

UNIVERSITÄTSKLINIKUM HAMBURG- EPPENDORF

Klinik für Strahlentherapie und Radioonkologie

Direktorin: Prof. Dr. med. Cordula Petersen

Bereich Strahlentherapie Ambulanzzentrum UKE GmbH

Direktor: PD Dr. med. Andreas Krüll

Global quality of life during the acute toxicity phase of multimodality treatment for patients with head and neck cancer: Can we identify patients most at risk of profound quality of life decline?

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
an der Medizinischen Fakultät der Universität Hamburg

vorgelegt von:

Elena Reemts

aus Achim

Hamburg 2014

Angenommen von der Medizinischen Fakultät der Universität Hamburg am 3.11.2014.

Veröffentlicht mit Genehmigung der Medizinischen Fakultät der Universität Hamburg.

Prüfungsausschuss, der/die Vorsitzende: Prof. Dr. med. Cordula Petersen.

Prüfungsausschuss, zweite/r Gutachter/in: Prof. Dr. med. Dr. phil. Martin Härtter.

Prüfungsausschuss, dritte/r Gutachter/in: PD Dr. med. Silke Tribius.

Table of content

	Page
1 Publication:	1
Global quality of life during the acute toxicity phase of multimodality treatment for patients with head and neck cancer: Can we identify patients most at risk of profound quality of life decline?	
2 Background	9
2.1 Introduction	9
2.2 Scientific overview	11
2.2.1 Health- related quality of life	11
2.2.1.1 Definition	11
2.2.1.2 Historical considerations	12
2.2.1.3 Aims of quality of life research	12
2.2.1.4 Quality standards in quality of life measurement	13
2.2.1.5 Instruments for measuring quality of life	14
2.2.1.6 Analyzing quality of life data	17
2.2.1.7 Quality of life measurement in head and neck cancer patients	18
2.2.2 Head and neck cancer	21
2.2.2.1 Clinical presentation and risk factors	21
2.2.2.2 Treatment options and side effects	21
2.2.2.3 Treatment outcome and prognosis	25
2.3 Methods	28
2.3.1 Patients	28
2.3.2 Measuring instruments	29
2.3.2.1 Quality of life measurement	29
2.3.2.2 Socioeconomic and medical factors measurement	30
2.3.3 Study design	31
2.4 Data analysis	33
2.5 Results	34
2.5.1 Patient characteristics	34
2.5.2 Quality of life before radiation treatment (baseline) (T1)	36

2.5.3	Quality of life at the end of radiation treatment (T2)	37
2.5.4	Quality of life at first follow- up (T3)	40
2.5.5	Predictors for quality of life	42
2.6	Discussion	44
2.6.1	Reduced quality of life before radiation treatment	44
2.6.2	Deterioration of quality of life during radiation treatment	48
2.6.3	Quality of life- recovery until first follow- up	49
2.6.4	Predictor for quality of life: Pretreatment quality of life	52
2.6.5	Critiques	56
2.7	Summary	60
2.8	Appendix	61
2.8.1	Ethics committee application	61
2.8.2	Ethics committee approval	75
2.8.3	Patient's informed consent	77
2.8.4	Socioeconomic questionnaire	81
2.8.5	Medical questionnaire	87
2.8.6	Questionnaire about radiation treatment data	89
2.8.7	Index of tables	91
2.8.8	Index of figures	92
2.8.9	Index of abbreviations	93
2.9	References	95
3	My contribution to the dissertation	107
4	Acknowledgements	108
5	Curriculum vitae	109
6	Statutory declaration	110

1 Publication:

Global quality of life during the acute toxicity phase of multimodality treatment for patients with head and neck cancer: Can we identify patients most at risk of profound quality of life decline? (Tribius and others (et. al.) 2012a)



ELSEVIER

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology



Global quality of life during the acute toxicity phase of multimodality treatment for patients with head and neck cancer: Can we identify patients most at risk of profound quality of life decline?

S. Tribius ^{a,*}, E. Reemts ^a, C. Prosch ^a, M. Raguse ^a, C. Petersen ^a, A. Kruell ^a, S. Singer ^b, C. Bergelt ^c

^a Department of Radiation Oncology, University Medical Center Hamburg-Eppendorf, Martinistra. 52, 20246 Hamburg, Germany

^b Department of Medical Psychology and Medical Sociology, University of Leipzig, Philipp-Rosenthal-Str. 55, 04103 Leipzig, Germany

^c Department of Psychosocial Medicine, Institute for Medical Psychology, University Medical Center Hamburg-Eppendorf, Martinistra. 52, 20246 Hamburg, Germany

ARTICLE INFO

Article history:

Received 12 January 2012

Accepted 16 March 2012

Available online 12 April 2012

Keywords:

Treatment intensification

Radiotherapy

Quality of life

EORTC QLQ-C30

EORTC QLQ-HN35

SUMMARY

Purpose: Treatment intensification has improved outcomes for patients with head and neck cancer (HNC), but little has been reported on health-related quality of life (QoL) consequences. We investigated changes in QoL after (chemo)radiotherapy to identify patient characteristics that predict those whose QoL deteriorates most profoundly in the acute post-treatment period.

Materials and methods: Patients with locally advanced HNC treated with curative intent received intensity-modulated radiotherapy (60–70 Gy) in this prospective study. (Chemo)radiotherapy was either definitive or adjuvant. Induction chemotherapy consisted of three cycles of docetaxel, cisplatin, and 5-fluorouracil; responders received (chemo)radiotherapy; nonresponders underwent salvage surgery followed by (chemo)radiotherapy if appropriate. Patients completed the EORTC QLQ-C30 and HNC-specific HN35 module before and at the end of (chemo)radiotherapy and 6–8 weeks after therapy completion.

Results: Ninety-five patients participated. At baseline, patients reported significantly lower Global health status, functioning, and symptom scale scores than a reference German population (all $p < 0.001$). At the end of (chemo)radiotherapy, patients had significantly lower QoL scores vs. baseline on all functioning scales ($p < 0.05$). Most symptom and HN35 scores worsened during (chemo)radiotherapy but many recovered 6–8 weeks post-treatment. QoL deteriorated more in patients with high vs. low baseline QoL; no clinical or sociodemographic characteristics of patients most likely to experience a significant deterioration in QoL during treatment were identified.

Conclusion: These standard QoL instruments did not predict patients at risk of profound global QoL impairments during acute treatment. Other than baseline QoL, no patient characteristics associated with significant QoL deterioration were identified.

© 2012 Elsevier Ltd. All rights reserved.

Introduction

The concept of health-related quality of life (QoL) refers to aspects of life that are important to an individual and that may be affected – positively or negatively – by health and illness. The development of intensive cancer treatment regimens has improved response rates, but toxicities have become more burdensome and

difficult to quantify.¹ However, little information is available on the QoL consequences of these more aggressive approaches.

Randomized studies defining new oncology therapies are often not applicable in practice because the general health status of many patients is too poor. For example, the recommended (chemo)radiotherapy regimen for head and neck cancer (HNC) is cisplatin 100 mg/m² every 3 weeks, combined with 70 Gy radiation delivered in 1.8–2.0 Gy daily fractions. This regimen causes severe toxicities, e.g. nephro-, oto-, and neuro-toxicities, nausea and vomiting, and severe mucositis, which in daily practice means the regimen is suitable only for patients with normal creatinine clearance and good performance status. To limit toxic effects, and so get patients through therapy, reduced administration schedules are used, but without equivalent efficacy being established.

* Corresponding author. Tel.: +49 40 7410 56140/54033; fax: +49 40 7410 59895.

E-mail addresses: tribius@uke.uni-hamburg.de (S. Tribius), elenareemts@web.de (E. Reemts), c.prosch@uke.uni-hamburg.de (C. Prosch), marieclaire.raguse@googlemail.com (M. Raguse), cor.petersen@uke.uni-hamburg.de (C. Petersen), kruell@uke.uni-hamburg.de (A. Kruell), Susanne.Singer@medizin.uni-leipzig.de (S. Singer), Bergelt@uke.uni-hamburg.de (C. Bergelt).

Patients undergoing multimodal regimens experience functional and psychosocial consequences of treatment.² QoL measurement should be integrated into all clinical studies in patients with HNC to provide data for treatment planning and to try to identify patients at most risk of profound QoL deterioration. Methods for measuring QoL in patients with cancer include generic instruments that apply to all cancer populations, those that are specific to the disease in question, and treatment-, symptom-, and site-specific instruments.³

The present study was designed to examine the evolution of QoL in patients with advanced HNC, initially during and just after (chemo)radiotherapy, and then over 5 years. The initial goal was to identify patient characteristics that may predefine those in need of support before treatment and immediately after treatment. In future studies, the effect of such support could then be assessed for any meaningful impact on QoL.

Patients and methods

Patients

Enrollment into this prospective study was offered to patients with locally advanced HNC who were treated with curative intent at a single institution. Approval was obtained from the local ethics committee and all patients provided written informed consent.

All patients received intensity-modulated radiotherapy (total dose 60–70 Gy at 2 Gy/fraction with conventional fractionation). (Chemo)radiotherapy was definitive or adjuvant. Induction chemotherapy consisted of three cycles of TPF (docetaxel 75 mg/m² 1-h infusion day 1, cisplatin 75 mg/m² 1-h infusion day 1, and 5-fluorouracil 750 mg/m² continuous infusion days 1–5). Subsequently, responders received chemoradiotherapy and nonresponders underwent salvage surgery [followed by (chemo)radiotherapy depending on risk factors]. Adjuvant (chemo)radiotherapy consisted of radiotherapy (60–66 Gy at 2 Gy/fraction) with or without platinum-based chemo-therapy.

QoL measurement

General cancer-related QoL was measured with the German-language version of the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30).⁴ HNC-related QoL was measured using the EORTC 35-item Head and Neck Module (HN35).⁴ The QLQ-C30 consists of a global health scale and five functioning scales (Emotional, Physical, Cognitive, Social, and Role). The QLQ-C30 also includes three multi-item and six single-item scales: Fatigue, Pain, Nausea and Vomiting, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, and Financial difficulties. The HN35 includes seven head and neck-specific multi-item scales (Pain in the mouth, Swallowing, Senses, Speech, Social eating, Social contact, and Sexuality) plus six single-item scales (Problems with teeth, Problems opening mouth, Dry mouth, Sticky saliva, Coughing, and Feeling ill). The HN35 includes five yes/no items relating to the use of painkillers, nutritional supplements, feeding tube, weight loss, and weight gain.

Questionnaires were self-completed in the physician's office before the start of (chemo)radiotherapy (t1), at the end of (chemo)radiotherapy (t2), and 6–8 weeks after completion of (chemo)radiotherapy (t3).

Mean scores (\pm standard deviation) for the QLQ-C30 and HN35 were calculated according to the EORTC scoring manual.⁵ Scores for each scale range from 0 to 100. Higher scores on functioning scales indicate better health-related QoL; conversely, higher scores on symptom scales indicate more severe symptoms and worse QoL.

Data analysis

Data were analyzed using SPSS (Windows) Version 15.0. Missing data in QoL items were treated according to the EORTC scoring manual.⁵

Data for men and women were compared using analysis of variance (ANOVA). QoL was compared with published QLQ-C30 data for a reference German population. This reference group of 2081 randomly selected adults (mean age 49.4 years [standard deviation 17.2 years]) were interviewed in their own homes by skilled interviewers.⁶ The present study used the cohort aged 60–69 years ($n = 390$) from this population, as 48% of our sample were in this age category. Comparisons were conducted using one-sample *t*-tests. QoL changes during (chemo)radiotherapy and follow-up were investigated by multivariate ANOVA with repeated measurements.

To determine potential predictors of QoL 6–8 weeks after (chemo)radiotherapy, two-step linear regression analyses were performed. First, univariate analyses were performed on the association between potential predictors and QoL at follow-up. The following independent predictors were investigated dichotomously: (A) disease- and treatment-related variables: (A1) tumor stage (T1/2 vs. T3/4/x), (A2) nodal stage (N0/1 vs. N2/3), (A3) grading (G1/2 vs. G3), (A4) previous surgery (yes/no), (A5) previous chemotherapy (yes/no), (A6) chemoradiotherapy (yes/no), (A7) body mass index (median split), (A8) Karnofsky index (median split) and (A9) hemoglobin (median split); (B) sociodemographic variables: (B1) age (median split), (B2) sex (male/female), (B3) marital status (married/not married), (B4) years of schooling (≤ 9 years vs. > 9 years), (B5) employment (employed vs. unemployed/retired) and (B6) household income ($\leq \text{€}2000$ vs. $> \text{€}2000/\text{month}$); (C) life-style factors: (C1) current smoking (yes/no) and (C2) current alcohol consumption (yes/no). For the analysis of QoL at follow-up, we also investigated (D) global health status at the beginning of radiation treatment: (D1) initial QoL (median split).

The second step was a multivariate stepwise regression. Age and sex were included as predictors because QoL changes with age and QoL-norm data are generally reported for each sex separately and according to age group. Additional variables were included that were associated with QoL at follow-up at a 10% significance level in the univariate analysis.

The dependent variable in the regression model was global health status. All predictors were included as either interval-scaled (age, initial QoL) or dichotomized (tumor stage, sex, current smoking status).

Results

This is an analysis of the first three timepoints (t1, t2, and t3) of the ongoing study, which commenced in April 2009. As of April 2011, 99 patients had enrolled. Table 1 summarizes clinical and demographic characteristics of 95 patients with data. One patient died shortly after completion of therapy and three were lost to follow-up.

There were no significant differences between men and women for any clinical, sociodemographic, or lifestyle variables.

Quality of life at baseline

The whole sample had statistically significantly lower QoL scores than the reference German population. QoL functioning scores in the study sample were between 10 (Physical function; $p < 0.001$) and 30 (Social function; $p < 0.001$) points lower than those of the reference group.⁶ The study sample also had significantly lower global health status ($p < 0.001$) and symptom scale scores (Table 2). Domains particularly affected (difference of > 20 points) included Role, Emotional, and Social function, as well as

Table 1
Sample characteristics of patients at the beginning of (chemo)radiotherapy ($n = 95$).

Characteristic	Whole sample	Women ($n = 30$)	Men ($n = 65$)	<i>p</i>
Mean age, years (SD)	59.1 (8.6)	57.6 (8.7)	59.8 (8.5)	0.240
Mean Karnofsky score (SD)	81.5 (10.7)	80.2 (11.5)	82.2 (10.4)	0.404
Mean hemoglobin (SD)	11.7 (1.9)	11.4 (1.6)	11.8 (2.0)	0.348
Tumor stage, %				
T1/2	43.2	36.7	46.2	0.426
T3/4	48.4	50.0	47.7	
Tx	8.4	13.3	6.2	
N0/1	40.0	46.7	36.9	0.368
N2/3	60.0	53.3	63.1	
Grading, %				
G1	1.1	3.3	0	0.310
G2	51.6	53.3	50.8	
G3	47.4	43.3	49.2	
Squamous cell carcinoma, %	91.6	86.7	93.8	0.241
Induction chemotherapy, %	20.0	26.7	16.9	0.270
Adjuvant (chemo)radiotherapy, %	76.8	66.7	81.5	0.110
Total chemoradiotherapy, %	57.9	50.0	61.5	0.290
Tumor site, %				
Oral cavity	33.7	40.0	30.8	
Oropharynx	36.8	26.7	41.5	0.523
Hypopharynx/larynx	15.8	20.0	13.8	
Others	13.7	13.3	13.8	
Smoking status, %				
Smoker	30.9	37.9	27.7	
Former smoker	51.1	48.3	52.3	0.556
Non-smoker	18.1	13.8	20.0	
Current alcohol consumption, %				
Regular	9.5	6.7	10.8	
Sometimes	34.7	30.0	36.9	
No consumption	55.8	63.3	52.3	0.578

SD = standard deviation.

Fatigue, Pain, Insomnia, Appetite loss, and Financial problems (all $p < 0.001$).

Women reported lower scores than men on all QLQ-C30 functioning scales and higher QLQ-C30 symptom scales other than Financial problems; none of these differences were statistically significant (Table 2).

The overall population had substantial head and neck symptoms at the beginning of (chemo)radiotherapy as measured using the HN35 (Table 3). The highest scores, indicating greatest symptom burden, were for Sexuality, Opening mouth, and Feeling ill. Men and women did not differ significantly with regard to head and neck symptoms at the beginning of (chemo)radiotherapy.

Patients who underwent surgery before (chemo)radiotherapy did not differ significantly on any QLQ-C30 scale from those who did not. A significant difference between patients with vs. without prior surgery was only found for Opening mouth (data not shown).

Scores for all HN35 symptom scales increased by >20 points between t1 and t2, with the exception of the Social contact and Teeth subscales (Table 4). Most HN35 scores had recovered to near baseline levels (or better) 6–8 weeks after (chemo)radiotherapy. Senses, Dry mouth, and Sticky saliva scores were 22, 39, and 28 points higher than at baseline and other scores were 1–10 points higher than at baseline. With the exception of the Teeth scale, for which there was no apparent time main effect ($p = 0.673$), Repeated-measures ANOVA revealed statistically significant time main effects for all functioning and symptom scales (all $p < 0.001$).

The proportion of patients requiring a feeding tube increased from 27% at baseline to 78% at the end of (chemo)radiotherapy, with only a small reduction after 6–8 weeks. There was an increase in patients reporting weight loss during treatment, with a more substantial reduction in the weeks after the completion of therapy (Table 4).

Changes in QoL over time

At the end of (chemo)radiotherapy, patients reported significantly lower QoL scores vs. baseline on all QLQ-C30 functioning scales (all $p < 0.05$). Differences between baseline and end of (chemo)radiotherapy were largest for Role (−20 points; $p < 0.001$) and Social functioning (−19 points; $p < 0.001$). Symptom scores increased during (chemo)radiotherapy, with the greatest increases in Fatigue, Nausea/vomiting, and Appetite loss (+26, +27, and +34 points, respectively; all $p < 0.001$). However, recovery was observed in most domains 6–8 weeks after treatment completion; only Nausea/vomiting, Appetite loss, and Constipation remained >10 points higher than at baseline. Repeated-measures ANOVA revealed statistically significant time main effects for all functioning and most symptom scales (Table 4).

Regression analysis

As baseline QoL was the only significant predictor for QoL at first follow-up, we divided the sample according to initial QoL and investigated the EORTC function scales. Repeated-measures ANOVA, with initial global QoL as a group factor (median split), revealed a statistically significant interaction of time and group factor for Global health status, Role, Emotional, and Social function (Table 5). Patients with low baseline QoL experienced little change over time in functioning scores, while patients with high baseline QoL reported larger decreases in functioning scores during (chemo)radiotherapy, although some recovery was apparent during follow-up ($p < 0.001$; repeated measures ANOVA). A statistically significant effect was also seen for Role, Emotional, and Social functioning scores.

Table 2

General quality of life at the beginning of (chemo)radiotherapy ($n=95$) assessed with the European Organisation for Research and Treatment of Cancer 30-item QoL questionnaire.

Scale	Women ($n=30$)		Men ($n=65$)		p^b	Whole sample		Reference group ^a	
	Mean	SD	Mean	SD		Mean	SD	Mean	p^c
Functioning scales									
Global health status	43.3	30.9	49.0	24.6	0.344	47.2	26.7	65.6	<0.001
Physical function	69.6	23.6	79.3	22.3	0.056	76.2	23.1	86.5	<0.001
Role function	51.1	36.9	60.2	36.7	0.269	57.3	36.8	84.5	<0.001
Emotional function	49.1	29.7	56.5	30.5	0.270	54.2	30.3	80.5	<0.001
Cognitive function	71.7	34.8	79.0	23.8	0.235	76.7	27.8	88.3	<0.001
Social function	48.3	35.4	59.7	32.5	0.126	56.1	33.7	86.7	<0.001
Symptom scales									
Fatigue	49.6	29.3	38.5	28.0	0.081	42.1	28.7	18.6	<0.001
Nausea/vomiting	8.3	20.4	5.9	11.9	0.467	6.7	15.1	2.2	0.005
Pain	47.8	38.1	38.2	33.8	0.221	41.2	35.3	20.3	<0.001
Dyspnea	32.2	35.5	24.6	27.8	0.260	27.0	30.5	12.6	<0.001
Insomnia	50.0	36.9	38.5	35.5	0.149	42.1	36.1	19.5	<0.001
Appetite loss	34.5	44.1	24.9	33.8	0.254	27.9	37.4	6.2	<0.001
Constipation	13.3	28.5	8.2	22.8	0.350	9.8	24.7	3.5	0.014
Diarrhea	15.6	30.0	12.8	22.6	0.623	13.7	25.0	2.1	<0.001
Financial problems	32.2	37.6	33.8	37.0	0.844	33.3	37.0	10.2	<0.001

SD = standard deviation.

^a Reference data from Schwarz and Hinz⁶; data were compared against reference data for the group aged 60–69 years as the majority of the study sample (48%) were in this age category.

^b Analysis of variance.

^c One-sample *t*-test.

Analysis of patient demographics and clinical characteristics according to high vs. low baseline QoL did not reveal any statistically significant differences that would account for the different evolution of QoL (Table 6).

Discussion

Key findings from this longitudinal QoL analysis were: (1) patients with HNC had considerably worse QoL before treatment than a reference population of German adults of a similar age; (2) QoL deteriorated during (chemo)radiotherapy but most domains recovered in the immediate follow-up period; (3) patients with higher

QoL at baseline had the most substantial fall in scores; and (4) baseline global QoL was the only predictor for QoL observed between the independent variables assessed and change in QoL over the treatment and follow-up period.

Unsurprisingly, patients with HNC had significantly worse baseline Global health status, functioning, and symptom scale scores than a similar-aged reference German population.⁶ At the start of the study, patients were coming to terms with their prognosis, and 77% had already had surgery and 20% had prior chemotherapy, all of which are likely to have impacted on their QoL. Borggreen et al. reported significantly worse pretreatment EORTC QLQ-C30 scores for Role function, Emotional function, Pain, Insomnia, and Appetite loss in patients with oral and oropharyngeal cancer vs.

Table 3

Symptoms related to head and neck cancers at the beginning of (chemo)radiotherapy ($n=95$): European Organisation for Research and Treatment of Cancer 35-item Head and Neck Module.

Scale	Whole sample		Women ($n=30$)		Men ($n=65$)		p^a
	Mean	SD	Mean	SD	Mean	SD	
Multi-item symptom scales							
Pain	31.9	28.3	24.3	23.9	35.4	29.6	0.074
Swallowing	40.0	32.9	34.2	33.1	42.6	32.7	0.244
Senses	23.8	31.1	18.4	25.7	26.2	33.1	0.265
Speech	36.1	30.2	37.4	31.5	35.5	29.8	0.773
Social eating	40.4	33.6	45.0	35.0	38.2	33.0	0.362
Social contact	22.4	24.8	27.8	28.1	19.9	22.9	0.152
Sexuality	45.4	38.8	45.2	40.8	45.5	38.2	0.976
Single-item symptom scales							
Teeth	28.5	36.9	28.7	38.5	28.4	36.4	0.970
Opening mouth	43.5	39.5	40.0	45.0	45.1	37.0	0.559
Dry mouth	33.3	32.4	32.2	32.1	33.9	32.8	0.821
Sticky saliva	41.4	38.5	33.3	39.1	45.1	37.9	0.166
Coughing	40.7	31.2	45.6	32.1	38.5	30.7	0.305
Felt ill	45.4	35.9	50.0	35.8	43.2	36.0	0.397
Additional items, % patients							
Use of pain killers	61.7		66.7		59.4		0.498
Nutritional support	22.0		17.9		23.8		0.527
Feeding tube	28.0		20.7		31.3		0.293
Weight loss	66.7		44.8		76.6		0.003
Weight gain	13.2		17.9		11.1		0.380

SD = standard deviation.

^a Analysis of variance.

Table 4
Change in quality of life during (C)RT ($n = 95$).

Instrument	Start of (C)RT (t1)		End of (C)RT (t2)		6–8 weeks after treatment (t3)		p^a (time)	Change t1–t2	Change t1–t3			
	Mean	SD	Mean	SD	Mean	SD						
EORTC QLQ-C30												
<i>Functioning scales</i>												
Global health status	46.6	26.3	35.3	22.4	48.5	22.4	<0.001	-11.3	+1.9			
Physical function	76.2	23.1	59.6	23.9	68.2	23.2	<0.001	-16.6	-8.0			
Role function	57.3	36.8	37.8	33.9	48.8	30.8	<0.001	-19.5	-8.5			
Emotional function	54.2	30.3	45.7	25.1	55.9	29.3	0.001	-8.5	+1.7			
Cognitive function	76.7	27.8	66.8	25.3	75.1	25.5	0.001	-9.9	-1.6			
Social function	56.1	33.7	37.4	29.4	48.1	30.5	<0.001	-18.7	-8.0			
<i>Symptom scales</i>												
Fatigue	42.3	28.8	68.2	25.3	51.0	27.2	<0.001	+25.9	+8.7			
Nausea/vomiting	6.8	15.2	34.1	33.8	18.8	25.9	<0.001	+27.3	+12.0			
Pain	41.2	35.3	57.4	33.9	39.3	34.5	<0.001	+16.2	-1.9			
Dyspnea	26.5	29.7	35.1	31.2	28.7	30.5	0.054	+8.6	+2.2			
Insomnia	43.5	35.9	55.8	34.6	42.4	36.0	<0.001	+12.3	-1.1			
Appetite loss	27.5	36.8	61.6	36.2	42.4	35.4	<0.001	+34.1	+14.9			
Constipation	9.9	24.8	30.5	35.5	20.2	31.4	<0.001	+20.6	+10.3			
Diarrhea	13.8	25.1	18.8	31.5	12.4	21.9	0.155	+5.0	-1.4			
Financial problems	32.3	36.6	38.4	35.1	38.4	35.8	0.220	+6.1	+6.1			
EORTC HN35												
<i>Multi-item symptom scales</i>												
Pain	31.9	28.3	56.9	28.6	36.6	24.7	<0.001	+25.0	+4.7			
Swallowing	39.7	32.8	69.4	24.9	45.9	31.5	<0.001	+29.7	+6.2			
Senses	23.8	31.1	59.6	29.1	45.9	30.5	<0.001	+35.8	+22.1			
Speech	36.3	30.2	62.6	30.3	40.0	28.9	<0.001	+26.0	+3.4			
Social eating	41.1	34.2	68.0	29.9	51.3	33.3	<0.001	+26.9	+10.2			
Social contact	22.4	24.8	37.5	28.9	26.9	26.3	<0.001	+15.1	+4.5			
Sexuality	49.2	38.0	72.6	35.4	56.2	37.0	<0.001	+23.4	+7.0			
<i>Single-item symptom scales</i>												
Teeth	27.1	35.8	29.4	35.8	25.5	35.9	0.673	+2.3	-1.6			
Opening mouth	43.5	39.5	66.7	37.3	47.7	38.8	<0.001	+23.2	+4.2			
Dry mouth	32.6	31.8	68.1	36.4	71.3	33.5	<0.001	+35.5	+38.7			
Sticky saliva	41.8	38.5	86.2	23.7	70.2	33.0	<0.001	+44.4	+28.4			
Coughing	40.1	31.3	62.4	31.9	41.9	31.4	<0.001	+22.3	+1.8			
Felt ill	43.7	35.2	66.7	32.4	47.0	32.0	<0.001	+23.0	+3.3			
<i>Additional items, %</i>												
Use of pain killers	61.1		70.5		53.7							
Nutritional support	21.1		45.3		47.4							
Feeding tube	27.4		77.9		70.5							
Weight loss	65.3		72.6		46.3							
Weight gain	12.6		4.2		22.1							

(C)RT = (chemo)radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; HN35 = 35-item Head and Neck Module; QLQ-C30 = 30-item quality of life questionnaire; SD = standard deviation.

^a Repeated measures analysis of variance.

normative data from the general Norwegian population.⁷ Pourel et al. reported significantly worse global health status, QLQ-C30 functioning scores, Pain, and Fatigue in long-term oropharyngeal cancer survivors vs. the general Swedish population.⁸

Significant worsening of functioning and symptom scale scores were observed in the study sample between the beginning and end of (chemo)radiotherapy. These were greatest in domains related to the function of the parotid glands, which are most affected by (chemo)radiotherapy to the head and neck, i.e. Appetite loss in the QLQ-C30 and Swallowing, Dry mouth, and Sticky saliva in the HN35 module. The effect of (chemo)radiotherapy on these key functions was further reflected in the high proportion of patients who needed a feeding tube during treatment and beyond. Similar reductions in QoL during treatment have been described previously.^{9–12}

We observed a recovery in scores to near baseline values for many QLQ-C30 and HN35 domains and items, although items relating to swallowing tended to remain affected at the 6–8 week timepoint. In the longer term, QoL deterioration can be expected when the late side effects of radiotherapy, such as persistent

xerostomia, osteoradionecrosis, and fibrosis, begin to appear. Scores have been shown to recover as patients adapt, even if physical function does not return to pretreatment levels.⁹

Baseline QoL appeared to be the only statistically significant predictor of subsequent QoL reductions among the variables tested. Patients with QoL scores >median at baseline had significantly greater deterioration in QoL during (chemo)radiotherapy than those with low baseline QoL. Falls of 18–37 points were observed in patients with high baseline QoL vs. 0–13 points in those with low baseline QoL. Jabbari et al. reported an effect of baseline QoL on post-therapy QoL scores in their study of the Xerostomia Questionnaire and Head and Neck Quality Of Life instruments, although no subsequent analysis of this effect was reported.¹³ In the present study, further analysis of patient characteristics that might have resulted in greater QoL deterioration in patients with good baseline QoL failed to identify any statistically significant factors.

Return to pretreatment levels was observed in patients with low baseline QoL 6–8 weeks after the completion of (chemo)radio-

Table 5

Change in quality of life during (chemo)radiotherapy in patients with low vs. high (median split) initial Global health status (repeated measures analysis of variance).

Functioning scales	QoL at baseline	Start of (C)RT (t1)		End of (C)RT (t2)		6–8 weeks after (C)RT (t3)		p (time)	p (time * group)
		Mean	SD	Mean	SD	Mean	SD		
Global health status	Low	31.3	17.9	30.3	17.2	43.9	21.3	<0.001	<0.001
	High	74.5	12.3	44.4	27.6	56.8	22.3		
Physical function	Low	67.4	24.0	54.0	21.3	62.4	23.6	<0.001	0.165
	High	91.6	9.3	69.4	25.3	78.4	18.6		
Role function	Low	42.4	33.8	30.2	30.9	40.1	27.9	<0.001	0.035
	High	81.9	27.0	49.5	35.4	62.3	30.2		
Emotional function	Low	41.0	27.5	41.1	21.4	46.7	28.8	<0.001	<0.001
	High	77.7	19.3	52.9	29.1	72.3	23.0		
Cognitive function	Low	69.2	29.6	63.6	23.7	70.6	26.5	<0.001	0.094
	High	89.7	18.8	71.6	27.4	82.8	22.3		
Social function	Low	41.9	30.0	33.1	27.9	37.8	28.9	<0.001	0.001
	High	79.9	24.9	43.1	29.9	65.2	25.1		

QoL = quality of life; SD = standard deviation.

therapy. QoL returned to a lesser extent in patients with high baseline QoL, although values were generally lower at 6–8 weeks after (chemo)radiotherapy than at baseline. Many early side effects of (chemo)radiotherapy, including fatigue, skin reactions, mucositis, and dysphagia, resolve spontaneously 1–2 months after (chemo)radiotherapy, therefore improvement in QoL is not unexpected. Xerostomia can persist after the completion of radiotherapy, but Ringash et al. showed that QoL recovers to baseline after radiotherapy in the presence of persistent xerostomia, possibly because of response shift or because xerostomia without acute mucositis has a relatively small influence on overall QoL.¹⁴ In contrast, Langendijk et al. demonstrated a link between QoL and

swallowing and xerostomia in patients with HNC.¹¹ The slower recovery in patients with high baseline QoL is surprising, however, and may be related to expectations that come from good initial health.

The ability to eat, swallow, chew, and talk, functions that are substantially affected in patients with HNC, is important to patients with HNC and nonpatients. In a study of patient preferences, being cured of their cancer, living as long as possible, and having no pain were most commonly ranked in the top three priorities of patients (90%, 61%, and 34%, respectively) and nonpatients (80%, 60%, and 52%, respectively).¹⁵ Patients and nonpatients also ranked highly the ability to swallow and having a normal sense of taste and smell,

Table 6

Sample characteristics of patients at the beginning of radiation treatment: QoL median split (median = 50).

Characteristic	Whole sample (n = 94)	Low initial QoL (n = 60)	High initial QoL (n = 35)	p
Mean age, years (SD)	59.1 (8.6)	59.5 (8.5)	58.3 (9.0)	0.506
Mean Karnofsky status (SD)	81.5 (10.7)	80.9 (11.4)	82.6 (9.6)	0.457
Mean hemoglobin (SD)	11.7 (1.9)	11.6 (1.9)	11.8 (1.9)	0.718
Tumor stage, %				
T1/2	43.2	40.0	50.0	0.294
T3/4	48.4	48.3	47.1	
TX	8.4	11.7	2.9	
N0/1	40.0	36.7	47.1	0.324
N2/3	60.0	63.3	52.9	
Grading, %				
G1	1.1	0.0	2.9	0.371
G2	51.6	53.3	47.1	
G3	47.4	46.7	50.0	
Squamous cell carcinoma, %	91.6	93.3	88.2	0.395
Previous chemotherapy, %	20.0	16.7	26.5	0.255
Previous surgery, %	76.8	75.0	79.4	0.627
Combined chemoradiotherapy, %	57.9	56.7	58.8	0.839
Tumor site, %				
Oral cavity	33.7	28.3	41.2	0.528
Oropharynx	36.8	41.7	29.4	
Hypopharynx/larynx	15.8	15.0	17.6	
Others	13.7	15.0	11.8	
Smoking status, %				
Smoker	30.9	33.9	26.5	0.061
Former smoker	51.1	55.9	44.1	
Non-smoker	18.1	10.2	29.4	
Current alcohol consumption, %				
Regularly	9.5	11.7	5.9	0.504
Sometimes	34.7	31.7	41.2	
No consumption	55.8	56.7	52.9	

QoL = quality of life; SD = standard deviation.

indicating that compromising these functions may profoundly affect QoL, regardless of whether one has HNC or not.

No predictors for QoL at follow-up were observed between the independent variables assessed and QoL during and after treatment. Surgery, prior chemotherapy, and tumor site did not emerge as significant variables in the multivariate analysis. Identification of baseline QoL as being relevant to subsequent changes in QoL leads us to speculate that some patients are psychologically highly susceptible to the changes that occur during HNC treatment. However, the standard QoL instruments used in this study may not be sensitive enough to differentiate specific problems influencing QoL in this complex group of patients. We therefore propose that new or additional instruments be developed to pre-select those at greatest risk of substantial deterioration. The EORTC HN35 is currently being revised to improve the ability to distinguish between patients with and without chemoradiotherapy.¹⁶

The HN35 module was developed on the basis of a combination of scales and single items, with each scale designed to assess a clinically meaningful concept. In some studies, it might be of clinical interest to report the results for each item separately to allow review of specific problems reported by patients. However, in using the questionnaire as a research tool, use of the global health status is preferred as it reflects the "whole" patient.

Patients in this study had a variety of tumor types affecting different anatomical areas of the head and neck. As a result, adverse events associated with treatment have the potential to vary, which may affect QoL.^{17–19}

In conclusion, this initial analysis has demonstrated that (chemo)radiotherapy has a significant impact on QoL in patients with HNC in the immediate post-treatment period although it was not possible to identify patient characteristics that were associated with changes in particular aspects of QoL. These results underline the importance of assessing QoL in patients with HNC and suggest that more sensitive or multiple instruments may be needed to predefine patients in need of support before treatment and in the immediate post-(chemo)radiotherapy period. Long-term QoL assessment continues in this group of patients to provide additional information regarding changes in post-treatment QoL.

Conflicts of interest statement

None declared.

References

- Trotti A, Pajak TF, Gwede CK, Paulus R, Cooper J, Forastiere A, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol* 2007;8(7):613–24.
- Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, et al. Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2004;130(4):401–8.
- Sayed SI, Elmiyeh B, Rhys-Evans P, Syrigos KN, Nutting CM, Harrington KJ, et al. Quality of life and outcomes research in head and neck cancer: a review of the state of the discipline and likely future directions. *Cancer Treat Rev* 2009;35(5):397–402.
- Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck cancer patients. EORTC Quality of Life Group. *Eur J Cancer* 2000;36(14):1796–807.
- Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M. On behalf of the EORTC Quality of Life Study Group. *The EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
- Schwarz R, Hinz A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. *Eur J Cancer* 2001;37(11):1345–51.
- Borggreven PA, Verdonck-de Leeuw IM, Muller MJ, Heiligers ML, de Bree R, Aaronson NK, et al. Quality of life and functional status in patients with cancer of the oral cavity and oropharynx: pretreatment values of a prospective study. *Eur Arch Otorhinolaryngol* 2007;264(6):651–7.
- Pourel N, Peiffert D, Lartigau E, Desandes E, Luporsi E, Conroy T. Quality of life in long-term survivors of oropharynx carcinoma. *Int J Radiat Oncol Biol Phys* 2002;54(3):742–51.
- Mehanna H, West CM, Nutting C, Paleri V. Head and neck cancer—Part 2: Treatment and prognostic factors. *BMJ* 2010;341:c4690.
- Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. *J Clin Oncol* 2007;25(16):2191–7.
- Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26(22):3770–6.
- van Herpen CM, Mauer ME, Mesia R, Degardin M, Jelic S, Coens C, et al. Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323). *Br J Cancer* 2010;103(8):1173–81.
- Jabbari S, Kim HM, Feng M, Lin A, Tsien C, Elshaikh M, et al. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. *Int J Radiat Oncol Biol Phys* 2005;63(3):725–31.
- Ringash J, Warde P, Lockwood G, O'Sullivan B, Waldron J, Cummings B. Postradiotherapy quality of life for head-and-neck cancer patients is independent of xerostomia. *Int J Radiat Oncol Biol Phys* 2005;61(5):1403–7.
- List MA, Rutherford JL, Stracks J, Pauloski BR, Logemann JA, Lundy D, et al. Prioritizing treatment outcomes: head and neck cancer patients versus nonpatients. *Head Neck* 2004;26(2):163–70.
- Singer S, Hofmeister D, Spiegel K, Boehm A. Aktuelle Entwicklungen bei der Erfassung der Lebensqualität mit Instrumenten der European Organisation for Research and Treatment of Cancer (EORTC). *Laryngo-Rhino-Otolgie* 2011;90(10):595–8.
- Huguenin PU, Taussky D, Moe K, Meister A, Baumert B, Lütfi UM, et al. Quality of life in patients cured from a carcinoma of the head and neck by radiotherapy: the importance of the target volume. *Int J Radiat Oncol Biol Phys* 1999;45(1):47–52.
- Hammerlid E, Silander E, Hörenstam L. Health-related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck* 2001;23(2):113–25.
- Morton RP. Life-satisfaction in patients with head and neck cancer. *Clin Otolaryngol Allied Sci* 1995;20(6):499–503.

2 Background

2.1 Introduction

A growing interest in adding life to years and not years to life in an ageing and more diseased society has also focused medical disciplines on research in quality of life in the last decades (Galbraith 1964, Elwood 1972). This development introduced more and more patient's unique view into the assessment of diverse fields of medicine and especially into evaluation of outcome of highly disabling and long- lasting entities, for example (e.g.) pharmaceutical assessment and cancer treatment (Karnofsky and Burchenal 1949, Spiers et al. 1975) and treatment of chronic diseases (Forrest 1976). In this context, the terminus of "health- related quality of life" (QoL) refers to an individual's perception of its well- being considering an impact by illness, disability or disease treatment (Centers for Disease Control and Prevention (CTC) 2013).

Until today, the inhomogeneous construct of QoL as defined by the World Health Organization (WHO) in 1946 confronts clinicians as well as scientists with a lot of methodological difficulties: Because of individual, intercultural and time- dependent interactions in the perception of QoL (WHO 1946), research suffers from various sources influencing outcome and complicating comparability (Murphy et al. 2007). Nevertheless, the QoL- construct remains, especially in cancer patients, an irreplaceable parameter of therapy outcome and is focused on clarifying patient's view on medical treatment further on. A sufficient QoL is for most – healthy and diseased – people the most important goal in their daily life (Bullinger and Hasford 1991).

Functional integrity, perception and structure of the head and neck region are particularly known to be important for positive social and emotional interactions (List et al. 2004). Many basic sensual functions are localized in this region as speech, taste, smelling and hearing. If someone suffers from cancer in the head and neck region (HNC), oftentimes these basic functions become limited not only by the life- threatening disease itself but additionally by medical treatment and its adverse effects (Trotti et al. 2007). Patients suffering from this cancer entity are known to experience a high impact in their biosocial perception and behavior and in their QoL (Bonner et al. 2006, Hammerlid et al. 2001a).

As Trotti et al. (2007) showed, during the preceding fifteen years, the implementation of intensified multimodal treatment into HNC- therapy had led to a multiplication of acute

and long- term side effects – compromising QoL in a growing manner – without having improved the actuarial survival rate significantly.

HNC- treatment as it is practiced today must take care of the individual risk to lose QoL and it must adapt treatment planning to the risk of a substantial impact in QoL. Therefore, it would be helpful for patients as well as for professionals to be able to predict the individually expected QoL- change before a treatment starts. At this time, preferable modalities, supplementary care and other support are supposed to be planned according to a patient's individual prognosis of QoL. Possible pretreatment predictors for the subsequent QoL- change are therefore necessary and evaluated in this study.

In the past years, QoL- research has already evaluated a number of possible pretreatment predictors for HNC- patients. For example, age, sex, tumor site and stage, treatment and depressive mood before therapy were shown to be correlated to a QoL- change under treatment and in the phase of rehabilitation (Wan Leung et al. 2011, Langendijk et al. 2008, Hammerlid et al. 2001b). Long- term data was rarely reported (Murphy et al. 2007).

The aim of this study was to find potential predictors for QoL in the acute phase after multimodality treatment in HNC- patients. A prospective clinical trial was designed and initiated by PD Dr. Silke Tribius in April 2009 in the Department of Radiation Oncology of the University Medical Center of Hamburg- Eppendorf (UKE), Germany.

2.2 Scientific overview

2.2.1 Health- related quality of life

2.2.1.1 Definition

Quality of life was defined by the WHO in 1946 as follows:

"Health- related quality of life is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broad ranging concept incorporating in a complex way the persons' physical health, psychosocial state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment" (WHO 1998).

If the term "health- related quality of life" (QoL) is used, the impact of a disease, disability, disorder or treatment on a person's perception of these criteria is commonly referred to quality of life. Hence, QoL as well as quality of life in general is a subjective and multidimensional construct (Ringash and Bezjak 2001).

The perception of QoL differs in every individual person depending on many factors as stated in the definition by the WHO. Thus, QoL is predominantly an individual's perception. The measurement of this and an eventual comparison to other people's individual perception was often criticized because of the various disturbances in assessing it (Bullinger et al. 1993, Rogers et al. 2007). In 1992, Bjordal and Kaasa proposed a model of the perception of subjective well- being. This model is shown in figure 1.

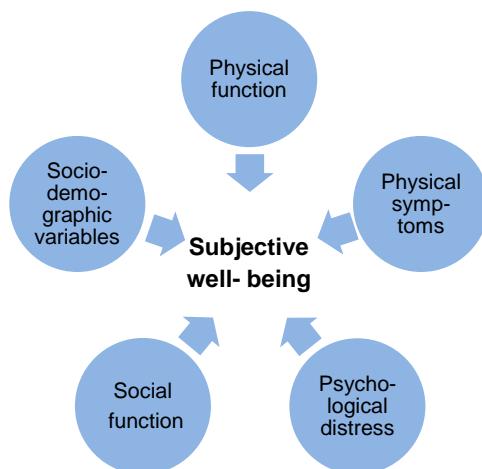


Figure 1: Factors influencing the subjective well- being (from Bjordal and Kaasa 1992).

2.2.1.2 Historical considerations

The WHO- definition (1946) showed early influences of patient's perception into the medical world. Health was described "not merely by the absence of disease and infirmity, but additionally by physical, mental and social well- being" (WHO 1946). In the following decades, research in oncology (e.g. Karnofsky and Burchenal 1949, Spiers et al. 1975) and chronic diseases (e.g. Forrest 1976) developed and applied various ways to evaluate QoL- data. Later on, the implementation of QoL- assessment into medical practice was in the focus of clinicians (Joyce et al. 2003). Insofar, physicians judged outcomes of treatments no more by technical and clinical parameters alone but also by psychosocial values.

For medical research, high- quality measurement instruments were required. When the development of these instruments started in the second half of the last century, a generally accepted definition for QoL itself was not yet found (Aaronson 1989, Bullinger et al. 1993). Although the psychometric evaluation was oftentimes not satisfying, many different instruments were developed and applied (Anderson et al. 1996). This accelerated development might picture some professional's feeling, that QoL- improvement made and makes "health care the basic humanistic transaction" (WHO 1998).

2.2.1.3 Aims of quality of life research

Depending on the discipline and target, in which QoL is examined, different emphases can be made:

- In clinical research, QoL is one under three parameters to judge treatment outcome, next to therapy- efficacy and adverse effects (Güthlin 2006).
- In public health care, particularly the confrontation to demographic aging raised interest in QoL- data: Arising numbers of people with chronic diseases and better possibilities to treat those conflicted limited financial resources. This led to the implementation of "quality- adjusted life years" (QALYs) into research in order to weigh the cumulative QoL- gain after a medical intervention (Smith 1987). In the following, a judgment of the cost- effectiveness of treatments by the resulting "costs per QALY" was and is discussed. Following this, today's public health care policies provide predominantly primary and secondary prevention of disease strategies affecting long- term QoL (Smith 1987).

- In personal life planning, a high everyday- QoL is an important goal – according to a study by Bullinger and Hasford (1991) in a German sample.
- In politics, QoL- data serve as a parameter for social well- being. Existential questions arise in this field: high and furthermore growing QoL- expectations (yielding to the prosperity of western industrial nations) face limited resources and financial reserves (Deutscher Bundestag 2013). Thus, e.g. the German Bundestag requested in 2010 for a committee of inquiry called “Wachstum, Wirtschaft, Lebensqualität – Wege zu nachhaltigem Wirtschaften und gesellschaftlichem Fortschritt in der Sozialen Marktwirtschaft” (Deutscher Bundestag 2013) (“Increase, economy, quality of life – pathways of sustainable economics along with social progress in a social market economy”).
- In economics, personal QoL is viewed competitively to the economic progress of affiliated groups (Galbraith 1964). In contrast, companies advertise their products often by promising a better well- being to customers after application or use (Kroeber- Riel et al. 1999).

Monitoring QoL in clinical settings in medical research can improve medical care in different dimensions according to Sayed and colleagues (2009): It can help to

- understand patient’s problem prioritization (particularly when many problems exist as in HNC),
- picture patient’s preferred outcome goals,
- investigate change and response under treatment,
- increase awareness of health care providers towards patient’s concerns,
- develop informed rehabilitative and patient educational services.

Therefore, not only the clinical setting, but also staff training, reviewing and improving care for the future become more patient- focused if QoL is assessed.

2.2.1.4 Quality standards in quality of life measurement

To provide high quality of QoL- data, questionnaires should fulfill different psychometric values (according to Aaronson 1989, Ringash and Bezjak 2001):

- *Objectivity* assures that test results are independent of the experimental set- up (e.g. study manager, measuring instruments and analytical methods).
- *Reliability* (measureable e.g. as internal consistency or test- retest- reliability), assures the stability of results in repeated measurements.

- *Validity* (also known as construct- validity), answers the question: “Does the instrument measure the subject it is supposed to measure?”
- *Sensitivity* answers the question: “Is a change in the observed subject pictured in the instrument’s result?”

Additionally, most scientists agree nowadays that questionnaire completion should be performed in self- administration, because patients “experience their QoL” and therefore they are the best “experts in rating” it (Bullinger and Hasford 1991). If a translated questionnaire version is applied, back- translation and testing should have been done to ensure the psychometric criteria also for the translated version (Anderson et al. 1993). Ringash and Bezjak (2001) stated that these values should have been shown in field testing among a sufficient number of patients to guarantee high quality results in this sample. Sayed et al. (2009) proposed an ideal QoL- instrument to contain an overall score as well as domain scores and to have no ceiling or floor effects (data crowding in one extreme of the scale, compare 2.6.4).

2.2.1.5 Instruments for measuring quality of life

Several instruments have been developed for QoL- measurement. As described in 2.2.1.1, QoL is a highly complicated construct. For measuring it as well as comparing it to other’s QoL, it is necessary to reduce it to a feasible size e.g. in questionnaires. Covering all the QoL- influencing domains would be a very detailed and time consuming way of QoL- assessment that is often not feasible in clinical routine practice (Sprangers et al. 1998). That is, why different instruments for QoL- assessment, each focusing on special domains of the construct, have been developed in the last decades (Tschiesner et al. 2008). Furthermore, this problem explains also why a standard QoL- instrument does not exist (Trotti et al. 2007, Sayed et al. 2009, Tribius and Bergelt 2011): Depending on the emphasis of a study, different instruments, a combination of them or even a combination with other (e.g. clinical) parameters or instruments can be suitable.

Despite the varying content of the instruments, five basic variables appear in most of the QoL- questionnaires (from Sayed et al. 2009): biological/ physical variables, symptoms, functioning, general health perception and health- related QoL.

Different types of QoL- questionnaires can be distinguished (as pictured in figure 2).

Generic questionnaires

contain **major health aspects**.

examples:

MOS- (Medical Outcomes Study) Short Form- 36.

WHOQOL (World Health Organization-Quality- Of Life- instrument).

Sickness Impact Profile.

Specific questionnaires

contain **health aspects in special situations**.

Disease- specific

Contains items, which are particularly relevant to a disease and its treatment.

Site- specific

Contains frequently appearing problems caused by a special disease- site (e.g. head and neck for HNC) and treatment.

Domain- specific

Contains dysfunctions of domains and related problems.

Treatment- specific

Contains issues and problems related to a particular treatment.

Symptom- specific

Contains issues caused by a symptom and frequently appearing disabilities.

examples:

EORTC- QLQ-C30.

FACT-G.

examples:

QLQ-H&N35.

UWQOL (University of Washington QoL questionnaire).

examples:

Voice- related QoL questionnaire.

MD Anderson Dysphagia inventory.

examples:

UWQOL for surgical patients.

Quality of Life Radiation Therapy Instrument - Head and Neck Module (**QOL-RTI/H&N**) for radiotherapy patients.

examples:

Brief pain inventory.

Brief fatigue inventory.

Figure 2: Types of QoL- questionnaires (according to Sayed et al. 2009).

Some questionnaires are difficult to group as they belong to more than one category (e.g. QOL- RTI/H&N is cancer-specific and treatment- specific); these are listed in one of the possible categories.

Generic questionnaires evaluate general QoL (including functioning, physical well-being and social relationships) without focusing intensively on specific problems (Bullinger and Hasford 1991). These instruments can explore QoL in any possible situation and they allow comparison between different groups as e.g. diseased and healthy people (Bullinger and Hasford 1991). Because of the non- specificity of items, the sensitivity for specific problems – particularly in case of illness – is not very high (Aaronson 1989). Especially, QoL- reducing problems of diseased people are often underrepresented in generic questionnaires and can lead to a (relatively) overestimated QoL- scoring compared to healthy people, because these special problems are not in the focus of interest (Aaronson 1989).

Specific QoL- questionnaires address people with specific problems. Therefore, they focus on specific items and may underreport other QoL- influencing parameters. People suffering from these specific problems are able to be judged more exactly in their QoL. However, comparisons to the general populations are problematic, because issues resulting in a reduction of QoL in healthy people often remain underrepresented - they are out of focus (Aaronson 1989). The more specialized a questionnaire becomes, the less applicable it will be for a generalization. Depending on the population they refer to, different kinds of specific questionnaires have been developed (shown in figure 2).

Disease- specific questionnaires focus on patients suffering from a certain disease (e.g. Quality of Life Scale (QOLS) addressing patients with chronic illness (Burckhardt and Anderson (2003)). Cancer- specific questionnaires also belong to this group, as for example the core version of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (called QLQ- C30 in the following), the Functional Assessment of Cancer Treatment (FACT) - General questionnaire (FACT-G) and the Quality Of Life - Radiation Therapy Instruments questionnaire (QOL- RTI). These instruments deal with cancer- and cancer- treatment- specific items and symptoms (Ringash and Bezjak 2001, Tribius and Bergelt 2011). A comparison between patients suffering from different subtypes of cancer is possible with these instruments but without specifying their cancer- subtype- specific problems in- depth. As a result, these issues might remain underreported.

Tumor- site- specific questionnaires form a second subgroup of specific QoL- questionnaires. They are primarily focused on site-, treatment- and symptom- specific problems of a particular cancer- subtype (Tribius and Bergelt 2011). The EORTC-

Quality of Life Questionnaire for head and neck cancer (called QLQ- H&N35 in the following) and the FACT- H&N (Functional Assessment of Cancer Therapy- Head and Neck Version) belong to this subgroup. These questionnaires are highly sensitive for site- specific cancer- symptoms, complications, side effects of treatment and functional limitations.

Domain-, treatment- and symptom- specific instruments are other specific QoL- questionnaires. Specific symptoms and problems appearing in subgroups are explored; application in non- concerned samples might give a blurred picture of their QoL.

Combination of a more general QoL- instrument to a specific instrument allows comparison of general issues between different samples but also provides specific information (Aaronson 1989, Bullinger and Hasford 1991, Bjordal et al. 1994a, Sprangers et al. 1998). Some questionnaires have already been designed for combined application (e.g. EORTC- questionnaires, FACT- questionnaires).

2.2.1.6 Analyzing quality of life data

Problems in interpreting QoL- data can be a problem due to several issues:

The theoretical construct of QoL defined by the WHO (1946) depends on a wide range of health- related, cultural, spiritual, economic, social, lifestyle- related and environmental influences. Often, these influences are not considered. They are so numerous that implementation of all of them is not feasible (Bullinger 2006). However, patients usually rate these items differently, so that similar answers do not necessarily mean, that patients feel the same. Vice versa, different results must not be interpreted as real differences for patients (Güthlin 2006). Accumulated QoL- data can give information about tendencies in overall behavior and perception. Although interactions, misunderstandings in completing questionnaires and weighted ratings result from differences in the individual perception, research in QoL has gained a high importance in modern medicine. On the one hand, QoL- research has to try a sufficient generalization to allow comparisons. On the other hand, it has to detect specific issues and problems of patients. The challenge is to take care of these interactions and to pay attention to the resulting limitations.

In medical research, studies often use specific questionnaires to pay attention to special issues patients might have. Nevertheless, it is possible, that the specific and subjective QoL- determining issues are not necessarily pictured. For example, a HNC-

patient can reach a relatively high QoL in a HNC- specific questionnaire, but indeed feels having a low QoL because his whole family died recently in an accident. This patient's QoL is determined predominantly by his social situation and not by his health status. Although he is seriously diseased, a specific QoL- questionnaire will not give a real assessment of his QoL. Measuring QoL in a clinical setting as in cancer treatment always tends to create a relationship between the medical situation and QoL/ QoL-changes (Sayed et al. 2009).

Vice versa, generic questionnaires picture a big variety of possible influences on QoL, but often they cannot provide the information that is necessary to mark the point of interest for QoL- improvement in diseased people (Le Pen et al. 1998), as discussed in detail in 2.2.1.5.

Another challenge in QoL- research is the fact that patients with highly disabling symptoms are sometimes very much focused on these. They are not likely to realize an increase in "general" QoL as long as they feel tortured by these specific symptoms (Sayed et al. 2009). These coping processes commonly interfere in QoL- research (Güthlin 2006). Particularly, if QoL is assessed longitudinally over a long time, coping mechanisms often interfere so that patients develop a greater tolerance towards their symptoms. The resulting problem is called response shift (Güthlin 2004).

Schlenk et al. (1998) found higher QoL- scorings in patients with life- threatening conditions as opposed to patients with less severe/ chronic disease burden. These findings support that conclusions from comparing QoL- data between different groups should be drawn with caution.

2.2.1.7 Quality of life measurement in head and neck cancer patients

HNC- specific QoL- instruments have emerged relatively early in QoL- research. For example, QLQ- H&N35 was one of the first cancer- specific modules evaluated by the EORTC quality of life group (EORTC 2011b), first published in 1992 by Bjordal and Kaasa. One reason for this was probably that HNC patients suffer from a dramatic decrease in their well- being and body image caused by disease related symptoms, treatment and its side effects (Trotti et al. 2007). Each of the questionnaires has its advantages in content and application. All of them were tested for validity and reliability (Rogers et al. 2007, Tschiesner et al. 2008), but testing in sufficient sample sizes has not been accomplished yet for all of them. No single questionnaire reflects all issues of

HNC patients (Ringash and Bezjak 2001). A list of different QoL- instruments in HNC-research is shown in table 7.

Numerous clinical trials have already investigated QoL in HNC- patients using different instruments for assessment (Rogers et al. 2007, Murphy et al. 2007). QoL research in HNC- patients was and is complex due to specific problems. Application of different questionnaires or of different parts of one questionnaire often interdicts comparison of QoL- data (Murphy et al. 2007). Many studies in the past were biased because they were conducted in a cross- sectional design (Sayed et al. 2009). Small sample size oftentimes precludes significance for observed differences. However, HNC is not a very frequent disease (Bettag et al. 2010) and therefore it takes much effort to investigate larger sample sizes. Retrospective design or lack of randomization of patients was oftentimes another possible source for bias (Murphy et al. 2007). Long- term- data are rarely reported, because HNC is a life- threatening disease and still, half of the patients die from it within five years of treatment (Trott et al. 2007, Meyer et al. 2012). Many patients are lost to follow- up because of incompliance or death (Murphy et al. 2007). Inclusion and exclusion criteria show a great variance (different tumor subtypes, different therapies) which make a comparison between study results difficult (Murphy et al. 2007).

Properties of questionnaires	EORTC ¹	FACT ²	QOL- RTI ³	UW-QOL ⁴	HNQOL ⁵	PSS- HN ⁶	LORO ⁷	VHI ⁸	Xerostomia ⁹
Author(s)	EORTC-Quality of life-group	D. Cella et al.	Casey, Johnson	Weymuller	Terrell	List	Rogers	Benninger	Eisbruch
Number of items	65	38	39	12	30	21	40	30	8
Completion time (minutes)	22	10	20	5	8-10	n. a. ¹⁰	15	n. a.	5
Administration modus	Self	Self	Self	Self	Self	Interviewer	Self	Self	Self
Scaling	4-7 points Likert type/binary	5 points Likert type	10 points Likert type	5 points Likert type	5 points Likert type	5-11 points Guttman type	10 points Likert type	5 points Likert type	10 points Likert type
Time frame for answers (weeks)	1	1	1	1	4	n. a.	1	None	None
Available languages	Multiple	Multiple	English, Japanese, German, Chinese	Multiple	English	English	English	English, German, Polish	English

¹⁾ QLQ- C30 combined with QLQ- H&N35.

²⁾ FACT- G with FACT- H&N.

³⁾ Quality Of Life- Radiation Therapy Instruments, core questionnaire QOL-RTI combined with its Head and Neck module QOL- RTI HN.

⁴⁾ University of Washington Quality of Life questionnaires (Version 4).

⁵⁾ Head and Neck Quality of Life instrument.

⁶⁾ Performance status scales for HNC patients.

⁷⁾ Liverpool oral rehabilitation questionnaire (Version 3).

⁸⁾ Voice handicap index.

⁹⁾ Xerostomia- specific questionnaire.

¹⁰⁾ Not available.

Table 7: Comparison of a choice of QoL- instruments applied in HNC- research (modified from Tschiesner et al. 2008).

2.2.2 Head and neck cancer

2.2.2.1 Clinical presentation and risk factors

HNC is the sixth frequent cancer worldwide (Osthus et al. 2011). In Germany, 5% of malignant tumors in men and 1- 2% of those in women are localized in this region (Bettag et al. 2010). During the last years, a rising prevalence particularly for oropharyngeal cancer was detectable in Europe and North America (Mehanna et al. 2012). In Germany, the mean age at diagnosis varies between 55 and 65 years (Bettag et al. 2010). Histology shows nearly exclusively (>95%) squamous cell carcinoma and these tumors are known to develop from dysplastic lesions (Bettag et al. 2010). At the time of diagnosis, many patients have already tumor spread into the locoregional lymph nodes, meaning (i.e.) locally advanced head and neck cancer (LAHNC).

High doses and frequent consumption of alcohol or tobacco or both respectively and poor oral hygiene are the main known risk factors for the classic type of HNC (Bettag et al. 2010). Oral colonization with the human papilloma virus (HPV, mostly subtype 16) is another important risk factor to develop HNC, as Mork and colleagues published in 2001. In contrast to the classic risk profile, HPV- DNA- positive tumors have been predominantly found in the oropharynx and were not associated with the above mentioned, classical risk factors. HPV- associated HNC is considered a separate tumor (Mork et al. 2001, Gillison et al. 2008) and occurs predominantly in younger males. The incidence of these tumors has been increased during the last decades (Gillison et al. 2008, Näsman et al. 2009) which is assumed to be due to a general change in sexual behavior (early oral sex practice, multiple partners) (Gillison et al. 2008). Actually, up to 70% of all oropharyngeal cancer detected in Europe is HPV- DNA- positive (Mehanna et al. 2012). Impressive regional differences in HPV- infection- status have been shown e.g. between Northern America and Europe (Mehanna et al. 2012) but also between different regions within Europe (Hoffmann et al. 2012).

HNC is commonly staged using the TNM- system by the International Union Against Cancer (UICC) (currently 7th edition from 2009 (Sabin et al. 2009)). T stands for tumor size, N for nodal spread and M for distant metastases.

2.2.2.2 Treatment options and side effects

After establishing the diagnosis, every HNC- case is discussed in an interdisciplinary conference with experts in head and neck surgery, medical and radiation oncology,

diagnostic radiology and pathology. The aim of this tumor board is to recommend an individually adapted therapy strategy. Multimodal treatment has become the standard of care for HNC (Tribius et al. 2012a). One or a combination of two or more of the treatment modalities can be suitable depending on tumor site and stage (National Comprehensive Cancer Network (NCCN) - guidelines by Pfister et al. 2000, complemented by Pfister et al. 2013). In addition, the patient's performance status as well as comorbidities should be considered. The different possibilities are shown in figure 3.

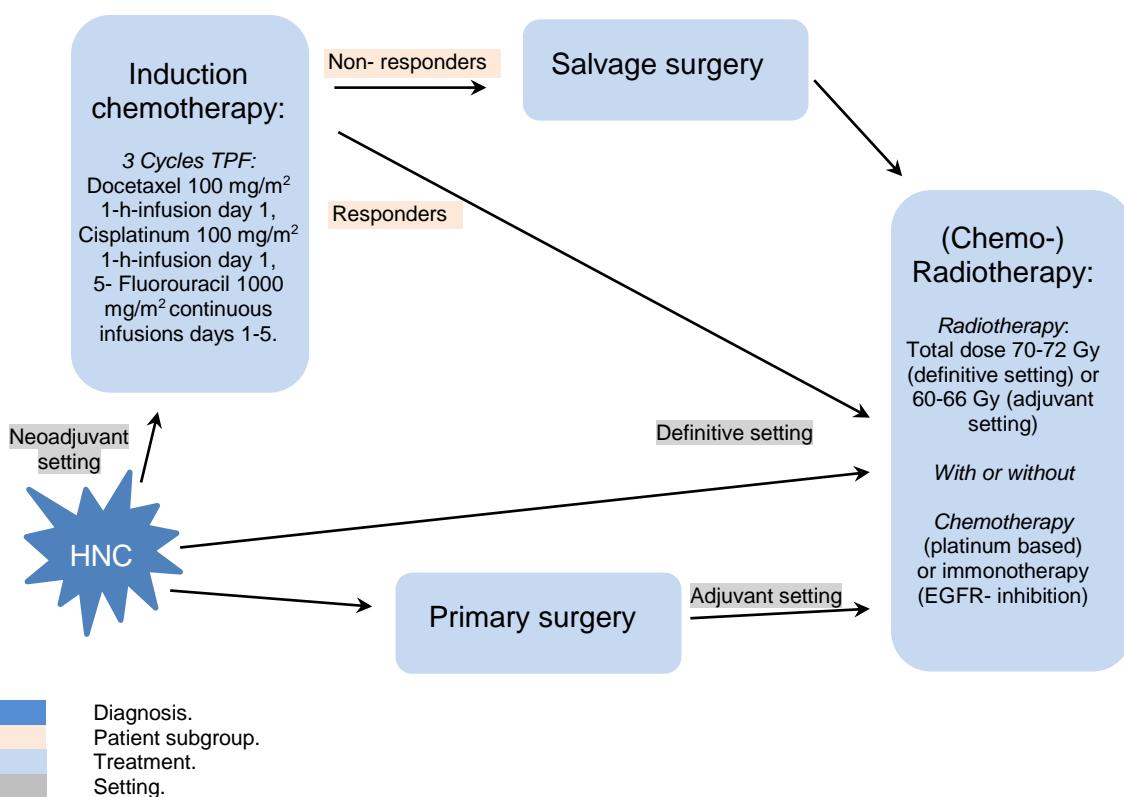


Figure 3: Treatment options in HNC.

Early stages of HNC can be treated with surgery alone (Bettag et al. 2010). In LAHNC, surgery is performed when the tumor is felt to be functionally resectable. Microsurgical techniques have been recently used allowing better organ and function preservation (Hinni et al. 2007). The classical radical neck dissection (RND) as the standard treatment for the neck in LAHNC has been replaced by less extensive procedures such as modified radical neck dissections (MRND) and selective neck dissections (SND). RNDs oftentimes left the patients with severe functional impairment such as partial

shoulder paresis after resection of the accessory nerve (Kuntz and Weymuller 1999, Nibu et al. 2010, Orhan et al. 2007, Hamoir et al. 2012).

If the tumor was found to be unresectable primary CRT is the standard of care (Pfister et al. 2000).

To improve treatment for patients whose survival and recurrence risk is increased after surgery, additional treatment i.e. adjuvant RT or chemoradiotherapy (CRT) can be worthwhile: A benefit from adjuvant RT or CRT has been proven for patients in a satisfactory performing status with extracapsular nodal spread and/ or remaining tumor cells in the resection margins (Bernier et al. 2004 and 2005, Cooper et al. 2004). Evidence for an increased risk in HNC because of increased T- stage 3 or 4 (classified according to Sabin et al. 2009), presence of vascular embolisms, perineural infiltrations and/ or lymph node affection at levels IV and V (in cases of oropharyngeal/ oral tumors) has not always been found but sometimes as e.g. by Bernier and colleagues (2004). The American College of Radiation (ACR) - criteria (Salama et al. 2011) stated also lymphovascular invasion, every lymph node involvement and bone involvement to define high- risk HNC. Low- risk tumors are defined vice versa.

Radiation therapy (RT) can be performed alone (e.g. in early stage HNC, Pfister et al. 2011) or combined with other modalities in LAHNC. If after surgery one of the above mentioned risk factors were identified on pathology, adjuvant treatment is recommended consisting of RT or CRT. The primary tumor as well as lymph node metastases usually receive a total dose of 70- 72 Gray (Gy); high risk regions for nodal spread receive 60 Gy and clinically unaffected locoregional lymph node areas receive 50 Gy (Pfister et al. 2000, Karstens et al. 2005).

In RT, Intensity modulated radiation therapy (IMRT) has become the standard of care over the past years (Bettag et al. 2009, Tribius and Bergelt 2011). IMRT uses computerized treatment planning processes and a computer- driven treatment delivery system to generate multiple small radiation beams of varying intensities to precisely irradiate a tumor/ target volume (Tribius 2012). The radiation intensity of each beam is controlled, and the beam shape changes throughout each treatment, allowing the radiation dose distribution to be conformed to the target volume while minimizing the dose delivered to the organs at risk (OAR) – particularly spinal cord, brain stem, salivary glands, optical nerves, inner ears (Wan Leung et al. 2011, Vergeer et al. 2009, Tribius 2012). A better QoL and disease- control in patients treated with IMRT

compared to conventionally treated patients has been repeatedly observed (Jabbari et al. 2005, van Rij et al. 2008, Wan Leung et al. 2011). However, it remains unclear, whether IMRT can also improve survival.

Systemic treatment in HNC, mostly cisplatin-based, has been shown to be most effective when given as concomitant chemoradiation (Pignon et al. 2009). Several schedules are being used depending on the institutional preference and/or comorbidities and performance status (weekly 30 or 40 mg/m² body surface area or 100 mg/m² body surface area every 21 days or daily 20 mg/m² during the first and fifth week of RT).

More recently, targeted therapies with EGFR-receptor- antibodies, particularly Cetuximab®, have emerged (blocking the epithelial-growth-factor-receptor, which is known to be overexpressed in most cases of HNC (Ishitoya et al. 1989)). EGFR-inhibition has been shown to improve HNC-survival in combination with RT compared to RT alone (Bonner et al. 2010). This kind of treatment is well established for metastatic or recurrent HNC (summed in the term of ‘advanced HNC’) (Burtness et al. 2005), but is also performed in cases of primary LAHNC (Pfister et al. 2011).

Generally, adverse side effects in cancer treatment are classified as ‘early’ if they appear under treatment or within 90 days after the end of treatment (LENT-SOMA-criteria (Late Effects on Normal Tissues, Subjective Objective Management Analysis) from 1992 by the National Cancer Institute (NCI 2009)). ‘Late’ adverse side effects are side effects persisting for more than 90 days or developing after that 90 day period.

In and after surgical treatment, nearby tissues are at risk to get hurt (esophagus, pleura, thyroid gland, nerves, salivary glands, teeth, swallowing and speaking structures) and may keep an impairment or loss of function (such as dysphagia, dysphonia/aphonia, hoarseness, reduced sensibility in mouth, loss of taste, shoulder or arm dysfunction). Bleedings, infections, circulation problems and thrombosis/embolia, cardiorespiratory troubles or organ dysfunctions can interfere. Wound healing may result in unaesthetic scarring or disfigurement and associated problems in social interactions (Forastière et al. 2001).

Typical early adverse side effects of RT in HNC are fatigue, radiation dermatitis and mucositis, sticky saliva, xerostomia and dysphagia and weight loss which oftentimes requires placement of a gastrostomy tube (Tribius and Bergelt 2011). Late side effects

of RT for HNC include xerostomia, dental decay, dysphagia, soft tissue fibrosis, thyroid dysfunction and osteoradiation necrosis of the jaw (NCI 2009).

Most common effects of the platinum- based chemotherapy include central emesis and vomiting, fatigue, mucositis, potential renal failure, impaired hearing and peripheral neuropathy (Karow and Lang- Roth 2011). As for all chemotherapeutic agents rapidly dividing cells are most attacked, resulting in mucositis and xerostomia, neutropenia/ pancytopenia with risk of severe infections or neutropenic fever, disturbance or loss of gonad function and hair loss (Lüllmann et al. 2003).

EGFR- inhibitors can cause an acneiform skin rash, allergic reactions and headaches (Bonner et al. 2010).

2.2.2.3 Treatment outcome and prognosis

Generally, overall and progression- free survival in patients with HNC depend on the initial extent of disease and the above (2.2.2.2) mentioned risk- factors (extracapsular extension of lymph node metastases, positive surgical margins) (Bernier et al. 2004 and 2005, Cooper et al. 2004). Forastière and colleagues (2001) calculated median survival times of LAHNC- patients depending on these risk factors (compare table 8).

Risk factors	Local/ regional recurrence within three years after therapy	Median survival
None	14%	5,6 years
Positive lymph nodes and/ or extra- capsular extension	27%	2,5 years
Positive surgical margin	49%	1,5 years

Table 8: Frequency of recurrence and median survival in LAHNC- patients depending on risk factors (from Forastière et al. 2001).

There is an increasing body of evidence that prognosis in patients with oropharyngeal cancer (OPC) is strongly influenced by the HPV- infection status. Nonsmokers with HPV- positive tumors were shown to have a 2- year overall progression- free survival rate of 90% (Rischin et al. 2010). In contrast, patients with HPV- negative oropharyngeal cancer had a 50% chance of tumor recurrence (Rischin et al. 2010, Ang et al. 2010, Tribius et al. 2010).

Several studies have shown that QoL is a predictive factor for survival in HNC- patients (Curran et al. 2007, Meyer et al. 2009, Osthuis et al. 2011): Patients with high initial

QoL- scores (measured before or after primary treatment), showed better survival outcomes than patients with a low score at this point in time.

Because medical research has increasingly focused on QoL- during the last decades (compare 2.2.1.2), numerous predictors for the QoL- development during and after HNC- treatment have been investigated and summarized in table 9.

QoL- predictor	Influence on QoL	References
Tumor site	Larynx: ↑ ¹ Hypopharynx: ↑ Oropharynx/ oral: ↓ ²	Wan Leung et al 2011 Alicikus et al. 2009 Fang et al. 2005 Hammerlid et al. 2001a Hammerlid et al. 2001b Hammerlid and Taft 2001
Age	younger: ↑ older: ↓	Wan Leung et al. 2011 Langendijk et al. 2008 Hammerlid et al. 2001b
Sex	Male: ↑ Female: ↓	Wan Leung et al. 2011 Hammerlid et al. 2001b
Tumor stage	Low: ↑ Advanced: ↓	Wan Leung et al. 2011 Alicikus et al. 2009 Hammerlid et al. 2001a Hammerlid and Taft 2001
Performance status (according to Karnofsky)	High: ↑ Low: ↓	De Graeff et al. 2000
Treatment	Unimodular: ↑ Combined: ↓	Wan Leung et al. 2011 Alicikus et al. 2009 Langendijk et al. 2008 De Graeff et al. 2000
Type of surgery	Conservative: ↑ Wide extend: ↓	Bjordal et al. 1994b
Type of radiation	IMRT: ↑ Conventional RT (2- dimensional RT or 3- dimensional RT): ↓	Wan Leung et al. 2011 Vergeer et al. 2009 Jabbari et al. 2005
QoL (HNQOL)	Satisfactory QoL: ↑ Poor QoL: ↓	Jabbari et al. 2005
Physical function (QLQ- C30)	Satisfactory phys. Function: ↑ Poor phys. Function: ↓	Hammerlid and Taft 2001
Depression	Non- depressive mood: ↑ Depressive mood: ↓	Hammerlid and Taft 2001 De Graeff et al. 2000
Anxiety	No anxious characteristic: ↑ Anxious characteristic: ↓	De Graeff et al. 2000
Type of induction- chemotherapy	Docetaxel plus PF ³⁾ : ↑ PF alone: ↓	Van Herpen et al. 2010
Xerostomia	Little extend: ↑ Marked extend: ↓	Langendijk et al. 2008 Jabbari et al. 2005
Family income	High annual family income: ↑ Low annual family income: ↓	Wan Leung et al. 2011

¹⁾ Improving influence on QoL- development.

²⁾ Reducing influence on QoL- development.

³⁾ Cisplatinum and 5- Fluorouracil.

Table 9: Predictors for post- treatment QoL- development in HNC- patients.

Although more intense treatment regimens established to improve outcome of HNC-treatment, Trott and colleagues showed in 2007, that there was no survival benefit in 13 HNC- studies evaluated between 1991 and 2000 by the Radiation Therapy Oncology Group (RTOG). According to these data, HNC- treatment schedule intensification has led to a fivefold increase in risk of serious adverse events without any prove for a survival benefit at all (calculated in TAME- analysis® (short- term toxicity (T), adverse long- term- effects (A) and mortality risk (M) generate an end score (E); compare figure 4). Lefebvre et al. (2012) recently published once again no significant survival benefit in long- term results of a highly intensified HNC- treatment protocol (5- year survival 33%, 10- year survival 13%).

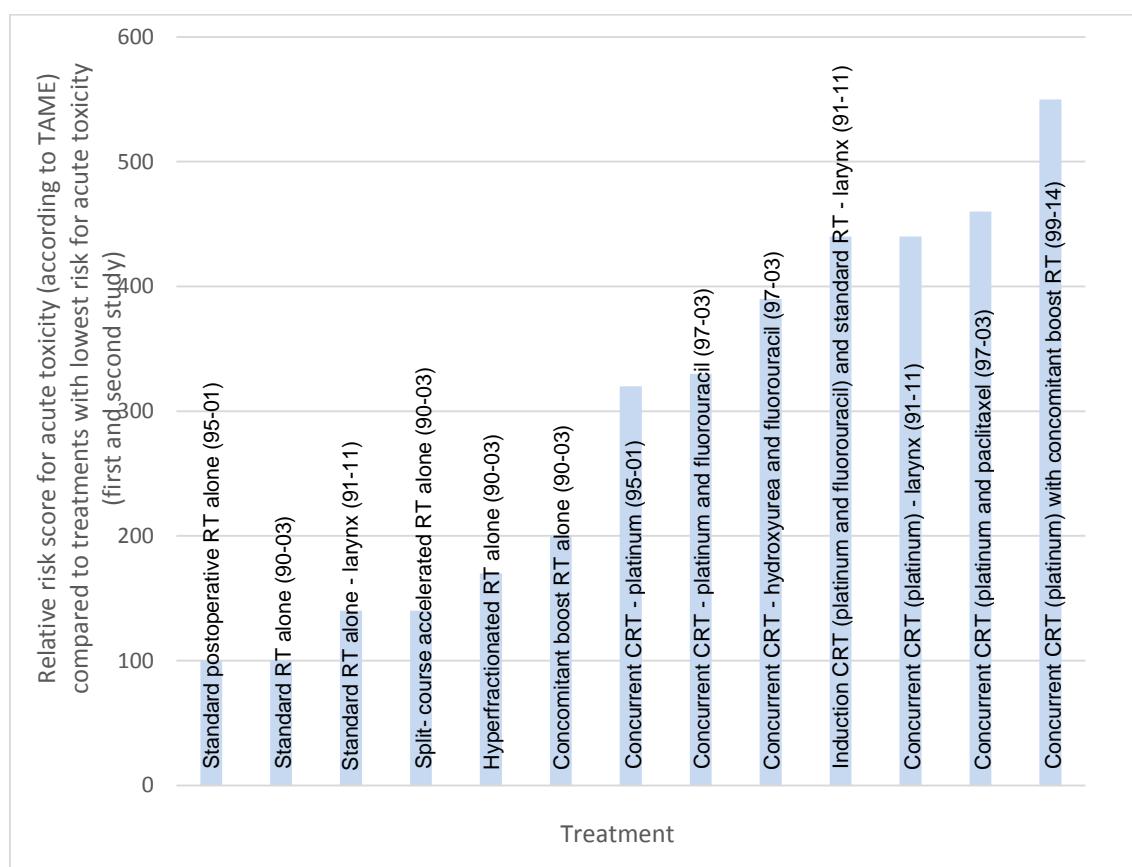


Figure 4: Acute toxicity in HNC- treatment according to the TAME- analysis (Trotti et al. 2007): 13 RTOG- trials between 1991 and 2000 (chronological order).

2.3 Methods

2.3.1 Patients

This prospective study recruited patients with newly diagnosed LAHNC before RT combined with or without chemotherapy ((C)RT) between April 2009 and May 2011 at the Department of Radiation Oncology of the UKE, Germany.

Patients included in the study had to have LAHNC to receive (C)RT with curative intent.

Patients had to sign the study specific informed consent (see 2.8.3).

2.3.2 Measuring instruments

2.3.2.1 Quality of life measurement

QoL was measured using the EORTC- instruments: the “core module” QLQ- C30 (version 3.0, EORTC 2011a) and the HNC- specific module QLQ- H&N35.

We used the German translation of the 3.0 version of the QLQ- C30, because it has shown high psychometric values in the past and is commonly used particularly in Europe, so that a comparison with results of other studies would be possible. The questionnaire has shown its high validity (Schwarz and Hinz 2001, Singer et al. 2009) as well as the original version (Bjordal et al. 2000).

Validity of the QLQ- H&N35 was also shown by Bjordal et al. in 2000. Singer and colleagues demonstrated in 2009 the validity of the German translation of this module.

Both questionnaires evaluate different function and symptom scales influencing QoL. Most answers are given on an ordinal scale and some items just allow a dichotomous manner of answering (“Yes/ No”). The resulting scores can range between 0 and 100 points. Different items are combined and summarized in functional and symptom scores. Higher absolute levels in functioning scores represent a better QoL (higher integrity of functions) whereas higher absolute levels in symptom- scores indicate reduced QoL (higher severity of symptoms) as shown in figure 5. Detailed information concerning content and calculation can be found in the publication by Tribius et al. (2012a). Osoba and colleagues (1998) proposed for the QLQ- C30 a minimum difference score of 10 points to represent a clinically meaningful difference.

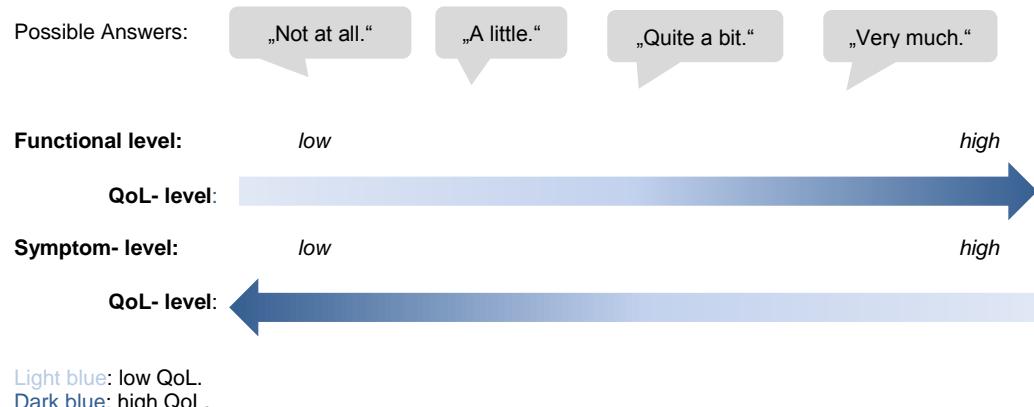


Figure 5: Score levels indicate diametrical QoL- levels for functioning and symptom scores in the EORTC- questionnaires (except dichotomously answered items).

The reference data to which we later compared our patients' QoL- data were published by Schwarz and Hinz (2001). The publication of Tribius et al. (2012a) describes the sample characteristics and methods of Schwarz' and Hinz' study in detail.

2.3.2.2 Socioeconomic and medical factors measurement

To evaluate socioeconomic and medical factors potentially influencing QoL, self-created questionnaires were used including variables concerning patient's social, educational and economic background and life- style- influences on health (see 2.8.4). Other information was collected including radiation data, details of treatment and disease- related items (e.g. tumor stage, performance status, nutritional support) with a potential QoL- reducing value (see 2.8.5 and 2.8.6).

2.3.3 Study design

The study was designed to be a prospective, non- interventional therapy- study in a single institution. Approval was obtained by the local ethics committee (see 2.8.1 and 2.8.2).

As shown in figure 6, data were collected per protocol at three specific points in time: At baseline before (C)RT (called T1 in the following), at the end of (C)RT (T2) and at first follow-up at six to eight weeks after completion of (C)RT (T3). All questionnaires were filled in by the patients during their appointments at the Radiation Department.

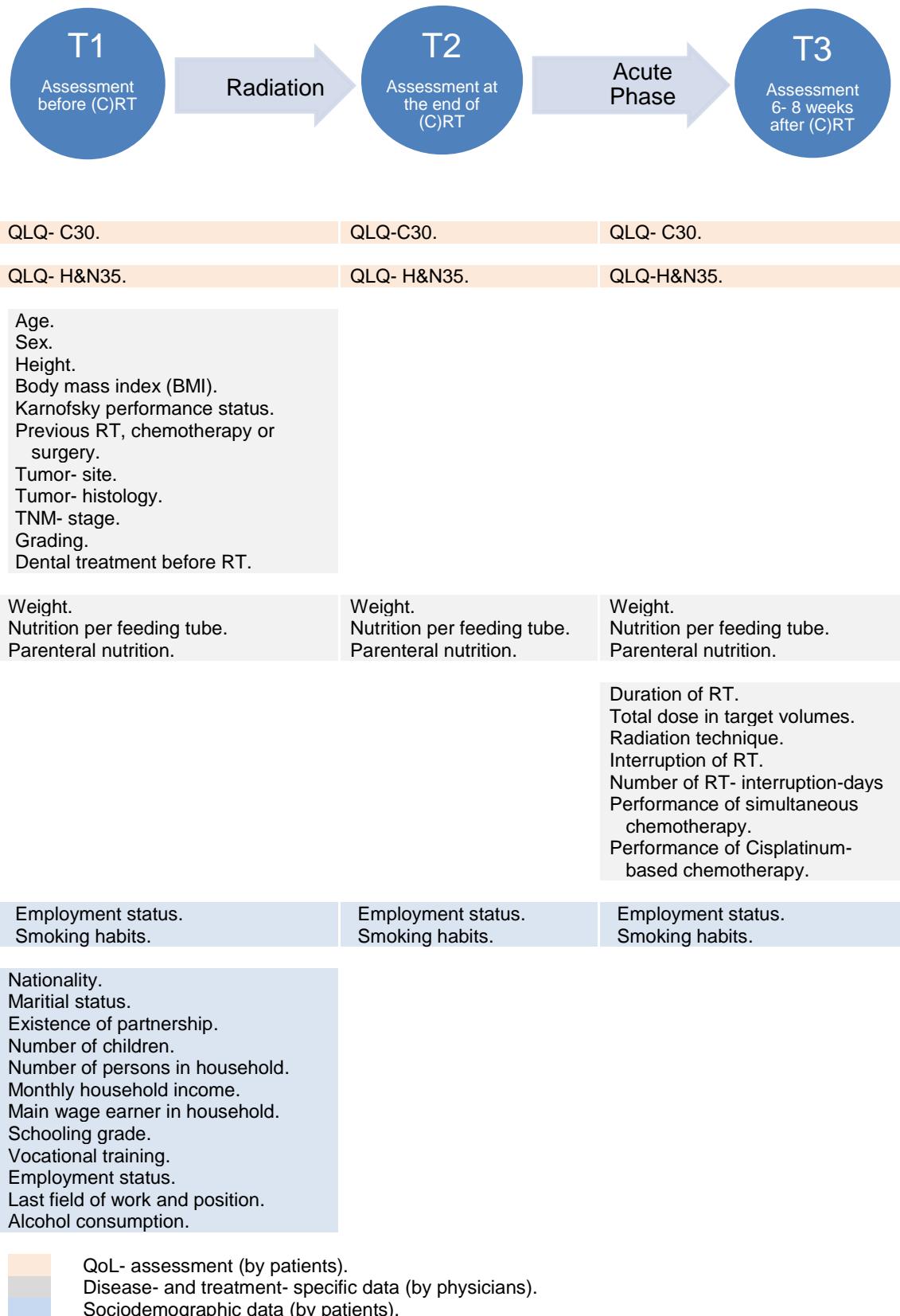


Figure 6: Assessment times and data collection.

2.4 Data analysis

According to the EORTC- scoring manual, mean scores (\pm standard deviation (SD)) were calculated for both QoL- questionnaires. We used the Windows- SPSS® program (version 15.0) for data analysis. Missing QoL- data were treated according to the EORTC- manual.

First, we looked at QoL- data for men and women by analysis of variance (ANOVA) (see table 1 at Tribius et al. 2012a). Then, we compared these results to the reference data of Schwarz et al. (2001) using one- sample t- tests (see table 2 in Tribius et al. 2012a). For the comparison, we chose the data of the 60- until 69- year- old subgroup of the reference sample, because the biggest group of our interviewees (48%) belonged to this age group, too. For our patients of another age, we assumed a balance of elderly and younger patients.

The changes in QoL under therapy as well as until the first follow- up were analyzed by ANOVA (see table 4 in Tribius et al. 2012a).

To examine a potential relationship between potential QoL- predictors and the QoL measured at T3, we used a univariate analysis. The potential predictors were separated dichotomously as mentioned (Tribius et al. 2012a). In this analysis, global health status after RT was the dependent variable and the independent variables were the potential predictors. We noted potential QoL- predictors in an interval scaled manner if possible (e.g. age, body mass index), but in most cases they had to be nominal scaled (e.g. chemotherapy vs. no chemotherapy, marital status, smoking status).

Secondly, we performed a multivariate stepwise regression. Because we knew from Schwarz' and Hinz' results (2001) that sex and age might influence QoL, we performed this analysis after having separated our results by sex and age.

2.5 Results

2.5.1 Patient characteristics

Among 99 patients enrolled in the study, data of 95 participants could be analyzed (see table 1 in Tribius et al. 2012a). One patient died on a myocardial infarction shortly after having completed CRT. Two patients were lost to follow- up before T3 because they relocated. Another patient refused further follow- up visits without a specific reason. Thus, data analysis was performed on 30 (31.6%) female and 65 (68.4%) male patients. Mean age was 59.1 years (SD 8.5) and 65 patients (67.7%) had a Karnofsky performance status of 80% or even better. At this point in time, 30 patients (30.9%) were current smokers, 50 patients (51.1 %) were former smokers and 18 patients (18.1%) reported never having smoked before. Pretreatment regular alcohol consumption was indicated by 9 patients (9.5%) and occasional alcohol consumption by 33 patients (34.7%). 54 patients (55.8%) denied regular alcohol consumption.

Pathology of the malignant tissue showed in 87 cases squamous cell carcinomas (91.6%). In 34 Patients (35%) the primary tumor site was located in the oral cavity (see figure 7), in 32 patients (32.9%) in the oropharynx, in 17 patients (17.5%) in the hypopharynx/ larynx and in 7 patients (7.2%) in the nasopharynx. Less common sites were nasal cavity or paranasal sinuses in 3 patients (3.1%) and carcinoma of unknown primary (CUP) in 4 patients (4.1%).

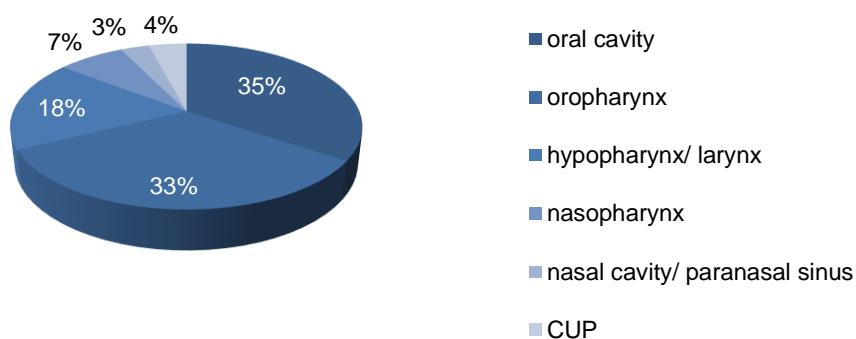


Figure 7: Tumor- site.

All patients showed locally advanced disease stage: 47 patients (48.4%) had stage T3- or T4- diseases (according to the TNM- classification), 42 patients (43.2 %) were staged T1 or T2. 36 Patients (40%) had N0/N1 disease and 54 diseased (60%) were diagnosed N2/N3. The majority of tumors were moderately or poorly differentiated (49 cases of G2- grading (51.6%) and 45 cases of G3- grading (47.4%)).

The data about the medical treatment (see table 1 in Tribius et al. 2012a) showed that 73 patients (77%) were treated adjuvantly and 19 patients (20%) had induction-chemotherapy prior to (C)RT. 55 Patients (57.9%) received combined (C)RT. Most patients received IMRT (see table 10): 55 patients (56.2%) were treated using the Tomotherapy® machine (computer- tomography based system) and 27 patients (28.1%) were treated on a linear accelerator. Only 15 patients (15.6%) received 3-dimensional conformal radiation therapy (3D- CRT).

Characteristic	N ¹⁾ (%)
Radiation technique	
3D- CRT	15 (15.6)
Tomotherapy®	55 (56.2)
Linear accelerator	27 (28.1)

¹⁾ population

Table 10: Radiation technique (n=95).

Before RT, we calculated no statistically significant differences between male and female patients for any of the disease- and therapy- specific, sociodemographic or life-style- variables shown in table 1 (all probability measure (p) indices > 0.001).

2.5.2 Quality of life before radiation treatment (baseline) (T1)

Before RT (compare table 2 in Tribius et al. 2012a), patients ranked their QLQ- C30 global health status at 47.2 points. We found the highest functioning score in physical functioning (76.2 points) and the lowest score in this category for emotional functioning (54.2 points). The highest absolute scores were found in our patients for the items feeling to be ill (45.4 points), sexuality (45.4 points) and opening mouth (43.5 points). Lowest symptom scores were indicated for nausea/ vomiting (6.7 points, SD 15.1) and constipation (9.8 points, SD 24.7). The additional items weight loss and the use of pain killers were reported by the majority of patients (64 patients (66.7%) and 58 patients (61.7%), respectively). Supportive care to improve their nutrition had been given to 20 patients (22.0%) as nutritional support and to 26 patients via feeding tube (28.0%).

Analysis of the QLQ- H&N35 before (C)RT (compare table 3 in Tribius et al. 2012a) brought up highest symptom scores (all 40 points or more) for the items feeling to be ill (45.4 points), sexuality (45.4 points), opening mouth (43.5 points), sticky saliva (41.4 points), coughing (40.7 points), social eating (40.4 points) and swallowing (40.0 points). Lowest scores (all less than 30 points) were found for social contact (22.4 points), sensual limitations (23.8 points) and the teeth scale (28.5 points).

We found in our sample, that diseased women reported a higher burden in functioning scales and higher symptom scores compared to diseased men. For example, social function was reported 12.4 points lower and physical function 9.7 points lower than in male patients. The highest gender- specific differences in symptoms were found for fatigue (11.1 points more in the female patient subgroup) and insomnia (11.5 points more in the female patient subgroup). Only the indications of weight loss and financial problems appeared more often in male patients. ANOVA revealed a tendency in the male subgroup to report more often weight loss ($p=0.003$), but statistical significance for all these gender- specific differences was rejected (all $p>0.001$).

2.5.3 Quality of life at the end of radiation treatment (T2)

After RT, our HNC- patients reported a decrease in global QoL, worse functioning and an increased symptomatology compared to the pretreatment assessment as analysis of the QLQ- C30- results show (see table 4 in Tribius et al. 2012a). Highest differences in functioning scales were found for role (−19.5 points), social (−18.7 points) and physical function (−16.6 points), pictured in figure 8. Patients reported also a reduced global QoL (−11.3 points) and more limitations in cognitive (−9.9 points) and emotional function (−8.5 points).

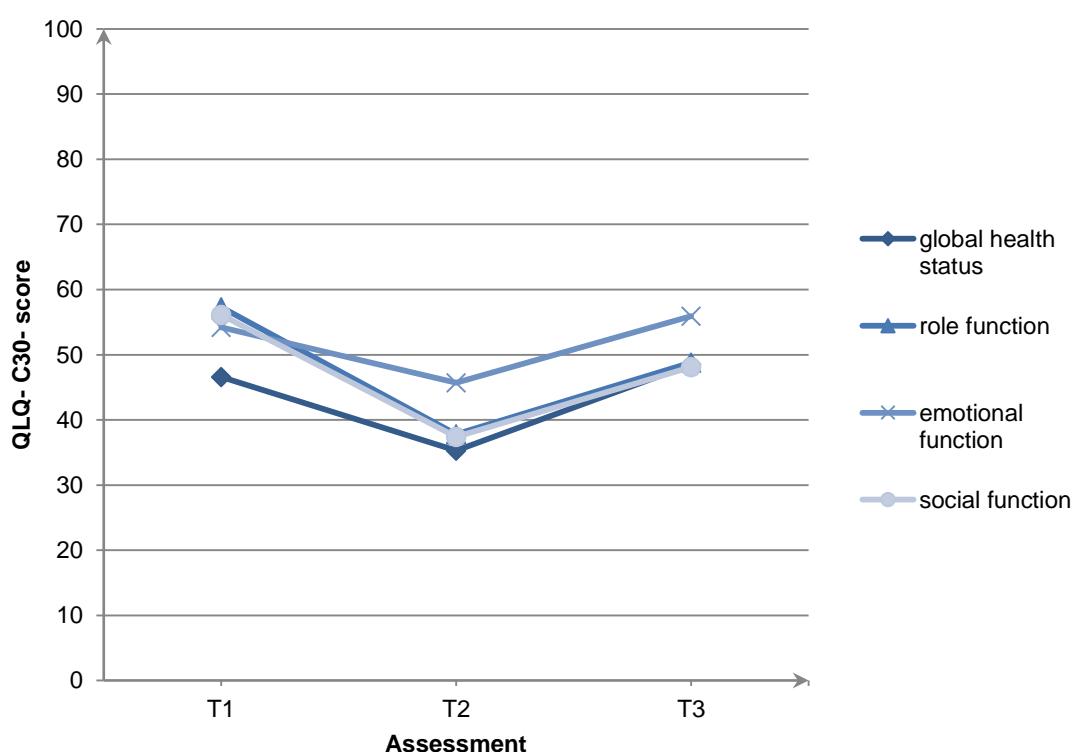


Figure 8: Changes in global health status and functions (QLQ- C30).

The interviewees indicated an increase in most of the cancer- specific symptoms. The highest absolute increase was found for loss of appetite (+34.1 points). The items nausea/ vomiting (+27.3 points), fatigue (+25.9 points), constipation (+20.6 points), pain (+16.2 points) and insomnia (+12.3 points) were also reported markedly more often compared to T1 (figure 9).

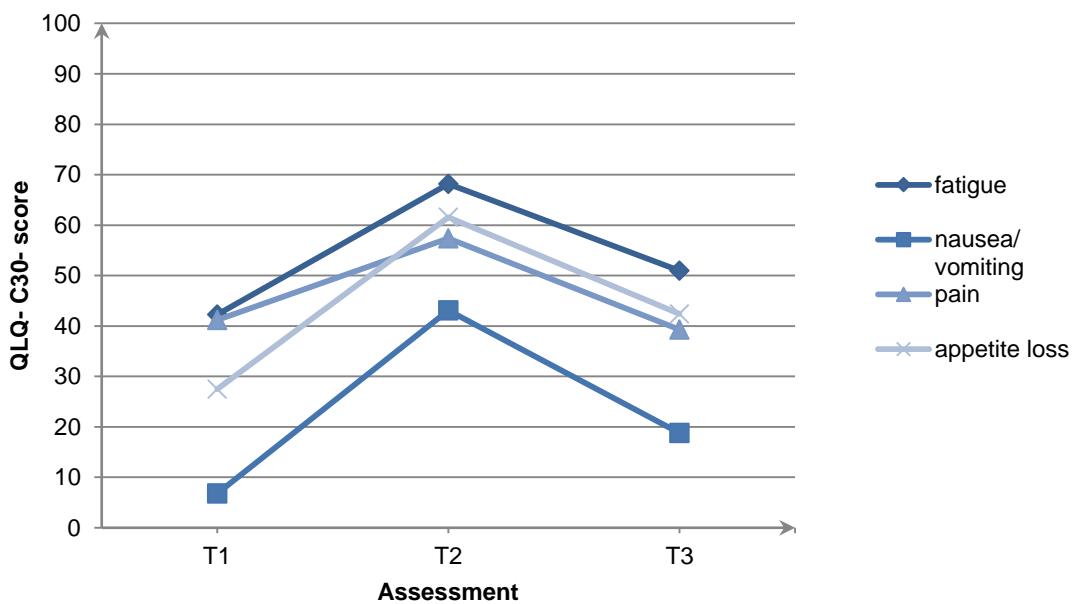


Figure 9: Changes in chosen cancer- specific symptoms (QLQ- C30).

Results of the second inquiry per QLQ- H&N35 showed that most of the HNC- specific symptoms were reported more often than before RT. All of the multi- item scales showed an increase, under which the highest was seen for sensual limiting (+35.8 points). Patients felt more problems in swallowing (+29.7 points), social eating (+26.9 points), speech (+26.0 points), pain (+25.0 points), sexuality (+23.4 points) and social contact (+15.1 points) than before RT (figure 10).

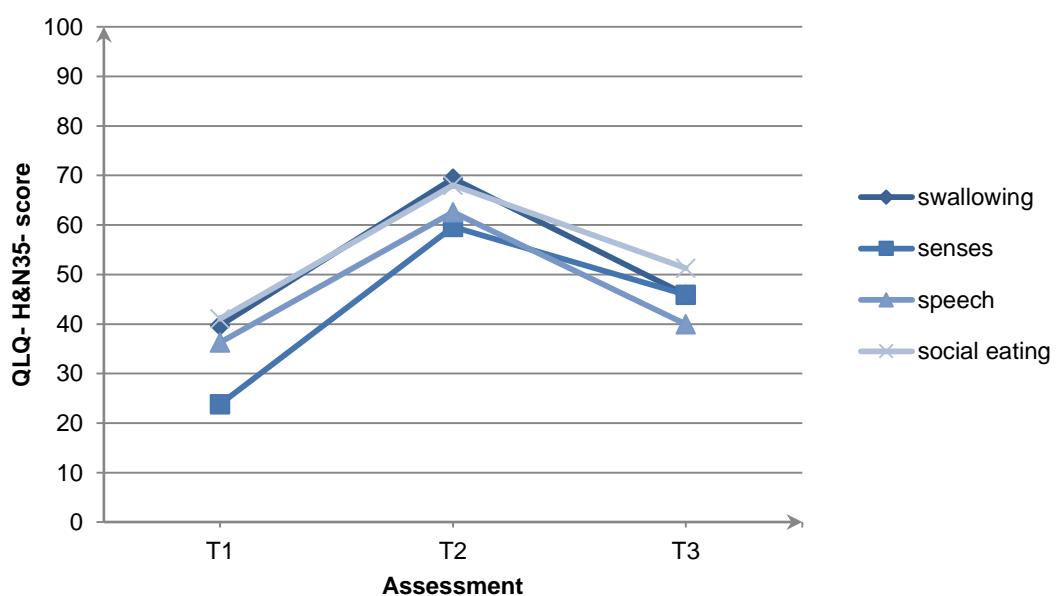


Figure 10: Changes in HNC- specific- symptoms, selection (QLQ- H&N35).

An increase was also marked for all of the QLQ- H&N35 single-items: Patients reported more often problems with sticky saliva (+44.4 points), dry mouth (+35.5 points), opening mouth (+23.2 points), feeling ill (+23.0 points), coughing (+22.3 points) and teeth (+2.3 points) (figure 11, selection).

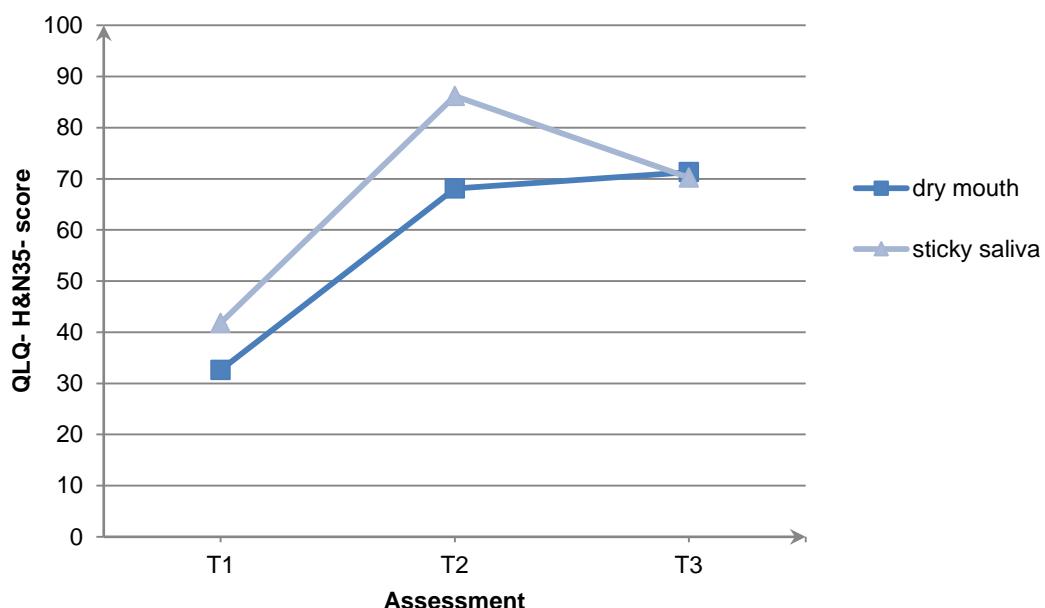


Figure 11: Changes in dry mouth and sticky saliva (QLQ- H&N35).

Analyzing the QLQ- H&N35- additional items, we observed an increase in nutrition via feeding tube (+50.0%) and in nutritional support (+24.2%). Patients reported more about the application of pain killers (+9.2%) and about weight loss (+7.3%), whereas weight gain was less often indicated (-8.4%) as illustrated in figure 12.

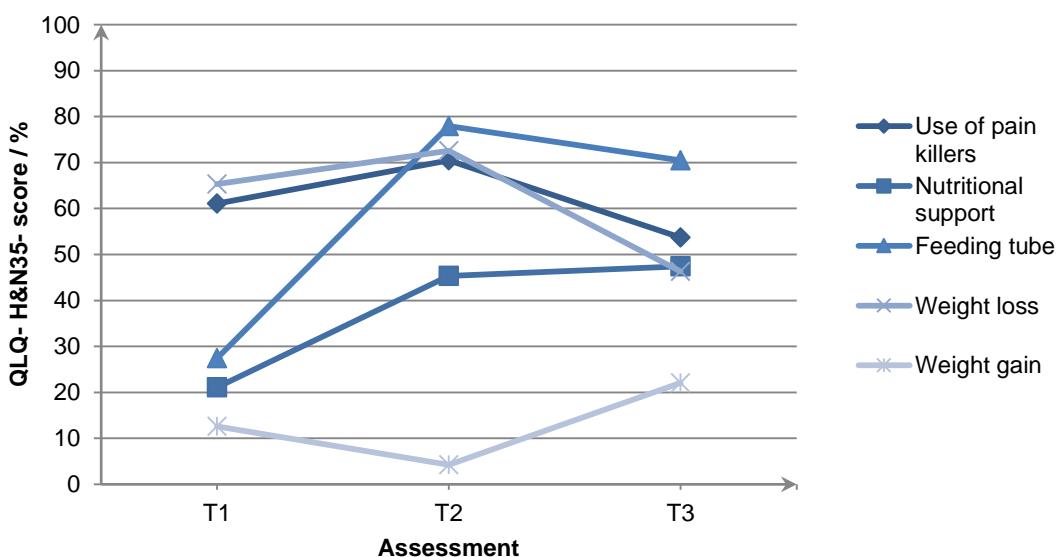


Figure 12: Changes in additional HNC-specific issues (QLQ- H&N35).

2.5.4 Quality of life at first follow- up (T3)

The third assessment (six to eight weeks after completion of RT) showed a trend towards recovery of function and symptoms.

At T3, we observed a recovery in patients' global QoL (1.9 points higher than initially and 13.4 points higher than after RT, see figure 8) and in their functional status: Physical, role and social function were still reduced compared to the initial levels (physical function -8.0 points; role function -8.5 points; social function -8.0 points). These items improved compared to the assessment at the end of RT (physical function +8.6 points; role function +14.9 points; social function +10.7 points). Emotional function scored in the third assessment 1.7 points over the initial measurement and 10.2 points higher than directly after RT. A decrease of 1.8 points remained in cognitive function compared to the assessment at baseline (+8.3 points compared to the second inquiry). Statistical significance for changes in global QoL, physical, role and social function were confirmed by analysis of variance ($p<0.001$). In contrast to this, the changes in emotional and cognitive function missed the evidence of significance ($p=0.001$).

Considering the cancer- specific symptoms, we also observed a tendency for recovery compared to the second inquiry (compare figure 9): A score reduction was found for loss of appetite (-19.2 points), pain (-18.1 points), fatigue (-17.2 points), nausea/vomiting (-15.3 points), insomnia (-13.4 points), constipation (-10.3 points), dyspnea (-6.4 points) and diarrhea (-6.4 points). Financial problems were reported unaltered compared to T2. Comparison of these symptom scores to baseline showed, that most patients had felt an increase in symptoms: loss of appetite (+14.9 points), nausea/vomiting (+12.0 points), constipation (+10.9 points), fatigue (+8.7 points), financial problems (+6.3 points) and dyspnea (+2.2 points). A slightly lower symptom score, representing less problems than at baseline, was observed for the items pain (-1.9 points), diarrhea (-1.4 points) and insomnia (-1.1 points). ANOVA showed a statistical significance ($p<0.001$) for the changes over time concerning fatigue, nausea/ vomiting, pain, insomnia, loss of appetite and constipation.

Analysis of the QLQ- H&N35 revealed a similar tendency: Compared to the second inquiry, all multi- item symptom scores had reduced: swallowing (-23.5 points), speech (-22.6 points), pain (-20.3 points), social eating (-16.7 points), sexuality (-16.4 points), senses (-13.7 points) and social contact (-10.6 points). Comparing the results to the data at baseline, patients reported more problems in all of these items (highest

differences in senses (+22.1 points) and social eating (+10.2 points)). All of these effects were shown to be statistically significant in ANOVA ($p<0.001$).

When we analyzed the QLQ- H&N35- single- item- results of the first follow- up (T3), we saw that most of these had a recovering tendency, too. Compared to T2, patients reported fewer problems with coughing (-20.5 points), feeling ill (-19.9 points), opening their mouth (-19.0 points), sticky saliva (-16.0 points) and teeth (-3.9 points), whereas the score for dry mouth increased in the same period (+3.2 points, figure 11). Reflecting the results of the pretreatment assessment, most of these symptoms were scored higher than initially. Xerostomia was observed as having increased during the whole observation period (+38.7 points from T1 until T3). A score increase of 28.4 points bewteen T0 and T3 was seen for the item sticky saliva. Meanwhile, opening mouth (+4.2 points), feeling ill (+3.3 points), coughing (+1.8 points) and dental problems (-1.6 points) had recovered to near baseline level. ANOVA showed all these differences to be statistically significant ($p<0.001$), except dental problems ($p>0.001$).

Fewer patients reported to use pain killers compared to baseline (-8.0%) and compared to the end of RT (-16.0%). More patients indicated to need nutritional support than at T2 (+2.1%; increase of 26.3% between T1 and T3). The number of patients requiring a feeding tube decreased between T2 and T3 (-7.4%), but stayed high compared to the initial assessment (+43.1%). Patients experienced weight gain more often than before RT (+9.5%) or at the end of RT(+17.9%). In accordance with these findings, weight loss was observed less often than at T1 (-19.0%) or T2 (-24.3%, figure 12).

2.5.5 Predictors for quality of life

In order to define potential predictors for the QoL- change, we performed a linear stepwise regression analysis. Tested variables were pretreatment QoL, tumor stage, combined CRT and persistent habit of smoking before RT. Only the variable pretreatment QoL showed a non- incidental relationship to the following QoL- change ($p=0,001$).

Knowing this, we performed repeated measurements of ANOVA with the variables 'change over time' and 'initial QoL' after having split the sample according to the median pretreatment QoL. Tested variables were the QLQ- C30- scales for global health status and functions (see table 5 in Tribius et al. 2012a). This combination of time factor (change over time) and group factor (QoL before treatment) showed, that initially reported high QoL resulted in a statistically significant stronger deficit of global health status during RT (-30.1 points) than low baseline- QoL (-1 point) ($p<0,001$). This is illustrated in figure 13.

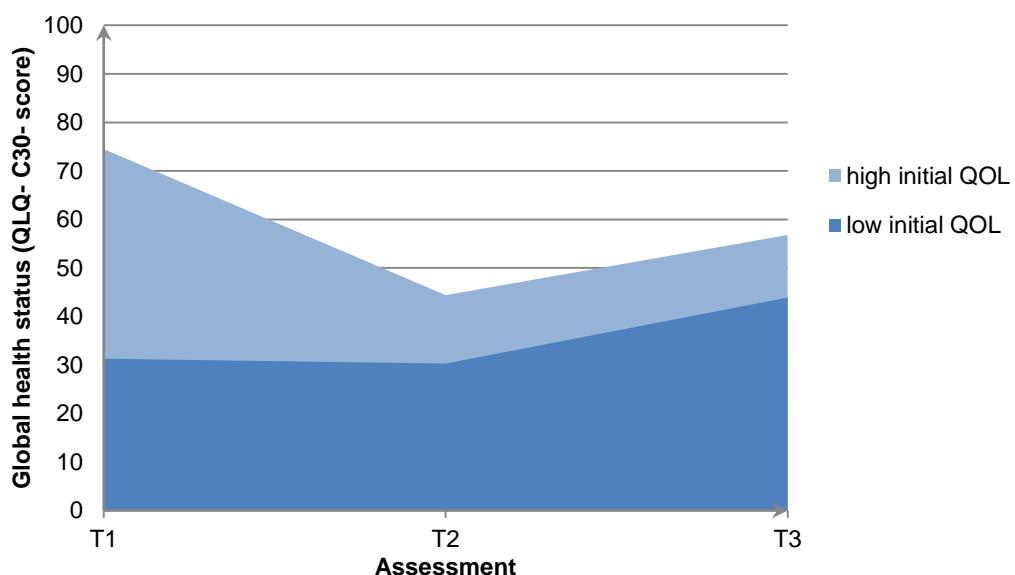


Figure 13: Change in global health status after dichotomization by initial QoL (QLQ-C30).

During the whole observation period, patients with a high initial QoL neither touched nor crossed the low QoL- level that the low- pretreatment- QoL- subgroup reported.

Emotional functioning showed a similar relationship to the initial QoL- status: Patients with a high initial QoL- score realized a stronger impact in their emotional function during RT (-24.8 points) than those with a low initial QoL- score, who reported a nearly

steady level in this item (+0.1 point, $p<0.001$). During the whole observation, the subgroup with a low initial QoL never reached the high emotional function level of the other subgroup (high pretreatment QoL). This is illustrated in figure 14.

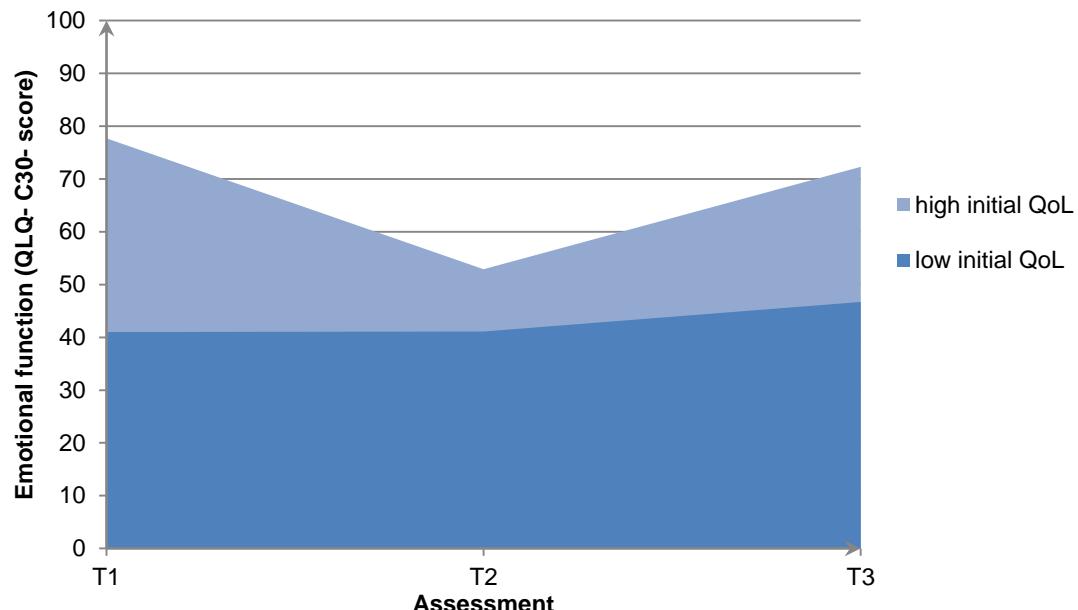


Figure 14: Change in emotional function after dichotomization by initial QoL (QLQ-C30).

The data showed that at T3, patients with low initial QoL reached higher or similar functions compared to their baseline scorings in global health status (+12.6 points), emotional (+5.7 points), cognitive (+1.4 points) and role function (-1.3 points). The other subgroup (high initial QoL) did not reach its initial level of QoL or functions. These patients reported the most marked persisting deficits between T1 and T3 in role function (-19.6 points), global health status (-17.7 points), social (-15.7 points) and physical function (-13.2 points).

In the next step, we combined the identified QoL-predictor 'initial QoL-score' in repeated measurements of ANOVA with the other collected disease- and treatment-specific and sociodemographic data (see table 6 in Tribius et al. 2012a). None of the tested variables showed a significant QoL-impact for either group (all $p>0.001$).

2.6 Discussion

2.6.1 Reduced quality of life before radiation treatment

We saw that patients being diagnosed with HNC reported a low global health status and problems in functioning and symptom scales already before RT started.

Comparing the pretreatment results of the QLQ- C30- questionnaire at T1 to a historical non- disease reference population (Schwarz and Hinz 2001) (see table 2 in Tribius et al. 2012a), we noted that our patients showed a significant lower global health status and worse functioning scores (figure 15, all $p<0.001$).

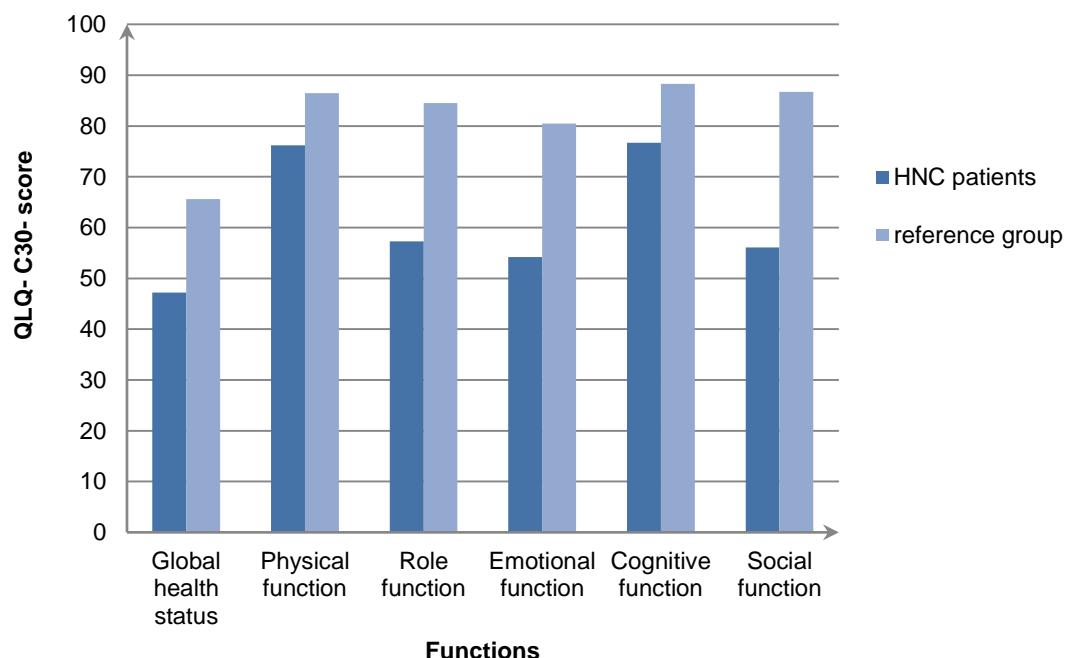


Figure 15: Initial functional status of our sample compared to the reference group (for all shown score differences $p<0.001$).

Considering the findings of Osoba et al. (1998), we found clinically meaningful differences in QoL and all functioning scores between the two contrasted groups. QLQ-C30- global health status was rated 17.8 points lower than in the non- diseased reference sample and social (-30.6 points), emotional (-26.3 points) and role function (-27.2 points) were also reported reduced. We also observed a reduction in physical (-10.3 points) and cognitive function (-11.6 points).

Most QLQ- C30- symptom scales also scored statistically significant lower in our patients than in the reference sample (see table 2 in Tribius et al. 2012a) as pictured

exemplarily in figure 16. Highest absolute score differences between the two samples were found for fatigue (23.5 points), pain (20.9 points), insomnia (22.6 points) and financial problems (23.1 points). Most of the other symptoms also rated statistically significantly lower in the non- diseased reference group compared to the HNC patients ($p<0.001$), but statistical significance could not be shown for nausea/ vomiting and constipation ($p>0.001$).

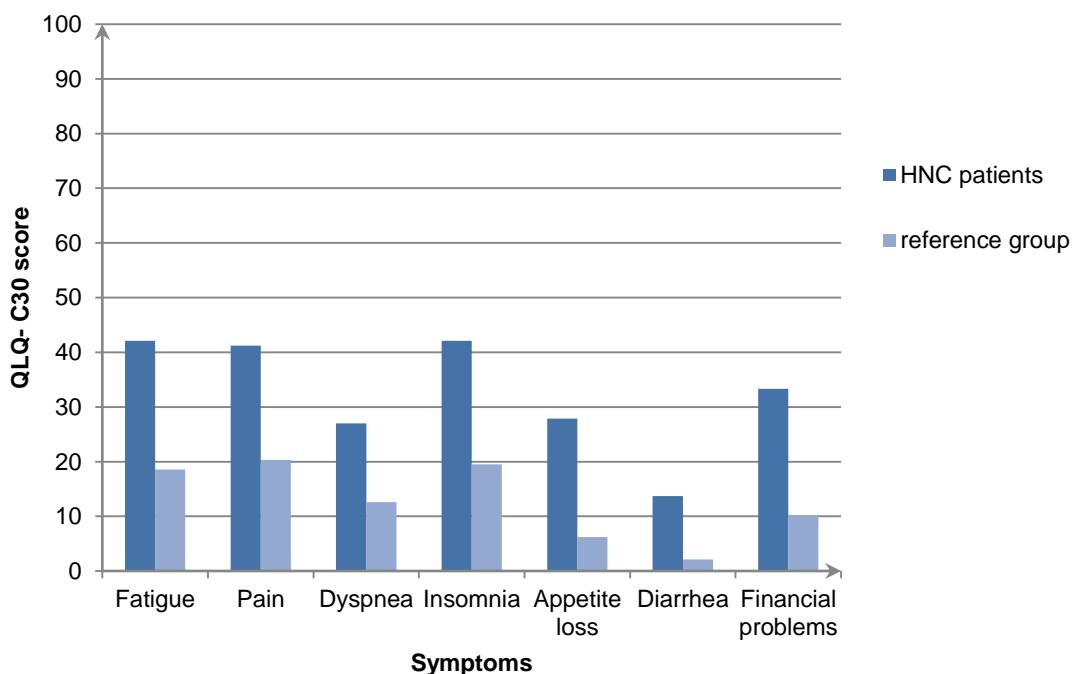


Figure 16: Initial QLQ- C30- symptoms of our sample compared to the reference group (for all shown differences $p<0.001$).

Comparable differences between HNC- patients and non- disease reference groups have already been found in other European countries (Pourel et al. (2002) in Sweden, Borggreven et al. (2007) in Norway, see Tribius et al. 2012a). We found high significance levels for most differences and therefore we expect our patients to feel the marked pretreatment QoL- loss and disability that have been described before.

This difference in QoL before RT started might be due to the typical symptomatology of HNC itself such as e.g. hoarseness, swallowing problems and weight loss (Bettag et al. 2010) that could have reduced QoL. In addition, before our first assessment, many patients had already received HNC- treatment and were eventually going through the

associated adverse effects (as described in 2.2.2.2): 78% of our patients had surgery and 21% received induction chemotherapy prior to (C)RT.

The variables that were identified to be most affected before treatment support the specific psychological distress patients are confronted with in this period: The items role, emotional and social functioning scored clearly lower compared to a non- HNC-reference group. Additionally, we showed a higher rating in the symptoms fatigue and pain that are known to be markedly psychologically modulated (Bingel and Tracey 2008). Insomnia, financial problems, feeling to be ill, sexual problems, weight loss and the use of pain killers were also reported much more frequently. In an Australian sample of 102 HNC- patients, Neilson and colleagues found a prevalence of 15% for mild to severe depression (2010). A group around Karnell (2006) described depression- rates between 20% and 40% in HNC- patients before treatment and stated that depressive moods increase during and directly after HNC- treatment with a recovery to pretreatment frequencies within the first post- treatment year. Davies et al. (1986) observed that HNC- patients, compared to patients with HNC- specific symptoms but non- malignant biopsy- results, showed higher scores of depression even before the biopsy was taken. They proposed depression to be a common symptom of HNC. Although we did not investigate which possible reasons and risk factors for depression were predominant in our sample, this accumulation of strongly psychologically modulated variables suggests, that patients' psyche suffered already in the pretreatment period. A possible reason for this can be a preexisting depressive mood which has been observed in other studies.

The fact that predisposing socioeconomic risk factors for this type of cancer such as alcohol and tobacco abuse, low economic and social status and low education level also predispose for depression (Rodda et al. 2011) might be another possible explanation for the high rate of this psychological comorbidity in HNC- patients. A correlation between lower QoL and depression is described not only in HNC- patients but in QoL- evaluation in general: De Leval (1999) observed depressive patients to be influenced strongly by their mood in rating their QoL and questioned the comparability of QoL- evaluation in a depressive mood to other (non- depressive) ratings.

Another possible reason for this predominance of strongly psychologically influenced QoL- subdomains might have been, that patients were newly diagnosed as having a highly disabling and frightening disease. Knowing about their reduced, actual health state and often being in process to reorganize health concepts and future plans as well

as daily life and social structures, patients might have been questioning their existing standards about their health status in the first assessment (Güthlin 2006). Regarding this, it seems possible that the QoL- scoring of our sample might have been influenced by the diagnosis- related psychological restructuring processes, insecurity and anxiety.

Other studies showed similar reductions in QoL before HNC- treatment: Shepherd et al. (2004) and de Graeff et al. (2000) described in their HNC- patients a statistically relevant dependency of pretreatment QoL- levels on depression- and anxiety- scales. They reported, that patients had the highest scorings in depression- and anxiety- items before the start of RT.

One consequence of these findings could be that not only physicians but also other medical professionals as well as caregivers should be more aware about the discussed limitations and burden of HNC- patients: acceptance of the diagnosis of HNC and restructuring their 'internal reference, their conceptualization of QoL, and their priorities' (Schwartz 1999), multimodal HNC- treatment and associated side effects, psychological distress particularly with depression and anxiety and possible substance abuse.

This should enable professionals to support patients better in the early period. Implementing specific support, counselling early and planning it more individually might help to identify psychologically burdened patients to plan treatment and support tailored to their needs. In this context, proposing a psycho- oncological contact for patients in need before any treatment commences might be of great benefit for these patients in long- term.

2.6.2 Deterioration of quality of life during radiation treatment

Our second finding was that during RT, HNC- patients experience a substantial decline in their QoL, in all function and symptom scales, especially the HNC specific items: loss of appetite, sensual limitations, dry mouth and sticky saliva. Patients more often required nutritional support and gastrostomy tube feedings.

Radiation therapy is associated with acute side effects typically appearing during the third week of radiation therapy. If combined with chemotherapy the onset is usually one week earlier (see 2.2.2.2). In this patient population different treatment modalities were included which might have contributed to the observed differences in QoL compared to other reported series: 73 patients (77%) underwent primary surgery, 19 patients (20%) received induction chemotherapy and 55 patients (58%) had concurrent (C)RT (Richter and Feyerabend 2002). Sticky saliva, sensual limitations and nutritional problems with subsequent loss of appetite or dysphagia are typical symptoms of mucositis and xerostomia, typical adverse effects of surgery, RT and/ or chemotherapy. These are serious and frequent problems during and after HNC- treatment known to influence QoL- scoring negatively (Langendijk et al. 2008, Maurer et al. 2011, Tribius et al. 2012b), which might explain why patients needed much more often nutritional support at T2 than before.

It is assumed that in HNC tumor- and treatment- related symptoms predominantly effect QoL negatively during RT. Meyer and colleagues (2012) found in a Canadian HNC- population a proportion of 23% of patients suffering from grade 3/ grade 4 severe acute toxicity, classified according to RTOG- ARMC (RTOG- Acute Radiation Morbidity Criteria). As in our series, similar QoL- development during RT has been described in multiple studies observing QoL in HNC- patients during the acute phase period (e.g. de Graeff et al. 2000, Bairati et al. 2005, Fang et al. 2005).

2.6.3 Quality of life recovery until first follow- up (T3)

Our third finding is that we saw that most of the QoL- domains showed a recovering tendency by first follow- up (6- 8 weeks after the end of RT), but sticky saliva and nutritional support had not improved. Most of the items had not yet reached the pretreatment levels, which we expected paying attention to a potentially persisting cluster of treatment- related side- effects. Nevertheless, emotional function, pain, diarrhea, insomnia, difficulty opening the mouth, feeling ill, coughing and dental problems returned to the initial assessment level. Bairati et al. (2005), Fang et al. (2005), de Graeff et al. (2000) and Shepherd et al. (2004) saw a comparable, significant recovery in different QoL- domains with a return to the pretreatment levels in most scores a few months until to one year after the end of RT.

Particularly in the HNC- specific symptoms from QLQ- H&N35, we noted our patients score still lower than before RT. We ascribe this to the emphasis of this questionnaire on problems that are common for our patients, particularly the items sticky saliva and nutritional support. These symptoms had undergone a marked increase over the whole assessment period (see figure 11). These problems are well documented (Richter and Feyerabend 2002). Many effects of RT appear with a delay in time, particularly xerostomia (Tribius et al. 2012b, Rathod et al. 2013) and the development of function-limiting lymphatic edema (Richter and Feyerabend 2002). Obviously, these problems play a meaningful role in patient's everyday life and compromise QoL markedly after the end of HNC- treatment. This is pictured in our results and it underlines the importance for physicians to be aware of the delay in which some adverse effects of treatment will occur. Making patients aware of the time frame is important to help patients to manage these limitations without uninformed false expectations of fast resolution, leading to disappointments and affecting mood.

In our study, the variables global health status and emotional functioning scored higher at the third assessment compared to the pretreatment time. Obviously, our patients ranked their overall QoL better than before RT – in spite of the above mentioned limitations. At first sight, this seems to be a discord, but we assume it to be due to the adjustment processes during and after treatment, which might have empowered some patients to hope for a more healthy future (Schwartz 1999, Sprangers and Schwartz 1999, Güthlin 2004): During completion of a comprehensive course of treatment and in the period of recovery and rehabilitation, possibly some patients developed another and more positive attitude towards their health and future. Despite increasing

symptoms (sticky saliva, nutritional support) patients perceive their level of QoL as "better". Ringash et al. (2005) found a QoL- recovery under persisting xerostomia in HNC- patients, too, and they proposed that xerostomia without acute mucositis might not reduce QoL as much as expected before. Further research seems to be necessary to decode possible interactions between QoL and different stages of mucositis as this is one of the predominant QoL- limitations that persists after treatment according to the EORTC- questionnaires (Bjordal et al. 1994b, Tribius et al. 2012b).

Facing the difference between obviously burdening symptoms and QoL- scoring, Schlenk and colleagues published data in 1998 about Canadian patients with advanced prostate cancer. These patients reported similar QoL- levels as a non-diseased reference population. These findings picture the multimodal WHO- definition from 1946 (WHO 1998): Schlenk's patients ranked their QoL according to their environment, health- dependent experiences and also according to their cultural and social experiences. In the diagnosis- and treatment- period as well as after cancer-treatment, they had probably experienced a quite different social situation than before. They had perceived the importance and vulnerability of their own health and the importance of social contacts; maybe they had gone through the fear to die. These challenges and coping to them might have "changed their internal standards for QoL- conceptualization" (Sprangers and Schwartz 1999), which can result in a statistical interference in longitudinal QoL- studies called response shift (Schwartz 1999). Also in our patients, this shifting effect can have made the QoL- score "better" 6- 8 weeks after RT, although a burdening and increasing symptomatology (xerostomia, nutritional support) probably compromised them intensively.

Xerostomia after treatment for HNC is a well- recognized issue because of the close proximity of the major salivary glands to the radiation target volume (Hammerlid and Taft 2001, Bjordal et al. 1994b, Wan Leung et al. 2011, Rathod et al. 2013). To better spare these radiation- sensitive structures from radiation exposure without compromising target volume coverage, great efforts are made as e.g. the implementation and research on patients benefitting from IMRT (van Rij et al. 2008, Vergeer et al. 2009, Wan Leung et al. 2011, Tribius et al. 2012b). McMillan et al. (2006) and Wan Leung et al. (2011) have seen an improvement in QoL after IMRT compared to conventional RT. IMRT has not yet been shown to add to survival time over 3D-CRT. Because time, economic and personal effort in IMRT- planning is much higher than in the other, conventional RT techniques (see 2.2.2.2), research is focused on

identifying patients benefitting most from IMRT. In the UKE- Radiation Department, patients with complex tumor volumes or difficult- to- reach- locations underwent IMRT (84% of patients in the study) but nevertheless rates of xerostomia were very high after RT in this study. In the future, further work on this issue could enable physicians to better recommend individual treatment options. Information about differences in costs per QALY between different radiation techniques in different patient groups could help to judge the applicability and cost effectiveness of IMRT in clinical routine.

The documented change in QoL in the post- treatment period confirms the importance of following patients regularly and frequently after the end of treatment. We showed that some symptoms had not yet reached their highest level at the end of RT (dry mouth, nutritional support). During the course of treatment, patients are evaluated on a regular basis in terms of side effects. Results of this study emphasize the importance of continued care for these patients as it is aimed in most HNC- centers already today. The implication in everyday routine must be focused further on. To guarantee high-quality treatment to patients, they must be recommended to take part in these follow-ups – if necessary also repetitively.

2.6.4 Predictor for quality of life: Pretreatment quality of life

Our data enable us to define pretreatment QoL to be predictor for QoL after RT in HNC- therapy. This predictor significantly influenced global health status and emotional functioning in the following. For a lot of other parameters that we expected to influence subsequent QoL, we could not show a predictive value (initial QoL, tumor stage, smoking status before RT, combined CRT). As already mentioned by Tribius et al. (2012a), this finding has not often been investigated or reported before. But in contrast to our results, various other pretreatment conditions were found to have a significant impact on QoL (summarized in table 9).

Before focusing on baseline QoL as a QoL- predictor, we had expected patients with low pretreatment QoL to be weaker and to suffer more during treatment so that they would report even worse QoL- scores after therapy. Surprisingly, we saw a contradictory relationship: We showed that patients with a high initial QoL- score experienced a stronger impact on QoL than patients with a low initial QoL- score. Different reasons can hold responsible for this development as deepened in the following.

We assume, that patients in the subgroup of high pretreatment QoL were not used to high limitations in their QoL and so they perceived them as highly interfering stressors. Therefore they might have felt the impact of treatment and associated limitations in a more pronounced way than the other subgroup. Lazarus et al. (1965) showed in the sixties of the last century that patients perceive the strength of a stressor differently, depending on different coping strategies. Coping behavior is a learned quality of people. Lazarus et al. showed how to shift these strategies in adults to better enable them facing to a stressor (as e.g. a disease). Regarding these findings, we assume patients with a high pretreatment- QoL to have had worse coping mechanisms towards health- related and general problems before their cancer- diagnosis. Facing HNC they had to go through a more intensive learning to better adapt their coping behavior to their situation. In contrast, patients who already suffered from serious problems before the diagnosis of HNC – whether health- related or non- health- related issues – might have scored already initially low in their QoL because of other QoL- compromising influences (see WHO 1946). Adaption to their low level of QoL might have taken place. In this case, they might not have felt as much limited as the patients of the other subgroup, because they were already used to a reduced QoL before HNC was diagnosed. Additionally, they had already learned to adapt to these limitations

(although they still felt them) before treatment and learned coping mechanisms along the way.

An avoidance coping pattern has been shown by Beisland and colleagues (2013) to predict the general health level (scored with the General Health Questionnaire (GHQ)) and QoL in Norwegian longtime- survivors of HNC. Regarding these findings, it seems possible that people with these preexisting coping patterns tried to avoid confrontation with their disease- problems as long as possible. That could have been the reason for them to score better before treatment but to have had less resources to cope the highly disabling HNC- treatment. Patients using “better” coping patterns might have acquired these in problems of other domains of the QoL- construct than health and disease. Insofar they might have had the possibility to learn how to face live- threatening dangers. As we did not investigate coping mechanisms in our patients, the psychosocial coping pattern and their possible relationship to the different QoL- developments in our HNC- patients remain outstanding for further research.

Although we observed this strong QoL- decline in the first subgroup, we must focus on the fact, that the initially low scoring patients reported worst total QoL- scores over the whole survey. Their low QoL- level was always under the “high initial QoL”- subgroup – although they lacked the dramatic QoL- change. These patients received the same treatment as the high- baseline- QoL- subgroup (no treatment- related differences detectable in ANOVA, compare table 6) and therefore we expected them to suffer from the same cluster and intensity of symptoms and limitations.

A possible reason for this low scoring over the whole period is probably the so- called “floor”- or “ceiling”- effect (Urban and Mayerl 2008). This statistical parameter describes the difficulty to detect (existing) differences in a sample because of an accumulation of answers at one end of an interval- scaled item in psychosocial studies (Urban and Mayerl 2008) and it raises the likelihood to negotiate a (true) difference. The explanation for this is, that changes in longitudinal studies are difficult to report in a non- appropriate scale (showing data accumulation as described above). In short and drawn to our study: Patients who already performed poor before treatment (low initial QoL) were not able to report a further QoL- impact on the same scale in following assessments, because the scale was already near its end. To prevent this effect, a shift of the scale towards the accumulated results can be helpful, so that different changes can be reflected (Urban and Mayerl 2008). In this context, the concept of the applied questionnaires could be questioned, because in QoL- research, particularly the

results of the low scoring patients are very important. One must reflect, that Bjordal and colleagues postulated (1994a) and showed (2000) high sensitivity for the applied questionnaires and it was also shown for the translated versions later (see 2.3.2.1). We assume our data to be influenced by the floor- effect. Further research seems to be required to find out whether this effect plays a more important role in the applied instruments than thought before. This could better enable patients to score their QoL in case of a low QoL level.

Regarding previous research in HNC, the QoL- predicting value of pretreatment QoL has not often been reported before. In a study by Jabbari and colleagues (2005), it was identified to predict subsequent QoL in an American sample of 30 HNC- patients, although this survey was designed to focus on the effect of IMRT on QoL.

Interestingly, pretreatment QoL as a predictor for survival has been investigated and proven before in larger populations of HNC- patients (Meyer et al. 2009, Osthuis et al. 2011). Reviewing different designed studies in different cancer subpopulations with application of EORTC- questionnaires, Quinten and colleagues (2009) also showed a survival- predicting value of pretreatment QoL, particularly if QoL- data and sociodemographic data are considered together. All these findings confirm that HNC- patients with a high QoL before treatment show better survival compared to patients with a low initial QoL- scoring.

Viewing these results together with ours, HNC- patients with a higher QoL before RT suffer from a stronger QoL- decrease, but patients with a lower pretreatment QoL die more often because of their disease. Summarized, it seems as if patients with a low initial QoL- score do not realize their QoL- loss but are in the higher risk to die. Estimating the acuity of problems, one must take into account that it is possible that a high QoL- change cannot be reported by the patients that performed worse already before treatment (floor- effect). On the one hand, physicians should be better educated in paying attention to these patients: Patients who will ask less for help themselves, but probably are in highest need. On the other hand, this subgroup should be empowered to take better care of changes in symptoms and QoL and report these to professionals.

Observing QoL in HNC- patients, Hammerlid et al. (2001b) observed a lower QoL- scoring more often reported by female sex. Schwarz and Hinz found lower QoL- levels in older patients (Schwarz and Hinz 2001) in each, diseased and non- diseased populations. Oftentimes, older people suffer from comorbidities and their risk to die is

higher anyway – including death from comorbidities. Pignon and colleagues (2007) showed that the survival benefit from adjuvant CRT reduces with increasing age. Because of these results, they proposed that patients older than 70 years have no survival benefit from additional chemotherapy and should be treated with RT only. In our patient sample, except the pretreatment QoL- score, we could not find these predictors related to the subsequent QoL- development.

Regarding this substantial QoL- decline during RT, one must also ask the question, whether HPV- positive HNC- patients really require such intense treatment regimens. We know this subgroup to have a much better prognosis than HPV- negative, classical HNC- patients (Rischin et al. 2010, Mehanna et al. 2012), but we do not yet know enough about whether less intense treatment protocols give a similar survival prognosis. This issue is especially important considering the late effects associated with the contemporary multimodality treatment prescribed in LAHNC. HPV- status was not subject of this study, but further research is required to find out more about treatment options for this subgroup.

2.6.5 Critiques

During the last decade, different potential predictors for QoL in HNC- patients have been researched and conflicting results were reported (see table 9). The one predicting factor for subsequent QoL in our study was the initial QoL- level.

For example, we could not find any significant difference between patients who had received prior surgery before RT and those who had not. This was surprising, because we had expected patients after combination of surgery and (C)RT to be affected by a more substantial QoL- loss. These patients experienced adverse effects of both modalities, surgery and (C)RT. Nevertheless, we could not observe any differences between these two groups.

In the same manner, we could not detect any differences between QoL of patients who received chemotherapy additional to RT compared to those who were treated with RT alone. We did not expect this, too, because adverse effects of chemotherapy usually stress additionally on patients of the first subgroup and therefor a stronger QoL- loss seemed expectable.

Different disease stages did also not influence QoL- results, although we had thought higher stages to score their QoL worse (oftentimes the tumor itself makes more symptomatology and treatment is more intensive). This could not be shown by our data, too.

Although we could also not find any correlation between QoL and tumor- site, this was observed in other settings before: Hammerlid et al. reported in 2001 (c), that tumor-site, age, sex and tumor- stage influenced QoL- levels before treatment. They found in a Norwegian and Swedish population of 357 HNC- patients QoL- levels correlated with tumor- sites and site- specific symptoms. For example, laryngeal carcinoma often caused speech problems and coughing; gingival cancer was associated with dental problems; carcinoma of the tongue often resulted in pain and nutritional support. These findings suggested that not only general, but site- specific pretreatment support could play a meaningful role for HNC- patients. Different sites in HNC require different options of help: Nutritional support, speech and swallowing exercises, dermatologic or dental care, breathing support, hearing or speaking aid, analgesic therapy and others. Further research is necessary to show, whether QoL- levels improve, if such pretreatment support is implemented.

To explain this lack in statistically significant results, one has to take into account the total number of 95 patients evaluated in this analysis. This sample might have been too small for the potential predictors to reach significance level. To resolve this problem, the study is still going on including “new” patients and later publications will describe the results from larger study samples and longer term follow- up.

Secondly, the observation time might have been too short to prove the significance of other predictors. Because the study protocol continued after the assessments that were included into the publication by Tribius et al. (2012a), additional long- term data is expected. These results might better enable to reveal other potential predictors.

The different domains of the QoL- construct are known to be highly dynamic in this short but important period of cancer treatment (Weisman and Worden 1976). We also saw large dynamics in different domains: e.g. change over 200% in xerostomia. To find out, when patients feel the highest impact on their QoL and when professional help is mostly needed, a higher frequency of QoL- assessments in this period is required. However, we could show that patients undergo a wide range of QoL- change during the observed period. Three assessment times might have been too few to reflect the dynamic sufficiently.

Another issue interfering the reveal of significant changes could have been the floor-effect (Urban and Mayerl 2008, described already in 2.6.4.). Regarding our results, the subgroup with a low initial QoL showed relatively cumulated low scorings at one end of the interval- scaled issues (about 30 points) during the whole observation. Insofar, a floor- effect might also count responsible for further lacking significances of other QoL- predictors, because it could have hided (existing) correlations. An adaption of the measuring scale in shifting it to the accumulated data could help to prevent this effect, but such a shift causes problems: It would make comparisons between new and ongoing studies (applying “different” EORTC- questionnaires) difficult.

An additional interference by response shift (described already in 2.6.3) cannot be excluded. If response shift interferes in QoL- studies, QoL- scores are usually higher than expected as patients get used to their changed health status: Their initially highly reduced QoL decreases again, not reflecting a similar change in everyday life but reflecting an adaption process. In the same way, limiting mechanism can appear in QoL- research as ours, because patients can undergo a fatiguing process in longitudinal studies. These patients do not get used to their limitation but suffer more

and more from it; they report a decreasing QoL. These different possibilities of patients to react on chronic limitations are illustrated summarized in figure 17.

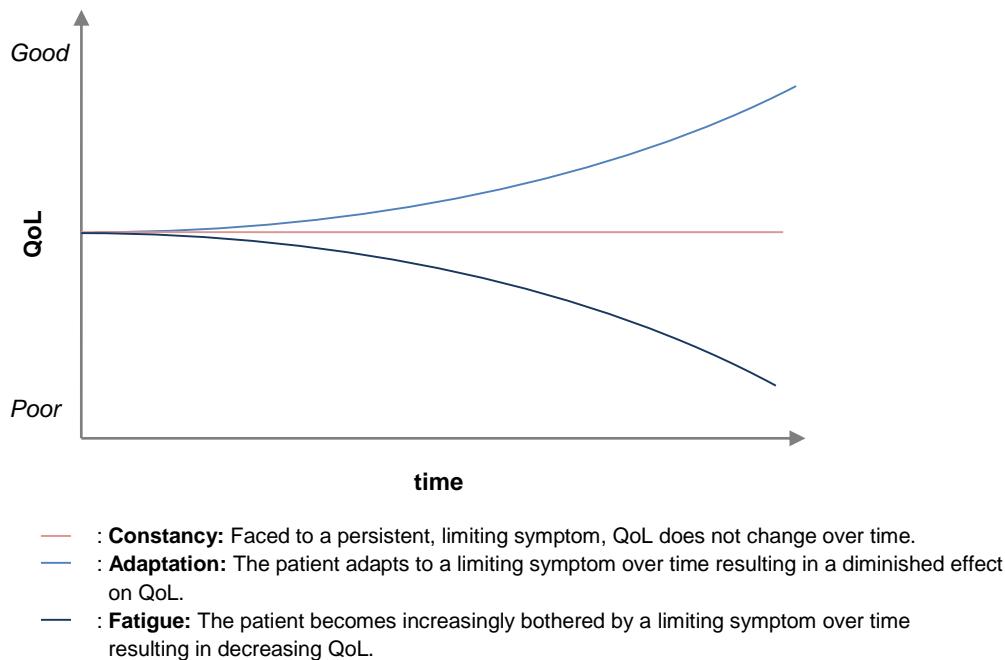


Figure 17: Potential relationship between persisting QoL-reducing symptoms and QoL (from Murphy et al. 2007).

HNC- treatment has undergone a significant increase in intensity during the last years as Trott et al. (2007) showed impressively. We have compared our data to studies from a time in which different treatment protocols were commonly used. Radiation techniques, systemic therapies as well as surgical techniques have changed significantly. It could be possible, that adverse effects of the modern treatments are not entirely reflected by the currently used EORTC- questionnaires designed more than 20 years ago. Currently, revision of the EORTC- H&N35 module is under way and phase III- testing initiated (EORTC 2012, Singer et al. 2013).

When comparing our results to those studies, we have to take also into account that longitudinal data on QoL in HNC patients have mostly been reported mainly based on patient- data from the non- IMRT era. To define the impact of new treatment techniques and strategies in HNC adequately, there is a need for prospective data on QoL in patients receiving contemporary state- of- the- art treatment. Comparison to such studies seems more appropriate for our data as we included e.g. a high percentage of IMRT- treated patients. Not only changes in QoL but also predictors

might have changed in this time so that comparing our data to “older” ones might be inadequate.

Other possible sources of bias that could have influenced the significance of our results are the Hawthorne- effect that describes the phenomenon that people change their behavior when they know that they are taking part in a survey (McCarney et al. 2007). Feeling the need to be positive in such answers might interfere, but these problems are difficult to exclude in a self- administered questionnaire- survey (and self-administration is the preferred performance of QoL- assessments as e.g. described by Bullinger 2006). The placebo- effect as a source of bias describes a change in patients, that is not caused by the expected reason (diagnosis, medical treatment), but by the expectation of the patient to undergo a change. To reveal the importance of this effect, a placebo- controlled trial would be required which would of course be unethical.

2.7 Summary

We know that HNC- patients suffer from a low QoL, compromised QoL- related functions and many cancer- and HNC- specific symptoms already before RT.

During treatment, these limitations increase strongly, but most of them show some recovery by 6- 8 weeks after the end of RT. The symptomatology of sticky saliva and nutritional support continue to increase in this period.

In addition, we showed that the pretreatment QoL- level (assessed with the EORTC-QLQ- C30- questionnaire) predicts the subsequent QoL and emotional functioning. Patients with a high initial QoL experience a stronger decline in QoL and emotional function during treatment. Patients with a low initial QoL experience a further decrease in their strongly compromised QoL and emotional functioning and remain beneath the QoL- scores of the other subgroup until 6- 8 weeks after completion of RT.

Several risk factors for the QoL- development in HNC- treatment have been described before and we extended this cluster of QoL- predictors: Pretreatment QoL predicts the QoL in HNC- patients after therapy. QoL is a valid endpoint in clinical trials for HNC patients and it helps to define patient populations most at risk. The knowledge of another predictor for changes in QoL enables physicians to plan early intervention and appropriate supportive care. HNC- patients' QoL can therefore benefit from these results in the future.

2.8 Appendix

2.8.1 Ethics committee application

Ausführungen für die Ethik-Kommission

„Lebensqualität bei Patienten mit fortgeschrittenen HNO- Tumoren“

Anmerkung:

Bei diesem Antrag handelt es sich nicht um eine klinische Prüfung, sondern alle Patienten erhalten eine leitliniengerechte Tumortherapie und werden zusätzlich bzgl. Ihrer Lebensqualität befragt.

1. Persönliche Angaben

- e.8 Namen und Dienststellungen des Leiters der Klinischen Prüfung (LKP) (entspr. § 40 AMG oder § 17 MPG) und seiner Mitarbeiter

Dr. med. Silke Tribius (LKP)
Ambulanzzentrum UKE GmbH
Bereich Strahlentherapie
Universitätsklinikum Hamburg-Eppendorf
Martinstr. 52
20246 Hamburg
Tel.: 040- 7410- 56140
Fax: 040- 7410- 59895
Email: tribius@uke.uni-hamburg.de

Dr. phil. Corinna Bergelt
Institut und Poliklinik für Medizinische Psychologie
Universitätsklinikum Hamburg-Eppendorf
Martinstr. 52- S35
20246 Hamburg
Tel.: 040- 7410- 54939
Fax: 040- 7410- 54940
Email: bergelt@uke.uni-hamburg.de

- 1.2 Nachweise (nur bei erstmaliger Anfrage erforderlich) über die wissenschaftliche Qualifikation des LKP entsprechend § 40 (1) 4. AMG; § 17 (1) 4. MPG.

Antragstellung und
Projektleitung:

Dr. med. Silke Tribius
Fachärztin für Strahlentherapie und Palliativmedizin am
UniversitätsklinikumHamburg- Eppendorf seit 2003,
wissenschaftliche Mitarbeiterin seit 2001; Facharztausbildung am
Albert Einstein College of Medicine, Bronx, New York
langjährige Forschungstätigkeit u.a. im Labor Neuroonkologie/
Strahlentherapie am Albert Einstein College of Medicine sowie
klinische Forschung/ Rekrutierung von Patienten in klinische
Phase II und III- Studien der RTOG und verschiedenen
Studiengruppen in Deutschland und Europa, GCP Zertifikat

1.3 Finanzierung der Studie (Sponsor)?

Das Projekt „Lebensqualität von Patienten mit fortgeschrittenen HNO- Tumoren“ wird im Rahmen des klinischen Alltags durchgeführt werden und wird nicht gesondert finanziert/ gesponsert.

- e.8 Anfragen an die Ethik-Kommission sind gemäß der Gebührenordnung der Ärztekammer Hamburg gebührenpflichtig:
An welche Person/Institution soll der Gebührenbescheid gerichtet werden?
Entfällt, da es sich um nicht um eine klinische Prüfung handelt.

2. Beschreibung und wissenschaftliche Begründung des Projektes, insbesondere:

2.1 Erläuterung des Versuchsziels

Der Begriff der Lebensqualität wurde Anfang der 80iger Jahre als eigenständiger Terminus in die Medizin eingeführt (Gandek B et al 1998). Die gesundheitsbezogene Lebensqualität wird definiert als ein SELBSTBERICHT von sozialen, psychischen, körperlichen und alltagsnahen Aspekten von Wohlbefinden und Alltagsfähigkeit.

In der medizinischen Forschung nimmt das Konstrukt „Lebensqualität“ zunehmend die Rolle ein, die dem Anspruch an einen ganzheitlichen Gesundheitsbegriff näher kommen. So wird beispielsweise versucht, Einzelheiten der medizinischen Therapie und Wirkmechanismen unterschiedlicher therapeutischer Verfahren bis hin zu Nebenwirkungen ebenso zu integrieren wie psychische Krankheitsverarbeitungsprozesse.

Im Mittelpunkt der Betrachtungen steht damit der individuelle Gesundheitsstatus des Krebspatienten zu unterschiedlichen Zeitpunkten im Verlauf der Erkrankung, Therapie und Rekonvaleszenz. Des Weiteren ist das Konzept so angelegt, dass es die vielfachen Interaktionen zwischen körperlichen, psychischen und sozialen Ebenen der Gesundheit berücksichtigt und darüber hinaus auch soziodemographische Co- Variablen in Betracht zieht.

Die EORTC (European Organization for Research and Treatment of Cancer) hat mehrere grundsätzliche Überlegungen und Ergebnisse zum Konzept der Lebensqualität formuliert (Aaronson et al 1986; 1993). Auf dieser Basis wurde der Fragebogen **QLQ C-30** entwickelt, der vor allem konstruktive und teststatistische Mängel bislang vorgestellter Erfassungsverfahren (z.B. Karnofsky Performance Index, Spitzer Index, QLI, LASA, FLIC, POMS etc.) ausgleichen soll. Da sowohl die Datenerhebung als auch die Datenauswertung vereinheitlicht und standardisiert sind, setzte dieser methodische Zugang einen Mindeststandard, der somit Leitlinie für alle weiteren wissenschaftlichen Anwendungen wurde.

Der EORTC-QLQ-C30 misst die Lebensqualität neben der Skala „Globale Lebensqualität“ anhand von fünf Funktionsskalen sowie neun Symptomskalen.

Die Funktionsskalen sind:

- Körperliche Funktion
- Rollenfunktion
- Emotionale Funktion
- Kognitive Funktion
- Soziale Funktion

Die Symptomskalen sind:

- Fatigue
- Übelkeit und Erbrechen
- Schmerzen
- Atemnot
- Schlaflosigkeit
- Appetitverlust
- Verstopfung
- Durchfall
- Finanzielle Probleme

Darüber hinaus wurden in der Folgezeit von der EORTC sogenannte Zusatzmodule entwickelt und standardisiert, die spezifisch für die einzelnen Krankheitsentitäten bzw. Lokalisationen sind. Für den Einsatz bei Tumoren im HNO-Bereich steht das „Head & Neck Cancer module“ (**QLQ-HN35**) zur Verfügung, welches maßgeblich von K. Bjordal (Bjordal K et al 1992; 1994) erarbeitet wurde. Dieses Modul wurde gemäß den Richtlinien der EORTC im Rahmen einer cross-cultural study (EORTC Protocol 15941) validiert und besteht aus 35 Einzelfragen.

2.2 Darstellung des bisherigen Wissensstandes

Die hier beantragte Studie fokussiert sich auf ein Patientenkollektiv, dass in vielfacher Hinsicht ein besonderes ist. Es werden Patienten untersucht, die an einer lokal fortgeschrittenen Krebserkrankung des HNO- Bereiches, also des Kehlkopfes, des Oropharynx, der Mundhöhle, der Nasenhaupt- und Nebenhöhlen sowie des Nasopharynx oder der Speicheldrüsen leiden. Diese Tumore betreffen also Bereiche, die strukturell und funktionell wichtig sind für kritische Funktionen wie Sprechen und Schlucken, Schmecken und Riechen. Außerdem haben Veränderungen im Aussehen als Therapiefolge weitreichende emotionale und soziale Folgen. Daher ist die Evaluation von biopsychosozialen Therapiefolgen bei HNO- Tumoren so wichtig (Murphy BA et al 2004).

Die Therapie ist multimodal und besteht aus einer Kombination von Operation, Strahlentherapie und Chemotherapie. Die Empfehlung der Therapie erfolgt im Rahmen einer interdisziplinären Konferenz, in der a) tumorspezifische Charakteristika wie Lokalisation, Stadium, Tumorprogress, b) patientenspezifische

Faktoren wie Performance Status, physiologisches Alter, und Co- Morbiditäten, c) soziales/ familiäres Umfeld und Begleitumstände und d) eigene institutionale Erfahrungen und Resourcen eine Rolle spielen. Während des Tumor Boards wird versucht, die für den Patienten geeignete Therapie zu empfehlen. Diese Entscheidungen basieren hauptsächlich auf subjektiver Wahrnehmung der Kollegen, die die Patienten primär betreuen. Wünschenswert wäre hier ein objektiveres Instrument, das bei der Therapieentscheidung hilft und den Wunsch des Patienten im Hinblick auf das Therapieergebnis (Überlebens- und Heilungswahrscheinlichkeit) UND die Lebensqualität widerspiegelt.

Murphy et al haben in einer Übersichtsarbeit herausgearbeitet, dass die Interpretation der Literatur über die Lebensqualität bei HNO- Patienten sehr schwierig ist, denn oftmals handelt es sich um sehr kleine Patientenkollektive, Studien mit schlechtem Design und Fehlen von prospektiven Daten (Murphy BA et al 2007). Dennoch wurde zusammengefaßt, dass allgemein die Lebensqualität der HNO- Patienten unmittelbar nach der Therapie massiv sinkt und nach circa 12 Monaten zur Baseline zurückkehrt. Dabei wurden Faktoren beschrieben, die die Lebensqualität negativ beeinflussen: Magensonde, Co- Morbidität, Tracheostoma, Tumorlokalisierung und -stadium.

In verschiedenen Bereichen haben Daten über HRQOL (health related quality of life- gesundheitsbezogene Lebensqualität) Therapiemaßnahmen verändert. So z.B. wird eine radikale Lymphknotendissektion im Halsbereich nur noch selten durchgeführt. Man ist vielmehr dazu übergegangen, sog. Funktionelle Lymphknotendissektionen durchzuführen, die sich an der Tumorgröße und -lage orientieren ohne Mitnahme funktionell wichtiger Strukturen wie z.B. des N. accessories. Außerdem hat der vermehrte Einsatz der Chemotherapie bei HNO-Tumoren zu einem großen Durchbruch des Organ- (z.B. Larynx) und damit Funktionserhalts und Verbesserung der HRQL geführt.

Seit ca 15 Jahren wird zunehmend die postoperative oder auch definitive kombinierte Radiochemotherapie durchgeführt, die in einem Survival Benefit von circa 10% resultiert; die Lebensqualität dieser Patienten ist jedoch nicht zufriedenstellend, denn nicht nur akute Nebenwirkungen, sondern auch Spätnebenwirkungen treten häufiger auf (Machtay M et al 2007) und betreffen vor allem die Schluck- und Sprachfunktion der Patienten. Es konnte gezeigt werden, dass sich der Therapieerfolg umgekehrt proportional zum Alter der Patienten verhält und dass sogar bei über 70-jährigen Patienten kein benefit mehr gegeben war (Pignon et al . 2007).

Eine türkische Arbeitsgruppe (Alicikus ZA et al 2009) hat kürzlich eine Arbeit veröffentlicht, die den Einfluss tumor- und therapiebedingter sowie patientenspezifischer Faktoren auf die Lebensqualität bei HNO- Patienten untersucht hat. Ein wichtiges Ergebnis dieser Studie war, dass die Einschätzungen der Ärzte sich mit denen der Patienten oftmals nicht decken. Soziokulturelle, wirtschaftliche und intellektuelle Faktoren haben einen großen Einfluss darauf, wie

ein Patient mit der Diagnose „Krebs“ und der Therapie umgeht und entscheiden maßgeblich über die Lebensqualität nach einer Krebstherapie.

Außerdem konnte gezeigt werden, dass eine eingeschränkte Basis- Lebensqualität ein schlechter Prognosefaktor für das Therapieergebnis darstellt und dass Frauen generell nach der Therapie gesundheitlich stärker beeinträchtigt sind (de Graeff A et al 2001).

Auch die technologischen Entwicklungen in der Strahlentherapie (intensitätsmodulierte Technik wie IMRT/ Tomotherapie) machen eine immer präzisere Bestrahlungsplanung und damit Schonung von Risikoorganen (wie z.B. Speicheldrüsen) möglich, was sich wiederum in einer verbesserten Lebensqualität der Patienten widerspiegelt (Essen und Schmecken, weniger Karies). Vergeer et al haben kürzlich eine Arbeit veröffentlicht und konnten darstellen, dass die Schonung der Speicheldrüsen mit der IMRT im Vergleich zur dreidimensionalen konformalen Bestrahlungstechnik zu einer signifikanten Reduktion der Xerostomie (Mundtrockenheit) führte, was sich wiederum in einer verbesserten HRQOL zeigte (Vergeer MR et al. 2009).

Van Rij et al (van Rij CM et al 2008) zeigten, dass die Dosisbelastung im Bereich der Parotis mit der IMRT im Mittel 26 Gy oder weniger betrug und Xerostomie damit signifikant weniger ein Problem war, was sich wiederum in einem verbesserten Symptomen- Score widerspiegelte. Diese Ergebnisse konnten in einer Untersuchung von Tribius et al (Tribius S et al 2008) bestätigt werden. Hier wurde Patienten, die im HNO- Bereich mit der helikalen Tomotherapie bestrahlt wurden, retrospektiv betrachtet. Die Dosisbelastung der geschonten Parotis betrug in 23 Fällen im Mittel 15 Gy. Die Mehrheit der Patienten hatte eine klinisch kaum relevante Grad 1 Xerostomie. Eine prospektive Untersuchung und Erfassung der Lebensqualität und Korrelation mit patienten-, tumor- und therapiespezifischen Faktoren soll mit dieser hier beantragten Studie erfolgen.

- e.8 a) Ergebnisse der pharmakologisch-toxikologischen Vorprüfungen bei Arzneimittelstudien (§ 40 (1) 5. Und 6. AMG)
 entfällt
- b) oder Nachweise über die sicherheitstechnische Unbedenklichkeit des Medizinproduktes sowie Ergebnisse der biologischen Sicherheitsprüfung (§ 17 (1) 6. Und 7. MPG)
 entfällt
- c) Handelt es sich um eine Untersuchung, auf die die §§ 23/24 StrahlenschutzVO vom 20.07.2001 Anwendung finden?
Werden studienbedingt röntgenologische und/oder nuklearmedizinische Untersuchungen/Behandlungen durchgeführt?
- Entfällt

2.4 Begründung der Notwendigkeit von Humanversuchen

a) Experimente an gesunden Personen?

Entfällt

b) Heilversuche an Patienten?

Entfällt

2.5 Schilderung der geplanten Versuchsausführung einschließlich der statistischen Auswertung

Der EORTC- Fragespiegel besteht aus insgesamt 65 Einzelfragen (**QLQ-C30** und **QLC-HN35**).

Zeitpunkte der Datenerhebung:

Ersterhebung (T1) i.S. eines Referenz- bzw. Ausgangswertes unmittelbar vor der Therapie

1. (frühe) Nachsorge (T2) ca 6-8 Wochen nach der Therapie
2. Nachsorge (T3) ca. 6 Monate nach der Therapie
3. Nachsorge (T4) ca. 12 Monate nach der Therapie
4. Nachsorge (T5) ca. 18 Monate nach der Therapie
5. Nachsorge (T6) ca. 24 Monate nach der Therapie

Operationalisierungen und Messinstrumente:

Patientin / Patient: Für die Befragung der Patientinnen und Patienten werden standardisierte Instrumente verwendet (Lebensqualität: EORTC-QLQ-C30 und EORTC-QLQ-HN35; soziodemographische Daten: angepasst durch Institut für Medizinische Psychologie).

Arzt / Ärztin: Ergänzend werden Arztfragebögen eingesetzt, die Angaben zur Erkrankung und Behandlung enthalten.

Tabelle 1 gibt eine Übersicht über die Datenquellen und die einzusetzenden Messverfahren.

Tab. 1: Übersicht über die Datenerhebung

Visitendatum	Notwendiges Formular	Ausführende Person
Vor Bestrahlung	Erhebungsbogen (1) Therapieprotokoll (2) Patientenfragebogen Basisbefragung	Arzt Arzt Patient
3. Bestrahlungswoche	Therapieprotokoll (2)	Arzt
Letzte Bestrahlungswoche	Therapieprotokoll (2)	Arzt
1. Nachsorge (6-8 Wochen nach RT)	Therapieprotokoll (2) Bestrahlungsformular (3) Frühe Nachsorge (4-1) Patientenfragebogen 1. Nachsorge	Arzt Arzt Arzt Patient

2. Nachsorge (ca. 6 Monate nach RT)	Therapieprotokoll (2) Frühe Nachsorge (4-2) Patientenfragebogen 2. Nachsorge	Arzt Arzt Patient
3. Nachsorge (ca. 12 Monate nach RT)	Therapieprotokoll (2) Späte Nachsorge (5-1) Patientenfragebogen 3. Nachsorge	Arzt Arzt Patient
4. Nachsorge (ca. 18 Monate nach RT)	Therapieprotokoll (2) Späte Nachsorge (5-2) Patientenfragebogen 4. Nachsorge	Arzt Arzt Patient
5. Nachsorge (ca. 24 Monate nach RT)	Therapieprotokoll (2) Späte Nachsorge (5-3) Patientenfragebogen 5. Nachsorge	Arzt Arzt Patient

Statistische Auswertung:

Die Charakterisierung verschiedener Subgruppen insbesondere hinsichtlich der verschiedenen Therapiebedingungen (Operation und Strahlentherapie +/- Chemotherapie bzw. eine primäre Strahlentherapie +/- Chemotherapie) wird zunächst über deskriptive Statistiken erfolgen. Für Gruppenvergleiche bezüglich der Lebensqualitätsdaten werden t-Tests (bzw. beim Vergleich von mehr als zwei Gruppen entsprechend Varianzanalysen) berechnet. Neben deskriptiven statistischen Verfahren gestattet die Längsschnittbefragung unter Verwendung psychometrisch geprüfter Instrumente auch die Anwendung multivariater Analysestrategien. Bei der vergleichenden Analyse des mittel- bzw. längerfristigen Verlaufs werden Varianzanalysen für Messwiederholungsdesigns als das zentrale statistische Verfahren zur Anwendung kommen.

2.6 Literaturangaben

1. Murphy BA et al. Quality of life research in head and neck cancer: A review of the current state of science. Critical Reviews in Oncology/ Hematology 62 (2007) 251-67.
2. Murphy BA et al. Head and Neck Cancer. In: Doyle E et al. Oxford Textbook of palliative medicine. Oxford University Press; 2004. P. 658-72.
3. Bjordal K et al. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30- item version and a diagnosis- specific module for head and neck cancer patients. Acta Oncologica 31 (1992), 311-21
4. K. Bjordal K et al. on behalf og the EORTC Quality of Life Study Group: Development of a European Organization For Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncologica 33 (1994), 311-21
5. Aaronson NK et al. Prospects and problems in European Psychosocial Oncology: A survey of the EORTC Study Group on quality of life. J Psych Onc 4 (1986), 43-53.
6. (Aaronson et al NK: The European Organization for Research and Treatment of Cancer; QOL-C30: A quality-of-life instrument for use in international clinical trials in oncology. JNCI 85 (1993), 365-75

7. Gandek B et al. Methods for validating and norming translations of health status questionnaires: the IQOLA Project approach. International Quality of Life Assessment. J Clin Epidemiol 1998 Nov;51(11): 953-9
8. Vergeer MR et al. Intensity modulated radiotherapy reduces radiation- induced morbidity and improves health- related quality of life: Results of a nonrandomized prospective study using a standardized follow-up program. IJROBP 2009 *in press*
9. Alicikus ZA et al. Importance of patient, tumour and treatment related factors on quality of life in head and neck cancer patients after definitive treatment. Eur Arch Otorhinolaryngol 2009 *in press*
10. van Rij CM et al. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Rad Onc 3 (2008), 41
11. Tribius S et al. Sparing of parotid gland and larynx with helical tomotherapy in head and neck cancer. Oral presentation at the First International Conference on Clinical Use of Tomotherapy, Munich 2008
12. De Graeff A et al. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. Eur J Cancer 37 (2001): 332-39
13. Pignon JP et al; MACH-NC Collaborative Group. [Meta-Analyses of Chemotherapy in Head and Neck Cancer \(MACH-NC\): an update.](#) Int J Radiat Oncol Biol Phys. 2007;69 (2 Suppl):S112-4.

e.8 Bei Multicenter-Studien (LKP in Hamburg):

- a) Ist das Projekt schon in einem anderen Bundesland bei der für den dortigen Prüfarzt zuständigen Ethik-Kommission vorgelegt worden?
Wenn ja, bei welcher?

Das Projekt wird mit diesem Antrag zum ersten Mal einer Ethik- Kommission vorgelegt.

- b) Wie viele Zentren nehmen teil?

Studienzentrum ist der Bereich Strahlentherapie des Ambulanzzentrums des Universitätsklinikums Hamburg-Eppendorf. Diese Untersuchung ist nicht als Mulizenterstudie konzipiert.

2.8 Geplanter Studienzeitraum (Beginn/Ende)

01.04.2009 – 31.12.2010.

3. Schilderung der voraussehbaren Belastungen und Risiken für die Versuchspersonen

3.1 Eingehen auf etwaige Kontraindikationen, Ein- und Ausschlusskriterien

Kontraindikationen sind nicht relevant, da es sich nicht um eine Therapiestudie handelt. In die Studie eingeschlossen werden Krebspatientinnen und -patienten mit lokal fortgeschrittenen HNO- Tumoren (UICC Stadium III und IV).

Ein- und Ausschlusskriterien im Überblick:

Einschlusskriterien:

- Lokal fortgeschrittener HNO- Tumor
- Patient muß einwilligungsfähig sein
- Compliance bzgl. Nachsorge

Ausschlusskriterien: Die Ausschlusskriterien ergeben sich komplementär zu den beschriebenen Einschlusskriterien:

- kognitive Defizite (ärztliche Einschätzung)
- unzureichende Deutschkenntnisse (für das Ausfüllen der Fragebögen)
- Teilnahmeverweigerung/ Non- Compliance

3.2 Stellungnahme zur Möglichkeit weiterer, derzeit nicht überschaubarer Risiken

Risiken sind nicht bekannt, da es sich um eine Fragebogenstudie handelt. Bei entstehenden Fragen haben die Patientinnen und Patienten die Möglichkeit, mit dem behandelnden Arzt zu sprechen.

3.3 Abbruchkriterien (individuell und für die Gesamtstudie)

Abbruchkriterien sind nicht vorgesehen. Die Teilnahme an der Fragebogenstudie ist freiwillig. Aus einer Nicht-Teilnahme ergeben sich keine negativen Konsequenzen für die Patienten.

4. Darlegung der voraussichtlichen Vorteile und der Bedeutung des Versuches für den Menschen

- e) in der Heilkunde (namentlich unter Vergleich mit herkömmlichen diagnostischen resp. Therapeutischen Methoden)

Es handelt sich nicht um eine klinische Studie, sondern um ein Projekt zur Untersuchung der Lebensqualität vor, während und nach der Standardtherapie.

Darüber hinaus sollen Indikatoren identifiziert werden, die möglicherweise die Indikationsstellung einer Therapie beeinflussen.

- b) in der Forschung

Diese Studie wird prospektiv die Lebensqualität von Patienten mit lokal fortgeschrittenen Hals- Kopf- Tumoren erfassen. Es werden patienten-, tumor- und therapiespezifische Faktoren mit der HRQOL korreliert, um prognostische Faktoren herauszuarbeiten, die Einfluss auf die Therapieentscheidung und damit nicht nur den Therapieerfolg sondern auch die Lebensqualität nach abgeschlossener Therapie haben.

Besondere Überlegungen sind bei Randomisierung, Verblindung und

Placebo-Kontrollen angesichts der ungleichen Behandlung der Gruppen nötig
(u.a.: Ist die Vorenthalzung einer aussichtsreichen neuartigen Behandlung gegenüber
der Kontrollgruppe vertretbar? Gibt es eine Standardtherapie?)

entfällt

4.1 Bei minderjährigen gesunden Versuchspersonen
(vgl. dazu § 40 (1) 1.-3. Und (4) 1.-4.) AMG
bzw. § 17 (1) 1.-3. Und (4) 1.-4 MPG)

- a) Spezieller Bezug zu Krankheiten von Minderjährigen?
- b) Individuelle Indikation ?
- c) Möglichkeit der Prüfung an Erwachsenen ausgeschlossen?

Entfällt

4.2 Bei Patienten als Versuchspersonen:
Individuelle Indikation?

Entfällt

**e. Güterabwägung zwischen den Nachteilen und Risiken einerseits
und dem voraussichtlichen Nutzen andererseits**

- e.8 Berücksichtigung des Grundsatzes, dass stets die Belange der Versuchsperson den Vorrang haben müssen (vgl. dazu Ziff. I 5, 6, II. 4 und 6 der revidierten Deklaration von Helsinki; § 40 (1) 1. AMG, § 17 (1) 1. MPG)
Belange der Patientinnen und Patienten haben grundsätzlich Vorrang. Das Forschungsvorhaben greift nicht in die medizinische Behandlung und Nachsorge ein.
- e.8 Beschränkung der Zahl der Versuchspersonen auf das unbedingt notwendige Maß (einschließlich begründeter biometrischer Berechnungen)
Befragt werden sollen circa 150 Patientinnen und Patienten zu sechs Messzeitpunkten. Diese Gruppengröße ist mindestens erforderlich, da bei der vergleichenden Analyse des Verlaufs der Lebensqualitätsdaten der verschiedenen Gruppen Varianzanalysen für Messwiederholungsdesigns als das zentrale statistische Verfahren zur Anwendung kommen werden. Die geplante Stichprobengröße stellt den notwendigen Mindestumfang dar, den es bedarf, um die anstehenden Fragestellungen beantworten zu können, bei nur mehrere Zeitpunkte und Subgruppen berücksichtigt werden müssen.
- e.8 Bei Versuchen an gesunden Probanden, denen keine therapeutischen Vorteile aus dem Versuch erwachsen, gelten strengere Anforderungen an die Vertretbarkeit des Forschungsvorhabens als bei neuartigen Heilversuchen an Patienten (vgl. die unterschiedlichen Anforderungen in § 40 AMG gegenüber § 41 AMG)
entfällt

- e.8 Besondere Überlegungen sind bei Blind- und Doppelblindversuchen an Patienten angesichts der ungleichen Behandlung der beiden Gruppen nötig (u.a.: ist die Vorenthaltung einer aussichtsreichen neuartigen Behandlung gegenüber der Kontrollgruppe vertretbar?)
entfällt

e. Angaben über den Inhalt der Aufklärungsgespräche mit den Versuchspersonen

- 6.1 Bei Patienten:
- a) Diagnoseaufklärung
 - b) Alternative Verlaufserklärung (Prognoseaufklärung)
 - c) Risikoaufklärung, bezogen auf die Versuchsauswirkungen
 - d) Aufklärung über ein angebrachtes Verhalten der Versuchsperson während des Versuches und nach dem Versuch
 - e) Aufklärung über die Aufzeichnung von Krankheitsdaten und deren Weitergabe zur Überprüfung an den Auftraggeber, die zuständige Überwachungsbehörde (gemäß § 67 AMG) oder die zuständige Bundesoberbehörde (§ 40 (1) 2. AMG; § 20 (1) 2. MPG)
 - p) Studienbedingte röntgenologische/nuklearmedizinische Untersuchungen
 - ad a) und b)
entfällt
 - ad c)
Ansprechpartner in den teilnehmenden Institutionen stehen bei weiteren Fragen und einem Beratungsbedürfnis seitens der Patientinnen und Patienten bereit.
 - Ad d)
Eine Instruktion für die Ausfüllungsmodi des Fragebogens wird in dem Fragebogen auf der ersten Seite enthalten sein.
 - Ad e)
Die Patientinnen und Patienten werden in einem Aufklärungsschreiben über Ziel und Zwecke der Studie, Studienteilnehmer, Datenschutz, statistische Auswertung und Freiwilligkeit der Teilnahme hingewiesen. Da es sich bei der vorliegenden Studie um keine Arzneimittelstudie handelt, werden die Daten auch nicht an Auftraggeber, Überwachungsbehörde oder Bundesoberbehörde weitergeleitet.
 - Ad f)
entfällt.

6.2 Aufklärung über die Widerruflichkeit einer Einwilligung?

Im Informationsschreiben werden die Patientinnen und Patienten über die Freiwilligkeit der Teilnahme informiert, ebenso wie darüber, dass das Einverständnis zur Teilnahme jederzeit ohne Angabe von Gründen zurückgezogen werden kann. Bereits erhobene Daten werden dann nicht in die Auswertung einbezogen. Nachteile erwachsen daraus für die Untersuchungsteilnehmerinnen und -teilnehmer nicht.

- 6.3 Besondere Aufklärung über die Situation
a) bei der randomisierten Studie
b) beim Blind- und Doppelblindversuch
c) bei placebo-kontrollierten Studien

a), b) und c)
entfällt
- 6.4 Beachtung der Sonderregeln bei Minderjährigen und bei in ihrer Geschäftsfähigkeit beeinträchtigen Patienten
(§ 40 (4) 1.-4. Und § 41 2.-7. AMG; § 17 (4) 4. Und § 18 2. MPG)
entfällt

e. **Beifügung eines Musters für die (schriftlich) zu erteilende Aufklärung sowie die Einwilligungserklärung** (vgl. § 40 (2) 2. AMG; § 17 (1) 2. MPG)

s. Anlage

8. Nachweis einer ausreichenden Probandenversicherung

- entfällt
- 8.1 Aufklärung über das Bestehen und den Umfang einer Probandenversicherung (§ 40 (1) 8. AMG; § 17 (1) 9. MPG) und die danach von der Versuchsperson zu beachtenden Obliegenheiten im Falle des vermuteten Schadens und im Todesfall (s. Allgemeine Versicherungsbedingungen
-für klinische Prüfungen von Arzneimitteln
-für klinische Prüfungen von Medizinprodukten nach dem MPG

entfällt

9. Darlegung der Erfüllung etwaiger sonstiger Voraussetzungen für die Durchführung des Vorhabens (z.B. § 40 (1) 3., 6., 7. AMG, § 67 (1) AMG;)

entfällt

10. Maßnahmen bei Veränderung der Risikolage

- 10.1 Sicherstellung, dass bei Veränderungen der Risikolage während des Versuches die Güterabwägung im Sinne von Ziffer 5. Jeweils erneut durchgeführt wird und bei nachteiliger Veränderung der Risikolage auch erneute Aufklärungsgespräche mit den Versuchspersonen stattfinden
entfällt
- 10.2 Mitteilung der veränderten Abbruchkriterien an die Ethik-Kommission

Abbruchkriterien sind nicht vorgesehen. Die Teilnahme an der Fragebogenstudie ist freiwillig. Aus einer Nicht-Teilnahme ergeben sich keine negativen Konsequenzen für die Patientinnen und Patienten.

- 10.3 Mitteilung schwerwiegender oder unerwarteter Ereignisse an die Ethik-Kommission.

Wird eingehalten

Anlage

- Patienteninformation/ Einverständniserklärung
- Studienprotokoll
- Fragebögen

Hamburg, den 07.02.09

Dr. med. Silke Tribius

2.8.2 Ethics committee approval



Ärztekammer Hamburg · Postfach 76 01 09 · 22051 Hamburg

Frau
Dr. med. Silke Tribius
Ambulanzzentrum UKE GmbH
Bereich Strahlentherapie
Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg

ETHIK-KOMMISSION DER
**ÄRZTEKAMMER
HAMBURG**

Körperschaft des öffentlichen Rechts

05.03.2009

Bearb.-Nr.: PV3182 (Bitte stets angeben!)

Studie: „Lebensqualität bei Patienten mit fortgeschrittenen HNO-Tumoren“

Sehr geehrte Frau Kollegin Tribius,

über Ihr oben bezeichnetes, zur Primärberatung vorgelegtes Projekt hat die Ethik-Kommission ausführlich beraten.

Das Vorhaben entspricht den berufsrechtlichen bzw. gesetzlichen Anforderungen. Die Ethik-Kommission stimmt dem Vorhaben zu.

Die Kommission weist darauf hin, dass die Verantwortung des Versuchsleiters für das Forschungsvorhaben und seine Durchführung durch das obige Votum der Kommission nicht berührt wird.

Sie werden gebeten, die Ethik-Kommission über alle schwerwiegenden oder unerwarteten Ereignisse, die während der Studie auftreten und die die Sicherheit der Studienteilnehmer gefährden, in Verbindung mit Ihrer Stellungnahme zu unterrichten.

Die Kommission geht davon aus, dass die personenbezogenen Daten der Probanden/ Patienten den datenschutzrechtlichen Vorschriften entsprechend behandelt werden.

Die Ethik-Kommission erwartet, dass ihr nach Abschluss des Projektes unaufgefordert ein Abschluss-Bericht übersandt wird (unter Angabe der Bearb.-Nr.), aus dem der Erfolg/Misserfolg der Studie sowie Angaben darüber, ob die Studie abgebrochen oder geändert bzw. ob Regressansprüche geltend gemacht wurden, ersichtlich sind.

Mit verbindlicher Empfehlung
Im Auftrage der Kommission:

Prof. Dr. med. Th. Weber

- Vorsitzender -

P.S. Die Ethik-Kommission arbeitet auf der Grundlage deutschen Rechts und Berufsrechts sowie in Anlehnung an die ICH-GCP

Bankverbindung:
Deutsche Apoth. u. Ärztebank, BLZ 200 906 02, Konto-Nr. 000 1346 113
BIC DAAEDEDD, IBAN DE71 3006 0601 000 1346 113

Humboldtstraße 67a · 22083 Hamburg
Telefon 040 / 20 22 99-240 · Fax 040 / 20 22 99-410
ethik@aekhh.de · www.aerztekammer-hamburg.de
Geschäftsleitung: Dr. Silke Schrum

2.8.3 Patient's informed consent



Universitätsklinikum Hamburg-Eppendorf

Ambulanzzentrum UKEGmbH

Martinstr. 52

20246 Hamburg

Ansprechpartnerin:

Dr. Silke Tribius; Tel.: 040-7410-54033

email: tribius@uke.uni-hamburg.de

Forschungsprojekt „Lebensqualität bei Patienten mit fortgeschrittenen Kopf-Hals- Tumoren“

**Sehr geehrte Patientin,
sehr geehrter Patient,**

Bei Ihnen wurde ein bösartiger Tumor im Kopf-Hals- Bereich diagnostiziert und es soll nun eine Standard- Strahlentherapie (mit/ ohne begleitende Chemotherapie) durchgeführt werden. Um in der Zukunft individueller Therapieempfehlungen aussprechen zu können, möchten wir die Lebensqualität unserer Patienten vor, während und nach der Therapie anhand standardisierter Fragebögen erfassen.

Deshalb führen wir gemeinsam mit dem Institut für Medizinische Psychologie des Universitätsklinikums Hamburg-Eppendorf eine wissenschaftliche Studie durch. Die Untersuchung mit dem Titel "Lebensqualität bei Patienten mit lokal fortgeschrittenen Kopf-Hals-Tumoren" beschäftigt sich mit Fragen der Basis- Lebensqualität und wie diese sich während und nach Abschluss der Therapie verändert. Wir möchten Faktoren herausarbeiten, die möglicherweise helfen einzuschätzen, welche Therapie oder Therapiekombination am ehesten verträglich für einen Patienten ist.

Die Studie soll die Wissensgrundlage zur Prognoseeinschätzung und Rehabilitation der einzelnen Patienten auf der Basis ihrer allgemeinen und organbezogenen Lebensqualität erweitern.

Wir möchten Sie um Ihre Mithilfe bei der Durchführung dieser wissenschaftlichen Arbeit bitten!

Wenn Sie sich für eine Mitarbeit entscheiden, würden wir Sie gerne zu Beginn der Therapie, während der ersten Nachsorge (6 bis 8 Wochen nach Therapieende) sowie alle 6 Monate für 2 Jahre befragen. Das Ausfüllen der Fragebögen dauert jeweils etwa 20-30 Minuten. Die wiederholte Befragung zu mehreren Zeitpunkten ist notwendig, um Veränderungen in Ihrer Situation und Ihrer Befindlichkeit im Zeitverlauf genau zu erfassen. Zusätzlich werden Daten aus Ihrer Krankenakte zu Ihrer Erkrankung sowie zu der durchgeführten Behandlung erfaßt. Diese Angaben sind notwendig, um die Wirksamkeit von Behandlungsmaßnahmen auf ihren Gesundheitszustand analysieren zu können

Im Folgenden ist der konkrete Ablauf der Studie beschrieben:

1. Wenn Sie zur Mitarbeit bereit sind, unterschreiben Sie bitte die beigefügte Einwilligungserklärung. Sie erhalten eine Kopie für Ihre Unterlagen.
2. Füllen Sie bitte die beiliegenden Fragebögen aus und geben Sie diese Ihrer zuständigen Ärztin/ Arzt.
3. Die Einwilligungserklärung mit Ihren Personalien verbleibt zur Dokumentation für die Dauer des Forschungsprojektes in der Abteilung für Strahlentherapie des Ambulanzzentrums des UKE GmbH.
4. Die Nachsorgeretermine, bei denen dann auch die Fragebögen auszufüllen sind, werden wir mit Ihnen vereinbaren.

Aufklärung zum Datenschutz:

Die im Rahmen der Studie nach Einverständniserklärung erhobenen persönlichen Daten, insbesondere Befunde, unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen. Sie werden in Papierform bei uns pseudonymisiert (verschlüsselt) – das heißt ohne Nennung Ihres Namens, Ihres Geburtsdatums, Ihrer Anschrift oder anderer Angaben, die Rückschlüsse auf Ihre Person zulassen – gespeichert. Dazu werden alle Erhebungsbögen, die Sie im Verlauf der Studie betreffen, mit einer einheitlichen Code-Nummer versehen. Im Bereich Strahlentherapie des Ambulanzzentrums des UKE GmbH wird eine Liste geführt, die Namen und Code-Nummern verbindet. Diese Liste verbleibt zu jedem Zeitpunkt dort; Zugriff haben nur die an der Studie beteiligten Ärzte und Studienmitarbeiter.

Die Nutzung der Daten erfolgt in pseudonymisierter Form: Die Dateneingabe und -auswertung der Angaben aus den mit Code-Nummern versehenen Fragebögen erfolgt räumlich getrennt im Medizinische Psychologie. Dort ist keine Verbindung von Fragebogenangaben mit Ihren persönlichen Daten (Name, Geburtsdatum, Anschrift etc.) möglich.

Eine Weitergabe der erhobenen Daten im Rahmen des Forschungszwecks erfolgt nur in pseudonymisierter Form. Gleiches gilt für die Veröffentlichung der Studienergebnisse.

Sie haben das Recht, über die von Ihnen stammenden personenbezogenen Daten Auskunft zu verlangen. Die Speicherung der Daten erfolgt für die Dauer von 10 Jahren.

Ihre Teilnahme ist selbstverständlich freiwillig und Sie können jederzeit, auch wenn Sie schon Ihre Einwilligung gegeben haben, aus der Studie ausscheiden. Falls Sie nicht an der Studie teilnehmen möchten, entstehen Ihnen keinerlei Nachteile. Im Falle eines Widerrufes Ihrer Einwilligung werden die bis dahin erfassten Daten gelöscht.

Eine Weitergabe der Daten an staatliche oder private Einrichtungen ist ausgeschlossen.

Falls Sie noch weitere Fragen haben, steht Ihnen Ihre behandelnde Ärztin bzw. Ihr behandelnder Arzt gerne zur Verfügung.

Vielen Dank für Ihre Mitarbeit!

EINVERSTÄNDNISERKLÄRUNG

Name: _____

Vorname: _____

Adresse: _____

Telefon: _____

Ich bin über Inhalt und Zweck der Studie „Lebensqualität bei Patienten mit fortgeschrittenen Kopf-Hals-Tumoren“, die von der Strahlentherapie des Ambulanzzentrums und dem Institut für Medizinische Psychologie des Universitätsklinikums Hamburg-Eppendorf durchgeführt und ausgewertet wird, informiert worden. Zu diesem Zweck habe ich ein Informationsschreiben erhalten.

Mir wurde versichert, dass keine personenbezogenen Angaben (Name, Geburtsdatum, Adresse oder sonstige Angaben, die Rückschlüsse auf meine Person zulassen) an Dritte weitergegeben werden und dass die in der Studie erhobenen Daten gelöscht werden, sobald sie für die weitere wissenschaftliche Auswertung nicht mehr erforderlich sind.

Ich möchte die Studie durch meine Beteiligung unterstützen und willige ein, Fragebögen auszufüllen, die mir ausgehändigt oder zugeschickt werden.

Ich bin damit einverstanden, dass medizinische Daten aus dem Arztbrief bzw. durch den behandelnden Arzt in pseudonymisierter Form den Forschungsunterlagen zugeführt werden.

Unter den in dem Informationsschreiben genannten Voraussetzungen erkläre ich mein Einverständnis für die Teilnahme an der Studie.

Arzt (Stempel und Unterschrift)

Patient

Hamburg, den

Hamburg, den

2.8.4 Socioeconomic questionnaire



Universitätsklinikum
Hamburg-Eppendorf

Ambulanzzentrum

Institut und Poliklinik für
Medizinische Psychologie

Code-Nr.: _____

Lebensqualität bei HNO-Patienten

Sehr geehrte Patientin, sehr geehrter Patient,
dieser Fragebogen enthält Fragen zu verschiedenen Bereichen Ihres körperlichen und psychischen Befindens, mit denen wir erfahren möchten, wie es Ihnen jetzt, zu Beginn Ihrer strahlentherapeutischen Behandlung geht.

Bitte lesen und beantworten Sie jede Frage. Es gibt keine „richtigen“ oder „falschen“ Antworten. Falls eine Frage weniger auf Sie zutrifft oder es Ihnen einmal schwer fällt, sich für eine Antwort zu entscheiden, kreuzen Sie bitte die Antwort an, die spontan am ehesten zutrifft. Bei einigen Fragen kann es zu Überschneidungen mit vorigen Fragen kommen, die aus technischen Gründen leider nicht zu vermeiden waren.

Bitte haben Sie Verständnis für die Länge des Fragebogens.

Beispielfrage

	gar nicht	kaum	etwas	ziemlich	sehr
Ich fühle mich über die laufende Behandlung informiert.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Wenn Sie sich zum Beispiel über die laufende Behandlung ***ziemlich*** informiert fühlen, kreuzen Sie das entsprechende Kästchen an.

Die Auswertung der Fragebögen erfolgt im Rahmen einer Kooperation mit dem Institut für Medizinische Psychologie des Universitätsklinikums Hamburg-Eppendorf. Die Fragebögen werden anonymisiert ausgewertet, d.h. Ihre Angaben im Fragebogen werden nicht mit Ihrer Person in Verbindung gebracht. Die Ergebnisse werden ausschließlich zu Forschungszwecken verwendet und nicht an Dritte weitergeleitet.

Sollten Sie noch Fragen haben, wenden Sie sich bitte an die für Sie zuständige Ärztin bzw. den Arzt oder die Studienleitung:

Dr. med. Silke Tribius Universitätsklinikum Hamburg- Eppendorf Ambulanzzentrum Martinstr. 52 20246 Hamburg Tel.: 040 42803 - 4031/ 6140 e-Mail: tribius@uke.uni-hamburg.de	Dr. phil. Corinna Bergelt Universitätsklinikum Hamburg-Eppendorf Institut und Poliklinik für Medizinische Psychologie Martinstr. 52 – S35 20246 Hamburg Tel.: 040/42803 4939 e-Mail: bergelt@uke.uni-hamburg.de
--	---

A Persönliche Daten

A1	geb	Monat	Jahr	
	Geburtsdatum (nur Monat und Jahr)			
geschl	Geschlecht	<input type="checkbox"/> weiblich	<input type="checkbox"/> männlich	
nat1	Nationalität	<input type="checkbox"/> deutsch	<input type="checkbox"/> anderes: _____ nat2	
fam1	Familienstand			
	ledig (nie verheiratet)	verheiratet (mit dem Ehepartner zusammenlebend)	verheiratet (in Trennung lebend)	geschieden verwitwet
	<input type="checkbox"/>	<input type="checkbox"/> ...seit →	<input type="checkbox"/> ...seit →	<input type="checkbox"/> ...seit → <input type="checkbox"/> ...seit → _____
	(Datum) fam1			
part1	Haben Sie zur Zeit einen festen Partner?		<input type="checkbox"/> ja... <input type="checkbox"/> nein... seit →	_____
kindz	Wie viele Kinder haben Sie?		Anzahl	<input type="checkbox"/> keine Kinder
(Datum) part2				
A2	Wie viele Personen leben insgesamt in Ihrem Haushalt, Sie selbst eingeschlossen? Zählen Sie dabei bitte auch Kinder mit und tragen Sie die Anzahl ein.			
wohn1	insgesamt <input type="checkbox"/> _____ Personen, davon → <input type="checkbox"/> _____ 2 unter 18 Jahre alt			
Wie hoch ist das monatliche Nettoeinkommen Ihres Haushalts insgesamt?				
A3	Nettoeinkommen: Die Summe aus Lohn/Gehalt/Einkommen usw., nach Abzug von Steuern und Sozialabgaben.			
netto	<input type="checkbox"/> bis unter 500 €	<input type="checkbox"/> 2000 € bis unter 3000 €		
	<input type="checkbox"/> 500 € bis unter 1000 €	<input type="checkbox"/> 3000 € bis unter 4000 €		
	<input type="checkbox"/> 1000 € bis unter 2000 €	<input type="checkbox"/> 4000 € und mehr		
A4	Sind Sie Hauptverdiener / Hauptverdienerin Ihres Haushaltes? <input type="checkbox"/> ja <input type="checkbox"/> nein			
A5	Welches ist Ihr <u>höchster</u> Schulabschluss?		A6 ausb1 Welches ist Ihr <u>höchster</u> berufsqualifizierender Abschluss?	
schul1	<input type="checkbox"/> ohne Schulabschluss abgegangen <input type="checkbox"/> Haupt-/Volksschulabschluss <input type="checkbox"/> Realschulabschluss/Mittlere Reife <input type="checkbox"/> Abschluss der Polytechnischen Oberschule 10. Klasse (vor 1965: 8. Klasse) <input type="checkbox"/> Fachhochschulreife <input type="checkbox"/> Allgemeine/fachgebundene Hochschulreife/Abitur <input type="checkbox"/> andere: <input type="checkbox"/> _____ schul2		<input type="checkbox"/> kein berufsqualifizierender Abschluss <input type="checkbox"/> abgeschlossene Lehre (beruflich-betriebliche Ausbildung) <input type="checkbox"/> Handelsschule/Berufsfachschule (beruflich-schulische Ausbildung) <input type="checkbox"/> Abschluss an Fachschule, Meister- Technikerschule, Berufs- oder Fachakademie <input type="checkbox"/> Fachhochschulabschluss, Ingenieurschule <input type="checkbox"/> Hochschulabschluss <input type="checkbox"/> andere: <input type="checkbox"/> _____ ausb2	

A6 Sind Sie zur Zeit erwerbstätig?

(Bitte auch ausfüllen, wenn Sie zur Zeit krankgeschrieben sind.)

w1_ty

- ja, Vollzeit
- ja, Teilzeit, und zwar _____ Stunden/Woche w2_ty
- nein, arbeitslos/erwerbslos seit _____._____._____ w3_ty
- nein, in Ausbildung/Umschulung
- nein, in Rente wegen verminderter Erwerbsfähigkeit seit _____._____._____ w4_ty
- nein, in Altersrente
- sonstiges: _____ w5_ty

A7 Welche berufliche Position nahmen Sie vor Ihrer Erkrankung ein?(Falls Sie arbeitslos, berentet oder aus anderen Gründen erwerbsunfähig waren bzw. sind, geben Sie bitte Ihre letzte Position an.)

arb

Arbeiter(in):

- ungelernte(r)
- angelernte(r)
- Facharbeiter(in)
- Vorarbeiter(in)
- Meister(in)

ang

Angestellte(r) mit

- einfacher Tätigkeit
- schwieriger Tätigkeit
- leitender Tätigkeit

Beamtin/Beamter

- im einfachen Dienst
- im mittleren Dienst
- im gehobenen Dienst
- im höheren Dienst

sel

Selbständige(r):

- selbständige(r) Landwirt(in)
- Akademiker(in) im freien Beruf
- Selbständige(r) im Handel, Gewerbe, Handwerk, Industrie, Dienstleistung
- Mit helfende(r) im Familienbetrieb

→ Anzahl Mitarbeiter(innen): seit

son

Sonstiger, hier nicht aufgeführter Beruf:

C Fragen zu Alkohol- und Nikotinkonsum

C1 Alkoholkonsum: Welche Aussage trifft am ehesten auf Sie zu?

- alc1_ty
- Ich trinke regelmäßig alkoholhaltige Getränke
 - Ich trinke gelegentlich alkoholhaltige Getränke
 - Ich habe früher regelmäßig alkoholhaltige Getränke getrunken (seit _____ Jahren nicht mehr)
 - Ich habe früher gelegentlich alkoholhaltige Getränke getrunken (seit _____ Jahren nicht mehr)
 - Ich trinke keinen Alkohol

Welche alkoholhaltigen Getränke trinken Sie durchschnittlich in einer Woche oder haben Sie getrunken?

Wieviel?

- | | alcxa_ty | alcxb_ty |
|---------|---|--|
| alcx_ty | <input type="checkbox"/> Bier (ca.5%) | _____ (Flaschen ca. 0,33 l) |
| | <input type="checkbox"/> Wein (ca. 12%) | _____ (Gläser ca. 0,2 l) oder _____ (Flaschen ca. 0,7 l) |
| | <input type="checkbox"/> Leichte Spirituosen (ca. 20%) | _____ (Gläschchen 2 cl) oder _____ (Flaschen ca. 1 l) |
| | <input type="checkbox"/> Mittlere Spirituosen (ca. 30%) | _____ (Gläschchen 2 cl) oder _____ (Flaschen ca. 1 l) |
| | <input type="checkbox"/> Harte Spirituosen (ab 40%) | _____ (Gläschchen 2 cl) oder _____ (Flaschen ca. 1 l) |

C2 Nikotinkonsum: Welche Aussage trifft am ehesten auf Sie zu?

- nic1_ty
- Ich rauche
 - Ich habe früher geraucht (seit _____ Jahren nicht mehr)
 - Ich rauche nicht

Wenn sie rauchen oder geraucht haben, beantworten Sie bitte folgende Fragen nach der Menge

	Was haben Sie geraucht?	Wieviel Stück pro Tag?	Wie viele Jahre?
nicx_ty	<input type="checkbox"/> Zigaretten	_____	_____
	<input type="checkbox"/> Zigarillos	_____	_____
	<input type="checkbox"/> Zigarren	_____	_____
	<input type="checkbox"/> Pfeife	_____	_____

dat_ty

Ausfülldatum:

				Tag	Monat	Jahr
				2	0	

**Vielen Dank für die Beantwortung des Fragebogens
und die Unterstützung unserer Studie!**

2.8.5 Medical questionnaire

Nebenwirkungen und Lebensqualität bei und nach Bestrahlung von Kopf-Hals-Tumoren
Erhebungsbogen (1)

Allgemein

- 1) Identifikationsnummer des Pat.
 - 2) Initialen des Patienten
 - 3) Geburtsdatum (TT MM JJJJ)
 - 4) Geschlecht (1=männlich, 2=weiblich)
 - 5) Körpergewicht (kg)
 - 6) Körpergröße (cm)
 - 7) BMI (kg/m²)
 - 8) Allgemeinzustand nach Karnofsky (10-100)
 - 9) Vorhergegangene Strahlentherapie im Kopf-Hals-Bereich (0=nein, 1=ja)
 - 10) Vorhergegangene Chemotherapie (0=nein, 1=ja)
 - 11) Datum der letzten Blutentnahme (TT MM JJJJ)
 - 12) Hämoglobin-Wert bei unter 11) genannter Blutentnahme (g/dl)
-

Tumor

- 13) Histologisch gesicherte Diagnose eines Plattenepithelkarzinoms (0=nein, 1=ja)
- 14) Lage /Sitz des Primärtumors (1=Mundhöhle, 2=Oroph., 3=Hypoph./ Larynx, 4=Nasoph.)
- 15) T-Stadium (1=T1, 2=T2, 3=T3, 4=T4)
- 16) N-Stadium (0=N0, 1=N1, 2=N2, 3=N3)
- 17) Wenn N-Stadium = N2, bitte spezifizieren (1=2a, 2=2b, 3=2c)
- 18) M-Stadium (0=M0, 1=M1)
- 19) Grading (1=G1, 2=G2, 3=G3)
- 20) Vorhergegangene Operation (0=R0, 1=R1, 2=R2, 3=keine OP)
- 21) Wenn operiert, bitte Operationsdatum (TT MM JJJJ)
- 22) Art der OP (1=Laryngektomie, 2=Larynxeilresektion, 3=Defektresektion, 4=selektive ND, 5=modifiziert radikale ND, 6=radikale ND, 7=andere OP (bspw. Kombinationen))
- 23) Wenn andere OP-Art ,bitte erläutern _____
- 24) Zahnsanierung vor Beginn der Strahlentherapie (0=nein, 1=ja)

2.8.6 Questionnaire about radiation treatment data

Nebenwirkungen und Lebensqualität bei und nach Bestrahlung von Kopf-Hals-Tumoren
Bestrahlung (3)

Initialen des Pat.: Geburtsdatum: . . Identifikationsnr. Des Pat.:

- 45) Erster Tag der Bestrahlung (TT MM JJJJ)..... . .
46) Letzter Tag der Bestrahlung (TT MM JJJJ)..... . .
47) Behandlungszeit in Tagen inkl. Wochenenden.....
48) Gesamtdosis am Zielvolumen 1. Ordnung (Gy)..... .
49) Gesamtdosis am Zielvolumen 2. Ordnung (Gy)..... .
50) Gesamtdosis am Zielvolumen 3. Ordnung (Gy)..... .
51) Bestrahlungstechnik (1=3D konformal, 2=IMRT, 3=Tomo).....
52) Wurde die Strahlentherapie vorübergehend unterbrochen?

0= nein

- 53) 1= ja, wegen Nebenwirkungen, *bitte genaue Angabe:* _____
2= ja, aus administrativen/ technischen Gründen
54) 3= ja, aus anderen Gründen, *bitte genaue Angabe:* _____
55) Wenn ja, Anzahl der Unterbrechungstage.....
56) Simultane Chemotherapie? (0= nein, 1= ja).....
57) Wenn ja, platinhaltige Chemotherapie? (0= nein, 1= ja).....

2.8.7 Index of tables¹⁾

Table	Title	Page
1	Sample characteristics of patients at the beginning of (chemo-) radiotherapy (n=95).	4
2	General quality of life at the beginning of (chemo-) radiotherapy (n=95) assessed with the European Organisation for Research and Treatment of Cancer 30- item QoL questionnaire.	5
3	Symptoms related to head and neck cancers at the beginning of (chemo-) radiotherapy (n=95): European Organisation for Research and Treatment of Cancer 35- item Head and Neck Module.	5
4	Change in quality of life during (C)RT (n=95).	6
5	Change in quality of life during (chemo-) radiotherapy in patients with low vs. high (median split) initial Global health status (repeated measures analysis of variance).	7
6	Sample characteristics of patients at the beginning of radiation treatment: QoL median split (median=50).	7
7	Comparison of a choice of QoL- instruments applied in HNC- research (modified from Tschesner et al. 2008).	20
8	Frequency of recurrence and median survival in LAHNC- patients depending on risk factors (from Forastière et al. 2001).	25
9	Predictors for post- treatment QoL- development in HNC- patients.	26
10	Radiation technique (n=95).	35

¹⁾ Table 1- 6 are part of the publication by Tribius et al. (2012a).

2.8.8 Index of figures

Number	Title	Page
1	Factors influencing the subjective well-being (from Bjordal and Kaasa 1992).	11
2	Types of QoL- questionnaires (according to Sayed et al. 2009).	15
3	Treatment options in HNC.	22
4	Acute toxicity in HNC- treatment according to the TAME- analysis (Trotti et al. 2007): 13 RTOG- trials between 1991 and 2000.	27
5	Score levels indicate diametrical QoL- levels for functioning and symptom scores in the EORTC- questionnaires (except dichotomously answered items).	29
6	Assessment times and data collection.	32
7	Tumor- site.	34
8	Changes in global health status and functions (QLQ- C30).	37
9	Changes in chosen cancer- specific symptoms (QLQ- C30).	38
10	Changes in HNC- specific- symptoms, selection (QLQ- H&N35).	38
11	Changes in dry mouth and sticky saliva (QLQ- H&N35).	39
12	Changes in additional HNC- specific issues (QLQ- H&N35).	39
13	Change in global health status after dichotomization by initial QoL (QLQ- C30).	42
14	Change in emotional function after dichotomization by initial QoL (QLQ- C30).	43
15	Initial functional status of our sample compared to the reference group (for all shown score differences p<0.001).	44
16	Initial QLQ- C30- symptoms of our sample compared to the reference group (for all shown differences p<0.001).	45
17	Potential relationship between persisting QoL- reducing symptoms and QoL (from Murphy et al. 2007).	58

2.8.9 Index of abbreviations

Abbreviation	Meaning
3D- CRT	3- Dimensional conformal radiation therapy.
ACR	American College of Radiation.
ANOVA	Analysis of variance.
BMI	Body mass index.
CRT	Chemoradiotherapy.
(C)RT	Radiation treatment combined with or without chemotherapy.
CTC	Centers for Disease Control and Prevention.
CUP	Carcinoma of unknown primary.
e. g.	For example (latin: exempli gratia).
EGFR	Epithelial growth factor- receptor.
EORTC	European Organisation for Research and Treatment of Cancer.
et al.	And others (latin: et alii/ aliae/ alia).
FACT	Functional Assessment of Cancer Treatment.
FACT- G	Functional Assessment of Cancer Treatment – General questionnaire.
FACT- H&N	Functional Assessment of Cancer Therapy- Head and Neck Version.
ff.	And following.
Gy	Gray.
HNC	Head and neck cancer.
HNQOL	Head and Neck Quality of Life instrument.
HPV	Human papilloma virus.
i.e.	Meaning (latin: id est).
IMRT	Intensity modulated radiation therapy.
LANHC	Locally advanced head and neck cancer.
MRND	Modified radical neck dissection.
N	Population.
n. a.	Not available.
NCCN	National Comprehensive Cancer Network.
NCI	National Cancer Institute.
OAR	Organs at risk.
OPC	Oropharyngeal cancer.
p	Probability measure.
PF	Chemotherapy- protocol consisting of Cisplatin and 5- Fluorouracil.
QALY	Quality- Adjusted Life Year.
QLQ- C30	EORTC Quality of Life Questionnaire core version.
QLQ- H&N35	EORTC Quality of Life Questionnaire for Head and Neck cancer.
QoL	Health- related quality of life.
QOL- RTI	Quality Of Life – Radiation Therapy Instruments general questionnaire.
QOL- RTI/ H&N	Quality of Life Radiation Therapy Instrument – Head and Neck Module.
QOLS	Quality of Life Scale.
RND	Radical neck dissection.

RT	Radiation treatment.
RTOG	Radiation Therapy Oncology Group.
SND	Selective neck dissection.
SD	Standard deviation.
T1	First data assessment in our study (before (chemo-) radiotherapy)
T2	Second data assessment in our study (at the end of (chemo-) radiotherapy)
T3	Third data assessment in our study (six until eight weeks after completion of (chemo-) radiotherapy).
TAME	Analysis of short-term toxicity, adverse long- term- effects and mortality risk in head and neck cancer by Trott et al. (2009).
TNM	Cancer- classification- system by the UICC (for HNC: Sabin et al. 2009), where T stands for tumor size, N for nodal spread and M for distant metastases.
UICC	International Union Against Cancer.
UKE	University Medical Center Hamburg- Eppendorf.
UWQOL	University of Washington QoL questionnaire.
WHO	World Health Organization.
WHOQOL	World Health Organization- Quality- Of Life- instrument.

2.9 References

- Aaronson NK (1989): Quality of life assessment in clinical trials: methodological issues. *Control Clin Trials*, 10 (4 Suppl), 195S-208S.
- Alicikus ZA, Akman F, Ataman OU, Dag N, Orcin E, Bakis B, Kinay M (2009): Importance of patient, tumor and treatment related factors on quality of life in head and neck cancer patients after definitive treatment. *Eur Arch Otorhinolaryng*, 266 (9), 1461-1468.
- Anderson RT, Aaronson NK, Wilkin D (1993): Critical review of the international assessments of health-related quality of life. *Qual Life Res*, 2 (6), 369-395.
- Anderson RT, Aaronson NK, Bullinger M, McBee WL (1996): A review of the progress towards developing health-related quality-of-life instruments for international clinical studies and outcomes research. *Pharmacoeconomics*, 10 (4), 336-355.
- Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML (2010): Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*, 363(1), 24-35.
- Bairati I, Meyer F, Gelinas M, Fortin A, Nabid A, Brochet F, Mercier JP, Tetu B, Harel F, Abdous B, Vigneault E, Vass S, Del VP, Roy J (2005): Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. *J Clin Oncol*, 23; 5805-5813.
- Beisland E, Aarstad AK, Osthus AA, Aarstad HJ (2013): 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. *Acta Otolaryngol*, 133 (2), 209-217.
- Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931 (2004): Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*, 350 (19), 1945-1952.
- Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefèvre JL (2005): Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*, 27(10), 843-850.

- Bettag M, Blatt- Bodewig M, Bokemeyer C, Claßen J, Distler L, Dornoff W, Folprecht G, Frick S, Glaß B, Goldschmidt H, Graf N, Hagmann FG, Hertel F, Hofheinz R, Honecker F, Hübner G, Huwer H, Koch P, Köhne CH, Kortmann RD, Krämer I, Liersch R, Link H, Lordick F, Mahlberg R, Matzdorff A, Ohlmann C, Preundschuh M, Preiß J, Schmidberger H, Schmieder A, Schneeweiß A, Seegenschmiedt MH, Siemer S, Stasche N, Trümper L, Ukena D, Uppenkamp M, Voigt H, Voigt HJ, Voswinkel J, Wilhelm H, Wulf G, Zwick C (2010): Taschenbuch Onkologie, Interdisziplinäre Leitlinien zur Therapie 2010/11. Preiß, Dornoff, Hagmann, Schmieder (pub.), 15th edition, W. Zuckerschwerdt Verlag, München (DE), 137-144, 384.
- Bingel U, Tracey I (2008): Imaging CNS modulation of pain in humans. *Physiol (Bethesda)*, 23, 371-380.
- Bjordal K, Kaasa S (1992): Psychometric validation of the EORTC core quality of life questionnaire, 30- item version and a diagnosis- specific module for head and neck cancer patients. *Acta Oncol*, 31 (3), 311-321.
- Bjordal K, Ahlner- Elmquist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, Kaasa S (1994): Development of a European organization for research and treatment of cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. *Acta Oncol*, 33 (8), 879-885.
- Bjordal K, Kaasa S, Mastekaasa A (1994): Quality of life in patients treated for head and neck cancer: a follow- up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys*, 28 (4), 847-856.
- Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, Ahlner- Elmquist M, Maher EJ, Mayza JW, Brédart A, Söderholm AL, Arraras JJ, Feine JS, Abendstein H, Morton RP, Pignon T, Huguenin P, Bottomly A, Kaasa S (2000): A 12 country field study of the EORTC QLQ- C30 (version 3.0) and the head and neck cancer specific module (EORTC- QLQ- H&N35) in head and neck cancer patients. EORTC Quality of life Group. *Eur J Cancer*, 36 (14), 1796-1807.
- Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK (2006): Radiotherapy plus Cetuximab for Squamous- Cell Carcinoma of the Head and Neck. *N Eng J Med*, 354 (6), 567-587.
- Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK (2010): Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*, 11 (1), 21-27.

- Borggreven PA, Verdonck- de Leeuw IM, Muller MJ, Heiligers ML, de Bree R, Aaronson NK, Leemans CR (2007): Quality of life and functional status in patients with cancer of the oral cavity and oropharynx: pretreatment values of a prospective study. *Eur Arch Otorhinolaryngol*, 264 (6), 651- 657.
- Bullinger M (2006): Methodological basis and aspects of quality of life. *Dtsch Med Wochenschr*, 131 (19 Suppl 1), 5-7.
- Bullinger M, Hasford J (1991): Evaluating Quality- of- Life- Measures for Clinical Trials in Germany. *Control Clin Trials*, 12, 91S-105S.
- Bullinger M, Anderson R, Cella D, Aaronson N (1993): Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. *Qual Life Res*, 2 (6), 451-459.
- Burckhardt CS, Anderson KL (2003): The Quality of Life Scale (QOLS): Reliability, Validity and Utilization. *Health Qual Life Outcomes*, 1, 60.
- CDC (2013): Health- Related Quality of Life (HRQOL). Conceppoints, Atlanta, Georgia (USA). [online] URL: <http://www.cdc.gov/hrqol/> [date: 15.10.2013, 22:41h].
- Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK; Radiation Therapy Oncology Group 9501/Intergroup (2004): Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*, 350 (19), 1937–1944.
- Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Lustig R, Ensley JF, Thorstad W, Schultz CJ, Yom SS, Ang KK (2012): Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*, 1;84(5), 1198-1205.
- Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS, Jassem J, Baselga J, Rowinsky EK, Amellal N, Comte S, Bonner JA (2007): Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. *J Clin Oncol*, 25(16), 2191-2197.
- Davies AD, Davies C, Delpo MC (1986): Depression and anxiety in patients undergoing diagnostic investigations for head and neck cancers. *Br J Psychiatry*, 149, 491-493.
- De Graeff A, de Leeuw J, Ros W, Hordijk GH, Blijham, Winnubst J (2000): Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head Neck*, 22 (4), 398-407.

- De Leval N (1999): Quality of life and depression: symmetry concepts. *Qual Life Res*, 8(4), 283-291.
- Deutscher Bundestag (2013): Schlussbericht der Enquete- Kommission "Wachstum, Wohlstand, Lebensqualität – Wege zu nachhaltigem Wirtschaften und gesellschaftlichem Fortschritt in der sozialen Marktwirtschaft, Bundestagsdrucksache 17/13300, Berlin (DE), 20-28.
- Elwood TW (1972): Old age and the quality of life. *Health Serv Rep*, 87 (10), 919-931.
- EORTC- AISBL/ IVZW (2011): EORTC Quality Of Life Group Activities. Brussels (BE). [online] URL: http://groups.eortc.be/qol/qolg_activities.htm [date: 14.01.2012, 16:15h].
- EORTC- AISBL/ IVZW (2011): EORTC Quality Of Life Group History. Brussels (BE). [online] URL: http://groups.eortc.be/qol/qolg_history.htm [date: 25.01.2012, 11: 08h].
- EORTC- AISBL/ IVZW (2012): EORTC Quality Of Life Group Projects. Brussels (BE). [online] URL: http://groups.eortc.be/qol/qolg_projects.htm#H&N35_rev [date: 24.04.2012, 14:06h].
- Fang FM, Tsai WL, Chien CY, Chiu HC, Wang CJ, Chen HC, Hsiung CY (2005): Changing quality of life in patients with advanced head and neck cancer after primary radiotherapy or chemoradiation. *Oncol*, 68 (4-6), 405-413.
- Forastière A, Koch W, Trott A, Sidransky D (2001): Head and Neck Cancer. *N Engl J Med*, 345 (26), 1890-1900.
- Forrest WA (1976): Oxprenolol in hypertension: a report on 2,770 patients in general practice originally treated with methyldopa. *Scott Med J*, 21 (1), 28-30.
- Galbraith JK (1964): Economics and the Quality of Life. *Science*, 145 (3628), 117-123.
- Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R (2008): Distinct risk factor profiles for human papillomavirus type 16- positive and human papillomavirus type 16- negative head and neck cancers. *J Natl Cancer Inst*, 100 (6), 407-420.
- Güthlin C (2004): Response shift: old problems and their new application on quality of life research. *Zeitschr Med Psych*, 13 (4), 165-174.
- Güthlin C (2006): Die Messung gesundheitsbezogener Lebensqualität: ausgewählte psychometrische Analysen und Anwendungsprobleme. Wirtschafts- und verhaltenswissenschaftl. Dissertation Universität Freiburg, Freiburg (DE).
- Hammerlid E, Taft C (2001): Health- related quality of life in long- term head and neck cancer survivors: a comparison with general population norms. *Br J Cancer*, 84 (2), 149-156.

- Hammerlid E, Silander E, Hörnestam L, Sullivan M (2001): Health- related quality of life three years after diagnosis of head and neck cancer – a longitudinal study. *Head Neck*, 23 (2), 113-125.
- Hammerlid E, Bjordal K, Ahlner- Elmquist M, Boysen M, Evensen J, Björklund A, Jannert M, Kaasa S, Sullivan M, Westin T (2001): A prospective Study of Quality of Life in Head and Neck Cancer Patients. Part I: At diagnosis. *Laryngoscope*, 111, 669-678.
- Hamoir M, Ferlito A, Schmitz S, Hanin FX, Thariat J, Weynand B, Machiels JP, Grégoire V, Robbins KT, Silver CE, Strojan P, Rinaldo A, Corry J, Takes RP (2012): The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease. *Oral Oncol*, 48 (3), 203-210.
- Hinni ML, Salassa JR, Grant DG, Pearson BW, Hayden RE, Martin A, Christiansen H, Haughey BH, Nussenbaum B, Steiner W (2007): Transoral laser microsurgery for advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg*, 133 (12), 1198-1204.
- Hoffmann M, Hoffmann AS, Tribius S (2012): Public awareness of human papilloma virus infection in the head and neck area. An appeal for precision in diagnostics and for public health awareness. *HNO*, 60 (11), 968-973.
- Ishitoya J, Toriyama M, Oguchi N, Kitamura K, Ohshima M, Asano K, Yamamoto T (1989): Gene amplification and overexpression of EGF receptor in squamous cell carcinomas of the head and neck. *Br J Cancer*, 59 (4), 559-562.
- Jabbari S, Kim HM, Feng M, Lin A, Tsien C, Elshaikh M, Terrel JE, Murdoch- Kinch C, Eisbruch A (2005): Matched case- control study of quality of life and xerostomia after intensity- modulated radiotherapy or standard radiotherapy for head and neck cancer: initial report. *Int J Radiat Oncol Biol Phys*, 63 (3), 725-731.
- Joyce CRB, Hickey A, McGee HM, O'Boyle CA (2003): A theory- based method for the evaluation of individual quality of life: the SEIQoL. *Qual Life Research*, 12, 275-280.
- Karnell L, Funk G, Christensen A, Rosenthal E. Magnuson J (2006): Persistent post-treatment depressive symptoms in patients with head and neck cancer. *Head Neck*, 28 (5), 453-461.
- Karnofsky DA, Burchenal JH (1949): Clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of chemotherapeutic agents. Mc Leod CM, Ed. New York: Columbia University Press (USA), 196.

- Karow T, Lang- Roth R (2011): Immunsuppressiva/ Grundlagen Hämatologie und Onkologie. In: Allgemeine und spezielle Pharmakologie und Toxikologie. 19th Edition, Thomas Karow Verlag, Pulheim (DE), 898-900.
- Karstens JH, Kremer M, Meyer A, Warszawki A, Bruns F (2005): Kopf- Hals-Karzinome. In: Strahlentherapie und Radioonkologie aus interdisziplinärer Sicht. Karstens JH (pub.), 4th edition, Lehmanns Media LOB.de, Hannover (DE), 71-85.
- Kroeber- Riel W, Weinberg P, Kröppel- Klein A (1999): 2. Teil: Psychische Determinanten des Konsumentenverhaltens. In: Vahlens Handbücher: Konsumentenverhalten. 9th Edition, Verlag Franz Vahlen, München (DE), 142-143.
- Kuntz AL, Weymuller EA Jr. (1999): Impact of neck dissection on quality of life. *Laryngoscope*, 109 (8), 1334-1338.
- Langendijk JA, Doonaert P, Verdonck- de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ (2008): Impact of Late Treatment- Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy. *J Clin Oncol*, 26, 3770-3776.
- Lazarus RS, Opton EM, Nomikos MS, Rankin NO (1965): The principle of short-circuiting of threat: further evidence. *J Pers*, 33, 622–635.
- Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, de Raucourt D, Langendijk JA (2012): Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10- year results of EORTC trial 24891. *Annal Oncol*, e- publication ahead of print, doi: 10.1093/annonc/mds065.
- Le Pen C, Lévy E, Loos F, Banzet MN, Basdevant A (1998): “Specific” scale compared with “generic” scale: a double measurement of the quality of life in a French community sample of obese subjects. *J Epidemiol Community Health*, 52 (7), 445-450.
- List MA, Rutherford JL, Stracks J, Pauloski BR, Logemann JA, Lundy D, Sullivan P, Goodwin W, Kies M, Vokes EE (2004): Prioritizing treatment outcomes: head and neck cancer patients versus nonpatients. *Head Neck*, 26 (2), 163-170.
- Lüllmann H, Mohr K, Wehling M (2003): Kapitel 17: Antineoplastische Wirkstoffe. In: Pharmakologie und Toxikologie. 15th Edition, Georg Thieme Verlag, Stuttgart (DE), 472-476.
- Maurer J, Hipp M, Schäfer C, Kölbl O (2011): Dysphagia – Impact on Quality of Life after Radio(chemo)therapy of Head and Neck Cancer. *Strahlenther Onkol*, 11, 744-749.
- McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P (2007): The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*, 7 (30) doi: 10.1186/1471-2288-7-30.

- McMillan AS, Pow EH, Kwong DL, Wong MC, Sham JS, Leung LH, Leung WK (2006): Preservation of quality of life after intensity- modulated radiotherapy for early- stage nasopharyngeal carcinoma: results of a prospective longitudinal study. *Head Neck*, 28 (8), 712-722.
- Mehanna H, Beech T, Nicholson T, El- Hariy I, McConkey C, Paleri V, Roberts S (2012): Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer – systematic review and meta-analysis of trends by time and region. *Head Neck*, e- publication ahead of print, doi: 10.1002/hed.
- Meyer F, Fortin A, Gélinas M, Nabid A, Brochet F, Tétu B, Beirati I (2009): Health-related quality of life as a survival predictor for patients with localized head and neck cancer treated with radiation therapy. *J Clin Oncol*, 27 (18), 2970-2976.
- Meyer F, Fortin A, Wang CS, Liu G, Bairati I (2012): Predictors of severe acute and late toxicities in patients with localized head- and- neck cancer treated with radiation therapy. *Int J Radiat Oncol Biol Phys*, 82 (4), 1454-1462.
- Mork J, Lie AK, Glattre, E, Hallmans G, Jellum E, Koskela P, Møller B, Pukkala E, Schiller JT, Youngman L, Lehtinen M, Dillner J (2001): Human papillomavirus infection as a risk factor for squamous- cell carcinoma of the head and neck. *N Engl J Med*, 344 (15), 1125-1131.
- Murphy BA, Ridner S, Wells N, Dietrich M (2007): Quality of life research in head and neck cancer: A review of the current state of the science. *Crit Rev Oncol Hematol*, 62, 251-267.
- Näsman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, Ährlund- Richter S, Marklund L, Romanian M, Lindquist D, Ramqvist T, Lindholm J, Sparén P, Ye W, Dahlstrand H, Munck- Wikland E, Dalianis T (2009): Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: An epidemic of viral- induced carcinoma? *Int J Cancer*, 125, 362-366.
- NCI, National Institutes of Health of the United States Department of Health and Human Services (2009): Common Terminology Criteria for Adverse Events Version 4.0, NIH Publication No. 09-5410. Bethesda, Maryland (USA). [online] URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [date: 15.5.2012, 18:03h].
- Neilson KA, Pollard AC, Boonzaier AM, Corry J, Castle DJ, Mead KR, Gray MC, Smith DI, Trauer T, Couper JW (2010): Psychological distress (depression and anxiety) in people with head and neck cancers. *Med J Aust*, 193 (5 Suppl), S48-S51.
- Nibu K, Ebihara Y, Ebihara M, Kawabata K, Onitsuka T, Fujii T, Saikawa M (2010): Quality of life after neck dissection: a multicenter longitudinal study by the Japanese

Clinical Study Group on Standardization of Treatment for Lymph Node Metastasis of Head and Neck Cancer. *Int J Clin Oncol*, 15 (1), 33-38.

- Orhan KS, Demirel T, Balso B, Orhan EK, Yücel EA, Güldiken Y, Değer K (2007): Spinal accessory nerve function after neck dissections. *J Laryngol Otol*, 121 (1), 44-48.
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998): Interpreting the significance of changes in health- related quality of life scores. *J Clin Oncol*, 16 (1), 139-144.
- Osthus AA, Aarstad AK, Olofsson J, Aarstad HJ (2011): Head and neck specific Health Related Quality of Life scores predict subsequent survival in successfully treated head and neck cancer patients: A prospective cohort study. *Oral Oncol*, 47 (10), 974-979.
- Pfister DG, Ang K, Brockstein B, Colevas AD, Ellenhorn J, Goepfert H, Hicks WL Jr, Hong WK, Kies MS, Lydiatt W, McCaffrey T, Mittal BB, Ridge JA, Schuller DE, Shah JP, Spencer S, Trott A 3rd, Urba S, Weymuller EA Jr, Wheeler RH 3rd, Wolf GT; National Comprehensive Cancer Network (2000): NCCN Practice Guidelines for Head and Neck Cancers. *Oncology (Williston Park)*, 14(11A), 163-194.
- Pfister DG, Ang KK, Brizel DM, Burtness BA, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW, Gilbert J, Gillison ML, Haddad RI, Haughey BH, Hicks WL, Hitchcock YJ, Kies MS, Lydiatt WM, Maghami E, Martins R, McCaffrey T, Mittal BB, Pinto HA, Ridge JA, Samant S, Sanguineti G, Schuller DE, Shah JP, Spencer S, Trott A 3rd, Weber RS, Wolf GT, Worden F (2011): NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 9(6), 596-650.
- Pfister DG, Ang KK, Brizel DM, Burtness BA, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW, Gilbert J, Gillison ML, Haddad RI, Haughey BH, Hicks WL Jr, Hitchcock YJ, Kies MS, Lydiatt WM, Maghami E, Martins R, McCaffrey T, Mittal BB, Pinto HA, Ridge JA, Samant S, Schuller DE, Shah JP, Spencer S, Weber RS, Wolf GT, Worden F, Yom SS, McMillian NR, Hughes M (2013): Head and neck cancers, version 2.2013. Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*, 11(8), 917-923.
- Pignon JB, le Maître A, Bourhis J on behalf of the MACH- NC collaborative group (2007): Meta- analysis of chemotherapy in head and neck cancer (MACH- NC): An update. *Int J Radiat Oncol Biol Phys*, 69 (2 suppl.), 112-114.
- Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group (2009): Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*, 92 (1), 4-14.

- Pourel N, Peiffert D, Lartigau E, Desandes E, Luporsi E, Conroy T (2002): Quality of life in long- term- survivors of oropharynx carcinoma. *Int J Radiat Oncol Biol Phys*, 54 (3), 742- 751.
- Quinten C, Coens C, Mauer M, Comte S, Sprangers M, Cleeland C, Osoba D, Bjordal K, Bottomley A (2009): Baseline quality of life as a prognostic indicator of survival: a meta- analysis of individual patient data from EORTC clinical trials. *Lancet Oncol*, 10 (9), 865-871.
- Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J (2013): Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol*, 49 (6), 634-642.
- Richter E, Feyerabend T (2002): Kapitel 4.3: Strahlenfolgen. In: Grundlagen Strahlentherapie. 2nd Edition, Springer Verlag, Berlin (DE)/ Heidelberg (DE)/ New York (USA), 74 ff (and following).
- Ringash J, Bezjak A (2001): A structured review of quality of life instruments for head and neck cancer patients. *Head Neck*, 23 (3), 201-213.
- Ringash J, Warde P, Lockwood G, O' Sullivan B, Waldron J, Cummings B (2005): Postradiotherapy quality of life for head- and neck cancer patients is independent of xerostomia. *Int J Radiat Oncol Biol Phys*, 63 (3), 725-731.
- Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, Solomon B, Choi J, O'Sullivan B, Kenny LM, McArthur GA (2010): Prognostic Significance of p16^{INK4A} and Human Papillomavirus in Patients With Oropharyngeal Cancer Treated on RTOG 02.02 Phase III Trial. *J Clin Oncol*, 28 (27), 4142-4148.
- Rodda J, Walker Z, Carter J (2011): Depression in older adults. *BMJ*, 343, d5219.
- Rogers SN, Ahad SA, Murphy AP (2007): A structured review and theme analysis of papers published on 'quality of life' in head and neck cancer: 2000-2005. *Oral Oncol*, 43, 843-868.
- Salama JK, Saba N, Quon H, Garg MK, Lawson J, McDonald MW, Ridge JA, Smith RV, Yeung AR, Yom SS, Beitzel JJ; Expert Panel on Radiation Oncology-Head and Neck (2011): ACR appropriateness criteria® adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol*, 47(7), 554-559.
- Sayed SI, Elmiyeh B, Rhys- Evans P, Syigos KN, Nutting CM, Harrington KJ, Kazi R (2009): Quality of life outcomes research in head and neck cancer: A review of the state of the discipline and likely future directions. *Cancer Treat Rev*, 35, 397-402.

- Schlenk EA, Erlen JA, Dunbar- Jacob J, McDowell J, Engberg S, Sereika SM, Rohay JM, Bernier MJ (1998): Health- related quality of life in chronic disorders: a comparison across studies using the MOS- SF 36. *Qual Life Res*, 7 (1), 57-65.
- Schwartz CE (1999): Teaching coping skills enhances quality of life more than peer support: results of a randomized trial with multiple sclerosis patients. *Health Psychol*, 18 (3), 211-220.
- Schwarz R, Hinz A (2001): Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. *Eur J Cancer*, 37, 1345-1351.
- Shepherd K, Fisher S (2004): Prospective evaluation of quality of life in patients with oral and oropharyngeal cancer: from diagnosis to three months post- treatment. *Oral Oncol*, 40, 751-757.
- Singer S, Wollbrück D, Wulke C, Dietz A, Klemm E, Oeken J, Meister EF, Gudziol H, Bindewald J, Schwarz R (2009): Validation of the EORTC QLQ-C30 and EORTC QLQ-H&N35 in patients with laryngeal cancer after surgery. *Head Neck*, 31 (1), 64-76.
- Singer S, Arraras JI, Chie WC, Fisher SE, Galalae R, Hammerlid E, Nicolatou-Galitis O, Schmalz C, Verdonck-de Leeuw I, Gamper E, Keszte J, Hofmeister D (2013): Performance of the EORTC questionnaire for the assessment of quality of life in head and neck cancer patients EORTC QLQ-H&N35: a methodological review. *Qual Life Res*, 22(8), 1927-1941.
- Smith A (1987): Qualms about QALYs. *Lancet*, 329 (8542), 1134-1136.
- Sabin LH, Gospodarowicz MK, Wittekind C (2009): TNM Classification of Malignant Tumors. UICC (pub.), 7th edition, Wiley- Blackwell, Oxford (GB).
- Spiers AS, Baikie AF, Galton DA, Richards HG, Wiltshaw E, Goldman JM, Catovsky D, Spencer J, Peto R (1975): Chronic granulocytic leukaemia: effect of elective splenectomy on the course of disease. *Br Med J*, 25:1 (5951), 175-179.
- Sprangers MA, Schwartz CE (1999): Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*, 48 (11), 1507-1515.
- Sprangers MA, Cull A, Gronevold M, Bjordal K, Blazeby J, Aaronson NK (1998): The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. *Qual Life Res*, 7 (4), 291-300.
- Tribius S (2012): Therapy for locally advanced head and neck cancer: Time to focus from precision in technique to precision in therapy. Habilitation treatise. University of Hamburg (DE).

- Tribius S, Bergelt C (2011): Intensity- modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: Is there a worthwhile quality of life gain? *Cancer Treat Rev*, 37, 511-519.
- Tribius S, Reemts E, Prosch C, Raguse M, Petersen C, Kruell A, Singer S, Bergelt C (2012): Global quality of life during the acute toxicity phase of multimodality treatment for patients with head and neck cancer: Can we identify patients most at risk of profound quality of life decline? *Oral Oncol*, 48 (9), 898-904.
- Tribius S, Prosch C, Raguse M, Reemts E, Kruell A, Petersen C, Bergelt C, Singer S (2012): Dry Mouth and Sticky Saliva: Quality of Life Domains Most Affected in the Acute Toxicity Phase of Radiation Therapy. Poster 3137 presented during the 54th annual meeting of the American Society for Radiation Oncology (ASTRO) October 28th - 31th 2012 in Boston, Massachusetts (USA).
- Trott A, Pajak TF, Gwede CK, Cooper RPJ, Forastiere A, Ridge JA, Watkins-Bruner D, Garden AS, Ang KK, Curran W (2007): TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol*, 8, 613–624.
- Tschiesner U, Rogers SN, Harréus U, Berghaus A, Cieza A (2008): Content comparison of quality of life questionnaires used in head and neck cancer based on the international classification of functioning, disability and health: a systematic review. *Eur Arch Otorhinolaryng*, 265, 627-637.
- Urban D, Mayerl J (2008): Regressionsanalyse: Theorie, Technik und Anwendung – Lehrbuch, Studienskripten zur Soziologie. 3rd Edition, VS Verlag für Sozialwissenschaften, Wiesbaden (DE), 318-319.
- Van Herpen CML, Mauer ME; Mesia R, Degardin M, Jelic S, Coens C, Betka J, Bernier J, Remenar E, Stewart JS, van den Weyngaert D, Bottomley A, Vermorken JB (2010): Short- term health- related quality of life and symptom control with docetaxel, cisplatin, 5- fluorouracil and cisplatin (TPF), 5- fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 2471/TAX 323). *Br J Cancer*, 103, 1173-1181.
- Van Rij CM, Oughlane- Heemsbergen WD, Ackerstaff AH, Lamers EA, Balm AJ, Rasch CR (2008): Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. *Radiat Oncol*, 3 (41), doi: 10.1186/1748-717X-3-41.
- Vergeer MR, Doornaert MA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA (2009): Intensity- modulated radiotherapy reduces radiation- induced morbidity and improves health- related quality of life: results of a non- randomized prospective

study using a standardized follow- up program. *Int J Radiat Oncol Biol Phys*, 74 (1), 1-8.

- Wan Leung S, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM (2011): Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC- QLQ- C30 and EORTC- QLQ- H&N35 questionnaires. *BMC Cancer*, 11, 128.
- Weisman AD, Worden JW (1976): The existential plight in cancer: significance of the first 100 days. *Int J Psychiatry Med*, 7 (1), 1-15.
- WHO (1946): Health topics: Mental health. Geneva (CH). [online] URL: http://www.who.int/topics/mental_health/en/ [date: 25.01.2012, 10:37h].
- WHO, Division of mental health and prevention of substance abuse (1998): Draft, Programme on mental health, WHOQOL User Manual. Geneva (CH). [online] URL: http://www.who.int/mental_health/evidence/who_qol_user_manual_98.pdf [date: 15.5.2012, 18:07h], 10-11.

3 My contribution to the dissertation

I was involved in designing the case report forms as well as contributed to the patient informed consent form.

Once the study was approved I actively supported patient recruitment with screening patients while attending the clinic with PD Dr. Silke Tribius. I also was involved in building and maintaining the database as well as checking the completeness of files and questionnaires. I researched for missing data and was responsible for patient recall to make sure we are not missing any patients.

I was actively involved in planning and performing the statistical analysis as well as data interpretation, preparing and approving the manuscript.

4 Acknowledgements

Firstly, I would like to thank PD Dr. med. Silke Tribius for her never ending professional support as well as for the emotional empowerment to start, continue and finish this work. My special admiration is based on the language help and patience that she gave to me in every moment of the work, although I needed sometimes more than one hint.

Also, I would like to thank all the colleagues at the Ambulanzzentrum and the Radiation Oncology Department of the UKE who supported this work with their patience in completing so many questionnaires. Marieclaire Raguse has continued my data collection and she added important patient information for this work. Also, my thanks go to PD Dr. med. Corinna Bergelt and PD Dr. med. Susanne Singer for their expertise and help to manage the statistics. I would like to thank Prof. Dr. med. Cordula Petersen, Director of the Department of Radiation Oncology, PD Dr. med. Andreas Krüll, Director of the Ambulanzzentrum GmbH, for their support.

Particularly, I would like thank all the patients who let us dive so deeply into their lives, sometimes in hard and painful hours. Without their motivation to improve the future – and if not their own than the future of the next patient generation – this work could never have existed.

Dr. med. Raphaela Borowka spent so many hours with me to manage troubles and disasters, and I am so thankful that her emotional support facilitated me irreplaceably in hard moments. Also, I would like to thank Henning Stern for his support.

With great admiration I thank my family, particularly my partner Raj Kotian, my children Jonathan and Maria to have empowered, supported and let me finish this work over this long time period. They have tolerated my absence and my changing moods in hard hours and always made the best of it.

5 Curriculum vitae

entfällt aus datenschutzrechtlichen Gründen

(because of protection of privacy not applicable)

6 Statutory declaration

Ich versichere ausdrücklich, dass ich diese Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

.....
Elena Reemts