Nutritional aspects of advanced Head and Neck Cancer and impact of different factors in Head and Neck Cancer of Unknown Primary

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Cover illustration: Human muscle anatomy of the Face and Neck, realistic 3D rendering. Photo purchased from 123RF.

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ABSTRACT

Background/Aims: Swallowing problems and malnutrition are common in advanced head and neck (HN) cancer. The aim of paper I was to study whether percutaneous endoscopic gastrostomy (PEG) affected the long-term swallowing function. Phase angle (PA) is a measure of the electrical permeability of tissues and has been found to be a prognostic factor in different diseases; the aim of papers II-III was to investigate the PA in HN cancer. Head and neck cancer of unknown primary (HNCUP) is a rare type of HN cancer. The aim of papers IV-V was to investigate the importance of human papillomavirus (HPV), different clinical factors and treatment in HNCUP.

Methods/Results: Paper I: Randomized, controlled, long-term study of 134 patients with advanced HN cancer: half of the patients had a prophylactic PEG, and the remaining patients received nutritional support. There was no significant difference in swallowing function according to the quality of life questionnaires or oral intake scale, esophageal disease, body mass index or survival between the groups. **Papers II-III:** Prospective study of the same patients as in paper I. The patients were measured with bioelectric impedance analysis at diagnosis and during follow-ups. Low value of PA at diagnosis and at 1, 2, 3, 6, 12 and 24 months after the start of treatment and after 8 years were significant negative factors for survival. At diagnosis, a cut-off value at 5.95° provided the best prediction of 5-year survival. The PA decreased after start of treatment, was lowest at 3 months and returned to the baseline value at 12 months. **Paper IV:** Retrospective study of 68 patients with HNCUP treated with curative intent. The tumors were HPV-positive in 69% of the cases. The overall 5-year survival was 82%. Advanced age, negative HPV status and higher N stage were negative factors for survival. **Paper V:** National, multicenter, register study of 260 patients with HNCUP. Treatment with neck dissection and radiation resulted in similar outcome as did (chemo)radiation. Advanced age, worse performance status and higher N stage were negative factors for survival.

Conclusions: The use of PEG in advanced HN cancer does not increase the risk for long-term swallowing problems. The PA at diagnosis and during and after the treatment predicts survival in HN cancer. HPV infection is common in HNCUP and is associated with better survival. Age and N stage are significant prognostic factors for survival. Treatment with neck dissection and radiation seem to result in a similar survival as (chemo)radiation.

Keywords: Head and neck cancer, swallowing problems, percutaneous endoscopic gastrostomy, bioelectrical impedance analysis, phase angle, unknown primary, human papillomavirus, prognostic factors, treatment, survival.

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SAMMANFATTNING PÅ SVENSKA

Huvud-hals (HH) cancer är den sjätte vanligaste cancerformen i västvärlden och ca 1500 personer drabbas årligen i Sverige. Sväljningssvårigheter och undernäring är vanligt vid avancerad HH cancer och beror både på smärta från tumören och biverkningar av behandlingen. Ett vanligt sätt att understödja näringstillförseln hos dessa patienter är att använda en s k perkutan endoskopisk gastrostomi (PEG; anlagd kanal via bukväggen). PEG har visats kunna ge en bättre livskvalitet och motverka undernäring under tumörbehandlingen, men användning av PEG har, i vissa studier, visats kunna ge bestående sväljningssvårigheter.

I studie I studerades 134 patienter med avancerad HH cancer som randomiserades antingen till PEG eller näringsstöd enligt sedvanlig rutin vid diagnos. Sväljningsfunktionen följdes vid totalt 8 tillfällen under ca 8 års tid. Resultatet visade att det inte fanns någon skillnad mellan grupperna avseende: sväljningsfunktion, förekomst av förträngning i matstrupen, kroppsvikt eller överlevnad.

Sammanfattningsvis visade studie I att PEG kan användas hos patienter med HH cancer utan ökad risk för bestående sväljningssvårigheter.

Bioelektrisk impedansanalys studerar kroppsvävnadernas elektriska genomsläpplighet och kan användas för att beräkna den s k fasvinkeln (FV). Värdet på FV har visats ha ett samband med överlevnad vid olika typer av cancer och andra sjukdomar, men är inte väl studerat för HH cancer.

I studie II och III studerades samma patienter med avancerad HH cancer som i studie I. FV mättes vid diagnos och vid ytterligare 7 tillfällen upp till ca 8 år efter diagnos. Analyserna visade att ju lägre värdet var på FV vid diagnos desto sämre överlevnad hade patienterna, sambandet var statistiskt säkerställt. Vid ett FV värde på 5,95° påvisades den största möjligheten för att förutspå överlevnaden. FV sjönk 1, 2, 3 och 6 månader efter behandlingsstart och återvände till ursprungsvärdet efter 12 månader, FV var som lägst efter 3 månader. Studierna visade även att FV värdet vid alla andra mättillfällen under och efter tumörbehandlingen också hade ett statistisk säkerställt samband med överlevnaden hos patienterna.

Sammanfattningsvis visade studierna II och III att patients FV-värde kan prediktera överlevnad vid HH cancer.

Huvud-hals cancer med okänd primärtumör (engelska HNCUP) är en ovanlig typ av HH cancer och betydelsen av olika faktorer och behandlingen är inte väl studerat vid denna sjukdom. Det är oklart vilken tumörbehandling som ger bäst överlevnad. Humant papillomvirus (HPV) är en känd orsak till livmoderhalscancer och har på senare år även visats vara betydelsefull för utvecklingen av cancer i svalget. Intresset för HPV har även ökat för HNCUP men enbart ett fåtal studier har hittills publicerats.

I studie IV studerades 68 patienter med HNCUP som behandlats med botande avsikt. Resultaten visade att HPV var vanligt, det förekom i 69% av tumörerna. 5-årsöverlevnaden var 82%. Ålder, HPV-status och tumörens körtelstadium var statistiskt säkerställda faktorer för överlevnad.

I studie V studerades 260 patienter i Sverige med HNCUP från det nationella kvalitetsregistret för HH cancer. Resultatet visade att behandling med halskörtelutrymning kombinerat med strålbehandling gav jämförbar överlevnad med strålning kombinerat med cellgiftsbehandling. Patientens ålder, allmäntillstånd och tumörens körtelstadium hade ett statistiskt säkert samband med överlevnad.

Sammanfattningsvis visade studie IV och V att HPV är vanligt vid HNCUP och en viktig faktor för överlevnad. Patients ålder, allmäntillstånd och tumörens stadium är viktiga faktorer för överlevnad. Behandling med halskörtelutrymning och strålning ger liknande överlevnad som strål- och cellgiftsbehandling.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E.
Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: A randomized controlled study.
Head Neck. 2017;39(5):908-915.

II. Axelsson L, Silander E, Bosaeus I, Hammerlid E.
Bioelectrical phase angle at diagnosis predicts survival in advanced head and neck cancer.
Manuscript-Submitted.

III. Axelsson L, Silander E, Bosaeus I, Hammerlid E.
Bioelectrical phase angle over time as prognostic factors for survival in advanced head and neck cancer.
Manuscript-Submitted.

IV. Axelsson L, Nyman J, Haugen-Cange H, Bove M, Johansson L, De Lara S, Kovács A, Hammerlid E.
Prognostic factors for head and neck cancer of unknown primary including the impact of human papilloma virus infection.
J Otolaryngol Head Neck Surg. 2017;46(1):45.

V. Axelsson L, Holmberg E, Nyman J, Högmo A, Sjödin H, Gebre-Medhin M, von Beckerath M, Ekberg T, Farnebo L, Talani C, Norberg Spak L, Notstam I, Hammerlid E.
Swedish national register multicenter study on head and neck cancer of unknown primary: Impact of treatment on survival.
Manuscript-Submitted.

TABLE OF CONTENTS

ABBREVIATIONS

AC	Alternating current
ASPEN	American Society for Parenteral and Enteral Nutrition
AUC	Area under the curve
BIA	Bioelectric impedance analysis
BMI	Body mass index
CT	Computer tomography
DC	Direct current
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECE	Extracapsular extension
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire
EORTC-QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Head and Neck 35 questionnaire
ESPEN	The European Society for Parenteral and Enteral Nutrition
FFM	Fat-free mass
FFMI	Fat-free mass index
FFM%	Fat-free mass percent
HN	Head and neck
HNCUP	Head and neck cancer of unknown primary

HPV	Human papillomavirus
HR	Hazard ratio
ISH	In situ hybridization
MRI	Magnetic resonance imaging
NGT	Nasogastric tube
PA	Phase angle
PCR	Polymerase chain reaction
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
ROC	Receiver operating characteristic
R	Resistance
SCC	Squamous cell carcinoma
SD	Standard deviation
SMR	Standardized mortality rates
SPA	Standardized phase angle
SweHNCR	Swedish Head and Neck Cancer Register
TNM	Tumor, Node, Metastasis
WHO	World Health Organization
X_c	Reactance (capacitive)

1 INTRODUCTION

The term *cancer* originates from the same Latin word that means *crab*. Cancer is a term for diseases in which *abnormal cells divide without control* and may *invade nearby tissues*. Cancer cells may also *spread to other parts of the body* through the lymph systems and blood.[1]

Cancer may be grouped according to the type of cell they start in. There are 5 main types:

1. *carcinoma* – cancer that begins in the skin or tissues that line or cover internal organs. There are different subtypes, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma
2. *sarcoma* – cancer that begins in the connective or supportive tissues, such as bone, cartilage, fat, muscle or blood vessels
3. *leukemia* – cancer that starts in blood forming tissues, such as the bone marrow, and causes abnormal blood cells to be produced and enter the blood
4. *lymphoma and myeloma* – cancers that begin in the cells of the immune system
5. *brain and spinal cord cancers* – cancers referred to as central nervous system cancers

Cancers are also, and more commonly, classified according to where they start in the body, such as lung cancer or head and neck (HN) cancer.

1.1 Head and neck cancer

HN cancer comprises cancer in the *lips*, *oral cavity*, *nasal cavity/sinus, naso-, oro-* and *hypopharynx*, *larynx*, *salivary glands* and *cervical unknown primary* (in this thesis referred to as head and neck cancer of unknown primary, HNCUP).

HN cancer accounts for approximately 4% of malignant tumors in the Western world.[2] In 2016, 1514 cases of HN cancer were reported in Sweden.[3] The most common type of HN cancer is oral cancer, followed by oropharyngeal cancer.[3] In Sweden the incidence of HN cancer increases, particularly oropharyngeal cancer.[3] It is well established that a majority of all HN cancer is squamous cell

carcinoma (SCC) or undifferentiated carcinoma. The mean age for patients with HN cancer is approximately *65 years*, and there is a male dominance, in which approximately 2/3 are *males*.[2,3]

Alcohol overconsumption and *tobacco smoking* are established etiologic factors for HN cancer.[4] Excessive exposition for *wood dust* increases the risk for nasal and sinus cancer.[5] *Epstein-Barr virus* (EBV) has been shown to cause nasopharyngeal cancer.[6] *Ultraviolet radiation* is a risk factor for the development of lip cancer.[7] Exposition to *ionizing radiation* has been linked to salivary gland cancer.[8] A *weakened immune system* has been identified in patients with HN cancer.[9] Poor dental status and *oral hygiene* are more common in patients with oral cancer and have been linked to oral and oropharyngeal cancer.[10,11] Other factors suggested as risk factors for HN cancer include poor nutrition, gastroesophageal and laryngopharyngeal reflux diseases and marijuana use.[2] In recent years, *human papillomavirus* (HPV) has been highlighted as an etiologic factor for several types of HN cancer, refer to chapter 1.6.

1.1.1 Classification and prognostic factors

HN cancer is classified according to the *TNM* (Tumor, Node, Metastasis) *classification*.[12] A new version of the TNM classification (8th edition) has recently been released, however, the studies in this thesis follow the former TNM classification (7th edition), which is shown in a summarized form regarding HN cancer in Table 1. The results from the TNM classification are used to *stage* the tumor in one of four stages, I-IV. Classification and staging the tumors aim to: aid *treatment planning*, provide an indication of *prognosis*, assist in the *evaluation* of treatment results, facilitate the *exchange of information* between treatment centers, contribute to continuing *investigations* of human malignancies and support cancer control activities, including through *cancer registries*.[12]

Apart from the tumor TNM classification and stage, there are other *prognostic factors* for survival in HN cancer. The survival differs between the different HN cancer *types*. Patients with lip cancer have the best prognosis for survival (92% relative 5-year survival), whereas hypopharyngeal cancer has the worst prognosis (26% relative 5-year survival).[3] *Age* and the patient's *performance status* are considered prognostic factors in all cancer as well as in HN cancer. A study showed *co-morbidity* to be a prognostic factor in elderly patients with HN cancer.[13] The role of HPV as a prognostic factor is discussed in chapter 1.6.

Table 1. *Summary of TNM classification 7th edition for most HN cancer.*

Classification	T Primary Tumor	N Lymph Nodes	M Distant Metastasis
0	No evidence of tumor	No regional nodes	No metastasis
1	≤2cm	Single ipsilateral <3cm	Metastasis
2	>2 – ≤4cm	a. One ipsilateral 3 – ≤6cm b. Multiple ipsilateral ≤6cm c. Bilateral or contralateral ≤6cm	.
3	>4cm	>6cm	.
4	a. Invades adj. structures b. Invades critical adj. structures or encases carotid art.	.	
Stage			
I	T1N0M0		
II	T2N0M0		
III	T3N0M0 or T1–3N1M0		
IV a–c	T4anyNM, N2–3anyTM or M1anyTN		

1.1.2 Treatment

In general, the treatment of patients with HN cancer in Sweden follows the *National care program for head and neck cancer*.[14] All patients with HN

cancer are discussed at a *multidisciplinary tumor conference* for staging and treatment recommendation. The treatment differs between the different tumor locations. In less advanced tumor stages (I-II), oral and salivary gland cancers are generally treated with *surgery*, whereas pharyngeal and laryngeal cancers are treated with *radiation*. For patients with advanced stages (III-IV) of HN cancer, the recommended treatment generally consists of a combined treatment when possible, a combination of surgery and radiation or *chemoradiation*.

The surgery of HN cancer consists of both the *removal of the primary tumor* and the removal of the lymph nodes in the neck, i.e., *neck dissection*. The most common surgery of the primary tumors includes excisions of oral cancers; however, the excision of the salivary glands, larynx and operation of nasal-sinus cancer are also performed.

Radiation is administered at a *full dose* (approximately 68 Gy) to the area of the primary tumor and the lymph node areas with evident metastases or at high risk to develop metastases. For areas with a lower risk of tumor development, an *adjuvant* dose is administered (approximately 2/3 of the full dose). The radiation schedule has changed at our institution over time; it is currently administered continuously over *6 weeks* with 2-Gy-fractions six times per week (*slightly accelerated radiation*) to a dose of 68 Gy. During the time for papers I-IV, was the most common fractionation schedule, however, a *hyperfractionated, accelerated radiation* with two daily fractions of 1.7 Gy 5 days per week with a total dose of 64.6 Gy with a 1-week break at 40.8 Gy. The radiation schedule currently employed at the different cancer centers in Sweden are relatively similar.

The *chemotherapy* is not curative when administered alone in HN cancer; however, addition of chemotherapy to radiation has shown survival advantages for advanced HN cancer.[15] It may be administered prior to the radiation, as *induction* therapy, or at the same time as the radiation, *concomitant*. Different agents have been used, mainly cisplatin and 5-fluorouracil. The chemotherapy has changed during the years of the papers in this thesis and concomitant chemotherapy is currently preferred over induction treatment.[15]

1.1.3 Side effects

The treatment has *side effects*. The surgery has *perioperative risks*, e.g., large bleedings, cardiac infarction and stroke, and a low risk of death. The risks depend on the patient's co-morbidity and the tumor status, and careful preoperative examinations are performed to select patients suitable for surgery and optimize the patient's status to minimize the risks. After the surgery, there

are expected side effects related to the *loss of function* following the removal of tissue. In oral surgery it includes impaired function of the tongue or lack of teeth, and for larger surgery including for example mandibelectomy is surgical *reconstruction* necessary. The neck dissection is associated with risks for permanent *damage* to critical cranial *nerves*, for example the accessory nerve leading to impaired movement of the shoulder or the facial nerve impacting movement in the face.

The radiation has very low risk for death, however, in many cases results in severe permanent side effects. During and immediately after radiation, *acute side effects* with pain, swelling from the radiated area and difficulties eating and swallowing frequently occur. *Late side effects* occur after the acute reactions have disappeared, and they often persist. Examples of late side effects include dry mouth, caries and fibrosis in the throat that lead to swallowing problems, discussed in chapter 1.2. Radiation is associated with a long-term risk for the development of a secondary cancer in the irradiated tissues.

Chemotherapy provides an additional chance for survival; however, it has *toxicity* and can induce severe *acute side effects*. In the patients treated in this thesis, the most common side effects of the chemotherapy included nausea and vomiting, infections, diarrhea and dehydration. The risk for interruption of the radiation is increased when chemotherapy is simultaneously administered, and there is a low mortality associated with chemotherapy.

1.2 Dysphagia

1.2.1 Definition and association with diseases

Swallowing problems (dysphagia) represent a common problem in many different diseases, including stroke[16] and other neurological diseases such as Parkinson's disease.[17] It is more common in elderly individuals.[18] In patients with advanced HN cancer, dysphagia is an important problem, and studies have reported the prevalence of dysphagia at 54%.[19,20]

Dysphagia may be divided based on the level at which the problem is located, i.e., oral, oropharyngeal or esophageal dysphagia (Figure 1). The cause of the dysphagia varies between diseases. In Parkinson's disease the cause is multifactorial and includes an incomplete upper esophageal relaxation and a reduced upper esophageal sphincter opening.[21] Among patients with HN cancer, such as in this thesis, the dysphagia is caused by pain or obstruction from the tumor and/or side effects of the treatment.[22]

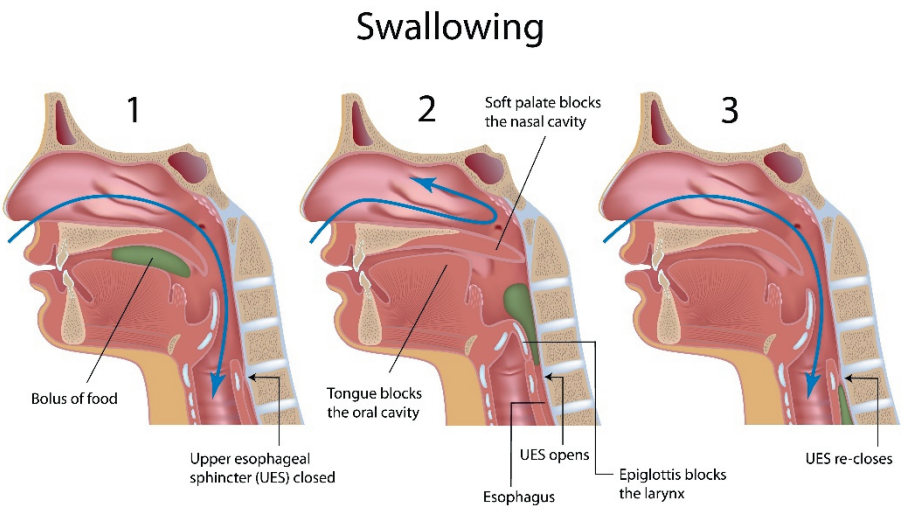


Figure 1. *Schematic presentation of the swallowing process. Swallowing may be divided into three phases: 1. oral, 2. pharyngeal and 3. esophageal. Swallowing is a complicated mechanism and involves 22 different muscles. Illustration and right to use purchased from 123RF.*

Dysphagia can lead to malnutrition, refer to chapter 1.3. Dysphagia has been associated with a worse quality of life, depression and anxiety in a study of patients with HN cancer.[23]

1.2.2 Methods that visualize swallowing

There are many different methods to evaluate the swallowing function and diagnose dysphagia. There are methods that *visualize* the patient's swallowing to assess the swallowing function, and there are methods that assess the swallowing function *without visualization* of the swallowing (questionnaires and scales). An advantage of methods that visualize the swallowing is that asymptomatic swallowing problems (silent aspirations) may also be detected[24]; however, a disadvantage is that the patient must perform an extra examination.

Fiberoptic endoscopic evaluation of swallowing (FEES) is a common method that visualizes swallowing with a fiber endoscope during the intake of liquid and food of different textures.[25] The speed and power of the swallowing is assessed along with aspiration to the larynx and lungs. To assess aspiration, the *penetration aspiration scale* (PAS) is used.[26] Another common method that

visualizes swallowing is a *video fluoroscopic swallowing exam* (VFSE).[27] The patient is observed and X-ray is performed as the patient swallows food of various consistencies and textures mixed with barium contrast, and the swallowing is evaluated.

1.2.3 Questionnaires and scales

There are many different questionnaires and scales in which the patient assesses his/her swallowing function. In the quality of life questionnaire, the European Organization for Research and Treatment of Cancer Quality of Life Head and Neck 35 questionnaire (*EORTC QLQ H&N35*), the swallowing function is assessed by a swallowing scale and a social eating scale, both of which are calculated from questions in the questionnaire, refer to chapter 3.3.2. The M.D. Anderson Dysphagia Inventory (*MDADI*) is a questionnaire with 20 questions used to assess the effects of dysphagia on the quality of life of patients with HN cancer. It includes 3 domains (emotional, functional, and physical) and 1 global question. Each subscale has five possible responses. Total scores range from 0 (extremely low functioning) to 100 (higher functioning).[28] The Swallowing Quality of Life Questionnaire (*SWAL-QOL*) is a 44-item tool that instructs patients to rate several factors regarding 10 quality-of-life concepts related to swallowing on a 5-point scale.[29,30] The Functional Oral Intake Scale (*FOIS*) is a swallowing scale with 7 levels (1-7), in which 1 = nothing by mouth and 7 = total oral diet with no restriction.[31]

In this thesis, in paper I, the swallowing function was assessed by the EORTC QLQ H&N35 together with the oral intake scale, refer to chapter 3.3.2.

1.3 Malnutrition

There are many different definitions of malnutrition and undernutrition and different criteria to diagnose these conditions. The World Health Organization (WHO) states: "*Malnutrition* refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. The term malnutrition covers two broad groups of conditions. One is *undernutrition*—which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals). The other is *overweight*, obesity and diet-related noncommunicable diseases (such as heart disease, stroke, diabetes and cancer)."[32]

The Swedish National Board of Health and Welfare has the following definition of *malnutrition*: "Conditions where lack of or imbalance of energy, protein and/or other nutrients have caused measurable and adverse changes in the composition of the body, function or of a person's disease. Malnutrition includes both undernutrition and overnutrition but is usually incorrectly used as a synonym to undernutrition"[33]

Because of the far more common use of the term malnutrition than undernutrition in the literature, the former term will be used in this thesis.

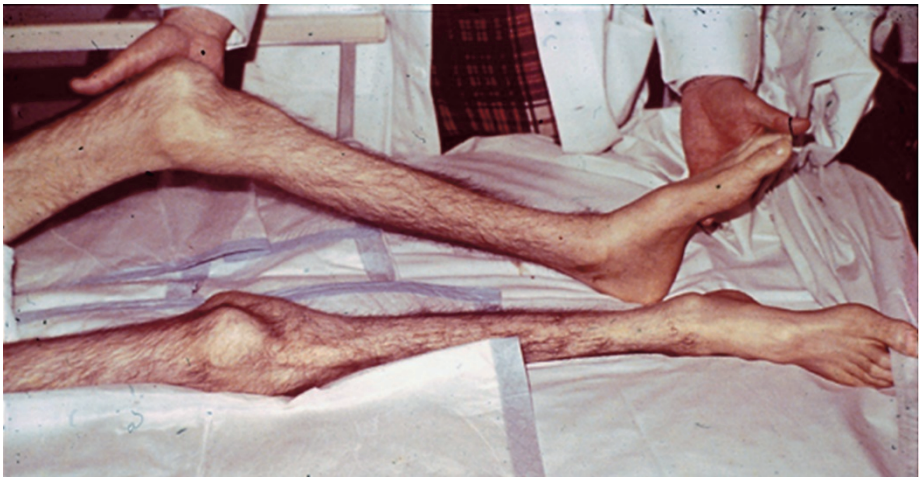
1.3.1 Diagnostic criteria for malnutrition

The European Society for Parenteral and Enteral Nutrition (*ESPEN*) suggests two alternative ways to diagnose malnutrition. However, before the diagnosis of malnutrition is considered, it is mandatory to fulfill criteria for being "at risk" of malnutrition using a validated risk screening tool. Alternative 1: BMI <18.5 kg/m^2. Alternative 2: Weight loss (unintentional) >10% indefinite of time or >5% over the last 3 months combined with a body mass index (BMI) <20 kg/m^2 if <70 years of age or <22 kg/m^2 if ≥70 years of age or a fat-free mass index (FFMI) <15 and 17 kg/m^2 in women and men, respectively.[34]

The American Society for Parenteral and Enteral Nutrition (*ASPEN*) suggests that the identification of 2 or more of the following 6 characteristics is recommended for the diagnosis of adult malnutrition (undernutrition): insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may, in some cases, mask weight loss and diminished functional status as measured by handgrip strength.[35]

1.3.2 Occurrence in diseases and consequences

Malnutrition has many different causes and is associated with several different disorders. Malnutrition in *children* is a substantial problem worldwide and is caused by starvation.[36] In developed countries, most adult malnutrition is associated with disease and may arise as a result of the following: reduced dietary intake, reduced absorption of nutrients, increased losses or increased energy expenditure.[37] Malnutrition is common in *elderly* individuals[38] and *neurologic diseases*, such as Alzheimer's disease[39] and Parkinson's disease[40]. It is common among *hospitalized patients*, including patients with malignancies, inflammatory bowel disease, chronic heart failure and benign lung diseases.[41]



Male patient showing signs of severe malnutrition with loss of weight and muscle mass. Slide adopted and reused with permission from Ingvar Bosaeus.

Malnutrition is common among patients with *cancer*,[42,43] and advanced malnutrition is an important problem in the later stages of the disease, referred to as *cancer cachexia*.[44] Numerous symptoms and complications of advanced cancer, anticancer treatment, or medical co-morbidities may interfere with patients' appetite and ability to eat or digest food and may be referred to as *nutrition impact symptoms*. They include taste and smell alterations, mucositis, nausea, constipation, pain and its treatment, or shortness of breath.[45]

Among patients with HN cancer, important nutritional impact symptoms before, during and after treatment include *dysphagia*, *mouth sores*, *pain*, *xerostomia*, *trismus*, *salivary issues* and *mucositis*.[46,47] The prevalence of malnutrition in patients with HN cancer included 19% in a study by Jager-Wittenaar et al.[48] and in patients with advanced HN tumors, it was 36% and 57% in two other studies, respectively.[49,50]

The *consequences* of manifest malnutrition are severe. Malnutrition is considered to impair the function and recovery of nearly all organ systems; it affects the muscle function, cardio-respiratory system, gastrointestinal function, immunity, and wound healing and has psychosocial effects.[37] Malnutrition has been shown to decrease function and quality of life, increase the risk for treatment interruption, morbidity and mortality and increase the frequency and length of hospital stays, as well as results in higher healthcare costs.[35,51-53]

1.3.3 Treatment of malnutrition

Malnutrition is thus relatively common in many diseases, including HN cancer, and it has severe negative consequences for patients. It is therefore important to treat malnutrition in the best possible way. The first important step is the early *identification* of whether a patient is malnourished or has a high risk of developing malnutrition. Unfortunately, many malnourished patients are not identified.[54] Malnourished patients and patients at a high risk for developing malnutrition should receive *nutritional counseling* and monitoring of the nutritional status. Malnourished patients should receive *oral nutritional supplements* as a first measure. In HN cancer, it has been shown that patients who received nutritional counseling and oral nutritional supplements had better weight maintenance, increased protein-calorie intake, improved quality of life and better anti-cancer treatment tolerance.[55]

For some HN cancer patients, oral intake, including nutritional supplements, is not sufficient to cover the need for energy. In these cases, the enteral nutrition may be ascertained with a *nasogastric tube* (NGT) or a *percutaneous endoscopic gastrostomy* (PEG, described in chapter 3.3.1). NGT has the advantage of being a non-surgical method; however, for many patients, it is not possible to use for longer periods because of severe discomfort.

PEG cannot be used when there are pharyngeal or esophageal obstruction (instead a radiologic gastrostomy may be placed), coagulopathy, prior upper abdominal surgery, abdominal wall metastases, open abdominal wounds, hepato-splenomegaly, ascites and gastric varices.[56] The *complications* with PEG are divided into minor and major, and there is a low mortality. Major complications include peritonitis, aspiration or wound infection, and minor complications include local infection, granulation formation, small bleeding or leakage from the PEG stoma.[57] The incidence of complications after PEG differs between studies. Löser at al. determined that 4% of the patients had major complications and 20% had minor complications[57], whereas Burney et al. reported a lower risk for complications[58] and Ehrsson et al. identified higher risks.[59] A concern against PEG has been raised that suggests the *swallowing function* is impaired permanently because of the use of PEG.[60,61] The aim of paper I was to examine whether the use of PEG leads to an increased risk of permanent dysphagia compared to nutritional treatment according to clinical praxis in patients with advanced HN cancer. It is, to our knowledge, the only randomized study that has examined this issue.

1.4 BIA

Impedance is an expression of the opposition that an electronic component, circuit, or system provides an alternating electric current. Impedance is a vector (two-dimensional) quantity that consists of two independent scalar (one-dimensional) phenomena: resistance and reactance.[62] *Resistance* (R) is a measure of the extent to which a substance opposes the movement of electrons among its atoms. The more easily the atoms give up and/or accept electrons, the lower the resistance, which is expressed in ohms. Resistance is observed with both alternating current (AC) and direct current (DC). *Reactance* (X) is an expression of the extent to which an electronic component, circuit, or system stores and releases energy as the current and voltage fluctuate with each AC cycle. Reactance is measured in ohms. It is observed for AC, but not for DC. When AC passes through a component that causes a phase shift, energy might be stored and released in the form of a magnetic field, in which case the reactance is inductive (X_L); or energy might be stored and released in the form of an electric field, in which case the reactance is capacitive (X_C).[62]

1.4.1 Principles of BIA

Bioelectrical impedance analysis (BIA) determines the impedance through body tissues. The principles of BIA are complex and have been described by Kyle et al.[63] The R of a length of homogeneous conductive material of uniform cross-sectional area is *proportional to its length* and *inversely proportional to its cross-sectional area*. Because it is easier to measure height than the conductive length (wrist to ankle), the empirical *relationship between lean body mass* (fat-free mass) and $height^2/R$ is used. As a result of the field inhomogeneities in the body, the term $height^2/R$, which describes an equivalent cylinder, must be matched to the real geometry by an appropriate *coefficient*. This coefficient depends on various factors, which include the anatomy of the segments under investigation. Therefore, *errors* occur when there are alterations in the resistivity of the conductive material, variations in the ratio height to conductive length, and variations in the shape of the body and body segments (body segments behave as if they are in series with each other, with shorter and thicker segments contributing less to the total R).[63]

Another complexity with BIA is that the body has two types of resistances to an electrical current, described as impedance: R and X_c. The R arises from *extra- and intracellular fluid*, and X_c arises from *cell membranes*. Several electrical circuits have been used to describe the behavior of biological tissues in vivo, and a commonly used circuit is *Fricke's circuit*. In this circuit, the R

of the extracellular fluid is arranged in parallel to a second arm which consists of X_c and R of intracellular fluid, Figure 2.[63]

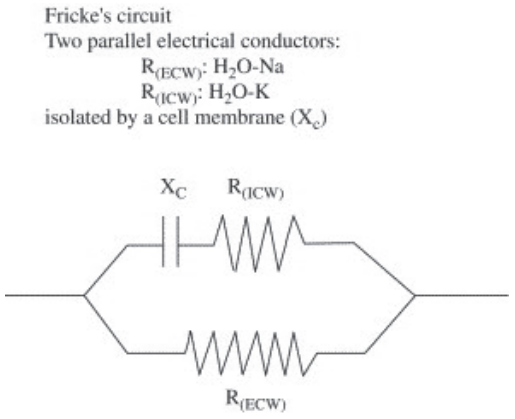


Figure 2. *Electrical model of biological tissues in vivo, the so-called Fricke's circuit. The electricity passes the tissues in two parallel ways with different resistances: intracellular (resistance constitutes of X_c and R_{ICW}) and extracellular (resistance R_{ECW}). ICW = intracellular water. ECW = extracellular water. H_20 = water. Na = sodium. K = potassium. Adopted from Kyle et al.[63] and reprinted with permission from Elsevier.*

R and X_c vary with the frequency of the AC. At zero (or low) frequency, the current does not penetrate through the cell membrane, which acts as an insulator; therefore, the current only passes through the extracellular fluid, and R_0 is equal to R_{ECW}. At infinite frequency (or very high frequency), the cell membrane acts as a perfect (or near perfect) capacitor; therefore, the current passes through both the extracellular and intracellular fluid, and R_∞ is equal to a combination of R_{ECW} and R_{ICW}. However, practical constraints and the occurrence of multiple dispersions prevent the use of a direct current (zero frequency) or very high frequency AC currents. The R values at the ideal measurement frequencies are predicted using a Cole–Cole plot, Figure 3.[63] R_0 theoretically represents the R of the extracellular fluid, and R_∞ represents the R of the intra- and extracellular fluid (total body water). At *50 kHz*, the current passes through both intra- and extracellular fluid, although the proportion varies from tissue to tissue.[63,64] The BIA machine that was used in papers II and III measured R and X_c at a frequency of 50 kHz.

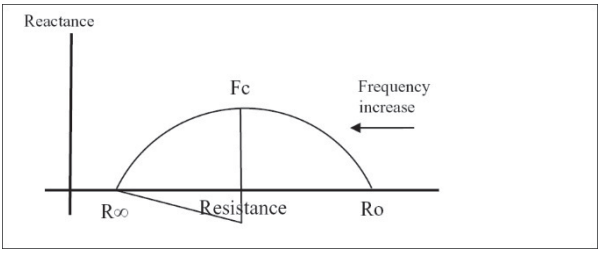


Figure 3. *Relations between resistance and reactance at different frequencies described in a so-called Cole-Cole plot. Fc = characteristic frequency (frequency of maximum reactance).* R_o *= resistance at zero frequency.* R_∞ *= resistance at infinite frequency. Adopted from Kyle et al*[63] *and reprinted with permission from Elsevier.*

1.4.2 Applications of BIA

BIA can be used to estimate the *body composition*.[64,65] The *total body water* (TBW), *extracellular* and *intracellular water volumes*, *fat-free mass* (FFM), *body cell mass* (BCM), and *body fat content* are predicted using different equations.[65,66] Assessment of body composition with BIA is used by healthy individuals in association with *training* and fitness, to motivate for further training and among elite athletes to monitor the results of the training.[64] At the hospitals, BIA is mainly used in various *research* projects.

A potentially important application of the assessment of body composition is as a *prognostic factor*. As stated in chapter 1.3, malnutrition defined as weight loss or low weight has been associated with decreased survival in various cancers. Fat is, however, mainly an energy depot and is not actively used in most different organ processes. The loss of the *fat-free mass* (FFM) is, therefore, especially interesting to investigate as a prognostic factor in diseases associated with malnutrition. FFM has been shown to be a prognostic factor in, for example, chronic obstructive pulmonary disease[67], chronic heart failure[68] and cancer.[69]

The so-called *phase angle* (PA) has received increasing interest as a prognostic factor for survival during recent years. PA is derived and calculated from the BIA values R and X_c, refer to chapter 3.3.6. PA has been shown to be significantly associated with survival in different severe diseases, including patients in intensive care units[70], and different types of cancer, such as breast and colorectal cancers;[71-74] however, it is not well-studied for HN cancer. Furthermore, the change of PA over time during and after tumor treatment and

the prognostic value of PA at different time points have not been explored. The aim of papers II and III was to investigate the prognostic impact of PA in HN cancer.

1.5 HNCUP

Head and neck cancer of unknown primary (HNCUP) is defined as HN cancer with carcinoma in cervical lymph nodes with no evidence of a primary tumor. The condition was first described by von Volkmann in 1882, who regarded it as a carcinoma in a branchial cleft cyst.[75] In 1950, after a study by Martin et al., it was generally considered that the condition in almost all cases included cystic lymph node metastasis from undetected pharyngeal primaries.[76] Only a few exclusive cases of branchial cleft cyst carcinoma have been described.[77]

1.5.1 The occult primary tumor

Two important questions may be raised regarding HNCUP; first, *why* is there no evident primary tumor in HNCUP? Either there was never a primary tumor, which has been ruled out in almost all cases as previously discussed. Alternatively, there is a primary tumor; however, it is too small to be detected when the diagnosis of the lymph node metastasis is made. Evidence of this explanation has been found in cases in which, after the treatment, a primary HN tumor of the same type as the HNCUP occurred. Another possibility is that there was a primary tumor, but the primary tumor has been killed by the body. Supporting this idea is that the immune system is known to interact with tumors and remove damaged cells.[78]

Another important question regarding HNCUP is *where* the occult primary tumor is located. The *location* of the lymph node metastasis in the neck provides an indication regarding where the most likely locations are for the primary tumor because different HN tumors metastasize to certain neck areas.[79] The *observed recurrences* in HNCUP in the form of the occurrence of a primary tumor was most frequently identified in the base of the tongue in the study by Grau et al.[80] During the *examination* of a supposed HNCUP, not clinically evident primary tumors are often identified. In a study by Rusthoven et al., the primary tumor was identified in various locations in the HN area and most often in the tonsils or base of the tongue.[81] In summary, it is generally considered that the occult primary tumor in HNCUP, in most cases, is/has been located in the *tonsils*, *base of the tongue* or *nasopharynx*.

1.5.2 Diagnostic work-up and etiologic factors

The diagnostic work-up of HNCUP aims to identify the primary tumor, and it is a diagnosis of exclusion. If the primary tumor is identified, the tumor may be staged correctly, and the treatment may be more accurately targeted, with less side effects for the patient. The diagnostic work-up for HNCUP is more extensive than for other types of HN cancer. The radiologic examination includes, in many cases, positron emission tomography and computer tomography (PET-CT, Figure 4). To identify hidden primaries, a panendoscopy together with a bilateral tonsillectomy and biopsies from the base of the tongue and the nasopharynx are performed with general anesthesia.

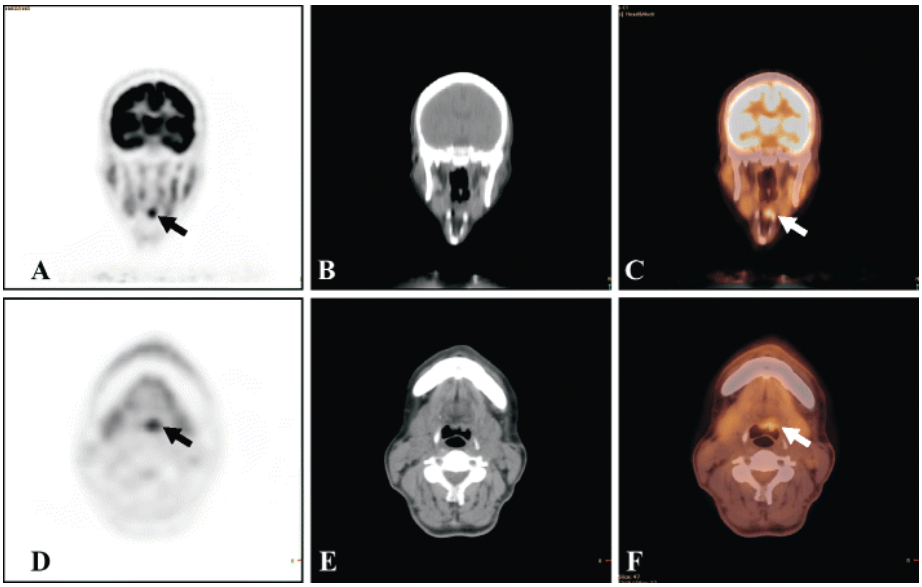


Figure 4. *PET-CT of a 52-year-old male who presented with a pathologically enlarged lymph node in the left side of the neck. Excision biopsy of the lymph node and subsequent histopathological examination showed metastatic squamous cell carcinoma of unknown primary. Laryngo-bronchoscopy was performed with biopsies and tonsillectomy; subsequent histopathological examination only showed reactive changes in the tonsils, pyriform sinus, and left tongue base. A PET-CT was performed, and there was in the coronal (a) and axial plane (b) intense uptake in the left supraglottic region (arrows), which likely represents the primary tumor. Corresponding CT and fused PET-CT images in the coronal (b and c, respectively) and axial plane (e and f, respectively) localize the lesion at the base of the tongue (arrows). Histopathological examination of a directed biopsy of the lesion showed squamous cell carcinoma and confirmed the diagnosis base of the tongue cancer. Image adopted from Kwee et al.*[82] *and reused with permission from Springer Nature.*

HNCUP is rare; the incidence is approximately 0.49 per 100000 individuals per year, and approximately 50 patients are diagnosed with HNCUP annually in Sweden.[3] The fact that HNCUP is rare has made it less well studied than other HN cancer types. The importance of the different etiological and prognostic factors is not well investigated, and, to my knowledge, no randomized treatment study has been performed.

Factors that are known to be more common and are considered etiological factors for HNCUP are *alcohol overconsumption* and *tobacco smoking*. *EBV* is also considered an etiological factor.[83] During previous years, HPV has been shown to be an important factor in the related oropharyngeal cancer[84] and is increasingly studied in HNCUP, refer to chapter 1.6.

1.5.3 Prognostic factors

The most important prognostic factor for survival in HNCUP is whether the patient may be treated with *curative intent*. Patients undergoing palliative intent treatment have a poor prognosis.[85] Factors that make it impossible to treat with curative intent are both patient-related, including too poor performance status, too severe comorbidities or the patient refuses treatment, or tumor-related, most often occurrence of distant metastases.

Among the curative intent patients, the impact of different prognostic factors for survival differed in previous studies. The patient's *age* at diagnosis was a significant factor for survival in two studies[80,86], but not in another study[85]. The performance status of the patient was a significant prognostic factor for survival in the study by Grau et al.[80] Patients who smoked 10 cigarettes or more per day had a worse prognosis for survival.[87] Tumor *N classification* was a prognostic factor for survival in several studies. In a study by Erkal et al. a higher N classification was associated with worse survival[88], N3 was a negative factor compared to N1-2 in a study by Huang et al.[86], and N2b-N3 was a negative factor compared to N1-N2a in another study.[89] Extracapsular tumor extension (*ECE*) was a significant prognostic factor in two studies[90,91] but not in another.[92] In recent years, HPV tumor status has been investigated as a prognostic factor, refer to chapters 1.6 and 5.3. The importance of different prognostic factors in HNCUP was investigated in papers IV and V.

1.5.4 Treatment

The curative intent treatment of HNCUP varies between different cancer centers in Sweden and internationally. The most common treatments include *neck dissection combined with radiation* or primary *(chemo)radiation*. Previous studies comparing treatments of HNCUP are retrospective, include relatively small numbers of patients, and the patients in the different treatment groups have differences in patient and tumor factors, which make the comparisons uncertain. The results differ, some studies have indicated there was no significant difference in survival between neck dissection and radiation versus (chemo)radiation.[80,93,94] Two studies have indicated that neck dissection in combination with radiation resulted in significantly improved survival compared to (chemo)radiation.[95,96] In a study from 1992, surgery alone showed comparable outcomes compared to treatment with postoperative radiation in patients with N1 tumors.[97] In papers IV and V, the survival after treatment with neck dissection and radiation compared to primary (chemo)radiation is analyzed.

1.6 HPV

1.6.1 The virus and infection mechanism

Human papillomavirus (HPV) is a virus that can cause infection in humans, and the oncogenic role of HPV was first identified in the 1980s (in cervical cancer).[98] HPV is a small, non-enveloped deoxyribonucleic acid (DNA) virus, and the viral diameter is approximately 55 nm (Figure 5).[99] Many *different types* of HPVs have been characterized; there are more than 200 known types, and new types are continuously discovered. The virus is classified into *mucosal* and *cutaneous* HPV, depending on the tissue that it infects. HPV is also classified in *high risk* or *low risk* HPV depending on the risk to cause cancer.[100] *HPV-16* is considered the most important high-risk HPV; however, many more types are considered high risk, including: HPV-18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.[101] HPV-6, 11, 13 and 42 are examples of low risk HPV.

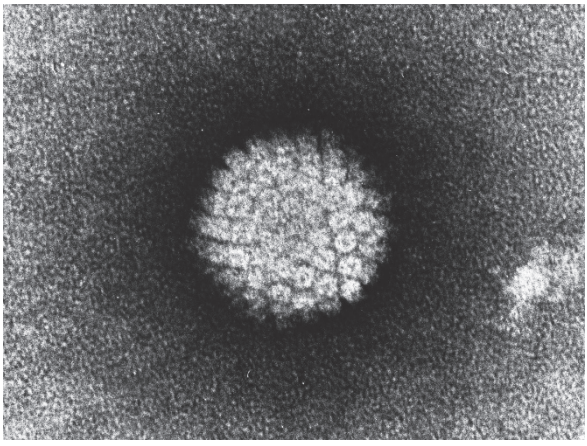


Figure 5. *Transmission electron micrography of an HPV virus particle. The particle is approximately 55 nm (55/1000000000 m) in diameter. Originally published by and reused with permission from the National Cancer Institute.*

The HPV genome is circular and may be divided into three major portions: an early (*E*) region that encodes nonstructural proteins (E1–E7), a late (*L*) region that encodes the two capsid proteins (L1–L2), and a noncoding long control region (*LCR*) that contains various elements, which regulate viral replication and gene expression.[99]

HPV only infects *basal epithelial cells*.[102] These cells are located in the deepest layer of the epithelium above the basement membrane, and they are the only cells in the epithelium that divide.[103] HPV-16 binds to a certain receptor (LN332) at the cell for infectious entry; however, this receptor is not used for all HPV types and this difference may explain the anatomical-site preference differences for the HPV types.[104] The virus enters the cell, the virus capsule is removed and the HPV DNA transports to the cell nucleus. The viral DNA is *maintained at a low copy number* in the nuclei of infected cells as they undergo differentiation and move toward the surface of the epithelium. In terminally differentiated cells, the virus replicates to a high copy number, L genes are expressed, and progeny virus is produced.[99] HPV is a *nonlytic* virus, and progeny virus is passively shed into the environment as a cargo.

1.6.2 Transmission, incubation time and clinical manifestations

HPV is transmitted between humans with direct contact. It is the most common sexually transmitted disease.[105] Skin-skin contact, genital-genital, genital-oral,

mother-baby transmission at delivery and inoculation have been described.[99,106-108] It is considered that HPV preferentially binds to and infects sites of trauma.[109]

The low-risk HPVs cause many different types of *warts* and other conditions in the *skin and mucosa*, including verruca plantaris, verruca vulgaris, verruca plana, condyloma acuminatum and laryngeal papilloma.[110] The high-risk HPVs cause nearly all *cervical cancer*; however, they are also an etiologic factor for many other types of cancer, including anal, penile, vulvar cancer, cutaneous squamous cell carcinoma, laryngeal cancer, as well as, in later years, they have been shown to cause *oral* and *oropharyngeal cancer*.[110-112] In a review article by Kreimer et al. regarding healthy individuals 1.3% had evidence of an oral infection with HPV-16, 3.5% with any high-risk HPV and 4.5% with any HPV.[113] These findings indicate that *asymptomatic* infection with high risk HPV in the oral cavity is not uncommon.

The incubation time from HPV infection to *epithelial changes* is studied in the cervix uteri. In a study by Woodman et al., the incubation time from detectable infection with HPV-16 to epithelial changes was most often 6–12 months.[114] The HPV infection *heals by itself* in most cases, and after approximately 12–24 months, a previously positive HPV test is negative.[115] A *persistent HPV infection* has been shown to be an important risk factor for the development of premalignant epithelial changes in the cervix.[116] The *incubation time* from infection to the development of cancer is for cervical cancer considered to be approximately 12–15 years.[117]

1.6.3 Mechanism of malignant transformation

The oncogenic mechanism of HPV is complicated.[99] One of the key events of HPV-induced oncogenesis is the *integration of the HPV* genome into a host chromosome. HPV genome integration often occurs near fragile sites of the human genome[118]; however, the integration can occur at different locations in the genome without specific hot spots, and in most cases, the normal genes are not mutated in this process.[119] Expression of the viral *E6* and *E7* genes is consistently maintained, whereas other portions of the viral DNA are deleted or their expression is disturbed.[120] *Loss of expression of the E2* transcriptional repressor is critical, as it removes the regulation of HPV E6 and E7. The fact that the loss of E2 repressor function may be critical for the oncogenesis is supported by experiments that showed re-expression of E2 in cervical cancer cell lines causes growth suppression.[121] The critical steps for HPV oncogenesis is shown in Figure 6. The oncogenic mechanism for HPV is *different from that of tobacco smoking*.[122]

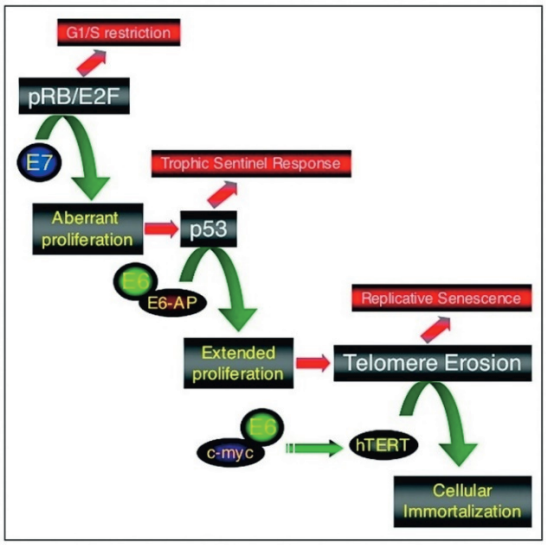


Figure 6. *Schematic presentation of three critical steps in high-risk HPV-induced oncogenesis. 1. Inactivation of pRB leads to aberrant proliferation. 2. Inactivation of p53 tumor suppressor leads to extended proliferation. 3. Expression of hTERT leads to telomere erosion and cellular immortalization. These steps are a subset of the steps that have been shown to be necessary in the oncogenesis of HPV. Illustration by Münger et al.*[99] *and reused with permission from the American Society for Microbiology.*

1.6.4 Detection methods, p16 immunostaining

HPV infection in tissues can be detected by many different methods.[123] There are *direct* HPV tests, in which parts of HPV are identified and *indirect* HPV tests, in which changes caused by HPV are identified.[123] The different methods have their advantages and disadvantages with regard to the sensitivity and specificity of the test, what types of samples that can be analyzed, how technically complicated they are and the cost.

The most widely used method for HPV detection in HN tumors is *p16 immunostaining*. P16 is a protein that plays an important role in cell cycle regulation and acts to slow down the cell cycle; thus, it is a *tumor suppressor*. Accumulation of p16 has been identified in different forms of cancer, including melanoma, glioma, lung cancer and leukemia, and is caused by mutations or deletions in the gene that codes for p16.[124] In HPV-induced HN cancer the mechanism is different. P16 is an inhibitor of cyclin-dependent kinases 4 and 6 that activate the negative cell cycle regulator protein pRB (Figure 6), which,

in turn, downregulates p16 expression. It has been shown in neoplastic cells that *E7 protein* of the high-risk HPVs can interfere with this regulatory circuit because of its capacity to *inactivate pRB,* and it thus leads to the *overexpression of p16*.[125]

The p16 method is described in chapter 3.3.8. P16 immunostaining has many advantages, including high sensitivity, high accessibility at most laboratories, is easy to use on the commonly used formalin-fixed paraffin-embedded samples, detects transcriptionally active virus and is relatively inexpensive. The disadvantages of the p16 analysis include that it is a surrogate marker for HPV infection as previously discussed, it has less sensitivity for non-p16 overexpressing HPV subtypes and it does not have an ideal specificity.[123] In a study by Jordan et al., p16 analysis of oropharyngeal specimens had a sensitivity of 96.8% and specificity of 83.8% (compared to polymerase chain reaction)[126] and in another study by Pannone et al., the sensitivity was 100% and the specificity was 93% for p16 analysis.[127]

The *staining pattern*, *intensity* and *percentage of positive cells* determine whether a p16 test is considered positive or negative.[128] Diffuse staining with a strong intensity is considered positive and is common in high-risk HPVs, whereas focal and weak staining is common in low-risk HPVs and considered negative.[129]

Another common method for HPV detection is polymerase chain reaction (*PCR*). The method was described by Mullis et al. and amplifies a copy or several copies of a segment of DNA to many million copies.[130] The advantages of PCR include that it has a high sensitivity, is cost effective, assesses for papillomavirus other than HPV-16 and is capable of amplifying highly degraded DNA samples. The disadvantages of PCR include that it has low specificity, does not provide a quantitative measure of the amount of virus and does not provide confirmation of transcriptionally active virus.[123]

A third common method for HPV detection is in situ hybridization (*ISH*). In ISH, specific marked complementary DNA sequences are hybridized (hybridization, fusion of two compatible DNA strands) with the genome of the sample cells. It can detect where in the cell the specific DNA sequence is localized.[131] ISH has the advantages that it can provide evidence that there is active oncogene transcription, the specificity is 100% and it can distinguish between integrated and non-integrated DNA. The disadvantages of ISH include the low sensitivity and that it is technically difficult to use in routine clinical examinations.[123]

In this thesis, p16 immunostaining was used for the HPV analysis in papers IV and V; however, in paper V PCR was used in some cases.

1.6.5 HPV vaccination and HPV in HNCUP

There is no curative medical treatment against an active HPV infection; however, there are *vaccines* against the disease. There are three types of vaccines: 2-valent (protects against HPV-16 and 18), 4-valent (protects against HPV-6, 11, 16 and 18) and 9-valent (protects against HPV-6, 11, 16, 18, 31, 33, 45, 52 and 58).[132] The HPV vaccine is administered in two or three doses.[132] HPV vaccination is administered to girls in many countries[133] and in Sweden, the HPV vaccine is recommended for girls at the age of 11–12 years as part of the general vaccination program.[132]

As previously discussed, HPV is considered a common cause of and an important prognostic factor for oropharyngeal cancer.[134] HNCUP is related to oropharyngeal cancer and may therefore also be caused by HPV in many cases and HPV status may be an important prognostic factor for survival. These aspects are investigated in papers IV and V.

2 AIMS

The main purposes of this thesis on patients with advanced HN cancer were:

-to determine whether there were differences in the severity and frequency of long-term dysphagia for patients who received enteral nutrition from a PEG versus nutrition according to clinical praxis.

-to investigate whether PA at diagnosis was predictive for overall survival in patients with advanced HN cancer.

-to investigate how PA changed over time during and after the cancer treatment and whether changes in PA and PA at different time-points were predictive for survival in HN cancer.

- to investigate the overall survival and the prognostic importance of different factors, including p16/HPV status, in patients with HNCUP.

- to compare the survival for the two major treatments, neck dissection combined with radiation and (chemo)radiation, in patients with HNCUP.

3 PATIENTS AND METHODS

3.1 Study design and patient selection

The papers in this thesis investigated patients with advanced HN cancer. The study design and patient selection of the papers are shown in Table 2. Paper I was a *randomized controlled trial*.[135] It compared patients who received an active intervention, a PEG (study group), with patients who were treated according to clinical praxis (control group) with regard to the swallowing function. The two groups were stratified for different clinical factors (age, gender, tumor site and tumor stage), and the two groups were comparable. It was a *post hoc* study, which indicates that it was a long-term follow-up study on a previous study.[136] Papers II and III were *prospective studies on a diagnostic test* (phase angle). Paper IV was a *retrospective study* on a *cohort* of HNCUP patients. Paper V was a *register* and *multicenter study*; the study was carried out at more than one medical institution.

Papers I, II and III were based on the same patient cohort, which included patients with advanced HN cancer treated with curative intent in the Western Region during 2002–2006 and followed until 2013. Most patients had oropharyngeal or oral cancer. Paper IV investigated patients with HNCUP in the Western Region during 1993–2009 who were treated with curative intent. Paper V was a national multicenter study on patients with HNCUP; the patients were recruited from the Swedish Head and Neck Cancer Register (SweHNCR)[3], and were treated during 2008–2012 at the university hospitals (and at some of the bigger county hospitals) in Sweden.

Table 2. *Study characteristics of the papers.*

	Paper I	**Paper II**	**Paper III**	**Paper IV**	**Paper V**
Study design	Randomized controlled trial	Prospective study on diagnostic test	Prospective study on diagnostic test	Retrospect-ive study	Register multicenter study

Study population	Advanced HN cancer	Advanced HN cancer	Advanced HN cancer	HNCUP Western Region	HNCUP Sweden
No. of subjects	134	128	128	68	260
Start of treatment	2002–2006	2002–2006	2002–2006	1993–2009	2008–2012
Censor date	Aug 2013	May 2016	May 2016	May 2016	Nov 2017
Study aim	Compare PEG vs controls	Compare PA vs other prognostic factors	Investigate PA over time as prognostic factor	Study impact of different prognostic factors and treatment	Compare treatment and other clinical factors
Primary outcome	Swallowing function	Overall survival	Overall survival	Overall survival	Overall survival
Secondary outcome(s)	Tube dependence BMI Overall survival Global quality of life	Cause of death	Change of PA from inclusion	Disease-free survival P16 prevalence Recurrence-free probability	Disease-free survival HPV/p16 prevalence

3.2 Ethical considerations

All studies in this thesis were performed following ethical approval by the Regional Ethics Committee in Gothenburg: Paper I Dnr: 927-11. Paper II S: 445-01. Paper III S: 445-01 and Dnr: 927-11. Paper IV Dnr: 421-13. Paper V Dnr: 299-14. Written informed consent was obtained in accordance with the Helsinki Declaration[137] from all patients that were included in papers I, II and III at the start of the original study.[136]

The potential negative effects of participation in the original study were taken into account when the study started in 2002 and were considered limited because PEG was a well-established method used for many years with reported low morbidity and mortality and probable positive effects on nutrition. We found no additional risks for the patients to also participate in papers I, II and III because BIA is a safe method without known side effects. We found no potential negative effects for the patients to participate in papers IV and V.

3.3 Methods

3.3.1 PEG

Half the patients in papers I, II and III received a PEG, i.e., a surgically placed tube through the abdominal wall to the ventricle.[138] A flexible gastrostomy was used in the procedure to enable the placement of the tube and ensure a correct position of the tube. PEG placements were performed according to the *Pull method* (Figure 7). Two different gastrostomy tubes were used: Novartis Compat® Nuport PEG 22FR and Bard PEG Fastrac 20FR. The patients received intravenous antibiotic prophylaxis (Cefuroxim 1.5 g) administered 1–3 times perioperatively.

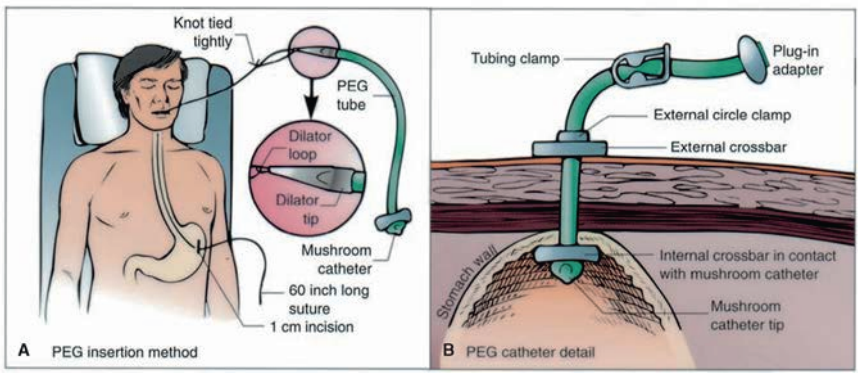


Figure 7. *Schematic illustration of how the PEG is inserted (Pull method) (A) and when it is in position through the abdominal wall (B). Adopted and reused with permission from diagramcharts101.com.*

3.3.2 Quality of Life Questionnaires

In paper I, two validated quality of life questionnaires were used to assess the swallowing function and the global quality of life. The European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (*EORTC-QLQ-C30*) was used (Appendix I).[139] The questionnaire consists of 30 items and asks for the patient's symptoms and problems during the past week. From the core questionnaire the patient's global health status was calculated from questions (items) 29 and 30. In this scale, the value ranges from 0–100, and a higher value represents a better quality of life. The Head and Neck 35 questionnaire (*EORTC-QLQ-H&N35*) is designed for patients with HN cancer (Appendix II).[140] In paper I, five different scales were used and were calculated from selected items: swallowing (items 35–38), social eating (items 49–52), pain (items 31–34), dry mouth (item 41) and opening mouth (item 40). In the scales. The value ranges from 0–100, and a higher value on these symptom scales represents increasing problems. A difference of *10 points or more* was considered a clinically significant difference in both the EORTC-QLQ-C30 and H&N35.[141,142]

3.3.3 Oral intake scale

In paper I, a 5-level ordinal scale was used to assess the oral intake, the "Oral intake scale". The score ranges from 1–5 with the following definitions: 1 = normal diet, 2 = semisolid diet, 3 = puréed diet, 4 = liquid diet and 5 = unable to eat. The scale is very easy to use; however, it is not validated.

3.3.4 Performance status

Two different performance statuses were used in this thesis. The *Karnofsky performance status*[143] was used in papers I, II and III (Table 3). It is an 11-point rating scale; the score ranges from 0–100%, and a higher percent indicates a better performance status. The *WHO performance status*[144] was used in paper V (Table 4). The score ranges from 0–5, and a lower score indicates a better performance status.

Table 3. *Karnofsky performance status.*

100% – normal, no complaints, no signs of disease
90% – capable of normal activity, few symptoms or signs of disease
80% – normal activity with some difficulty, some symptoms or signs
70% – caring for self, not capable of normal activity or work
60% – requiring some help, can take care of most personal requirements
50% – requires help often, requires frequent medical care
40% – disabled, requires special care and help
30% – severely disabled, hospital admission indicated but no risk of death
20% – very ill, urgently requiring admission, requires supportive measures
10% – moribund, rapidly progressive fatal disease processes
0% – death

Table 4. *WHO performance status.*

0 – asymptomatic (fully active, able to carry on all pre-disease activities without restriction).
1 – symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work).
2 – symptomatic, < 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours).
3 – symptomatic, > 50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours).
4 – bedbound (completely disabled, cannot carry on any self-care, totally confined to bed or chair).
5 – death

3.3.5 BMI

In papers I, II and III the body weight and height were measured. The BMI was calculated with the following formula: BMI = weight/height^2 (kg/m^2). A BMI 18.5–24.9 was considered normal weight, <18.5 underweight, 25–30 overweight and >30 obesity.

3.3.6 BIA

Results from BIA were presented in papers II and III. BIA was performed by a registered dietician (Ewa Silander) using a Bioelectrical Impedance Analyzer (Model BIA-101Q: RJL Systems, Clinton Township, MI, USA). All patients had fasted for at least two hours prior to the measurement. BIA was conducted with the patient lying supine on a bed or exam table, with the legs apart and arms not touching the torso. Evaluations were conducted on the patients' right side using the standard four surface electrode (*tetrapolar*) technique on the hand and foot (Figure 8).[145] The resistance (R) and reactance (X_c) were measured in Ω at *50 kHz*, 800 μA. One measure of R and X_c was performed for each patient at each time point.

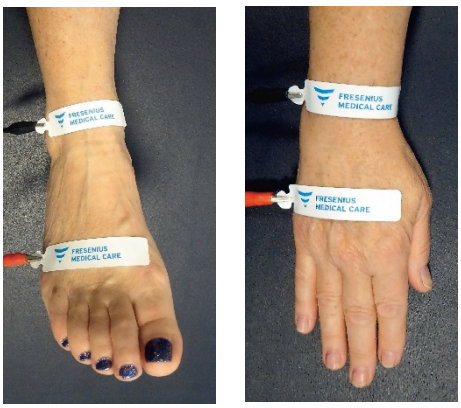


Figure 8. *Placement of electrodes at the BIA measurements. The AC current flows between the current source electrodes (connected with red cables) placed distal at the right foot and the right hand. The electrical values are detected in the detection electrodes (connected with black cables) placed proximal to the current source electrodes. Photos by the author.*

The fat-free mass (*FFM*) was calculated using Lukaski's equation: FFM = 0.734(height^2/R) + 0.116weight + 0.096Xc + 0.878sex - 4.03. Sex: women = 0, men = 1.[146,147] The fat-free mass percent (*FFM%*) was calculated as follows: FFM% = FFM/weight. The fat-free mass index (*FFMI*) was calculated as follows: FFMI = FFM/height^2 (kg/m^2). The *PA* was calculated with the following formula: PA = arc-tangent(X_c/R) * (180/π). The standardized phase angle (*SPA*) was obtained from the PA using the BMI, age, and gender

reference values from the study by Bosy-Westphal et al.[148] Patients with SPA values greater than +3 SD or less than -3 SD at inclusion were considered outliers with values caused by errors in the impedance measures, and these patients were excluded from papers II and III.

3.3.7 Diagnostic work-up

In all papers patients with advanced HN cancer were investigated, in papers IV and V patients with HNCUP. All patients were examined by a specialist in Otolaryngology – Head and Neck Surgery. A *biopsy* was obtained from the area of the primary tumor if present and in the cases of lymph node involvement a *fine-needle aspiration* was performed from the neck mass to obtain a histopathological diagnosis. *Radiological examinations* of the HN area were performed on all patients with MRI (magnetic resonance imaging) or CT (computer tomography). The thorax was also radiologically examined, in most cases with CT and in some early cases with plain X-ray.

The patients with HNCUP were examined more *extensively*, with the aim to identify the primary tumor. A fine-needle aspiration was performed from the neck mass to obtain a histopathological diagnosis and was complemented with a core-needle and/or an open biopsy if required to obtain a diagnosis. Radiological examinations of the HN and thorax were performed on all patients with *PET-CT*, MRI or, in a few patients, CT. A *panendoscopy* was performed in the HNCUP patients, including an examination of all parts of the pharynx, larynx, lungs and esophagus. At the same time, tonsillectomy was performed, and biopsies were obtained from the base of the tongue and the nasopharynx.

All patients with HN cancer were discussed at a multidisciplinary tumor conference for staging and treatment decisions.

3.3.8 P16 and HPV analyses

Results from p16 and HPV analyses were presented in papers IV and V.

In paper IV, all HPV analyses consisted of p16 analyses. The histopathological specimens were retrospectively analyzed with p16 immunostaining using light microscopy by a pathologist (Anikó Kovács) blinded for clinical data and outcomes. Formalin-fixed and paraffin-embedded blocks were used to prepare 4-µm-thick sections applied onto positively charged slides (Flex IHC Microscope Slides, Ref K8020, DAKO). Subsequently, the tissue sections were subjected to deparaffinization and rehydration followed by heat-induced epitope retrieval (HIER) Tris/EDTA buffer (pH 9.0) for 20 min at 97 °C using

PT Link instrument (PT Link, Dakocytomation, DAKO). The tissue sections were immunostained with the p16 (CINtec Histology kit, Ref 9511, Roche) mouse monoclonal antibody (clone E6H4) using DAKO visualization system (Envision Flex High pH, Link, Ref 8000, DAKO) and DAKO stainer for IHC (Autostiner Plus, Dakocytomation, Denmark) following the manufacturer's instruction. Peroxidase-catalyzed diaminobensidine tetrahydrochloride was used as the DAB+ chromogen to determine protein expression levels in tumors from HNCUP and then the slides were counterstained with hematoxylin. The stained slides were rinsed with deionized water followed by the dehydration process in ethanol 70%, ethanol 95%, absolute ethanol, cleared in xylene and added cover glass (Coverslipper, DAKO). P16 was interpreted as positive if more than 5% of tumor cells showed brown nuclear or nuclear and cytoplasmic staining.[149,150] The lowest positive value in paper IV was 20%.

Paper V comprised a national multicenter study, and the HPV analyses were performed at the time of diagnosis at the different hospitals by various pathologists. None of the analyses were performed retrospectively. P16 immunostaining was used for HPV analysis and, in some cases, in combination with or only as PCR analysis. The p16 analyses were performed similar to the description for paper IV; however, the manufacturer for the histological staining agents was not known for the different hospitals and the limit when p16 was considered positive were not discussed between the hospitals.

3.3.9 SweHNCR

The Swedish Head and Neck Cancer Register (SweHNCR)[3] is a national register on all patients with HN cancer in Sweden. It started in 2008. It covers approximately 98–99% of all patients with HN cancer in Sweden. The SweHNCR includes data from different time points: at diagnosis (patient age and gender, tumor data and the diagnostic work-up), treatment (surgical and oncologic) and at follow-ups up to 5 years after diagnosis including any relapse and whether the patients deceased with the tumor or not (Appendix III).

In paper V, data from the SweHNCR were used together with additional data from the medial records, including more detailed information regarding the radiological examination, medical work-up, radiation, chemotherapy and recurrence.

3.3.10 Tumor treatment and follow-up

The treatment recommendations for the patients in this thesis depended on the patient's performance status, the tumor site and the tumor stage. Nearly all patients in this thesis (except 44 of 260 patients in paper V) had a tumor stage

and performance status that enabled curative treatment. All patients had advanced (stage III-IV) HN cancer. The treatment depended on tumor location. The patients with oral cancer were treated with excision of the primary tumor and neck dissection followed by (chemo)radiation, the patients with oro-, naso- and hypopharyngeal cancer were treated with (chemo)radiation and the patients with HNCUP were treated, in most cases, with neck dissection and radiation or (chemo)radiation.

The patients in papers I-IV were treated at the Sahlgrenska University Hospital (or, in a few cases, at one of the county hospitals), whereas the patients in paper V were treated at one of the Swedish university hospitals (or at some of the bigger county hospitals). No change in treatment guidelines occurred for the treatment in papers I-III during the time period 2002–2006. No major treatment changes were made regarding treatment of HNCUP in Sweden between 2008 and 2012, in paper V. For the patients in paper IV; however, the time period for inclusion of patients was long (1993–2009), and the treatment changed during this period. More patients were treated with (chemo)radiation during the 1990s through approximately 2004, whereas thereafter neck dissection in combination with radiation were more common. The radiation schedule varied, and three different schedules were used. The target volumes differed over time, radiation to the nasopharynx was common in the early part of the period.

After the completion of treatment, all patients in paper I-V had regular follow-ups over 5 years, including every 3 months during the first two years and every 6 months during years 3–5. A radiologic examination, CT or MRI, was performed 3 months after the completion of the radiation and thereafter at the suspicion of tumor recurrence during the surveillance.

3.4 Statistics

The results were presented as means, standard deviations, medians and ranges for continuous variables and as numbers and percentages for categorical variables.

To compare the results between independent groups, the Mann-Whitney U test was used for continuous variables. For ordered categorical variables the Mantel-Haenszel chi-square test was used in papers I-IV and the non-parametric test was used in paper V. Fisher's exact test was used for dichotomous variables in all papers and for non-ordered categorical variables in paper V, whereas the chi-square test was used for non-ordered categorical

variables in papers I-IV. For paired data of a continuous variable (in paper III), the Wilcoxon signed-rank test was used.

Survival analysis was performed with Kaplan-Meier curves and Cox proportional hazard regression analyses. In the Kaplan-Meier curves, comparisons of mortality and recurrence between subgroups were analyzed with a log-rank test for dichotomous and non-ordered categorical variables and a log-rank test for trend for ordered categorical variables. Standardized mortality rates (SMR) were used in paper IV to analyze survival adjusted for age (reference population in Statistics Sweden 2016). Comparisons between the SMR results were performed with Monte Carlo methods.

Multivariable analysis of risk of survival was performed with a forward stepwise Cox proportional hazard regression analysis in papers II and IV and a multivariable Cox proportional hazard regression analysis in paper V.

In paper II, a receiver operating characteristic (ROC) curve was used to analyze the association of predicted probabilities and observed responses. The area under the curve (AUC) was calculated for each ROC curve.

All significance tests were two-tailed and were conducted at the 5% significance level. SAS, System Version 9.4 (SAS Institute, Inc, Cary, NC, USA), was used for the statistical analyses in papers I-IV, and StataCorp (2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC.) was used in paper V. Statisticians from the Statistiska Konsultgruppen Gothenburg were consulted for the statistics in papers I-IV, and a statistician in RCC was consulted for paper V.

4 RESULTS

4.1 PEG effect on swallowing in HN cancer (Paper I)

Paper I included *134 patients* with advanced HN cancer (stage III and IV), including 64 patients who had a prophylactic PEG (study group) and 70 patients who had clinical support according to clinical praxis (control group). The groups were stratified for age, gender, tumor site and tumor stage, and there were no significant differences in age, gender, tumor site, T classification, N positivity, tumor stage, treatment, weight, BMI and performance status between the groups. Most patients had *oropharyngeal cancer* (58%) and *oral cancer* (31%). The mean age at inclusion was 62 years, and the patients had a normal weight with a mean BMI at 24.8 kg/m^2.

There was no significant difference in the *swallowing scale* in the EORTC-QLQ-H&N35, at any time point between the study and control groups (Figure 10, Table 5).

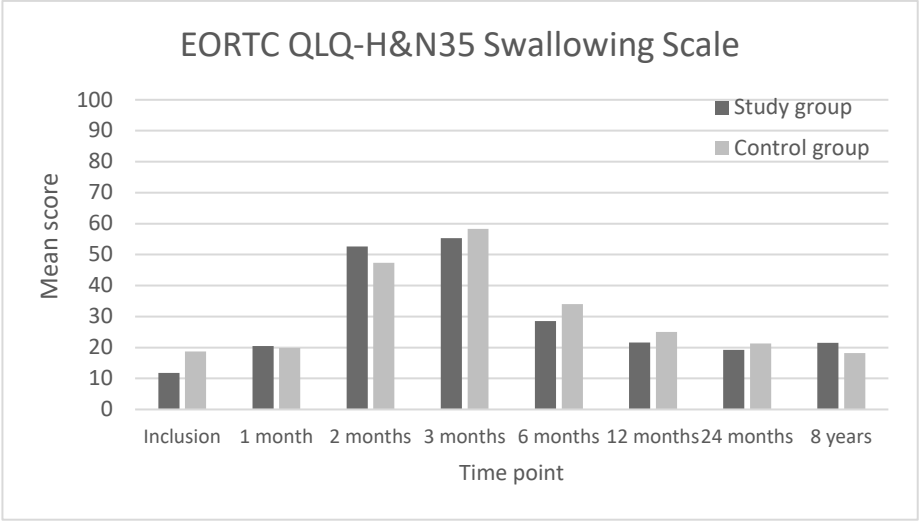


Figure 9. *Results from the swallowing scale in the EORTC QLQ- H&N35 for the study and control groups at different time points. The results are shown as the mean values. A higher value indicates more problems.*

Table 5. *Results from selected scales and items in the EORTC QLQ-C30 and QLQ-H&N35, the oral intake scale, remaining feeding tube, and the BMI for the study and control groups at different time points.*

	Inclusion			12 months			24 months			8 years		
Randomization group	Study	Control	*p* value	Study	Control	*p* value	Study	Control	*p* value	Study	Control	*p* value
Subjects *n*	64	70		54	54		48	46		32	30	
EORTC QLQ-C30*												
Scales (score) mean												
Global health status	67	63	.27	68	66	.43	77	70	.27	71	79	.083
EORTC QLQ-H&N35†												
Scales (score) mean												
Swallowing	12	19	.20	22	25	.51	19	21	.88	21	18	.97
Social eating	15	20	.32	25	26	.80	20	20	.96	17	14	.36
Pain	25	28	.74	29	27	.51	21	22	.66	16	18	.41
Dry mouth	19	21	.59	72	72	.95	66	67	.89	58	63	.59
Opening mouth	15	19	.28	33	33	1.0	23	33	.19	34	38	.72
Items *n* (%)												
Swallow liquids‡												
1-2	59 (95)	63 (91)		52 (96)	48 (89)		45 (96)	39 (91)		29 (91)	28(100)	
3-4	3 (5)	6 (9)	.60	2 (4)	6 (11)	.27	2 (4)	4 (9)	.61	3 (9)	0	.28
Swallow solid food‡												
1-2	47 (76)	47 (69)		35 (65)	36 (67)		32 (68)	34 (79)		23 (72)	22 (79)	
3-4	15 (24)	21 (31)	.51	19 (35)	18 (33)	1.0	15 (32)	9 (21)	.32	9 (28)	6 (21)	.93
Oral intake scale§												
1	46 (72)	46 (66)		36 (67)	29 (54)		33 (69)	32 (70)		27 (84)	26 (87)	
2	12 (19)	13 (19)		14 (26)	14 (26)		12 (25)	8 (17)		4 (13)	2 (7)	
3	6 (9)	4 (6)		1 (2)	3 (6)		1 (2)	0		1 (3)	1 (3)	
4	0	6 (9)		2 (4)	3 (6)		0	6 (13)		0	1 (3)	
5	0	1 (1)	.14	1 (2)	5 (9)	.057	2 (4)	0	.60	0	0	.84
mean scale value	1,4	1,6		1,5	1,9		1,5	1,6		1,2	1,2	
Remaining tube	0	0	1.0	4 (7)	4 (7)	1.0	1 (2)	1 (2)	1.0	0	0	1.0
BMI¶ mean	24.9	24.8	.91	22.5	21.8	.40	23.4	23.0	.63	25.1	24.8	.84

*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer 30. †European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Head & Neck 35. A high score on global quality of life scale represents a high function, while a high score on the other scales represents a high level of problems. ‡Have you had problems to swallow liquids / swallow solid food: 1 not at all, 2 a little, 3 quite a bit, and 4 very much. §The oral intake scale: 1 normal diet, 2 semi-solid diet, 3 pureed diet, 4 liquid diet, and 5 unable to eat. ¶Body mass index.

Furthermore, there were no significant differences between the study and control groups with regard to the *global quality of life*, *social eating*, pain, dry mouth, and opening of the mouth at the different time points (Table 5).

The patients' swallowing function was assessed by a dietitian with a 5-level *oral intake scale* (1 normal diet – 5 unable to eat, refer to section 3.3.3) and the results are shown in Table 5. At inclusion, there were more patients with level 4 and 5 swallowing function but fewer patients with level 3 swallowing function in the control group than in the study group, the difference was not significant. Twelve months after the start of treatment, the difference was more pronounced between the groups but not significant. After 24 months and 8 years there was no significant difference between the groups.

There was no significant difference between the study and control groups with regard to *remaining feeding tube*, clinical *evidence of esophageal disease*, *weight* or *BMI* after 12, 24 months or 8 years. The *overall survival* was similar between the two groups.

4.2 BIA, PA and SPA as prognostic factors in HN cancer (Paper II)

The study population consisted of the same patients with advanced HN cancer as in Paper I, with the exception of 6 patients who were excluded due to erroneous BIA values, thus resulting in a study cohort of *128 patients*. The patients' mean weight at inclusion was 75.1 kg, BMI was 24.9 kg/m^2 and unintentional weight loss 6 months before diagnosis was 3.15%.

Univariable analyses of overall survival showed that *age* (hazard ration (HR) 1.075 per year, p<.001) and *performance status* (HR=1.85, p<.001) were significant factors (Table 6). *Tumor site* was not a significant factor for survival when divided into 5 tumor sites (HR=1.35, p=.31); however, it was significant when divided into oral cancer and non-oral cancer (HR=3.90, p<.001, Table 6). Tumor *T classification* was a significant prognostic factor for survival (HR=1.88, p<.001). *Unintentional weight loss* (HR=1.066, p=.001), *weight* (HR=.975, p=.005), *height* (HR=.78, p=.005) and *BMI* (HR=.913, p=.010) were all significant factors for survival.

Table 6. *Uni- and multivariable Cox regression analyses on overall survival for patient characteristics, tumor and nutritional factors.*

	Univariable analyses			Multivariable analysis		
	n	HR (95 % CI)	*p*	n	HR (95 % CI)	*p*
Age (years)	128	1.075 (1.051–1.100)	<.001	128	1.030 (1.000–1.062)	.050
Gender				.	.	.
Male	87	1				
Female	41	.95 (.57–1.59)	.85			
Performance status†	128	1.85 (1.43-2.43)§	<.001	128	1.47 (1.14–1.90)§	.003
100	62	1				
90	47	1.64 (.94–2.87)	.085			
80	15	5.40 (2.77–10.54)	<.001			
70	4	4.08 (1.40–11.88)	.010			
Tumor site				128	NS	NS
Non-oral	87	1				
Oral	41	3.90 (2.04–7.47)	<.001			
T classification	128	1.88 (1.48-2.39)§	<.001	128	1.49 (1.15–1.94)§	.003
T0	10	no deaths				
T1	17	1				
T2	32	1.29 (.45–3.72)	.64			
T3	20	2.16 (.75–6.21)	.15			
T4	49	4.42 (1.74–11.24)	.002			
N classification	128	.85 (.66-1.09)§	.20	.	.	.
N0	32	1				
N1	34	.88 (.47–1.63)	.68			
N2	49	.51 (.27–.95)	.033			
N3	13	1.08 (.48–2.43)	.86			
Stage				.		
III	33	1			.	.
IV	95	1.35 (.76–2.39)	.39			
Weight loss‡ (%)	128	1.066 (1.025–1.107)	.001	128	NS	NS
Weight (kg)	128	.975 (.958–.992)	.005	.	.	.
Height (cm)	128	.78 (.65-.93)	.005	.	.	.
Body mass index (kg/m^2)	128	.913 (.852–.978)	.010	128	NS	NS
Resistance (Ω)	128	1.002 (.999–1.005)	.29	.	.	.
Reactance (Ω)	128	.955 (.931–.979)	<.001	.	.	.
Fat free mass percent (%)	128	1.034 (.996–1.073)	.078	.	.	.
Fat free mass index (kg/m^2)	128	.912 (.831–1.001)	.052	.	.	.
Phase angle (°)	128	.47 (.36–.62)	<.001	128	.69 (.50–.96)	.026
SPA (SD)	128	.66 (.52–.84)	<.001	.	.	.

Abbreviations: *SPA*, Standardized phase angle. *HR*, hazard ratio; *CI*, confidence interval. *NS,* not significant with significance level 0.05 in the multivariable analysis. †Karnofsky Performance Status. ‡Unintentional weight loss 6 months before diagnosis. §The overall hazard ratio for the ordered categorical variables corresponds to the hazard ratio for each step in the ordinal scale.

The mean resistance value was 512 Ω, and the mean reactance value was 52.3 Ω. *Reactance* was a significant prognostic factor for survival (HR=.955, p<.001), in contrast to resistance. The mean FFM% was 77.6% and the FFMI was 19.2 kg/m^2, which were not significant factors for survival.

The mean *PA* was *5.85°* and the median PA was *5.91°*. PA was a significant prognostic factor for survival (HR=.47, p<.001, Table 6). The patients with the lower half of PA values had significantly shorter survival than the patients with higher values (median PA 5.91°, p<.001, Figure 11). An ROC curve of how PA predicted 5-year survival showed an AUC of 0.73. The cut-point PA value that provided the most accurate prediction of 5-year survival was *5.95°* (Figure 12, 70.3% correct predictions, sensitivity 64% and specificity 81%).

The mean SPA was -0.013 SD (Table 6). *SPA* was a significant prognostic factor for survival (HR=.66, p<.001), and the patients with the lower half of SPA values had significantly shorter survival than the patients with higher values (p<.001). The area under the ROC curve for SPA to predict 5-year survival was 0.66.

Multivariable analysis indicated the following independent significant factors for survival: *age* (HR=1.030, p=.050), *performance status* (HR=1.47, p=.003), *T classification* (HR=1.49, p=.003) and *PA* (HR=.69, p=.026, Table 6).

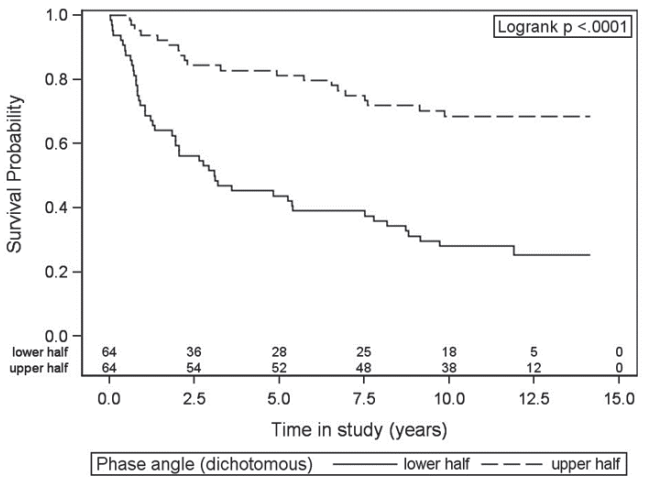


Figure 10. *Overall survival probability for patients with phase angle values in the lower half versus upper half (median PA 5.91°).*

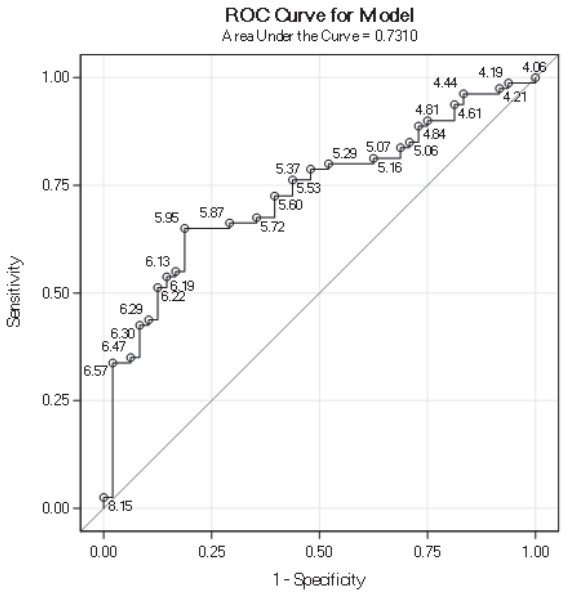


Figure 11. *ROC-curve of how phase angle predicts 5-year survival. Points labeled by the phase angle value.*

4.3 PA changes and prognostic importance over time (Paper III)

One hundred twenty-eight patients with advanced head and neck cancer were included in this study, the same population as in Paper II. BIA was performed at *eight* different *time points*: at diagnosis, 1, 2, 3, 6, 12 and 24 months after the start of treatment and after 6–10 years, and the PA was calculated (Table 7). The mean PA at diagnosis was 5.85°. The PA decreased after diagnosis and was *significantly lower* than at diagnosis after 1, 2, 3 and 6 months after the start of treatment. The lowest PA was identified 3 months after the start of treatment, and at this time point, the mean PA was 5.34°. After 12 and 24 months, there was no significant difference in the PA compared to at diagnosis.

Table 7. *Phase angle values at different time points for all patients with available data at each time point and for only the patients with data from all time points.*

Phase angle (°)	n	All patients	n	All-time-point patients
Diagnosis, mean (SD) median (range)	128	5.85 (0.98) 5.91 (4.06-8.45)	58	6.25 (0.94) 6.23 (4.06-8.45)
1 month, mean (SD) median (range)	118	5.79 (1.30) * 5.54 (3.40-11.31) *	56	6.22 (1.24) 5.94 (3.40-9.71)
2 months, mean (SD) median (range)	120	5.64 (1.01) * 5.78 (3.45-8.26) *	58	6.05 (0.93) * 6.11 (3.45-8.26) *
3 months, mean (SD) median (range)	119	5.34 (1.32) * 5.35 (2.57-12.55) *	56	5.69 (1.06) * 5.64 (3.40-8.55) *
6 months, mean (SD) median (range)	114	5.46 (1.20) * 5.39 (2.56-12.77) *	57	5.88 (1.24) * 5.62 (3.93-12.77) *
12 months, mean (SD) median (range)	104	5.82 (1.12) 5.73 (2.81-9.03)	58	6.20 (1.11) 6.31 (3.17-9.03)
24 months, mean (SD) median (range)	92	6.07 (1.02) 6.05 (4.24-8.89)	58	6.18 (1.01) 6.14 (4.24-8.81)
6–10 years, mean (SD) median (range)	58	5.88 (1.27) * 5.72 (3.47-11.58) *	58	5.88 (1.27) * 5.72 (3.47-11.58) *

Significant difference in phase angle compared to at inclusion is shown as *.

The patients with a high PA at diagnosis had a significantly higher PA during all seven follow-up time points than the patients with a low PA at inclusion. The decrease in the PA from diagnosis to the 3-month follow-up was larger for the patients with higher than lower PA values at diagnosis.

Half the patients had a *PEG*, and the other half nutritional support. The PA at diagnosis was higher in the nutritional support group than in the PEG group but the difference was not significant. There was no significant difference between the groups at 1, 2, 3, 6, and 12 months after treatment, but the PA was significantly higher in the nutritional support group than in the PEG group after 24 months and 6–10 years.

PA was a significant factor for survival at *all 8 time points*, i.e., not only at diagnosis. The decrease in the PA between diagnosis and 3 months after treatment was not significantly correlated with survival; however, the increase

in the PA 3 to 12 months after the start of treatment was a significant factor for survival.

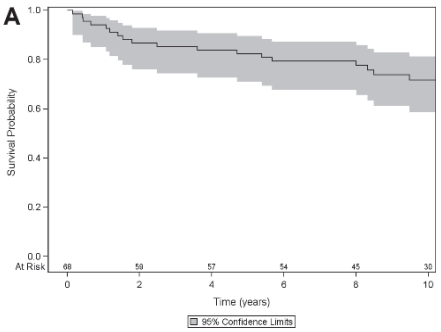
4.4 Results from the Regional HNCUP study (Paper IV)

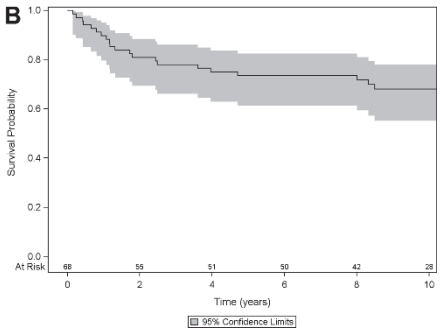
Sixty-eight patients with HNCUP treated with curative intent were included in paper IV. The patients' mean age was 59 years, and the majority of the patients were males, 81%. The most common tumor N classification was N2 (63%), whereas 19% were N1 and 18% were N3. The tumor histopathology was SCC in 85% of the cases and undifferentiated carcinoma in the remaining cases. Extracapsular tumor extension was identified in 27%.

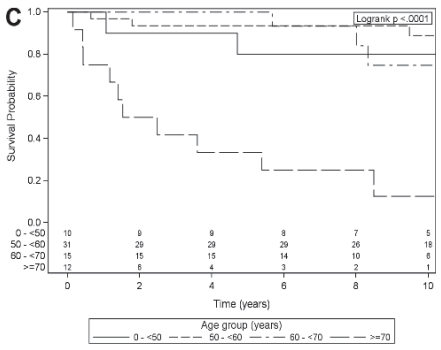
The 2-, 5- and 10-year overall survival rates for all patients were 87%, *82%*, and 72%, respectively (Figure 13A), and the corresponding disease-free survival rates were 81%, 74%, and 68%, respectively (figure 13B).

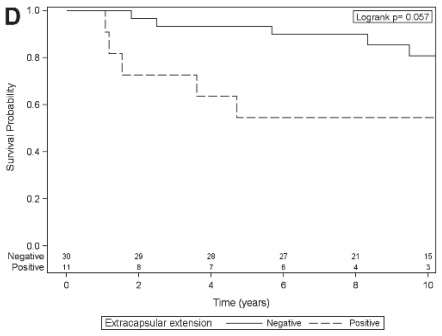
There was a significant difference in the overall survival between different age groups ($p<.001$, Figure 13C). The patients who were *70 years old or older* had a significantly worse overall survival rate than the other age groups together ($p<.001$). Standardized mortality rates (SMR) were calculated, and the patients 70 years or older had an SMR of 22.5 ($p<.001$) whereas the patients younger than 70 years had an SMR of 4.2 ($p=.002$). There was a significant difference in the comparison of these SMR values ($p=.014$), which indicated that an age >70 years was a significant prognostic factor for survival in these patients with HNCUP following correction for normal aging.

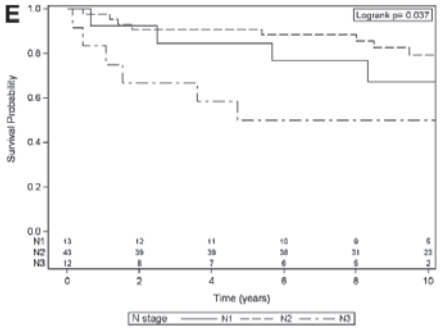
Men and women had no significant difference in survival (Figure 13C). *Extracapsular tumor extension* gave a worse survival rate than tumors limited to the lymph glands, but the difference was not significant ($p=.057$, Figure 13D). There was a significant difference in survival between patients with N1-, N2-, and N3-class tumors ($p=.037$, Figure 13E). *N3* tumors had a significantly worse prognosis than the combined N1 and N2 tumors ($p=.010$).

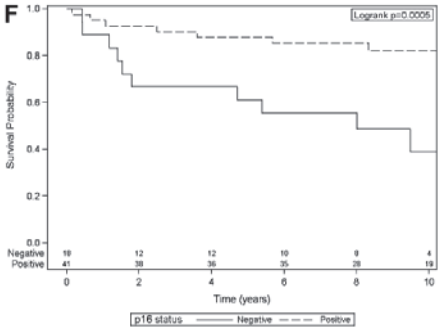

A
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
At Risk
68
59
57
54
45
30
0
2
4
6
8
10
Time (years)
95% Confidence Limits

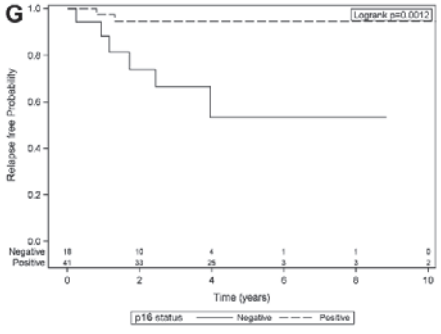

B
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
At Risk
68
55
51
50
42
28
0
2
4
6
8
10
Time (years)
95% Confidence Limits


C
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 - <50 10 9 9 8 7 5
50 - <60 31 29 29 29 26 18
60 - <70 15 15 15 14 10 8
>=70 12 6 4 3 2 1
0
2
4
6
8
10
Time (years)
Age group (years)
0 - <50
50 - <60
60 - <70
>=70


D
Logrank p= 0.057
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Negative 30 29 28 27 21 15
Positive 11 8 7 6 4 3
0
2
4
6
8
10
Time (years)
Extracapsular extension
Negative
Positive


E
Logrank p= 0.037
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
N1 13 12 11 10 9 6
N2 43 39 38 38 31 23
N3 12 8 7 6 6 2
0
2
4
6
8
10
Time (years)
N stage
N1
N2
N3


F
Logrank p=0.0005
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Negative 19 12 12 10 9 4
Positive 41 38 36 35 28 19
0
2
4
6
8
10
Time (years)
p16 status
Negative
Positive


G
Logrank p=0.0012
Relapse free Probability
1.0
0.8
0.6
0.4
0.2
0.0
Negative 18 10 4 1 1 0
Positive 41 33 25 3 3 2
0
2
4
6
8
10
Time (years)
p16 status
Negative
Positive

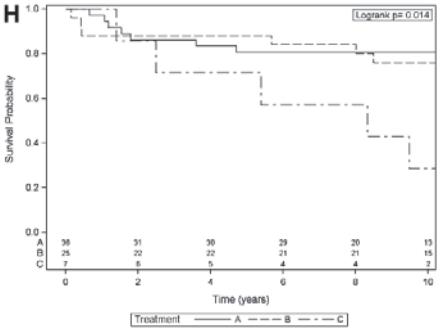

H
Logrank p= 0.014
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
A 36 31 30 29 20 13
B 25 22 22 21 21 15
C 7 6 5 4 4 2
0
2
4
6
8
10
Time (years)
Treatment
A
B
C

Figure 12. *Kaplan-Meier plots for different prognostic factors. The overall survival is shown in A, C, D, E, F and H, in B the disease-free survival, and in G the relapse-free probability. The number of patients at risk is shown at the bottom of the figures. Significance levels were calculated with a log-rank test. A, B The whole study population, the shaded area shows the 95% confidence limits. C Age groups. D N stage. E Extracapsular tumor extension. F, G p16 status. H Treatment. Treatment A = neck dissection and postoperative radiation, treatment B = (chemo)radiation, and treatment C = neck dissection.*

P16 staining was possible in 59 of the 68 tumors, and *69%* of the tumors were p16 positive whereas 31% were p16 negative. The p16-positive patients were 6 years *younger* than the p16-negative patients, but the difference was not significant. N1-class tumors were more common, and N2 was less common, among the p16-positive than the p16-negative patients. The *survival* was significantly *better* for the patients with p16-positive tumors than with p16-negative tumors ($p<.001$, Figure 13F). There was a significantly higher risk for *recurrence* among the patients with p16-negative tumors than p16-positive tumors, 38% vs 4%, respectively ($p=.001$).

Thirty-six patients were *treated* with neck dissection and postoperative radiation, 25 patients were treated with (chemo)radiation and 7 patients were treated with neck dissection. The patients treated with neck dissection and postoperative radiation and with (chemo)radiation had *no significant difference* in overall survival (Figure 13H), and the risks for recurrence were similar in the two treatments. The two groups had similar age and gender distributions, and tumor histology; however, the patients treated with (chemo)radiation had less advanced tumor N class than the neck dissection and postoperative radiation group (not a significant difference). There were significant differences regarding the radiation schedule and radiation to the nasopharynx between the groups, and more patients had chemotherapy in the (chemo)radiation than in the neck dissection and postoperative radiation group (72% vs 17%, respectively, $p<.001$).

In the multivariable analysis, *age* (HR=2.73 per 10 years, $p<.001$), *N3* classification (HR=6.25, $p=.001$), and *p16 status* (HR=4.30, $p=.003$) were significant factors for overall survival.

4.5 Results from the National HNCUP study (Paper V)

In paper V, *260 patients* with HNCUP were included, including 216 patients treated with curative intent and 44 patients treated with palliative intent. The mean age for the curative intent patients was *62.5 years*, and 76% were *males*. Approximately 9/10 of the patients treated curatively had a performance status WHO 0 and the tumor histopathology was SCC (94%) or undifferentiated carcinoma (6%). The most common N class was N2, which comprised 65% of the patients, whereas 25% were N1 and 11% were N3. The palliative intent patients were older, had worse performance status and had a more advanced N class than the curative intent patients; 32% of the palliative intent patients had M1 tumors.

The overall 2-, 5- and 8-year survival rates for the patients treated with curative intent were 86%, *71%* and 68%, respectively and the 2- and 5-year disease-free survival rates were 83% and 70%, respectively.

Age was a significant factor for overall survival (HR=1.076, p<.001, Table 8). The overall survival significantly differed between the different age groups (p<.001), as well as the disease-free survival (p<.001). The patients 70 years old or older had significantly worse overall 5-year survival than the patients younger than 70 years (p<.001). The patients 60-69 years old had significantly worse survival than the patients younger than 60 years (p<.001).

There were no significant differences in overall survival between genders and according to smoking history. Survival significantly differed between patients with different *performance statuses* (p<.001, Table 8). There was no significant difference in overall survival between the patients with tumor histology SCC and undifferentiated carcinoma. The overall survival significantly differed for patients with different tumor *N classes* (p=.002, Table 8). The patients with N3 tumors had a significantly worse prognosis than the other patients (p=.003). The patients with N2 tumors had a significantly worse prognosis than the patients with N1 tumors (p=.045, Table 8).

HPV analysis was performed in 95 of 216 patients treated with curative intent. Of the curatively treated patients, *84%* had HPV-positive tumors. These patients were significantly *younger* and had significantly more *SCC* than undifferentiated carcinoma than the patients with HPV-negative tumors. The overall survival for the curative treated patients was better for the

patients with HPV-positive than HPV-negative tumors but the difference was *not significant* (p=.39, Table 8) nor was the disease-free survival (p=.45).

Table 8. *Uni- and multivariable Cox regression analyses on overall survival for patients treated with curative intent.*

	Univariable analyses			Multivariable analysis		
	n	HR (95 % CI)	*p*	n	HR (95 % CI)	*p*
Age (years)						
Continuous	216	1.076 (1.053–1.099)	<.001	201	1.072 (1.042–1.102)	<.001
Gender						
Male	165	1		.	.	
Female	51	.79 (.43–1.44)	.44	.	.	.
Smoking habits						
Never smoker	17	1		.	.	
Former smoker*	22	.73 (.18–2.94)	.66	.	.	.
Smoker	12	1.01 (.23–4.53)	.99	.	.	.
Performance status†						
0	179	1		179	1	
1	19	3.90 (2.04–7.47)	<.001	19	2.12 (1.05–4.26)	.036
2	3	5.58 (1.72–18.1)	.004	3	2.92 (.80–10.7)	.10
Tumor histology						
SCC	202	1		.	.	
Carcinoma N/S	14	1.54 (.66–3.58)	.31	.	.	.
HPV status						
Positive	80	1		.	.	.
Negative	15	1.54 (.57–4.16)	.39	.	.	.
N stage						
N1	53	1		51	1	
N2	139	2.08 (1.01–4.27)	.045	130	1.82 (.88–3.81)	.11
N3	23	4.39 (1.85–10.4)	.001	20	2.63 (1.02–6.78)	.046
Treatment						
A	122	1		110	1	
B	87	1.11 (.66–1.86)	.70	84	1.44 (.83–2.50)	.20
C	7	3.07 (1.20–7.87)	.019	7	.63 (.20–1.97)	.42

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval. *SCC,* squamous cell carcinoma. *Former smoker quit smoking at least 1 year ago. †WHO Performance status. Treatment A, neck dissection in combination with (chemo)radiation. Treatment B, (chemo)radiation. Treatment C, neck dissection.

The curatively treated patients were divided into 3 groups based on the treatment: neck dissection in combination with (chemo)radiation (122 patients, (chemo)radiation (87 patients), and only neck dissection (7 patients). There were *no significant differences* in the overall or disease-free survival between the patients treated with neck dissection in combination with (chemo)radiation and (chemo)radiation alone (Table 8). The overall 5-year survival for the patients treated with neck dissection in combination with (chemo)radiation was 73% and with (chemo)radiation alone 71%. The patients who received both treatments had similar age, smoking habits, performance status, tumor histology and HPV status; however, there were significantly more males in the group treated with neck dissection in

combination with (chemo)radiation than (chemo)radiation alone. The patients who received (chemo)radiation had a significantly higher radiation dose, more radiation to the bilateral neck and more chemotherapy than the patients who received neck dissection in combination with (chemo)radiation.

In the multivariable analysis, *age* (HR=1.072 per year, p<.001), *performance status* (HR=2.12 WHO 1 versus 0, p=.036) and *N classification* (HR=2.63 N3 versus N1, p=.046) were significant factors for overall survival. Treatment was not a significant factor for overall survival.

5 DISCUSSION

This thesis investigates different aspects of patients with advanced HN cancer. It examines whether use of PEG for enteral nutrition increases the risk for permanent dysphagia. It investigates how useful PA is at diagnosis and at different time points during and after the cancer treatment as a prognostic factor for survival. It also examines the importance of HPV and other prognostic factors in HNCUP and compares the survival after the most common treatments.

5.1 PEG and swallowing in HN cancer

Many patients with advanced HN cancer have dysphagia and are malnourished. It is important to detect and treat malnutrition in these patients. Different methods may be used to treat the malnutrition, including enteral tube feeding with an NGT or a PEG. Studies have indicated that the use of PEG can lower the risk for malnutrition in HN cancer during treatment and have recommended use of the method.[58,151] However, concerns have been raised regarding PEG that it may increase the risk for permanent dysphagia.

In paper I, *no significant difference* in the swallowing function was identified between the patients who received a PEG and nutritional support according to clinical praxis (in most cases, including the use of an NGT). A study by Prestwich et al. supported the finding in paper I and indicated that PEG and NGT provided a similar risk for dysphagia[152], whereas other studies have identified higher rates of dysphagia after PEG than after NGT.[60,61,153-157] However, these previous studies were not randomized (and have other methodological issues). A major advantage of paper I was that the patients were *randomized* and prospectively assessed, which made the comparison between the groups reliable. To my knowledge, no other randomized controlled study on PEG in HN cancer has been performed; thus, in this respect, paper I is unique.

The patients were assessed for approximately 8 years. This is a long time compared to most previous studies, in which patients were evaluated for up to 6 months[155] or 1 year[153,154,157], even though some studies have assessed the swallowing after 5 years.[60] Changes in swallowing may occur more than 1 year after the cancer treatment; thus, a long-term assessment of swallowing function as in paper I is interesting. Because patients with advanced HN cancer have a 5-year survival at approximately 50%, this paper investigates the *long-term*

survivors. The loss of patients was consequently relatively high; however, it was similar in both groups, and there were still enough patients in order to evaluated the outcomes even after eight years.

A discussion could be raised on the outcome data in paper I. The swallowing scale in the *EORTC QLQ H&N35* was used as the primary outcome to assess the swallowing function. The EORTC QLQ H&N35 is a validated and well-established questionnaire.[140] It is a method that does not visualize the swallowing but relies on the patient's perception of his/her swallowing function. It is established that methods that visualize swallowing may identify more subtle changes in the swallowing process than questionnaires, including silent aspiration.[24] On the other hand, it may be questioned how important it is to identify asymptomatic changes in these patients. Furthermore, additional factors linked to the swallowing function were investigated in paper I, including tube dependence, clinical evidence of esophageal disease, BMI and global quality of life, and there were no significant differences between the groups at the long-term follow up in these factors. There are a number of other validated questionnaires that may be used to evaluate swallowing; however, many of these were not well-established methods during the time when the study started in 2002, for example, the MDADI, SWAL-QOL and FOIS.[28,29,31] The oral intake scale is not validated but was employed because it was very easy to use and it served as a complement to the EORTC QLQ H&N35.

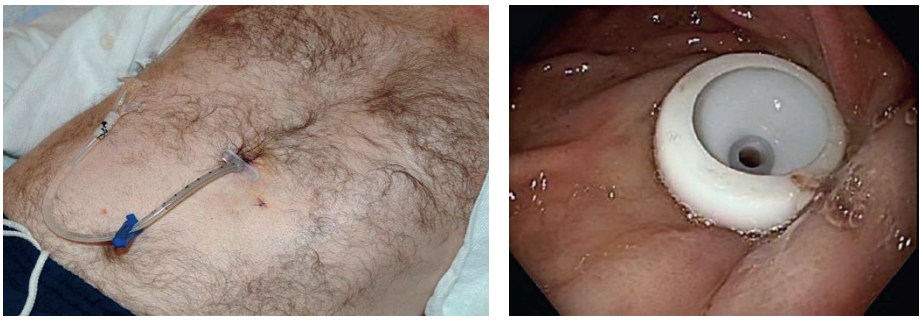


Photo of a 61-year-old male with tonsil cancer with a PEG tube (left photo). The tube was placed on the left side of the abdomen a few centimeters below the ribs arc. The patient participated in papers I-III and is still alive. Photo by Ewa Silander. Right photo on another patient with a PEG tube seen from the ventricle with a gastroscope. The right photo adopted from Waghray et al.[158] and reused with permission from the Annals of Gastroenterology.

In all randomized controlled studies, there is an established problem that patients in the treatment groups may have different *compliance* to the study.[159] One example is a study by Corry et al. on PEG, in which the randomization process had to be interrupted because too many patients withdrew their informed consent to participate in the study.[155] In paper I this was not a problem; only 11 of 145 patients (8%) were excluded after randomization, including 8 patients (11%) in the study group and 3 patients (4%) in the control group. At the follow-up after approximately 8 years, a large part of the surviving patients was examined. In summary, the study had a good compliance. One may speculate in the reasons for this, and probably factors such as good personal contact with the research team and easily performed tests at the follow-ups contributed to the good compliance.

PEG is a surgical method and has other side effects and risks in addition to the considerations on swallowing. The complications may be divided into minor and major, and there is a low risk for mortality. The risks for complications vary in the literature, as described in chapter 1.3.3. Among the patients who received PEG in paper I, most complications were mild. The most common side effect was granulation tissue in the stoma which was treated locally. Benign peristomal infection also occurred in some patients. One patient had abdominal pain and underwent a diagnostic laparotomy; however, no leakage or peritonitis was identified. One fatal complication occurred in a patient who had a PEG and dislodged the tube during a delirium tremens at home. He developed peritonitis, general organ failure and died after 6 days. It was a fragile patient with advanced hypopharyngeal cancer who had no complication during the PEG surgery. In the control group, there were no serious complications. Twenty-eight patients lost their NGT unintentionally on one or more occasions and had a new NGT as soon as possible. Fifteen patients had tube-blocking and received a new tube.

In conclusion, PEG may be used in patients with advanced HN cancer without increased risk of clinically relevant permanent swallowing problems. The specific patients with HN cancer who should be recommended for a PEG must be decided from case to case and has to weight the probable gains with the procedure against the risks.

5.2 PA as a prognostic factor in HN cancer

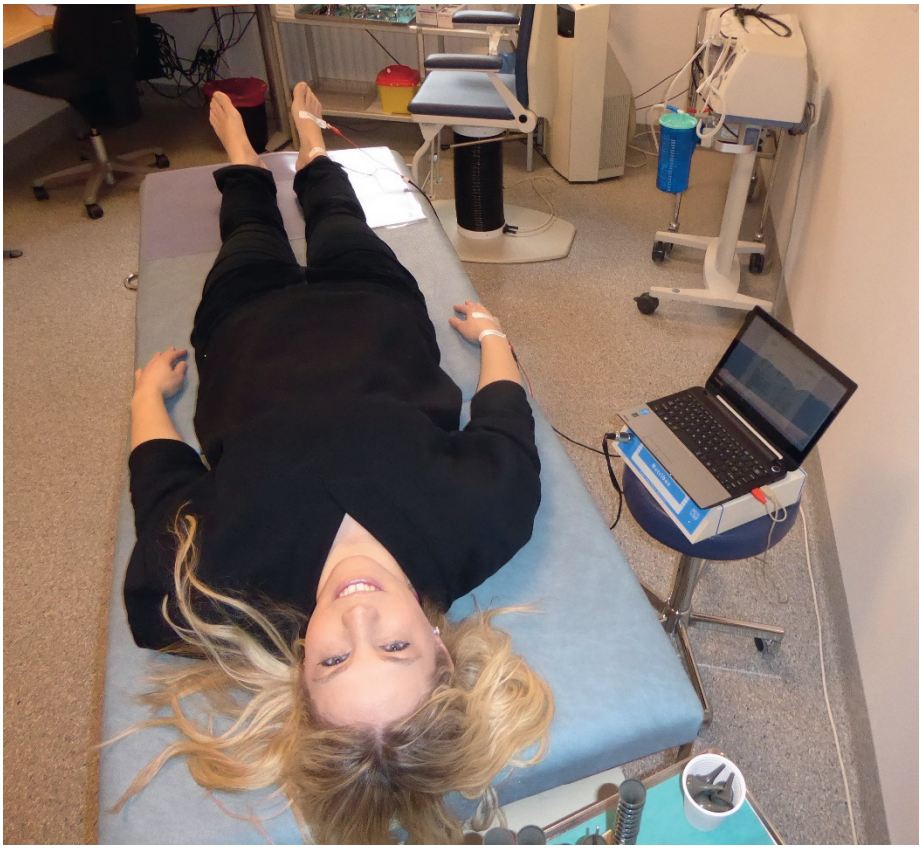
Patients with advanced HN cancer have a difficult situation. The treatment required to cure the disease has considerable side effects, and after completion of the treatment, a considerable risk that the disease is not cured remains. Thus,

it is important to consider different prognostic factors and plan the treatment carefully to avoid over- and undertreatment of the patient. Patients with HN cancer are often malnourished at diagnosis and during treatment. FFM and PA have been associated with the nutritional status of the patient and the prognosis for survival in different types of cancer. In papers II and III, the prognostic importance of PA on survival was investigated for patients with HN cancer.

In paper II, we found that the PA at diagnosis was a *significant predictor for survival* in patients with advanced HN cancer, also in the multivariable analysis. A study by Władysiuk et al. on patients with HN cancer also identified the PA at diagnosis to be a prognostic factor for survival, thus supporting paper II.[160] The prognostic importance of the PA on survival is considered a main finding. It makes the PA interesting to study further, and it has the potential to be used together with other important factors, such as age and performance status, in treatment planning.

PA was a *stronger predictor* for survival than other nutritional factors, including weight, weight loss and BMI. PA was also better in predicting survival than the BIA-derived factors FFM% and FFMI. This is interesting as these nutritional factors are part of the definition of malnutrition and are established prognostic factors for survival.[34,53] PA thus seems to measure the effect of malnutrition on survival better than the previously used methods.

Why is the PA good in predicting survival? The PA is calculated from R and X_c. R is considered to depend on the resistance of intra- and extracellular fluid, and X_c depends on the function of the cell membranes (Figure 2).[63] Analyzing paper II, it may be noted that X_c is far more determining for the predictive power of PA than R, even if R also has a minor contribution. Thus, *dysfunction of the cell membranes* and the *total cell volume* seem to be the most critical factors for why PA predicts survival. This could be considered logical, as transport through cell membranes is energy dependent[161], and this transport system likely works less well during malnutrition.



BIA tetra polar examination on a 39-year-old woman. In this case, a BIA Nutribox machine was used. Photo by the author.

PA is *dependent on gender, age and BMI*. In paper II, *SPA* was also investigated as a predictive factor for survival. SPA was identified as a significant predictor of survival. However, when analyzing how well SPA predicted survival with an ROC curve, it was not as accurate as PA. This finding was interesting and demands further discussion. One could attempt to explain this observation based on the knowledge that patients with HN cancer are different from the reference population of healthy German individuals. Surprisingly, the mean PA and the SD in paper II were similar to that of the healthy reference population; the mean SPA was approximately 0, and the SD was near 1. Thus, from a PA perspective, the patients in paper II seem similar to the reference, which does not provide an explanation as to why PA was better than SPA. (Another reference population in the study by Barbosa-Silva

et al. had a higher mean PA than the reference population we used, and if we had employed the Barbosa-Silva population, the SPA would have been lower.[162]) The explanation may instead be found when examining the reference values. The PA is lower in females, at a higher age and at a lower BMI.[148] Increased age and lower BMI were both significant negative factors for survival in paper II, and correction for these factors with SPA compared to PA will thus impair the prediction of survival.

In paper II, the cause of death within 5 years was analyzed and grouped for the patients. To my knowledge, this has not been done previously for PA in HN cancer. In the patients with high PA, with a *good prognosis*, no patients died of the treatment and most patients died of the initial cancer. This finding suggests that these patients both have a treatment that works well and may simultaneously benefit from escalated cancer treatment. In the patients with a low PA, with a *worse prognosis*, most patients died of the initial cancer; however, some patients also died of the treatment. This finding suggests that these patients have a more difficult situation in which they would benefit from an escalated cancer treatment and simultaneously have a risk of death from the treatment because of side effects. This group of patients requires careful monitoring both during and after the treatment to improve the rehabilitation and find recurrences.

What *cut-off value* of PA at diagnosis should be used? In paper II, PA *5.95°* was the value at which the best discrimination between the good and worse prognosis groups was achieved. This value is slightly above and relatively near the median at 5.91°, which makes the two prognosis groups similar in size (good prognosis group contained 47% of the patients and the worse prognosis group included 53%). Norman et al. suggested the use of the median as the cut-off value.[163] Previous studies on PA in cancer have used this approach, including studies on advanced pancreatic cancer where the cut off was 5.0°[73], advanced colorectal cancer 5.57°[72] and breast cancer 5.6°[71]. In a study of mixed cancer patients who were planned for radiation, the median PA was 5.95° and the cut-off value was set to 5.2°.[164] In a study on patients with advanced HN cancer, the mean PA was 5.04° and the cut off was 4.73°. In summary, the median and cut-off values of PA in paper II appear to be relatively higher than most previous studies.

To use a PA cut-point value, the BIA machine must be regularly *calibrated* (which was performed for papers II and III at the hospital's medical-technical department). The measures must be performed in a correct body position and after standardized times of fast and rest prior to the measurement. Before PA may be implemented in clinical praxis, larger groups of patients with HN

cancer must be investigated to reproduce the findings in papers II and III and provide more certainty of the PA cut-point value that discriminates between different subgroups of HN cancer.

How does *PA change* over time in patients with HN cancer? In paper III, it was determined that PA decreased during the first 3 months after the start of treatment, subsequently increased at 6 months and returned to the value at diagnosis after 12 months. This finding was expected and follows the nutritional status of these patients during the treatment and recovery phases. To my knowledge, the change of PA over time in patients with HN cancer or cancer in general has not previously been studied.

In paper III we found that PA was a significant factor for survival at *all measured time points* during and after treatment, which has also not previously been studied. This finding is interesting because it further shows the prognostic value of PA. It may suggest the use of repeated PA measures in HN cancer patients, even though the most useful measure is at the treatment planning, at diagnosis. However, the *change in PA* from diagnosis to 3 months after the start of treatment was not a significant factor for survival, and the patients who had a larger decrease in PA had better survival. The change in PA from 3 months to 12 months was a significant factor for survival; however, it was not as strong as the absolute values at the different time points. Thus, one may conclude that PA at any time point may be used to predict survival (though with another median and cut-point value of PA than at diagnosis); however, the changes in PA between time points seem less suited for use in predicting survival.

There are many *advantages* with BIA as a clinical method, which may make it easy to use in the clinical work. It is a non-invasive method, which indicates that it does not involve the introduction of instruments into the body. When performed, you cannot perceive the current, only the electrodes. It is a safe method with no reported side effects, but the manufacturers of the BIA machines dissuade for safety reasons from measures in patients with an implantable cardioverter defibrillator or with an older model of pacemaker. It is an easy to use method that may be introduced to different care professionals. The test only requires approximately 3–5 minutes. The equipment is inexpensive.

Are there no *problems* with BIA? Approximately 4% of the measures in papers II and III provided erroneous or *extreme PA values* despite the correction of the electrodes and retesting. Both the R and X_c could be extreme and both extremely high and low PA values were observed. These patients had, in most

cases, normal PA values at the other time points measurements. The reason for the extreme values is not known. It is important to perform the *measurements under standardized conditions* as previously discussed to minimize the risk for errors. Furthermore, in general, BIA values are considered more uncertain in situations where the patients are *extremely hydrated*, for example, at the intensive care unit or at patients with profuse edema.[165] Medication with *diuretics* may also influence the BIA values. BIA used to calculate FFM is also considered not as accurate in patients with *extreme body composition*, at the extremes of BMI[165]. It is not known how predictive PA is for survival in these patients.

The number of patients in papers II and III was 128, which reflects, to our knowledge, the largest study on the prognostic value of PA in HN cancer. However, a *limitation* of papers II and III was that relevant factors were not included that would have been interesting to investigate in relation to PA. Smoking status was not included because of unreliable data. HPV status was not known to be an important factor at the time of the start of the study and was not included. CRP and albumin were unfortunately not analyzed; however, they are known to influence PA.[166]

In conclusion, PA is a significant prognostic factor for survival in advance HN cancer. PA has many methodological advantages that make it a promising tool to use. Further studies are required on PA in patients with HN cancer before it may be implemented in clinical praxis.

5.3 Importance of p16/HPV in HNCUP

HNCUP is a diagnosis of exclusion where an extensive medical investigation is performed to attempt to identify the primary tumor, and despite being a rare disease, HNCUP is an important diagnosis in HN departments. HPV has been found to be a dominating cause for cervical cancer,[98] and during later years, it has also been identified to be an important factor in HN cancer, particularly oropharyngeal cancer.[111] There is an increasing interest regarding the importance of HPV in HNCUP; however, it is not well studied.

Papers IV and V indicated that HPV is common in patients with HNCUP, in which 69% of the HNCUP were positive in paper IV and 82% in paper V. In two previous studies on patients with HNCUP, the HPV prevalence was 74% and 91%, i.e., similar to papers IV and V.[167,168] Thus, HPV is prevalent in a majority of HNCUP tumors and is likely an *etiological factor* in most cases of HNCUP. Because HPV infection is most common in the genitals, the probable

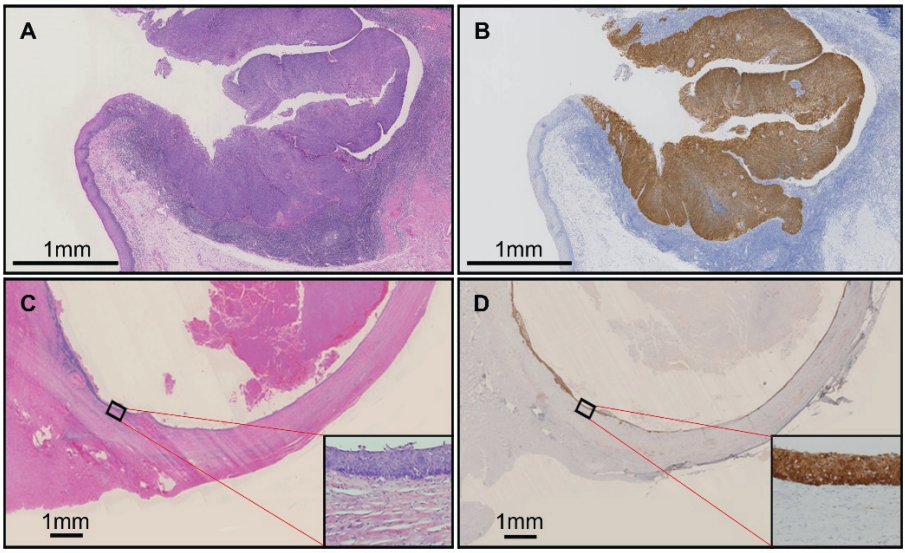
transmission route of HPV is genital-oral, i.e., *sexually transmitted*. Because HPV is an important causal agent for HNCUP, the prevention of HPV may also prevent many cases of HNCUP. To date, girls are routinely *vaccinated* for high-risk HPV. Given that HPV is an etiological factor for HNCUP (and for several other types of cancer) and that HNCUP (and some other types of cancer) most often affects males, one may suggest that boys should also be recommended HPV vaccination (considering that the effect of herd immunity is not complete). This has also been suggested.[169] Because vaccination is performed, it is likely that the prevalence of HNCUP will decrease in the coming years.

In paper IV and V, we found that patients with p16/HPV-positive tumors had *better prognosis for survival* than patients with p16/HPV negative tumors. The difference was significant in paper IV but not in paper V. The non-significant result in paper V and the differences between the two studies are interesting and merit consideration, particularly as more patients with HPV were analyzed in paper V than IV. The difference in background factors between HPV positive and negative patients was relatively similar in the two studies and does not seem to explain the different result. In paper V, many patients did not undergo HPV analysis in contrast to in paper IV, and a selection bias cannot be excluded, even if no bias is evident. Methodological aspects in paper V (previously discussed) may have influenced the result.

Nevertheless, after summarizing the results from papers IV and V, HPV may be regarded as an important prognostic factor in HNCUP that should be considered in treatment planning. Moreover, HPV status has been implemented in clinical praxis as it is considered in the recently published 8th edition of the *TNM classification* of malignant tumors. The staging of HNCUP includes the HPV status (as well as the EBV status and ECE).[170,171] Studies by Sivars et al. and Keller et al. both indicated significantly better survival for patients with HPV-positive than HPV-negative HNCUP.[167,172] A further support for the importance of HPV status as an important clinical factor in HNCUP was that patients in paper IV with HPV-positive tumors had significantly *fewer tumor recurrences* than patients with HPV-negative tumors.

The patients with HPV-positive tumors were significantly *younger* in paper V and non-significantly younger in paper IV than the patients with HPV-negative tumors. Previous studies have supported this finding, and a significant difference was identified in two studies[167,168] with a non-significant difference in another study.[172] The difference in age is not unexpected because of differences in the oncogenic mechanisms between HPV-positive and negative

tumors. With respect to other cancers, this age difference is also present; cervical cancer known to be caused by HPV has a median age of 49 years[173], whereas lung cancer known to be caused mainly by tobacco smoking has a median age of 69 years.[174] Patients with HPV-positive tumors had a better performance status, lower rate of tumor extracapsular extension, and better N and M classes than patients with HPV-negative tumors; however, the differences were not significant. These findings are also likely caused by differences in the formation and characteristics of HPV-positive and negative tumors.



Histopathologic examination of an occult tonsillar cancer (A and B) with cystic node metastasis (C and D). Hematoxylin and eosin staining is shown in A and C, and p16 immunostaining is shown in B and D. The scale bar corresponds to 1 mm. The superficial mucosal layer of the tonsil was found to be intact; however, cancer cells were prominent in a crypt layer with invasion into the submucosal layer. The cancer expressed p16 (brown color). Cancerous tissue was also identified in a thin cystic wall and diffusely expressed p16. Image from Yasui et al.[175]and reused with permission from PLOS ONE.

There are different methods to detect HPV in tumors. In this thesis, *p16* immunostaining was the method employed to determine the HPV status in papers IV and V, in the latter paper in combination with/or only with PCR in some cases. P16 is the most widely used method to assess HPV status, and it

has many advantages, including a *high sensitivity*, *high accessibility*, is easy to use on formalin-fixed paraffin-embedded samples, detects *transcriptionally active virus* and is relatively inexpensive.[123] However, P16 also has several disadvantages, including a *lower specificity*. In a study by Schache et al., the differences in the accuracy and prognostic value of different HPV tests were discussed, and the different tests, including p16, were not considered sufficiently specific to be recommend for use as the only test for HPV analysis when used in clinical trials.[176] Furthermore, p16 cannot discriminate between the specific subtype of high risk HPV that is in the tumor, which may be interesting, not least with regard to vaccination that only covers some HPV types. Nevertheless, the disadvantages with p16 may be considered relatively limited, and p16 analysis has been a recommended method for use in the determination of the HPV status in previous studies[177-179] and clinical practice.[180]

Another point of discussion regarding p16 is the specific *criteria* used for determining positive and negative p16 results. In paper IV, the lowest percentage of positive cells considered a positive p16 result was 20%. In paper V, this exact value was not known for the different centers; however, the values were 50% or higher at most hospitals. The specific staining kits that were used at the different regions were not known, and different clinical pathologists performed the p16 analysis in paper V. In paper IV, the same p16 staining kit was used and the same pathologist, blinded for the results, performed the p16 analysis for all patients. In summary, the HPV analyses were more uniform in paper IV than in paper V.

A limitation in both papers IV and V with regard to the HPV investigation was that the number of patients was relatively low to identify smaller significant differences in the uni- and multivariable survival analyses. This situation is unfortunately common in studies of patients with HNCUP. Particularly in paper V, we had hoped for more patients to be HPV analyzed; however, many regions had not started to perform HPV analysis during the time of the study. The methodological aspects of HPV analysis previously discussed, particularly in paper V, may also be considered a limitation.

In summary, it is concluded that HPV is common in HNCUP, and HPV is likely the most important etiological factor for HNCUP. P16/HPV status is a prognostic factor for survival in HNCUP and should be considered in staging and treatment planning.

5.4 Importance of other prognostic factors in HNCUP

Many factors other than HPV are considered in the treatment planning of HNCUP. However, because it is a rare disease, there are no larger recently performed studies on the importance of different prognostic factors in HNCUP.

The factor that had the most importance for survival was, as is well established, whether the patient could be treated with *curative intent*. In paper V, palliative intent patients had a fundamentally worse prognosis than curative intent patients. Linked to palliative treatment were the *M1* tumor class and *poor performance status / advanced comorbidity*, which consequently are the most important prognostic factors.

With respect to curatively intent patients, *age* was a significant prognostic factor for survival in both papers IV and V in both uni- and multivariable analyses. Age was the strongest prognostic factor for survival in both studies. This finding is in line with healthy individuals, where advanced age is known to increase the risk for death.[181] In paper IV, an attempt for statistical adjustment for normal aging was performed using the standardized mortality rates, and it was determined that patients with HNCUP 70 years old or older had a relatively more impaired prognosis for survival than younger patients with HNCUP than healthy individuals 70 years old or older compared to healthy younger patients. Thus, age per se does not explain more than a part of the decreased survival. The fact that age is a significant prognostic factor for survival in HNCUP is both supported[80,86] and not supported[85] in previous studies.

Performance status was shown to be a significant factor for overall survival for the curative intent patients in the uni- and multivariable analyses in paper V. This finding was also identified in a previous study on HNCUP.[80] Performance status is routinely assessed at the tumor conference and is considered in the treatment recommendation; the finding in this thesis emphasizes the importance of this factor.

N classification was a third significant prognostic factor for survival both in uni- and multivariable analyses. Patients with *N3* class tumors had a significantly worse prognosis for survival than the other patients in papers IV and V. The survival for patients with N2 tumors compared to N1 was similar in paper IV and better but with no significant difference in paper V. Previous studies support the findings in papers IV and V and have indicated a worse

prognosis for survival for advanced N class[88,89,182] and N3 versus N1 and N2.[86] In summary, papers IV and V confirm the importance of the N stage, particularly N3, as a prognostic factor in HNCUP.

The histologic tumor type (SCC or undifferentiated carcinoma) was not a significant factor for survival in paper V or in a study by Grau et al.[80] ECE of the tumor was a negative prognostic factor; however, it was not significant among the 41 analyzed patients in paper IV. ECE has been a significant factor in several previous studies of HNCUP.[89-91,183] Gender was not a significant factor for survival in papers IV and V or in two previous studies.[80,88]

One limitation in paper IV with respect to the investigation of the importance of prognostic factors was, as stated in chapter 5.3, that relatively few patients were included. Paper V had substantially more patients; however, unfortunately, there were missing data for several factors, such as smoking status, and no ECE data.

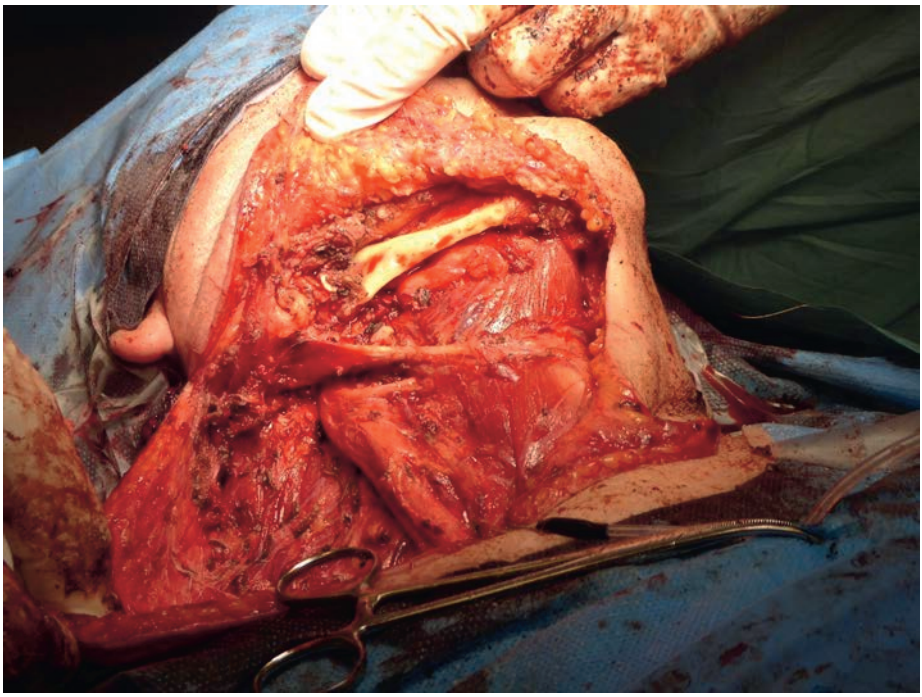
In conclusion, age, performance status and N stage are particularly important prognostic factors for survival in HNCUP, and these factors should be considered in the treatment planning.

5.5 Considerations for treatment of HNCUP

Different treatments are employed in HNCUP. The most common curative intent treatments include neck dissection and radiation or (chemo)radiation; however, only neck dissection is also performed in less advanced HNCUP. The optimal treatment for HNCUP is not established, and to my knowledge, there are no randomized treatment studies.

Papers IV and V investigated patients treated for HNCUP with the main aim to compare the outcome after treatment with neck dissection and radiation and (chemo)radiation; paper V included a large cohort of patients with HNCUP. Both papers IV and V indicated there is *no significant difference in survival* between the two treatments. Previous studies have supported this finding and indicated there was no significant difference in survival between the two treatments[80,93,94]; however, two studies obtained better results for the treatment with neck dissection and radiation compared to (chemo)radiation.[95,96] Both treatments resulted in relatively *favorable survival* compared to advanced HN cancer in general. The 5-year survival after the treatments was greater than 80% in paper IV and greater than 70% in paper V compared to the mean 5-

year survival for all HN cancer in Sweden, which was 67%.[3] In this respect, both treatments seem adequate.



Surgical treatment with a right sided radical neck dissection, in this case, on an 83-year-old male with cancer in the upper lip. Because of advanced lymph node tumor growth, the accessory nerve, the mandibular nerve, the digastric muscle and part of the mylohyoid muscle were divided and part of the mandible was free dissected, and the bone cortex was removed with a bone drill. The largest lymph node metastasis was located in the submandibular area next to the mandible; however, there were also metastases in the posterior neck area. This patient will be subject to postoperative radiation. Photo by the author

One limitation with the comparison of the two treatments was that the groups were not randomized. In both papers, there were *differences in the background factors* between the groups, such as age, gender and tumor N stage. Although these differences, in most cases, were not significant, they likely impact the results. Multivariable analyses were performed on survival in papers IV and V, including the treatment and the factors that were significant in the univariable analysis, and confirmed the result that there was no significant

difference between the treatments. In paper V, the HR for death in the multivariable analysis was 1.44, p=.20, which thus indicates non-significantly better results for neck dissection and radiation than (chemo)radiation. In summary, the differences in background factors cannot be fully corrected, and a randomized study is required to accurately evaluate the survival after both treatments.

Another problem with the comparison was the *heterogenous nature of the treatment* within and between the two groups. In paper V, there were significantly higher radiation doses, more patients who were irradiated bilateral and more patients who received chemotherapy in the (chemo)radiation group than in the neck dissection and radiation group. This indicates that postoperative radiation has been given less radical than primary radiation. This may have an impact on the comparison of the outcome between the groups.

In both papers IV and V, there was a small group of patients treated with *only neck dissection*, which thus did not follow the cancer care program for the recommended treatment. These patients were older and had a worse performance status. It is therefore not possible to draw firm conclusions regarding these patients. One may note in paper IV that these patients statistically had a higher risk of recurrence and lower survival than the other patients in the univariable analysis, i.e., not correcting for other background factors.

An important aspect of the treatment of cancer and HNCUP, apart from the survival and recurrence rates, is the *quality of life* patients have after the treatment. These aspects were not investigated in papers IV and V.

In conclusion, treatment with neck dissection in combination with radiation and (chemo)radiation seem to result in similar survival in patients with HNCUP. However, a randomized treatment study is required to establish the optimal treatment and should also include quality of life aspects.

5.6 Limitations

Specific limitations of the different studies have been discussed in more detail in the different sections. In summary, the main limitation with paper I was that no method was used that visualized swallowing. In papers II-II, relevant factors for nutrition and cancer prognosis were not included. In papers IV-V, the non-randomized design was a limitation.

6 CONCLUSIONS

- Our studies suggest that PEG may be used without an increased risk for clinically relevant permanent swallowing problems in patients with advanced HN cancer.

- PA at diagnosis and at various time points during and after cancer treatment are significant prognostic factors for survival in advanced HN cancer. PA decreases during cancer treatment and return to baseline value after approximately 12 months. It has many methodological advantages and is a promising tool to use in HN cancer. Further studies on PA are required before it can be implemented in clinical praxis.

- Higher age, worse performance status and higher N stage are negative prognostic factors for survival in patients with HNCUP treated with curative intent, and these factors should be considered in the treatment planning.

- HPV is common in and likely the most important etiological factor for HNCUP. P16/HPV status is a prognostic factor for survival and risk for recurrence in HNCUP. HPV status should be included in staging and treatment planning.

- Treatment with neck dissection and radiation compared to (chemo)radiation seems to result in similar survival in HNCUP. A randomized treatment study is required to establish the optimal treatment and should also include side effects and quality of life aspects.

7 FUTURE PERSPECTIVES

The findings in this thesis will hopefully be useful for future patients with HN cancer and will facilitate future research in the fields of this thesis. PEG is a method that has been used since 1980; however, it has been used more restrictively because of concerns for permanent swallowing problems. Hopefully, this specific concern is now less, and PEG may be used for future patients to prevent malnutrition, taking into account the risks of the procedure.

BIA has many methodological advantages, and it is mainly used to measure the body composition. In this thesis, the focus has been on the use of BIA to measure PA. PA is a promising method to use as a prognostic factor in HN cancer. Further studies should be performed on larger groups of HN cancer patients to further confirm the prognostic importance of PA and obtain more reliable reference values of the mean, median and cut-off values. The measures should be performed under standardized conditions. In the future, PA may be part of a risk-grading system at diagnosis for HN cancer patients alongside other important factors, such as performance status and age. PA also has potential in other diseases and healthy individuals that should be further explored.

HNCUP is a rare disease, and it has not been as thoroughly investigated in many aspects as other HN cancers. This thesis has shown the importance of HPV, and this importance has been recognized in the new classification system (8th edition). The other most important prognostic factors in HNCUP, including age, performance status and N stage, are also recognized factors in the treatment planning. A substantial remaining question in HNCUP is the treatment. A randomized treatment study is required to define the optimal treatment. This study should randomize for all known prognostic factors. It should also include evaluation of side effects and quality of life aspects. An international cooperation is needed to recruit sufficient patients in such a study. Over time, the SweHNCR will include an increasing number of patients, and future studies that include large numbers of patients with HNCUP should be performed.

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APPENDIX I

EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer: ____

När är Du född? (Dag, Månad, År): __ __ __ __ __ __

Dagens datum (Dag, Månad, År): 31 __ __ __ __ __ __

		Inte alls	Lite	En hel del	Mycket
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en lång promenad?	1	2	3	4
3.	Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbys eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfådd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:		**Inte alls**	**Lite**	**En hel del**	**Mycket**
17.	Har Du haft diarré?	1	2	3	4
18.	Har Du varit trött?	1	2	3	4
19.	Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20.	Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21.	Har Du känt Dig spänd?	1	2	3	4
22.	Har Du oroat Dig?	1	2	3	4
23.	Har Du känt Dig irriterad?	1	2	3	4
24.	Har Du känt Dig nedstämd?	1	2	3	4
25.	Har Du haft svårt att komma ihåg saker?	1	2	3	4
26.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28.	Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

APPENDIX II

EORTC QLQ - H&N35

Patienter uppger ibland att de har följande symptom eller problem. Var vänlig och ange i vilken grad Du har haft dessa besvär under veckan som gått. Sätt en ring runt den siffra som stämmer för Dig.

Under veckan som gått :	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Har Du haft smärtor i munnen ?	1	2	3	4
32. Har Du haft smärtor i käken ?	1	2	3	4
33. Har Du haft sveda i munnen ?	1	2	3	4
34. Har Du haft smärtor i svalget ?	1	2	3	4
35. Har Du haft problem med att svälja flytande ?	1	2	3	4
36. Har Du haft problem med att svälja mosad mat ?	1	2	3	4
37. Har Du haft problem med att svälja fast föda ?	1	2	3	4
38. Har Du "satt i halsen" när Du svalt ?	1	2	3	4
39. Har Du haft problem med tänderna ?	1	2	3	4
40. Har Du haft problem med att gapa ?	1	2	3	4
41. Har Du varit torr i munnen ?	1	2	3	4
42. Har saliven varit seg ?	1	2	3	4
43. Har Du haft problem med luktsinnet ?	1	2	3	4
44. Har Du haft problem med smaksinnet ?	1	2	3	4
45. Har Du hostat ?	1	2	3	4
46. Har Du varit hes ?	1	2	3	4
47. Har Du känt Dig sjuk ?	1	2	3	4
48. Har Ditt utseende besvärat Dig ?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått :	**Inte alls**	**Lite**	**En hel del**	**Mycket**
49. Har Du haft problem med att äta ?	1	2	3	4
50. Har Du haft svårt att äta inför familjen ?	1	2	3	4
51. Har Du haft svårt att äta inför andra människor ?	1	2	3	4
52. Har Du haft svårt att njuta av måltiderna ?	1	2	3	4
53. Har Du haft svårt att prata med andra människor ?	1	2	3	4
54. Har Du haft problem med att prata i telefon ?	1	2	3	4
55. Har Du haft svårt att umgås med din familj ?	1	2	3	4
56. Har Du haft svårt att umgås med Dina vänner ?	1	2	3	4
57. Har Du haft svårt för att gå ut offentligt bland andra människor ?	1	2	3	4
58. Har Du haft svårt för fysisk kontakt med Din familj eller Dina vänner ?	1	2	3	4
59. Har Du känt Dig mindre intresserad av sex ?	1	2	3	4
60. Har Du känt mindre sexuell njutning ?	1	2	3	4

Under veckan som gått:	**Nej**	**Ja**
61. Har Du använt smärtstillande mediciner ?	1	2
62. Har Du tagit något näringstillskott ? (förutom vitaminer)	1	2
63. Har Du haft matsond ?	1	2
64. Har Du gått ner i vikt ?	1	2
65. Har Du gått upp i vikt ?	1	2

APPENDIX III

RCC VÄST 2017-08-27

SVENSKT KVALITETSREGISTER FÖR HUVUD- OCH HALSCANCER

Canceranmälan – ledtider – behandlingsbeslut

Blanketten används som underlag för elektronisk rapportering

1

Inrapporterande sjukhus/klinik

Anmälande läkare

Rapporteringsdatum (20ÅÅMMDD) | 2 | 0 |___|___|___|___|___|___|

Ange personnummer och namn.

Canceranmälan (ANMÄLAN om tumörer och tumörliknande tillstånd från klinisk verksamhet)

Diagnosdatum | 2 | 0 |___|___|___|___|___|___|

Tumörens lokalisation:

.....

ICD10-kod |___|___|___| . |___|

Morfologisk diagnos.....

☐ Skivepitelcancer ☐ Adenoid-cystisk cancer ☐ Mukoepidermoid cancer

☐ Acinic cellcancer ☐ Adenocarcinom ☐ Odifferentierad cancer

☐ Malignt slemhinne-melanom ☐ Lymfoepiteliom, Schminketumör ☐ Annan cancerform

Sida

☐ Höger ☐ Vänster ☐ Ej tillämpligt

Patienten vidareremitterad till (sjukhus/klinik)

.....

Tumörutbredning/klinisk TNM-klassifikation[1]

| T |___|___| | N |___|___| | M |___|

Diagnostiserande patologi-/cytologiavdelning

.....

Preparatnummer/år |___|___|___|___|___|___|___|___|___|___|

Nummer År

Diagnosgrund

☐ Klinisk undersökning

☐ Röntgen, scintigrafi, ultraljud, MR, CT eller motsv undersökning

☐ Provexcision eller op m histopatologisk undersökning

☐ Obduktion m histopatologisk undersökning

☐ Cytologisk undersökning

☐ Operation utan histopatologisk undersökning

☐ Obduktion utan histopatologisk undersökning

☐ Annan laboratorieundersökning

Ledtider[2]

Remissankomst/sökt själv
Datum: | 2 | 0 |___|___|___|___|___|___|

Första besök på utredande ÖNH-mottagning | 2 | 0 |___|___|___|___|___|___|

Utredande enhet (sjukhus/klinik)

.....

☐ Patient ej handlagd på ÖNH-klinik

Cytologi/px Provtagningsdatum | 2 | 0 |___|___|___|___|___|___|

Cytologi/PAD Provsvarsdatum | 2 | 0 |___|___|___|___|___|___|

Rökvanor

☐ Rökare (daglig rökning under minst ett år) ☐ Före detta rökare (rökfri > ett år) ☐ Aldrig rökare (eller endast feströkt) ☐ Uppgift saknas

HPV - analys

p16	☐ Negativt	☐ Positivt	☐ Ej Utfört
HPV DNA-analys	☐ Negativt	☐ Positivt	☐ Ej Utfört
Metod:			
PCR/Lumiex	☐ Nej	☐ Ja	
ISH (In situ hybridisering)	☐ Nej	☐ Ja	

Annan metod
Om annan metod specifiera nedan:

.....

Om HPV DNA Positiv, vilken virustyp

Typ16	☐ Nej	☐ Ja
Typ18	☐ Nej	☐ Ja
Typ 31	☐ Nej	☐ Ja
Typ 33	☐ Nej	☐ Ja

Annan
Om annan, ange typ, kod:

.....

Ej typat men påvisat högriskgenom ☐ Nej ☐ Ja

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Behandlingsbeslut

Beslutande sjukhus/klinik	Beslutsdatum *(datum för behandlingsbeslut)* | 2 | 0 |__|__|__|__|__|__|__|
Beslutet taget vid multidisciplinär konferens? ☐ Nej ☐ Ja	
Syfte med behandling ☐ Kurativt ☐ Palliativt	WHO performance status vid beslutet[3] ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Ej känt

Beslutad tumörbehandling, primärtumör och hals

Ingen tumörbehandling planerad	☐	Ange orsak ……..……
Kirurgi, primärtumör	☐ Nej	☐ Ja
Kirurgi, hals	☐ Nej	☐ Ja
Extern strålbehandling	☐ Nej	☐ Ja
Brachyterapi	☐ Nej	☐ Ja
Medicinsk tumörbehandling	☐ Nej	☐ Ja
Annan behandling	☐ Nej	☐ Ja, ange vilken: ……

Behandlande sjukhus/klinik 1	Behandlande sjukhus/klinik 2

Beslutet i enlighet med regionalt/lokalt vårdprogram eller lokal terapitradition

☐ Ja ☐ Nej. Motivering:

……

Uppföljande enhet (sjukhus/klinik)

……

2017-11-22

Kommentarer

1. TNM-klassifikation av huvud- och halscancer

T1: ≤ 2 cm T2: > 2-4 cm T3: > 4 cm

Läpp, munhåla, orofarynx, hypofarynx	TX, T0, T1, T2, T3, T4a, T4b
Spottkörtlar	TX, T0, T1, T2, T3, T4a, T4b

T1-T4: utbredning till en eller flera lokaler/linjer

Käkhåla, näshåla o etmoid, supra- och subglottis	TX, T0, T1, T2, T3, T4a, T4b
Nasofarynx	TX, T0, T1, T2, T3, T4
Glottis	TX, T0, T1a, T1b, T2, T3, T4a, T4b

För alla HH-cancer utom nasofarynxcancer:

NX
N0
N1 – Ipsilateral körtel ≤ 3 cm
N2a – Ipsilateral körtel > 3-6 cm
N2b – Ipsilaterala körtlar, alla ≤ 6 cm
N2c – Bilaterala körtlar, alla ≤ 6 cm
N3 – Körtlar > 6 cm

Nasofarynx:

N1 – Unilateral körtel ≤ 6 cm, ovan fossa supraclavikularis
N2 – Bilaterala körtlar ≤ 6 cm, ovan fossa supraclavikularis
N3a – Körtlar > 6 cm
N3b – Körtlar i fossa supraclavikularis

Specialfall: Slemhinnemelanom (oavsett lokal) T-klassificeras endast med T3,T4a och T4b och N-klassificeras endast med N0 och N1

För M-klassificering gäller M0 och M1 för alla tumörtyper. MX har i den nu aktuella klassificeringen utgått helt och får inte användas. Så länge man inte vet om metastaser föreligger gäller M0

Referens: UICC, TNM-Classification of Malignant Tumors 7-th edition. Edited by Lesie Sobin et al 2009.

2. Ledtider

Remissankomst/sökt själv – Datum för remissankomst till resp. datum för första kontakt med utredande ÖHN-klinik.
Cytologi/px – Datum för cytologipunktion/px som ger slutlig diagnos.
Cytologi/PAD – Datum för det svar som ligger till grund för terapibeslut.

3. Performance status enligt WHO

0 – Klarar all normal aktivitet utan begränsning.
1 – Klarar inte fysiskt krävande aktivitet men är uppegående och i rörelse mer än 50% av dygnets vakna timmar.
2 – Är uppegående och kan sköta sig själv men klarar inte att arbeta. Är uppe och i rörelse mer än 50% av dygnets vakna timmar.
3 – Kan endast delvis sköta sig själv. Är bunden till säng eller stol mer än 50% av dygnets vakna timmar.
4 – Klarar inte någonting. Kan inte sköta sig själv. Är bunden till säng eller stol.

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SVENSKT KVALITETSREGISTER FÖR HUVUD- OCH HALSCANCER

Kirurgisk behandling

2a

Blanketten används som underlag för elektronisk rapportering

Inrapporterande sjukhus/klinik
Anmälande läkare
Rapporteringsdatum (20ÅÅMMDD) I 2 I 0 I___I___I___I___I___I___I

Plats för patientbricka, alternativt ange personnummer samt namn.

Genomförd primär kirurgisk behandling

Kirurgi, primärtumör ☐ Nej ☐ Ja
Kirurgi, hals ☐ Nej ☐ Ja

Annan planerad/genomförd primär tumörbehandling ☐ Nej ☐ Ja

Extern strålbehandling ☐ Nej ☐ Ja
Brachyterapi ☐ Nej ☐ Ja
Medicinsk tumörbehandling ☐ Nej ☐ Ja
Annan primär tumörbehandling ☐ Nej ☐ Ja
Ange vilken: .....

Behov att omklassificera tumören vid beh. start ☐ Nej ☐ Ja

Patienten ingår i klinisk behandlingsstudie ☐ Nej ☐ Ja

☐ Ingen kirurgisk behandling utförd.
Orsak: .....

Sjukhus och klinik som utför onkologiska behandlingen:
.....

Kirurgi (Avser ej provexcision från tumören, frånsett när den kan anses som en del i den primära behandlingen)

Datum för operation 1 I 2 I 0 I___I___I___I___I___I___I
primärtumör

Sjukhus/klinik
.....

Operationskoder* (första koden huvudop) I___I___I___I___I___I
I___I___I___I___I___I I___I___I___I___I___I
I___I___I___I___I___I I___I___I___I___I___I
Rekonstruktion ☐ Nej ☐ Ja

Datum för operation 2 I 2 I 0 I___I___I___I___I___I___I
primärtumör

Sjukhus/klinik
.....

Operationskoder* (första koden huvudop) I___I___I___I___I___I
I___I___I___I___I___I I___I___I___I___I___I
I___I___I___I___I___I I___I___I___I___I___I
Rekonstruktion ☐ Nej ☐ Ja

Operation halskörtelutrymning, höger

Datum för operation I 2 I 0 I___I___I___I___I___I___I
Sjukhus/klinik

Tömt area ☐ I ☐ II ☐ III ☐ IV ☐ V ☐ VI
Sparat interna vena jugularis ☐ Nej ☐ Ja
Sparat m. sternokleidomastoideus ☐ Nej ☐ Ja
Sparat n. accessorius ☐ Nej ☐ Ja

Operation halskörtelutrymning, vänster

Datum för operation I 2 I 0 I___I___I___I___I___I___I
Sjukhus/klinik

Tömt area ☐ I ☐ II ☐ III ☐ IV ☐ V ☐ VI
Sparat interna vena jugularis ☐ Nej ☐ Ja
Sparat m. sternokleidomastoideus ☐ Nej ☐ Ja
Sparat n. accessorius ☐ Nej ☐ Ja

***Se operationskoder på baksidan av blanketten!**

Kommentarer

Operationskoder (andra än nedanstående operationskoder kan vara tillämpliga)

DH Operationer på näsan (exkl septum)
DHB10 Exstirpation endonasalt
DHB40 Konkotomi
DHW99 Annan operation på näsan
DJ Operationer på nässeptum
DJB10 Resektion av nässeptum
DJW99 Annan operation på nässeptum
DM Operationer på sinus maxillaris
DMA10 Exploration av sinus maxillaris
DMB00 Endonasal öppning av sinus maxillaris
DMB10 Trepanation av sinus maxillaris med bred öppning och radikaloperation
DMB20 Endoskopisk öppning av sinus maxillaris
DMB30 Transmaxillär operation
DMB40 Lateral rinotomi
DMW99 Annan operation på sinus maxillaris och överkäken
DN Operationer på sinus ethmoidalis
DNB00 Yttre etmoidektomi
DNB10 Endonasal etmoidektomi
DNB20 Endoskopisk etmoidektomi
DNB30 Exstirpation av lokal förändring i sinus etmoidalis
DNW99 Annan operation på sinus ethmoidalis
DP Operationer på sinus frontalis och sfenoidalis
DPB00 Resektion av förändring i sinus frontalis
DPB20 Resektion av förändring i sinus sphenoidalis
DPW99 Annan operation på sinus frontalis eller sinus sphenoidalis
DQ Operationer på larynx
DQB00 Resektion av larynxtumör
DQB10 Endoskopisk exstirpation
DQB30 Laryngektomi
DQB40 Supraglottisk laryngektomi
DQB50 Hemilaryngektomi
DQB60 Arytenoidektomi
DQB70 Exstirpation av stämband
EA Operationer på läppar
EAA10 Exstirpation av lokal förändring på läpp
EAA20 Resektion av överläpp
EAA30 Resektion av underläpp
EAA99 Annan incision eller resektion av läpp
EC Operationer på gingiva och alveolarutskott
ECA30 Resektion av gingivaförändring
ECA99 Annan incision, biopsi eller excision av gingiva och alveolarutskott

ED Operationer på underkäken
EDB00 Resektion av underkäke
EDB10 Exstirpation av underkäke
EDB20 Hemimandibulektomi
EDB99 Annan resektion av underkäke
EE Operationer på överkäken
EEB00 Resektion av överkäke
EEB10 Exstirpation av överkäke
EEB20 Hemimaxillektomi
EEB99 Annan resektion av överkäke
EH Operationer på gommen
EHB00 Excision av lokal förändring i gom
EHB99 Annan resektion av gom
EJ Operationer på tunga och munbotten
EJB10 Exstirpation av tungtumör
EJB20 Exstirpation av tungbastumör
EJB30 Exstirpation av munbottentumör
EJB40 Hemiglossektomi
EJB50 Glossektomi
EJB60 Resektion av munbotten
EJB99 Annan resektion av tunga och munbotten
EK Operationer på kinden
EKB00 Exstirpation av lokal förändring i kind
EKB99 Annan resektion av kind
EL Operationer på spottkörtlar
ELB00 Exstirpation eller exploration av lokal förändring i spottkörtel
ELB10 Exstirpation av glandula salivaria minor
ELB20 Exstirpation av glandula sublingualis
ELB30 Exstirpation av glandula submandibularis
ELB40 Resektion av glandula parotis
ELB50 Exstirpation av glandula parotis
ELB99 Annan resektion eller excision av spottkörtel
EM Operationer på tonsiller och adenoider
EMB00 Exstirpation av tumör i tonsill eller adenoid
EMB10 Tonsillektomi
EN Operationer på farynx och närliggande mjukdelar
ENB00 Excision eller exploration av lokal förändring i farynx
ENB20 Faryngektomi
ENB30 Laryngofaryngektomi
ENB99 Annan resektion av farynx eller närliggande mjukdelar
GB Operationer på trakea
GBB00 Trakeostomi
PJ Operationer på lymfsystemet
PJD51 Radikal utrymning av cervikala lymfkörtlar
PJD41 Exstirpation av cervikala lymfkörtlar

SVENSKT KVALITETSREGISTER FÖR HUVUD- OCH HALSCANCER

Onkologisk behandling

2b

Blanketten används som underlag för elektronisk rapportering

Inrapporterande sjukhus/klinik

Anmälande läkare

Rapporteringsdatum (20ÅÅMMDD)
I 2 I 0 I___I___I___I___I___I___I

Plats för patientbricka, alternativt ange personnummer samt namn.

Genomförd primär onkologisk behandling

Extern strålbehandling ☐ Nej ☐ Ja ☐ Ja, men avbruten
Brachyterapi ☐ Nej ☐ Ja
Medicinsk tumörbehandling ☐ Nej ☐ Ja ☐ Ja, men avbruten

Annan planerad/genomförd primär tumörbehandling ☐ Nej ☐ Ja

Kirurgi, primärtumör ☐ Nej ☐ Ja
Kirurgi, hals ☐ Nej ☐ Ja
Annan primär tumörbehandling. ☐ Nej ☐ Ja
Ange vilken: .....

Behov av att omklassificera. tumören vid beh. start ☐ Nej ☐ Ja

Patienten ingår i klinisk. behandlingsstudie ☐ Nej ☐ Ja

☐ Ingen primär onkologisk behandling utförd.
Orsak: .....

Enhet för kirurgisk behandling
.....

Extern strålbehandling

Datum för behandlingsstart I 2 I 0 I___I___I___I___I___I___I___I
Datum för behandlingsavslut I 2 I 0 I___I___I___I___I___I___I___I
Sjukhus/klinik .....

Totaldos I___I___I , I___I Gy
Dos/fr1 I___I___I , I___I Gy/fr
Dos/fr2 I___I___I , I___I Gy/fr

Brachyterapi

Datum för behandlingsstart I 2 I 0 I___I___I___I___I___I___I___I
Sjukhus/klinik .....

Dos I___I___I , I___I Gy
Behandlingstyp ☐ HDR ☐ LDR ☐ PDR

Medicinsk tumörbehandling

☐ Cytostatika
☐ Annan medicinsk tumörbehandling
Datum för behandlingsstart I 2 I 0 I___I___I___I___I___I___I___I

Datum för behandlingsavslut I 2 I 0 I___I___I___I___I___I___I___I
Sjukhus/klinik .....

Uppföljande enhet (sjukhus/klinik)
.....

SVENSKT KVALITETSREGISTER FÖR
HUVUD- OCH HALSCANCER - Uppföljning

Blanketten används som underlag för elektronisk rapportering

3

Inrapporterande sjukhus/klinik
Anmälande läkare
Rapporteringsdatum (20ÅÅMMDD) I 2 I 0 I___I___I___I___I___I___I

Plats för patientbricka, alternativt ange personnummer samt namn.

Denna uppföljning avser: **Välj diagnos (Diagnosdatum, ICD-10 klartext, Stadie)**

Översikt på inrapporterad primär behandling

Kirurgi, primärtumör	I 2 I 0 I___I___I___I___I___I___I
Kirurgi, hals	I 2 I 0 I___I___I___I___I___I___I
Extern strålbehandling	I 2 I 0 I___I___I___I___I___I___I
Brachyterapi	I 2 I 0 I___I___I___I___I___I___I
Medicinsk tumörbehandling	I 2 I 0 I___I___I___I___I___I___I

Om primär tumörbehandling givits men saknas ovan, var god sänd in behandlingsuppgifter på ny behandlingsformulär!

Ny kontrollinformation	**Tidigare inrapporterad kontrollinformation**
Datum för kontroll av tumörstatus I 2 I 0 I___I___I___I___I___I___I	Datum för föregående inrapporterat tumörstatus I 2 I 0 I___I___I___I___I___I___I
Om kontrollerna överförs till annan enhet, ange sjukhus/klinik	Om kontrollerna överförs till annan enhet, ange sjukhus/klinik .....

Aktuellt tumörstatus	**Tidigare inrapporterad tumörstatus**
☐ Tumörfri efter primärbehandling	☐ Tumörfri efter primärbehandling
☐ Ej tumörfri (efter primärbehandling eller då ingen primärbehandling givits)	☐ Ej tumörfri (efter primärbehandling eller då ingen primärbehandling givits)
☐ Ej bedömbart om tumörfri efter primärbehandling	☐ Ej bedömbart om tumörfri efter primärbehandling
☐ Recidiv, nytt eller kvarvarande	☐ Recidiv, nytt eller kvarvarande
☐ Tumörfri efter behandling av recidiv	☐ Tumörfri efter behandling av recidiv
☐ Ej bedömbart om tumörfri efter behandling av recidiv	☐ Ej bedömbart om tumörfri efter behandling av recidiv
*Första bedömning av tumörfrihet efter primärbehandling skall utföras **senast 6 månader** efter avslutad behandling. Recidiv får endast anges om patienten tidigare bedömts vara tumörfri efter primärbehandling*	.

Information angående första recidiv	**Tidigare inrapporterad information om recidiv**
Datum för första recidiv I 2 I 0 I___I___I___I___I___I___I	Datum för första recidiv I 2 I 0 I___I___I___I___I___I___I
Ange lokalisation	Lokalisation
☐ Lokalt ☐ Regionalt ☐ Fjärrmetastasering	☐ Lokalt ☐ Regionalt ☐ Fjärrmetastasering

Avslut av kontroller eller avliden patient

Datum för avslutade kontroller I 2 I 0 I___I___I___I___I___I___I	Datum för avslutade kontroller I 2 I 0 I___I___I___I___I___I___I
Om kontrollerna avslutats innan 5-årsläkning, ange orsak	Om kontrollerna avslutats innan 5-årsläkning, ange orsak .....
Patienten avliden, datum I 2 I 0 I___I___I___I___I___I___I Avliden med huvud-halstumör ☐ Nej ☐ Ja ☐ Vet ej	Patienten avliden, datum I 2 I 0 I___I___I___I___I___I___I Avliden med huvud-halstumör ☐ Nej ☐ Ja ☐ Vet ej