions and therefore it is easy to make comparisons between studies[105]. Well-known questionnaires used in studies of patients with H&N cancer include The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), a cancer-specific questionnaire with 30 items relevant for different cancer groups[111]. The EORTC QLQ-C30 is often combined with the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire - Head and Neck (EORTC QLQ-H&N35)[112]. The latter questionnaire includes 35 questions on disease, treatment, related symptoms, social functions and sexuality. The University of Washington Quality of Life questionnaire (UW-QoL) version 4 is another questionnaire that looks at the clinical outcome from the H&N cancer patient's perspective. It consists of 15 questions: 12 disease-specific and 3 general and a section where patients can provide comments[113-115]. The Performance Status Scale for Head and Neck (PSS-HN) cancer patients is an instrument to measure speech and swallowing outcome. It consists of three subscales: normalcy of diet, understandability of speech and eating in public[116]. The Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT-H&N) is a questionnaire containing 12 disease-specific items to be used together with FACT-General (FACT-G), which includes 27 questions in four domains: Physical, Social/family, Emotional and Functional[117]. Instead of using these standardised QoL questionnaires, there are individual-based instruments to apply such as the Schedule for the Evaluation of Individual Quality of Life – Direct Weighting (SEIQoL-DW). The SEIQoL instrument has not previously been used on patients with H&N cancer. SEIQoL is a semi-structured interview-based questionnaire module developed to assess individual perspectives of QoL without using predetermined variables. The questionnaire assesses both positive and negative aspects of life[118,119].

1.2 RATIONALE

Patients with H&N cancer are known to have specific as well as substantial needs. They are known to be a challenging patient group for health care professionals because central parts of their identity and fundamental functions (e.g., drinking, eating, speaking and breathing) may be affected by the disease and by side effects of the treatment. Nutritional problems are acknowledged as very important to prevent complications, recurrence and even death. Furthermore, nutritional problems may lead to decreased QoL. Assessments of the patient's nutritional status, nutritional therapy and outcome measures are important to use in this patient group. It would be of great interest to be able to predict which patients will actually lose body weight with the risk for undernutrition. Different metabolic measures of inflammation and metabolism could therefore be of interest to examine. Severe body weight loss can lead to treatment interruptions, which could have a negative effect on disease outcome. Several interventions in the form of regular follow-up and weekly measurements of body weight during treatment are suggested to be important in this patient group. However, the importance of nutritional management in the long-term is unknown in this group. Today, there is an ongoing debate (clinical and academic) about whether to use enteral nutrition in patients with H&N cancer and there is no consensus as to when enteral nutrition should be initiated and which enteral nutrition method to use (NGT or PEG). Although the literature seems to favour the use of PEG over NGT, scientific evidence is scarce regarding this issue. In this debate the patients' personal experience of NGT or PEG is seldom included. It would be of interest in relation to the decision-making process to have more information about patients' experiences of having NGT or PEG.

2 AIMS

General aim

The ultimate goal of this thesis is to identify patients in need of nutritional support and to improve nutritional surveillance for patients with H&N cancer. The following specific aims are proposed to move toward that goal:

Study I

1. To explore the predictive value of systematic inflammatory and metabolic markers in patients with H&N cancer undergoing RT.

Study II

1. To describe the incidence of fatal, severe and minor complications in patients with H&N cancer receiving PEG at a teaching hospital from 1992-1999.
2. To describe the duration of PEG use and the long-term survival rate after PEG tube placement in patients with H&N cancer.
3. To evaluate whether the complication rate is related to the method of PEG tube placement.

Study III

1. To evaluate if therapeutic approach, tumour site, tumour stage, BMI, sex, age and civil status predict body weight loss in H&N cancer patients.
2. To examine the association between body weight loss on postoperative infections and mortality in a cohort of patients with H&N cancer during RT and up to 2 years after the termination of RT.

Study IV

1. To describe patients with H&N cancer from the time of diagnosis up to 3 months after the termination of RT and to assess the patient's views on (1) overall QoL, (2) aspects of life affected by the disease, (3) aspects of life affected by having enteral nutrition or oral feeding and (4) aspects of life affected by the feeding tube (NGT or a PEG tube).

3 METHODS

3.1 SETTING

All patients were recruited from the Department of Otolaryngology and Head and Neck Surgery, Karolinska University Hospital (until 2004 Karolinska Hospital), Stockholm, Sweden. The different anatomical sites of the H&N tumours were the lip, oral cavity, oropharynx, hypopharynx, nasopharynx, larynx and salivary glands. In addition to these tumour sites, there were unknown primary tumours. RT treatment was given mainly as a single modality treatment or preoperatively at Karolinska University Hospital, Radiumhemmet or Karolinska University Hospital Södersjukhuset. Surgery was performed at the Department of Otolaryngology and Head and Neck Surgery.

In 1992, with the experience from previous studies and information about nutritional problems in patients with H&N cancer in connection with surgical treatment, a nurse-led outpatient clinic was started. The aim of the nurse-led outpatient clinic was to support, inform and educate patients about side effects and nutritional problems, as well as to help patients handle social and emotional issues before, during and after treatment. Another important task was to help patients come in contact with other professionals (e.g., physicians and to arrange regular appointments with a registered dietician for assessment of nutritional requirements.

3.2 SAMPLES

Study I. Fifty consecutive patients were asked to participate and 32 agreed and were enrolled into the study. Of these 32 patients, 5 did not fulfil the study, leaving a final sample of 27 patients. They were enrolled shortly after receiving a H&N cancer diagnosis and were planned for RT. Exclusion criteria were a 5% pre-therapy body weight loss at diagnosis, diabetes mellitus, severe alcoholism, evident secondary malignant disease, not fluid in the Swedish language and having dementia or a psychiatric disorder.

Study II. A total of 171 consecutive patients with H&N cancer who were candidates for PEG between January 1992 and December 1999 were included in this retrospective study on complications of PEG insertion. Indications for PEG were swallowing disorders and 5% body weight loss or more or advanced tumour stage with expected nutritional problems.

Study III. Totally, 232 patients with H&N cancer were offered nutritional follow-up at a nurse-led outpatient clinic before start of RT. Of the 232 patients who were offered nutritional follow-up support, 178 (77%) agreed to participate.

Study IV. Seventy-three patients were allocated at a weekly multidisciplinary team conference. Sixty-four of these 73 patients were eligible according to the inclusion criteria (i.e. patients planned to receive RT with a curative intention either as a single modality treatment or in combination with other treatment modalities). Of these 64 patients, 41 agreed to participate and 36 completed the whole study. The number of participants at the three interview occasions was as follows: n=41 at T1, n=38 at T2 and

n=36 at T3. Exclusion criteria were severe alcoholism, unable to speak fluent Swedish and dementia or a psychiatric disorder.

3.3 DATA COLLECTION

Study I. This study involved a follow-up between the time of diagnosis and 4 weeks after the termination of RT. During this period, serial (non-fasting) blood tests were collected and measurement of body weight and assessment of oral mucositis were performed according to the WHO scale for acute and subacute toxicity[120]. The schedule for assessments was pre-RT, at week 3 of RT, at the end of RT and within 2-4 weeks after the termination of RT. The WHO scale for acute and subacute toxicity is graded as follows: Grade 0=no changes; Grade 1=smarting pain, discomfort or erythema; Grade 2= erythema, ulceration, can eat solids; Grade 3=ulceration, requires liquid diet only; and Grade 4=ulceration, alimentation not possible[120]. The following inflammatory and metabolic parameters were analysed in serum: highly sensitive C-reactive protein (hsCRP), an acute-phase protein used to determine small changes in concentrations of inflammation, with a reference range of <2 mg/L, albumin, a protein marker for inflammation and malnutrition, with a reference range of 35-48 g/L and insulin-like growth factor 1 (IGF-1) (µg/L), a liver-synthesised mediator of growth hormone with a number of important metabolic effects and may be associated with malnutrition and systematic inflammation. IGF-1 is an age-dependent marker that decreases with increasing age. Hilding et al.[121] have described a more efficient way to look at aberrations of IGF-1 by using the age-transformed value - insulin-like growth factor I, standard deviation score (IGFSD). Insulin-like growth factor binding protein 1(IGFBP-1) (µg/L) is an IGF-1 binding protein in circulation. Plasma concentrations of the multifunctional peptide hormone ghrelin were also determined. Ghrelin is produced by endocrine cells in the stomach and has been reported to influence appetite, food intake and body weight[122,123]. Ghrelin levels increase during starvation and decrease during re-feeding[122]. Data on ghrelin levels will be presented as ng/L divided by body weight (kg).

Study II. Data in this study were collected from medical records during the period January 1992 to June 2001. The patients were retrospectively followed from diagnosis to June 2001 or until death. PEG has been used since 1992 at Karolinska Hospital. Three PEG methods were used during the study period: 'introducer' technique, 'push' technique and 'pull' method (these methods are described in more detail in study II). A data matrix was developed to collect information about the patient and PEG. The following information was collected: diagnosis, TNM classification, stage, RT, surgery, date of insertion of the PEG, PEG related to RT and surgery, type of PEG method, indications for PEG, duration of PEG, deceased, PEG at time of death, survival after PEG tube placement and complications.

Study III. In this study nutritional data (BMI and body weight) were collected from a nurse-led outpatient clinic from the first clinical visit and up to 2 years after the termination of RT. Body weight was measured at initial diagnostic endoscopy, at start of RT, after 2 weeks of RT, after 4 weeks of RT, at the end of RT, 1 month after RT completion, at the time of surgery, 6 months after the termination of RT and 1-2 years after RT. In addition, information about nutritional support was collected: enteral nutrition or no enteral nutrition and when nutritional support was given to the patient in

relation to the treatment. Demographic and disease-specific data were collected from the medical files.

Study IV. An evaluated Swedish version of the SEIQoL-DW[118,119] was used in this study, including a generic (SEIQoL-G) and a disease-related (SEIQoL-DR) part[124,125]. For the purpose of this study, a third part was developed to capture patient perceptions and problems related to enteral nutrition (SEIQoL-EN). This version has not been used previously. However, it is used in the same way as the other two evaluated versions (SEIQoL-G and SEIQoL-DR). The patients were interviewed at three time points: at start of RT (T1), 2 weeks after the termination of RT (T2) and 3 months after the termination of RT (T3). Three persons trained to use the instrument conducted the interviews. The patients were asked the following questions: In the SEIQoL-G the respondents were asked, "If you think about your life as a whole, what are the most important things, both good and bad, in your life at present, and which are crucial for your QoL?" The respondents could identify as many areas as they wanted. SEIQoL-DR and SEIQoL-EN were used in the same way but with different questions. For SEIQoL-DR, the question was, "If you think about the fact that you will/are being/have been treated for cancer, what things in your life are influenced, both positively and negatively, by the disease?" For SEIQoL-EN, the question was, "If you think about the feeding tube (NGT or PEG), what things in your life are influenced, both positively and negatively, by this experience?" Demographic and clinical data were collected and before each interview, the patient's body weight was measured.

An overview of the design, samples, sex, follow-up and data collection included in the studies are shown in Table I. The age of the patients ranged from 29-85 years.

Table I. Overview of the design, samples, sex, follow-up and data collection for study I-IV.

	Design	**Samples (Male/female)**	**Follow-up**	**Data collection**
Study I	Prospective Explorative	n=27 (19/8)	At diagnosis to 4 weeks after RT	Blood tests Body weight Oral mucositis
Study II	Retrospective Case-control	n=171 (115/56)	From PEG insertion up to 9.5 years or until death	Matrix from medical records
Study III	Retrospective Non-randomised	n=178 (125/53)	First clinical visit to 2 years after RT	Matrix from medical records
Study IV	Prospective Descriptive	n=41 (28/13)	At start of RT 2 weeks after RT 3 months after RT	Semi-structured interviews (SEIQoL)

3.4 ANALYSES

SigmaStat (version 3.0), GraphPad Prism and SPSS software were used for analysis of the data. Statistical significance was set to $p<0.05$ in all four studies.

Study I. All patients could initially eat orally. The patients were divided into three clinical groups based on maximum body weight loss in relation to their initial body weight at diagnosis: <5%, 5-10% and >10%. Results of body weight reduction, oral mucositis and nutrition as well as systematic inflammatory and metabolic markers were described and analysed. Kruskal-Wallis test or the rank sum test was used for comparison between groups and linear regression was applied to determine the association between two variables.

Study II. Treatment, duration of PEG use (in weeks), PEG complications and the PEG method are described. Chi-square analysis was used to compare the complication rate and the relation to the PEG technique used. PEG complications were categorised into three groups: fatal, severe and minor. Patients with fatal complications all died directly related to the PEG procedure or indirectly because of the PEG tube placement that was caused by a non-surgical origin. Severe complications signified major discomfort for the patient, such as subileus, septicaemia, indurations that were caused by the PEG, subcutaneous emphysema around the PEG incision, bleeding, peritonitis, major leakage, wound infections with a positive culture or treated with antibiotics and pneumonia. Minor complications were annoying but of no major threat for the patient and included abdominal pain around the PEG, minor leakage, food regurgitation, granulation tissue, wound that was caused by the PEG, minor bleeding, problems with the PEG material, accidental tube extrusion, occlusion of tube lumen and the PEG attaching itself to the abdominal wall.

Study III. The data were stratified and analysed according to the therapeutic approach and outcome: either RT as single modality treatment with complete response (the RT group) or combined modality treatment with preoperative RT and surgery with radical surgery or no evidence of microscopic tumour (the RT & surgery group). The lowest registered body weight loss during the entire study period was compared with the first pre-treatment body weight and defined as the maximum body weight loss expressed in per cent. Analyses of group differences were done with the unpaired t test or one-way ANOVA. Comparison of proportions between groups was done with Fisher's exact test. To predict maximum body weight loss linear regression was used to analyse the relationship between selected variables (independent variables) and maximum body weight loss in percent (dependent variable). The independent variables used in the linear regression analysis were tumour stage (1=I, 2=II, 3=III, 4=IIII), tumour site (1=larynx, 2=oropharynx or oral cavity), surgery (1=no, 2=yes), sex (1=men, 2=women) and age (numerical).

Study IV. In all, 115 semi-structured interviews were performed. Most interviews (n=93, 81%) were conducted at the Karolinska University Hospital but some interviews at T2 and T3 were performed by telephone (n=22, 19%). The mean interview time was 26 minutes (range 10-60 minutes). Three registered nurses conducted the interviews. Before the interviews were carried out, the nurses' practiced together on how to use the

instrument and then interviews were practiced on patients admitted to the ward. The analysis was performed according to Elo and Kyngäs[126] using content analysis with a deductive approach. Briefly, an unconstrained matrix was used and then categories were determined. From the text of the interviews, a transcript was made and meaning units were derived and coded with specific labels. Next, sub-categories and categories were created from the codes and then selected quotations were used to illustrate the categories. Frequencies of patients that mentioned each category are presented. Fisher's exact test was performed to determine proportional differences between groups. Mann-Whitney's U test was used to test any difference between the groups regarding percentage of body weight loss.

4 ETHICAL CONSIDERATION

All studies were considered by the Regional Ethical Review Board in Stockholm, Sweden. Studies III and IV were reviewed and approved by the Regional Ethical Review Board and studies I and II were judged as clinical development programmes. Permission to carry out the studies was given by the head of the Department of Otolaryngology and Head and Neck Surgery, Karolinska University Hospital (until 2004 Karolinska Hospital), Stockholm, Sweden.

Ethical principles of clinical research are based on several principles, including autonomy, beneficence (i.e. doing good for the patients, meaning that the benefits of the research for the patient has to be considered), the principal of not harming the patient and the justice principle, i.e. equal care for all patients according to the Swedish Research Council[127] and the Declaration of Helsinki[128]. The principle of autonomy was considered in study I, III and IV in that the patients were given oral and written information about the study (including the aim and outline of the research) and information about the researchers involved in the study. Patients' participation was voluntary and confidentiality was maintained. In the prospective studies (study I and IV) the patients could terminate their participation at any time. The patients were given their informed consent in writing in study I and IV and orally in study III. In study II the patients were not informed about this retrospective study. In all the studies the patients' confidentiality was preserved by use of a unique patient identification number. Decoded data were stored and looked at separately from the code list used in these studies. The data in the studies have been presented in a way that the risk of identification of individuals is minimised.

5 RESULTS

5.1 STUDY I

All participants (n=27) lost body weight, with the lowest body weight observed at the end of RT. Eight patients lost <5%, 12 patients from 5-10% and 7 patients >10%. Nineteen patients needed enteral nutrition. The grade of oral mucositis (according to WHO scale) is presented in Table II. At the end of RT, all patients had mucositis.

Table II. Radiation-induced oral mucositis according to the WHO scale in patients with H&N cancer

Occasion	n	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pre-RT	26	26	-	-	-	-
Three weeks of RT	26	7	13	3	3	-
End of RT	27	-	1	2	18	6

The higher the grade, the more severe is the mucositis

For the four assessments occasions (pre-RT, 3 weeks of RT, at end of RT and within 2-4 weeks after the termination of RT) only small changes were observed in IGF-1, IGFBP-1 and ghrelin. A decrease of 18.2% was seen in the albumin concentration. HsCRP significantly increased during RT and decreased during the recovery period, although it did not return to pre-therapy levels. For all patients, maximum hsCRP was 35.8±8.5 mg/l, which can be compared with 5.2±1.0 mg/l at diagnosis (p<0.01). HsCRP of more than 40 mg/l was noted in seven patients. No significant correlation was detected between hsCRP and body weight loss or grade of mucositis. Albumin or mucositis was not related to body weight loss. The regression analysis showed that the metabolic markers were not predictive of body weight loss; nor were the values of the age-transformed IGFSD.

5.2 STUDY II

Totally, 171 attempts to place a PEG tube were made and 156 (91%) were placed successfully, i.e. there were 15 failed attempts. Two of the patients in which the failed attempts occurred died because of the procedure. One patient died because of a needle puncture of the abdominal wall leading to pneumoperitoneum with renal failure and the other one died because of cardiac arrest during the PEG procedure. Of the 156 patients that received PEG, 120 (77%) had tumour stage III or IV. RT was given to 144 (92%) of the 156 patients. The PEG procedure was done in 29 patients before RT, 37 patients during RT and 78 patients after RT.

Twenty-two senior and junior general surgeons performed the PEG procedure. The methods used were the “introducer” technique (n=89), the “pull” method (n=59) and the “push” technique (n=1). Information about which PEG method was used was missing in seven patients. No significant difference in complication rate (including fatal, severe and minor complications) was seen between the two most commonly used methods, i.e. the “introducer” technique and “pull” method (chi-square analysis).

Complications occurred in 65 (42%) of the 156 patients. Seven patients (5%) had fatal complications, 33 (21%) had severe complications and 25 (16%) had minor complications.

Fatal complications were either procedure-related (two with postoperative lethal peritonitis and one with pneumoperitoneum with renal failure) or PEG-related (one with necrotising fasciitis around the PEG site, two with gastrointestinal bleeding and one with paralytic ileus). All seven patients died directly or indirectly (within 12 weeks) because of PEG tube placement.

Severe and minor complications affected 58 (37%) patients, with some patients having more than one complication. Twenty-eight (18%) patients had one complication, 14 (9%) had two, 11 (7%) had three and 5 (3%) had four complications. Numbers and types of the most frequently occurring severe and minor PEG complications are listed in Table III.

Table III. The most frequently occurring severe and minor PEG complications in 156 patients with H&N cancer

Type of complication	n
Severe complications	
Wound infections	26
Major leakage	5
Peritonitis	4
Minor complications	
Abdominal pain around the PEG site	22
Minor leakage	12
Granulation tissues	11
Problems with the PEG material	10

The duration of PEG use varied considerably (see Table IV). Two groups were identified: short-term users [PEG <12 weeks (25%)] and long-term users [PEG >12 weeks (72%)]. Information about duration of PEG use was missing in 3% of the patients. Fifty-seven (37%) patients died within 6 months and 52 had PEG tube at the time of death. One year after PEG tube placement, 47 (30%) patients still needed enteral feeding for nutritional support.

Table IV. Duration of PEG use in 156 patients with H&N cancer

		Dead patients		Living patients	
Duration	n (%)	With PEG	Without PEG	With PEG	Without PEG
<1 week	4 (3)	4			
≥I week but <4 weeks	14 (9)	8	5		1
≥4 weeks but <12 weeks	21 (13)	13	4		4
≥12 weeks but <1 year	65 (42)	55	3		7
≥1 year but <2 years	19 (12)	15			4
≥2 years	28 (18)	17		11	
Information missing	5 (3)				

In the group of short-term users (n=39) fatal, severe and minor complications were seen in 16 patients and in the group of long-term users (n=112) severe and minor complications were seen in 49 patients (no fatal complications occurred in this group). Forty-one per cent of the long-term users had complications that occurred after 12 weeks.

5.3 STUDY III

This cohort (n=178) was stratified according to the therapeutic approach. Sixty of the patients received single modality RT and 118 received combined modality treatment. Of the 60 patients given RT, 52 showed clinical complete response and thereby constituted the RT group. Of the 118 patients receiving combined modality treatment, 105 had radical surgery or no evidence of microscopic tumours after RT and thus constituted the RT and surgery group.

Table V shows the BMI of the RT group and RT and surgery group at time of diagnosis. In the RT group there was no significant difference in maximum body weight loss between the patients with different BMI classifications: BMI 1 (5%), 2 (9%), 3 (6%) and 4 (10%). In the RT and surgery group a significant difference in maximum body weight loss ($p<0.05$) was noted between patients with BMI 1 (7%), 2 (9%), 3 (13%) and 4 (12%).

Table V. BMI at time of diagnosis in the RT group (n=52) and in the RT and surgery group (n=105)

BMI	RT group n (%)	RT and surgery group n (%)
1. Underweight (<70 years=<20/>70 years=<22)	8 (15)	10 (10)
2. Normal weight (>20/>22-24.9)	19 (37)	41 (39)
3. Overweight (25.0-29.9)	17 (33)	38 (36)
4. Obese (>30.0)	8 (15)	16 (15)

Both groups showed an increase of body weight between start of RT up to 2 weeks of RT; thereafter, a decrease was seen for both groups, with the lowest point coming 6 months after RT (Figure 2). Maximum body weight loss was significantly greater in the RT and surgery group than in the RT group.

Figure 2. Mean body weight during the study period for the RT group (n=52) and RT and surgery group (n=105)

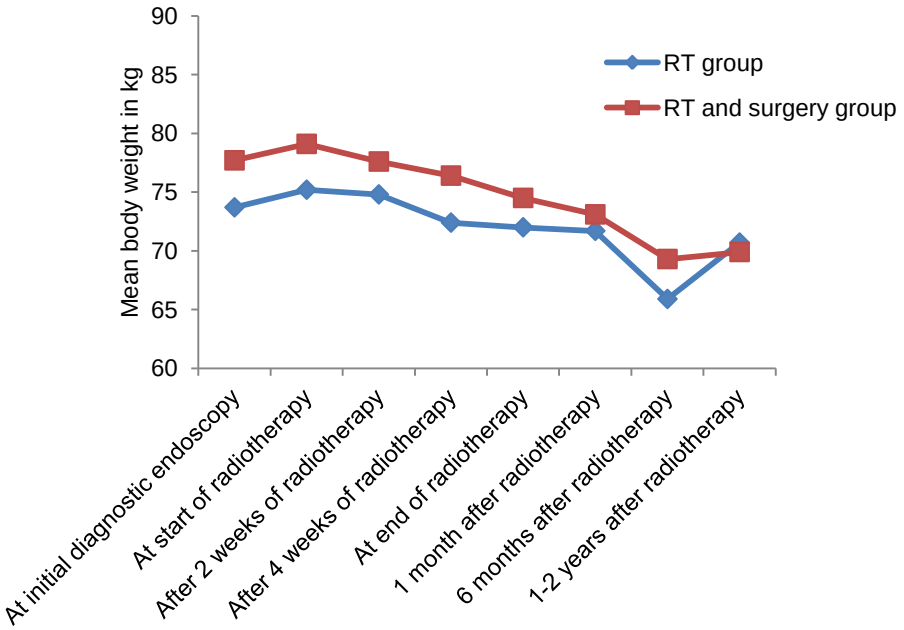


Table VI presents the maximum body weight loss during the study period in the RT group and RT and surgery group. In the RT group 21 patients (40%) needed enteral nutrition and 31 (60%) maintained oral eating. In the RT and surgery group 71 patients (68%) needed enteral nutrition and 34 (32%) did not. This difference between the groups was statistically significant (p=0.002). Mean maximum body weight loss for patients receiving enteral nutrition (n=92) was 13% and per oral feeding (n=65) 6% (p<0.001).

Table VI. Maximum body weight loss in the RT group (n=52) and RT and surgery group (n=105)

Body weight loss	RT group n (%)	RT and surgery group n (%)
Retained/gained	12 (23)	4 (4)
<5%	11 (21)	16 (15)
>5<10%	9 (17)	29 (28)
>10%<20%	16 (31)	44 (42)
≥20%	4 (8)	12 (11)

Maximum body weight loss was not significantly related to risk for postoperative infection or mortality. Predictive factors of maximum body weight loss were diagnosis (oropharynx 11%, oral cavity 10% and larynx 5%, p<0.001), tumour stages (stage I 3%, II 9%, III 10% and IV 12%, p<0.0001) and treatment modality (RT alone 7% and RT with surgery 11%, p<0.005). There were no significant differences in maximum body weight loss between sex, different age groups (29-49, 50-59, 60-69 and 70-85 years old) and civil status (married/cohabiting and living alone).

The linear regression analysis showed that only tumour stage was significantly predictive of maximum body weight loss. In total, the model explained 19.7% of the variance.

5.4 STUDY IV

This study involved two groups of patients, namely those who could maintain oral feeding during the study period (OF group, n=18) and those who received enteral nutrition (EN group, n=23). In the EN group 14 patients received PEG and 9 NGT. At the 3-month follow-up, no significant difference was found in body weight loss between the OF group (median 9.4%) and the EN group (median 6.8%). Median body weight loss in the NGT group was 9.6% and in the PEG group 5.9% (this difference was not statistically significant).

SEIQoL-G. Thirteen categories describe areas that the participants nominated as most important in their life. There were significant differences over time in two of the categories: Interest/leisure activities ($p<0.001$) and Housing/living conditions ($p<0.01$). The two categories were more often mentioned as being important before RT than after treatment. The three most frequently reported categories were Family/relation to family, Personal health and Interest/leisure activities.

SEIQoL-DR. Table VII presents the most common categories and examples of statements describing what is influenced by the disease and number of patients giving statements on any of the three interview occasions. There were no significant differences in the life categories influenced by disease between the OF group and EN group at T2 and T3.

Table VII. SEIQoL-DR. Listed are the most common categories and examples of statements reported by the patients at any of the time points. (T1: start of RT, T2:2 weeks after the termination of RT and T3: 3 months after the termination of RT)

Categories	n	Examples of statements
Health aspects		
Fatigue/loss of energy	24	I am not recovering in the way I thought. I am getting impatient. It affects my daily life - and cleaning the house, etc., is difficult. I am tired both psychologically and physiologically. I get tired when I am walking.
Psychological impact	18	I am psychologically affected and I feel worried. I feel slightly depressed sometimes.
Symptoms		
Pain	20	It hurts inside my mouth and throat and the skin on my neck also hurt.
Xerostomia	14	My mouths is very dry because of the radiotherapy.
Sleeping problems	11	I have sleeping problems and wake up many times during the night. It is hard to fall asleep again.
Skin/mucous impairment	10	I am sore in my mouth as I have blisters and the skin on my neck is red and itchy.
Nutrition		
Eating prob/dysphagia	20	I have problems with chewing and swallowing food.
Eating habits/ taste changes	14	I have no taste. I am eating normal food again but feel it is boring when there is no taste, except sometimes the first bite tastes.
Loss of appetite	9	I have problems with my appetite.
Social restrictions		
Social life	14	Restrictions in my social life, especially in contacts with other people and friends.
Family life	13	I am worried about my family – what they think about the situation.
Work/financial	13	My economy is affected because of the cancer. The money I get when I am sick does not cover our expenses. I have to take from our savings and it affects the whole family. We cannot do fun things with the children that are costly.
Thoughts about disease	22	My whole life is affected by the cancer. I am thinking about it all the time, even though I am trying not to.
Treatment-related concerns	17	The disease changes your entire life. My life is now about treatment, the intake of calories and to kill time in between. It is a full-time job.
Opinions on health care	9	The rehabilitation has taken much longer than what they said it would take, and I am surprised over the fact of having 12 meetings with 9 doctors during my radiotherapy treatment. Insufficient information about side effects and that everything takes such a long time. Also, the appointments with different doctors each time is so frustrating.
Positive aspects		
View of life and oneself	11	I am living in the present and trying to enjoy life (e.g., the spring, flowers and grandchildren).
Thoughts of disease and treatment	11	I am very happy and at ease now when I have talked to the doctor who told me the cancer is cured.
Opinions on health care	9	A good continuity of the nurses. Both the staff and doctors have been answering my questions.

SEIQoL-EN. Table VIII presents examples of statements given by the patients with NGT or PEG. The table further describes the different categories and the total number of patients who made a statement in relation to each category. Significant differences were found in two categories: Confined to a tube ($p<0.05$), which was more frequently mentioned in patients with PEG, and Social limitations ($p<0.01$), which were more commonly referred to by patients with NGT.

Table VIII. SEIQoL-EN. Examples and frequencies of statements in relation to each category given by patients received enteral nutrition by either NGT or PEG tube.

Categories (%)	Examples of statements Sub-categories	Number of patients NGT n=9	PEG n=14
Nutrition			
Nutritional comfort	It is positive. I do not have to panic about meals. I get nutrition without having to worry about being able to swallow.	6 (67)	13 (93)
Maintaining and gaining weight	Positive as I realise that I would have lost weight without it.	4 (44)	5 (36)
Long feeding time	It takes lots of time. To take all three bags in one day is hard to manage.	3 (30)	6 (43)
Missing oral eating	I cannot eat. I miss eating orally. It is hard. I cannot chew.	3 (30)	4 (29)
Losing weight	It is hard to maintain my weight.	0 (0)	2 (14)
Symptoms			
Feel unhygienic	I feel unhygienic – it smells bad.	1 (11)	6 (43)
Gastrointestinal probl	I easily feel nauseous in connection to tube feeding.	4 (44)	2 (14)
Nose and throat probl	My nose feels irritated by the NGT.	2 (22)	1 (7)
Pain	It hurts around the PEG tube.	0 (0)	5 (36)
Function			
Functioning well	I have learned to live with tube feeding	5 (56)	9 (64)
Difficult to handle	Practically, it is difficult to handle the tube, the syringe and tube feeding.	2 (22)	4 (29)
Limitations			
Confined to a tube	It is negative because the tube is in the way. The tube disturbs my sleep. I feel confined to the tube when feeding.	1 (11)	8 (57)
Social limitations	I feel embarrassed to have the NGT in my nose.	6 (67)	1 (7)
Miscellaneous	I only use the PEG in the mornings, so I am hoping to get rid of it soon.	0 (0)	4 (29)

6 DISCUSSION

Eating is not only a vital function that provides us with an abundance of nutrients, it is also something that gives us pleasure and is associated with social activities and traditions[44]. For patients with H&N cancer, are these fundamental aspects of life often affected by disease and treatment. Treatment of eating problems and swallowing difficulties in patients with H&N cancer are a serious challenge to health care professionals. Special attention must be paid before, during and after therapy[98]. There are many factors that have to be considered, such as tumour location and size, mucositis and oesophagitis induced by RT. In addition, functional changes that are caused by surgical resection and individual factors have to be taken into consideration[42].

6.1 ASSESSMENT OF NUTRITION

In the four studies of this thesis all patients received nutritional counselling and were informed that a high-caloric intake is important in order to avoid body weight loss during RT. In addition, most patients were followed-up at a nurse-led outpatient clinic. Because of this approach, many patients gained body weight before the start of RT. Despite this support with nutritional counselling, almost all patients in study I, III and IV suffered to some extent to body weight reduction during and after treatment. Seventy-percent lost >5% in body weight in study I, 73% in study III and 65% in study IV. In all, as much as 70% (study I), 59% (study III) and 56% (study IV) needed enteral nutrition. In study III a nadir of mean body weight loss was seen 6 months after the termination of RT and patients receiving combined modality treatment (RT followed by surgery) had significantly greater body weight loss than patients only given RT. The components underlying body weight loss are complex. To be able to predict body weight loss and eventually identify patients who will suffer from undernutrition specific measures for metabolic changes would be of considerable value because then more efficient nutritional support could be given to patients with the greatest problems. In study I an attempt was made to predict body weight loss using systematic inflammatory and metabolic markers. The purpose was to find markers that could easily become a clinical routine if they could demonstrate a correlation between serum levels and body weight loss. We studied repetitive blood markers that could be important in predicting body weight loss. This was done together with measurement of body weight and assessment of oral mucositis. The results from the blood tests showed that hsCRP increased during RT, most probably as a response to irradiation-induced inflammation. It was found that hsCRP >40 mg/ml indicated a poor prognosis (results not shown). It can be speculated that the hsCRP measurement could have highlighted a biomarker of great clinical importance if a larger cohort had been studied. A few studies on H&N cancer patients have shown a similar pattern of CRP changes during RT[129,130]. CRP may therefore be a reliable and feasible marker to use as an add-on for metabolic monitoring together with grade of mucositis for patients with H&N cancer. In a study on patients with advanced haematological and gastrointestinal cancer prognosis was affected by CRP levels, performance status and energy intake[131]. In contrast, in a study by Kruse et al.[132] on patients with oral cancer no correlation was noted between preoperative CRP levels and development of metastasis or recurrence. In study I the age-transformed value IGFSD[121] was generally low, indicating a

catabolic state. However, the hypothesis that the systematic inflammatory and metabolic markers (hsCRP, albumin, IGF-1, IGFBP-1 and ghrelin) could predict body weight loss was not established. When using univariate analysis to look at different factors to predict body weight loss in study III, tumour site, tumour stage and treatment modality were correlated to maximum body weight loss. However, when applying multivariate analysis the only predictive variable of maximum body weight loss was tumour stage. In a study by Nourissat et al.[64] on patients with H&N cancer tumour site and stage were also found to be associated with body weight loss. In patients with H&N and gastrointestinal tract cancer Ravasco et al.[54] found that the median percentage of body weight loss was significantly greater for patients with stage III or IV than for patients with stage I or II. These findings indicate that nutritional management should make provisions to provide special attention to patients with higher tumour stage and with tumours located in the oral cavity and oropharynx. Even though, in study III, the patients with laryngeal cancer lost less body weight (compared with patients with oropharyngeal and oral cavity cancer), these patients also require nutritional follow-up. This argument is supported by a study in which 44% of the patients with laryngeal cancer (stage I or II) exhibited a weight loss of >5% (n=238)[133]. Mucositis, which can lead to serious eating problems, is a grievous problem for patients with H&N cancer[60-62]. Two major mechanisms (epithelial cell death and inflammatory response) are probably the pathogens underlying irradiation-induced oral mucositis[134]. In study I, we used the WHO scale for acute and subacute toxicity in that it is a simple and reliable method[120] that has been used for over 30 years in clinical care[135]. Oral mucositis was found to gradually increase during RT and at the end of RT all patients in study I were suffering from oral mucositis. Oral mucositis was not related to body weight loss, however.

Several screening tools are available for nutritional follow-up (e.g., MUST[73,76] and MNA[77-79]). These tools are easy to use, but they need complementation. Clinical experience and research on patients with H&N cancer have shown that these patients should always be considered as being at risk for undernutrition[54,58]. Consequently, there are other more complex issues that need to be considered than what is captured by screening instruments and therefore a more prominent nutritional assessment is required to make an appropriate nutritional care plan. The most important nutritional assessments verified in study I are measurements of body weight and assessment of oral mucositis. The laboratory test to consider is CRP in that other blood markers seem to have less value in this patient group. Questions that need to be addressed to each patient concerns whether there are problems in transporting food in the oral cavity, chewing problems, alteration in smell and taste, loss of appetite, xerostomia, thick saliva, irritation in the throat, dysphagia, drooling, pain, nausea, vomiting, diarrhoea, constipation and fatigue[42,43,58,61,64,68].

In nutritional assessment and screening BMI is often used to detect undernutrition. The definition of underweight differs. According to WHO, underweight is a BMI of <18.5 kg/m²[136]. To detect underweight in study III we used the Swedish national recommendations for sick adults[74]: BMI <20 kg/m² in patients <70 years old and <22 kg/m² in patients >70 years old. Consequently, fewer patients would have been classified with underweight in study III if the WHO scale had been used. However, in study III a low BMI before the start of treatment was not found to be a risk factor for

body weight loss in patients that received RT and surgery. Thus, the number of patients classified as being underweight will depend on the BMI definition in use. One can, therefore, discuss the value of BMI in detecting undernutrition in patients with H&N cancer. Nevertheless, BMI is a well-established method that is used worldwide to detect undernutrition[73].

6.2 NUTRITIONAL MANAGEMENT

There is an ongoing clinical and scientific debate concerning when enteral nutrition should be initiated in patients with H&N cancer. The two main alternatives of nutritional management are a "wait and see" approach or a "prophylactic" approach. Moreover, there is no consensus on which method to use (i.e. NGT or PEG).

NGT and PEG have both advantages and disadvantages. Complications that are caused by the two methods must be considered in the decision-making process of which method to use in patients with H&N cancer. Clinical studies have different ways of looking at side effects of nutritional treatment. For instance, some studies report all types of complications, whereas others only report fatal and severe side effects. These differences could depend on what researchers consider to count as complications e.g., of complications that is not always reported but rather frequently are existent are pain and granulation tissues. Table VIIII illustrates the different types of complication reported in the literature and in study II. Almost all the PEG tube complications were found in study II (except for some of the severe complications e.g., oesophageal perforation and transcolic puncture).

Table VIIII. NGT and PEG tube complications reported in the literature

NGT[86,137-140]	**PEG tube**[86,88,141-145] and study II
Tube dislodgements	Accidental removal of PEG tube
Tube blocking	Feeding end of tube dislodged/tube migration
Obstruction	Obstructed PEG tube
Rhinorrhea	Minor/major tube leakage
Irritation	Subcutaneous emphysema/abscess at PEG site
Pain	Granulation tissues
Lump sense	Bleedings
Infections	Skin excoriations around PEG site
Pharyngeal ulceration	Pain/discomfort around PEG site
Pulmonary aspiration	Problems with the PEG-material
Pneumothorax	Infections/Pneumonia
Transbronchial intubation	Ileus
	Pneumoperitoneum
	Peritonitis
	Septicaemia
	Indurations caused by PEG
	Gastric perforation/bleedings
	Oesophageal perforation with mediastinitis
	Transcolic puncture
	Bleedings/abscess/necrosis of the abdominal wall

Another important factor when deciding on the most suitable method for enteral feeding is to consider the estimated duration of enteral nutrition and the risk for dysphagia after cancer treatment. A NGT can easily be administered for a short period and thus a PEG insertion can be avoided. Choice of method might affect the duration of enteral feeding and increase the risk for prolonged dysphagia. Enteral nutrition dependence seems to be longer for PEG than for NGT. In study II the PEG duration varied considerably: 25% of the patients had PEG for <12 weeks and 72% had PEG for >12 weeks. Studies show that the median duration of enteral nutrition use with NGT is considerably shorter than use with PEG[86,146]. One reason for prolonged duration for patients with PEG could depend on that PEG is more frequently used in patients with expected long-term use. In the study by Mekhail et al.[146] dysphagia was more persistent among PEG patients than among NGT patients at 3 and 6 months after the start of treatment; however, at 12 months, the difference had disappeared. No significant difference in dysphagia was noted between patients with NGT and PEG in a study by Corry et al.[86]. Rosenthal et al.[147] recommend delaying tube feeding as long as is deemed appropriate to maximize post-RT swallowing recovery. The authors also suggest the use of NGT over PEG tube feeding. Ahlberg et al.[65] found that patients receiving enteral nutrition with NGT or PEG before, during or immediately after RT had more strictures. These authors suggested that continued swallowing might prevent stricture of the upper oesophagus and that enteral nutrition should be selectively used. The risks with NGT concern disturbance in the swallowing process, with PEG the problem is that the patients might be less inclined to swallow. Another thing to consider is the cost for the material and insertion of the feeding tube. According to Corry et al.[86], the costs are almost 10 times higher for PEG than for NGT. Even if NGT dislodges more often, one can insert almost 12 NGTs for the same cost as 1 PEG.

In the four studies of this thesis a "wait and see" approach has been used in which patients with swallowing problems and loss of >5% of their pre-treatment body weight were offered enteral nutrition. Patients with expected nutritional problems that were caused by advanced tumour (stage IV) were also offered enteral nutrition. Numerous authors argue for "prophylactic" enteral nutrition[88-90]. Madhoun et al.[144] studied whether all prophylactic PEGs were used by patients with H&N cancer and found that 35% were never used and 13% were used only on a limited basis (<2 weeks). In addition, the authors found no association for diagnosis, stage and treatment between patients with used and non-used PEG. Considering the complication risks that can occur with enteral nutrition using PEG and that a certain number of PEGs will never be used or used limitedly with a "prophylactic" approach, a "wait and see" approach must be regarded as safer and the better choice in most cases. When deciding on an enteral nutrition method (NGT or PEG), there are several factors to consider, particularly complications. In study II 42% of the patients had fatal, severe or minor PEG complications. Complications reported in the literature are many times of a more serious nature for patients with PEG than for patients with NGT. Another alternative could be to use parenteral nutrition. Comparisons between NGT and parenteral nutrition have shown similar results concerning nutritional outcomes, number of complications, overall recovery, hospital stay and commencement of oral feeding[140]. Disadvantages of the parenteral nutrition method are higher cost, risk for systemic infections[140] and dependence on help when administering parenteral nutrition at the

home of the patient by a registered nurse. All these disadvantages of parenteral nutrition support the use of a NGT.

In the Corry et al.[86] study in which 73 patients received NGT and 32 PEG significant more patients with PEG reported pain and more patients with NGT reported inconvenience and greater impact on body image. In study IV the patients with enteral nutrition were asked how their life was influenced by having PEG or NGT. The results of the study revealed significant differences in two categories. Patients with PEG felt confined to the tube in that they experienced the tube as disturbing and uncomfortable. In addition, patients with PEG reported that it was harder to sleep and that they were required to stay at home. On the other hand, because the tube is visible, patients with NGT experienced embarrassment and felt hindered from participating in social activities. The patients' statements influenced by enteral nutrition in study IV showed few major differences between NGT and PEG use. Thus, from these findings of the patients' experiences, it is not possible to conclude which method to recommend. Importantly, rather often the patients seemed to be aware of its benefits with enteral nutrition and acknowledged the possibility to hinder further body weight loss.

In study IV the patients mentioned a variety of different issues or problems that indicate the importance of asking the patients individually what their expected specific needs are and to follow-up their problems. When discussing which method to employ (i.e. NGT or PEG), risks and benefits and the estimated time of enteral nutrition use should be considered together with each patient's individual preferences and needs. Shared decision making between patient and health care givers is often a goal, even though it is not always easy to apply in clinical practice. One study reported that only 10% of the decisions on PEG were based on shared decision making[148]. In the decision-making process information is crucial in increasing patient autonomy and patient needs and should be based on clinical experiences and scientific results[149]. However, the need for information may vary substantially among patients and their needs may be in conflict with those of the care providers[149]. Numerous studies have reported that shared decision making is preferred among patients[150-152], but a tendency to overvalue the patient's desire to have an active role in decision making has also been reported[153,154]. One should therefore be aware of that the patients may have diversified views regarding how active a role they would like to have in the decision-making process concerning choice of methods for enteral nutrition (i.e. NGT or PEG).

6.3 CLINICAL IMPLICATIONS

The main purpose of enteral nutrition is to provide patients with nutritional ingredients in order to restore body weight loss and avoid undernutrition. The mechanisms underlying body weight loss are often complex in patients with H&N cancer. Silver et al.[155] studied whether changes occur in body mass and body composition in patients with H&N cancer before and after chemo-RT in relation to energy balance, inflammatory state and physical function. Despite intake of energy and macronutrients, the patients experienced lost body weight. It was calculated that almost 72% of the body mass loss was related to loss of lean body mass and 28% to loss of fat. The changes in metabolism, body composition and inflammatory state were associated with reduced physical performance and function. Study III indicated that enteral nutrition

could not restore body weight loss. The patients that could maintain oral feeding lost significantly less body weight than patients who needed enteral nutrition. This finding is in accordance with Nguyen et al.[89] who reported that 98% of 104 patients with H&N cancer that received prophylactic PEG (before chemoradiation) lost weight despite enteral nutrition and nutritional assessment from a dietician. In study IV the patients were followed-up for a shorter time (3 months) and no significant difference in body weight loss was found between patients that could maintain oral feeding and patients with enteral nutrition. Another important issue concerns the implications of body weight loss for patients with H&N cancer. Larsson et al.[44] interviewed patients with H&N cancer about their experiences with eating problems during RT. The eating problems worsened during treatment, which resulted in serious consequences on the daily life of the patients (e.g., loss of meals, eating alone and spending time alone rather than with family and friends). Moreover, the patients experienced tiredness as a result of treatment, changes in self-image and feelings of shame over not being able to eat normally, as well as fears about the negative effects of not being able to eat. However, when looking at the consequences of not being able to have normal nutrient intake, the therapeutic results 1-2 years after termination of treatment did not seem to be influenced by body weight loss (study III). In contrast, Pedruzzi et al.[156] found that loss of body weight was a significant predictor of treatment response for the survival of patients with cancer in the oropharynx. Moreover, in study III the loss of body weight was not identified as a risk factor for postoperative infection, which has been reported as a risk factor elsewhere[42,60]. One should keep in mind that nutritional support has generally been accepted as being beneficial in maintaining the patient's health, but discussions have also questioned the role and benefits of nutritional support. In this respect, Rabinovitch et al.[72] reported poorer 5-year loco-regional control and survival rate in patients with H&N cancer who had received nutritional support.

When comparing the outcome of body weight loss between patients with NGT and PEG, the two methods were shown to be equally effective in study IV and confirmed by Nugent et al.[92]. Six months post-treatment, Corry et al.[86] also showed no significant difference in body weight loss between patients receiving enteral nutrition via a NGT or PEG.

Over half of the patients' statements in study IV had some link to eating and the effect of disease and treatment upon this basic function. There were no major differences in these statements concerning QoL in patients with oral eating and patients with enteral nutrition. This finding is not in line with that of Ringash et al.[157], who found that patients with H&N cancer who received enteral nutrition at some time points during the study period showed significantly less improvement in their QoL (at 6 and at 12 months) than patients not requiring enteral nutrition. QoL in their study was measured by physical (e.g., lack of energy, nausea and pain) and functional well-being (e.g., work, enjoying life and acceptance of the illness). In another study Silander et al.[158] compared patients with advanced H&N cancer (stage III or IV) who either received prophylactic PEG or followed clinical praxis i.e. the patients received standard nutritional advice and support with NGT or PEG when necessary. The most noticeable difference between the prophylactic PEG group and the clinical praxis group was seen 6 months after the start of treatment, where the prophylactic PEG group had a significantly better overall QoL and less body weight loss. The different outcomes

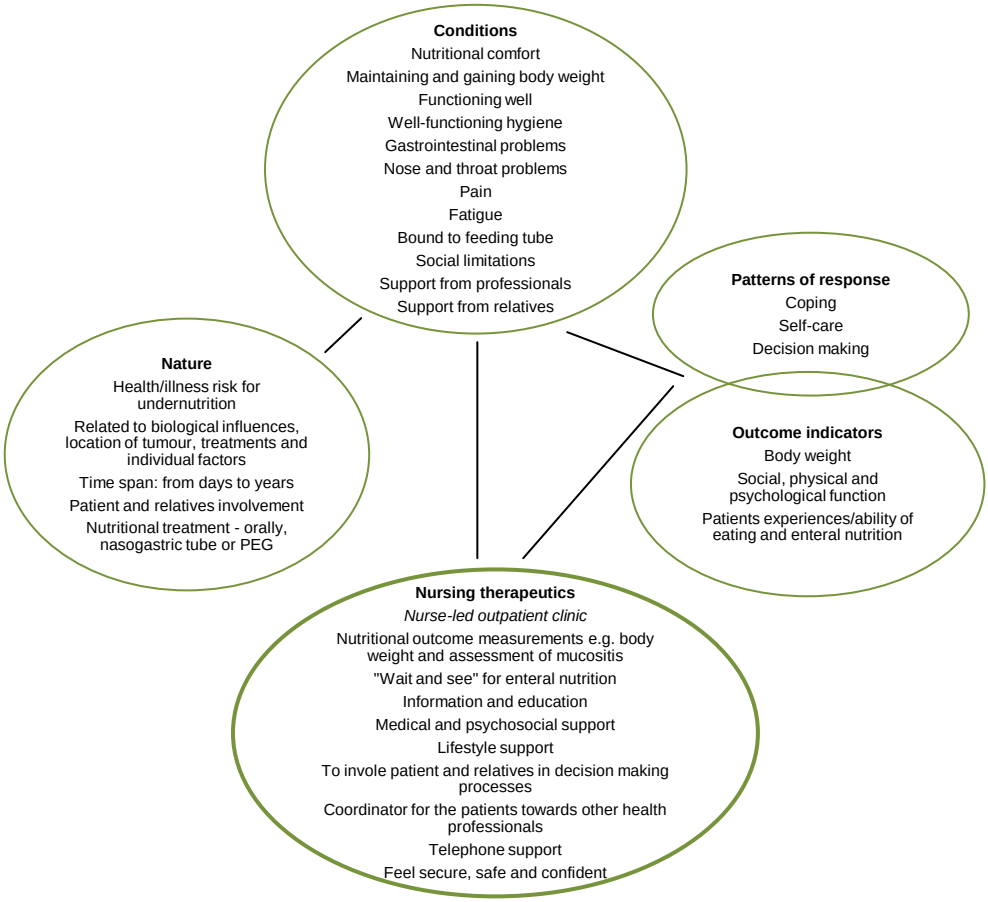
reported in the Ringash et al.[157] and Silander et al.[158] studies and in study IV may be related to the time points in which the studies were conducted. The patients in study IV were followed-up for only 3 months after termination of RT, which could be too short to detect any differences. Moreover, the results could have been affected by the fact that all patients in study IV were given nutritional counselling with follow-up at the nurse-led outpatient clinic.

The framework of the thesis illustrates nutritional areas of importance for patients with H&N cancer. The four studies provide different aspects on the major aims of a nurse-led outpatient clinic at an H&N cancer centre. A basic task involves the measurement of body weight and assessment of oral mucositis as shown in study I. The results from study II imply that a nurse-led outpatient clinic could provide medical and psychosocial support before and after PEG tube placement. This nurse-led support extends to a longer perspective in that it was shown that complications occurred long after PEG tube insertion. Study III demonstrated that nutritional management is an important feature of effective clinical care, regardless of less obvious effects on survival and infection prevention. In study IV the various statements regarding fatigue/loss of energy, pain and eating problems/dysphagia and other dysfunctions show that these symptoms mean different things to the patients and may therefore influence them in different ways. Thus, it is obviously important to have an individual approach towards problems related to nutrition and that the patients are seen at nurse-led outpatient clinic before, during and after treatment.

The eating problems that patients with H&N cancer must confront can be summarised relative to the theory of transition[159]. The transition theory can be used to understand and interpret knowledge in the area of nutrition and H&N cancer. According to Meleis et al.[160], transition theory can be understood as a change from one place, state, subject or stage to another. Transition is both a result in and of changes in life, health, relationships and environments and is characterised by flow and movements over time[160,161]. Transition can also be explained as the way people adapt and respond to new situations in their life over time[160]. Transition is associated with specific situations or life development stages that constitute a period of uncertainty and instability for the individual[160]. Transition is a central concept in nursing in that it focuses on individuals and what they go through in life (e.g., developmental and lifespan transitions, situational transitions, organisational transitions and health-illness transitions). Developmental and lifespan transitions can be about pregnancy to becoming a parent. A situational transition is about various educational and professional roles. Organisational transitions are changes in the economic, social or political context. Health-illness transition can be from diagnosis to recovery, from illness to well-being or well-being to illness. However, it can also be about how individuals and families respond to illness[160,162]. To be able to assist people to go through transition processes related to health, health care professionals have to understand the process[160].Transitions are both complex and multidimensional. A framework for developing a theory or a model of a specific transition process is described by Meleis et al.[160]. They suggest that a transition theory or model should include a description of the nature of the transition conditions (facilitators and inhibitors), patterns of response (progress and outcome indicators) and nursing therapeutics. The model can be used to explain evidence-based knowledge by linking research with clinical experience. In this thesis the transition theory has been inspirational in the process of describing the context of eating problems in relation to H&N cancer from a health-illness transition (Figure 3). The nature of

eating problems is broad and includes risk for undernutrition, influences on biological processes, location of tumour, treatment and individual factors, time factor, the importance of involvement and the need for nutritional treatment. The transition conditions are the importance of nutritional comfort and not losing body weight; however, conditions also refer to the patients' experiences of functioning well, well-functioning hygiene, gastrointestinal problems, nose and throat problems, pain and fatigue. The patients might also feel bound to the tube (when a tube is necessary) and experience social limitations. Furthermore, support from professionals and relatives is important in the transition process. The patients' response to the problems depends on their coping ability, self-care ability and the ability to make decisions. Important outcomes are body weight, physical, social and psychological functioning, patients own experiences and ability in eating and nutritional management. There are indications that a nurse-led outpatient clinic will enhance the patient's daily life. Larsson et al.[98] have shown in a non-randomised study that to make the patient feel secure, safe and confident a nurse-led outpatient clinic is of great importance for the patient, especially before and directly after treatment when the patient often lacks regular contact with the healthcare system. In addition to the tasks identified in the present thesis, another important role for a nurse at a nurse-led outpatient clinic is to work as a co-ordinator for the patient. A nurse co-ordinator could play a central role for both the patient and the healthcare system because communication gaps may occur between patient and different specialists[100]. The nurse co-ordinator could initiate enteral nutrition when needed in collaboration with a physician (a "wait and see" approach towards enteral nutrition). Information and education on different issues are also a very important part of a nurse-led outpatient clinic, including giving medical and psychosocial support. This could be done by repeating information given by the physician, educating the patient on how to take enteral nutrition and providing lifestyle support about the importance of physical training and the dangers of smoking and alcohol abuse. The competence of a nurse co-ordinator implies specific professional knowledge from education and training in the areas of H&N cancer and nutrition. Other health professionals of great importance for this patient group should be linked to the nurse-led outpatient clinic (e.g., physicians, dieticians, almoners and physiotherapists). Telephone support is another important area leading to increased availability and utilisation of resources for the patient and their relatives. Nurse-led telephone follow-up in patients with other diagnosis have shown to be effective in maintaining contact (e.g., to give support and providing information) and reducing the needs of clinical visits[163-165]. The purpose of a nurse-led outpatient clinic is to make the patient feel secure, safe and confident in new situations (e.g., with how to handle the tube).

Figure III. A model of the transition of nutrition in relation to H&N cancer, based on this thesis. Inspired by Meleis[160]



To ensure improvement of the patients QoL follow-up of each patient's individual needs is important before, during and after treatment. A nurse-led outpatient clinic could provide nutritional, lifestyle and psychosocial support, as well as education for the patients. The transition model presented in this thesis could work as a support tool in the management of nutritional problems in patients with H&N cancer but can also be of model for experimental studies (hypothesis testing).

6.4 METHODOLOGICAL CONSIDERATIONS

Because the patients in this thesis had different types of H&N cancer, the treatment modalities differed between groups. The different treatment modalities could have affected some of the present results. However, in a 25-month long-term follow-up study of patients with advanced oropharynx cancer different treatment modalities did not affect pain, swallowing, chewing, speech, salvia, mood and appearance[166]. Another general remark is that almost all patients received nutritional surveillance and when needed nutritional treatment with a "wait and see" approach towards enteral nutrition. This non-strict clinical approach may have been somewhat beneficial for the patients and could have influenced the results in study I, III and IV in an unpredictable way.

One limitation in study I is the small sample size. Fifty patients were asked to enter the study and 32 (64%) agreed to participate. There were five dropouts, leaving 27 eligible patients that completed the study. The reason for this small sample size was the problem of recruiting patients to participate in this study. One major concern for the patients was the number of blood samples collected. Another limitation of study I was that the serial of blood samples collected was of non-fasting origin. The blood samples were taken after the patients had been irradiated which mostly occurred at midday. Furthermore, it would be unethical to have them fast as this is a very vulnerable group of patients who are in need of regular nutrition surveillance to maintain body weight. Daily variations in IGF-1, IGFBP-1 and ghrelin could also occur but this would be impossible to assess because the patients in general were not hospitalised during and after RT treatment.

The contraindications for PEG reported in the literature should be considered, even though problems such as bleedings, tumour obstruction and therapy-induced oesophageal stricture will always be a risk in patients with H&N cancer. In the PEG study (study II) a cohort was constructed of consecutive patients receiving PEG at Karolinska hospital during the period 1992-1999. Of the 171 patients planned for a PEG tube, placements were completed in 156 (91%) Altogether 22 senior and junior general surgeons performed the PEG procedure. Reasons for failed attempts were obstructing tumour, obesity and the patient's poor general condition. Of the 15 failed PEG attempts, there were two deaths because of procedure-related complications. In another study (conducted in 2005-2009, thus after study II, at the Endoscopic unit at the Karolinska University Hospital) by Blomberg et al.[167] the PEG procedure was performed on patients (n=535) mainly with cancer (including H&N cancer) and neurological diseases by an experienced surgeon (from an upper GI team) and assisted by an experienced endoscopist. Despite this, there was still a relatively high insertion failure rate of PEG catheters of 10%. The Blomberg et al.[167] study indicates that a combination of low albumin and high CRP levels increases the risk for mortality after PEG insertion.

Today, the "pull" method is mostly used in the placement of PEG catheters. In study II silicone PEG catheters were primarily used. However, many clinics now use polyurethane PEG catheters. There are many benefits with polyurethane in that the material is thinner but with the same inner diameter of the catheter. Therefore, a smaller French size can be used that could be of benefit to patients with H&N cancer.

Moreover, polyurethane material can be used for a longer period because it is not as complex as silicone, which tends to change over time. Finally, polyurethane material has a further advantage in that there is almost no growth of fungal or bacterial organisms. Despite these advantages of polyurethane material, no differences were found in local complications in a retrospective study comparing 228 patients with polyurethane PEG tubes with 69 patients with silicone PEG tubes[168]. A significant difference, however, was found in tube deterioration that caused PEG removal in 36/228 patients with polyurethane PEG tubes and in 25/69 patients with silicone PEG tubes[168].

Comparisons between retrospective studies are generally difficult to perform in that the data have been collected from previously recorded material, such as in study II and III in the present thesis where cases were taken from nursing and medical records. The disadvantages with retrospective cohort studies are that information is sometimes missing and different clinics/countries can have different ways of documenting information. Furthermore, there is the risk of researcher bias because of the researchers' preconceptions when collecting retrospective material from medical records. In general, results that are more reliable can be obtained by using a prospective design.

The 2-year follow-up of these patients regarding loss of body weight is a unique material (study III). However, the optimal design in studying the value of nutritional surveillance of patients with H&N cancer during and after treatment would be to compare a study group with a control group. On the other hand, to provide nutritional support to one group and not to another during the treatment phase would be unethical. In study III the linear regression model was able to explain 19.7% of the variance. It is plausible that this figure could have been even larger if other variables would have been included, such as grade of mucositis and cigarette smoking. The retrospective material in study III, lack adequate power analysis (as there are two independent groups with repeated measures), which restricts generalisation. In any event, to detect a significant difference with a power of 0.80 and a *p*-value of < 0.05, a power analysis was performed on body weight loss between patients who received enteral nutrition and those that maintained oral feeding. The analysis indicated that 49 patients in each group would be sufficient.

QoL is a broad concept and in study IV the patients' nominated generic areas were rather similar to findings in studies of patients with other diagnoses (e.g., haematological malignancies and prostate cancer)[169,170], as well as similar to what the general population regard as important in life[124,171]. However, the overall QoL is not similar to how the patients' experience symptoms and problems related to the disease and nutritional problems. The SEIQoL instrument version used proved to be a good method to capture areas in life that were affected by disease. The method allows the patients to express their present life situation in their own words. On the other hand, a disadvantage of the SEIQoL instrument is that it is more time-consuming compared with self-reported questionnaires. The latter are easier to administer, may have a lower dropout rate and are self-administered by the patient[105]. Recently, studies with the SEIQoL instrument have been administered by computer (touch screen), which has proven to be a feasible and valid alternative to semi-structured interviews[172,173].

In Table X contents of two standardised QoL tools that are often used in H&N cancer studies (the EORTC-QLQ-C30[111] with the H&N35-module[112] and the UW-QoL[113,115]) are compared with the categories obtained with the SEIQoL disease-related and enteral nutrition versions used in study IV. The most important difference is that the standardised questionnaires do not capture issues pertaining to nutritional problems as expressed by the patients in study IV. Only a few of these categories are mentioned in the EORTC and none in the UW-QoL. The UW-QoL has tried to solve this problem by adding an open-ended question at the end of the questionnaire. One reason why more issues about nutrition were captured in study IV is probably because the patients were specifically asked about what things in life were influenced by NGT or PEG tube feeding. Therefore, from a nutritional perspective, the SEIQoL tool might be a better choice.

Table X. Examples of disease and enteral nutrition-related areas obtained from three QoL tools

Category	SEIQoL-DR and -EN	EORTC- QLQ C30 and H&N35	UW-QoL
Negative aspects			
Health aspects			
Fatigue/loss of energy	X	X	X
Psychological impact	X	X	X
Symptoms			
Pain	X	X	X
Xeorstomia	X	X	X
Sleeping problems	X	X	
Skin/mucous impairment	X	X	
Viscous phlegm	X	X	
Speaking problems	X	X	X
Hearing problems	X		
Tooth extraction	X	X	
Altered body appearance	X	X	X
Loss of hair	X		
Impact on sexual life	X	X	
Felt ill		X	
Loss of breath		X	
Coughing		X	
Nutrition			
Eating problems/dysphagia	X	X	X
Eating habits/taste changes	X	X	X
Loss of appetite	X	X	
Enteral nutrition	X	X	
Losing weight	X	X	
Nutritional supplements		X	
Senses of smell	X	X	
Social restrictions			
Social life	X	X	
Family life	X	X	
Work/financial	X	X	

Thoughts about disease	X		X
Treatment-related concerns	X		
Opinions on health care	X		
Positive aspects			
Social improvements			
Family life	X	X	
Social life	X	X	
View of life and oneself	X		
Thoughts about disease and treatment	X		X
Opinions on health care	X		
Enteral Nutrition			
Nutrition			
Nutritional comfort	X		
Maintaining and gaining weight	X	X	
Long feeding time	X		
Missing oral eating	X		
Losing weight	X	X	
Symptoms			
Feel unhygienic	X		
Gastrointestinal problems	X	X	
Nose and throat problems	X		
Pain	X	X	
Function			
Functioning well	X		
Difficult to handle	X		
Restrictions/Limitations			
Bound to tube	X		
Social limitations	X	X	

SEIQoL-DR --- The Schedule for the Evaluation of Individual Quality of Life-Disease-Related

SEIQoL-EN --- The Schedule for the Evaluation of Individual Quality of Life-Enteral Nutrition

EORTC QLQ-C30--- The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire-Cancer[111]

EORTC-H&N35 --- The European Organization for Research and Treatment with the head and neck cancer-specific module[112]

UW-QoL v4 --- The University of Washington Quality of Life Scale version 4[113,115]

7 GENERAL CONCLUSIONS

The strongest prognostic predictor for maximum body weight loss was tumour stage (body weight loss was greater in patients with more advanced stage tumours). Mean body weight was lowest at about 6 months after termination of RT. Patients who underwent combined modality treatment (RT and surgery) lost significantly more body weight and more often required enteral nutrition than patients who underwent RT only. Regular measurements of body weight, as well as assessment of oral mucositis and CRP were important to carry out in the nutritional follow-up of patients with H&N cancer before, during and after treatment.

More than 50% of the patients manifested eating-related problems that affected their daily life. The patients' level of disease-related QoL was not negatively affected by having enteral nutrition. Suitable candidates for PEG should be identified with respect to the risk for fatal complications. Regardless of type of feeding tube (NGT or PEG), the patients seem to present similar problems. Although inter-individual variations were observed, patients with NGT or PEG expressed positive and negative attitudes towards enteral nutrition. The major differences between NGT and PEG patients were that patients with NGT expressed negative views regarding social limitations and patients with PEG felt confined by the tube. The patient's perspective should be incorporated into the decision-making process in how best to treat and provide nutrition to the target groups.

In conclusion, it is suggested that a nutritional surveillance programme through a nurse-led outpatient clinic might be of great value before, during and not in the least after treatment to support and educate patients during the illness trajectory. With appropriate pre-assessment and high standards of aftercare and follow-up, the risks for feeding tube-related complications might be significantly reduced. NGT should be the first method to consider for enteral nutrition because it is easy to use, relatively safe, cost-effective and acceptable to most patients. Moreover, NGT has a relatively low rate of complications and the length of use seems to be shorter than PEG. On the other hand, PEG is preferred to NGT when prolonged treatment is anticipated or for patients who cannot eat orally because of advanced cancer.

8 FUTURE STUDIES

A high number of different general surgeons performed the PEG procedure (study II), which might have influenced the outcome. After this study was published and presented to the Endoscopic unit at the Karolinska University Hospital, the hospital changed their routine so that a smaller group of specialists now performs the procedure. In addition, they started a nurse-led outpatient clinic. For that reason, it would be of interest to replicate this study prospectively and to determine whether the complication rate differs. Both NGT and PEG have advantages and disadvantages. Consequently, it would be worthwhile to follow-up patients with NGT prospectively in order to determine the complication rate, the duration of NGT and how many patients are switched to PEG.

An experimental randomised study designed to follow-up patients with H&N cancer at a nurse-led outpatient clinic and to develop and test the transition model from this thesis are suggested.

Furthermore, it would be of interest to follow-up patients (e.g., at 6 months, at 1 year and at 2 years) after termination of treatment with the SEIQoL instrument that includes a general, disease-related section and specific sections on enteral nutrition.

9 SUMMARY IN SWEDISH

Nutritionsuppföljning av patienter med huvud- och halscancer
Huvud- och halscancer utgör cirka 5,1 % av alla cancerfall i världen och 2,2 % i Sverige. Det är en heterogen grupp av elakartade solida tumörer lokaliserad till läpp, munhåla, näsa, bihåla, svalget och struphuvudet. Behandlingen består i regel av en kombination av två eller flera olika behandlingsformer, främst extern strålbehandling och kirurgi. Många patienter drabbas av problem orsakade av tumör och behandling. Behandlingsrelaterade besvär och komplikationer kan ha inverkan på de mest fundamentala funktionerna i livet såsom sväljning, andning, tal och utseende. Patienterna kan drabbas av bl.a. smärta i mun och svalg, mukosit (slemhinneinflammation), svårigheter att gapa, minskad salivproduktion och segt sekret i munnen vilket kan medföra betydande tugg- och sväljproblem. Vidare kan patienterna drabbas av lukt- och smakförändringar, illamående, kräkningar, diarré och förstoppning samt fatigue. Besvären kan leda till viktnedgång och undernäring. Patienternas förmåga att äta och tillgodose sig näring är ett stort och komplicerat problem som medför utmaningar i vården av patienter med huvud- och halscancer. Om en patient drabbas av sväljsvårigheter och har en fungerande magtarmkanal, är vanligen enteral nutrition att föredra, antingen via nasogastrisk sond (NGT) eller perkutan endoskopisk gastrostomi (PEG). Det övergripande målet med avhandlingen är att identifiera patienter i behov av nutritionsstöd och förbättra nutritionsövervakningen.

Studie I
Syftet var att förutse viktsförlust hos patienter med huvud- och halscancer som genomgår strålbehandling. Tjugosju patienter följdes prospektivt med undersökning av inflammatoriska och metaboliska markörer i blodprover. Samtliga patienter förlorade vikt under strålbehandlingen. Störst viktförlust hade patienterna i slutet av behandlingen. Alla patienter drabbades även av mukosit. Hög sensitivt C-reaktivt protein (hsCRP) ökade signifikant under strålbehandlingen. Ingen av de inflammatoriska och metaboliska blodproverna var associerad med viktförlust.

Studie II
Syftet var att retrospektivt följa 171 patienter som planerades för PEG utifrån eventuella komplikationer och hur länge patienterna hade PEG. PEG-ingreppet misslyckades på 15 patienter, varav två patienter avled direkt till följd av ingreppet. Totalt lyckades ingreppet på 156 patienter. Av dessa hade 25 % PEG mindre än 12 veckor och 72 % hade PEG mer än 12 veckor. Av de 156 patienter som fick PEG drabbades 42 % av någon typ av komplikation. Fem procent fick komplikationer med dödligt utfall direkt eller indirekt relaterat till ingreppet. Svåra komplikationer drabbade 21 % av patienterna t ex sårinfektion, större läckage och peritonit (bukhinneinflammation). Lättare komplikationer drabbade 16 % såsom smärta runt PEG-området, mindre läckage, granulationsvävnad och problem relaterade till PEG-materialet.

Studie III
Syftet var att retrospektivt hitta faktorer som kan förutse viktförlust och att undersöka om det finns ett samband mellan viktförlust, postoperativa infektioner och dödlighet. Totalt följdes 178 patienter med huvud- och halscancer via en sjuksköterskeledd mottagning. Data från patienternas journaler samlades in från första besöket på kliniken och fram till två år efter avslutad strålbehandling. De patienter som var tumörfria efter

behandlingen (n=157) indelades i två grupper, en stålbehandlingsgrupp och en strålbehandlings- och kirurgigrupp. Totalt gick 73 % av patienterna ner mer än 5 % i vikt. Den största viktförlusten sågs 6 månader efter avslutad strålbehandling. Av patienterna i strålbehandlings- och kirurgigruppen var 68 % i behov av enteral nutrition och i strålbehandlingsgruppen 40 %. De patienter som var i behov av enteral nutrition hade signifikant högre maximal viktförlust jämfört med de patienter som klarade av att inta föda på vanligt vis. Vid en linjär regressionsanalys var tumörstadium den enda oberoende variabeln som kunde förutse viktförlust. Det fanns inget samband mellan maximal viktförlust och postoperativa infektioner. Det fanns heller inget samband mellan maximal viktförlust och dödlighet.

Studie IV
Syftet var att prospektivt via semistrukturerade intervjuer följa patienter med huvud- och halscancer (n=41). Patienterna intervjuades vid tre tillfällen, vid start av strålbehandlingen, två veckor efter avslutad strålbehandling och slutligen tre månader efter avslutad strålbehandling. Patienterna fick beskriva hur de såg på sin allmänna livskvalité och på vilket sätt sjukdomen och näringsintag (försörjning på vanligt vis alternativt via NGT eller PEG) påverkade deras livssituation. Mer än 50 % av patienterna gjorde uttalanden om problem relaterat till ätandet som påverkade dem i vardagen. Patienter som kunde försörja sig på vanligt vis jämfördes med patienter som fick enteral nutrition angående deras utsagor om olika livsområden relaterat till sjukdomen, t ex fatigue, smärta, nutrition, sociala aspekter och familjelivet. Inga väsentliga skillnader mellan grupperna kunde ses. De patienter som erhöll NGT och de patienter som erhöll PEG uttalade inte heller några direkta skillnader i vad som var påverkat i det dagliga livet. Förutom att fler uttalanden gjordes av patienter med NGT angående sociala begränsningar (t ex att de skämdes över att ha sondslangen i ansiktet och att träffa andra) och patienter med PEG gjorde fler uttalanden angående att de kände sig bundna till sondslangen (t ex att sondslangen var i vägen, störde sömnen, att de upplevde bundenhet till att ta sondmat).

Implikationer
Nutritionsstatus hos patienter med huvud- och halscancer kan med fördel kontrolleras via en sjuksköterskeledd mottagning. Avhandlingen visar på viktiga nutritionsaspekter som bör undersökas regelbundet. En modell är gjord i avhandlingen som visar på hur detta skulle kunna se ut.

Konklusion
Tumörstadium kan förutse viktförlust (patienter med mer avancerad tumör förlorade mer i vikt). Största viktförlusten sågs 6 månader efter avslutad strålbehandling. De patienter som fick kombinationsbehandling med strålbehandling och kirurgi förlorade mer i vikt och var i behov av enteral nutrition oftare än de patienter som endast fick strålbehandling. Värdefulla variabler att kontrollera vid nutritionsövervakning av patienter med huvud- och halscancer är vikt, CRP och mukosit.

Mer än 50 % av patienterna uttryckte att de hade problem relaterat till ätandet som påverkade deras dagliga liv. Patienternas sjukdomsrelaterade livskvalité var inte negativt påverkad av enteral nutrition. Patienter med huvud- och halscancer bör vara delaktiga i beslutet av val av nutritionsbehandling.

Vid val av enteral nutritionsmetod bör risken för komplikationer orsakade av PEG övervägas. NGT bör väljas vid korttidsanvändning och PEG vid långtidsanvändning.

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11 REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* Dec 2010;127(12):2893-2917.
2. Social styrelsen. The National Board of Helath and Welfare in Sweden. Cancer incidence in Sweden 2009. Official statistics of Sweden. Statistics - Helath and medical care. *Available from: http://www.socialstyrelsen.se* 2010.
3. Swedish Head and Neck Cancer Register (SweHNCR). Svenskt kvalitets-register för huvud- och halscancer. *Available from: http://www.incanet.se* (In Swedish).
4. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc.* Apr 2008;83(4):489-501.
5. Parker RG, Sherman EJ, Lee SP, Rice DH, Casciato DA. Head and Neck Cancers. In: Casciato DA, Territo MC, eds. *Manual of Clinical Oncology. 6 ed.* Philadelphia: Lippincott Williams & Wilkins; 2008:141-168.
6. Dufour X, Beby-Defaux A, Agius G, Lacau St Guily J. HPV and head and neck cancer. *Eur Ann Otorhinolaryngol Head Neck Dis.* Sep 2011.
7. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. *Nat Rev Cancer.* Jan 2011;11(1):9-22.
8. Mehta V, Yu GP, Schantz SP. Population-based analysis of oral and oropharyngeal carcinoma: changing trends of histopathologic differentiation, survival and patient demographics. *Laryngoscope.* Nov 2010;120(11):2203-2212.
9. Gourin CG, Boyce BJ, Vaught CC, Burkhead LM, Podolsky RH. Effect of comorbidity on post-treatment quality of life scores in patients with head and neck squamous cell carcinoma. *Laryngoscope.* May 2009;119(5):907-914.
10. Paleri V, Wight RG, Silver CE, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. *Oral Oncol.* Oct 2010;46(10):712-719.
11. Ahlberg A, Lagerlund M, Lewin F, Friesland S, Lundgren J. Clinical outcome following radiotherapy and planned neck dissection in N+ head and neck cancer patients. *Acta Otolaryngol.* 2008;128(12):1354-1360.
12. Huang SH, O'Sullivan B, Weinreb I, et al. Patterns of failure and histopathologic outcome predictors following definitive radiotherapy and planned neck dissection with residual disease. *Head Neck.* Sep 2011.
13. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet.* May 17 2008;371(9625):1695-1709.
14. Swedish Cancer Society and The National Board of Health and Welfare in Sweden. Cancer i siffror 2009. *Available from: http://www.socialstyrelsen.se 2009.* (In Swedish).
15. Anniko M, Mercke C, Vedung S. Huvud- och halscancer (head and neck cancer). In Anniko M, eds. *Öron-, näs- och halssjukdomar, huvud- och halskirurgi, 3 ed*. Stockholm, Liber; 2006:321-332. (In Swedish).
16. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* Feb 2006;354(6):567-578.
17. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a

phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* Jan 2010;11(1):21-28.
18. Lind MG, Lewin F, Lundgren J, Nathanson A, Strander H, eds. Vårdprogram Huvud-hals- och esopahguscancer. Diagnostik, behandling och uppföljning i Stockholm-Gotlandregionen (Head-neck and oesphagus cancer. Diagnostics, treatment and follow-up in the Stockholm-Gotland region). Karolinska University Hospital, Stockholm: Oncological Centrum. *Available from: http://www.karolinska.se/oc* 2001. (In Swedish).
19. Sharp L, Lewin F, Hellborg H, Lundgren J, Hemmingsson E, Rutqvist LE. When does my treatment start?--The continuum of care for patients with head and neck cancer. *Radiother Oncol.* Jun 2002;63(3):293-297.
20. Halle M, Bodin I, Tornvall P, Wickman M, Farnebo F, Arnander C. Timing of radiotherapy in head and neck free flap reconstruction--a study of postoperative complications. *J Plast Reconstr Aesthet Surg.* Jul 2009;62(7):889-895.
21. Wennerberg J. Pre versus post-operative radiotherapy of resectable squamous cell carcinoma of the head and neck. *Acta Otolaryngol.* Jul 1995;115(4):465-474.
22. Zackrisson B, Nilsson P, Kjellén E, et al. Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma - The ARTSCAN study. *Radiother Oncol.* Jul 2011;100(1):41-48.
23. Wehage IC, Fansa H. Complex reconstructions in head and neck cancer surgery: decision making. *Head Neck Oncol.* 2011;3:14.
24. Ebrahimi A, Ashford BG, Clark JR. Improved survival with elective neck dissection in thick early-stage oral squamous cell carcinoma. *Head Neck.* Jul 2011.
25. Guibert M, David I, Vergez S, et al. Brachytherapy in Lip Carcinoma: Long-Term Results. *Int J Radiat Oncol Biol Phys.* Dec 2010.
26. Tselis N, Ratka M, Vogt HG, et al. Hypofractionated accelerated CT-guided interstitial ^{192}Ir-HDR-Brachytherapy as re-irradiation in inoperable recurrent cervical lymphadenopathy from head and neck cancer. *Radiother Oncol.* Jan 2011;98(1):57-62.
27. Choong N, Vokes E. Expanding role of the medical oncologist in the management of head and neck cancer. *CA Cancer J Clin.* 2008 Jan-Feb 2008;58(1):32-53.
28. Chitapanarux I, Tharavichitkul E, Lorvidhaya V, Sittitrai P, Pattarasakulchai T. Induction chemotherapy with paclitaxel, ifosfamide, and cisplatin followed by concurrent chemoradiotherapy for unresectable locally advanced head and neck cancer. *Biomed Imaging Interv J.* Jul 2010;6(3):e23.
29. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol.* Sep 2007;25(26):4096-4103.
30. Tejwani A, Wu S, Jia Y, Agulnik M, Millender L, Lacouture ME. Increased risk of high-grade dermatologic toxicities with radiation plus epidermal growth factor receptor inhibitor therapy. *Cancer.* Mar 2009;115(6):1286-1299.
31. Biazevic MG, Antunes JL, Togni J, de Andrade FP, de Carvalho MB, Wünsch-Filho V. Survival and quality of life of patients with oral and oropharyngeal cancer at 1-year follow-up of tumor resection. *J Appl Oral Sci.* 2010 May-Jun 2010;18(3):279-284.
32. Langius A, Bjorvell H, Lind MG. Functional status and coping in patients with oral and pharyngeal cancer before and after surgery. *Head Neck.* Nov-Dec 1994;16(6):559-568.

33. Mallis A, Goumas PD, Mastronikolis NS, et al. Factors influencing quality of life after total laryngectomy: a study of 92 patients. *Eur Rev Med Pharmacol Sci.* Aug 2011;15(8):937-942.
34. Eades M, Chasen M, Bhargava R. Rehabilitation: long-term physical and functional changes following treatment. *Semin Oncol Nurs.* Aug 2009;25(3):222-230.
35. Semple CJ, Sullivan K, Dunwoody L, Kernohan WG. Psychosocial interventions for patients with head and neck cancer: past, present, and future. *Cancer Nurs.* Nov-Dec 2004;27(6):434-441.
36. Sherman AC, Simonton S. Advances in quality of life research among head and neck cancer patients. *Curr Oncol Rep.* May 2010;12(3):208-215.
37. Neilson KA, Pollard AC, Boonzaier AM, et al. Psychological distress (depression and anxiety) in people with head and neck cancers. *Med J Aust.* Sep 2010;193(5 Suppl):S48-51.
38. Swore Fletcher B, Cohen MZ, Schumacher K, Lydiatt W. A Blessing and a Curse: Head and Neck Cancer Survivors' Experiences. *Cancer Nurs.* Jul 2011.
39. Lauchlan DT, McCaul JA, McCarron T, Patil S, McManners J, McGarva J. An exploratory trial of preventative rehabilitation on shoulder disability and quality of life in patients following neck dissection surgery. *Eur J Cancer Care (Engl).* Jan 2011;20(1):113-122.
40. Buckwalter AE, Karnell LH, Smith RB, Christensen AJ, Funk GF. Patient-reported factors associated with discontinuing employment following head and neck cancer treatment. *Arch Otolaryngol Head Neck Surg.* May 2007;133(5):464-470.
41. Hofstra EI, Hofer SO, Nauta JM, Roodenburg JL, Lichtendahl DH. Oral functional outcome after intraoral reconstruction with nasolabial flaps. *Br J Plast Surg.* Mar 2004;57(2):150-155.
42. Batty J. Nutrition. In: Feber T, ed. *Head and Neck Oncology Nursing*. London: Whurr Publishers Ltd; 2000:171-188.
43. García-Peris P, Parón L, Velasco C, et al. Long-term prevalence of oropharyngeal dysphagia in head and neck cancer patients: Impact on quality of life. *Clin Nutr.* Dec 2007;26(6):710-717.
44. Larsson M, Hedelin B, Athlin E. Lived experiences of eating problems for patients with head and neck cancer during radiotherapy. *J Clin Nurs.* Jul 2003;12(4):562-570.
45. McQuestion M, Fitch M, Howell D. The changed meaning of food: Physical, social and emotional loss for patients having received radiation treatment for head and neck cancer. *Eur J Oncol Nurs.* Apr 2011;15(2):145-151.
46. Gritz ER, Carmack CL, de Moor C, et al. First year after head and neck cancer: quality of life. *J Clin Oncol.* Jan 1999;17(1):352-360.
47. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. *Dysphagia.* Jun 2011;26(2):155-170.
48. Ahlberg A, Engström T, Nikolaidis P, et al. Early self-care rehabilitation of head and neck cancer patients. *Acta Otolaryngol.* May 2011;131(5):552-561.
49. Stratton R, Green C, Elia M. *Disease-related malnutrition: an evidence-based approach to treatment.* Oxon, UK: Cabi Publishing; 2003 (page 3).
50. Lochs H, Allison SP, Meier R, et al. Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics. *Clin Nutr.* Apr 2006;25(2):180-186.

51. O'Neill JP, Shaha AR. Nutrition management of patients with malignancies of the head and neck. *Surg Clin North Am.* Jun 2011;91(3):631-639.
52. Bozzetti F. Nutrition support in patients with cancer. In Payne-James J, Grimble G, Silk D, eds. *Artificial Nutrition Support in Clinical Practice* 2 ed. London, Greenwich Medical Media Ltd; 2001:639-680.
53. Blum D, Omlin A, Fearon K, et al. Evolving classification systems for cancer cachexia: ready for clinical practice? *Support Care Cancer.* Mar 2010;18(3):273-279.
54. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol (R Coll Radiol).* Dec 2003;15(8):443-450.
55. Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. *Radiother Oncol.* Feb 2006;78(2):152-158.
56. Newman LA, Vieira F, Schwiezer V, et al. Eating and weight changes following chemoradiation therapy for advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg.* May 1998;124(5):589-592.
57. Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. *Head Neck.* Aug 2007;29(8):779-792.
58. Epstein JB, Huhmann MB. Dietary and nutritional needs of patients undergoing therapy for head and neck cancer. *J Am Dent Assoc.* Oct 2011;142(10):1163-1167.
59. Lees J. Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care (Engl).* Sep 1999;8(3):133-136.
60. Capuano G, Grosso A, Gentile PC, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck.* Apr 2008;30(4):503-508.
61. Hayward MC, Shea AM. Nutritional needs of patients with malignancies of the head and neck. *Semin Oncol Nurs.* Aug 2009;25(3):203-211.
62. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol.* Mar 2003;66(3):253-262.
63. Sonis ST. Oral mucositis. *Anticancer Drugs.* Aug 2011;22(7):607-612.
64. Nourissat A, Bairati I, Fortin A, et al. Factors associated with weight loss during radiotherapy in patients with stage I or II head and neck cancer. *Support Care Cancer.* Mar 2011.
65. Ahlberg A, al-Abany M, Alevronta E, et al. Esophageal stricture after radiotherapy in patients with head and neck cancer: experience of a single institution over 2 treatment periods. *Head Neck.* Apr 2010;32(4):452-461.
66. Elia M, Russell CA, Stratton RJ. Malnutrition in the UK: policies to address the problem. *Proc Nutr Soc.* Nov 2010;69(4):470-476.
67. Barber MD. The pathophysiology and treatment of cancer cachexia. *Nutr Clin Pract.* Aug 2002;17(4):203-209.
68. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. *Head Neck.* Apr 2011;33(4):490-496.
69. Kubrak C, Olson K, Jha N, et al. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of

patients with head and neck cancer before treatment. *Head Neck.* Mar 2010;32(3):290-300.
70. Nguyen NP, Frank C, Moltz CC, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* Mar 2005;61(3):772-778.
71. Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. *Crit Rev Oncol Hematol.* Jun 2000;34(3):137-168.
72. Rabinovitch R, Grant B, Berkey BA, et al. Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: a secondary analysis of RTOG trial 90-03. *Head Neck.* Apr 2006;28(4):287-296.
73. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, Educational and Clinical Practice Committee ErSoPaENE. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* Aug 2003;22(4):415-421.
74. Livsmedelsverket (The National food administration in Sweden). *Mat och näring för sjuka inom vård och omsorg* (Food and nutrition to sick individuals in hospitals and community care). 2003:23. (In Swedish).
75. Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiation therapy. *Otolaryngol Head Neck Surg.* Dec 2001;125(6):645-648.
76. Malnutrition Advisory Group (MAG) a Standing Committeé of BAPEN. Malnutrition Universal Screening Tool (MUST). *Available from: http://www.bapen.org.uk/*
77. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev.* Jan 1996;54(1 Pt 2):S59-65.
78. Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature--What does it tell us? *J Nutr Health Aging.* 2006 Nov-Dec 2006;10(6):466-485; discussion 485-467.
79. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging.* Nov 2009;13(9):782-788.
80. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr.* 1987 Jan-Feb 1987;11(1):8-13.
81. Kerrebijn JD, Simons PJ, Tas M, et al. The effects of thymostimulin on immunological function in patients with head and neck cancer. *Clin Otolaryngol Allied Sci.* Oct 1996;21(5):455-462.
82. van Bokhorst-De van der Schuer MA, von Blomberg-van der Flier BM, Riezebos RK, et al. Differences in immune status between well-nourished and malnourished head and neck cancer patients. *Clin Nutr.* Jun 1998;17(3):107-111.
83. Garcia JM, Garcia-Touza M, Hijazi RA, et al. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *J Clin Endocrinol Metab.* May 2005;90(5):2920-2926.
84. Goodwin WJ, Byers PM. Nutritional management of the head and neck cancer patient. *Med Clin North Am.* May 1993;77(3):597-610.
85. Clavel S, Fortin B, Despres P, et al. Enteral feeding during chemoradiotherapy for advanced head-and-neck cancer: a single-institution experience using a reactive approach. *Int J Radiat Oncol Biol Phys.* Mar 1 2011;79(3):763-769.
86. Corry J, Poon W, McPhee N, et al. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in

patients with head and neck cancer undergoing (chemo)radiation. *Head Neck.* Jul 2009;31(7):867-876.
87. Piquet MA, Ozsahin M, Larpin I, et al. Early nutritional intervention in oropharyngeal cancer patients undergoing radiotherapy. *Support Care Cancer.* Sep 2002;10(6):502-504.
88. Assenat E, Thezenas S, Flori N, et al. Prophylactic Percutaneous Endoscopic Gastrostomy in Patients with Advanced Head and Neck Tumors Treated by Combined Chemoradiotherapy. *J Pain Symptom Manage.* Apr 2011.
89. Nguyen NP, North D, Smith HJ, et al. Safety and effectiveness of prophylactic gastrostomy tubes for head and neck cancer patients undergoing chemoradiation. *Surg Oncol.* Dec 2006;15(4):199-203.
90. Scolapio JS, Spangler PR, Romano MM, McLaughlin MP, Salassa JR. Prophylactic placement of gastrostomy feeding tubes before radiotherapy in patients with head and neck cancer: is it worthwhile? *J Clin Gastroenterol.* Sep 2001;33(3):215-217.
91. Lees J. Nasogastric and percutaneous endoscopic gastrostomy feeding in head and neck cancer patients receiving radiotherapy treatment at a regional oncology unit: a two year study. *Eur J Cancer Care (Engl).* Mar 1997;6(1):45-49.
92. Nugent B, Parker MJ, McIntyre IA. Nasogastric tube feeding and percutaneous endoscopic gastrostomy tube feeding in patients with head and neck cancer. *J Hum Nutr Diet.* Jun 2010;23(3):277-284.
93. Cresci G, Mellinger J. The history of nonsurgical enteral tube feeding access. *Nutr Clin Pract.* Oct 2006;21(5):522-528.
94. Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg.* Dec 1980;15(6):872-875.
95. Payne-James J. Enteral nutrition: tubes and techniques of delivery. In: Payne-James J, Grimble G, Silk D, eds. *Artificial Nutrition Support in Clinical Practice 2 ed*. London: Greenwich Medical Media Ltd; 2001:281-302.
96. Siddiqi AM, Hamilton RD, Minocha A. Malignant seeding of percutaneous endoscopic gastrostomy tract in patient with head and neck cancer. *Am J Med Sci.* Sep 2008;336(3):291-292.
97. Sinclair JJ, Scolapio JS, Stark ME, Hinder RA. Metastasis of head and neck carcinoma to the site of percutaneous endoscopic gastrostomy: case report and literature review. *JPEN J Parenter Enteral Nutr.* 2001 Sep-Oct 2001;25(5):282-285.
98. Larsson M, Hedelin B, Athlin E. A supportive nursing care clinic: conceptions of patients with head and neck cancer. *Eur J Oncol Nurs.* Feb 2007;11(1):49-59.
99. Lewis R, Neal RD, Williams NH, et al. Nurse-led vs. conventional physician-led follow-up for patients with cancer: systematic review. *J Adv Nurs.* Apr 2009;65(4):706-723.
100. Wiederholt PA, Connor NP, Hartig GK, Harari PM. Bridging gaps in multidisciplinary head and neck cancer care: nursing coordination and case management. *Int J Radiat Oncol Biol Phys.* 2007;69(2 Suppl):S88-91.
101. Holder H. Nursing management of nutrition in cancer and palliative care. *Br J Nurs.* Jun 12-25 2003;12(11):667-668, 670, 672-664.
102. Ouwens MM, Hermens RR, Hulscher MM, et al. Impact of an integrated care program for patients with head and neck cancer on the quality of care. *Head Neck.* Jul 2009;31(7):902-910.
103. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients

improves dietary intake compared with standard practice. *J Am Diet Assoc.* Mar 2007;107(3):404-412.
104. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck.* Aug 2005;27(8):659-668.
105. Haberman MR, Bush NE. Quality of life methodological and measurement issues. In: King CR, Hinds PS, eds. *Quality of life from nursing and patient perspectives. Theory, research, practice 3 ed.* London, Jones and Bartlett Learning; 2012:167-195.
106. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med.* Nov 1995;41(10):1403-1409 (page 1405).
107. Doward LC, McKenna SP. Defining patient-reported outcomes. *Value Health.* Sep-Oct 2004;7 Suppl 1:S4-8.
108. Naughton MJ, Shumaker SA. The case for domains of function in quality of life assessment. *Qual Life Res.* 2003;12 Suppl 1:73-80.
109. U.S. Department of Health and Human service FDA Center for Drug Evaluatin and Research et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes.* 2006;4:79.
110. Bateman E, Keefe D. Patient-reported outcomes in supportive care. *Semin Oncol.* Jun 2011;38(3):358-361.
111. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* Mar 3 1993;85(5):365-376.
112. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol.* Mar 1999;17(3):1008-1019.
113. Hassan SJ, Weymuller EA, Jr. Assessment of quality of life in head and neck cancer patients. *Head Neck.* Nov-Dec 1993;15(6):485-496.
114. Laraway DC, Rogers SN. A structured review of journal articles reporting outcomes using the University of Washington Quality of Life Scale. *Br J Oral Maxillofac Surg.* Jan 2011.
115. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA, Jr. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head Neck.* Jun 2002;24(6):521-529.
116. List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer.* Jun 1996;77(11):2294-2301.
117. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* Mar 1993;11(3):570-579.
118. Browne JP, O'Boyle CA, McGee HM, McDonald NJ, Joyce CR. Development of a direct weighting procedure for quality of life domains. *Qual Life Res.* May 1997;6(4):301-309.
119. Hickey AM, Bury G, O'Boyle CA, Bradley F, O'Kelly FD, Shannon W. A new short form individual quality of life measure (SEIQoL-DW): application in a cohort of individuals with HIV/AIDS. *BMJ.* Jul 6 1996;313(7048):29-33.

120. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* Jan 1981;47(1):207-214.
121. Hilding A, Brismar K, Degerblad M, Thorén M, Hall K. Altered relation between circulating levels of insulin-like growth factor-binding protein-1 and insulin in growth hormone-deficient patients and insulin-dependent diabetic patients compared to that in healthy subjects. *J Clin Endocrinol Metab.* Sep 1995;80(9):2646-2652.
122. Levin F, Edholm T, Schmidt PT, et al. Ghrelin stimulates gastric emptying and hunger in normal-weight humans. *J Clin Endocrinol Metab.* Sep 2006;91(9):3296-3302.
123. Peeters TL. Central and peripheral mechanisms by which ghrelin regulates gut motility. *J Physiol Pharmacol.* Dec 2003;54 Suppl 4:95-103.
124. Wettergren L, Björkholm M, Axdorph U, Bowling A, Langius-Eklöf A. Individual quality of life in long-term survivors of Hodgkin's lymphoma--a comparative study. *Qual Life Res.* Aug 2003;12(5):545-554.
125. Wettergren L, Kettis-Lindblad A, Sprangers M, Ring L. The use, feasibility and psychometric properties of an individualised quality-of-life instrument: a systematic review of the SEIQoL-DW. *Qual Life Res.* Aug 2009;18(6):737-746.
126. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs.* Apr 2008;62(1):107-115.
127. Vetenskapsrådet (Swedish Research Council). Riktlinjer för etisk värdering av medicinsk human forskning. Forskningsetisk policy och organisationer i Sverige. (Guidelines for ethical assessment of medical research on humans. Policy and organisation of research ethics in Sweden). *Available from: http://www.vr.se* (In Swedish).
128. WMA Declaration of Hesinki - Ethical Principles for Medical Research Involving Human Subjects. *Available from: http://wma.net*
129. Ki Y, Kim W, Nam J, Kim D, Park D. C-reactive protein levels and radiation-induced mucositis in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* Oct 2009;75(2):393-398.
130. Koc M, Taysi S, Sezen O, Bakan N. Levels of some acute-phase proteins in the serum of patients with cancer during radiotherapy. *Biol Pharm Bull.* Oct 2003;26(10):1494-1497.
131. Paillaud E, Bories PN, Aita SL, et al. Prognostic value of dietary intake and inflammation on survival in patients with advanced cancer: relationship with performance status, pain, and digestive disorders. *Nutr Cancer.* 2003;45(1):30-35.
132. Kruse AL, Luebbers HT, Grätz KW. C-reactive protein levels: a prognostic marker for patients with head and neck cancer? *Head Neck Oncol.* 2010;2:21.
133. Langius JA, Doornaert P, Spreeuwenberg MD, Langendijk JA, Leemans CR, van Bokhorst-de van der Schueren MA. Radiotherapy on the neck nodes predicts severe weight loss in patients with early stage laryngeal cancer. *Radiother Oncol.* Oct 2010;97(1):80-85.
134. Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. *J Support Oncol.* Oct 2007;5(9 Suppl 4):3-11.
135. Quinn B, Potting CM, Stone R, et al. Guidelines for the assessment of oral mucositis in adult chemotherapy, radiotherapy and haematopoietic stem cell transplant patients. *Eur J Cancer.* Jan 2008;44(1):61-72.
136. Global Database on Body Mass Index World Healt Organisation (WHO). Body Mass Index BMI. *Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html*

137. Lo JO, Wu V, Reh D, Nadig S, Wax MK. Diagnosis and management of a misplaced nasogastric tube into the pulmonary pleura. *Arch Otolaryngol Head Neck Surg.* May 2008;134(5):547-550.
138. Marderstein EL, Simmons RL, Ochoa JB. Patient safety: effect of institutional protocols on adverse events related to feeding tube placement in the critically ill. *J Am Coll Surg.* Jul 2004;199(1):39-47; discussion 47-50.
139. Pancorbo-Hidalgo PL, García-Fernandez FP, Ramírez-Pérez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. *J Clin Nurs.* Jul 2001;10(4):482-490.
140. Ryu J, Nam BH, Jung YS. Clinical outcomes comparing parenteral and nasogastric tube nutrition after laryngeal and pharyngeal cancer surgery. *Dysphagia.* Dec 2009;24(4):378-386.
141. Chadha KS, Thatikonda C, Schiff M, Nava H, Sitrin MD. Outcomes of percutaneous endoscopic gastrostomy tube placement using a T-fastener gastropexy device in head and neck and esophageal cancer patients. *Nutr Clin Pract.* Dec 2010;25(6):658-662.
142. Chandu A, Smith AC, Douglas M. Percutaneous endoscopic gastrostomy in patients undergoing resection for oral tumors: a retrospective review of complications and outcomes. *J Oral Maxillofac Surg.* Nov 2003;61(11):1279-1284.
143. Lloyd CJ, Penfold CN. Insertion of percutaneous endoscopic gastrostomy tubes by a maxillofacial surgical team in patients with oropharyngeal cancer. *Br J Oral Maxillofac Surg.* Apr 2002;40(2):122-124.
144. Madhoun MF, Blankenship MM, Blankenship DM, Krempl GA, Tierney WM. Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)? *World J Gastroenterol.* Feb 2011;17(8):1004-1008.
145. Zuercher BF, Grosjean P, Monnier P. Percutaneous endoscopic gastrostomy in head and neck cancer patients: indications, techniques, complications and results. *Eur Arch Otorhinolaryngol.* Apr 2011;268(4):623-629.
146. Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer.* May 2001;91(9):1785-1790.
147. Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *J Clin Oncol.* Jun 2006;24(17):2636-2643.
148. Hanson LC, Garrett JM, Lewis C, Phifer N, Jackman A, Carey TS. Physicians' expectations of benefit from tube feeding. *J Palliat Med.* Oct 2008;11(8):1130-1134.
149. Brundage MD, Feldman-Stewart D, Tishelman C. How do interventions designed to improve provider-patient communication work? Illustrative applications of a framework for communication. *Acta Oncol.* 2010;49(2):136-143.
150. Degner LF, Kristjanson LJ, Bowman D, et al. Information needs and decisional preferences in women with breast cancer. *JAMA.* May 1997;277(18):1485-1492.
151. Gattellari M, Butow PN, Tattersall MH. Sharing decisions in cancer care. *Soc Sci Med.* Jun 2001;52(12):1865-1878.
152. Keating NL, Guadagnoli E, Landrum MB, Borbas C, Weeks JC. Treatment decision making in early-stage breast cancer: should surgeons match patients' desired level of involvement? *J Clin Oncol.* Mar 2002;20(6):1473-1479.

153. Feldman-Stewart D, Brundage MD, Hayter C, et al. What prostate cancer patients should know: variation in professionals' opinions. *Radiother Oncol.* Nov 1998;49(2):111-123.
154. Florin J, Ehrenberg A, Ehnfors M. Patient participation in clinical decision-making in nursing: A comparative study of nurses' and patients' perceptions. *J Clin Nurs.* Dec 2006;15(12):1498-1508.
155. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head Neck.* Oct 2007;29(10):893-900.
156. Pedruzzi PA, Kowalski LP, Nishimoto IN, Oliveira BV, Tironi F, Ramos GH. Analysis of prognostic factors in patients with oropharyngeal squamous cell carcinoma treated with radiotherapy alone or in combination with systemic chemotherapy. *Arch Otolaryngol Head Neck Surg.* Nov 2008;134(11):1196-1204.
157. Ringash J, Lockwood G, O'Sullivan B, et al. Hyperfractionated, accelerated radiotherapy for locally advanced head and neck cancer: quality of life in a prospective phase I/II trial. *Radiother Oncol.* May 2008;87(2):181-187.
158. Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer - a randomized study. *Head Neck.* Mar 3 2011.
159. Meleis AI. *Theoretical nursing: development and progress 5 ed.* Philadelpia, Lippincott Williams & Wilkins; 2012.
160. Meleis AI, Sawyer LM, Im E-O, Hilfinger Messias DA, Schumacher K. Transition theory. In Meleis AI, ed. *Transitions theory. Middle-range and situation-specific theories in nursing research and practice.* New York, Springer Publishing Company; 2010:52-83.
161. Meleis AI, Trangenstein PA. Facilitating transitions: redefinition of the nursing mission. *Nurs Outlook.* 1994 Nov-Dec 1994;42(6):255-259.
162. Schumacher KL, Meleis AI. Transitions: a central concept in nursing. *Image J Nurs Sch.* 1994;26(2):119-127.
163. Cox K, Wilson E. Follow-up for people with cancer: nurse-led services and telephone interventions. *J Adv Nurs.* Jul 2003;43(1):51-61.
164. Al-Dawoud M, Thompson L, Al-Khaffaf H. Evaluation of a telephone clinic for patients with intermittent claudication. *Br J Nurs.* 2009 Apr 23-May 13 2009;18(8):495-497.
165. Kimman ML, Dirksen CD, Voogd AC, et al. Nurse-led telephone follow-up and an educational group programme after breast cancer treatment: results of a 2 × 2 randomised controlled trial. *Eur J Cancer.* May 2011;47(7):1027-1036.
166. Mowry SE, Ho A, Lotempio MM, Sadeghi A, Blackwell KE, Wang MB. Quality of life in advanced oropharyngeal carcinoma after chemoradiation versus surgery and radiation. *Laryngoscope.* Sep 2006;116(9):1589-1593.
167. Blomberg J, Lagergren P, Martin L, Mattsson F, Lagergren J. Albumin and C-reactive protein levels predict short-term mortality after percutaneous endoscopic gastrostomy in a prospective cohort study. *Gastrointest Endosc.* Jan 2011;73(1):29-36.
168. Sartori S, Trevisani L, Nielsen I, Tassinari D, Ceccotti P, Abbasciano V. Longevity of silicone and polyurethane catheters in long-term enteral feeding via percutaneous endoscopic gastrostomy. *Aliment Pharmacol Ther.* Mar 2003;17(6):853-856.

169. Stone PC, Murphy RF, Matar HE, Almerie MQ. Measuring the individual quality of life of patients with prostate cancer. *Prostate Cancer Prostatic Dis.* 2008;11(4):390-396.
170. Wettergren L, Sprangers M, Bjorkholm M, Langius-Eklof A. Quality of life before and one year following stem cell transplantation using an individualized and a standardized instrument. *Psychooncology.* Apr 2008;17(4):338-346.
171. Bowling A. What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life. *Soc Sci Med.* Nov 1995;41(10):1447-1462.
172. Ring L, Lindblad AK, Bendtsen P, Viklund E, Jansson R, Glimelius B. Feasibility and validity of a computer administered version of SEIQoL-DW. *Qual Life Res.* Sep 2006;15(7):1173-1177.
173. Wettergren L, Lindblad AK, Glimelius B, Ring L. Comparing two versions of the Schedule for Evaluation of Individual Quality of Life in patients with advanced cancer. *Acta Oncol.* Jun 2011;50(5):648-652.