Effects on quality of life of new radiotherapy techniques in treatment of head and neck cancer

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"Well, I can’t put it any more clearly, sir, for it isn’t clear to me."

- Alice

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ABSTRACT

The treatment of head and neck cancer (HNC) with radiotherapy has greatly evolved during the last twenty-five years with the introduction of new algorithms and techniques such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). The aim of this thesis was to investigate short- and long-term effects of new radiation therapy techniques on patients' quality of life and contribute to the implementation of the results in the everyday clinical care for these patients.

In a longitudinal study health-related quality of life (HRQOL) questionnaires were used to prospectively study patient-reported outcome measures (PROM) in patients with advanced HNC treated with IMRT versus 3D-CRT. We found better HRQOL scores regarding symptoms such as dry mouth and head and neck-specific pain as well as functional aspects, like cognitive functioning and sexuality, favoring the IMRT group.

In a five-year follow-up of HNC patients treated with IMRT, most HRQOL domains returned to baseline values with exception of local symptoms like dry mouth, taste alterations and problems with teeth. A comparison with an age and sex matched cohort from the normal population showed even more HRQOL effects in the treated patients.

Cancer-related fatigue (CRF) was evaluated in the same group of patients with a fatigue-specific HRQOL questionnaire. A significant increase of CRF within the first three months after start of treatment was found. CRF scores returned to baseline values within twelve months. Radiation mean dose to the cerebellum, age < 60 years, lower performance status and lower tumor stage were predictive for higher levels of CRF.

Keywords: Head and neck cancer, IMRT, HRQOL, fatigue, predictive

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SAMMANFATTNING PÅ SVENSKA

Huvud-halscancer drabbar cirka 1700 personer i Sverige årligen och 5-års överlevanden (d.v.s. chansen till bot) är ca 67 %. Strålbehandling ger möjlighet till kuration i många fall, antingen som enda behandling eller i kombination med kirurgi och/eller cellgifter. Emellertid ger strålbehandlingen i regel upphov till besvärliga biverkningar både på kort och lång sikt med betydlig påverkan på patienternas livskvalitet. Målet med denna doktorsavhandling har varit att utvärdera effekter av nya strålbehandlingstekniker i behandlingen av huvud-halscancer med fokus på patienternas livskvalitet.

Huvud-halscancerpatienter remitterade för kurativt syftande strålbehandling inkluderades i en prospektiv studie mellan 2008 och 2010 på Öron-näs-halskliniken och Onkologiska kliniken på Sahlgrenska Universitetssjukhuset i Göteborg. För att utvärdera patienternas egenupplevda livskvalitet använde vi oss av enkäter utgivna av European Organization for Research and Treatment of Cancer (EORTC), som har utvecklats gemensamt med experter från hela Europa och sedan validerats för respektive språk, bland annat svenska. Livskvalitetformulären EORTC QLQ-C30 (allmän livskvalitet), QLQ-HN35 (livskvalitet kopplad till symtom från huvud och halsregionen) samt QLQ-FA-12 (livskvalitet kopplad till cancerrelaterad trötthet, s.k. *fatigue*) delades ut innan start av behandling, månadsvis under behandling samt 6 mån, 1, 2 och 5 år efter behandling. Totalt 186 patienter tillfrågades varav 156 tackade ja till att delta i studien.

I delarbete ett undersöktes om införandet av ny strålbehandlingsteknik med förbättrad möjlighet till att spara känsliga organ, s.k. intensitetsmodulerad radioterapi (IMRT), förbättrade livskvaliteten jämfört med konventionell strål-behandling. Vi fann signifikant förbättrad livskvalitet avseende muntorrhet och smärta ett år efter behandling hos de patienter som behandlats med IMRT, talande för att möjligheten till att minska stråldosen till känslig vävnad, bidrar till att öka livskvaliteten. Livskvaliteten hos patienterna behandlade med IMRT fem år efter behandling beskrivs i delarbete två. Sammanfattningsvis kunde vi se att den allmänna livskvaliteten är förbättrad jämfört med innan behandlingsstart, men symtom kopplade till huvud-halsregionen, som muntorrhet, gapförmåga, seg saliv och tandproblem är klart försämrade. Vid en jämförelse med ett köns- och åldersmatchat urval från en svensk normalpopulation såg vi kvarstående betydande problem hos de behandlade patienterna.

Delarbete tre och fyra undersöker specifikt upplevelsen av fatigue under och efter behandling hos patienter behandlade med IMRT. Formuläret QLQ-FA12 utvärderar graden av fatigue utefter tre olika skalor; fysisk, emotionell respektive kognitiv fatigue. Vi fann att alla tre skalorna följde ett liknande mönster med en tydlig ökning från innan behandlingsstart till 3 månader efter behandling, men sedan en lika tydlig nedgång mellan 3 till 12 månader och därefter fann vi relativt små förändringar upp till fem år. Påverkan var mest tydlig i den fysiska fatiguen och här kunde vi också se en möjlig koppling till given stråldos. De patienter som fått högre medeldos till lillhjärnan utvecklade högre grad av fatigue tre månader efter behandling. Förekomsten av fatigue var också mer sannolik hos yngre personer (under 60 år), hos patienter med sämre allmäntillstånd vid diagnos och de patienterna med mindre avancerat tumörstadium vid diagnos.

Nya strålbehandlingstekniker som IMRT bidrar till minskad påverkan på huvud-halscancerpatienters livskvalitet, även om betydande problem kvarstår lång tid efter behandling. Fatigue förefaller vara mest uttalad den närmaste tiden efter behandling och nivån påverkas av både kliniska parametrar och givna stråldoser till riskorgan. Denna nya kunskap bör tas hänsyn till vid utformandet av nya kliniska studier och protokoll.

LIST OF PAPERS

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

I. **Abel E**, Silander E, Nyman J, Bove M, Johansson L, Björk-Eriksson T, Hammerlid E. Impact on quality of life of IMRT versus 3-D conformal radiation therapy in head and neck cancer patients: A case control study. *Adv Radiat Oncol. 2017 May 12;2(3):346-353.*

II. **Abel E**, Silander E, Nyman J, Björk-Eriksson T, Hammerlid E. Long-Term Aspects of Quality of Life in Head and Neck Cancer Patients Treated with Intensity Modulated Radiation Therapy: A 5-Year Longitudinal Follow-up and Comparison with a Normal Population Cohort *Adv Radiat Oncol. 2019 Aug 2;5(1):101-110.*

III. **Abel E**, Silander E, Nordström F, Olsson, C, Brodin NP, Nyman J, Björk-Eriksson T, Hammerlid E. Fatigue in head and neck cancer patients treated with radiotherapy: a prospective study of patient-reported outcomes and their association with radiation dose to the cerebellum. *Adv Radiat Oncol. 2022 Apr 8;7(5):100960.*

IV. **Abel E**, Brodin NP, Viswanathan S, Nordström F, Nyman J, Hammerlid E, Björk-Eriksson T. Analysis of radiotherapy induced fatigue in head- and neck cancer patients using longitudinal data analysis. *Manuscript*

CONTENT

ABBREVIATIONS

3DCRT	Three-dimensional Conformal radiotherapy
ART	Adaptive radiotherapy
CT	Chemotherapy
CTV	Clinical Target Volume
DVH	Dose-Volume Histogram
EORTC	European Organization for Research and Treatment of Cancer
EQD_2	Equivalent Dose at 2 Gy
FNAC	Fine-needle aspiration Cytology
GTV	Gross Tumor Volume
HNC	Head and neck cancer
HPV	Human Papilloma Virus
HRQOL	Health-Related Quality of life
IMPT	Intensity-Modulated Proton Therapy
IMRT	Intensity-Modulated Radiotherapy
LINAC	Linear Accelerator
MLC	Multi-Leaf Collimator
NTCP	Normal Tissue Complication Probability
OAR	Organ at risk
OS	Overall Survival
PROM	Patient-Reported Outcome Measures

PTV	Planning Target Volume
RCT	Randomized Controlled Trial
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
TCP	Tumor Control Probability
TPS	Treatment Planning System

1 INTRODUCTION

Head and neck cancer (HNC) is most frequently a local or loco-regional disease where radiotherapy has been used successfully for curative treatment since the middle of the last century. [1] During the last decades, technical innovations in radiotherapy including image guidance have increased the potential to deliver high radiation doses to tumors in the head and neck region and at the same time minimize doses to normal tissues. Consequently, new techniques like intensity-modulated radiotherapy (IMRT) have rapidly become a new standard in HNC treatment. Combined with improved surgical techniques and medical treatments, survival rates have improved, with a growing proportion of long-term HNC survivors. Therefore, researching side-effects including treatment-related Health-related Quality of Life (HRQOL) and providing prospective clinical data on the benefits of new techniques on HRQOL is of great interest.

1.1 HEAD AND NECK CANCER

1.1.1 EPIDEMIOLOGY

Head and neck cancer (HNC) is with nearly 900000 new cases in 2020 the eighth most common cancer worldwide. [2] The corresponding number for Sweden is close to 1700 new cases per year in 2020, and since 2008 the number of cases have increased with about 4 % per year. [3] The median age at diagnosis varies between 60 years (oro- and nasopharyngeal cancer) and 75 years (lip cancer). Gender distribution is also dependent on site, where oropharyngeal and laryngeal cancers are more common in males (70-80%), whereas oral cancers are evenly distributed between the sexes. Traditionally the disease is associated with older age and excessive tobacco and alcohol use, but in the last decades there's a rising incidence of Human Papilloma Virus (HPV)-associated cancers in North America and northern Europe, predominantly comprising of tumors in the oropharynx.[4]

HNC in the scope of this thesis, refers to squamous cell carcinoma (SCC) located in the oral cavity (lip, gingiva, buccal mucosa or tongue), pharynx (naso-, oro or hypopharynx) or larynx, all of which represent a majority of cases in the clinic. It also includes cancers of unknown primaries presenting as SCC in lymph nodes of the neck. Other cancers in the head and neck area, such as salivary gland tumors and thyroid neoplasms have distinctively different histopathological and clinical features and are therefore not included in this thesis.

1.1.2 DIAGNOSIS AND STAGING

Symptoms leading patients to seek care for HNC include a growing lump on the neck, bleeding or pain from the throat or nose, hoarseness, unilateral nasal congestion or difficulties from swallowing. After physical assessment, fine-needle aspiration cytology (FNAC) from enlarged nodes or primary tumor biopsy gives an initial histologic diagnosis and combined with radiological imaging, yields the information necessary for staging. [5]

For prognostic purposes, staging is made using the Union for International Cancer Control (UICC) TNM classification of malignant tumors. [6] From the 8th edition classification (implemented from 2018), staging is split into whether the patient is HPV-positive or negative. However, patients included in the studies forming this thesis were diagnosed and staged prior to that implementation, why all stages herein are according to the 7th edition. (Table 1)

Treatment decisions and strategy requires a multidisciplinary approach, where ear-nose-throat (ENT) surgeons, pathologists, radiologists, medical and radiation oncologists, and often oral and maxillofacial surgeons collaborate in deciding the optimal treatment. To handle adverse treatment effects, supportive care, including nutritional aid, pain management and help with dental problems, is essential during and after treatment. [7, 8]

Table 1. Staging for tumors in the oral cavity, larynx, oropharynx and hypopharynx (TNM, UICC, Edition 7)

N	***T1***	***T2***	***T3***	***T4a***	***T4b***
N0	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
N1	Stage III	Stage III	Stage III	Stage IVA	Stage IVB
N2	Stage IVA	Stage IVA	Stage IVA	Stage IVA	Stage IVB
N3	Stage IVB	Stage IVB	Stage IVB	Stage IVB	Stage IVB

1.1.3 TREATMENTS OTHER THAN RADIOTHERAPY

1.1.3.1 SURGERY

Surgery aims at the complete removal of the primary tumor and is often combined with either a diagnostic or radical neck dissection. In the case of small tumors in the oral cavity the loss of function is often minimal. [9-11] By contrast, laryngectomy in advanced laryngeal cancer, which is the most efficient treatment, leads to obvious functional impairment. [12] In locally advanced disease with or without lymph node involvement, reconstructive surgery is common to achieve as good function as possible. However, radical surgery with negative margins can be hard to achieve, why adjuvant chemoradiotherapy often is needed. [13, 14]. As surgery, if possible to pursue, of naso-, oro, and hypopharyngeal cancers often result in severe functional loss, it is most commonly used as salvage treatment in recurrent disease. [15] The introduction of trans-oral robotic surgery (TORS) promises better functional and cosmetic outcomes compared to conventional techniques and studies comparing it with radiotherapy in oropharyngeal cancers are ongoing. [16, 17]

1.1.3.2 SYSTEMIC TREATMENT

The question if adding chemotherapy (CT) to radiotherapy (RT) in locally advanced disease is beneficial has been addressed in meta-analyses with individual patient data from approximately 100 randomized controlled trials (RCT). [18-21] They show an absolute benefit in overall survival (OS) of 6,3 % with concomitant cisplatin + RT compared to RT alone. The benefit is solely for concomitant CT and not for induction or adjuvant CT. Apart from CT, targeted therapy in the form of the monoclonal antibody Cetuximab has shown effect in combination with RT compared to RT alone, with fewer of the adverse effects typically associated with concomitant CT. [22] However, direct comparisons between concomitant CT versus concomitant cetuximab show worse tumor control and overall survival with cetuximab in HPV-positive patients and worse locoregional control if HPV-status is not considered. [23-25] Immunotherapy has in the recent years been introduced in the palliative setting showing superior response and survival compared to CT. [26, 27] This has spawned multiple RCT's comparing adding immunotherapy in locally advanced disease, but results are still pending.

1.1.4 SURVIVAL

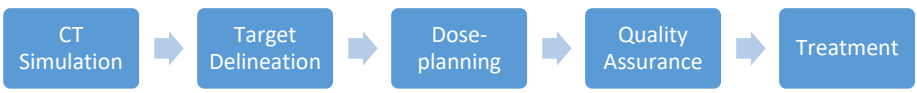
The relative 5-year survival for all HNC-patients in Sweden was 67 % during 2008-2020, with a slight increase during the timeframe (64,8 % 2008 to 68,1 % 2016). [3] The numbers vary greatly depending on site, from lip cancer (91 %), through oral cancer and oropharyngeal cancer (62 %-72 %), to cancers in the hypopharynx (26 %). Typically, survival decreases with higher tumor stage, with the notable exception of HPV-positive oropharyngeal cancer where stages I-IVA, according to the 7th edition of UICC's TNM staging manual, all have similar survival curves. [28] This has led to the revision of the staging procedure for HPV-positive oropharyngeal cancers in the 8th edition of the UICC staging manual. Besides tumor site, stage and HPV-status, smoking (defined as > 10 years of smoking one pack of cigarettes per day), is associated with poorer prognosis in oropharyngeal cancer. [29]

1.2 RADIOTHERAPY IN HEAD AND NECK CANCER

1.2.1 BASIC PRINCIPLES

Soon after the discovery of X-rays by Wilhelm Conrad Roentgen in 1895 and radioactivity by Henri Becquerel and Marie Curie in 1896, the first medical treatments with radiation were reported. [30, 31] In the first half of the 20th century, superficial treatment with X-rays and Radium brachytherapy against gynecological cancers were the dominating applications. From the 1940's and onwards the introduction of Cobalt-60 units and later Linear Accelerators (LINAC) paved the way for the modern external radiotherapy of today. [32] The modern radiotherapy treatment process includes a couple of fundamental steps: A computer tomography (CT) simulation scan is performed over the relevant treatment area. Radiation oncologists delineate treatment volumes (Gross tumor volume (GTV), Clinical tumor Volume (CTV) and planning tumor volume (PTV)) as well as organs at risk (OAR) on the CT scans. Radiographers and physicists develop distributed dose-plans in a treatment planning system (TPS) which are subsequently approved in cooperation with the radiation oncologist. Before treatment the calculated dose-plan is verified in a quality assurance process before finally being approved for treatment. (Figure 1)

Figure 1. The radiotherapy process

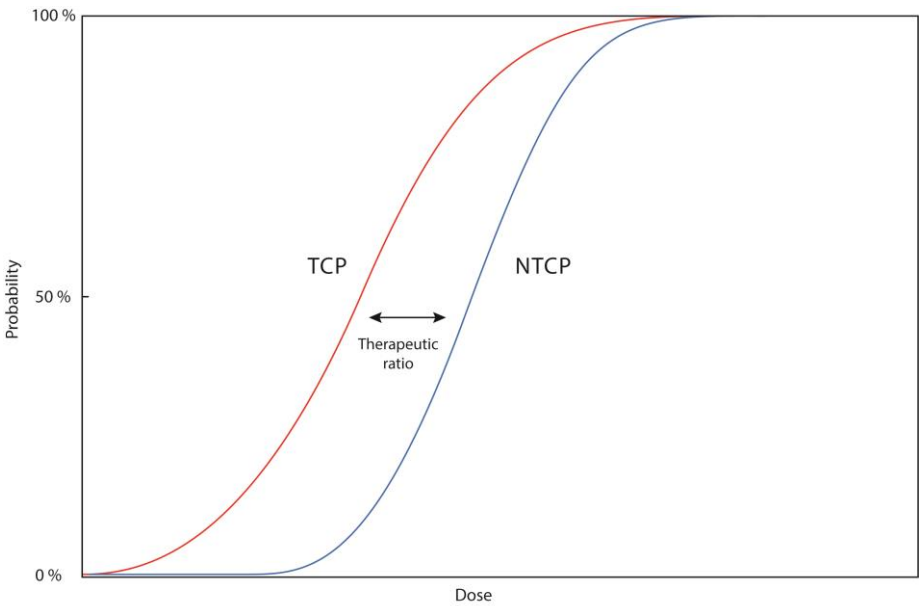


Several developments in the last few decades have increased the possibility to optimize each of these basic steps promising better treatment outcomes. Enhanced anatomical information has been provided by adding magnetic resonance imaging (MRI) simulation and fusing it with CT images, and the use of Artificial Intelligence (AI) and machine learning solutions has paved the way for automated target delineation and dose-planning. 3D-conformal radiotherapy (3D-CRT) followed by Intensity-modulated Radiotherapy (IMRT) and Volumetric Arc Therapy (VMAT) have vastly improved the

precision and conformity of radiotherapy.[33] Additionally, the attachment of on-board imaging like cone-beam computer tomography (CBCT) and MRI to LINAC's, has opened the possibilities for Adaptive radiotherapy (ART), i.e. the ability to adjust treatment plans after treatment start, reacting to tumor shrinkage and possibly reducing treatment volumes. [34]

At the heart of the radiotherapy process is the aim to deliver a high dose to the tumor (Tumor Control Probability, TCP) while keeping normal tissue doses as low as possible (Normal Tissue Complication Probability, NTCP). The difference in dose between avoiding normal tissue damage while maintaining tumor control is often referred to as the *therapeutic ratio*. (Figure 2).

Figure 2. Schematic model of TCP and NTCP



Increasing the therapeutic ratio was initially achieved by applying multiple angles for the incoming beam and using lead shields to block radiation to vulnerable tissues. LINAC-mounted shielding in the form of multi-leaf collimators (MLC) coupled with more powerful computers and improved dose calculation algorithms, made the concept of 3D-CRT possible. [35] Parallel to technical developments, the understanding of dose-volume effects in different tissues has improved, resulting in the comprehensive guidelines published by Emami et al in 1991. [36] These NTCP prediction models (and later updates) are based on pooled clinical data and are used to estimate risk of radiotherapy-induced complications in individual cases. [37, 38]

1.2.2 RADIOBIOLOGY IN HEAD AND NECK CANCER

In HNC, radiotherapy has proven to be an efficient treatment regarding tumor control and for locally advanced disease and chemoradiotherapy has become the recommended primary treatment for patients with a good performance status. [11, 39, 40]

The explanations to why HNC responds to radiotherapy, can be derived from some of the important factors influencing tissue response to ionizing radiation (the 5 R's of radiobiology): DNA damage Repair, Redistribution, Repopulation, Reoxygenation, intrinsic tumor cell Radiosensitivity. [41]

Fractionated radiotherapy (dividing the total radiation dose into multiple fractions to be delivered daily) takes advantage of the difference in radiosensitivity and ability of DNA damage repair as well as reoxygenation between normal and tumor cells leading to a higher proportion of tumor cell death at each fraction, increasing the therapeutic ratio. [42, 43] One commonly accepted way to explain the relationship of dose and fractionation and effect on cell survival is the *Linear Quadratic* (LQ)-model. DNA damage caused by radiation can be either lethal (i.e. unrepairable double-strand breaks) or sublethal (i.e. potentially repairable lesions). Lethal damages (α) represent the linear portion of a logarithmic cell survival curve and sublethal damage (β) represents the quadratic portion. These values determine the intrinsic radiosensitivity: cells with high α and β are more radiosensitive. The ratio α/β (the point of the curve where the linear and quadratic parts are equally responsible for the resulting cell death) measures the fractionation sensitivity. [44] A higher α/β-value corresponds to a higher proportion of cell death at a given dose and varies depending on which tissue is exposed. For example, an α/β of about 10 has been established in animal models for early skin reactions as well as for radiosensitive tumor cells. Conversely, late reacting tissues like kidneys and less radiosensitive tumors like prostate cancer have an α/β-value of appr 2-3. Thus, which fractionation schedule and dose per fraction that is optimal varies between different normal tissues and tumors. Early-reacting tissues (e.g. bone marrow) tend to be effected by RT at smaller doses per fraction than late-reacting tissues (lung, kidney) given the same total dose. [45] The radiosensitivity of HNSCC cell lines has been estimated as moderate, close to for example cervical cancer, but less sensitive than lymphomas. [46, 47]

By applying the LQ-model in conjunction with the α/β-values of different tissues, one can compare different fractionation schedules and total doses. Using the *Equivalent dose at 2 Gy* (EQD2)-formula:

$$EQD^2 = D\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$$

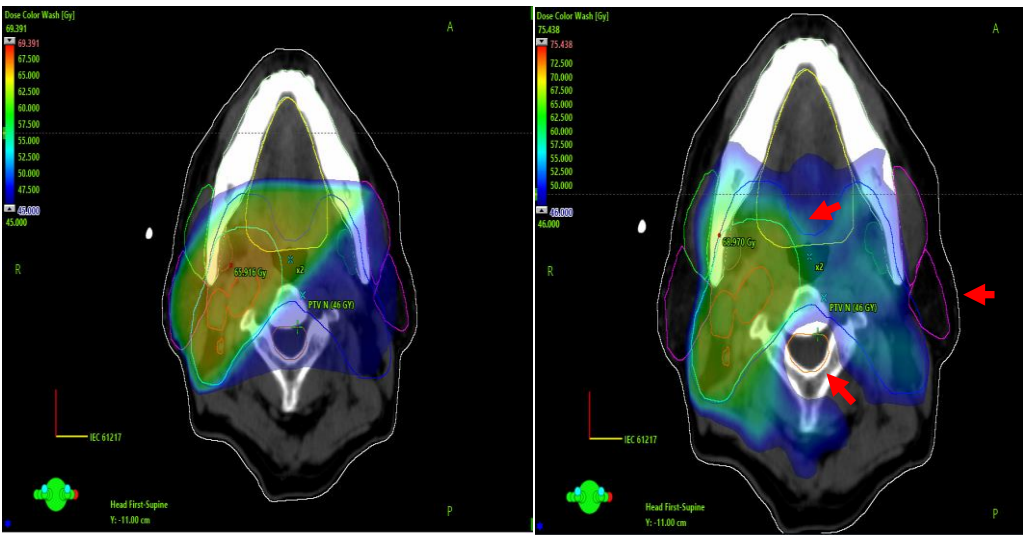
where *D* is total dose and *d* is dose per fraction, we can calculate the resulting dose, had it been given as the reference treatment of conventional fractionation (i.e 2 Gy, 1 fraction/ day, 5 fractions/week).

Conventionally fractionated radiotherapy in HNC is delivered with fractions of 2 Gy daily, 5 days a week, during 7 weeks to a total dose of 66-70 Gy. Since RT alone historically only shows 5-year survival rates around 35 %, altering the fractionation has been suggested to yield better outcomes.[18] Altered fractionation schedules in HNC typically refer to hyperfractionation and acceleration. In hyperfractionated radiotherapy dose per fraction is lowered to 1,0-1,2 Gy given twice daily, enabling an increase of the total dose, which otherwise is not possible due to late side-effects. Accelerated radiotherapy refers to the reduction of treatment time to 5-6 weeks with the same total dose (e.g., six fractions/week instead of five). It is known that head and neck SCC cells show an accelerated rate of repopulation (cell regeneration as a response to lethal damage) a few weeks after initiation of radiotherapy and prolonged treatment times increase the risk of local failure. [48] Thus, shortening overall treatment time could potentially yield better outcomes. Multiple RCT's have been made investigating the optimal fractionation schedule in HNC, summarized in a comprehensive meta-analysis.[49, 50] The survival benefit for altered fractionation is 3,1 % and it is wholly attributed to hyperfractionation, whereas acceleration does not seem to impact survival. Another factor impacting outcome of HNC radiotherapy is the increase of HPV-associated tumors. Studies show that HPV-associated p16 expression is a strong prognostic factor for response to radiotherapy and better local control and survival. [29, 51] In vitro studies confirms that an intrinsic higher radiosensitivity of HPV-positive HNC cell lines exists. [52-54] Preliminary data have shown promising results of lowering the total radiation dose in HPV-positive oropharyngeal carcinoma, leading to the initiation of ongoing RCT´s. [55]

1.2.3 INTENSITY-MODULATED RADIOTHERAPY (IMRT)

While 3D-CRT adds the possibility to shield off certain OAR's, it's hard to fit the desired dose-distribution to complex geometric shapes. Dynamically controlled MLC's gives the ability to shape the incoming beam during actual beam delivery, thus enabling dose-distributions that can adapt to irregular target shapes as well as avoid critical OAR's. (Figure 3). Combined with inverse dose-planning, where the use of an optimization process aids the dose-planner in producing a plan where relevant target volumes and OAR's have been prioritized, IMRT as a concept has been clinically implemented in the last decades. [56-58]

Figure 3. Example of 3D-CRT plan (left) vs IMRT plan(right). Notice how the spinal cord and left parotid gland are better spared and how the high dose is better shaped around the PTV (arrows).



A recent further development of modulated radiotherapy is Volumetric Modulated Arc Therapy (VMAT), which enables shorter treatment times, better dose conformity and possibly less dose to OAR's.[59]. The ability to reduce patient treatment times while maintaining the same dose-planning quality as IMRT, has made it widely adopted in many centers, but if it yields any clinical benefits is yet to be established. [60, 61]

In the treatment of HNC, the introduction of IMRT has opened possibilities potentially sparing crucial OAR's that are well-known to give severe adverse-effects both in the short- and long-term. Xerostomia due to radiation doses to the parotid glands is perhaps the most common long-term side effect of curative radiotherapy in the head and neck region. [62] In the guidelines most commonly used in the clinic, it is recommended to keep at least one parotid gland dose to <20 Gy or <25 Gy to both glands in order to avoid severe xerostomia. [63] This is very hard to accomplish with standard 3D-CRT, without compromising target volume coverage. Early adaptations of IMRT in HNC have shown the feasibility of avoiding dose to the parotids, and possibly preserve salivary gland function. [33, 64] Recovery of salivary flow rates after parotid-sparing treatment confirm this, while the locoregional control rates remain unaffected. [65-68] Saliva production is also dependent on the submandibular glands and reduction of xerostomia has been reported in submandibular gland-sparing treatments. [69, 70]

Radiotherapy-related dysphagia is associated with doses to the oral cavity, pharyngeal muscles, and larynx. [71] As all these areas, even with IMRT, are nearly impossible to spare at the same time, several critical risk volumes with relevant dose constraints have been proposed, but no clear candidate has emerged from the available literature. [72, 73] Thus, there is no established dose-volume relationship for avoiding dysphagia and current recommendations are to keep doses to relevant structures as low as possible. [74]

1.3 HEALTH-RELATED QUALITY OF LIFE

Apart from objective outcome measures like survival, time to progression and response rate, randomized controlled trials have increasingly incorporated Health-related quality of life (HRQOL) assessments to measure the treatments impact on a patient's general well-being. Quality of life can be defined as a set of outcomes that contribute to a person's health, usually established by measures or scales describing the patient's overall health. [75] The term health-related specifies measurements connected to a disease or medical treatment. Such measures include physical, emotional, and social functioning, pain, appetite, fatigue, but also organ-specific complaints like dysphagia and dryness of the mouth. In addition to describe the overall well-being of patients, HRQOL may also be an independent prognostic factor for survival. [76]

In the context of this thesis, evaluating new organ-sparing and therefore possibly less patient-burdening techniques, QOL assessment is of central interest.

1.3.1 PATIENT-REPORTED OUTCOME MEASURES (PROM)

As the name implies, Patient-reported outcome measures (PROM) are outcomes experienced from the patient's perspective, rather than the caregivers. To accomplish this, an array of different instruments or questionnaires for the patients to respond to, have been developed for clinical use. Questionnaires usually contains a set of questions where each question aims to describe an *item.* Some symptoms are relatively well defined and may be sufficiently described by a single question (e.g shortness of breath or lack of appetite). Other functions like emotional well-being and social interaction need multiple items to form a *scale.* As a single question may miss important aspects of a patient's current experience of its general QOL, items and scales are often combined to form a multidimensional instrument for assessment. To be useful in the clinic, PROM's need to be evaluated regarding their psychometric properties to fulfill basic criteria common for all health-related measurements: validity, reliability, sensitivity, and responsiveness. A validation process aims at confirming that the instrument actually measures what it is meant to be measured. Reliability means that the measurements are stable and reproducible over time, given that the situation is unchanged.

Sensitivity is a scale's ability to measure and discover differences between groups. Responsiveness refers to the ability to detect changes over time. [75]

Symptoms affecting HRQOL can also be graded by health professionals using tools like the Common Terminology Criteria for Adverse Events (CTCAE). [77] However, objective assessments have been shown to underestimate the severity of subjective symptoms, underscoring the importance of self-assessment. [78, 79]

The scores obtained by PROM's have no meaning by their own, instead they need to be related to a context. The clinical significance or minimal important difference is the change in score which the patient perceive as important. [80] In that case changing the score to the better (avoiding significant adverse effects), could be a relevant objective of an intervention. Investigations have shown that an absolute change in score of 10 % can be regarded as a "moderate" change to be used in the clinic. [81] However, minimal important differences between groups are not necessarily in the same magnitude as changes over time, i. e. a ten-point difference can be clinically significant between groups, but a change as small as 3-5 points can indicate important change over time. [82] In studies with large cohorts, the minimal important difference can be helpful in interpreting data, since small numerical differences can be statistically significant due to the big number of data-points.

In cases when absolute HRQOL scores need to be correlated to a reference, one method is to make comparisons to population-based reference values from the normal population. This is achieved by obtaining scores from a selection of people representing an average of the population. Such data exists for various countries and questionnaires. [83-85]

1.3.2 HRQOL IN HEAD AND NECK CANCER

The HRQOL of HNC patients at diagnosis is affected by site and size of the primary tumor. [86, 87] For example, problems with speech are more pronounced in laryngeal cancer patients, while pain and nutritional problems are more common in patients with oral and oropharyngeal cancer. Furthermore, a few studies suggest that HRQOL by itself may be a prognostic factor predicting survival and locoregional control. [88, 89]

The different treatment options add to the number of problems experienced. Surgery alone in the treatment of oral cavity tumors leads to minimal HRQOL effects, but in combination with adjuvant radiotherapy many domains are affected. [90] Laryngectomy, which is the gold standard treatment in advanced laryngeal cancer, obviously have a great impact on function and head and neck-specific quality of life. [91, 92] However, the impact on general symptoms like global quality of life is less pronounced. [93] Shoulder movement dysfunction can be an effect of radical neck dissection and result in an impact on physical and social functioning as well as global QOL. [94, 95]

In the first weeks of radiotherapy for HNC cancer, normal tissue reactions in the mucous membranes occurs that lead to often painful oropharyngeal mucositis affecting taste and the quality of saliva. Combined, this leads to swallowing difficulties requiring nutritional support in the form of adapted food stuffs and tube feeding during the treatment period. Therefore, many HRQOL domains typically worsens during and shortly after radiotherapy. [96] Besides effects on specific symptoms, there is an impact on general HRQOL. Specifically, moderate to severe xerostomia and dysphagia is linked to significantly reduced global quality of life and social functioning. [97] As patients begin to recover from the acute side-effects, HRQOL effects become less pronounced. However, notable exceptions are items regarding swallowing, dry mouth, sticky saliva, and taste/smell, which continue to be affected long time after the treatment has been completed. [98, 99] The addition of chemotherapy to radiotherapy aggravates typical radiotherapy-induced symptoms, compared to radiotherapy alone. [100] Consequently, HRQOL impact has been shown to be more severe in patients treated with chemo-radiotherapy. [101, 102]

1.3.3 CANCER-RELATED FATIGUE

One of the most common symptoms in cancer and cancer treatment is fatigue. Cancer-related fatigue (CRF) is characterized by tiredness/exhaustion not caused by physical activity, interfering with daily activities, and not remedied by rest or sleep. [103, 104] Already at diagnosis, up to 40 % of cancer patients report moderate to high fatigue levels, and that figure increases to 80-90 % at the end of treatment. [105, 106] For HNC alone there are few studies describing fatigue extensively. In one retrospective study of fatigue and in another about fatigue after treatment for nasopharyngeal cancer, around 20-50 % of long-time survivors experience some degree of fatigue. [107, 108] Moreover, the relative impact of fatigue on HRQOL in HNC patients has been reported to exceed that of many other symptoms, like xerostomia and weight loss. [109]

Although social factors like marital status and comorbidities (especially anxiety and depression) contribute to levels of fatigue, even patients without these co-factors experience significant fatigue levels during and after treatment. [110] Pathophysiological mechanisms that have been proposed to explain treatment-related fatigue, include the release of cytokines promoting inflammation, neuroendocrine dysregulation and altered immune responses. [111-114] There is data that support that these inflammatory changes associated with experience of fatigue, prevail long after treatment. [115] Radiotherapy increases CRF regardless of anatomical site being irradiated, possibly due to the activation of proinflammatory cytokines. [105, 112] However, doses to brain structures may also impact levels of fatigue as reported in studies on hippocampal-avoided whole brain radiotherapy and proton therapy in brain tumors, where lower brain doses seem to give lower levels of fatigue. [116, 117] Even if HNC radiotherapy generally does not result in high absorbed doses to the whole brain, structures close to the head and neck area may be affected by significant doses and has been proposed to play a part in the development of CRF. [118]

Fatigue is commonly included as one symptom in PROM's measuring overall HRQOL. However, given the impact on many aspects of daily life (i.e. physical, mental, emotional, etc.), a multidimensional approach has been widely accepted as appropriate to describe CRF. [119] Several fatigue-specific questionnaires have been developed to provide such multi-dimensional data, reflecting the fact that there exist various interpretations of how to exactly define CRF. [120-123]

2 AIM

The overall aim of this thesis is to explore the concept of HRQOL effects of new radiotherapy techniques in the treatment of HNC.

2.1 SPECIFIC AIMS

PAPER I

To compare general and HNC-specific HRQOL prospectively and longitudinally in patients with locoregionally advanced HNC treated with IMRT compared to a matched cohort of patients treated with 3D-CRT, hypothesizing that IMRT results in a clinically significant benefit in HRQOL.

PAPER II

To longitudinally, over five years, describe the impact of IMRT on HRQOL in HNC patients and compare their HRQOL with reference data from an age- and sex-matched normal population cohort.

PAPER III

To evaluate acute and long-term cancer-related fatigue (CRF) in patients with HNC treated with IMRT and to explore possible associations with organs at risk.

PAPER IV

To make a predictive model of fatigue changes over time in HNC patients considering relevant clinical and dosimetric parameters,

3 PATIENTS AND METHODS

3.1 STUDY POPULATIONS

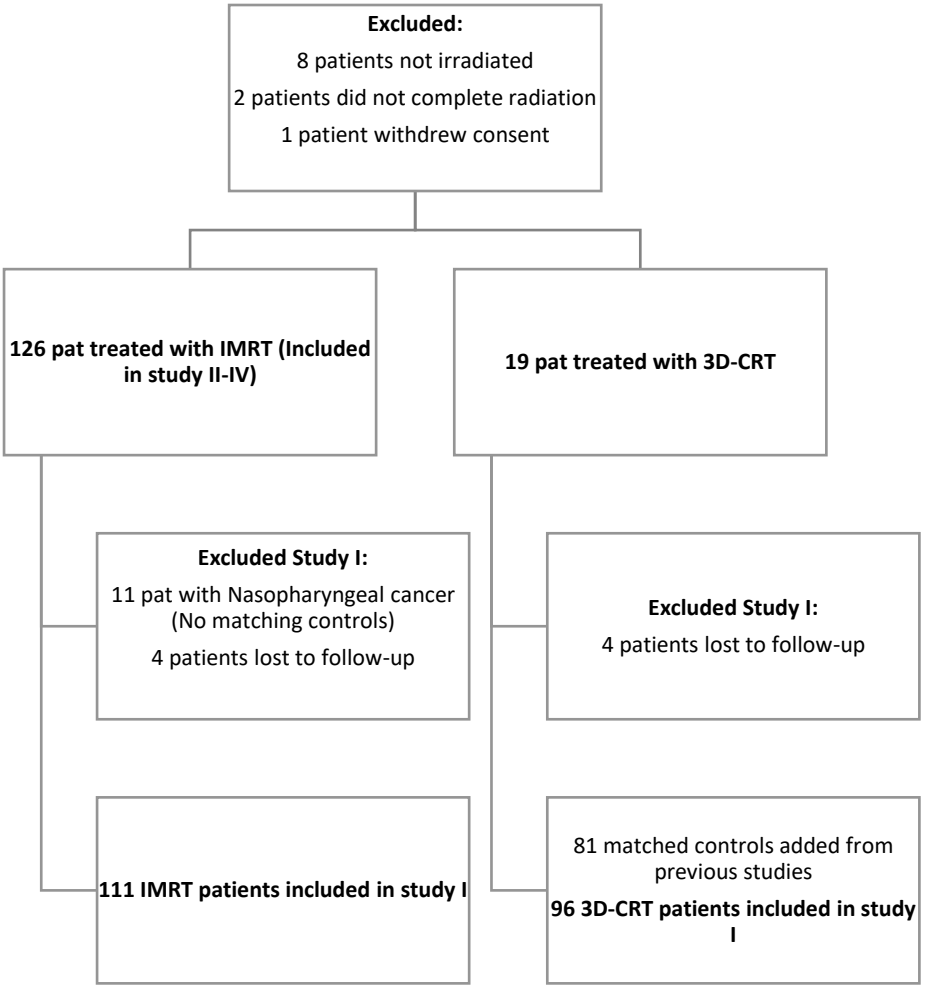
Between 2008 and 2010, patients with advanced HNC intended for curative radiotherapy who were discussed at the regional Head and neck multi-disciplinary tumor board at Sahlgrenska University Hospital were asked for inclusion in a prospective study. Out of 186 eligible patients, 156 accepted participation in the study.

In Paper I, this cohort was matched to a cohort of patients serving as HNC 3D-CRT controls included in two previous studies, who had utilized the same HRQOL questionnaires. [124, 125] Data regarding demographics (age, gender, Karnofsky Performance score (KPS), primary tumor location and stage, if surgery had been performed or chemotherapy given were retrieved from patient medical records.

The patients available for inclusion in the four papers included in this thesis are specified in Fig 4.

An age- and sex-matched normal population cohort drawn from of a random sample from the Swedish population registry, which had responded to the same PROM's used in the study, was used as a comparison to the treatment group in paper II. [84]

Figure 4. Flowchart of patient inclusion



3.2 STUDY TREATMENTS

RADIOTHERAPY

One of the aims of the study was to compare the effects of IMRT vs 3D-CRT on HRQOL. At the time of study initiation, it was postulated that a roughly equal number of patients were to be treated with either technique, in part since IMRT at the time was a time- and resource consuming technique and could therefore not be applied to all patients. However, this changed rapidly after the start of the study, leading to most patients being treated with IMRT, leaving only 19 patients treated solely with 3D-CRT.

Patients with oral and oropharyngeal cancers were initially treated with Hyperfractionated Accelerated radiotherapy (HART), 1,7 Gy/fraction given twice daily to a total dose of 64,6 Gy to primary tumor and involved lymph nodes and 40,8 Gy to adjuvant volumes. Overall treatment time was appr. 5 weeks with a 7-9 days split after 34 Gy to alleviate acute side-effects. [126] A small number of patients with stage I-II disease in the tonsillar fossa or base of tongue received a PDR-brachytherapy boost of 25 Gy ending external treatment at 40,8 Gy. During the study period a change of treatment recommendations occurred at our institution, introducing a moderately accelerated schedule of 2 Gy, 6 fractions/week to 68 Gy, and 1,55 Gy 6 fr/week to 52,7 Gy to adjuvant volumes given with SIMT-technique. [127] Nasopharyngeal tumors were given 72,6 Gy to the primary tumor using a concomitant boost of 2,2 Gy. Cancers in the hypopharynx were also treated with simultaneous integrated boost-technique, twice daily, 2 Gy/fr in the morning to the whole volume and a boost of 1,3 Gy to the tumor in the afternoon, raising the total dose to 72 Gy. [128] During IMRT planning, spinal cord dose < 46 Gy, PTV coverage and contralateral parotid dose < 25 Gy were prioritized criteria. [129] Eclipse (Varian Medical Systems, CA) was used to generate treatment plans and final absorbed doses were calculated using the pencil beam convolution algorithm.

To obtain comparable dose-volume histograms (DVH) between the respective fractionation schedules, absorbed doses were converted to EQD_2 using the scripting application programming interface in Eclipse v16.1. Corrections for incomplete repair between fractions were done using an adjusted version of the Linear-quadratic formula with an α/β–value of 3 Gy.

CHEMOTHERAPY

Chemotherapy was recommended for all patients with stage III-IV disease. Patients treated with HART fractionation were given two cycles of induction chemotherapy, cisplatin 100 mg/m^2 day 1 and 5-fluorouracil 1000 mg/m^2 day 1-5.[130] If treated with moderately acclerated radiotherapy, patients were given concomitant chemotherapy, cisplatin 40 mg/m^2, once weekly. [131]

SURGERY

Surgery of the primary tumor was performed in patients with oral cancers if it was considered technically possible. If there was evidence of positive lymph nodes, a radical neck dissection was performed simultaneously. If node involvement was unclear, a diagnostic modified ipsilateral neck dissection of lymph node areas I-III was performed. [132] Patients with head and neck cancer of unknown primary was treated with an ipsilateral radical neck dissection. [133]

3.3 PATIENT REPORTED OUTCOME MEASURES

HRQOL questionnaires (EORTC QLQ-C30, H&N-35 and FA-12) were distributed to patients at eight timepoints: At inclusion (before radiotherapy), 1, 2, 3, 6, 12, 24 and 60 months after start of treatment. Non-responders were reminded once via mail. In paper IV, MDADI was distributed to patients alive at five years.

EORTC QLQ-C30

The EORTC QLQ-C30 has been developed to assess the self-reported quality of life of all cancer patients. It has been validated in over 100 languages and is frequently used in studies around the globe. It comprises of 30 questions covering a stand-alone global quality of life item, five functional scales (Physical, role, emotional, cognitive, and social functioning) as well as nine symptom items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Questions involving the functional scales and symptoms use Likert scales with four possible answers: “Not at all”, “A little”, “Quite a bit” and “Very much”. Each answer corresponds to a value ranging from 1 to 4, the higher value corresponding to more symptoms in the symptom items, but less problems in the functional scales. The two questions covering global QoL are visual analog scales ranging from 1 to 7, where 1 represents “very poor” and 7 “excellent”. [134]

This approach applies as well to the two following EORTC questionnaires.

EORTC QLQ H&N 35

Apart from the EORTC QLQ-C30, the EORTC quality of life research group have developed diagnosis-specific questionnaires to examine symptoms that are related to organs and treatments involved in the disease. For HNC, the EORTC H&N 35 contains 35 questions covering symptoms including head and neck specific pain, dryness of mouth, mouth opening, teeth problems, coughing and sticky saliva as well as functional aspects like swallowing difficulties, taste alterations, speech problems, sexuality problems, problems with eating among other people and feeling ill. [135]

EORTC QLQ FA-12

To address cancer-related fatigue more comprehensibly than as just one scale in the QLQ-C30, the EORTC QLQ FA-12 has been developed and validated in several European languages, including Swedish. It is built upon 12 questions that are grouped into three dimensions of fatigue, namely physical, emotional, and cognitive. Moreover, there are two stand-alone questions regarding the interference of fatigue on daily activities and social functions. [136]

Scoring of EORTC Questionnaires

The scoring of EORTC questionnaires all follow the same general principles. High scores in **functional** scales or **global QoL,** signifies good function/health, whereas high scores in **symptom** items/scales, denotes worse symptoms. A RawScore (RS) for each scale/item is calculated by adding the value for each item and dividing it by the number of items in that scale. [137] A linear transformation from 0-100 is applied to the RS to obtain the score *S,* using the range between the highest and lowest possible value for each question. (i.e with four possible answers numbered 1 to 4 the range is 3). Thus, a universal 0-100 scale is produced for each item and scale.

MD Anderson Dysphagia Inventory (MDADI)

The MDADI is a validated PROM for evaluating swallowing dysfunction in HNC patients and its impact on HRQOL. [138] It consists of one question regarding overall effect of swallowing ability on daily functions and physical (8 questions), emotional (7 questions) and functional (5 question) subscales, in total 20 questions. Each question is scaled in five steps from “strongly agree” to “strongly disagree” and scored from 1 to 5. The sum for all responses in each subscale is divided with the number of questions and then multiplied with 20 to give a score of 0-100 for each scale.

All questionnaires are attached in the Appendix.

3.4 STATISTICS

In the initial study design, the difference in dry mouth score from EORTC QLQ-H&N-35 between 3D-CRT and IMRT was the primary study endpoint. A difference of 20 points was considered as a clinically relevant outcome and a power calculation at $p<0,05$ estimated that 150 patients were needed for inclusion, i.e., 75 patients in each treatment arm. Since HRQOL data is not normally distributed, non-parametric tests were used throughout.

Demographic and clinical characteristics of included patients was numerically summarized using descriptive statistics. Continuous scale variables were summarized using mean and standard deviation, while categorical variables were presented as frequency counts and percentages. In paper I to III, comparison between groups were made using Fisher's exact test for dichotomous variables, the Mantel-Haenszel chi square test for ordered categorical variables and the Mann-Whitney U-test or Fisher's non-parametric permutation test for continuous variables The chi-square exact test was used for non-ordered categorical variables. A significance level of 0.05 was applied throughout. In paper II and III, the Wilcoxon signed rank test was used for comparison over time for continuous variables. In Paper II, HRQOL mean score change in clinical subgroups with possible impact (radiotherapy only vs added surgery, oropharyngeal vs non-oropharyngeal, Stage I-II vs III-IV, added chemotherapy vs no chemotherapy and age <60 y vs >60 y) was compared. Mean age for the matching normal population cohort was chosen by adding 5 years to the mean age of IMRT patients at inclusion.

In paper III, the association between fatigue scores and gender, age (>60 years vs < 60 years), Karnofsky Performance Score (KPS=90-100 vs KPS< 90) and chemotherapy (yes vs no) was assessed. To estimate the effect of baseline fatigue levels, patients were split into no fatigue (score < 10) vs fatigue (score > 10) assuming a difference in score of 10 points as clinically relevant. [81]The median in the patient cohort for each OAR dose variable ($D_{2\%}$ and D_{mean} for brainstem and cerebellum) was chosen as the cutoff value to compare high vs. low dose effects. The difference in score between the time-point where fatigue levels peaked after start of treatment (3 months) and baseline values were used in the dose-fatigue analyses.

In paper IV, analyses of fatigue scores were focused on the dynamics within the first year following treatment, since only minor movements were seen after 12 months.

Clinical and dosimetric variables were tested in a univariable model and anything with a significance level of $p<0,15$ was included in a multivariable model build. Backward elimination was used to delete variables of no value. The predictors were chosen using a likelihood ratio test under the maximum likelihood estimation procedure. The choice of covariance structures and goodness of fit of the model were selected based on Akaike Information Criterion. Finally, the validity of the model was examined using assumption diagnostics.

4 RESULTS

4.1 PAPER I

Patients with HNC treated with IMRT from a prospective cohort followed longitudinally was compared to matched controls from a historic cohort of patients treated with 3D-CRT. 111 patients treated with IMRT, and 96 patients treated with 3D-CRT were included. EORTC QLQ-C30 and H&N-35 were used in both groups at diagnosis and 1, 2, 3, 6 and 12 months after treatment start. The two groups were evenly distributed regarding age, gender, primary tumor size, clinical stage, 1-year survival or additional treatment (surgery and/or chemotherapy). Out of patients alive, 83,7 % in the IMRT group and 83,1 % in the control group responded at 12 months.

At baseline, appetite loss, opening mouth and teeth were significantly worse in the control group. Social functioning, nausea, appetite loss, insomnia and diarrhea from the QLQ-C30 and coughing and senses/taste from the H&N-35 were significantly worse in the IMRT group at 1-3 months, but not from 6 months and later. At 12 months dry mouth, head and neck pain, social contacts and sexuality from the H&N-35 and cognitive functioning and financial difficulties from the C30 were all significantly better in the IMRT group. Most items and scales showed a similar pattern over time in both groups with an increase during and shortly after treatment and a return to near baseline values at 12 months, apart from dry mouth, sticky saliva and senses which were significantly worse at 12 months. Mean dose to the ipsilateral and contralateral parotid gland was 44,7 Gy and 28,2 Gy respectively in the IMRT group. Doses to OAR's were not available in the control group.

4.2 PAPER II

One hundred and twenty-six patients treated with IMRT available for evaluation of long-term Qol effects, were included in the study. HRQOL was assessed by the EORTC QLQ-C30 and QLQ-H&N-35 questionnaires at four time-points: before treatment (baseline), 1, 2 and five years after treatment. Furthermore, the MDADI was sent out to surviving patients at five years for specific assessment of swallowing. For reference, QLQ-C30 and H&N-35 values at five years were compared to scores from a sex- and age-matched cohort representing the Swedish normal population.

Average age of the study cohort was 60 years and male to female distribution was 3:1. Predominant primary tumor site was oropharynx (63,5 %) and most had advanced stage (III-IV) at diagnosis (85,7 %). Ninety-one patients (72,2 %) received induction or concomitant chemotherapy and 20 (15.5 %) had surgery prior to radiotherapy. Five-year survival rate was 95/126 patients (75,4 %) and out of these 95 patients, 73 (77 %) responded to the questionnaires at five years.

Comparing five-year results in responders at five years with baseline scores showed a significant increase in physical, emotional and role functioning, Global QoL, general and head and neck-specific pain, financial difficulties and feeling ill. Conversely, the items senses (i.e., taste alteration), sexuality, dry mouth, teeth, sticky saliva and opening mouth were significantly worse with dry mouth (19 vs 56) and sticky saliva (15 vs 40) showing the greatest numerical difference. Comparing patients with or without surgery, stage I-II vs III-IV or oropharyngeal vs non-oropharyngeal showed no significant differences. Significantly higher increase of scores in senses, dry mouth and diarrhea were observed in patients without added chemotherapy vs chemotherapy patients. Patients < 60 years had worse cognitive functioning but better social functioning than older patients.

The comparison to the normal population cohort showed significant worse scores for social functioning, appetite loss, senses, swallowing, head and neck pain, speech, social eating, problems with teeth, dry mouth, opening mouth and sticky saliva in the treated group.

The MDADI at five years showed a mean score of 80,3 for the global question and a composite score of 80,1. (physical: 80,8; emotional: 86,8; functional: 87,7)

4.3 PAPER III

One-hundred and twenty-six patients treated with IMRT for HNC cancer were included in a study following levels of fatigue before and after treatment. The EORTC FA-12 questionnaire was distributed before treatment start (baseline) and 1, 3, 6, 12, 24 and 60 months after baseline.

Physical fatigue increased significantly from baseline up to six months but reached baseline levels already at 12 months before decreasing to below baseline levels at five years. Physical fatigue peaked at three months (59 vs 29 at baseline). Emotional and cognitive fatigue showed similar patterns over time but with less pronounced numerical differences. Both were significantly increased at three months, but emotional fatigue was instead significantly decreaed from 12 months up to 60. Cognitive fatigue showed a significant derease at 24 months that was not sustained at 60 months.

Analysis of age (< 60 y vs >60 y), gender, performance status at baseline (karnofsky performance score 90-100 vs < 90) and if chemotherapy had been administered, showed that women and younger patients had significantly higher emotional and cognitive fatigue at baseline and younger patients and patients with low KPS had lower physical fatigue scores at baseline. Patients treated without added chemotherapy had significantly higher physical and emotional fatigue at 3 and 6 months, but not at any other time-point. Patients with no fatigue (<10) in any of the scales at baseline had significantly higher change in fatigue at all time-points.

Cerebellum and brainstem mean dose (Dmean) and near maximum dose (D2) in patients above or below the median value of each dose parameter was compared regarding the increase of physical fatigue from baseline to its highest value (3 months) to evaluate possible impact of delivered dose. This analysis showed that patients with a cerebellum Dmean > 3,5 Gy had significantly higher physical fatigue at three months.

4.4 PAPER IV

In the same cohort as in paper III fatigue scores for all three fatigue scales were summarized at each time-point. Analysis showed that all scores increased up to three months and then decreased to around baseline levels at 12 months to remain stable until 60 months follow-up. All following analyses was therefore focused on the fatigue score dynamics within the first year.

The response trajectory (i.e change in fatigue score means) could be described as two separate slopes, one increasing from baseline to 3 months and one decreasing from 3 m to 12 months. The slopes were steeper in physical fatigue and more modest in emotional and cognitive fatigue.

Clinical (age, sex, stage and Karnofsky Index) and dosimetric (Cerebellum Dmean and Brainstem D2) predictors were selected based on significance at p <0,15 in the univariable model.

In the multivariable model higher physical fatigue score was predicted by lower KPS (<100) and higher cerebellum mean dose (>3,5 Gy). High stage (stage IV) and higher age (> 62 y) had a negative predictive association (i.e. less fatigue), whereas lower KPS predicted more fatigue on the emotional scale and higher cognitive fatigue was predicted by female gender and younger age.

5 DISCUSSION

In HNC improved treatment strategies and a shift in etiological and prognostic factors have led to better survival rates, why evaluating HRQOL has gained increasing importance in the optimization of HNC treatment. Regarding radiotherapy, IMRT has rapidly become a gold standard in the treatment of HNC, based on its organ-sparing potential without compromising tumor control. Confirming improved HRQOL in patients treated with IMRT and to better understand predictive clinical and therapeutic factors is of big interest.

In the initial design of the study which most of the data in this thesis was derived from, IMRT was not, due to being relatively resource-consuming, available for all new patients. It was therefore assumed that asking every patient that was referred for radiotherapy from the multi-disciplinary tumor board for inclusion would lead to a roughly equal number receiving either 3D-CRT or IMRT. This changed quite rapidly after the study had started where we found that most patients were planned for IMRT as it became less costly and demanding. To have a numerically comparable control group treated with 3D-CRT in Paper I, we decided to use matched controls from a previous study using the same questionnaires at the same time-points.

It is known that patients' responses may change over time as they recalibrate their self-assessments, i.e. symptoms that were very prominent before treatment seem less problematic afterwards, so called *response-shift.* [139] Even if there is no clear evidence from the literature on this, it could possibly also be a concern when comparing two patient groups with the same questionnaires but treated during different time-periods.

We found a significant difference in patient-reported xerostomia 12 months after treatment favoring IMRT (63 vs 72). This finding is in line with previously reported results. Vergeer et al used HRQOL questionnaires distributed through a standardized follow-up program to compare 241 HNC patients (150 3D-CRT and 91 IMRT), before and after the introduction of parotid-sparing IMRT. [140] Both patient-reported and observer-rated xerostomia was significantly better for the IMRT group with a 20-point difference at six months post-treatment. A similar result was reported by van Rij et al, where 75 IMRT patients and 88 controls were compared regarding xerostomia related quality of life and they found significantly better scores in the IMRT group, especially in patients where mean parotid gland doses had

been below 26 Gy. [141] The largest prospective randomized trial is the PARSPORT trial, where 47 patients in each arm, were assigned to either conventional radiotherapy (3D-CRT) or parotid-sparing IMRT. [142] The primary endpoint was observer-assessed xerostomia at 12 months where the IMRT group had significantly lower grades. However, HRQOL scores for dry mouth (measured by EORTC H&N-35), though clinically in favor of IMRT (mean score difference of 8,5), were not statistically significant. The reported IMRT mean doses to the spared parotid gland in these three studies were 23,3, 27,1 and 25,4 Gy respectively, close to the 28,2 Gy in our study. That IMRT improves HRQOL compared to 3D-CRT is probable and given that it has become a global standard in the planning of HNC radiotherapy, more evidence in the form av prospective randomized trials, may be hard to obtain.

Long-term HRQOL effects of HNC treatment are well-known and important to identify during follow-up, which has been addressed in survivorship care guidelines. [143, 144] These guidelines are mainly based upon pre-IMRT data. The introduction of IMRT, given its positive effect on HRQOL compared with 3D-CRT during and shortly after radiotherapy, could potentially be beneficial in the long term.

As shown in Paper I, HRQOL scores were better in patients treated with IMRT compared to those treated with 3D-CRT at 12 months, but several symptoms, such as dry mouth, senses and sticky saliva was still significantly worse compared to baseline values. In Paper II we found that these items together with problems with opening mouth and problems with teeth remained significantly higher (i.e., more problems) five years after treatment. In comparison with a normal population cohort, even more symptoms, including head and neck pain, swallowing and social eating/contacts were affected in the treated population. Interestingly, scores from general symptoms including global QoL, role and emotional function and pain from the QLQ-C30 questionnaire showed significantly better functioning compared to baseline and did not differ from normal population levels.

As mentioned earlier, dysphagia with related HRQOL effects has historically been one of the most common and distressing long-term side-effects in HNC radiotherapy with objective signs like gastric-tube dependency and risk of pneumonia associated with aspiration. There is not much data on long-term effects of IMRT available. In a study by Baudelet et al on HNC patients ≥ 8 years after IMRT, they found 48 % of patients with some degree of observer-rated dysphagia, but the impact on QOL could not be assessed since no PROM's had been used. [146] Better HRQOL scores on swallowing in patients treated with IMRT vs 3D-CRT in long-time follow up, has been reported by

Kraaijenga et al, albeit in a small subset of patients (n=22) and in a study not primarily focused on radiation technique. [147] We could not detect any significant change in swallowing scores compared to baseline levels. Furthermore, the MDADI scores at five years were indicative of high function compared to data from the literature. [148, 149] Still, when comparing to the normal population cohort in Paper II, dysphagia is indeed a prominent complaint and therefore prospective studies to establish which volumes to spare and determine critical dose-constraints are much needed.

Chemotherapy has become a valuable additional treatment for increasing survival in advanced HNC and around 70 % of the patients in our study received induction or concomitant chemotherapy. There were some unexpected findings when comparing the HRQOL of patients treated with or without chemotherapy. In paper II we reported that the change in scores from baseline to five years for the items dry mouth and taste alterations, were significantly higher in the group without added chemotherapy. Similarly, in paper III, we saw that physical and emotional fatigue was significantly higher in patients without chemotherapy treatment at six months. Since chemoradiotherapy compared with radiotherapy alone is known to exacerbate symptoms like dysphagia and xerostomia, it has been assumed that this also should be reflected in worse HRQOL. [14, 150] This has also been reported by Rosenthal et al, where patients with concurrent chemotherapy had more problems with mouth/throat mucus and taste sensation. [101] On the other hand, in a large study published by Van den Bosch et al, though reporting worse symptoms in chemoradiotherapy patients, the effect could be attributed to early-stage larynx cancers alone and not in other HNC sites. [102] There is no obvious explanation to the contradicting results in our study. Baseline scores did not differ significantly between the groups and radiation doses to the parotid glands were similar. In conclusion, further studies are needed to clarify this issue.

The (at the time of study design), recently validated fatigue questionnaire EORTC QLQ-FA-12 was included in the longitudinal HRQOL assessment, and these data were the basis for Paper III and IV. Previously developed fatigue instruments had for the most part been developed in a single language and cultural environment, but the interpretation of questions can vary between different cultural settings and may not be readily translatable. Therefore, the EORTC quality of life group decided on the development of a fatigue instrument with a multi-national approach (EORTC FA-12). [136] There are a few studies on long-term fatigue using the QLQ-FA12, but none with HNC patients included, making this study the first of its kind, according to our knowledge. [152-155]

We found that fatigue levels, especially physical fatigue, nearly doubled the first three months, but returned to near baseline levels at 12 months with no additional significant change from 1 to 5 years. Emotional and cognitive fatigue also significantly increased at three months before returning to, and in the case of emotional fatigue, significantly below baseline at five years. These figures are perhaps lower than expected considering the fatigue prevalence of 20-50 % in long-time HNC survivors mentioned in chapter 1.3.3, but those data are not adjusted to baseline values. In a study by Jellema et al, they found increased fatigue levels 2 years after treatment in patients with xerostomia. [99] Patients included in the study were exclusively treated with 3D-CRT and since IMRT reduces xerostomia rates, it might explain the lack of increased long-term fatigue in our study. Hammermüller et al have compared levels of anxiety and fatigue in HNC patients included in an aftercare survivorship program with values from a German normal population cohort. [156] They found significantly higher fatigue levels in the survivor group regardless of age or gender. However, more than half of the patients (52,6 %) were assessed within 9 months of treatment and patients with follow-up > 9 months after treatment had in comparison significantly lower scores. As the available data are conflicting, further studies are required to clarify the long-term effects of fatigue in HNC patients treated with IMRT.

In modern radiotherapy TPS's each individual treatment plan yields detailed data on distributed doses to individual tumor volumes and organs at risk. Relating dose data not only to effects on tumors and OAR's, but also to HRQOL outcomes could assist clinicians when deciding on the optimal treatment plan in each individual case. As shown by Van den Laan et al, fatigue has a relatively high impact on overall HRQOL in HNC patients. [109] Therefore, establishing which doses and organs that contribute to radiation-induced fatigue is necessary to be able to optimize individual dose-plans.

In paper III we found that patients that received more than 3,5 Gy in mean dose to the cerebellum had a significantly higher physical fatigue levels at three months after treatment. Our cutoff value cerebellum D_{mean} of 3,5 Gy was somewhat arbitrarily chosen as it was the median of the patient cohort. Also, as the patients had been treated with several different fractionation schedules, we performed recalculation of all absolute doses from the TPS into EQD2 doses, which required assumptions of α/β-values and incomplete repair times. More data is needed to establish a reliable dose-volume relationship. There are a few other studies reporting on the possible association of radiation dose to the brainstem and cerebellum and the development of fatigue during treatment. In the previously mentioned PARSPORT trial they unexpectedly found a significantly higher proportion of acute high-grade fatigue in patients treated

with IMRT. [157] Dosimetric analysis showed significantly higher mean and maximum doses to the brainstem and cerebellum in patients with high (n=42) vs low (n=25) fatigue grades. In another publication from the same group, on patients with nasopharyngeal cancer (NPC) treated with chemoradiotherapy, they found significantly higher cerebellum D_{mean} in patients with high-grade fatigue 4 to 8 weeks after treatment. [118] In contrast to our results, the cutoff dose was over 30 Gy, reflecting the population of only NPC patients where, for anatomical reasons, doses to the brain become much higher than in HNC cases in general. None of these studies used PROM's for fatigue assessment, unlike Ferris et al who found an association between maximum dose to the brainstem and medulla and patient-reported fatigue one month after treatment. [158] This was in a mixed HNC population not unlike our study and reported max and mean doses to the brainstem and cerebellum were similar. Based on these data, a prospective trial aiming at restricting doses to these OAR's to prevent the development of fatigue should be considered, even if the exact dose constraints still need to be worked upon.

In paper IV we found that levels of fatigue up to 12 months after treatment may be predicted by age, gender, performance status, tumor stage and cerebellum mean dose (D_{mean}).

Little is known about predictive factors that contribute to fatigue levels. In a study on 200 colo-rectal cancer patients before and after adjuvant chemotherapy, fatigue six months after treatment was dependent on baseline fatigue (for all dimensions) and older age (for physical fatigue). [159] We find instead that younger patients develop higher fatigue levels. Hammermuller et al show in their comparison that the difference of fatigue between HNC patients and the normal population was markedly higher in younger patients (<65 y). [156] A hypothesis could be that the impact of the cancer diagnosis and following treatment in patients of younger age (with effects on working ability, social contacts and daily life) is more severe than in older patients.

In the multivariable regression model we found that lower tumor stage (stage I-III) predicts for higher emotional fatigue. Higher tumor stage has been reported predicting for worsening global QoL but not affecting fatigue during treatment of HNC. [160] Other studies have failed to show any predictive value of tumor stage on any of the QoL dimensions. [161] More studies are needed to get a definitive answer on the possible impact of tumor stage.

6 CONCLUSIONS

Patients with locally advanced HNC treated with IMRT show improvement in several HRQOL domains compared to patients treated with 3D-CRT, one year after treatment start. These domains include dry mouth, head and neck-specific pain and social functioning. However, some items, such as problems with senses, coughing, insomnia, and appetite loss, are worsened in the IMRT group during and shortly after treatment is finished, but these differences do not remain further on. (Paper I)

Long-term HRQOL in HNC survivors treated with IMRT improves regarding global QoL, pain and emotional functioning five years after treatment compared to baseline values. Furthermore, head and neck specific items like dry mouth, senses, problems with teeth, sticky saliva, swallowing, and opening mouth are markedly worse compared to a normal population cohort after five years, even in patients treated with IMRT. (Paper II)

Cancer-related fatigue is more pronounced in HNC patients up to six months after treatment but is not affected in long-term follow-up. Physical fatigue levels three months after start of treatment show an association with mean dose to the cerebellum, where patients receiving a dose > 3,5 Gy have significantly higher fatigue. (Paper III)

Younger age (< 62 years), cerebellum Dmean < 3,5 Gy, female gender and low KPS (<100) may be predictive of higher fatigue scores. (Paper IV)

7 FUTURE PERSPECTIVES

Beyond IMRT, we should look at other newer techniques with the potential of HRQOL benefits. Intensity-modulated proton therapy (IMPT) is perhaps the most obvious choice, providing even better organ-sparing possibilities. So far, IMPT for HNC has been shown to give less dysphagia measured as severe weight loss and gastric tube-dependency under treatment compared to IMRT. [162] Results of longitudinal HRQOL studies show promising outcomes, but there are still no direct comparisons with IMRT. [163, 164] Even if proton therapy is more costly than photons, calculations from NTCP models show a possible cost-benefit for IMPT assuming better efficiency regarding HRQOL effects. [165] Protons have a relative biological effectiveness (RBE) of approximately 1,1 times the effect of photons, but data suggests an even higher RBE of protons in HPV-positive HNC. [166] Thus, IMPT may also be more effective against squamous cell carcinoma, especially if it is HPV-positive. Therefore, de-escalating the total tumor dose using IMPT, thus enabling lower doses to OAR's, is currently under investigation in clinical trials. [167]

Another promising treatment improvement is adaptive radiotherapy (ART). By using onboard imaging on modern LINACs to assess tumor shrinkage and movement, it is possible to adapt dose distribution plans during treatment, enabling decreased treatment volumes and doses to OAR's. There is data supporting that one re-planning during radiotherapy for nasopharyngeal cancer leads to improved HRQOL. [168] Recently LINAC's with either CT- or MRI-based imaging, have commercially been made available offering the opportunity to adapt treatment plans during daily treatment. [169-171] It is not unreasonable to assume that daily ART could lead to improved HRQOL, and this should be an important aim to confirm in future trials.

Incorporating the use of PROMs in the daily clinical practice would give enhanced possibilities to gather HQROL data and relate them to given radiotherapy doses. New applications on web pages as well as on cellular phones are available to facilitate the collecting of data. Some considerations must be made in the implementation of such tools, such as that the validation process is not compromised when transforming paper-based questionnaires into a digital format, but overall, they should be of great value in future studies. [172, 173]

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APPENDIX

EORTC QLQ-C30, H&N 35, FA-12 and MDADI questionnaires

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.

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 hobbyer 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 på saker som att läsa en tidning eller titta 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

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

EORTC QLQ - FA12

Patienter berättar ibland att de har följande symptom. Markera i vilken utsträckning som du har haft dessa symptom under den senaste veckan. Svara genom att ringa in den siffra som bäst passar in på dig.

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
1. Har du saknat energi?	1	2	3	4
2. Har du känt dig utmattad?	1	2	3	4
3. Har du upplevt att du varit tvungen att dra ner på tempot?	1	2	3	4
4. Kände du dig sömnig under dagen?	1	2	3	4
5. Hade du svårt för att sätta igång med saker och ting?	1	2	3	4
6. Kände du dig nedstämd?	1	2	3	4
7. Kände du dig hjälplös?	1	2	3	4
8. Kände du dig frustrerad?	1	2	3	4
9. Hade du svårt för att tänka klart?	1	2	3	4
10. Kände du dig förvirrad?	1	2	3	4
11. Störde du av trötthet i dina dagliga aktiviteter?	1	2	3	4
12. Kände du att dina närstående inte hade förståelse för din trötthet?	1	2	3	4

MDADI

INSTRUKTION: Detta formulär handlar om hur Du uppfattar Dina problem med att äta, dricka och svälja och hur Du tycker att det påverkar Dig. Besvara frågorna genom att ringa in det svarsalternativ Du tycker stämmer bäst in på Din situation de senaste 7 dagarna. Om Du är osäker, markera det alternativ som känns mest riktigt.

		Stämmer precis	Stämmer ganska bra	Osäker/ har ingen åsikt	Stämmer inte särskilt bra	Stämmer inte alls
1.	Mina vardagsaktiviteter begränsas av mina problem med att äta, dricka, svälja	1	2	3	4	5
E2.	Jag är generad över mitt ätande	1	2	3	4	5
E4.	Jag blir upprörd, illa berörd av mina problem med att äta, dricka, svälja	1	2	3	4	5
F1.	Det är svårt för andra att laga mat åt mig	1	2	3	4	5
P2.	Det är svårare att äta, dricka, svälja mot slutet av dagen	1	2	3	4	5
E7.	Jag känner mig besvärad när jag äter, dricker, sväljer	1	2	3	4	5
F5.	Jag har fått lägre inkomster på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
P3.	Andra frågar "Varför kan du inte äta det?"	1	2	3	4	5
P7.	Det tar längre tid för mig att äta på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
E3.	Andra blir irriterade på mina ätproblem	1	2	3	4	5
E6.	Jag har dålig självkänsla på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5

		Stämmer precis	Stämmer ganska bra	Osäker/ har ingen åsikt	Stämmer inte särskilt bra	Stämmer inte alls
P8.	Jag hostar när jag försöker dricka	1	2	3	4	5
F3.	Mitt privata och sociala liv begränsas av mina problem med att äta, dricka, svälja	1	2	3	4	5
F2.	Jag har problem med att gå ut och äta med vänner, grannar eller släktingar	1	2	3	4	5
P6.	Det är ansträngande att äta, dricka, svälja	1	2	3	4	5
E5.	Jag går inte ut på grund av mina sväljningsproblem	1	2	3	4	5
P5.	Jag begränsar mitt födointag på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
F4.	Jag känner mig utanför på grund av mina ätproblem	1	2	3	4	5
P1.	Jag kan inte behålla min vikt på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
P4.	Det känns som om jag sväljer för mycket mat åt gången	1	2	3	4	5