Health-related Quality of Life, Distress and Psychosocial Factors in Head and Neck and Renal Cancer Patients

Quality of Life in HNSCC and RCC patients

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Dissertation for the degree of philosophiae doctor (PhD)
at the University of Bergen

2015

Dissertation date: 11.12.15

"People don't care how much you know, until they know how much you care."

Josepha Campinha-Bacote

To Hans Christian, Jenny Elise and Iver August

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SCIENTIFIC ENVIRONMENT

This study has been a collaborative project among three institutions:

- Bergen University College, Department of Health and Social Sciences, Institute of Nursing;
- University of Bergen, Faculty of Medicine and Dentistry, Department of Clinical Medicine;
- Haukeland University Hospital, Departments of Otolaryngology/Head and Neck Surgery and Urology.

The study has been administered from the Bergen Postgraduate School of Clinical Medical Research, Department of Clinical Medicine. Funding was provided from Bergen University College, Department of Health and Social Sciences, Institute of Nursing.

ACKNOWLEDGMENTS

First and foremost, my greatest gratitude goes to my main supervisor, Professor Anne Kari Hersvik Aarstad. She introduced me to her research back in 2008, thereby inspiring, challenging and recruiting me into Quality of Life research and the field of Cancer Survivorship. Her companion, Professor Hans Jørgen Aarstad, my co-supervisor, also deserves my sincere gratitude. Together you have granted me your extensive academic experience, kindness, patience and steady guidance throughout the entire period of my doctoral work. I am forever thankful to you both!

Professor August Bakke`s contribution as co-supervisor has also been important. Your academic experience and special knowledge in the field of RCC has been shared when reviewing my preliminary abstracts and papers. For that, I am very grateful!

I have certainly experienced that research is cooperation! The Head of the Urological Department, Christian Beisland, granted us access to the nephrectomy database; thus it became pertinent to collaborate despite the fact that we are husband and wife. The mutually shared joy during the process of analysis and writing on data from the RCC patients has been continually evolving. My other co- authors Arild Andre Østhus, Leif Bostad and Karin Hjelle also contributed in different ways to obtain important data/information. Thanks to every one of you for your contributions!

Sissel Tollefsen, Head at the Department of Health and Social Sciences at Bergen University College deserves gratitude for giving me her unconditional support along my PhD journey. Without the faculty’s support in granting me the time to do this work, and your willingness to facilitate, my degree would never have been realized.

I would also like to express my gratitude to my closest colleagues for their patience and understanding for me being a part-time PhD student, not always being solely dedicated to tasks in our department during the last semester.

Furthermore, I would like to thank all the patients who voluntarily spent their time answering questions, being coherent to the study protocol and for sharing some of their important experiences with me. You have taught me quite a bit about living with serious conditions, and I am humbled by this!

I am forever grateful for the love, care and upbringing that my parents, Bjørg Jenny and (later) Hans gave me. You both taught me to rejoice in the work and to withstand challenges. The values that you gave me I hold very high!

My most important coworkers during this period of doctoral work have been my children Hans Christian, Jenny Elise, Iver August and my husband Christian. Without your positive setting, excellent skills in running a home and willingness to cooperate, this work could not have been carried out. You are my “dream team!”

Wernersholm, Bergen, September 2015

Elisabeth Beisland

LIST OF PAPERS

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ABBREVIATIONS

BDI - Beck Depression Inventory

COPE - Coping Inventory

CV - Common Variance

CT - Chemo Therapy

EORTC - European Organization for Research and Treatment of Cancer

EORTC QoL C-30 - EORTC Quality of Life Questionnaire Core 30

EORTC H&N35 - EORTC Quality of Life Questionnaire Head and Neck 35

EPI - Eysenck Personality Inventory

EPQ - Eysenck Personality Questionnaire

FCR - Fear of Cancer Recurrence

GHQ - General Health Questionnaire

Gy - Gray

HNC - Head and Neck Cancer

HNSCC - Head and Neck Squamous Cell Carcinoma

HRQoL – Health-related Quality of Life

ISS - Integrated Staging Systems

KPS - Karnofsky Performance Status

LRN - Laparoscopic Radical Nephrectomy

MRCC – Metastatic Renal Cell Carcinoma

NSS - Nephron Sparing Surgery

ORN - Open radical nephrectomy

PROM - Patient Reported Outcome Measure

QoL - Quality of Life

RCC – Renal Cell Carcinoma

RN - Radical Nephrectomy

RCT- Randomized Controlled Trials

RT- Radiation Therapy

SCC - Squamous Cell Carcinoma

SHQ - Svebak Humor Questionnaire

SPM - Second Primary Malignancies

SPSS - Statistical Package of Social Sciences

TNM - Tumor, Node, Metastasis

WHO - World Health Organization

SAMMENDRAG

Kreftsykdom og dens behandling representerer en stor helseutfordring på verdensbasis, og berører en betydelig andel av verdens befolkning. Tradisjonelt har studier av kreftbehandling evaluert endepunkter som total overlevelse eller progresjonsfri overlevelse. For bedre å kunne forstå og evaluere den samlede effekten av sykdommen og dens behandling, har forskere etter hvert også inkludert evaluering av helserelatert livskvalitet (HRQoL), som blant annet innbefatter spørsmål om symptomer og psykiske/sosiale endringer etter kreftbehandling. Kunnskap om hva som påvirker kreftpasienters helserelaterte livskvalitet og psykologiske tilpasning til behandling og overlevelse har også blitt stadig viktigere med tanke på det økende antall kreftpasienter som overlever.

I denne avhandlingen har vi studert forholdet mellom helserelatert livskvalitet (HRQoL) og psykososiale forhold som personlighet, anvendt mestrings strategi, og psykologisk stress (målt med GHQ) hos hode/hals kreft opererte pasienter. Hos nyrekreft opererte pasienter har vi studert de samme faktorene, men har foreløpig ikke analysert data om psykologisk stress (GHQ). Vi har også undersøkt betydningen av komorbiditet, forhold ved kreftsykdommenes biologi og andre behandlingsrelaterte faktorer.

Hode/hals kreft og nyrekreft forekommer omtrent like hyppig i Norge. De to sykdommene har omtrent lik risiko for tilbakefall og død. Den store forskjell mellom disse to pasientgruppene er behandlingsbetingelsene. Hode/hals kreft pasientene får omfattende behandling som kan bestå av strålebehandling, cellegift og/eller kirurgi, som ofte medfører følgetilstander med potensielt stor innvirkning på daglige funksjoner. Nyrekreftpasienter blir vanligvis behandlet med bare ett kirurgisk inngrep. Gruppene er derfor interessante å sammenligne i forhold til hva som avgjør oppfattet

helserelatert livskvalitet. Er det kreftsykdommenes utbredelse, behandlingsrelaterte faktorer, risikoen for tilbakefall og død, følgetilstander - eller er det andre mer personlighets relaterte egenskaper som er avgjørende.

Hos hode/halskreft pasienter har vi funnet at tilstedeværelse av personlighetstrekket nevrotisisme og bruk av unngåelses mestring er assosiert med, og predikerer høyt nivå av psykologisk stress (GHQ) med mye det samme mønsteret som for livskvalitet (HRQoL). Psykologisk stress (GHQ) kan derfor sies å være et livskvalitetsmål. Til personlighets trekket nevrotisisme er det vist opp mot 30% felles varians mot livskvalitet. Stor utbredelse av primærtumor (T- stadium), predikerer også høyt nivå av psykologisk stress hos hode/hals kreftopererte pasienter. Anvendt mestrings strategi er også viktig, delvis som medierende faktor mellom personlighet og livskvalitet, og delvis assosiert mot livskvalitet. Psykologisk stress og til en viss grad også livskvalitet ble funnet å være stabile målt over en fire års oppfølgingsperiode i hode/hals kreft gruppen.

I nyrekreft gruppen ble det gjort lignende funn. Nesten alle livskvalitets indeksene var signifikant negativt korrelert med personlighetstrekket nevrotisisme og til bruk av unngåelses mestring. Nyrekreft pasientene som var operert med åpen operasjonsmetode (flankesnitt eller snitt via bukhulen), rapporterte om nedsatt livskvalitet på flere områder, mens de som ble operert med kikhulls kirurgi, rapportere om livskvalitet på nivå med normalbefolkningsutvalget. På noen områder rapporterte de flanke opererte nyrekreft pasientene om lavere livskvalitet enn de laryngektomerte hode/halskreft pasientene som vi sammenlignet med. Valg av kirurgisk tilkomst ved nefronsparende kirurgi (partiell nefrektomi) bør muligens sees i lys av dette funnet, med tanke på pasientens livskvalitet. Komorbiditet, og spesielt hvorvidt pasienten hadde diabetes eller stod på lungemedisiner eller ikke, synes å være assosiert med nedsatt helserelatert livskvalitet hos nyrekreft opererte pasienter.

«European Organization for Research and Treatment of Cancer» har utviklet flere generelle og diagnose- spesifikke livskvalitets spørreskjema for kreft pasienter, men et diagnose spesifikt skjema for nyrekreft opererte pasienter har hittil manglet. Vi har derfor startet arbeidet med å utvikle et slikt. Vårt foreslåtte EORTC-kompatible, diagnose spesifikke livskvalitets spørreskjema for nyrekreft opererte pasienter tilfører viktig informasjon om denne pasientgruppens helserelaterte livskvalitet. Ved å legge til fire generelle spørsmål om smerter, mobilitet og sosial funksjon har skjemaet også potensiale til å brukes som en kortversjon for å kartlegge nyrekreft pasienters generelle livskvalitet i kliniske situasjoner.

Overraskende like mønster av selvrapportert helserelatert livskvalitet og psykologisk stress (bare hode/hals kreftpasienter) på den ene siden, og personlighet og mestring på den andre siden, mellom hode/hals- og nyre kreft pasienter ble funnet i denne studien. For begge gruppene ser det ut til at forholdet mellom psykososiale faktorer og helserelatert livskvalitet er tre til fire ganger så sterkt som korrelasjonen mellom følgetilstander av behandling og rapportert helserelatert livskvalitet. Komorbiditet var assosiert med lavere selvopplevd helserelatert livskvalitet.

SUMMARY

Cancer represents a major health challenge worldwide, and affects a substantial proportion of the human population. Studies of cancer treatment has traditionally assessed endpoints such as overall survival and progression free survival. In order to better understand and evaluate the overall impact of the disease and its treatment, researchers eventually also included evaluation of health related quality of life (HRQoL) after cancer treatment. Knowledge of patient’s HRQoL and what affects cancer patients' psychological adaptation to treatment and survival has become increasingly important considering the growing number of cancer patients who survive.

In this thesis, we have studied the relationship between HRQoL and psychosocial factors such as personality, choice of coping, and distress (GHQ) in patients treated for Head and Neck Squamous Cell Carcinoma (HNSCC). Except for distress, we have studied the same factors in patients treated for Renal Cell Carcinoma (RCC). We have also examined the importance of comorbidity, some aspects of cancer biology and other treatment-related factors.

HNSCC and RCC occurs about equally as frequently in Norway. The two cancer diagnosis groups have an approximately equal risk of recurrence and death. The big difference between the two patient groups is according to the conditions of treatment. HNSCC patients often receive an extensive treatment consisting of radiation therapy, chemotherapy and surgery, which may lead to sequelae of a potentially great impact on daily functioning. RCC patients are normally treated with one surgical procedure only. The groups are therefore interesting to compare in terms of what determines the perceived HRQoL. Is it the cancer prevalence, treatment related factors, risk of

recurrence and death, sequelae -or other more personality-related qualities that are decisive.

In HNSCC patients, we found that presence of the personality trait neuroticism and use of avoidance- coping, were both associated with and predicts increased distress with much the same pattern as for HRQoL. Furthermore we suggested that distress may possibly be regarded a HRQoL variable in HNSCC patients.

The personality trait of neuroticism showed up to 30% common variance with HRQoL. Large extent of primary tumor (T- stage), predicted increased distress in HNSCC patients. Utilized coping strategy was also important, partly as mediator between personality and HRQoL, and associated to HRQoL. Distress was found to be stable when measured over a four-year follow-up period in the HNSCC patient group.In our sample of RCC patients we made similar findings. Almost all HRQoL-indices were significantly negatively correlated with the personality trait neuroticism and to use of avoidance- coping. RCC patients treated with a flank incision and to some extent with open abdomen approach, reported impaired HRQoL in several indexes, while those treated with minimal- invasive surgery, reported HRQoL in line with the general population. In some areas, the flank treated RCC patients reported a decreased HRQoL compared to a group of laryngectomized HNSCC patients. Considering the patients HRQoL, selection of surgical access in nephron- sparing surgery (NSS) should be viewed in the light of this finding. Comorbidity and particularly whether the patient had diabetes or were on lung medication or not, seems to be associated with impaired HRQoL in patients surgically treated for RCC.

The “European Organization for Research and Treatment of Cancer” (EORTC) has developed several general and disease-specific quality of life questionnaires for cancer patients, but a disease-specific questionnaire for RCC patients have so far been lacking. We have therefore developed an EORTC-compatible RCC-specific quality of life questionnaire. Our proposed form adds important disease-specific information about RCC- patients' HRQoL. By adding four general questions about pain, mobility and social functioning, our form also has the potential as a stand- alone HRQoL questionnaire that can be clinically used among surgically treated RCC patients.

Surprisingly similar patterns of self-reported HRQoL and distress (only in head/neck cancer patients) on the one hand, and personality and coping on the other side, between the head/neck and renal cancer patients were found in this study. For both groups, it appears that the relationship between psychosocial factors and HRQOL is three to four times as strong as the correlation between sequelae of treatment and reported HRQOL. Comorbidity was associated with lower self-reported HRQoL.

1 INTRODUCTION

Worldwide cancer is a major health issue that affects a substantial proportion of the population. By the end of 2013, there were more than 232,000 Norwegians with at least one cancer diagnosis and who were still alive (1). The probability of surviving a cancer diagnosis seems to increase for almost all cancers (1). As a result of this, the knowledge of a cancer patient's Quality of Life (QoL) and psychological adjustment to treatment and survival has become increasingly important. Awareness of the experiences and type of issues concerning cancer patients is important. Identification and knowledge of what factors and how they influence patient's QoL, are vital for an accurate assessment of effective intervention.

Cancer treatment trials have traditionally assessed end points such as overall survival and progression-free survival (2). Increasing interest has gradually been drawn to a larger field of outcomes, ranging from pure physical entities (like the stenosis of ducts) via the entities of both physical and psychological aspects (like swallowing and pain) to more psychological entities such as mood. A development from health- worker-generated (physical) assessments to patient-reported outcome measures (PROMs) has also been recognized (3, 4). The use of PROMs has increased with the use of multimodal treatment- and new chemotherapy regimens.

To better portray the overall effects of the treatment of a disease, investigators have included Health Related Quality of Life (HRQoL) outcomes following cancer treatment (5-8), an assessment of outcomes presumably including both physical and mental aspects. For example, patients are asked to assess the level of strain imposed by physical symptoms such as pain, but also more general symptoms like mood changes and fatigue. The assessments of bodily functions are also often included. During recent years, an increasing number of publications reporting on patients' HRQoL represent an expanded view of clinical outcomes.

HRQoL is a complex entity, in which the discussion of the content of the concept is still not completely agreed upon (5, 9). A contemporary view is to use an empirical model in which the content of the mainstream HRQoL questionnaires defines the term. In any case, HRQoL assessment should contain both a general feeling of health or well-being and a level of general function and symptom-associated QoL from broad symptoms such as fatigue to specific symptoms like coughing (9, 10). Both general- and disease-specific HRQoL aspects are usually investigated (11).

It is generally agreed upon that to undergo cancer treatment may be demanding for the patient (12, 13). Concerns about life and death are probably similar in all major cancer diseases. Additionally, a cancer patient follow-up usually continues over a period of years because of, e.g. a risk of recurrence. In addition to HRQoL issues, fear of cancer recurrence (FCR) is among the most commonly reported problems and one of the most prevalent areas of unmet needs for cancer survivors and their carers (14). Lowered mood has also been recognized as an important sequel of living with a cancer disease (15, 16), whereas clinically and research-wise, lowered mood is often grouped together with anxiety, such as in the HADS inventory (17), and denoted distress. Distress has been suggested to be a particularly well suited concept to measure among cancer patients, as there will then be limited need to separate genuine depression and anxiety from naturally occurring distress among cancer patients. Distress is furthermore recommended to be targeted as a general screening entity in cancer clinics (18-20). The close relationship between distress and HRQoL scores among Head and Neck Squamous Cell Carcinoma (HNSCC) patients has been emphasized in this present investigation.

Some cancer disease treatments may leave specific sequels, while other cancer disease treatments seemingly leave limited or no sequels. In order to estimate the relative importance of physical sequels, as related to HRQoL and psychosocial factors, at least one cancer disease with many sequels and one cancer disease with few sequels had to be studied. As we had studied HNSCC patients along these lines, we extended our studies to also include Renal Cell Carcinoma (RCC) patients. Both of these cancer patient groups have a survival rate of approximately two-thirds, and recurrence mostly occurring within the first years after the primary diagnosis. However, the sequel levels of these patients vary. Treatment in HNSCC may be detrimental to both physical appearance and bodily functions such as breathing, swallowing and speech (21). On the other hand, RCC patients are primarily treated with a single curative tumor treatment surgery without any expected specific major physical sequels. Therefore, to what extent sequel levels are related to HRQoL or other psychological and treatment-related factors, is furthermore investigated in this thesis.

Another hypothesis emphasized in this thesis is that cancer patient's HRQoL is depending on psychosocial conditions such as personality and coping. Therefore studying to what extent personality and coping influence HRQoL levels regarding the two cancer diseases, has currently also been an aim.

Many studies have been published concerning cancer patients from the diagnosis time point and the first years thereafter (22-24). In addition, many studies have concentrated on patients following the recurrence of a cancer disease (25, 26). Cancer patients, who are presumably cured, should also be investigated regarding HRQoL and distress, and this has also currently been a focus of this study.

A variety of different HRQoL outcome measures are being used in the collection and interpretation of HRQoL information today, thus complicating the ability to draw conclusions across different data sets, with varying treatment regimens and different cancer types (27, 28). The European Organization for the Research and Treatment of Cancer (EORTC-QLQ) has developed a series of HRQoL questionnaires especially aimed at cancer patients. A disease-specific questionnaire on HNSCC patients is also available. This group of questionnaires has been used in this investigation. Concerning RCC patients, a disease-specific questionnaire was missing; therefore, one of this thesis' aims has been to develop a RCC disease-specific HRQoL questionnaire.

The overall aim of this thesis has been to study the relative importance of physical sequels related to psychosocial conditions with outcome measures such as HRQoL and distress as measured by GHQ in presumably cured HNSSC and RCC patients. In order to do so, knowledge of the two chosen cancer diseases will first be presented, in which current knowledge and measurement questionnaires of the utilized psychosocial concepts will be presented. Next, the aim, material and methods will be described, before the results of the thesis will be given. A discussion will then follow before a discussion about future aspects will conclude the thesis.

2 HEAD AND NECK CANCER

Head and neck cancer (HNC) includes a variety of malignant tumors, and is defined as cancers occurring in the oral cavity, pharynx, larynx, nasal cavity and sinuses.

2.1 Head and Neck Squamous Cell Carcinoma

The most common HNC is squamous cell carcinoma (SCC) and its variants (90-95% of cases) (29). In our study we have only included patients with a primary manifestation of the cancer from the mucosa in the head and neck area, denoted Head and Neck Squamous Cell Carcinoma (HNSCC) patients. The remaining 5 % of other HNC has not been studied in this thesis.

2.2 Epidemiology of HNSCC

In Norway, 536 persons were diagnosed with different HNC in 2013 (1). Men are more commonly affected than females, at a ratio of 2:1 (1). HNSCC is considered the sixth most common malignancy worldwide, accounting for approximately 55,000 cases and 12,000 deaths annually in the United States (29). Progress has been made during the last several years towards a better understanding of the molecular development of this cancer (30). The incidence rate and primary site differ according to geographic differences and the prevalence of risk factors. In Norway, as in the US, the highest rates of HNC are seen in older males, though the incidence rate is increasing in females as well. Up to 40% of patients with HNSCC present with metastatic disease to the neck lymph nodes. Other common sites of metastases may be the lungs, mediastinal nodes, the liver and bone (31).

2.3 Risk Factors for HNSCC

The most important known risk factors associated with head and neck cancer are smoking (32), alcohol consumption (33), human papillomavirus (HPV) infection (oropharyngeal cancers) (34) and Epstein-Barr virus (EBV) infection (naso-pharyngeal cancers in Asia) (35).

Genetic and ethnic factors, environmental and occupational exposures and cultural differences among populations, i.e. betel nut chewing (36, 37), radiation exposure, vitamin deficiencies, periodontal disease and immunosuppression also seem to play a role. Tobacco and alcohol consumption are also considered to have a synergistic effect (38). The exposure of the mucosa to the carcinogenic effects of the substances may cause multiple primary and secondary tumors in the mucosa, a phenomenon described as "field cancerization" (30).

2.4 Tumor States and Survival in HNSCC

Head and neck tumors may be classified according to the Tumor Node Metastases (TNM) classification system (39). Physical examination, imaging and histological confirmation are all part of the procedure, with the assessment of the following three components forming the basis for classification of the cancer diseases' anatomical extent in head and neck cancer patients:

T - The extent of the primary tumor (T-is, T1, T2, T3, T4);

N - The absence or presence and extent of regional lymph node metastases
(N0, N1, N2a, N2b, N2c, N3);

M - The absence or presence of distant metastases (M0, M1).

T-is indicates an in situ carcinoma, while a T1 in the oral cavity indicates a tumor of 2 cm or less in its greatest dimension. A T2 tumor has a diameter between 2.0 and 4.0 cm, and a T3 tumor has a diameter of 4.0 cm or more. Lastly, a T4 denotes whether the tumor has spread into nearby anatomical structures such as muscles, cartilage or bone (40).

In laryngeal and pharyngeal carcinomas, the T stage rules are more complex, though derived from the same principle that the more extended disease, the higher the T stage (40).

N0 denotes no spread to the regional lymph node. N1 denotes metastasis in a single ipsilateral lymph node of 3 cm or less in its greatest dimension. N2 denotes metastases in a single- or in multiple lymph nodes, ipsilateral or bilateral, between 3 and 6 cm, with N3 denoting metastasis in a lymph node of more than 6 cm in greatest dimension (40). M0 indicates no distant metastasis, and M1 indicates a distant metastasis (40). Moreover, the TNM grading system has been a mainstay in cancer outcome prediction for many years (41).

The five-year overall survival in HNSCC patients was between 60-70% in Norway in 2011 (42). Comorbidity has an increasing effect on mortality in HNSCC patients (41). Despite advances in systemic therapies, the median overall survival for patients with recurrent or metastatic HNSCC is less than one year (43).

2.5 Treatment of HNSCC

Treatment is traditionally based on an assessment of clinical factors such as histological diagnosis, primary site, tumor-, node-, and distant metastasis- status. A multidisciplinary team consisting of Head and Neck surgeons, oncologists, plastic surgeons, oral surgeons, radiologists, pathologists, prosthodontists, clinical nurse specialists, speech and language therapists and dieticians is often involved, and extensive treatment is sometimes necessary.

Surgery and radiation therapy (RT) have remained the mainstay of therapy in HNSCC patients (31). Intensity-modulated radiation therapy and the development of various fractionation schemes have allowed an improved delivery and tolerability of this treatment (38). Chemotherapy has been reintroduced as an integral part of the RT treatment to some selected patients, and may be administered before definitive treatment or simultaneously with radiation therapy (38, 44, 45).

2.6 Treatment Sequels in HNSCC Patients

Surgery may cause disfigurement and cosmetic changes, but also functional challenges in relation to swallowing (46, 47), speech and breathing difficulties (48). Radiation therapy may cause acute and lasting damage, skin inflammation and other complications such as xerostomia (dry mouth) and fibrosis, which may cause abnormal motility of the deglutition muscles, thus possibly leading to aspiration, dysphagia and stenosis (46).

Compared with standard treatments, new treatment protocols tested in order to improve survival in HNSCC patients provide an increased amount of side effects both during and after treatment. Sequels after surgery, radiation therapy and chemotherapy may have a potentially large impact on daily functioning in previous HNSCC patients (48). This is also an argument that the quality of life studies in previous head/neck cancer patients is important.

2.7 Secondary Cancers in HNSCC Patients

Patients with HNSCC are at elevated risk of second primary malignancies (SPM), most commonly of the head and neck, lung and esophagus (49).

3 RENAL CELL CARCINOMA

3.1 Renal Cell Carcinoma

For many years, these tumors were believed to originate from the adrenals, hence the term “hypernephroma,” which was clinically used for decades. With the introduction of the electron microscope, it became evident that these tumors actually originated from a mature tubular structure (50). Today, it is commonly accepted that most renal cell carcinomas (RCC) originate from the proximal tubule of the nephron (51). The term RCC includes many different histological subtypes (52). The most common subtype is clear-cell RCC, which constitutes approximately 70% of the cases, followed by papillary RCC with 10-15% of the cases and chromophobe RCC, with approximately 5% of the cases (52). The remaining 10% represents more rare types.

3.2 Epidemiology

In 2013, 757 cases of RCC were reported in Norway (53). RCC represents 2.5% of all new cancer cases in Norway, and after prostate- and bladder cancer, it is the third most common urological cancer (53). At the end of 2013, there were 5,693 persons living with a diagnosis of RCC in Norway (53). RCC affects men twice as often as women, and incidence peaks in the sixth and seventh decade. Renal cancer occurs more frequently in the developed world, and Scandinavia has a relatively high incidence of the disease (54). For example, in 2013 there were 265 deaths due to RCC, thereby constituting 2.5% of all cancer deaths in Norway (53).

3.3 Risk Factors

The causes of Renal cancer are not well enough understood, but some risk factors are generally acknowledged. These include smoking, hypertension, obesity and end-stage kidney disease (55). In addition, Renal cancer may be a result of genetic disorders. The most commonly known of this type of cancer is Von Hippel-Lindau disease, which causes clear cell RCC in affected patients. In most patients, however, it is not possible to identify any definitive single cause.

3.4 Tumor Staging and Prognosis

The TNM-system is the basis for staging in RCC, and is the most important prognostic factor in RCC. Primary RCC tumors are classified as T1 when the tumor is 7 cm in its greatest dimension or less, and limited to the kidney. The T1-stage is subdivided into T1a (≤4.0 cm) and T1b (4.1-7.0 cm). A T2 denotes a tumor found to be more than 7 cm in its greatest dimension, and limited to the kidney. A tumor is classified as T2a when more than 7 cm, but less than 10 cm, and T2b when more than 10 cm, and limited to the kidney. T3 denotes that the tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond the Gerota's fascia, whereas T4 denotes that the tumor invades beyond the Gerota's fascia.

Regional lymph nodes are classified as N0 when no metastases are found and N1 when metastasis is found in a single regional lymph node. The N2 classification denotes that metastasis is found in more than one regional lymph node (40). M0 indicates no distant metastasis, while M1 indicate the presence of such metastasis (40).

There are several other prognostic factors for RCC, but it is generally accepted that the second most important is tumor grade (56). To create an improved prognostication, TNM staging, tumor grade and other factors have been combined into so-called integrated staging systems (ISS). Several ISS exist, and have been externally validated (57-59). Such systems might also be used for tailoring follow-up programs after treatment.

3.5 Treatment of Localized RCC and Sequels

Over the last two decades, there has been a major change in how to perform surgery for RCC. Open radical nephrectomy (ORN) used to be the gold standard for RCC treatment. Laparoscopic radical nephrectomy (LRN) challenged this, and today it is generally accepted that LRN has a lower treatment morbidity than ORN (55). Nephron sparing surgery (NSS) has been introduced, and has steadily increased its role. Today, NSS is the recommended treatment for T1a tumors, and is further recommended for T1b tumors whenever surgically feasible (55). NSS may be performed by an open, pure laparoscopic- or robot-assisted technique based on the skills of the surgeon. Of importance here is that the European Association of Urology (EAU) guidelines highlight that LRN should not be performed in a tumor with a recommendation for NSS (55).

While surgery is the single recommended curative treatment for RCC, active surveillance or observation could be an option in selected patients with a limited life expectancy. In general, ablative techniques are not recommended, but may be offered to the latter patient group (55).

Neither radiotherapy nor chemotherapy treatment has a place in the curative primary, or as adjuvant therapy. Consequently, sequels that are commonly related to such treatment are therefore rarely seen in RCC (52).

Kidney function is significantly more affected by nephrectomy than by NSS. However, if the remaining kidney is functioning normally, most patients will not experience any problems with impaired kidney function (52).

RCC surgery is often said to have few long-term sequels. Nonetheless, incisional hernias and abdominal wall bulging are well known (60), but there is a possibility of underreporting in the existing literature.

3.6 Outcome of Treatment

Curation for RCC is heavily dependent on TNM stage (52). Smaller T1a tumors have a five-year survival rate of 95-99%, while primary metastatic RCC (MRCC) has a five-year survival rate of 10-15%. Of those experiencing a recurrence of the disease, approximately 50% will get this during the first two years and 80% within five years after primary treatment (52). RCC most commonly metastasizes to the lungs, liver, bone and brain (61). For patients with MRCC, there is currently no curative treatment available (52). Since 2006, fit patients with MRCC in Norway have been treated with antiangiogenic drugs (targeted therapy (TT)). This has significantly increased the length of overall survival within this group of patients (62).

4 QUALITY OF LIFE

The fact that illness affects QoL was recognized centuries ago by Lichtenberg (1742-1799), who declared that, "*The feeling of health is acquired only through sickness*." Despite this, QoL was rarely mentioned in the scientific literature before the 20th century. In daily life, QoL is often described by terms such as well-being, happiness, need fulfillment, life satisfaction, the meaning of life, goal attainment and functioning. Several more strict definitions have been proposed throughout history, and the definitions have generally changed from being observer-based to being based on the perspective of the patient (3, 4). Even so, no exact definition exists, despite extensive emphasis in research over the past 60 years.

4.1 Historical Development

From a health perspective, QoL has a long tradition. In ancient Greece, Aristotle (384-322 BC) described that one of the main goals of the existing health-care system was to improve patients' QoL (9, 63). The World Health Organization (WHO) stated in 1948 that health is "*physical, mental, and social well-being and not merely the absence of disease or infirmity*" (64). By this definition, the WHO showed a broadening of the health concept to include quality of life. Illness not only comprises the physiological or biological aspects of life, but also the psychological, social and economic well-being. Furthermore, a more holistic view of medical problems invokes QoL (65).

In 1996, the WHO Quality of Life group (WHOQoL) defined quality of life as: "*Individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns*" (66).

4.2 Definition and Content of QoL and HRQoL

The assessment of QoL within the medical community started at the end of the 1940s, with the publication of the Karnofsky Performance Scale (67), which is still in use in cancer therapy trials today. In 1995, Morton [39] provided a list of important domains to be included in a QoL questionnaire, including Physical functioning, Symptoms, Emotional functioning, Role functioning, Social functioning, Coping ability, Financial impact, Health status, Sexuality and a Global index. Today, coping is considered an explanatory variable (68), and in that sense not part of the HRQoLconcept.

Kaplan and Bush (69) were some of the first researchers to introduce the term "health-related quality of life" in the early 1980s. They claimed that disease does not necessarily or directly affect well-being and satisfaction, but that symptoms and dysfunction are attributes that affect these aspects. Furthermore they claimed that these attributes constitute a "health-related quality of life," and that these aspects are directly associated with satisfaction, desirability and utility. The extended term "health-related quality of life" (HRQoL) emerged to distinguish the interest of QoL in clinical health research from QoL in general (69).

Today, QoL is often specified to the term "health-related" QoL (HRQoL), thus denoting the scores of a QoL questionnaire (70). Numerous studies have addressed the impact of different diseases and their treatment on patients' HRQoL. Studies investigating HRQoL improvements or decline, or the importance of psychosocial conditions in relation HRQoL among groups of patients, seem to be an emerging interest in medicine and health research (71-75).

Padilla and co-workers (76) defined health-related QoL (HRQoL) as: "*A personal, evaluative statement summarizing the positivity or negativity of attributes that characterize one's psychological, physical, social, and spiritual well-being at a point in time when health, illness, and treatment conditions are relevant.*" Elements of the approach advocated by e.g. Padilla are reflected in most of today's QoL instruments.

In this thesis, the term HRQoL has been used, thus indicating a relatively broad definition of quality of life as scored by the patient. The questionnaires that have been used contain the items summed up, as required by Padilla (76) and Morton [39].

4.3 HRQoL in HNSCC Patients

Over the last decades there has been an increasing amount of published studies about the quality of life in patients who have survived head and neck cancer (21, 71, 77-80). A disease-specific EORTC QoL questionnaire for HNSCC patients has been developed (81).

Because this cancer affects structures that are critical for, e.g. speaking and swallowing, and treatment may lead to deformities that may result in loss of facial integrity and impact psychosocial functioning (71), it is particularly interesting to assess the HRQoL in these patients. Many researchers have shown a relatively limited reported decrease in HRQOL among survivors of head and neck cancer compared with the general population (6, 7). Additionally, minor differences are also seen in reported quality of life among patients who have received extensive treatment with many sequels, compared with those who have received limited treatment without specific expected sequels (82).

4.4 HRQoL in RCC Patients

HRQoL issues with regard to RCC patients have only been explored on a limited basis. Existing studies have rarely taken into consideration patient-reported quality of life, and are therefore characterized by being retrospective (72). Using domain-specific questionnaires, Ficarra et al. (83) comparatively assessed the psychological, social well-being and general state of health in patients with stage I RCC who either underwent elective nephron sparing surgery (NSS) (n=56) or radical nephrectomy (n=88). Surgery for localized RCC did not particularly negatively affect the overall HRQoL outcome. The comparative analysis showed that at long-term follow-up, a radical nephrectomy seemed to eventually cause a more relevant negative impact on the psychological well-being than nephron sparing surgery (NSS) (83).

Ames et al. (84) evaluated the psychological needs of individuals (n=28) undergoing nephrectomy for newly diagnosed, localized RCC, using a mixed qualitative-quantitative approach with semi-structured interviews and the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire. The investigation provided information that fatigue, anxiety and depressive symptoms were experienced in patients undergoing surgery for localized RCC (84). Health-care providers working with these patients were encouraged to be mindful of the psychological needs of these patients. Ames et al. (84) further recommends that in cases where patients are experiencing significant distress, a referral for adjuvant psychosocial services should be considered (84).

Other published studies have primarily focused on the chosen surgical procedure and its impact on HRQoL (24, 85). According to these studies RCC patients report a high quality of life regardless of operating method (24), and most patients regain their pre-operative HRQoL within 12 months (72).

Within the EORTC family, a disease-specific questionnaire in RCC patients is lacking. The development and validation of a disease-specific HRQoL questionnaire in RCC patients would increase the specificity and quality of RCC data, and make it possible to compare data across studies.

4.5 General HRQoL Questionnaires

The following presentation of questionnaires is based on an overview published by Tamburini in 2001 (86).

a. Karnofsky Performance Index

The Karnofsky Performance Index (67) is an observer-based, 11-point rating system to assess the performance status of the patient. It is still being used in both clinical situations and in research in order to validate new measurements, patient's self-care, physical activities, symptom burden and ability to work. It is scored from 0 (dead) to 100 (fully functional), and may also be a good predictor of survival (87).

b. Spitzer Quality of Life Index

The Spitzer Quality of Life Index (88) was one of the first HRQoL instruments, and is also an observer-based instrument, consisting of five questions assessing a patient's daily living, health, activity, support and outlook. Questions are scored on a three-point scale (0-2), and a sum score is calculated (range 0-10).

c. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QoL C-30)

The EORTC QoL C-30 questionnaire consists of nine multi-item scales, five functional scales, three symptom scales and one global health and HRQoL scale. Several single item symptom measures are also included. Questions are scored according to a Likert scale ranging from 1-4, except for the general questions, where a 7-point Likert scale is utilized (3, 77, 89). This questionnaire is described in detail in the "Material and Methods" section.

d. The Functional Assessment of Cancer Treatment –General (FACT- G)

The FACT-G is a multi-dimensional questionnaire published in 1993 by Cella et al. (90), which aimed to study HRQoL in cancer patients. The questionnaire consists of 28 questions, measuring five sub-scales: physical, functional, social and emotional dimensions, as well as a dimension measuring the patient's relationship with the doctor. Scores are made according to a Likert scale, from 0- 4 (the higher the score the better outcome). This instrument can be supplemented by disease-specific modules.

e. Rotterdam Symptom Checklist (RSCL)

The aim of the Rotterdam Symptom Checklist is to evaluate physical toxicity, social functions and psychological adjustment in cancer patients. The instrument originally had 30 items, eight measuring daily activities and 22 covering various symptoms. Scores are rated on a 4-point Likert scale, in which 0 denotes "not at all" and 3 denotes "very much." One overall score, and two sub-scales measuring physical and psychological dimensions, are sum scores derived from this questionnaire to be summed up (79).

f. The Cancer Rehabilitation and Evaluation System, Short Form (CARES-SF)

The CARES questionnaire originally consisted of 139 questions, but was later reduced to a short form version consisting of 59 items (91). The first 36 questions are answered by all cancer patients, while the last 23 questions are site-specific (92). Scales covering the physical, psychosocial, sexual and marital domains, in addition to a scale measuring medical interaction, are to be scored according to a five–point scale ranging from "not at all" (0) to "very much" (4). Low scores indicate few problems, and this test has been translated into Norwegian by Hjermstad (92).

g. Short Form-36 Health Survey (SF-36)

The SF-36 questionnaire is empirically based and has 36 questions, comprising eight multi-item scales concerning: physical functioning, physical role, emotional role, bodily pain, general health, vitality, social functioning, and mental health (93). It has become one of the most widely used general health status measures, and is also referred to as a health-related quality of life measure.

h. World Health Organization Quality of Life Abbreviated (WHOQoL-BREF)

This questionnaire is based on the WHO`s definition of QoL. The 26 questions cover physical, psychological, social and environmental domains. The test is scored according to a 5-point Likert scale, in which a high sum score indicates a good

HRQoL. The questionnaire has been translated into more than 30 languages, and is a general HRQoL questionnaire (66).

4.6 Head and Neck Cancer-specific HRQoL Questionnaires

Rogers et al. 1999 (79), Semple et al. 2004 (70) and Tschiesner et al. 2008 [58] have all published systematic reviews of the quality of life questionnaires used in head and neck cancer patients. The last paper also offers a content comparison of the quality of life questionnaires used, based on the international classification of functioning, disability and health (ICF). The following overview of questionnaires to specifically assess HRQoL in HNC patients is based on these three aforementioned reviews:

a. Rathmell Quality of Life Questionnaire

The Rathmell Quality of Life Questionnaire (94) contains 19 questions covering symptoms, performance, employment and social and emotional function, and is scored on a 4-point Likert scale. This test needs further validation, and has not been much used (79).

b. Mc Master University Head and Neck Radiotherapy Questionnaire - Browman

Browman and co-workers (95) developed this performance-related questionnaire to be used by clinicians in HNC patients previously treated with radiation therapy. The questionnaire consists of 23 items, most of them focusing on function- and symptom-related treatment consequences, and some few questions related to emotional issues.

c. European Organization for Research and Treatment of Cancer Quality of Life – Head and Neck 35 (EORTC QOL H&N35)

This HNC specific questionnaire was first developed by Bjordal et al. in 1994 (81). It consists of items related to HNC disease and treatment, social functioning and sexuality. The specific part consists of 14 symptom items with 18 questions, and eight functional items with 12 questions, all of which are scored according to a 4-point

Likert scale. Descriptive items about weight, nutrition and pain are also included, with this questionnaire described in detail in the “Material and Methods” section.

d. Functional Status in Head and Neck Cancer (FS H&N-SR)

This questionnaire was developed by Baker and Schuller in 1995 (96), and has 12 symptom categories and 15 items, including one on overall HRQoL. Ability as to chew, eat, swallow and shoulder function and appearance is being assessed. Questions are scored on a scale from 1 to 5, with a maximum score of 75 and the higher the score, the better the functioning.

e. Functional Assessment of Cancer Therapy – Head and Neck Scale (FACT-HNS)

In 1996, List et al. (97) developed a head and neck disease-specific part of the FACT questionnaire. It has 11 items, including questions on eating, swallowing, appearance, breathing, use of alcohol and smoking. The questions are scored according to a 4-point Likert scale. The general- and disease-specific questionnaire may be used as one entity.

f. Head and Neck Cancer-specific Quality of Life (H&NCSQL)

In 1997, Terrell et al. (74) published an instrument consisting of 11 questions about treatment satisfaction, response to treatment and HRQoL issues. Items covering communication, pain, eating and emotions are scored according to a 5-point Likert scale.

g. Head and Neck Survey (H&NS)

Gliklich et al. (98) published the Head and Neck survey questionnaire in 1997. It has 11 items summarized to three HN-specific domain scores about eating/swallowing (five items), speech/communication (two items) and appearance (four items). Scores from 0 (worst) to 100 (best) can be reported.

h. *Liverpool University Questionnaire*

Young et al. (99) developed this short HRQoL questionnaire in 1998 to be used in outpatient settings. Ten items cover state of mind, ability to perform daily living activities, well- being and function related to HNC symptoms.

i. *University of Washington Quality of Life Scale – revised*

The University of Washington Quality of Life Scale consists of nine categories related to daily living and symptoms following the treatment of HN cancer. The questionnaire originally consisted of 10 items (100) (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste and saliva), and was later supplied with items about mood and anxiety (101). In addition, "Which issues have been most important for you during the past 7 days?", and three questions about general health and overall HRQoL are asked. Each domain is scored from 1 (not important) to 5 (extremely important) (79).

4.7 RCC Patient-specific HRQoL Questionnaires

A disease-specific HRQoL questionnaire for RCC patients has thus far been lacking. However, several symptom burden indexes do exist (102-104). The Functional Assessment of Cancer Therapy (FACT) - Kidney Symptom Index (FKSI) was developed and validated in 2006 to enhance treatment decision-making, practice guidelines, symptom management and treatment efficacy for kidney cancer patients (105). Thirty-four symptoms related to the disease were identified and tested.

5 DISTRESS, DEPRESSION AND ANXIETY

According to the US National Comprehensive Cancer Network, distress is defined as: "*An unpleasant emotional experience of a psychological, social, or spiritual nature that may interfere with the patient`s ability to cope with cancer and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fear, to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis*" (106).

Kallay et al. (107) states that; "*Psychological distress can be described as a combination of symptoms, including anxiety, mood, cognitive, and behavioural impairments*", and that it is a concept used more in psychological research, rather than in medical research (107). The level of distress may be an indicator of mental disease (108, 109).

Despite progress in treatment strategies and increased overall survival rates, cancer may still be associated with suffering, pain and death (110, 111). A cancer diagnosis may create a greater sense of fear than other illnesses that possess a poorer prognosis (111). Impaired mood, anxiety, depression and increased distress are considered under-recognized and common in many different cancer patient groups (16, 112-116). Research suggests high prevalence rates of emotional distress in cancer populations globally (16, 117, 118). Previous prevalence studies of psychological distress indicate that 25-30% of all newly diagnosed and recurrent cancer patients experience significantly elevated levels of emotional distress (16, 119). According to Vachon (120), one-third of patients with cancer experience distress, and may benefit from psychosocial intervention.

Distress has been suggested to be a particularly valuable concept to help assess cancer patients in general throughout the entire cancer trajectory (121). In 2009, the

International Psycho-Oncology Society (IPOS) endorsed distress as the “sixth vital sign,” in addition to temperature, blood pressure, pulse, respiration and pain, and recommended regular screening for distress to be implemented (122).

Distress interacts with cancer patients quality of life (19), and may influence the patient’s decision-making, compliance and treatment outcome. The close relationship between distress and HRQoL scores among cancer patients has also been emphasized research-wise (108, 123, 124). The interest in screening for distress in cancer patients has grown substantially during recent years. Despite high prevalence rates, studies show that fewer than 10% are referred to psychosocial care (125).

5.1 Distress in HNSCC Patients

Distress has been reported to be high in former HNSCC patients (108, 126, 127), as these patients often undergo demanding multimodality treatment, including surgery and radiation therapy (RT), both with or without chemotherapy. RT, chemotherapy and organ-conserving treatments are increasingly being employed to preserve speech, swallowing and other regional functions (128). Visible and bothersome effects of the treatment, such as disfigurement, dry mouth, loss of taste and ability to eat may also enhance the experience of distress. Life as a former HNSCC patient with a fear of recurrence and new cancer disease (129), as well as experiencing sequels caused by the extensive cancer treatment (21), place a considerable demand on the patient. HNC patients may be more prone to experience distress than patients with other tumor sites (16, 127). Distress as measured by GHQ among long-term survivors of HNC, showed that up to 30% of patients may fulfill the criteria of mental illness (108). Distress and QoL scores seem to relate similarly to choice of coping and present personality (68).

Haman (127) reviewed in 2008 the literature on psychological distress in HNC patients, including the symptoms and diagnoses of depression, anxiety and substance abuse, and concluded that oncology professionals must be alert for clinically significant manifestations of distress in this particular patient group. If left unaddressed, distress may be associated with a variety of serious negative outcomes. According to Haman, giving the patients an opportunity to express their concerns and empathic listening may be an effective treatment for distress (127). Furthermore, Haman states that the type of treatment needed to address the concerns will depend on the patient's answers (127).

5. 2 Distress in RCC Patients

In a sample of 88 RN patients and 56 elective NSS patients, Ficarra et al. (83) showed in the case of RCC patients that distress as measured by the GHQ status was impaired in 12.5% of the RN patients and in 7% of the NSS patients. In general, distress in RCC patients has been poorly explored.

5.3 Depression and Anxiety

5.3.1 Definition of Depression

According to the American Psychiatric Association`s Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM- V) (130), at least five of the following symptoms must be present during a two-week period, as well as representing a change from the patient's previous functioning, to be criteria of depression:

1. Depressed mood most of the day;
2. Markedly diminished interest or pleasure in all, or almost all, activities;
3. Significant weight loss when not dieting, or gaining weight;
4. Insomnia or hypersomnia;
5. Psychomotor agitation or retardation;
6. Fatigue or loss of energy;

7. Feelings of worthlessness or excessive or inappropriate guilt;
8. Diminished ability to think or concentrate, or indecisiveness;
9. Recurrent thoughts of death.

One of the five criteria’s should be either depressed mood or loss of interest or pleasure. Symptoms should not be caused by other somatic or psychiatric diseases (130).

5.3.2 Definition of Anxiety

The American Psychiatric Association`s DSM – V criteria (130) state that an anxiety disorder is present when three or more of the following symptoms are present:

1. Restlessness or feeling keyed up or on edge;
2. Being easily fatigued;
3. Irritability;
4. Muscle tension;
5. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep).

Moreover, some of these symptoms should be present for more days, and should represent something new from the past six months.

5.3.3 Depression and anxiety in cancer patients

Due to the fact that cancer and its treatment can be life-threatening, fear is a common mental symptom in oncology patients. Due to the heterogeneity of samples with regard to the type of cancer, age and gender, and time since diagnosis, and also to methodological differences concerning data collection, criteria and instruments used, variations in prevalence are reported. Nevertheless, the prevalence of depression has been shown to be higher in cancer patients than in the general population (109). Approximately 25% of cancer patients develop depression during the first year after diagnosis. After two years and later there is still an incidence of 12% (131). In a prospective computerized screening study for emotional distress and referral rate to psychosocial care in a group of HNC patients, Verdonck-de Leeuw et al. (132) found that high levels of emotional distress were common, and that few patients were referred to psychosocial care. RCC patients have also been shown to have higher reported levels of depressive symptoms compared to a general population (133).

In a systematic review and meta-analysis of the prevalence of depression and anxiety in long-term cancer survivors compared with spouses and healthy controls, Mitchell et al. (134) showed that 18% of cancer patients filled the criteria of having an anxiety disorder during the first year after diagnosis. They concluded that efforts should be made to improve the recognition and treatment of anxiety in long-term cancer survivors and their spouses.

Aass et al. (135) investigated 716 evaluable cancer patients at the Norwegian Radium Hospital using the HADS, the EORTC QLQ-C33 and an ad hoc designed questionnaire, and found a prevalence of 13% and 9% of anxiety and depression, respectively. Female patients reported significantly more anxiety than men. Patients with a premorbid history of psychiatric distress, patients suffering from fatigue and impaired physical activity, impaired social role function or impaired social life represented high-risk groups for the development of depression and/or anxiety. A special awareness among health-care providers was recommended.

Aarstad et al. (136) have shown that depression and anxiety levels assessed at diagnosis did not predict the level of HRQoL at follow-up in HNSCC patients. They reported high anxiety scores and lower depression levels than control patients, although there was overlap between the groups (136). T stage was only associated with depression levels, whereas N stage was associated with high anxiety scores and depression levels. Both anxiety scores and depression levels at diagnosis predicted prognosis through an association with TNM stage, while a sense of humor at diagnosis predicted QoL and depression levels at follow-up (136).

5.4 Inventories Measuring Distress, Depression and Anxiety

A wide range of questionnaires for measuring distress, depression and anxiety are available.

General Health Questionnaire (GHQ)

Distress may be measured by the "General Health Questionnaire" (GHQ) (137). The questionnaire is scored according to a 4-point response matrix, and the responses calculated as Likert scores, with case scoring indicating response category 1 and 2 scored as 1, response and response category 3 and 4 scored as 2. This questionnaire is described in more detail in the "Material and Methods" section, as we have chosen to use it in our investigations.

Beck Depression Inventory (BDI)

The "Beck Depression Inventory" (BDI) (138) is one of the most widely accepted tools for measuring depressive state and mood (109). The BDI short form consists of 13 questions measuring mood with a scale in which 0 points refer to a neutral mood, and 39 points refer to maximum depression (0-4 points refers to no clinical depression, 4-7 points refers to possibly depressed, > 7 points indicates that the patient is likely depressed). The validity and reliability of this inventory is found to be satisfactory in several studies (109).

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (17) is a 14-item self-reported instrument developed for screening in a non-psychiatric population. It has the advantage of evaluating both depression and anxiety, and is sub-scaled into total (HADS-T), anxiety (HADS-A) and depression (HADS-D). It is considered a quick and reliable tool (139).

National Comprehensive Cancer Network- Distress Thermometer

The National Comprehensive Cancer Network (NCCN) distress thermometer (19) designates patients level of distress between 0 (no distress) and 10 (extreme distress).

The NCCN problem checklist should also be answered (yes/no), which consists of questions concerning practical-, family-, emotional-, spiritual/religious- and physical problems (19). The sensitivity and specificity of this test was found to be in line with the HADS (116).

EORTC QLQ C-30

The EORTC QLQ C-30 contains two questions specifically asking about anxiety and depression.

6 PERSONALITY

There are several approaches to conceptualizing personality. This brief presentation is based on the book "Personality. Theory and Research" by Cervone and Pervin (140).

6.1 Historical Development

The well-known psychoanalyst Sigmund Freud introduced his psychoanalytic theory around 1900. Freud's theory claimed that early life experiences, especially in the first years in life, are of great importance when referring to later life personality development. Freud's theory was criticized suffering from being ambiguous, lacking well-defined concepts and a hypothesis that could be tested (140). Early analysts therefore broke with Freud, emphasizing social aspects (Adler), life energy (Jung), cultural factors and interpersonal relations. Development- psychologist Erikson further broadened the concept by also comprising psychosocial development (140).

The Trait Concept

Eysenck was one of many psychologists who advocated the trait concept (141) in personality theory. He proposed that people had predispositions to respond in specific ways, which were called traits, and that personality had specific habitual response modes, which for example he named extroversion or neuroticism (142). Eysenck introduced the three-factor theory based on factor analysis, which included two basic dimensions named introversion-extroversion and neuroticism later adding a third dimension called psychoticism (143). By doing a factor analysis, clusters of items were identified and showed how the items responses related to each other. Cattell also had a factor analytic approach to the trait concept (144). He was concerned with the consistency of behavior and personality, as well as on motivation processes. He also used the concept of state when referring to mood and emotional changes.

Trait theorists agreed about the presence of broad personality dispositions, even though they differed in other approaches. Some were critical of factor analysis, and others disagreed on the number of traits in their description of personality. Still, there has been an emerging consensus about the "Big Five" dimensions (140).

Other investigators have found other concepts, besides the "Big Five," that may meet the definition of being a personality trait. Examples are a sense of humor (145) and optimism (146).

6.2 Modern trait definition of Personality

Pervin et al. (147) defined personality as "*those characteristics of the person that account for consistent patterns of feeling, thinking and behavior.*" McRae and Costa consider personality: "*A system defined by personality traits and the dynamic processes by which they affect the individual's psychological functioning*" (148). Wrosch and cowriters [79] state that personality can be considered the continuity, stability and consistency about what a person does, thinks and experiences.

The "Big Five" model, a broad framework for identifying personality constructs, has been developed by several independent sets of researchers over 60 years (149), and is still considered as state of the art theory (150). According to McCrae and John (151), this framework divides personality into five domains or dimensions:

1. *Neuroticism* is considered an emotionality factor. High scorers tend to be emotionally unstable people who are chronically anxious.
2. *Extraversion* is the quantity and intensity of interpersonal interaction, activity level, need for stimulation and capacity for joy, and is assessed and found to be high in these persons, who are often found to be person oriented, optimistic, fun-loving and affectionate. On the contrary, low scoring individuals are likely to be reserved, sober, task-oriented and quiet.

3. *Openness to experience* is linked to culture. High scoring individuals are curious, have broad interests and are creative and untraditional. Low scoring persons are conventional, with narrow interests and may also be non-analytical.
4. *Agreeableness* represents a positive attitude and compassion in thoughts, feeling and actions. High scorers are very often person-oriented, optimistic, fun-loving and affectionate, good-hearted, good-natured and helpful. Low scoring persons are characterized by being hostile, rude, cynical and manipulative.
5. *Conscientiousness* reflects the will and ability to achieve goals and to be responsible. High scorers are hard-working, self-disciplined and ambitious, whereas low scoring persons are characterized by being careless and weak-willed.

Empirical research has shown that the “Big Five” model trait structure shows a consistency that seems to be found across a range of participants in different cultures and of different ages (152).

6.3 Neuroticism

A thorough understanding of the neuroticism concept has not been reached, even though it is proven to be empirically important (153). Neeleman et al. define neuroticism as “*A broad pervasive dimension of normal personality whereby people vary in their tendency to experience dysphoric emotional states*” (154). Individuals high on neuroticism are assumed to have a predisposition towards worry regardless of the presence or absence of threats, and to report more subjective health complaints than do stable individuals (154). Neuroticism may also simply be defined as a lifelong tendency to experience negative emotions (155), which is associated with strong emotional reactions to fear-producing stimuli (140).

According to Neeleman et al. (154), various characteristics seem to be important in terms of defining the neurotic individual:

- Over reporting of physical symptoms (155);

- Higher levels of reported physical illness, which may be attributable to the psychiatric disorders they often suffer from (156), as their physical health is negatively influencing their lifestyle through factors such as smoking and alcohol abuse.

- Reverse causality may appear as illness (psychiatric or somatic) if it recurs, it may enhance increased levels of neuroticism, also described as the “scarring” phenomenon (157). This phenomenon nevertheless receives divided support, as other studies do not report this problem (158).

6.4 Research on Personality and HRQoL

Few studies are conducted investigating personality and HRQoL in cancer patients. However, in 1998 Yamaoka et al (73) compared the HRQoL scores with the Eysenck Personality Inventory questionnaire response pattern in a group of ventricular cancer patients and a group of healthy people in Japan. A positive association was seen between HRQoL and psychoticism and extraversion, but negative associations between neuroticism and HRQoL in both groups (73).

In a review, Sales et al. (159) investigated the associations between personality characteristics, depression, psychological distress and HRQoL in colorectal cancer patients. Evidence indicates that a type D (distressed) personality may predict distress among colorectal cancer patients. Other personality traits, such as specific ego defense mechanisms, influence the coping responses and HRQoL.

We and others (68, 73) have previously shown a close inverse association between level of neuroticism and level of QoL in HNSCC patients. A similar general relationship is shown between distress (GHQ) and neuroticism (160). Previous studies on RCC patients have rarely taken linking patient personality into account (24).

6.5 Personality Measurement Questionnaires

Within the factor analytic approach, testing personality by using questionnaires has a long tradition (140). Questionnaires are used by psychologists to detect and understand personality characteristics and psychiatric symptoms, as well as by researchers attempting to understand personality variables' correlation to different illness states and factors, critical events in life and other health-related and psychological variables. The testing of personality is closely associated to psychopathology (161).

The Minnesota Multiphase Personality Inventory (MMPI)

The Minnesota Multiphase Personality Inventory (MMPI) was developed in the late 1940s by Hathaway and Mc Kinley (162). Today, an updated version, the MMPI-2, which consists of 567 questions, is being used (163). Scoring generates six validity scales and 10 basic clinical or personality scales: hypochondriasis, depression, hysteria, psychopathic deviate, masculinity-femininity, paranoia, psych asthenia, schizophrenia, hypomania and social introversion. This test is voluminous when used in its original form, and therefore not particularly suitable for studying HRQoL in cancer patients.

The NEO-Personality Inventory-Revised NEO-PI-R

The NEO-Personality Inventory-Revised (NEO-PI-R) consists of 240 questions, and was developed in the US by Costa and McRae in 1985 (164). It is based on the Big Five personality model (five factors, subdivided into 5x6= 30 facets). It has been translated into Norwegian, and has a good validity and reliability (165).

The Eysenck Personality Inventory (EPI)

Eysenck first published a test measuring neuroticism and extra/introversion, together with a lie scale (166). The psychoticism scale was later added to the test (142). The neuroticism (24 questions), extra/introversion (24 questions) and lie score (9 questions) dimensions of the Eysenck Personality Inventory (EPI) are determined based on the subject responding YES or NO to all the questions (167). Sum scores are then calculated. The EPI test has been translated into Norwegian and is determined to have a satisfactory validity and reliability (168). This questionnaire is described in detail in the "Material and Methods" section.

7 COPING

7.1 Historical Development

Researchers have taken different approaches to coping throughout the years. In the beginning, life-threatening situations or crises were focused. Some researchers even defined the coping area as the study of responses and reactions to extreme situations (169). Later, everyday life responses, and the situation where the coping occurred, have also been included (170, 171).

In early research, coping was conceptualized as an unconscious defense mechanism. Recent research conceptualizes coping as a response to stressful or negative events. A change in the field of coping theory and research was seen in the late 1970s as the hierarchical view of coping, with a trait and style emphasis, was traded for the contrasting approach viewing coping as a process. The trait approach, classifying individuals according to their stable coping styles, was changed, now viewing coping as a process claiming that coping changes over time (172). From this perspective, coping changes over time and in accordance with the situational context in which it occurs (173).

7.2 Coping Definition

A widely accepted definition of coping in the management of psychological distress is Lazarus and Folkman's definition (173), who defined coping as "*constantly ongoing cognitive and behavioral efforts to manage specific external and/or internal demands judged to tax or exceed the resources of the person*".

Coping style is associated with the ways individuals tend to respond to different stressors (174). Coping is claimed to be one of the core concepts in medical and health psychology, as it is strongly associated with the regulation of emotions, and in particular distress, throughout the stress process (175).

7.3 Coping styles

The principal coping styles described and identified by Carver et al. (176) are problem-focused, emotional-focused and avoidance-focused coping styles. Problem-focused coping may be to actively do something to reduce the demand posed by the stressor. Emotion-focused coping may be to change the attitudes toward the demand by social support or by a cognitive re-interpretation such as: “I have grown as a human being because of having had cancer.” Avoidance coping may be to behave, act or to think, as if the cancer disease had never occurred (176).

7.3.1 Coping by humor

Sense of humor is regarded an important factor to cope in certain situations. Svebak and Martin (177) suggested coping by humor to be regarded a mode of coping. In Carver et al.`s (176) COPE questionnaire four questions related to humor is added. This index measure humor used as coping related to HRQoL.

7.4 Research on Coping in HNSCC and RCC Patients

In successfully treated HNSCC patients, the utilized choice of coping is shown to be related to both general and head and neck-specific HRQoL scores (178). The level of problem-focused coping style was associated with the T stage and whether or not the patient had been given neck radiotherapy. An avoidance-focused coping style seems to generally be associated with a lowered HRQoL (178, 179). The use of emotionally focused coping was associated with a low HRQoL among patients treated with surgery only, and an increased HRQoL among patients treated with radiation therapy only (178). The associations between HRQOL and coping style levels were stronger for

HRQoL indexes reflecting mental function, rather than for HRQoL indexes reflecting physical function (178).

In another study by Aarstad et al. (68), a high T stage, high neuroticism, coping by humor and coping by problem solving directly predicted low QoL, whereas neuroticism was also associated with QoL through avoidance coping in HNSCC patients. Studies of coping in RCC patients is lacking.

7.5 Coping Instruments

Several approaches to identifying utilized coping strategies have been described [83].

Ways of Coping Checklist/Questionnaire

Folkman and Lazarus' "Ways of Coping Checklist" (WCC) (171), later revised to "Ways of Coping Questionnaire" (WCQ) (180), is one of the most frequently employed questionnaires for individual coping measurement, and has also been used as examples to develop other coping measures.

The WCC was a self-reporting questionnaire consisting of 68 items concerning two basic coping dimensions: problem-focused and emotion-focused coping. The respondents were asked to respond Yes or No, and to answer in relation to a stressful situation. A cross-validation of the WCC factor structure has given mixed results (181), and the WCQ does not create constant factors (180). A factor analysis has to be conducted before answers can be incorporated into a study. Hence, a comparison with other studies is therefore complicated.

The Jalowiec Coping Scale

The Jalowiec Coping Scale (182) is based on Lazarus and Folkman's theory of stress and coping (172). The test can be used as both a self-administered or interviewer-administered questionnaire in adults of all ages. It takes 10-15 minutes to complete, and consists of 60 cognitive and behavioral coping strategies classified into eight coping styles:

-Confrontive: constructive problem solving

-Evasive: avoiding to confront the problem items

-Optimistic: positive thinking

-Fatalistic: pessimistic thinking

-Emotive: expressing/releasing emotions

-Palliative: doing things to make you feel better

-Supportive: using support systems

-Self-reliant: depending on yourself, rather than others, to deal with the situation

The COPE Scale

When developing the COPE Scale, Carver and co-workers (176) argued that problem-focused and emotional-focused coping had to be separated into subgroups in order to solve problems and regulate emotions. Three different scales were composed, employing a rational constructions procedure on 978 college students. The students were asked what they usually did when experiencing profound/considerable stress. The questionnaire assesses the level of:

-Problem-focused coping:

- active
- planning
- suppression of competing activity
- restrain
- seeking social support for instrumental reasons

-Emotional coping

- seeking social support for emotional reasons

- positive reinterpretation and growth
- acceptance
- focusing on- and venting of emotions
- coping by religion

-Avoidance coping

- denial
- behavioral disengagement
- mental disengagement

Furthermore, two scales concerning the use of alcohol and drugs, and one concerning humors, are included in the COPE scale:

- drinking to cope
- coping by humor

Schwarzer and Schwarzer (183) did a factor analysis of the scale, and found almost the same structure as was theoretically predicted. The COPE scale is theoretically derived and has fixed scales. It is translated into Norwegian, and seems to work well with Norwegian subjects (184-186). This questionnaire is described in further detail in the “Material and Methods” section.

Svebak Humour Questionnaire (SHQ)

Originally, the SHQ consisted of 27 questions. After a second revision, seven items on each of three dimensions theoretically founded on ideas of person-situation interactions remained. Research found that items on meta-message sensitivity (M-items) and liking of humorous situations (L-items) yielded fair alphas, whereas those on mirthful expression (E-items) did not. In our investigation we asked 7 questions from the M- items and 7 questions from the L- items of the “Sense of Humor Questionnaire” (145).

8 AIMS OF THE THESIS

The overall aim of this thesis has been to study the relative importance of physical sequels, cancer referring to biology and treatment, psychosocial factors like personality and coping, as well as comorbidity, related to HRQoL and distress (GHQ). In HNSCC patients, we have studied all the aforementioned factors. In RCC patients, we have not included studies of distress.

Paper I: The aim of the study was to explore the relationship between distress, HRQoL, personality and choice of coping in successfully treated HNSCC patients. Moreover, we aimed to study whether distress could be regarded a QoL variable.

Paper II: The aim of the study was to investigate the stability of distress and HRQoL in relation to neuroticism and choice of coping response in HNSCC patients during a follow-up period of four years. Furthermore we wanted to determine to what extent alcohol and smoking history, TNM stage as well as previously scored HRQoL and distress scores predict the level of current distress and HRQoL in successfully treated HNSCC patients.

Paper III: The aim of this study was to investigate the HRQoL outcome in long-term survivors after surgical renal cancer treatment, and to compare with both a general population cohort, successfully treated laryngectomized patients and successfully treated HNSCC patients. Furthermore we wanted to study the extent to which patient-, treatment-, and tumor- derived variables such as comorbidity, surgical access and TNM stage determined the subsequent HRQoL following primary treatment of RCC patients.

Paper IV: The aim of the study was to explore whether HRQoL depends on psychosocial factors, rather than on factors related to the cancer treatment in surgically treated RCC patients. We explored the associations between HRQoL, personality, choice of coping, clinical parameters such as surgical approach, as well as present comorbidities.

Paper V: The aim of the study was to develop an EORTC-compatible, RCC disease-specific HRQoL questionnaire in surgically treated RCC patients, and to test the proposed questionnaire in a broader setting.

9 MATERIAL AND METHODS

Because this thesis has been built up from five different studies, an overview of the different samples that have been investigated, and the respective methods will be presented here.

9.1 Patients

9.1.1 Study I and II

Study I: "*Distress, quality of life, neuroticism and psychological coping are related in head and neck cancer patients during follow-up"* [104].

In this study, data previously collected by my coworkers in the period from July 1, 1992 to October 1, 2001 were used. All patients diagnosed with HNSCC in Western Norway below 80 years of age in that particular period (n=162) were asked to participate. Eighteen patients were found to be not eligible. Three patients refused to participate, and two were lost to follow-up. A total of 139 HNSCC patients (96.5% response rate) successfully treated at Haukeland Hospital, with a minimum one-year observation period with no evidence of cancer recurrence, were included. Mailed questionnaires were answered at least one year after completed therapy. At inclusion, 31 of the patients were living alone, and the mean age of the included patients was 60 ±12 (mean ±SD) years. One hundred and four males and 35 females were included, and information about gender, age and educational level were also obtained.

Data on HRQoL, distress (GHQ), personality, coping style, and views on humor were obtained. Treatment level, TNM stage, alcohol consumption and smoking level, as well as demographic data were obtained.

The treatment record of each patient was reviewed, and it was determined whether or not the patient had been subjected to local surgery, re-constructive flap surgery or neck dissection (scored as yes or no (0/1). Radiation therapy was administered by the use of a two-dimensional external beam technique using five fractions (2.0 Gy) per week throughout the entire period. Neck dissection was performed unilaterally or bilaterally as a modified radical or supra-omohyoidal procedure.

Neck radiation therapy was scored on a scale in which one point was added if radiated to each of the fields: high left, high right, lower neck. The maximum cumulative dose of radiation therapy to a specific site in each patient was registered and categorized into five levels. Whether given radiation therapy to the primary tumor site was scored as 0/1 (Table I, study I).

Study II: "*Stability of distress and health-related quality of life, as well as relation to neuroticism, coping and TNM stage in head and neck cancer patients during follow-up*" [126].

This study was conducted using the same data as that in Study I. Since supplementary follow-up data was wanted, the GHQ and HRQoL questionnaires were sent by mail in 2007, asking the patients still alive and less than 78 years of age to answer a second set of questions. Of the 128 invited patients, 105 patients responded, yielding a response rate of 82%. Two patients were lost to follow-up. The secondary invited patients were asked to return the questionnaires only if no new serious disease had occurred during the last year, and that they understood the questions.

9.1.2 Study III, IV and V

Study III: "*Health-related quality of life in long-term survivors after renal cancer treatment"* [24].

Study IV: "*Health-related quality of life (HRQoL) personality and choice of coping is associated in renal cell carcinoma patients"* (187).

Study V: "*Development of a disease-specific health-related quality of life (HRQoL) questionnaire intended to be used in conjunction with the general European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) in renal cell carcinoma patients"* (188).

These three studies are all based on the same cross sectional sample. Patients suffering from RCC were identified from the nephrectomy database at Haukeland University Hospital, which serves Hordaland County in Western Norway. A total of 413 patients surgically treated with nephron sparing surgery (NSS) or radical nephrectomy (RN) between January 1st, 1997 and December 31st, 2010 were identified.

Patients with a histologically proven RCC on 1 February 2011 were recruited from the nephrectomy database. Three-hundred-and-nine were still alive at the inclusion time, of which 49 patients were excluded from the study due to reasons such as cognitive impairment, severe other disease or other malignant diseases. After exclusions, 260 patients younger than 85 years and still alive were invited to answer the mailed questionnaires. If the patients did not return the first mailed questionnaire, a second invitation was sent. After two rounds of invitations, a total of 185 patients (a 71% response rate) had returned the questionnaires.

Data on HRQoL, distress (GHQ), personality, coping style and views on humor were obtained, as well as demographic information, alcohol consumption and smoking level.

The clinical, demographic and disease characteristics were retrieved from the database, with tumor stage determined according to the TNM 2009 classification system (39). Histological subtypes and grade were scored according to the World Health Organization (WHO) classification, in addition to the Fuhrman nuclear grading system (56). Questionnaires were mailed to RCC patients operated on from 14 years to less than one year ago at the inclusion time point, thus representing cross sectional data.

9.1.3 Comparison groups

Data from a sample of general HNSCC patients (82), a sample of laryngectomized HNSCC patients (189) and a cohort from the general population of Norway (190) were used to compare the RCC patients' HRQoL scores in study III. HRQoL data were obtained using the EORTC QLQ C-30 questionnaire version 2.0 for the general population (comparison) and version 3.0 for the patients (3).

The General Population Cohort

A sample of 3,000 randomly selected people, reflecting the age and gender distribution of the adult Norwegian population, was obtained by a random draw from the adult Norwegian population by Hjermstad et al. in 1998 (190). The EORTC QLQ C-30 (2.0 +3) version and a questionnaire asking for demographic data and health were sent by mail. Reference data on HRQoL were obtained, and the results have been published previously (191).

The HNSCC sample

In the HNSCC patient group there were 75 men and 21 women, with a mean age of 61 years (25-79 years). The primary tumors were on the lip (one), tongue (15), salivary glands (two), gingiva (five), mouth floor (five), oral cavity (four), oropharynx (10), rhinopharynx (two), hypopharynx (four), sinus (three), larynx (42) or unknown primary site (three). The patient, tumor and surgical characteristics of this group have been previously published (82).

The Laryngectomy sample

In the group of 104 laryngectomized patients, there were 89 men and 15 women with a median age of 68 years (37-80 years). More than 90% of this group had received radiation therapy in addition to a laryngectomy. The patient-, tumor- and surgical characteristics of this group have also been previously published (189).

9.2 Methods

9.2.1 Measuring HRQoL and Related Concepts

Much research has focused on the development of valid and reliable instruments to measure the HRQoL concept and its covariates [36]. It is argued that these instruments are rarely based on theoretical or philosophical analyses, but rather on medical expert groups' agreements on operational definitions [37]. As a consequence of this, strict definitions of QoL are very seldom seen in medical papers and research reports [38].

Critics of the HRQoL concept emphasize the complexity of it, in addition to a lack of awareness of different conceptions of what it actually is, and what gives QoL [39]. The interconnectedness of health status with other aspects such as economic situation, social interaction, personal relationships, work status and mood, etc. must be kept in mind when assessing HRQoL [39].

Questionnaires available for the assessment of HRQoL can be categorized into four major groups according to Murphy (71).

-Generic

-Disease-specific

-Site- or treatment-specific

-Symptom-specific

It is common to combine questionnaires to provide the opportunity to compare data from different groups of cancer patients, and still be able to assess aspects specific to a subset of cancer patients.

9.2.2 General Requirements for Questionnaires/Tests Used

A substantial challenge when measuring phenomena such as HRQoL, distress and coping is that there is no gold standard. Careful consideration of psychometric properties should be made when choosing instruments. Of special importance is the validity, reliability, sensitivity, responsiveness and repeatability of the instruments used (192). The chosen instrument has to be easily understood and interpreted by the patients, and the number of questions must balance against the burden upon the respondents.

The validation concept encompasses that measurement and the use of instruments in studies are found to be trustworthy - that we actually measure what we intend to measure. Inner validity refers to the possibility that a study provides that the findings can be explained through the assumed hypothesis. Furthermore, a high internal validity presupposes that one has a good control of any possible bias (193). One example of a possible selection bias may be age. For some reason a specific age group may be more likely to be selected for a study than others, hence biasing the sample.

External validity refers to whether or not the results of a study of a limited scope can be more widely applicable (e.g. for an entire population) (193). Hypotheses that are strengthened and reach statistical significance do not directly imply that results can be implemented in clinical practice. Researchers must consider the transferring value of the results using clinical judgment.

Reliability refers to a measuring instrument`s or assay`s degree of stability and consistency in the measurements. Internal consistency is about the extent to which the various questions in a form register the same characteristics. This can be measured by Cronbach`s Alpha, which is satisfactory when > .70 or more (193).

Reliability in research is about the credibility of the performed measurements or results. If one repeats the same measurement many times (repeatability), the result is reliable if the same answer is obtained each time (assuming we then actually measure everything the same). A conclusion is reliable if others arrive at the same conclusion, using the same terms or tests.

9.3 Statistics

The statistical program package SPSS was employed (Ver. 22.0; SPSS Inc. Chicago, IL, USA) when performing all the statistical analyses. Correlation between variables was measured by Pearson's r. Correlation analysis and reliability analysis were performed. Statistical significance was considered at $p < 0.05$. Independent-samples t-test and Paired samples t- test was conducted in order to explore differences in mean (M) between groups (i.e. males, females, different T stage etc.). Correlation measures covariation were denoted from +1 to -1. Furthermore, if indicated, r^2 was calculated and denoted as common variance (CV). Cronbach`s α was calculated to estimate the reliability of the psychometrics.
Regression analysis is a statistical process used when estimating the relationship among variables that presumably have a clear causal pathway (194). Modelling and analyzing the relationship between a dependent and one or several independent variables can be done in different techniques (194). In our studies, multiple regression analyses helps understand how the typical value of the dependent variable (i.e. HRQoL) changes when any of the independent variables (i.e. neuroticism, smoking, coping, comorbidity) is varied, as the other independent variables are held fixed. Regression analyses are used to understand which among the independent variables and to what extent they are related to the dependent variable (194). Regression analyses were also used for prediction calculations (i.e. of GHQ/HRQoL scores by neuroticism, COPE scores, TNM stage). R^2=the explained variance (0-1) tells how much the predictor affects the dependent variable.

In study III multiple analysis of variance (M)ANOVA was performed to investigate HRQoL scores of the three RCC patient groups (laparoscopic/trans-abdominal/flank incision), HNSCC patients, laryngectomy patients and the general Norwegian population, to test if the groups had statistically significant differences in mean (M). Post hoc comparisons were applied if a significant main effect was found.

9.3.1 Factor Analysis in the Development of a Questionnaire

The term Factor Analysis is a general term, and encompasses a variety of different related techniques. One of the main distinctions is between what is termed Principal Component Analysis (PCA) and Factor Analysis (FA) (195).

There are two main approaches to factor analysis described in the literature - exploratory and confirmatory. Exploratory factor analysis explore the interrelationships among a set of variables in the early stages of research. Factors are estimated using a mathematical model, whereby only the shared variance is analyzed (196). A confirmatory factor analysis is a more sophisticated set of techniques used later in the process to test the structure underlying a set of variables (195).

When conducting an exploratory factor analysis, using the PCA technique, the original variables are transformed into a smaller set of linear combinations with all of the variance in the variables being used (195).

There are two main issues to consider when determining whether a dataset is suitable for factor analysis: the sample size and the strength of the relationship among the variables. The recommendation concerning how large the sample should be is; the larger the better (195). According to Nunnally (197), a 10 to 1 ratio is recommended. The correlation coefficients among the variables are less reliable in small samples. Tabachnick and Fidell (196) concede that a smaller sample size (e.g. 150 cases) may be sufficient if solutions have several high loading marker variables (above 0.8). To assess the factorability of the data, a Bartlett`s Test of Sphericity (198) and the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy (199) is recommended generated (195).

Factor extraction means determining the smallest number of factors that can represent the interrelationships among the set of variables. The most commonly used approach is a Principal Component Analysis (PCA) (195). Two conflicting needs are balanced using this approach: to find a solution with as few factors as possible, and the need to explain as much of the variance in the original dataset as possible (195). Using this exploratory approach, it is recommended that researchers experiment with a different number of factors until a satisfactory solution is found (196).

As the number of factors has been determined, the next step is to interpret them, a process in which the factors are rotated (195). There are a number of different techniques provided by SPSS to do this, with the most common being the Varimax method (195).

The EORTC Quality of Life Group has formulated a manual for development and the validation of questionnaire modules within the EORTC “family”(200).

9.4 Applied Inventories

Previously validated questionnaires were used in our collection of data.

9.4.1 The General HRQoL Questionnaire EORTC QLQ C-30

The general HRQoL data in our studies was determined by employing the validated Norwegian edition of the EORTC QLQ C-30, version 3.0 (3). The general part of the EORTC QLQ C-30 contains one question about global health status and one question of global QoL, five functional scales (physical, role, emotional, cognitive and social), and questions about symptoms like fatigue, dyspnea, pain, dizziness, insomnia, nausea, obstipation, anxiety, depression and memory, but also about economy.

The answers were given according to a 4-point Likert format, (i.e. «not at all,» «a bit,» «quite a lot» and «all the time»), with the exception of questions about general health and general quality of life, which were given according to a 7-point Likert format. The indexes were scored according to the EORTC guidelines.

The C-30 functional scales and the global scale were transformed, so that 100% indicates the best function and 0% the least function of the individual HRQoL index, whereas the C-30 symptom scales were transformed so that 0% indicated the least- and 100% the most symptoms.

The QLQ scores built up from more than one response were studied by Cronbach's α, and the general health/QoL scores were compiled to one sum score. Two additional sum scores were computed, compiling the functional indexes and the symptom indexes. The sum scores broadly have satisfactory Cronbach's α, thereby indicating that it is psychometrically valid to calculate these indexes. In order to avoid collinearity, only indexes underlying significant sum score associations were further studied. The general EORTC QLQ C-30 (version 3.0) is translated and validated into 81 languages, and is used in more than 3,000 studies (201).

9.4.2 The Disease-specific EORTC H&N35 Questionnaire

The EORTC has developed a disease-specific HRQoL questionnaire especially aimed at HNC patients (202, 203). It was first developed in Norway, and has later been translated and validated into 49 languages (201), and is also used worldwide as one of the standard instruments in measuring QoL in HNC patients. The HNC specific part consists of seven multiple –item scales (pain, swallowing, senses, speech, social eating, social contact and sexuality) and 11 symptom items (teeth problems, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, pain killers, nutritional supplements, feeding tube, weight loss and weight gain) (81).

The answers were given according to a 4-point Likert format, (i.e. «not at all,» «a bit,» «quite a lot» and «all the time») in questions 1-30. Items 31-35 are answered yes (2) or no (1). The indexes were scored according to the EORTC guidelines. The symptom scales were transformed so that 100 indicated the most- and 0 the least symptoms, and a HNC sum score was computed. Higher scores correspond to a lower quality of life.

9.4.3 Eysenck Personality Inventory

We determined personality by the Eysenck Personality Inventory (EPI) (167), which was originally published as a test measuring neuroticism, extra- introversion and a lie scale. Tambs et al. (204) translated the test into Norwegian, and documented the reliability and validity of the test. The neuroticism (24 questions) and lie score (nine questions) dimensions of the Eysenck Personality Inventory (167) were obtained. The subject responded YES or NO to the questions, and the scales were calculated as sum scores. The neuroticism scale consists of questions related to mental symptoms such as obsessive thoughts, anxiety, depression and low self-esteem, but also includes somatic symptoms such as muscle pain, tachycardia and sleeplessness. The scale assesses adjustment versus emotional instability, and identifies individuals prone to psychological distress, unrealistic ideas, excessive cravings or urges and maladaptive coping responses. Individuals with low scores are characterized as calm, relaxed, unemotional and self-satisfied (124). The lie scale is based on yes or no answers to nine questions such as: “Have you ever stolen anything?” Although originally introduced as a lie scale, it has later been suggested that the response pattern to this scale may be regarded as a measurement of a personality trait (205), with a focus on handling of moral issues.

9.4.4 The Coping Instrument

Carver, Scheier and Weintraub`s (176) COPE questionnaire is based on the conceptual framework by Lazarus (173). We have chosen to use this questionnaire, which is considered a general, and not cancer-specific coping instrument. The test is theoretically derived and has fixed scales. It has also been translated into Norwegian, and seems to work well with Norwegian subjects (206). The scores for each assessed coping indexes are calculated as the sum of the responses to four different questions, which are scored according to a 4-point Likert format. The scales were utilized to assess the level of suppression of competing activity (problem-focused coping), seeking social support for emotional reasons (emotional-focused coping) and coping by behavioral disengagement (avoidance-focused coping). The subjects were asked to relate the responses to their cancer disease.

9.4.5 Svebak humor questionnaire (SHQ)

We employed the SHQ (145) in our investigation. We asked 7 questions from the M-items (meta-message sensitivity) and 7 questions from the L- items (humorous situations) of the "Svebak Humor Questionnaire" (145). Each question in both item scale were answered according to a 4 point Likert scale and sum scores were calculated.

9.4.6 The General Health Questionnaire (GHQ)

Distress was measured by using the General Health Questionnaire (GHQ) (137). The GHQ is used when detecting psychiatric disorders in the general population within community or non-psychiatric clinical settings. The questionnaire assesses the respondent's current state and asks if that differs from his or her usual state. It is therefore more sensitive to short-term psychiatric disorders, but less to the long-standing attributes of the respondent.

Several versions of the GHQ are available, though differing in length with 12/28/30/60 questions, respectively. We have chosen the GHQ-12 version, which was prepared by removing the items endorsed by "physically ill" respondents from the GHQ-60. Items were then divided into those in which agreement indicated either health or illness. Within each group, items were selected that had the highest slopes in the original item analysis (207). The 12-question version of the GHQ is quick to administer and score, as it only contains 12 questions. It also has comparable psychometric properties to the longer versions, even though it only takes approximately two minutes to complete (208). Given its speed of administration, it is often used in research studies where it is impractical to administer a longer form (207). The GHQ-12 yields only an overall total score.

The 20/ 28 and 30 versions of the questionnaire were validated in Norwegian in 1989 by Malt et al (209), and in 1995 by Jacobsen et al. (210).

According to a report from the American Psychosocial Oncology Society (APOS), Association of Oncology Social Work (AOSW) and Oncology Nursing Society (ONS) Joint Task Force, the General Health Questionnaire (GHQ) was considered a sound instrument in current mental health assessments (211).

9.4.7 Demographic Variables

Demographic variables such as age and gender were obtained when reviewing the patient records. Level of education, level of smoking and alcohol levels were also determined at the interviews.

9.4.8 RCC Candidate Questions

To form the disease-specific questionnaire, we asked 13 candidate questions. Our candidate questions (cq) were based upon the review of a few studies on this topic (60, 133), as well as on urologists' and urology nurses' experiences concerning common complaints from treated RCC patients. Studies of living donors after nephrectomy (212) and common complaints from treated RCC patients observed in clinical practice were also taken into consideration. A review of other disease-specific parts of the EORTC QoL family questionnaires was also done, although the questions were not to overlap semantically. Answers were reported according to an EORTC-QLQ identical 4-point Likert format (i.e. "not at all," "a bit," "quite a lot" and "all the time"), and the scores were transformed in the same manner as with the symptom questions from the EORTC C-30 QLQ questionnaire.

9.5 Comorbidity

In this study, the term “Comorbidity” is used when studying patients additional illnesses that are not related to the cancer disease. Also referred to as intercurrent illness. In particular, we studied patients suffering from diabetes and whether or not on lung medication. In addition the Charlson Comorbidity Index (213), the Eastern Cooperative Oncology Group (ECOG) scores (214) and American Society of Anesthesiologists (ASA) scores (215) were analyzed.

9.6 Ethics

The ethical guidelines of the Helsinki Declaration (World Medical Association, 2000) are a prerequisite of this work. The Regional Committee for Medical and Health Research Ethics, Western Norway, approved and “Helseforetaket Helse Bergen” was responsible for the project. Written informed consent was obtained from all participating patients, and were informed that they could withdraw from the study at any time, without any consequence. They were given the opportunity to ask questions about the study and their participation at any time by contacting the project leader by phone. Anonymity was ensured and the data securely stored. “The Nürnberg trial recommendation” (the Nürnberg Code, 1947), makes clear that research and trials can only be performed on persons legally able to give their written consent (216, 217).

In our RCC sample used in studies III, IV and V, we decided to include patients younger than 85 years. Chronological age alone does not legitimize exclusion. In any case, we decided to do this due to serious considerations, and exclude individuals with cognitive impairment. Because this was difficult to assess, we made a choice to exclude persons more than 85 years. Furthermore, only patients treated by surgery are included in these studies. In general, patients with localized RCC not offered surgery, are elderly, have several comorbidities and have a limited life expectancy (218). Such impairments would most likely significantly affect the outcome of HRQoL questionnaire scores. For this reason, we decided not to include this group of RCC patients. However even in primary metastatic RCC (mRCC), approximately 50% will undergo kidney surgery (219). After initial treatment (tumor surgery and metastasectomy), only a few of these will achieve long-term survival without any signs of disease and without any further treatment. These patients are included. Primary MRCC patients not offered nephrectomy usually have a very short life expectancy (219), and hence, this latter group is excluded.

We probably lost some informants due to this limit, but avoided having to make a more thorough assessment of patients who were suspected to be cognitively impaired. On the other hand we were aware of the fact that such a limitation would reduce the possibility of gaining access to important information about vulnerable groups, such as the oldest cancer patients.

10 RESULTS OF THE THESIS

10.1 Paper I

In our first study, "*Distress, quality of life, neuroticism and psychological coping are related in head and neck cancer patients during follow-up*" (123), we found that distress (GHQ) and HRQoL indexes were quite similarly scored, with a common variance (CV) between 20 % and 35%. The measured variables accounted for 40-48% of the variance of the QoL/GHQ scores. Between 3% and 10% of the GHQ/general QoL scores and 10% of the variance of the H&N35 QoL scores were predicted by the TNM stage. The measured psychological factors accounted for 20% of the H&N35 QoL scores and 40% of the measured variance of the general QoL and GHQ responses. High neuroticism (CV≈20-35%), present avoidance coping (CV≈10-30%) and problem focused coping (coping by suppression of competing activity) (CV≈10-20%) were associated with low QoL and high distress (GHQ).

Furthermore the SHQ L- scale responses were inversely associated with HRQoL/GHQ levels with CV 3% and 9% (Table III, article I).

In conclusion GHQ and QoL were scored similar, and could to a certain extent be predicted by treatment-related factors, but shown to be 2.5 to 10 times more closely associated with psychological factors, such as personality and coping. We concluded that distress measured outside the disease level is a measure of quality of life in HNSCC patients, and that distress may possibly be regarded as a QoL variable. We presented a figure to depict the associations between the investigated variables (Figure I, paper I).

10.2 Paper II

In our study, "*Stability of distress and health-related quality of life as well as relation to neuroticism, coping and TNM stage in head and neck cancer patients during follow-*

up,” distress and to some extent HRQoL was found to be stable when measured over a four-year period in HNSCC patients (220). About one- third of the distress and HRQoL variances were accounted for in the present investigation with one- third from T stage, one- third directly from neuroticism and one- third from neuroticism via choice of coping response. Additionally, choice of coping response predicted directly 5% of the HRQoL variance.

A figure depicting the proposed relationship between distress and HRQoL versus neuroticism, choice of coping style and T stage by regression and correlation analyses was presented (Figure I, paper II).

10.3 Paper III

In our study of *“Health-related quality of life in long-term survivors after renal cancer treatment,”* we found that surgically treated RCC patients, in particular those treated by a flank approach, had a multifacetedly reduced HRQoL compared with a population cohort (221). In some of the flank-treated patients, HRQoL scores were lower than among laryngectomy- treated HNSCC patients. Those treated by minimally invasive surgery for RCC retained a HRQoL comparable to that of the general population. Patients suffering from comorbidities such as diabetes, or patients who were on lung medication reported lower HRQoL than patients without these diseases.

Performance status as measured by ASA score, and ECOG classification at diagnosis showed an inverse relation to HRQoL. Glomerulus Filtration Rate (GFR) was determined at diagnosis, and no relation with HRQoL level was detected. An inverse relationship was determined between GFR and general HRQoL scores at the time when HRQoL data was obtained. We furthermore found that RCC tumor variables at diagnosis, such as histology, maximum tumor diameter and whether metastases or not, did not predict the HRQoL scores (221).

10.4 Paper IV

In our study, *"Health-related quality of life (HRQoL) personality and choice of coping is associated in renal cell carcinoma patients,"* we found that HRQoL is affected by treatment-related factors, but in this present study shown to be more closely associated with psychosocial factors (187). The presence of the personality trait neuroticism and the use of avoidance coping was associated with a reduced quality of life and increased distress in surgically treated RCC patients. All the QoL indices except for one were significantly negatively correlated with neuroticism and avoidance coping. Reported coping by humor was to some extent negatively associated with HRQoL scores (CV_{max} 4%).

Patients with low HRQoL due to treatment, secondary to flank or open surgery, reported a closer association between problem- focused choice of coping and HRQoL than the other patients. Furthermore, we found that present comorbidity, in particular diabetes or whether or not on lung medication, seemed to be uniquely associated with lowered HRQoL scores (187).

10.5 Paper V

In our study, "*Development of a disease-specific health-related quality of life (HRQoL) questionnaire intended to be used in conjunction with the general European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)in renal cell carcinoma patients*" (188), we conducted a factor analysis using the extraction method called "Principal Component Analysis" (PCA). The original variables were transformed into a smaller set of linear combinations, with most of the variance in the variables being used (195). We also included the rotation method "Varimax with Kaiser Normalization," which includes a rotation converged in iterations (195). We drew the questions the most closely related to the formed factor, or questions clearly asking about the unique features of the RCC QoL. By including the 13 candidate questions and one EORTC C30 general health/QoL sum score in the factor analysis we ended up with 14 items, which yielded 176/14=12.5 participants per item. This was judged to be sufficient. A correlation matrix, including the different RCC disease-specific items, showed that the correlations between the different items were satisfactory in order to be included in a factor analysis.

Our performed factor analysis showed that five factors were formed; one general symptomatic, one general functional, one with disease specific questions (flank pain, blood in the urine, flank edema, urinary tract infection), one about sexuality and one about weight loss or gain. Factor one and two were closely associated to the EORTC general questionnaire response pattern, as analyzed by including sum scores derived from the EORTC general QLQ (C-30). We suggested a core RCC6 questionnaire with six questions derived from factors III-IV and a more complete RCC10 version including four questions related particularly to pain, mobility and social functioning, also representing a short version of the EORTC C30. The response patterns to these questions capture most of the information from the general EORTC QoL questionnaire. The psychometrics and the relation to other psychological and clinical variables were determined to be satisfactory.

11 DISCUSSION OF METHODOLOGICAL ISSUES

11.1 Discussion of Sampling Issues

Our sample of HNSCC patients represents initially curatively treated HNSCC patients in Western Norway who survived at least 12 months without evidence of disease, thereby constituting a defined cohort relative to the particular timeframe.

Our studies of surgically treated RCC patients are based on a sample representing all surgically treated patients from a specific geographic area, constituting a geographically defined cohort relative to a specific timeframe. The study is of a survey nature, though a better approach would be a longitudinal one. A higher percentage of the intended included patients could also have been included. Nonetheless, we have shown that the clinical characteristics of the responders and non-responders were the same (Table II, article V).

Our suggested RCC- specific questionnaire is intended for use in a surgically treated group of patients, which we recognize as a limitation. However, the vast majority of RCC patients are surgically treated. Those not surgically treated constitute a separate cohort, and could be interesting to study in a separate future study.

11.2 Discussion of Data Collection

Our survey consisted of 150 questions, thus representing a possible burden on the patients. Patients suffering from cognitive impairment, severe illness or high age were therefore not included. The heterogeneity of the elderly may be large, and information about the elderly patients' HRQoL is of great importance. Ideally, all clinical trials in oncology should be without an upper age limit to allow the entry of eligible older adults. Investigators should critically review whether sufficient justification exists for every exclusion criterion before incorporating it in trial protocols (222). The obligatory integration of a comparable form of geriatric assessment, to help meet the special needs of elderly subpopulations, may be a solution in future studies.

Our RCC data is collected by patients filling out questionnaires at home in their own surroundings, where domestic aspects may influence the results. A better quality of answers could perhaps be anticipated if the employed method was structured interviews.

In study V the number of candidate questions included in our factor analysis could perhaps have been higher, possibly providing a more thorough questionnaire. However, we aimed for the suggested questionnaire to include a limited number of questions, thus being user-friendly.

11.2.1 Use of Previously Validated Questionnaires

As previously shown several relevant questionnaires related to quality of life, distress, personality, coping, etc. are available. Several suitable instruments fulfilling the general criteria exists for head and neck cancer patient concerns, but according to Ringash et al.'s (223) review, efforts should be made in the future to harmonize PROM measurements across trials.

Our chosen "test battery", except our suggested disease specific RCC HRQoL questionnaire, is composed of standardized, validated and proven tests, with the aim of increasing the likelihood to obtain the information intended. The wording and ask target structure is tested and adjusted through several rounds, on several cohorts of patients, just to increase the level of precision to the questions and to obtain exact information. The questionnaires were all tested and adapted for self-reporting. They have all been translated into Norwegian in a recommended way, and are used in previously published studies.

11.2.2 Confounding Factors

Confounding can take place when you have a factor or variable that is associated both with the impact factor and the outcome of a study. An example of this from our study may be that the patients age directly affects patients' self-reported quality of life, or it may indirectly influence the choice of coping strategy, which in turn affects the quality of life. It is not possible to account for- or to uncover all such confounding factors, but one must exercise caution so that wrong conclusions are not drawn about causal relationships. We controlled for age, education and marital status, but social status, cognitive functioning and other more general social factors may also affect the outcome. Moreover, we did not observe any changed relationship pattern between the investigated variables, gender, age and level of education of the patients, when included in the analyses.

11.2.3 Selection Bias

A potential source of selection bias in cancer research is missing data, which is not accidental, as patients in poor health or elderly patients are non-compliers. To help avoid this, we decided to exclude patients aged more than 85 years of age, as well as patients suffering from other serious illnesses.

11.2.4 Missing Data

Patients may fail to answer a question (or several) in a questionnaire, thus we have to deal with missing values. It is of great importance to distinguish between items missing by random and items missing for a specific reason. Although it is difficult to determine why data is missing, several imputations techniques are available to estimate the missing items in SPSS (195). In our two cohorts, no imputation method has been applied, as missing values were not common. This is in line with the recommendations proposed in the scoring manual from the EORTC (192).

11.3 Discussion of Analysis Issues

The statistical program package SPSS was employed (Ver. 22.0; SPSS Inc. Chicago, IL, USA). Pearson's r, partial correlation analysis, reliability analysis and regression analyses were performed as indicated, and statistical significance was considered if $p<0.05$. Correlation measures co-variation were denoted from +1 to -1. Furthermore, if indicated, the r^2 was calculated and denoted as common variance (CV).

11.3.1 Likert Scales

Some of the questionnaires in our test battery are scored according to a 4-point or 7-point Likert Scale. It is common to have from three up to nine answer- alternatives on the Likert Scale. Consequently, in our studies of HRQoL using the EORTC questionnaires, we have calculated sum scores, including a functional sum score and a symptom sum score. This has previously been done in several studies by e.g. Aarstad (68, 82, 224) and Hinz et al. (225). Computing the score as a mean of the functional scales is a potential alternative of initial interpretation to the EORTC-derived indexes. For all the measured criteria: the Cronbach’s alpha, convergent validity and discriminant validity, as well as the sum scores were either significantly better or comparable to the original global QoL. The inclusion of sum scores adds unique information to whether the question of research was to compare the broader concepts to HRQoL. The sum scores results must nevertheless be interpreted in conjunction with the underlying indexes.

11.3.2 Factor Analysis and Development of a Disease-specific RCC Test

Before a factor analysis can be conducted, an important step is to generate the correlation matrix and check whether the variables do not correlate too highly or too lowly with other variables (195). If variables correlate too highly it becomes impossible to determine the unique contribution to a factor of the variables that are highly correlated. If a variable correlates lowly with many other variables, the variable probably does not measure the same underlying construct as the other variables. Both

the highly and lowly correlating items should be eliminated, so we therefore included a correlation matrix including the different RCC disease-specific items (Table II article V). This table shows that the correlations between the different items were satisfactory in order to be included in a factor analysis.
We included either the one or two questions in the final questionnaire most closely related to each formed factor, or questions clearly asking about unique features of the RCC HRQoL, since our goal was to keep the number of questions down in order to construct a simple test suited for use in clinical settings.

The Kaiser-Meyer-Olkin (KMO) (199) Measure of Sampling Adequacy (MSA) index was used to measure the appropriateness of each item in our factor analysis. To consider whether the sample size was sufficient to conduct a reliable factor analysis, a common rule of thumb is that a researcher needs at least 10-15 participants per item (195), and the authors also need to report the completeness of each single item in the questionnaire (Table II article V). We also performed a Bartlett's Test for Sphericity (198), which is a measure of sampling adequacy recommended to investigate in the variable ratio for the analysis being conducted. This test plays an important role for accepting the sample adequacy and relates to the significance of the study, thereby showing the validity and suitability of the responses collected to the problem being addressed through the study (195). For a Factor Analysis to be recommended as suitable, the Bartlett's Test of Sphericity must be less than 0.05 (195), which in our Factor Analysis showed a significant result. Hence, psychometrically speaking, all the employed questionnaires were satisfactory.

12 SPECIFIC DISCUSSION OF RESULTS

In this study we have investigated presumably cured cancer patients regarding the relative importance of physical sequels related to psychosocial conditions, with outcome measures such as HRQoL and distress.

12.1. Distress in HNSCC

Distress, depression and anxiety include symptoms that may be studied as part of the HRQoL concept, and are thus related concepts. Others have empirically proven these associations (226, 227), as well as our research group (123).

In successfully treated HNSCC patients, we found that distress as measured by GHQ and HRQoL indexes were scored with a common variance between 20% and 35%, with the measured variables accounting for 40-48% of the variance of the HRQoL/GHQ scores. Between 3% and 10% of the GHQ/general QoL scores, and 10% of the variance of the H&N35 QoL scores, were predicted by the TNM stage. Treatment level or a high T stage predicted a low-symptom QoL, but not level of distress. High neuroticism, present avoidance coping and coping by suppression of competing activity were generally associated with a low QoL and a high level of distress. In sum up, the measured psychological factors accounted for approximately one-third of the measured variance of the QoL and GHQ responses, while the treatment-related factors account for approximately 10%. This indicates that distress scores may possibly be regarded as a HRQoL variable (123).

Distress, and to some extent HRQoL, was further found to be stable when measured over a four-year period in HNSCC patients (220). We (228) and others (124) have shown a close association between the level of neuroticism and level of distress in HNSCC patients when simultaneously measured. It was therefore interesting and important to determine risk factors, duration and stability of distress.

Findings from a large Australian study demonstrate that the risk of psychological distress in individuals with cancer relates much more strongly to patients' level of disability than it does to the cancer diagnosis itself (229). The findings of this study also suggest that following the diagnosis and its treatment, psychological- and other forms of support services for people with cancer may be particularly important for those with a significant disability (229). Banks et al. (229) argue that screening measures should be implemented at the time of diagnosis in order to identify psychologically vulnerable patients and offer them evidence-based psycho-oncological support.

12.2 HRQoL in HNSCC Patients

We have shown that the extent of the primary tumor at diagnosis explains roughly 10% of the variance in the HRQoL of HNSCC patients (228). The personality trait of neuroticism had a 30% common variance (CV) with the quality of life in HNSCC patients, showing that this psychosocial factor is important according to how HRQoL is reported (228). This is also found for other cancer patients (230), and for patients suffering from chronic diseases (231, 232). The HRQoL scores of HNSCC patients declined slightly ($p<0.001$), but were found to some extent to be stable when measured over a four-year period (220). In sum, the general HRQoL scores were predicted by neuroticism, avoidant coping pattern, T stage and smoking history, but primarily HN-specific HRQoL was predicted by treatment-derived factors (220).

12.3 HRQoL in RCC Patients

In our cross sectional study of long-term survivors after RCC treatment, we found in particular that patients treated by a flank approach, but not those treated by minimally invasive surgery, had a multifaceted decreased HRQoL compared to a general

population cohort (187). We also found that RCC tumor variables at diagnosis, such as histology, maximum tumor diameter and whether metastases or not, did not predict the HRQoL scores to any important degree (187). In order to validate the RCC HRQoL scores, a cohort of laryngectomized HNSCC patients and a cohort from the general Norwegian population (190), as well as our previous results on HNSCC patients were compared to the RCC patients' HRQoL scores. HRQoL scores in RCC patients were more closely associated with psychological than somatic disease related factors, i.e. present neuroticism and avoidant coping were associated with a lowered HRQoL. The laparoscopically treated RCC patients had HRQoL scores at the level of the population, while the flank-treated RCC patients had lower scores on general QOL/health than patients treated otherwise (187).
Ficarra et al. (83) showed in 2002 that the HRQoL of patients who underwent surgery for RCC was not particularly negatively affected. Nevertheless, the comparative analysis of Ficarra et al. showed that, at a long-term follow-up, radical surgery seemed to cause a more relevant negative impact on the patient's psychological well-being than conservative surgery (83). This is in line with our results. NSS with preserved renal function should be the goal for RCC treatment. Therefore, if NSS is oncological feasible, the choice of surgical approach may to some extent be guided by our findings regarding HRQoL in RCC patients.

In general RCC patients have been understudied when it comes to measuring HRQoL. One of the major areas of confusion in the QoL literature is the failure to distinguish symptom surveys and quality of life measures. Symptom burden indexes are limited to assess symptoms, which do provide important information, but it does not place the symptom in the context of global well-being (71).

12.4 HRQoL / GHQ in relation psychosocial factors in HNSCC and RCC patients

12.4.1 HRQoL/GHQ in relation Personality and Coping in HNSCC patients

By applying regression analyses, we have shown that neuroticism and choice of coping is total uniquely explained on the order of 20-30% of the HRQoL in HNSCC patients, of which some were directly between personality and HRQoL, some from choice of coping directly to the HRQoL and some from personality through choice of coping (220). The GHQ/distress scores also correlated closely with neuroticism, avoidance coping and coping by suppression of competing activity (problem focused coping). A former study of HNSCC patients compared to Multiple Sclerosis patients conclude that adequate coping seems to be to limit avoidance coping and promote coping by acceptance (233).

12.4.2 HRQoL in relation Personality and Coping in RCC Patients

By applying regression analyses, we have shown that neuroticism and choice of coping in combination uniquely explained on the order of 20-30% of the HRQoL in RCC patients. Some were directly between personality and the HRQoL, as well as some from personality through choice of coping to the HRQoL as depicted in Figure 3 article IV. In particular, a high use of avoidant coping was associated with a reduced HRQoL. Such relationships have further been previously found for other urological cancer diseases such as prostate- (234, 235) and testicular cancer (236). Interestingly, Grov et al. (237) found that the personality trait of neuroticism is strongly associated with long-term morbidity in testicular cancer survivors.

In RCC patients, the indexes directly related to symptoms were less related to neuroticism and choice of coping than indexes related to cognition. It is therefore interesting to note that even indexes directly asking about somatic function were answered in association with the personality of the individual. An interesting extension of our study would be to investigate the relationship of personality, choice of coping and HRQoL to distress, anxiety and depression also in RCC patients. We have shown a close association between these concepts in head and neck cancer patients (220).

The reported choice of problem-focused coping was inversely correlated to HRQoL scores. This coping mode was originally labeled as active healthy coping, although previous research has also suggested that this may in some cases be harmful coping (123), as currently seems to be the case. Further studies are needed in order to answer this apparent paradox in more detail. To a certain degree, the choice of coping may be regarded as a result of the personality of an individual, with personality as a more basic characteristic of an individual than choice of coping (238). It may be that neuroticism determines choice of coping to a certain extent.

SHQ L- scale responses in HNSCC patients and reported coping by humor in RCC patients was to some extent negatively associated with HRQoL scores.

In conclusion remarkably similar findings were found in the pattern of HRQoL / distress on the one hand, and personality/coping on the other in respectively HNSCC and RCC patients. The relationship between psychological factors and HRQoL is three to four times as strong as the correlation between the prevalence of cancer and the given QoL.

12.5 Impact factors in HNSCC and RCC Patients' HRQOL and Distress Scores

12.5.1 Sociodemographic factors

In our cross-sectional sample of surgically treated RCC patients, there was a significant gender difference, as men reported a better HRQoL than females, accounting for 4% of the total variance. EORTC QoL sum scores were not associated with age at surgery.

2.5.2 Cigarette smoking and alcohol consumption history

Cigarette smoking history was inversely associated with HRQoL scores, both as measured by number of cigarettes smoked per week and years of smoking, thereby accounting for approximately 4% of the total variance of RCC patients HRQoL.

In the HNSCC patients, the correlations indicated an inverse relationship between alcohol consumption history and GHQ/QoL. Present level of smoking was inversely associated with QoL/GHQ scores. A prediction of common variance ranging between 5% and 27% as to number of years smoked on HRQoL, and a prediction of 5% on GHQ scores in HNSCC patients was found.

Our findings point to that factors such as age, smoking and drinking habits should be taken into consideration when measuring HRQoL and distress levels in HNSCC and RCC patients.

12.5.3 Comorbidity

Comorbidity has so far not been fully explored in terms of what impact it may have on RCC patients' HRQoL. We have shown that present comorbidity, in particular in relation to diabetes or whether or not on lung medication, seems to be uniquely associated with a lowered HRQoL (187). Levels of comorbidity have been shown to be significantly correlated with both the functional and general symptom HRQoL sum score in RCC patients (221). We have shown that comorbidity, independent of other known predictors of HRQoL scores, such as the personality trait of neuroticism, psychological coping, TNM stage and BMI, uniquely explains 5-12% of RCC patients' common variance of HRQoL sum scores. This is in accordance with Osthus et al.'s (23) study demonstrating that comorbidities, especially present lung disease, appear to have an important and unique influence on HRQoL scores in HNSCC patients.

Verdonck-de Leeuw (239) found that the course of the HRQOL of HNSCC patients during the first two years after chemoradio therapy was different for survivors compared to non-survivors, and associated with comorbidity and tumor subsite. They observed significant differences for the majority of HRQOL scales between patient and reference groups, both at baseline and follow-up. Patients with comorbidity reported worse physical functioning (239).

This is also in line with Vissers et al.'s (240) findings when analyzing data from the PROFILES registry, where the impact of comorbidity in the HRQoL of cancer survivors was investigated. The results showed that comorbidity explained more of a variance in physical and emotional functioning, pain and fatigue in comparison with socio-demographic- and cancer characteristics in cancer survivors, regardless of cancer type. These findings underscore the importance of adjusting for the presence of comorbid diseases when assessing HRQoL in cancer survivors in general.

Our findings could point to a strategy of a closer awareness and follow-up of cancer patients with comorbidity such as diabetes and respiratory diseases. The patient's general practitioner can probably best do this. To monitor and treat present comorbidities in former cancer patients in the best possible way may contribute to increase the HRQoL in such patients.

12.5.4 Tumor Characteristics, Level of Treatment and Sequels

Tumor Characteristics

The numerical T stage predicted the QoL level, with the C-30 functional sum score, the C-30 symptom sum score and the H&N35 sum score, though not the GHQ score in our HNSCC patients. The N stage predicted the GHQ scores and the H&N35 score.

The poor association between tumor characteristics and HRQoL scores in RCC patients is in accordance with the results from studies of several other cancer diseases, i.e. colorectal cancer (241), breast cancer (242) and lung cancer (243), as well as in our study of HNSCC patients (220). In our study of RCC patients, the fact that the presence of distant metastasis was not associated with HRQoL scores may be due to the fact that only 3% of the respondents had distant metastases.

Level of Treatment and Time Post-treatment

The level of treatment and the time post-treatment were also explored in regard to being explanatory variables. The HN-specific HRQoL was predicted by treatment-derived factors (220). HNSCC may be extensively treated with a combination of surgery, radiation therapy and chemotherapy, which often lasts for a while and results in sequels. Despite this, the relationships between HRQoL, personality and avoidant coping seem to be parallel from such treated patients to our cohort of RCC patients, who are most commonly treated by one surgical procedure only.

Sequels

RCC patients treated surgically by a flank- or open surgical approach showed closer associations between problem-focused coping and HRQoL than the laparoscopically treated patients. The association between problem-focused coping and HRQoL, seems to depend on to what extent the cancer has left sequels. A treatment producing sequels may influence more on the choice of coping than a treatment without troublesome physical sequels, and that problem-focused coping is more situationally dependent than avoidant coping, which is further in line with previously published research (123). In addition, similar causes may help explain the findings about coping through humor and HRQoL levels. A common feature of HNSCC and RCC patients is that the treatment may affect the muscles that are innervated by movement of the neck and upper body. This may be one among many explanatory factors of the lowered HRQoL scores following these diseases.

12.5.5 Mental Mechanisms

The aforementioned relationship between HRQoL, personality and coping points to that the mental mechanisms behind these determined associations are basically the same for many cancer diseases, as has been previously suggested by Dahl and co-workers (230). The same relationships as given above have also been determined with other chronic non-cancer diseases such as Parkinson's disease (231) and chronic back pain (232). Hence it is possible that our findings may be part of a general relationship between personality, avoidant coping and HRQoL. This could be better answered by including additional control groups, which is currently lacking. States such as mood, depression and anxiety can possibly be changed, e.g. by psychological treatment or psychotherapy. A question that has to be addressed in future intervention studies is whether and how traits such as neuroticism, and more permanent features of our personality, and coping strategies can be changed. Several studies have shown that up to two-thirds of cancer patients experience substantial physical, psychological and social challenges due to their disease and treatment (244, 245).

Many studies have been carried out to improve the quality of life of patients treated for cancer (246-248). The increasing incidence of cancer, combined with improved survival, challenges us to provide evidence-based rehabilitation services (249). In order to assure patients' and families' continuing quality of life, multidisciplinary rehabilitation should be an integral and continuous part of all cancer care (249).

Fear of cancer recurrence (FCR) is among the most commonly reported problems among cancer patients (250). In a review by Simard et al. (14), survivors reported low to moderate levels of FCR, but considered it to be one of the greatest concerns and the most frequently reported unmet need. Furthermore, Simard et al. (14) found FCR to be stable over the survivorship trajectory. Younger age, as well as the presence and severity of physical symptoms, psychological distress and lower quality of life, were all associated with a higher FCR. Limited data on interventions are available (14).
It is reasonable to resume that FCR and distress are related. To identify common key features of FCR and distress may stimulate the development of targeted interventions.

12.6 Therapy Aimed to Improve HRQoL

In a systematic Cochrane review, Semple et al. (251) assessed the effectiveness of seven trials of psychosocial interventions to help improve the quality of life and psychosocial well-being for patients with HNC. They found no evidence to suggest that psychosocial intervention promotes a global quality of life for patients with HNC at the end of the intervention (251).

Yet another systematic review and meta-analysis of psychosocial interventions, conducted by Preyde and Synnott (252), concludes that there is no strong evidence to support any specific type of psychosocial intervention. Small intervention effects were noted for some psychosocial interventions, particularly those in which a focus on stress and coping were included; however, the poor quality of reporting negated any conclusive results (252).

The evidence base regarding health-related benefits of increased physical activity, improved diet and weight control continues to expand. Results suggest that physical activity interventions are safe for cancer survivors and produce improvements in fitness, strength and physical function, as well as in cancer-related psychosocial variables (253).

13 CONCLUSIONS

We have made remarkably similar findings in the pattern of HRQoL/ distress on the one hand, and personality/coping on the other hand, between HNSCC patients and RCC patients. The presence of the personality trait of neuroticism and the use of avoidance coping is associated with a reduced HRQoL and an increased distress in HNSCC. For both groups, it appears to apply that the relationship between psychological factors and general HRQoL is three to four times as strong as the correlation between the sequels and the reported HRQoL (187). If an aim of treatment is to generally improve HRQoL in cancer patients, a psychosocial follow-up may be integrated into cancer treatment.

Conclusions from the various studies included in the thesis are accounted under:

Study I

We have found that distress and HRQoL are scored similarly among successfully treated HNSCC patients. A high T stage or treatment level predicts low symptom QoL, but not level of distress. The presence of neuroticism and use of avoidance coping are both associated with and predict increased distress, with much the same pattern as for the HRQoL in HNSCC patients. The measured psychological factors accounted for about one third of the measured variance of the HRQoL and GHQ responses while the treatment related factors account for about 10 %, especially for the HN indexes. We put forward a hypothesis that distress measured outside the disease level may be a measure of HRQoL for this group (123).

Study II

Distress was found to be stable when measured over a four-year period in HNSCC patients (220), as HRQoL sum scores declined slightly ($p<0.001$). The distress and HRQoL scores were predicted by neuroticism, avoidant coping patterns, T stage and smoking history scores, but HN-specific HRQoL was primarily predicted by treatment-derived factors.

Study III

Long-term survivors after RCC treatment, and in particular those treated by a flank approach but not those treated by minimal invasive surgery, have a multifaceted reduced HRQoL compared to a general population cohort (221). In some indices, the HRQoL of the flank- treated patients was lower than among laryngectomy- treated HNSCC patients. In contrast RCC patients treated by minimal invasive surgery, retained HRQoL scores comparable to levels of the general population. NSS with preserved renal function should be the goal for RCC treatment, when the tumor is found to be suitable for that. Choice of surgical approach may to some extent be guided by the present findings.

Study IV

HRQoL in RCC patients is affected by treatment-related factors, but in this study is shown to be more closely associated to personality and choice of coping. Moreover, we have shown that present comorbidity, in particular diabetes or whether or not on lung medication, seems to be uniquely associated with HRQoL scores (187).

Study V

A disease-specific EORTC QLQ-like questionnaire for RCC patients has been developed, seemingly adding important information about RCC patients HRQoL. Our proposed "EORTC - RCC 10" provides additional value to the EORTC C-30 questionnaire, and is psychometrically satisfying (188). The questionnaire has the potential as a stand alone HRQoL questionnaire for use in surgically treated RCC patients. Further testing of the questionnaire is needed.

14 FUTURE PERSPECTIVES

Further investigation of HNSCC and RCC patients regarding HRQoL, distress, personality and coping is needed. An awareness of the relationship between these phenomena and the careful monitoring and evaluation of symptoms, and patients' perceptions of how the symptoms affect their lives, seem to be crucial in understanding and providing useful help throughout the cancer trajectory.

14.1 Implications for Clinical Practice

The reporting of HRQoL data in oncology trials should be in such a way as to provide clinically meaningful data to health- providers, in order to link research to clinical practice (254). To integrate into clinical practice findings gained from research is an important goal for all health professions.

Screening for psychosocial distress and disease- specific HRQoL should cause a minimum of burden on patients and health-care providers. Researchers should provide information that allows the clinicians to meet the needs of the patient with evidence-based approaches. It is therefore important that researchers document issues concerning quality of life and distress in cancer patients. The separation between those who research distress in patients and those who provide care has been identified as a challenge (125), as a failure to detect and treat distress may jeopardize the outcome of cancer therapy, decrease the patient's HRQoL and increase health-care costs (16). Clinicians should take into consideration Mitchell et al.'s (255) conclusion after reviewing studies of distress/QoL, that the screening of distress/QoL is likely to benefit communication and a referral for psychosocial help, and that it has the potential to influence patient well-being.

Our findings have hopefully contributed to strengthening the evidence that psychological factors are important prerequisites to obtain a good quality of life in HNSCC and RCC patients, and possibly in cancer survivorship as such. Our results may contribute to an increased focus on identifying the most vulnerable patients early, so that inter-professional collaboration can be provided. Our suggested “RCC 10” questionnaire can provide information on surgically treated RCC survivors HRQoL and what specific issues they are dealing with, and it may help detect the most vulnerable survivors. The “RCC 10” may also help health professionals in the clinic provide more personalized help and treatment.

14.2 Implications for Further Research

Our findings regarding the relationship between psychological factors and HRQoL is three to four times as strong as the correlation between the sequels and the given quality of life in HNSCC and RCC patients, challenges us to continue investigating these phenomenon. A better understanding of to what extent psychosocial conditions generally affect cancer patients’ HRQoL, and to what degree psychosocial treatment of cancer patients must take into consideration the actual cancer disease from which the patients suffer needs to be further investigated (244).

A future aim is to investigate our baseline data on HRQoL and distress in newly diagnosed RCC patients, as well as longitudinal follow up data. We would like to investigate the stability of distress during follow-up in RCC patients, as well as the relationship of HRQoL, distress, personality, choice of coping, anxiety and depression in RCC patients. The poor association between tumor characteristics and HRQoL scores, is also an aspect that needs further investigation in a larger sample of RCC patients. Palliative patients and RCC patients not surgically treated constitute separate cohorts that would also be of great interest to study in separate future studies.

To conduct a comparative study of the associations between HRQoL, distress, personality and coping among HNSCC and RCC patients would be very interesting in future studies. Other tests, conceiving other psychosocial aspects, such as mood, optimism and FCR, would also be of interest to explore. To identify common key features of FCR and distress may stimulate the development of targeted interventions.

Our proposed disease-specific EORTC QLQ questionnaire concerning RCC patients needs further validation. It has to be translated and validated internationally, by administrating it into a large international group of RCC survivors (77). Translational procedures and adaption to different cultures will have to be taken care of, so that the psychometric properties of the questionnaire remain satisfactory (201). Hopefully, it will be approved by the EORTC as a disease-specific questionnaire in RCC patients, and used in future trials for RCC survivors. Our suggested disease- specific RCC questionnaire will help fill a gap, and hopefully contribute to a better understanding of surgically treated RCC patients HRQoL. It will be easier to compare samples across trials and to build stronger power databases by collaborate on study protocols.

Well-conducted, hypothesis-driven studies using validated tools to provide information on how health-care providers can guide patients in clinical treatment decisions is warranted (71). Future studies have to find more evidence of the different associations, also in other cancer patient groups, so that the evidence of what interventions may help will be found.

A common feature of HNSCC and RCC patients is that the treatment may affect the muscles that are innervated by movement of the neck and upper body. This may be one among many explanatory factors of the lowered HRQoL scores following these diseases, which must be explored in future studies. Another question that has to be addressed in future intervention studies is whether and how traits such as neuroticism, and more permanent features of our personality, can be changed.

Based on our findings that present comorbidities were uniquely associated with a lowered HRQoL in cancer patients, it would be interesting to study whether a closer follow up by i.e. their general practitioner regarding their intercurrent disease could contribute to a better HRQoL.

Lastly, it is also pertinent to carry out specific interventional studies such as RCTs to establish knowledge of what may contribute to reducing the patient's levels of neuroticism and improve HRQoL. Our findings support an emphasis on supportive treatment, including an intervention that may reduce the use of avoidant coping, and encourage coping by acceptance and positive reinterpretation (256). It would be of interest to study whether an intervention study (phase II study) based on the current findings could show an improved HRQoL among patients suffering from HNSCC or RCC.

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