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Cancer therapy-induced oral mucositis in head and neck cancer patients

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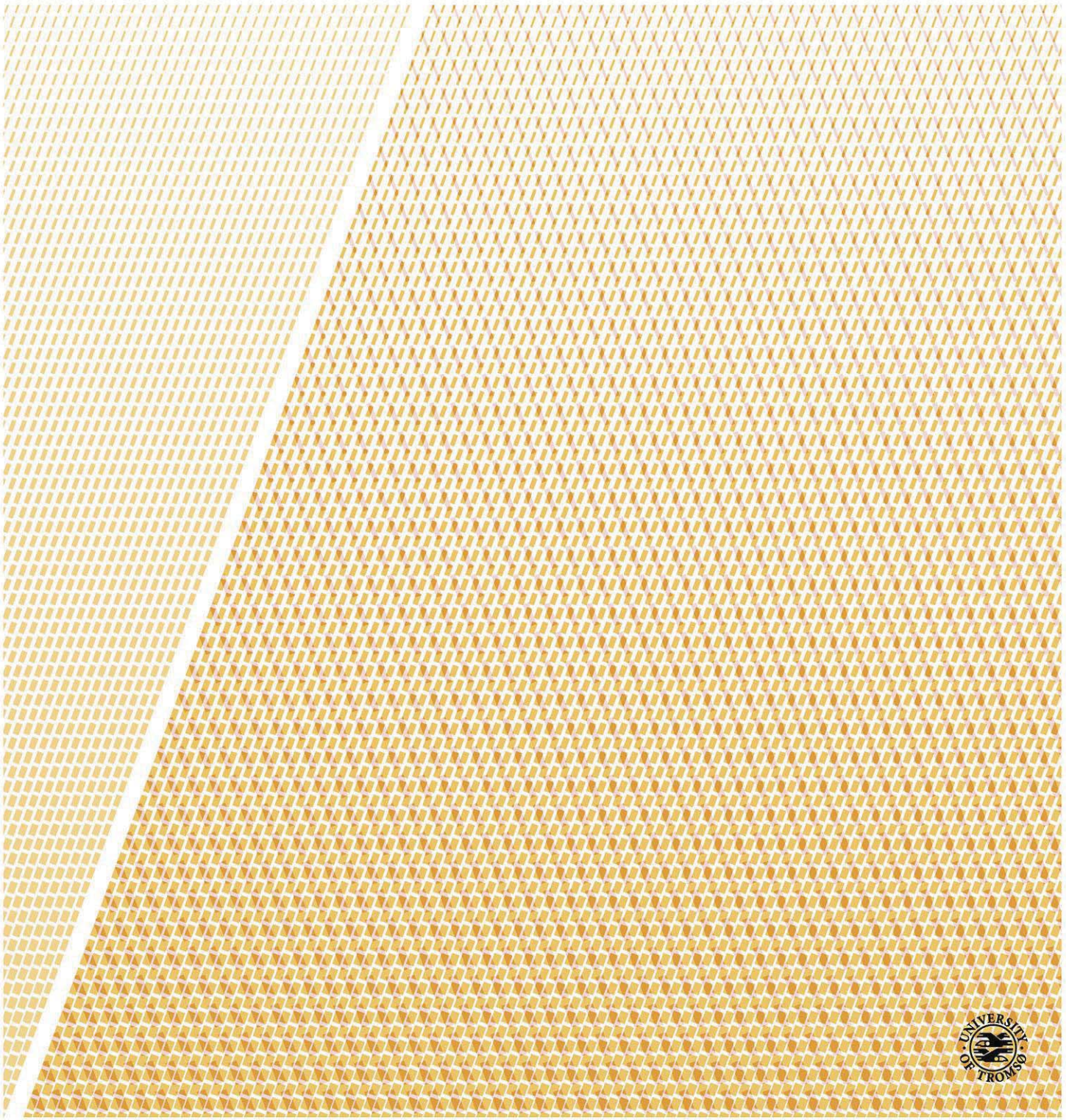
Anne Margrete Gussgard

A dissertation for the degree of Philosophiae Doctor –2015



CANCER THERAPY-INDUCED ORAL MUCOSITIS IN HEAD AND NECK CANCER PATIENTS

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Contents

1 Preface

Medicine has always fascinated me. Following high school, I deliberated whether I should study psychology, general medicine or dentistry. After graduating from the dental faculty as a DDS, Dr. Torbjørn Owren, the founder of Groruddalen Dyreklinikk, invited me to join him and his staff at his small-animal hospital. He gave me the opportunity to follow my dreams and assisted me in creating the first veterinary dentistry practice in Norway. While treating dogs and cats, I often observed that oral diseases in small animals could alter somatic and psychological health. It was quite common to see that dogs that suffered from e.g. chronic dermatological diseases showed major improvement of general health following dental treatment. Animals that had altered their behavior (being more passive, aggressive or working dogs being dysfunctional) showed positive behavioral changes after treatment of oral diseases. My experiences with animals initiated my interest in studies of the association between oral conditions and general health.

My spouse and I made a career change in 2005 when we moved to Toronto, Canada. In Toronto, I was privileged to meet and discuss my experiences and other scientific matters with a periodontist, Dr. Howard Tenenbaum. He introduced me to studies undertaken in Toronto on cancer patients who suffered extensively from oral mucositis due to chemotherapy. Our discussions led to collaborations with others and principally with Drs. Robert Wood and Andrew Hope at the Princess Margaret Cancer Centre (PMCC). In cooperation with other researchers of PMCC and the University of Toronto (UofT), we designed the study protocol which forms the basis for this PhD thesis. Concurrently, I was fortunate to be accepted into and complete a three-year specialty program in periodontology at the UofT. In my mind, periodontology is the most fascinating discipline in dentistry since much focus is on possible connections between oral health and general health.

All that I have achieved could never have happened without continuous encouragement and support from my two superb supervisors in Canada, Drs. Robert Wood and Howard Tenenbaum.

Bob; thank you for offering me space in your clinic and the use of your private office at PMCC so that I was able to see the study participants. Thank you for teaching me not only science, but also Canadian culture and bearing with me even when I in full sincerity told you that “no, I had never heard of Wayne Gretzky”. Howie; thank you for guiding me in the intricacies of clinical research, listening to me each time I was totally frustrated and for always being optimistic and enthusiastic.

I’m also grateful to my co-authors and wonderful colleagues for continuously reading and co-editing my multiple manuscript drafts. Valuable inputs from you have enriched the articles.

My sincere appreciation goes to all dentists and support staff at the PMCC, Dental Oncology Clinic and all personnel in the Radiation Medicine clinics for their kind assistance and support.

I would also express my gratitude to my Norwegian supervisor, Dr. Elin Hadler-Olsen who has provided valuable input to the thesis and guided me along the correct administrative pathways.

My husband, Dr. Asbjørn Jokstad has spent enormous time on deliberating and listening to me, several hours working on further statistical analysis, and assisting me with solving computer problems. Thank you for always being there for me.

My sons, Magnus and Thomas have grown into two fantastic young men despite all the time I have spent on studying. Your continuous and positive support has been especially valuable for me. Thank you for coping with your busy mother.

Special appreciation goes to my parents, Grete and Knut Gussgard who taught me the importance of critical thinking and that almost everything is possible if you believe in what you are doing.

Tromsø, February 2015

Anne Margrete Gussgard

2 Summary

Background: Radiotherapy causes oral mucositis (OM) that is painful and disrupts eating, talking, social activities and general health. OM may even interrupt cancer therapy. Any intervention that can reduce OM will lead to improvement in treatment and quality of life for patients. It is essential to have a suitable tool to measure potentially effective and new treatments against OM.

Objective: To determine if the Patient Reported Oral Mucositis Symptom (PROMS) scale provides a more accurate tool for assessment of oral mucositis than conventional methods based solely on clinician-assessed recordings in patients receiving radiation for head and neck malignancy.

Methods: Fifty study participants were examined clinically once before radiotherapy and thereafter twice weekly during the course of their 6-7 weeks treatments and once again post radiotherapy. OM was evaluated clinically according to commonly used clinical assessment tools. The patient-reported OM symptoms were recorded on PROMS-questionnaires. The relationships between PROMS data and clinical data were appraised with Spearman rank correlation tests at the different time points, using robust repeated measures mixed linear models. ANOVA were applied for comparisons of changes of PROMS scale values upon transitions between different sizes of OM ulceration. Simple bivariate tests were used for comparison of characteristics of study participants.

Results: Thirty-three participants completed the study. Significant correlations ($p<.001$) were seen between PROMS scores and other clinical assessments of OM at a group level. The correlation between different signs and symptoms over all time points varied markedly on the individual level. The major change in PROMS scale values occurred upon transition from small to medium size of ulceration, rather than from medium to large. The characteristics of the study participants in different sub-cohorts defined by high and low correlations, high manifestations & minor complaint and low manifestations & major complaints, were comparable, except for age.

Conclusion: The relationship between patient-reported impairment of oral functions and mouth pain caused by OM ulceration is not linear, but rather more curvilinear. Therefore, future interventional studies should adopt less severe outcomes than maximum clinical OM scores as primary outcomes. Patient-reported outcomes (PROs) should be incorporated in any interventional studies regarding OM and the changes of PROs values should be measured on the intra-individual rather than on any inter-individual levels. The PROMS questionnaire may be a useful tool to augment clinical assessment of OM, and a feasible substitute assessment in situations where patients cannot endure oral examinations.

3 List of papers

The thesis is based on the following papers:

Assessment of Cancer Therapy-Induced Oral Mucositis Using a Patient-Reported Oral Mucositis Experience Questionnaire.
Gussgard AM, Hope AJ, Jokstad A, Tenenbaum H, Wood R.
PLoS ONE 2014; Volum 9 (3). ISSN 1932-6203.s doi: 10.1371/journal.pone.0091733.

Symptoms reported by head and neck cancer patients during radiotherapy and association with mucosal ulceration site and size: an observational study
Gussgard AM, Jokstad A, Wood R, Hope AJ, Tenenbaum H.
Resubmitted

Head and neck cancer patients experiencing radiation-induced mucositis - should the signs or the symptoms be measured?
Gussgard AM, Jokstad A, Hope AJ, Wood R, Tenenbaum H.
Submitted

4 List of abbreviations

CRF	Case Report Form
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
FACT	Functional Assessment of Cancer
Gy	Gray (unit for absorbed radiation dose)
H&N	Head and Neck
HSCT	Haematopoietic Stem Cell Transplantation
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
IMRT	Intensity Modulated Radiation Therapy
IL	Interleukin
ISOO	International Society of Oral Oncology
MASCC	Multinational Association for Supportive Cancer Care
MMPs	Matrix Metalloproteinases
NCI	National Cancer Institute (USA)
NF-kB	Nuclear Factor-kappaB
OM	Oral Mucositis
OMAS	Oral Mucositis Assessment Scale
PMCC	Princess Margaret Cancer Centre (Previous name: Princess Margaret Hospital)
PROs	Patient Reported Outcomes
PROMS	Patient Reported Oral Mucositis Symptoms
QOL	Quality Of Life
RCT	Randomized Controlled Trial
REB	Research Ethics Board
ROS	Reactive Oxygen Species
SCC	Squamous Cell Carcinoma
TNF	Tumour Necrosis Factor
TNM	Tumour Node Metastasis (Classification system for malignant tumours)
UICC	Union for International Cancer Control
VAS	Visual Analogue Scale
WHO	World Health Organization

5 Introduction: Head and neck (H&N) cancer

H&N cancers are heterogeneous with regard to histopathology, localization and etiology. Histopathologically, H&N cancers are predominantly squamous cell carcinomas (SCC) that originate from the mucosal lining (epithelium) of these organs. Adenocarcinomas, melanomas, lymphomas and sarcomas may also occur, although less commonly. Based on location, H&N cancers are defined by cancer of the oral cavity and lips, salivary glands, pharynx, nasal cavity, paranasal sinuses, and the larynx (Figure 1).

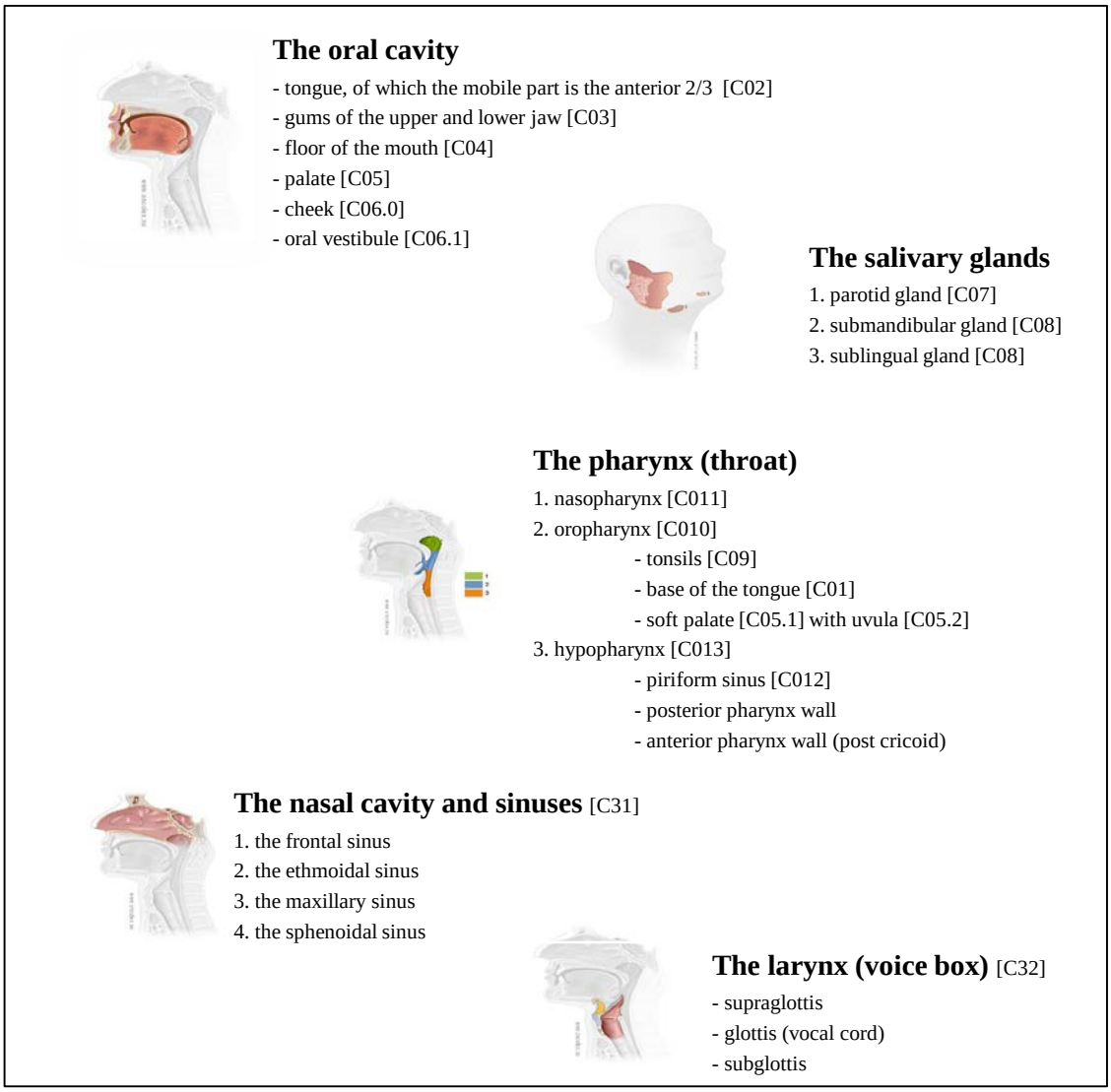

Figure 1: Anatomical location of Head and Neck Cancers. Adopted from: Oncolex Norway www.oncolex.no. (Permission for use obtained from editor).
[ICD-10- Diagnosis Codes] (www.who.int/classifications/icd/)

5.1 Classification of tumours

A tool for staging tumour malignancy or more accurately the extent of tumours was developed in the 1940s and later adapted by the Union for International Cancer Control (UICC) in the mid-seventies and named TNM. The latest version, number 7, was introduced in 2009 [1]. In brief, the TNM Staging System describes the extent of the original tumour (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M) (Table 1).

Table 1. The TNM Tumour Staging system

The T category describes the original (primary) tumour	
TX	Primary tumour cannot be evaluated
T0	No evidence of primary tumour
Tis	Carcinoma in situ (early cancer that has not spread to neighbouring tissue)
T1–T4	Size and/or extent of the primary tumour
The N category describes whether or not the cancer has reached nearby lymph nodes.	
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement (no cancer found in the lymph nodes)
N1-N3	Involvement of regional lymph nodes (number and/or extent of spread)
The M category tells whether there are distant metastases	
M0	No distant metastasis (cancer has not spread to other parts of the body)
M1	Distant metastasis (cancer has spread to distant parts of the body)

Recently there has been a discussion whether the TNM staging system should be revised, especially for H&N cancer patients, to account for human papilloma status and perhaps smoking [2].

Tumours and cancers are also classified according to the International Classification of Diseases (ICD). ICD was first developed around 1850 and originally for registration of deaths. The World Health Organization (WHO) took ownership of ICD in 1946. ICD is continuously under revision and the present version, ICD-10 has been used by WHO Member States since 1994 [3]. The official version of ICD-10 in Norway was developed by the Norwegian Centre for Informatics in The Norwegian Directorate of Health (Helsedirektoratet) [4].

The ICD-10 codes applied to tumours can indicate the site of the tumour, whether the tumour site is the primary or a metastatic site, the histological type of the tumour and whether the tumour is benign or malignant. The use of the ICD internationally greatly facilitates comparisons between populations and countries, and may even provide indications of potential etiological factors.

5.2 Epidemiology of H&N cancer

H&N cancers constitute about 2-5% of all new cancer cases each year worldwide. The prevalence of oral cancer and laryngeal cancer is respectively two times and four times more common in males than in females [5].

Most epidemiological registries report cancers according to ICD-10 codes. However, one should be aware when comparing statistics from different sources that e.g. in Canada, the term "oral cancer" encompass all ICD C0-C14 codes; that is cancers of the lip, tongue, salivary gland, mouth, nasopharynx and oropharynx while in Norway, the term that is applied for these locations is "mouth and pharynx" (Figure 2).

Cancer in Norway 2012

Number of new cases by primary site and sex, 2012

ICD-10	Site	Males	Females	Total
C00-96	All sites	16491	13608	30099
C00-14	Mouth, pharynx	359	181	540
C00	Lip	71	43	114
C01-02	Tongue	67	47	114
C03-06	Mouth, other	57	30	87
C07-08	Salivary glands	29	14	43
C09-14	Pharynx	135	47	182
C30-34, C38	Respiratory organs	1739	1342	3081
C30-31	Nose, sinuses	31	19	50
C32	Larynx, epiglottis	98	19	117

URL: http://kreftregisteret.no/Global/Cancer%20in%20Norway/2012/CIN_2012.pdf

Estimated New Cases and Age-Standardized Incidence Rates for Cancers by Sex, Canada, 2012

	New Cases			Cases per 100,000		
	Total*	M	F	Total*	M	F
All Cancers	186,400	97,600	88,800	406	456	368
Oral	4,000	2,700	1,350	9	12	5
Larynx	1,050	860	180	2	4	1

URL:http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2012---English.pdf

Figure 2: Estimates of incidence of H&N cancers in Norway and Canada in 2012.

Estimates of the incidence of various forms of H&N cancer vary globally, probably as a reflection of etiological factors. Norway ranks mid-to-high for pharynx (other than nasopharynx) as well as lip and oral cavity cancer and low for nasopharyngeal and laryngeal cancer (Figure 3a-d).

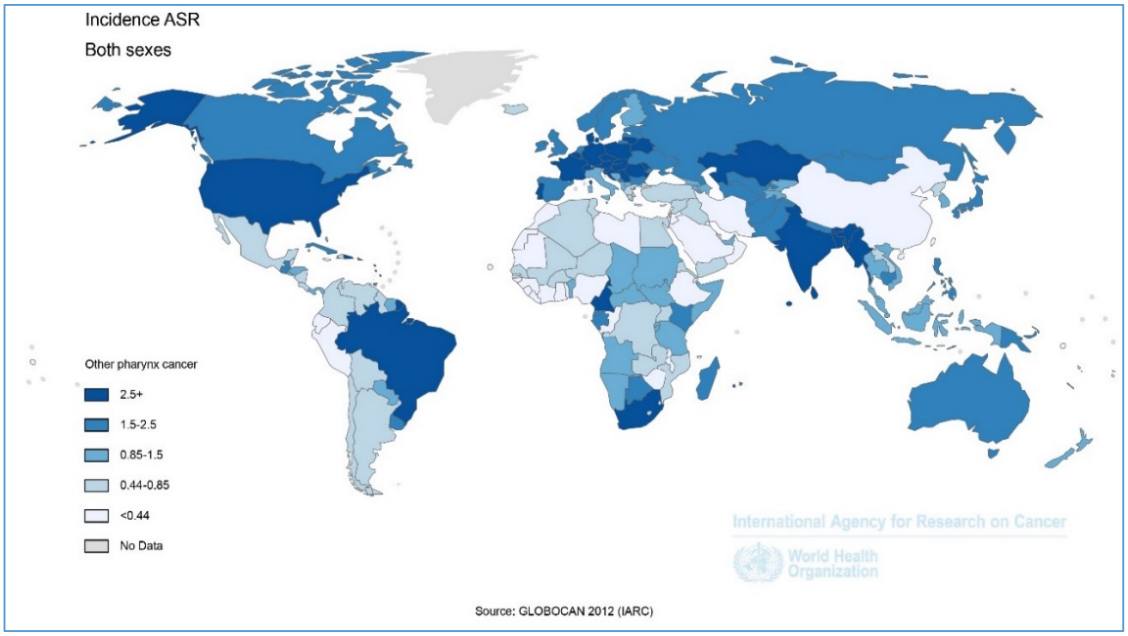

Figure 3a. Cancer of the pharynx other than nasopharynx

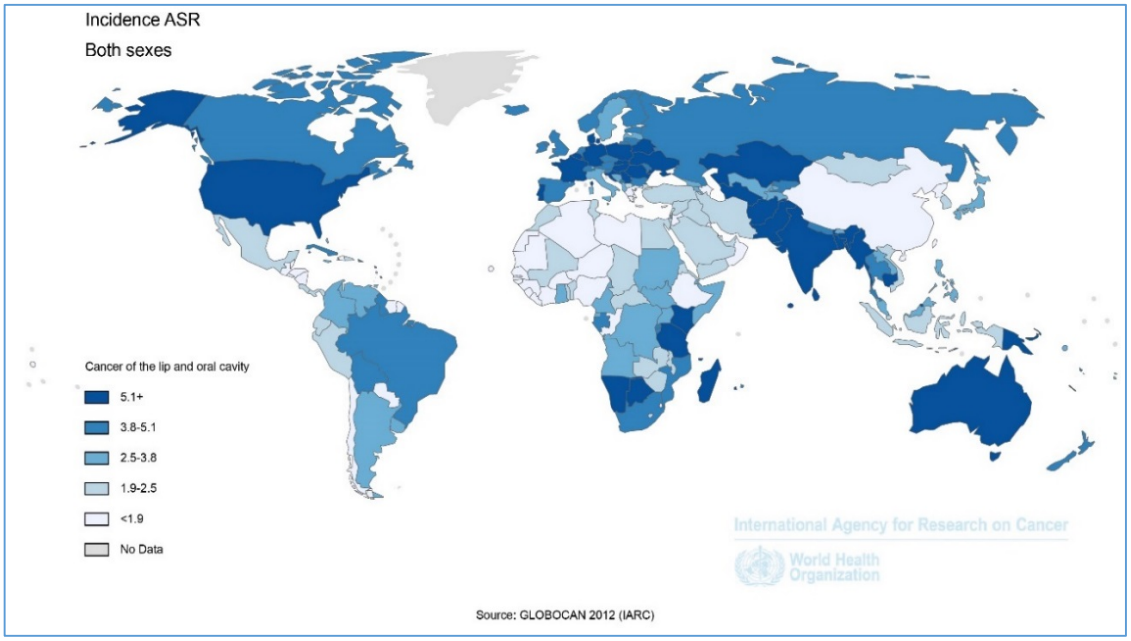

Figure 3b. Cancer of the lip and oral cavity

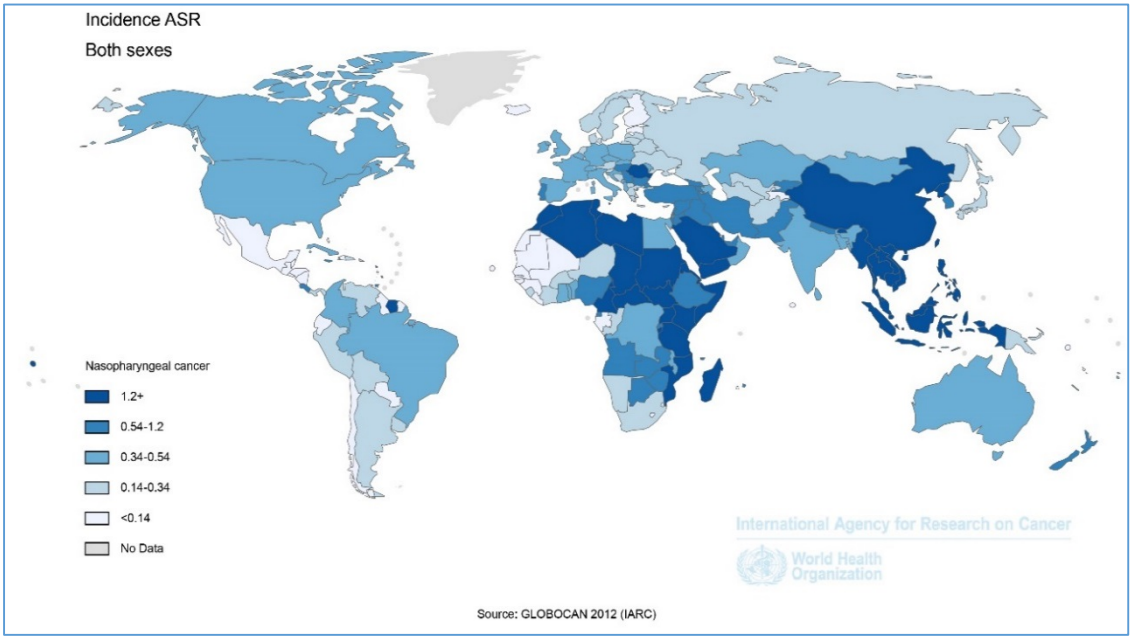

Figure 3c. Cancer of the nasopharynx

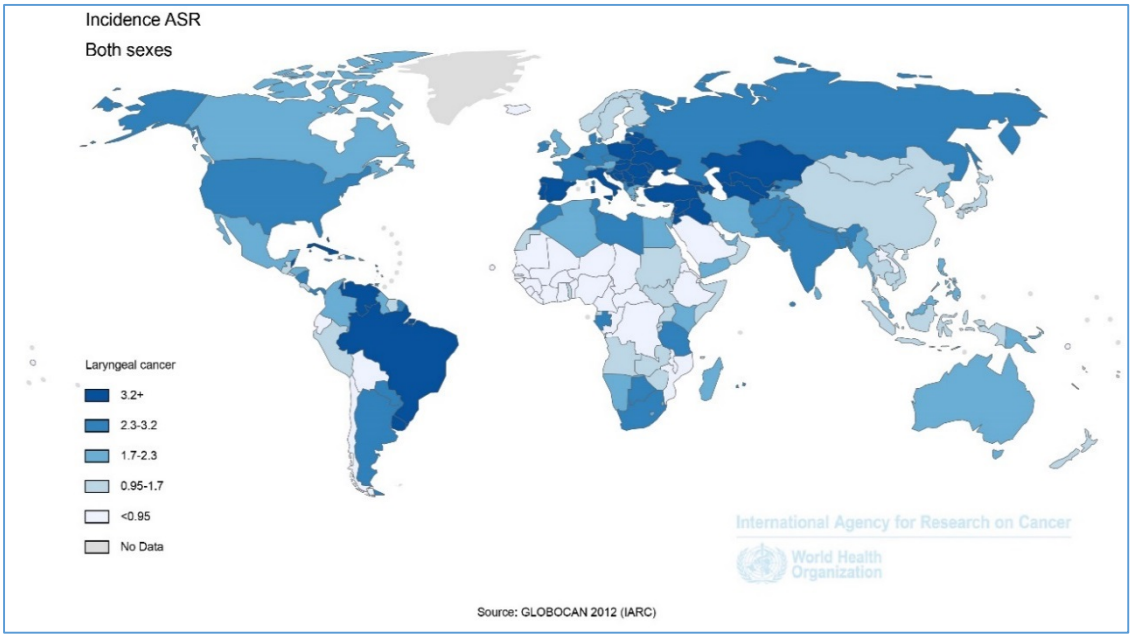

Figure 3d. Cancer of the larynx

Figure 3 a-d: Estimates of incidence of H&N cancers globally. Source: Ferlay et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 06/01/2015

5.3 Etiology of H&N cancer

H&N cancers have been associated primarily with excessive smoking and consumption of alcohol [6]. Some studies have reported synergism between smoking and alcohol consumption, indicating an increased risk for individuals who both smoke and drink heavily [7]. One emerging risk factor for cancer of the oropharynx amongst the young, non-smoker and non-drinker patients is the human papilloma virus (HPV), especially HPV-16 [8, 9]. Other etiological factors include Epstein-Barr virus, poor oral hygiene/dental status, chewing tobacco, betel quid chewing (betel quid is a combination of betel leaf, areca nut, and slaked lime, with or without added tobacco) and maté, a tea-like beverage habitually consumed by South Americans [5, 10]. The incidence rate for HPV-positive H&N cancer cases seems to have increased during recent years, while non-HPV-positive H&N cancer appears to have declined, most likely due to fewer heavy smokers in the population [11, 12].

5.4 Treatment of H&N cancer

Patients with H&N cancer undergo treatments that can consist of surgery, radiotherapy, chemotherapy, or combinations of these. The treatments can be delivered concurrently or in different temporal sequences. Moreover, over the last years, several innovative targeted molecular therapies have shown promising results [13, 14]. Radiotherapy is conventionally given as fractions of 1.8 – 2.0 Gray (Gy), once daily, 5 days weekly for 6 or 7 weeks (Total up to 70 Gy). For the treatment of H&N cancer, an accelerated schedule using six fractions per week appear to be superior to five visits per week [15, 16]. The predominant radiotherapy technical approach today is Intensity Modulated Radiation Therapy (IMRT), principally because the late toxicity effects are less severe than conventional radiotherapy [17]. With regard to H&N cancer, IMRT cause less collateral tissue damage (e.g., mucosa, connective tissues, and salivary glands) compared to other radiotherapy techniques [18]. Irrespective of technical approach, radiotherapy in the head and neck region cause acute toxic effects and the most common indicator of toxicity is oral mucositis (OM), followed by pain, difficulty with swallowing and taste disturbances [19-21].

6 Radiotherapy-induced Oral Mucositis (OM)

Mucositis of the oral mucosa progress from initial erythema to pinpoint ulceration(s) that often proceed to confluent ulceration(s) (Figure 4). OM occurs in virtually all patients who receive H&N radiotherapy and especially for those undergoing a combination of radiotherapy and chemotherapy [20, 22].

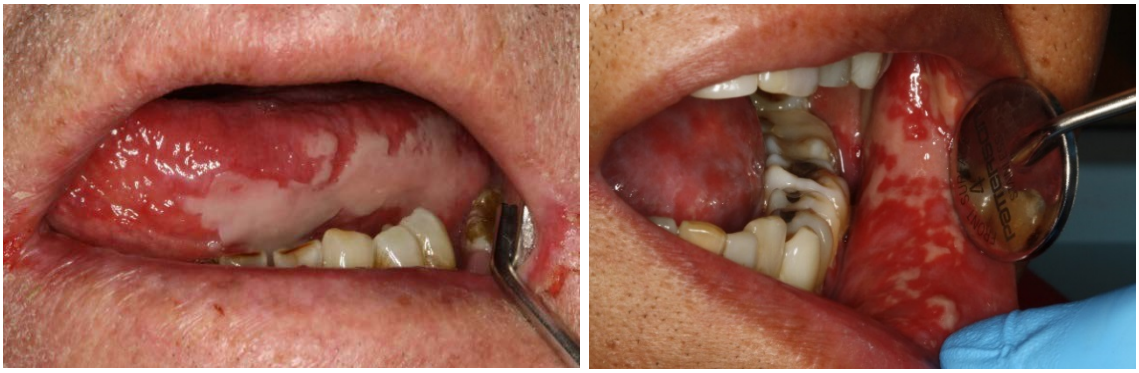

Figure 4: Oral mucositis is a side effect of radiation treatment that leads to pain and limitations of mouth opening and numerous oral functions. Photographs: AM Gussgard

6.1 Impact of OM

OM can become very painful, and so severe that the patient might limit food intake to the extent that clinically important weight loss occurs. For this reason, patients in many hospitals worldwide, including at PMCC, routinely have a feeding tube surgically inserted for prophylactic reasons before cancer therapy is initiated [23]. Moreover, analgesics appear to have limited effects on pain caused by OM [24], and patients may therefore at times appeal for a less aggressive therapy. Estimates of interruptions of cancer therapy caused by severe OM are in the range of 10-25% of all patients [25-27], although interruption rates as high as 47% has been reported [28]. The direct economic consequences of cancer-therapy induced OM are significant and require allocation of considerable hospital resources [22, 29, 30]. Severe manifestation of OM increases even more the use of healthcare resources and may require additional supportive care or even hospitalization [31]. On the individual level, the psychosocial consequences of high levels of OM can be dramatic and leading to anxiety and depression [32-35].

6.2 Pathogenesis and manifestation of OM

The prevailing theory purporting to explain the underlying mechanisms related to chemotherapy-induced OM was first suggested in 1998 [36], and has now been extended to all forms of cancer therapy-induced OM [37, 38]. However, the aetiology of radiotherapy-induced OM is still not understood in full [39-43]. It is postulated that the adverse biological events evolve in five steps starting from the initiation of primary damage followed by a primary damage response that cause a signal amplification leading to ulceration and eventually a healing [41, 42, 44, 45]. The more detailed aspects of the underlying pathophysiological processes thought to be involved in the development (and resolution) of OM are described below:

1. Initiation of primary damage

The radiation damages the DNA of cells in the basal epithelium and within the underlying submucosa. The injury triggers the production of Reactive Oxygen Species (ROS) leading to cell death within the basal and suprabasal epithelium. The largest contribution to injury is caused by the cell destruction in the underlying submucosa.

2. Primary damage response

The disintegration of the DNA-molecules activates transduction pathways that turn on different transcription factors. The most important transcription factor in relation to toxicity is considered to be nuclear factor-kappaB (NF-kB). The activation of NF-kB upregulates several genes that further result in an increase of pro-inflammatory cytokines. The cytokines, Interleukin (IL)-beta, IL-6 and Tumour Necrosis Factor (TNF)-alpha in particular, promote injury to the connective tissue and the endothelium. Additional mesenchymal-epithelial signaling lowers the epithelial oxygenation and causes injury and death of the epithelial basal-cells. The fibroblasts in the submucosa are also damaged, both directly by radiation and chemotherapy, and also indirectly by secretion of Matrix Metalloproteinases (MMPs).

3. Signal amplification

The net effect of the gene upregulation and activation of transcription factors is an accumulation of a wide range of biologically active proteins that targets the submucosal

tissues. Additional proteins, especially the pro-inflammatory cytokines damage the tissue. In addition, a positive-feedback loop is created, which increases the primary damage caused by the radiation (Figure 5a).

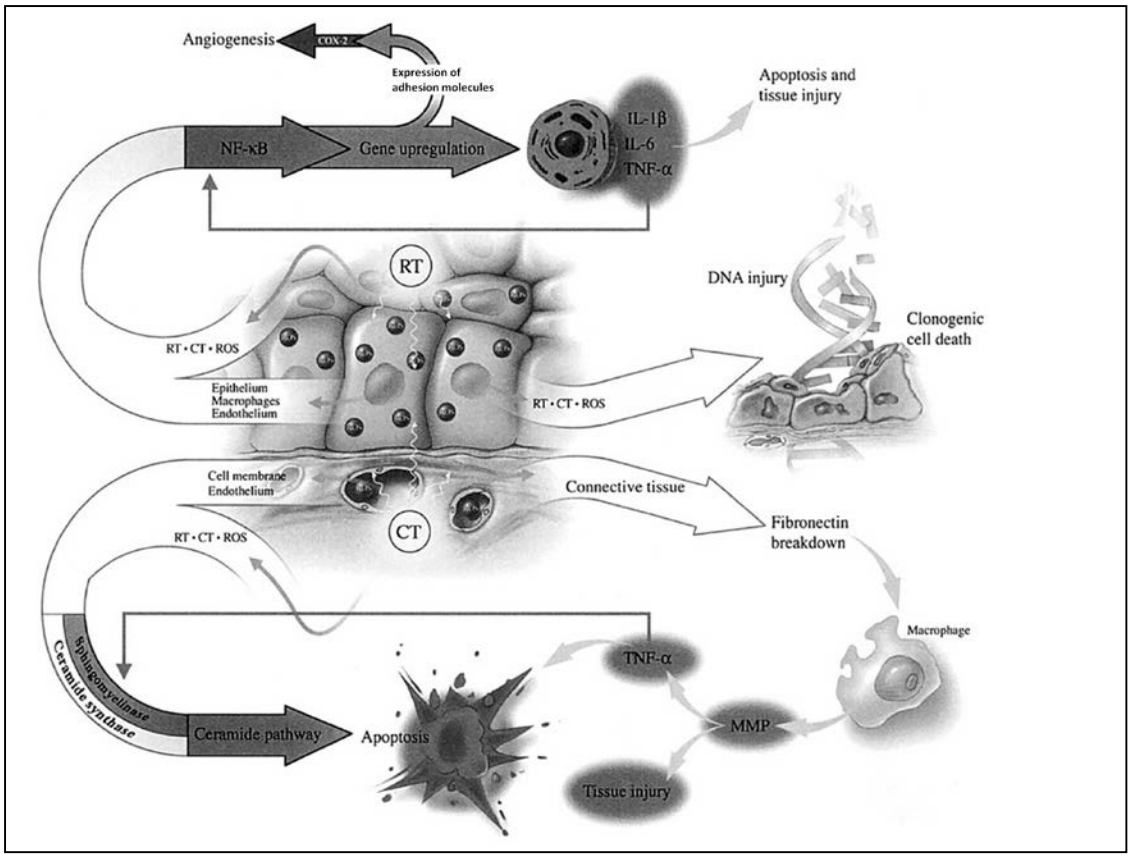

Figure 5a: Signaling and amplification phase. Illustration from [45] (Permission obtained from publisher). RT: radiotherapy, CT: chemotherapy, IL: interleukin, TNF: tumour necrosis factor, NF-kB: Nuclear Factor-kappaB, MMP: Matrix Metalloproteinases, ROS: Reactive Oxygen Species

4. <u>Ulceration</u>

Ulcerative lesions are susceptible to bacterial colonization, which may result in bacteremia and potential sepsis. Products from the cell wall of colonizing bacteria may also gain access into the submucosa and stimulate macrophages to discharge additional pro-inflammatory cytokines and MMPs (Figure 5b).

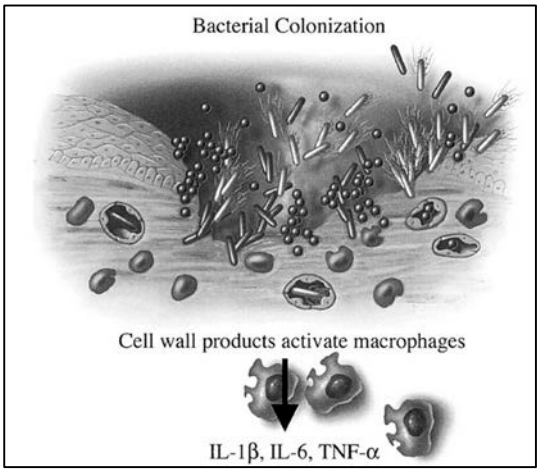

Figure 5b; Ulceration. Cell wall products from bacteria stimulate macrophages to release proinflammatory cytokines

5. Healing

Once the cancer treatment is completed, the radiation induced OM normally heals within weeks, however there are individual variations [46].

Clinical manifestation

The clinical manifestation of OM during the various stages of radiotherapy is depicted in a study participants shown below (Figure 6). For some participants erythematous areas developed in week one, followed by pinpoint ulcerations in week 2 with increasing confluent zones over the following weeks. Maximum extensions of the ulcerations were observed at the point of time when the radiotherapy was completed.

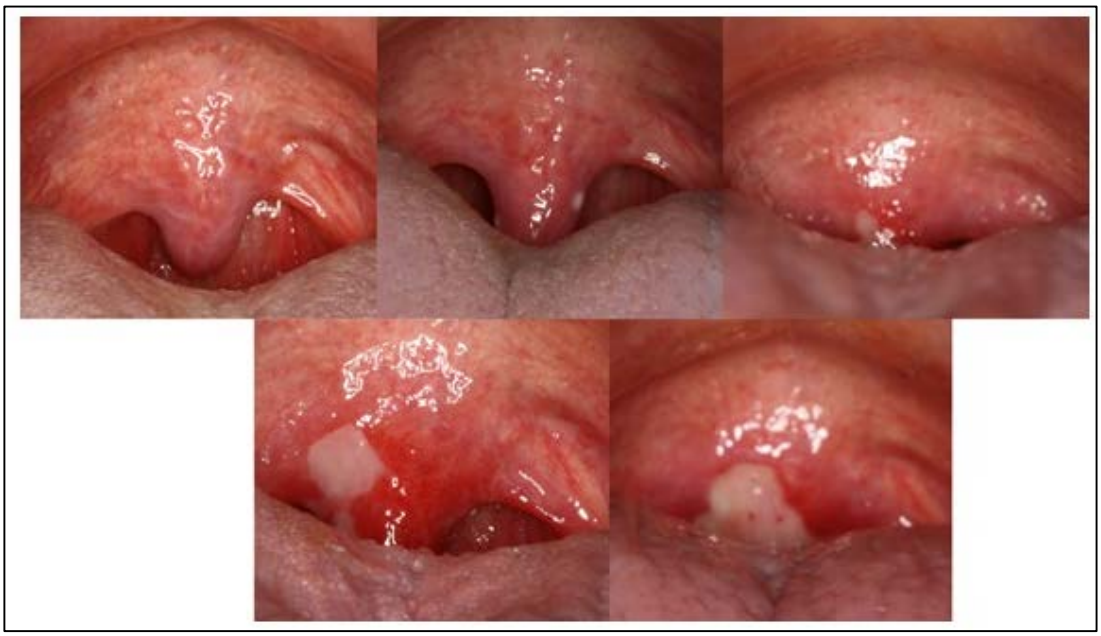

Figure 6: Development of OM in the soft palate. In this participant, the first clinical sign of ulceration developed in the midst of an erythematous area on the uvula (upper centre picture) during the 3rd week of radiotherapy. The size of the ulceration increased over the subsequent weeks 4 (upper right picture), 5 (bottom left picture) and 6 (bottom right picture). Photographs: AM Gussgard

6.3 Prevention and management of OM

Unfortunately, there is little compelling evidence that any current interventions fully prevent [47-49] or cure [50, 51] OM for H&N cancer patients, in spite of much dedicated efforts. Different therapies have been developed, and new interventions are being evaluated clinically, in conformity with the current understanding of pathogenesis of OM [52, 53]. The outcomes form the basis for the best practice guidelines for the management of patients with OM that have recently been updated by the Multinational Association for Supportive Cancer Care (MASCC) in collaboration with the International Society of Oral Oncology (ISOO) [54]. There are some promising data for the use of ice chips [55] as well as for recombinant human keratinocyte growth factor-1 [56], for OM caused by chemotherapy in patients suffering from haematological malignancies. Also low laser therapy may possibly prevent OM in cancer patients receiving haematopoietic stem cell transplantation together with chemotherapy and in H&N cancer patients undergoing radiotherapy [57].

6.4 Diagnosis and assessment of OM

There is no consensus as to which method or combination of methods that are the most appropriate and clinically relevant assessment tools for the appraisal of OM. It is reasonable to assume that the extent of visible OM ulceration correlate with patient-reported pain, yet other mechanisms for pain associated with OM cannot be ruled out [58, 59]. Multiple assessment tools presented in the literature categorize the manifestation of clinical signs or describe patient-reported symptoms, alternatively quantify a combination of signs and symptoms of OM. Efforts have also been dedicated to record patients' quality of life during and after the cancer treatment phase. The most common tools for the assessment of OM are shown in tables 2a and 2b. There is currently an international drive to include subjective experiences reported by study participants in prospective clinical cancer research, under the acronym "PROs", i.e., patient reported outcomes [60-63], with the recognition that such data are required for informed decision making.

Table 2a. Assessment of OM in H&N cancer patients by combination of clinical signs and by measuring patient symptoms.

Year	Instrument/Tool/Scale/Questionnaire	Appraises	Ref.
2009	Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4)	Functional/symptomatic (0-4)	[64]
2003	Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)	Clinical signs (0-4) + Functional/symptomatic (0-4)	[65]
1999	Common Terminology Criteria for Adverse Events (NCI-CTCAE v.2)	Clinical signs (0-4) + Pain (0-4)	[66]
1999	Oral Mucositis Assessment Scale (OMAS)	Erythema (0-2) & Ulceration(0-3) + Pt-reported: Pain & swallow(1-100VAS) + ability to eat & drink (categorical)	[67]
1995	Radiation Morbidity Criteria – Radiation Therapy Oncology Group /European Organization for Research (RTOG/EORTC)	Swallow, Speech, Pain, Dryness, Taste, Analgesics, Ulceration (0-4)	[68]
1979	World Health Organization (WHO) Oral Toxicity Scale	Erythema/ulceration + can eat solids / liquid diet only vs. alimentation not possible (0-4)	[69]

Table 2b. Assessment of OM H&N cancer patients by measuring patient symptoms.

Year	Instrument/Tool/Scale/Questionnaire	Ref.
2011	Children's International Mucositis Evaluation Scale (ChIMES)	[70]
2010	International Classification of Functioning, Disability and Health Comprehensive Core Sets for Head and Neck Cancer (ICF-CCS-HNC)	[71]
2010	Vanderbilt Head and Neck Symptom Survey (VHNSS)	[72]
2008	Patient-Reported Oral Mucositis Symptom (PROMS) scale	[73]
2007	FACT Head and Neck Symptom Index (FHNSI) scores	[74]
2007	MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN)	[75]
2007	Oral Mucositis Weekly Questionnaire- Head and Neck Cancer (OMWQ-HN)	[76]
2006	Oral Mucositis Daily Questionnaire (OMDQ) & Mouth and throat soreness (MTS)	[77]

6.5 Need to improve instruments for the assessment of OM

Extensive resources have been spent in research and hospitals to develop the most meaningful measurement of OM [78-84]. Nevertheless, it can be questioned whether the tools and criteria presently used in the assessment of OM are adequate to distinguish potentially small, though important effects of interventions. In the absence of a validated clinically-relevant measurement tool there is no reliable way to evaluate whether any particular intervention can be used to prevent or alleviate OM or whether one patient management is superior to another. Any intervention that reduces the incidence or severity of OM will improve supportive treatment and quality of life for patients and should similarly permit more effective and even more aggressive therapy for cancer.

There is a growing consensus that the best management of patients at risk for developing OM should include using a standardized tool, or a combination of tools that should measure physical, functional and subjective changes. Pain scoring, in particular by patient self-reporting should form part of any OM assessment. Such a diagnostic tool needs to be validated, easy to use and not perceived as a burden for the patient [82]. One measurement tool for subjective reporting, the PROMS scale [73], appear to fulfil these requirements, and the scale has also been validated in a study sample consisting of haematological cancer patients having received Haematopoietic Stem Cell Transplantation (HSCT) [73]. The question was raised whether the PROMS scale could be applied also to other populations of cancer patients, including but not limited to those with H&N cancer.

7 Aims of the thesis

7.1 Research objectives

Radiotherapy-induced OM has until recently been mostly quantified by clinicians according to criteria detailed in a clinical diagnostic instrument. The overall objective of the current research was to determine whether H&N cancer patients by using a novel PRO tool named PROMS [73], would provide symptom information that correlate with the clinical signs. Findings obtained with the use of the PROMS questionnaire might also provide care providers with clinically valuable information about the condition of the patient that might be unknown otherwise (e.g. suffering/pain despite possibly minor ulceration).

More specifically, could the PROMS be applied to (i) complement common clinician-determined assessments of OM and (ii) possibly substitute the common clinician-determined assessments of OM in situations where patients have difficulties in opening their mouths for a complete clinical assessment?

I pursued the stated research objective by conducting three separate studies, each with a different working hypothesis.

7.2 Hypotheses

The working hypotheses of the three studies were:

- Patient-reported OM experience assessed by the PROMS scale correlates with OM assessed by clinician based scoring tools at the group level. (Paper #1).
- Patient-reported pain and debilitating effects associated with OM may be influenced by the extent and possibly the location of OM lesions (Paper #2).
- Patient-reported pain and debilitating effects associated with OM may be influenced by factors beyond the local toxic effects of radiotherapy on oral tissues (Paper #3).

8 Materials and methods

8.1 Study design and setting

A prospective single cohort study was designed to appraise the merits of using the PROMS scale to measure how patients with H&N cancer were affected by OM during their cancer treatment. Approval was obtained from the Research Ethics Boards of the University Health Network (#09-0231-CE) and University of Toronto (# 24171). The study was conducted at the Princess Margaret Cancer Centre (PMCC), a leading cancer treatment centre in Canada.

8.2 Patient population

All patients that require treatment for H&N cancer at PMCC routinely undergo examinations and preparatory care in the dental department prior to their cancer treatment. The dental department faculty and staff informed potentially eligible participants about the current clinical study. Eligible participants were identified by predefined inclusion and exclusion criteria (Table 3).

Eligible individuals that had expressed an interest in participating received oral and written information about the objectives and details of the study. They were given time to review the written information and the opportunity to ask questions of an investigational team member. A copy of the signed and dated patient information/informed consent form was given to all study participants. The participants were informed that they had the right to withdraw from the study at any time, and that this would in no way prejudice any future treatment, in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice (ICH 1996) [85].

Table 3. Inclusion and exclusion criteria for study participation

Inclusion
• 18 years of age or greater
• Willing and able to provide written informed consent for study participation
• Carcinoma of the oral cavity, nasopharynx, oropharynx, salivary glands or maxillary sinus
• Scheduled to receive radiotherapy with a minimum prescription radiation dose of 54Gy, with or without concurrent chemotherapy
• Normal mucosa at baseline (i.e. NCI-CTCAE v.3 OM grade 0)
• Karnofsky score performance status ≥60% [86]
• Commit to twice weekly clinical examinations over the cancer therapy period, plus one post-operative examination
Exclusion
• Clinical evidence of active significant acute or chronic diseases that might compromise the ability to evaluate OM
• Individuals who, in the opinion of the investigator, were unlikely to comply with the study procedures, or were unlikely to complete the study due to different reasons like, e.g., language barriers or mental incapacity

8.3 Study participant examinations

The participants were scheduled for appointment sessions at baseline, twice weekly over the course of radiotherapy and once, four to six weeks after completion of the cancer therapy. At each session, one investigator conducted an examination of the intra-oral mucosa with the help of mouth mirrors and using a high-power headlamp as a light source. In addition, the investigator inquired about smoking and drinking habits since the last study visit, and recorded eventual need of pain medication or nutritional support and any in-hospital stays, based on information given by the participants. The study participants completed also a self-assessment questionnaire i.e., the PROMS-scale questionnaire [73].

8.4 Assessment of OM by measurement of clinical signs

The manifestations of OM were described according to three different clinical assessment tools, i.e., the clinical component of the NCI-CTCAE version 3 [65]; the clinical component of the Oral Mucositis Assessment Scale (OMAS) [67] (Table 4) and the Total VAS-OMAS grading scale [87].

Table 4. Characteristics of the NCI-CTCAE v.3 clinical part and OMAS clinical scales

Source	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
NCI CTCAE v.3 Mucositis (clinical exam)	Normal	Erythema of the mucosa	Patchy ulcerations or Pseudo-membranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
OMAS Ulceration	Normal	Less than 1 cm^2	Between 1-3 cm^2	Greater than 3 cm^2	N/A
OMAS Erythema	Normal	Not severe	Severe	N/A	N/A

According to the NCI-CTCAE v 3.0, the occurrence and severity of OM is graded between 0 (none) to 4, as observed at any site intraorally. The OMAS was used as described by the developers [67], whereby a score between 0 (none) and 3 (for ulceration) or 2 (for erythema) is assessed in nine different intra-oral locations. These are the upper lip, lower lip, right and left cheek, right and left ventro-lateral tongue, floor of mouth, soft palate and hard palate (Figure 7). The ulceration and erythema scores were not aggregated as in the original publication, but kept separate to better elucidate possible correlations with the other clinician-based scoring tools and the PROMS scale values. Hence, the maximum sum score of ulceration was 27 (9 sites x 3) and of erythema 18 (9 sites × 2).

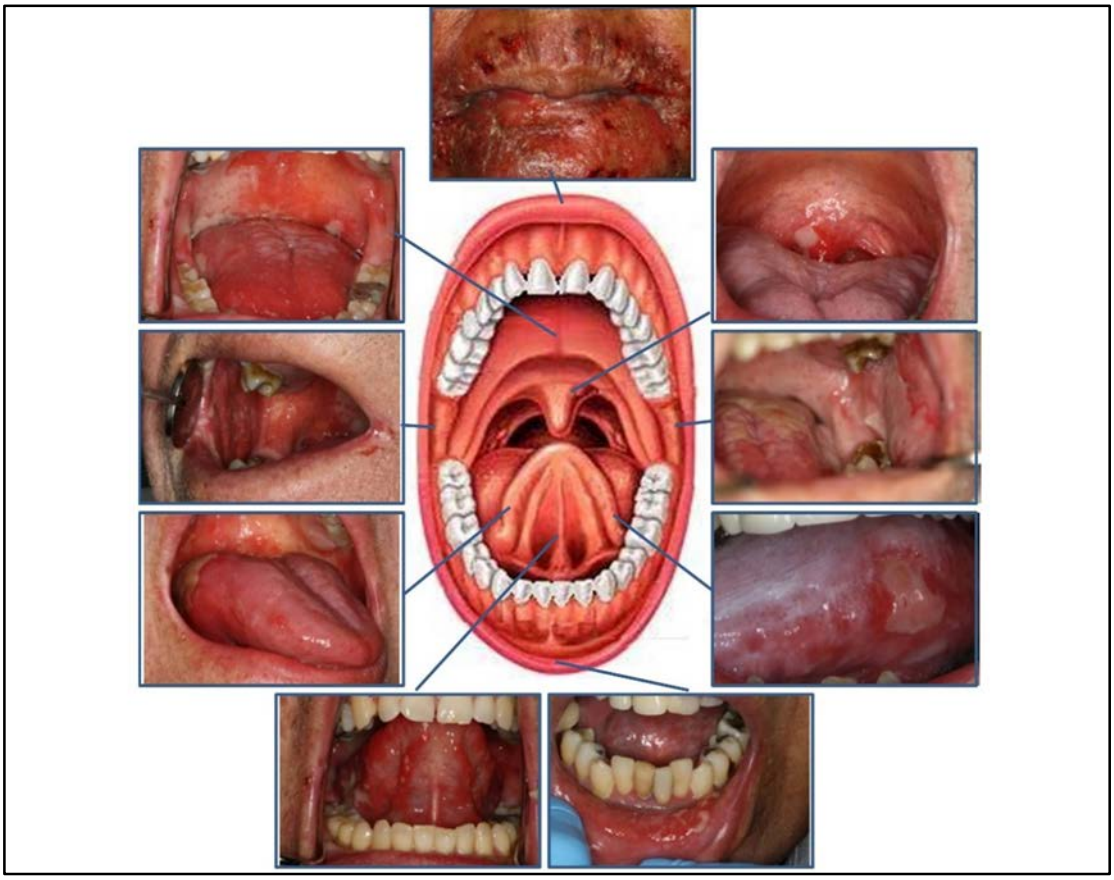

Figure 7: Clinical manifestations of OM in the nine anatomical sites according to the OMAS [67]. Photographs: AM Gussgard

The third clinical assessment tool, named "Total VAS-OMAS", was based on marking a whole mouth, i.e. "total" OM somewhere between 0-100 score on two linear visual analogue scales (VASs) [87]. One VAS value was set for extent of ulceration and the other for erythema (Figure 8).

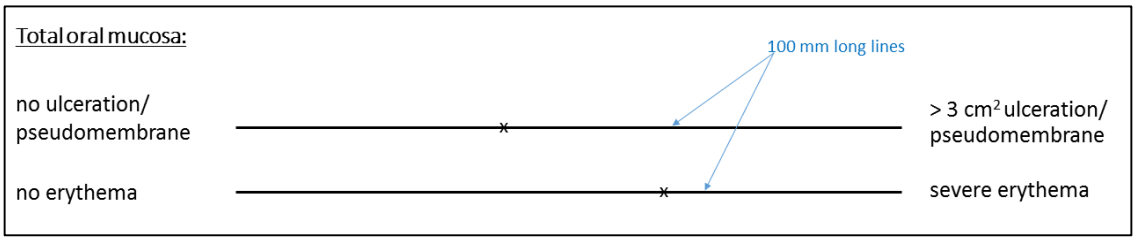

Figure 8. The "Total VAS-OMAS" concept. The "x"-marks set for illustration represent scores of 40 for ulceration and 65 for erythema, respectively.

We planned to use one main and one backup clinical examiner, with the recognition that seeing too many physicians at check-up appointments appears to be an important factor for negative experiences in cancer trial participants [88]. Moreover, having the clinical assessments done mainly by one examiner would presumably lead to less variability.

Training and calibration in the use of the OMAS tool was done prior to the study initiation, using a set of photographs kindly obtained from Dr. Monique Stokman at the University Medical Center Groningen, The Netherlands. Laminated booklets with clinical photographs of OM were used consistently during the study to avoid drifting of the intra-rater assessments of OM.

8.5 Assessment of OM by measurement of patient-reported symptoms

The participants' experience of OM throughout the study period where appraised by the PROMS scale questionnaire [73]. The questionnaire consists of 10 items, each with a 100-mm horizontal linear visual analogue scale addressing oral functions affected by the OM (Figure 9). The participants were asked to mark on the 100 mm line what best represented their present condition on the day of examination. All participants had undergone an exercise with dummy questions conducted at baseline to become familiarized with the linear VAS-style questionnaire.

Patient Reported Oral Mucositis Symptom (PROMS) Scale

1. Mouth* pain - *Mouth encompass also lips, cheeks, tongue, gums, palate and throat

no pain _____ worst possible pain

2. Difficulty speaking because of mouth* sores

no trouble speaking _____ impossible to speak

3. Restriction of speech because of mouth* sores

no restriction of speech _____ complete restriction of speech

4. Difficulty eating hard foods (hard bread, potato chips etc) because of mouth* sores

no trouble eating hard foods _____ impossible to eat hard foods

5. Difficulty eating soft foods (Jello, pudding etc) because of mouth* sores

no trouble eating soft foods _____ impossible to eat soft foods

6. Restriction of eating because of mouth* sores

no restriction of eating _____ complete restriction of eating

7. Difficulty drinking because of mouth* sores

no trouble drinking _____ impossible to drink

8. Restriction of drinking because of mouth* sores

no restriction of drinking _____ complete restriction of drinking

9. Difficulty swallowing because of mouth* sores

not difficult to swallow _____ impossible to swallow

10. Change in taste

no change in taste _____ complete change in taste

Figure 9: PROMS scale questionnaire with the ten items each detailing two extremes of pain, a functional characteristic and change in taste within a 100 mm horizontal linear Visual Analogue Scale (VAS).

8.6 Power, data management and statistical analyses

An *a priori* power analysis to establish a rank correlation between the PROMS scale and the NCI and/or OMAS tools of 0.90 yielded a sample group of 20 study participants (Alpha level 0.05 % and power of 80%, 2-tailed correlations) (Sample power, SPSS Inc. Chicago, USA). Since patients with H&N cancer could be considered as a challenging group to follow because of dropouts, no-show for follow-ups or treatments, it was considered prudent to sample 50 participants.

All recordings were documented using de-identified case report forms (CRFs). The information from the CRFs was uploaded to a relations database (MS Access, Microsoft Inc. Redmont, WA, USA). Repeated data entry verifications were made before exporting the data matrices for statistical analysis.

The measured clinical and participant-reported variables were checked for normal distribution to establish a potential need for log-transformation corrections to obtain more precise p-values before being subjected to Spearman rank correlation. Spearman rank correlations were applied to characterize the relationships between the PROMS scale values and the NCI-CTCAE v.3 as well as the OMAS & TOTAL-VAS-OMAS scores. The Spearman rank correlation tests were applied to address the relationships at both group as well as individual levels. To appraise the strengths of correlation at the different time points throughout the observation period, robust repeated measures mixed linear models, "PROC MIXED", were applied which account for the repeated nature of the measurements. Finally, a Bonferroni correction was applied to all statistical tests to account for multiple testing of the same measures. Correlations of <0.20 were considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and >0.80 very good [89]. The statistical procedure "PROC CORR" in the SAS System Version 9.2 software (SAS Institute, Cary, NC, USA) was used.

The secondary analyses presented in Paper #2, aimed to determine whether there was an association between oral mucositis symptoms and any specific extent or location(s) of OM. The changes of the aggregated PROMS scale values were measured when transitions occurred between OMAS score 0 to 1, 1 to 2 and 2 to 3, respectively in any of the nine intra-oral locations designated in the OMAS [67]. Prior to being subjected to

parametric or non-parametric statistical tests for comparative purposes, the PROMS scale values were checked for normal distribution and any need for log-transformation corrections. ANOVA with pairwise contrasts using the LSD procedure were applied for comparisons of mean changes of PROMS scale values upon transition between the three levels of OMAS scores (IBM SPSS ver. 22, IBM Corporation, Somers, NY).

In Paper #3 the correlations on the individual level were considered in light of the study participant characteristics. The study participants characterized with moderate correlations between signs and symptoms (n=5) were contrasted with the ones with very good correlations (n=10). As well, the study participants with the most extensive manifestations of OM, but with minor pain and adverse impact on oral functions (n=6) were contrasted with the ones with opposite traits (n=7). Simple bivariate tests were used, i.e., Fisher's exact or chi-squared tests for categorical variables and Student's-t test for comparison of the age of the study participants in the four identified sub-cohorts.

9 Main findings

Fifty study participants were recruited and followed throughout their radiation treatment conducted between August 17, 2009 and July 19, 2010. During this time 520 clinical examinations were undertaken, of which 500 were carried out by A.M.G. (Figure 10).

Pt #	Screen & baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		P	Sum # visits
1	X	X																2
2	X	X			X				X	X	X	X	X	X		X	X	11
3		X																1
4		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	15
5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	17
6		X	X	X	X	X	X		X	X	X	X	X	X			X	13
7	X	X	X	X	X	X	X	X	X	X	X	X	X	X				14
8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		15
9		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	16
10	X	X																3
11	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	17
12		X	X		X	X	X	X	X	X	X	X	X	X			X	13
13		X		X	X		X											4
14		X																1
15	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	15
16		X	X	X	X	X	X	X	X	X	X	X	X	X			X	14
17		X																1
18		X																1
19		X		X	X	X		X	X	X	X	X	X	X	X	X	X	14
20		X	X	X	X													4
21	X			X	X	X	X	X	X	X	X	X	X		X		X	15
22	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	15
23	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	15
24	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	16
25	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	15
26	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	15
27	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	14
28	X	X	X	X		X	X	X									X	7
29	X	X	X	X	X	X	X	X			X	X	X	X	X		X	14
30	X	X																1
31		X	X	X														3
32		X																1
33		X				X												2
34		X	X		X													3
35		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	15
36		X		X	X	X	X	X		X	X	X	X	X	X	X	X	14
37	X	X	X	X	X			X	X								X	8
38	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	15
39		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	15
40		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	15
41		X																1
42		X	X	X	X	X	X	X	X	X	X	X	X	X			X	14
43		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	15
44	X	X	X	X		X	X	X	X	X	X	X	X	X	X			14
45	X	X	X	X	X	X	X	X	X	X							X	11
46		X		X	X	X	X	X	X	X							X	9
47		X		X	X	X	X	X	X		X	X	X	X	X		X	12
48		X		X	X	X		X	X	X		X		X	X	X		11
49		X	X	X	X	X		X	X	X	X		X					10
50		X	X	X	X	X	X	X	X	X	X	X	X	X	X			14
	50	14	32	33	37	36	31	33	32	32	28	30	31	28	24	19	30	520

Figure 10: Clinical visits completed by-weekly over 6-7 week the study period marked by boxes in green with "x" (n=520). Boxes in left column indicate a combined screening and base-line visit (and also a few combined screening-baseline-first visits). Bottom line shows the number of study participants that completed the screening visit (n=50) of which n=30 were examined at the post therapy session.

Seven participants decided not to undergo cancer therapy or renounced further cancer treatment at some later stage. Three participants were excluded from the study because the prescribed radiation dose was below 54 Gy. Of the remaining 40, 33 participants completed the study, while 7 dropped out because of fatigue and exhaustion. The participants who completed the study received daily radiation fractions for six (n= 7) or seven weeks (n= 25), while one participant received radiation twice daily for 4 weeks. Tumours were principally T2 (n=9) and T3 (n=7), with node stage N0 (n=15) and N2 (n=12) and most often located in the oropharynx (n=13). (Table 5).

Table 5: Diagnoses of the study participants who completed the study, indicated by location and TN-stage (n=33).

	Total No (%)	T0/Tx	T1	T2	T3	T4
Oral cavity	5 (15)	N1	N0	N0	N2b	N0
Oropharynx	13 (39)	N0	N2b N2b N2b	N0 N2b N2b N3	N0 N1 N2c	N0 N2c
Salivary glands	6 (18)	-	N0	N0 N0	N0 N0	N0
Other*	9 (27)	N2b N2b N2b N2c	-	N1 N1	N1	N0 N0

*primary unknown, nasopharynx, sinus

All participants in this study experienced OM during the course of the radiotherapy, which for some patients became manifest as erythema after an approximate absorbed dose of 6 Gy and increasing thereafter in concert with increased absorption of therapeutic radiation. Some participants reported pain and impairment of oral functions in their first week of radiation treatment.

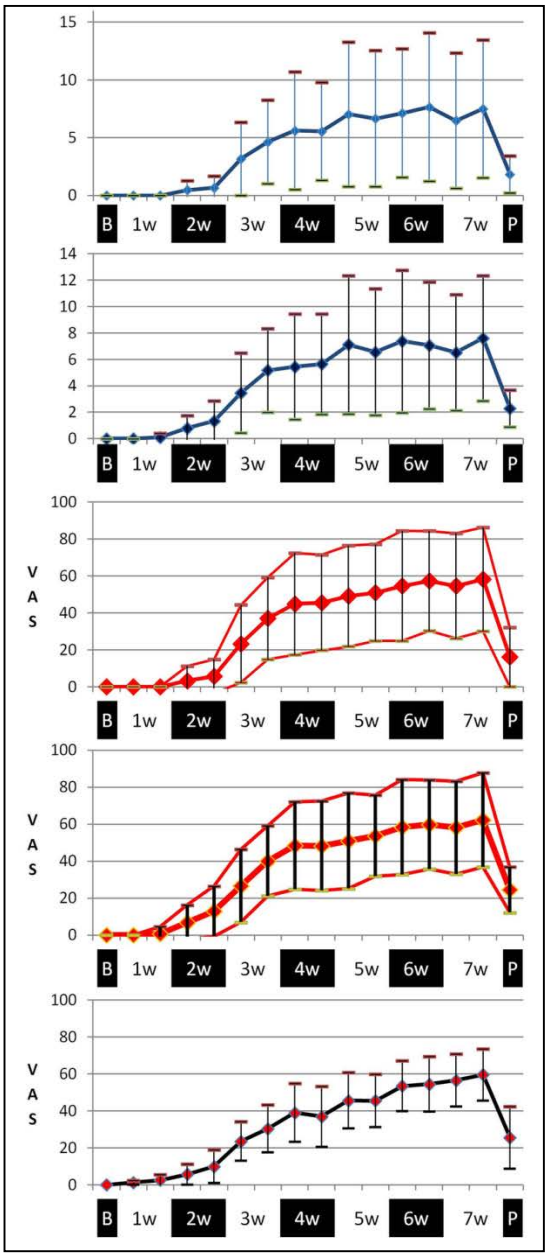

Figure 11. Clinical signs and patient symptoms recorded over the observation period (7 weeks) and at the 4-6 week post-therapy examination ("P").

From top to bottom: OMAS Scores for Ulceration (Means +/- SDs; maximum score = 27), OMAS Scores for Erythema (Means +/- SDs; maximum score = 18), TOTAL-VAS-OMAS Score for Ulceration (Means +/- SDs), TOTAL-VAS-OMAS Score for Erythema (Means +/- SDs) and PROMS scale value (Means +/- SDs).

(All VAS scales: maximum value = 100).

NCI-CTCAE scores for oral mucositis of "1" were observed as early as the first week of cancer treatment, while scores of "3" started occurring towards the end of the second week. By the end of the cancer treatment period, about half of the study participants had score "3". At the post treatment examination about 50% of the participants still demonstrated a NCI-CTCAE v.3 score of "2" (Figure 3 in Paper #1).

The OMAS-Ulceration and -Erythema as well as the TOTAL- VAS-Ulceration and -Erythema scores varied markedly amongst participants at the different time-points. However, the maximum scores were recorded consistently at the end of the 6-7 week radiotherapy period.

The PROMS-aggregated scores increased gradually during the cancer treatment period culminating with a visual analogue scale value of 60 by the end of treatment. Hence, all the clinical and patient-reported measurements of OM displayed similar patterns of increasing scores and values, with peaks at the end of cancer treatment. Signs and symptoms of oral mucositis were still present at the post-treatment examination carried out 4 to 6 weeks after ending cancer treatment (Figure 11).

While all items of the PROMS scale were affected by OM, two items in particular, i.e., "Change of Taste" and "Difficulties eating hard foods", were considerably more affected (Figure 12). Moreover, the participants reported that these two functions remained substantially affected even 6 weeks after the therapy had ended.

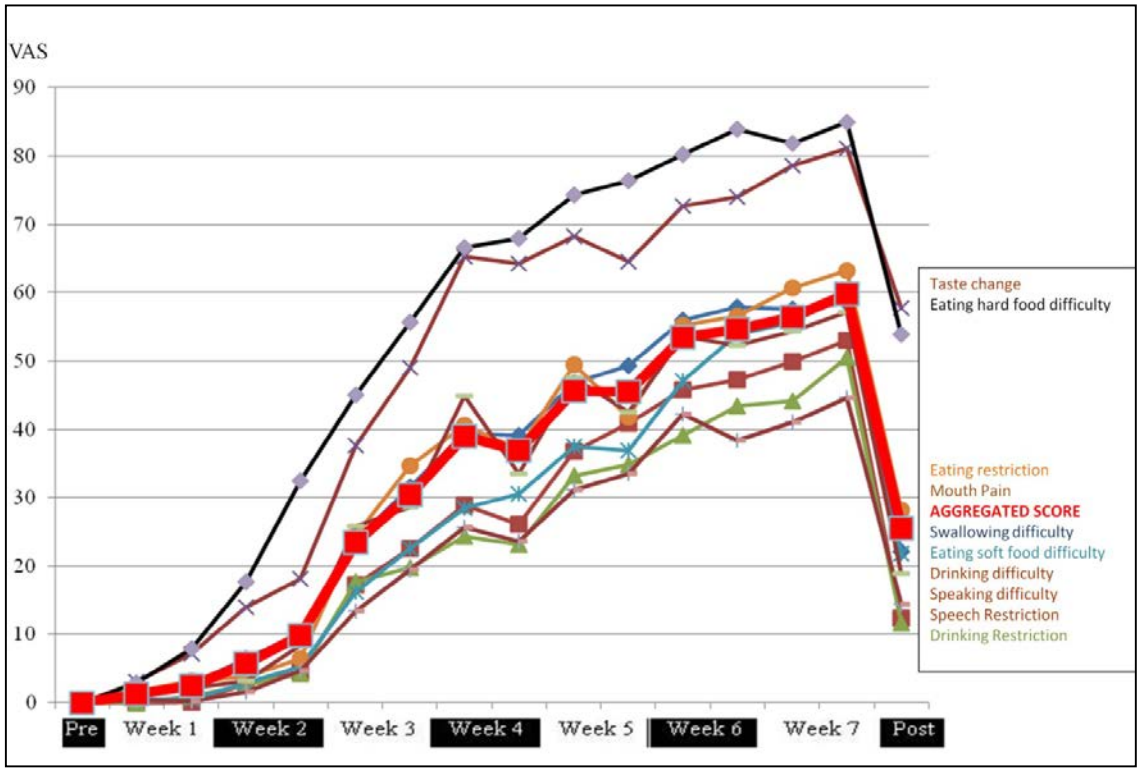

Figure 12. Patient-reported PROMS scale VAS-values experienced over the full course of the 7 weeks cancer therapy period. Left side indicate the mean PROMS scale VAS-values at baseline "Pre" before commencing therapy. Right side show the mean PROMS scale VAS-values at the post-therapy examination 4-6 weeks after the completed cancer therapy ("Post"). The mean aggregated PROMS scale average is emphasized in red, while the 10 separate components of the PROMS instrument (listed to the right) are shown in different colors. Higher VAS-values denote more impairment of oral functions (max VAS=100).

9.1 Paper #1

The participants' experience of OM according to the PROMS scale values demonstrated good correlations (Spearman's Rho 0.65 - 0.78, p<0.001) with the clinician-determined scores on the group level over all time points and poor to good correlations (Spearman's Rho -0.12 - 0.70, p< 0.001) on the group level at different time points during and after therapy (Figure 13)

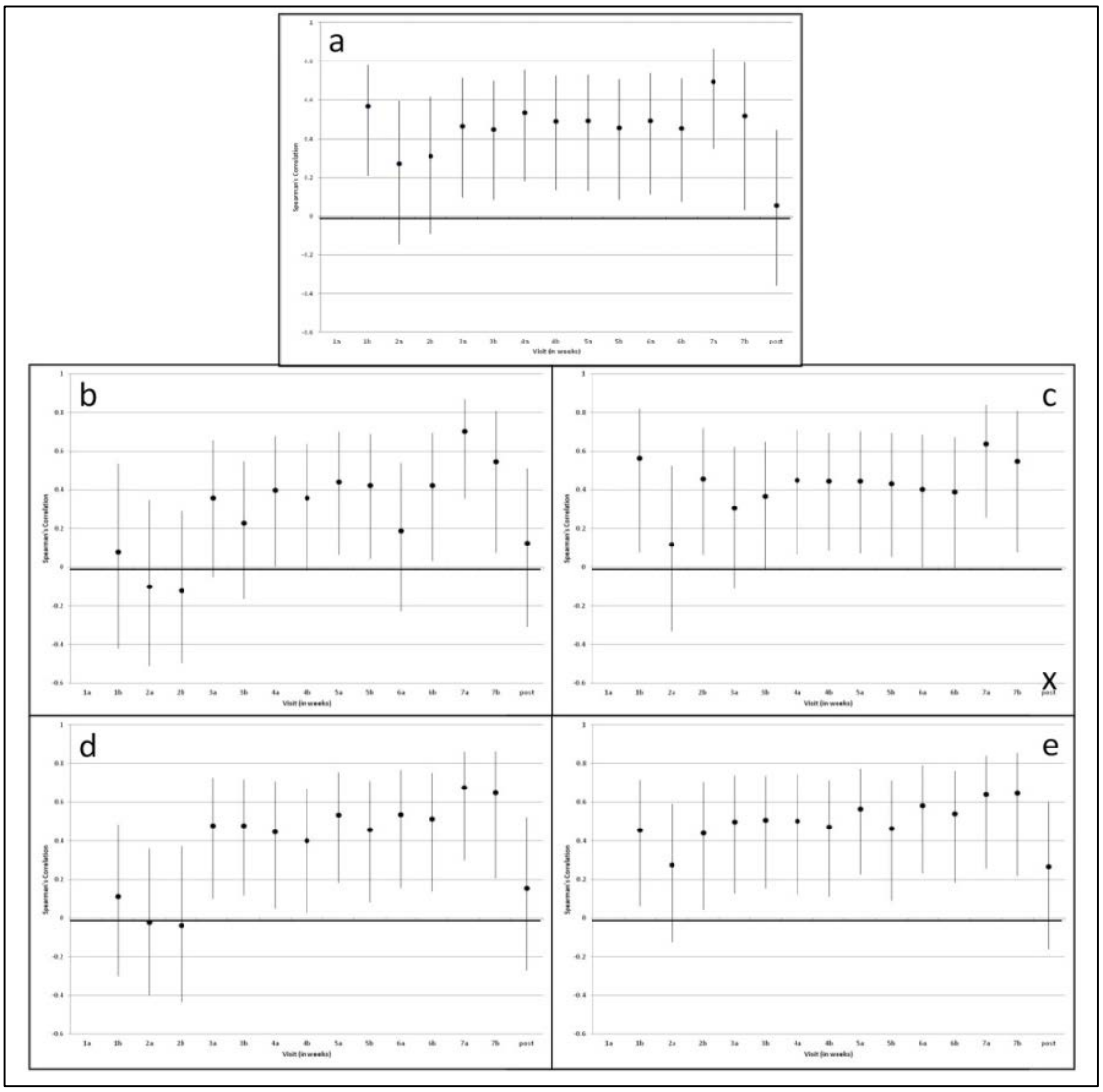

Figure 13. Spearman rho correlation coefficients over the observation period (6 or 7 weeks) and at the 4-6 week post-therapy examination between clinical signs of oral mucositis, as reported by different clinician-based scoring tools and the experience of oral mucositis by the participants, as reported by the PROMS scale. PROMS scale value vs. scores for: NCI-CTCAE v.3 (a), OMAS-Ulceration (b), OMAS Erythema (c), TOTAL-VAS-OMAS Ulceration (d) and TOTAL-VAS-OMAS Erythema (e).

9.2 Paper #2

Some study participants experienced major discomfort and oral dysfunction even with only a few affected locations or with a relatively small extent of ulceration. The patient-reported mouth pain associated with OM increased more upon transition of OMAS score for ulceration anywhere in the mouth from 1 to 2, compared to 0 to 1 (p=0.05) (Figure 14). Moreover, the difficulties of eating hard foods caused by the OM was more pronounced when the OMAS score for ulceration anywhere in the mouth changed from 1 to 2, compared to between score 0 and 1 (p=0.002) or between score 2 and 3 (p=0.001). The patient-reported PROMS score increased also more upon transition of OMAS score for ulceration anywhere in the mouth from 1 to 2, compared to 0 to 1 (p=0.009). The same applied for ulcerations located in the soft palate with more pronounced difficulty upon change from 1 to 2 compared to between score 0 and 1 (p=0.05) or between score 2 and 3 (p=0.02).

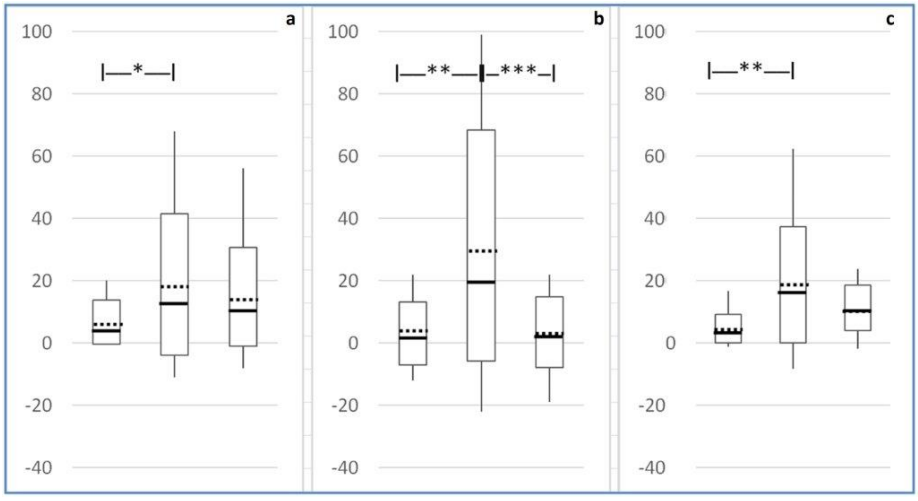

Figure 14. Change of patient-reported PROMS scale VAS-values upon transitions between OMAS scores 0 to 1, 1 to 2 and 2 to 3 anywhere in the mouth. The three boxplots within each graph show the dispersion of changes in VAS-values of mouth pain (a, left), difficulties eating hard food (b, centre) and aggregated PROMS (c, right) upon the transitions (maximum change = VAS value 100). The interrupted horizontal lines in the box centers represent the mean changes, with the upper and lower box edges indicating the SD. The horizontal full lines represent the median, and the whiskers represent the maximum and minimum changes of VAS values. Horizontal bars above box-plots indicate statistical significant differences (*= P< 0.05, **= p<0.01, ***=p<0.001).

In summary, the relationship between the patient-reported impairment of oral function and pain caused by OM ulceration, and the extent of the ulcerations is not linear, but rather curvilinear (Table 6).

Table 6: Change of patient-reported PROMS scale VAS-values upon transitions between OMAS scores 0 to 1, 1 to 2 and 2 to 3. Change of VAS-scores (original scale 0-100) upon transitions between OMAS scores from 0 to 1, 1 to 2 and 2 to 3 anywhere in the mouth, in the soft palate, on the tongue or cheek for the two items: mouth pain, and difficulties eating hard food and for the aggregated PROMS scale values. In each column: mean and (SD)

Intra-oral location	**PROMS item**		**0 to 1**	**1 to 2**	**2 to 3**
Any			n=14	n=23	n=17
	Mouth pain		7 (7)	19 (23)	15 (16)
	Difficulty eating hard food		3 (10)	31 (37)	3 (11)
	Aggregated PROMS		5 (5)	19 (19)	11 (7)
Soft palate			n=12	n=20	n=14
	Mouth pain		7 (7)	16(20)	12 (17)
	Difficulty eating hard food		6 (11)	23 (33)	3 (12)
	Aggregated PROMS		7 (7)	13 (19)	10 (9)
Ventral and lateral tongue		Side	Right n=7 - Left n=11	Right =15 - Left n=15	Right=5 - Left=6
	Mouth pain	Right	15 (11)	6 (20)	24(22)
		Left	17 (16)	9 (13)	10 (20)
	Difficulty eating hard food	Right	11 (23)	20 (37)	9 (10)
		Left	16 (29)	17 (28)	7 (18)
	Aggregated PROMS	Right	8 (10)	11 (11)	18 (7)
		Left	11 (14)	10 (11)	12 (10)
Cheek			Right n=9 - Left n=7	Right n=10 - Left n=13	Right n=8 - Left n=8
	Mouth pain	Right	19 (22)	9 (9)	6 (15)
		Left	11 (24)	15 (15)	10 (15)
	Difficulty eating hard food	Right	27 (35)	27 (40)	13 (37)
		Left	23 (35)	28 (33)	-1 (6)
	Aggregated PROMS	Right	17 (20)	12 (10)	9 (12)
		Left	14 (20)	16 (16)	7 (6)

9.3 Paper #3

The correlations between the different signs and symptoms over all time points varied markedly on the individual level. The characteristics of the study participants in the two sub-cohorts defined by high and low correlations were comparable, except perhaps with regard to age ($p < 0.05$, t-test) (Table 7a). Nor did the study participants in the two sub-cohorts defined by high manifestation and minor complaints and *vice versa* differ with regard to the recorded variables (Table 7b). An example of a stoical sufferer with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions is shown in figure 15.

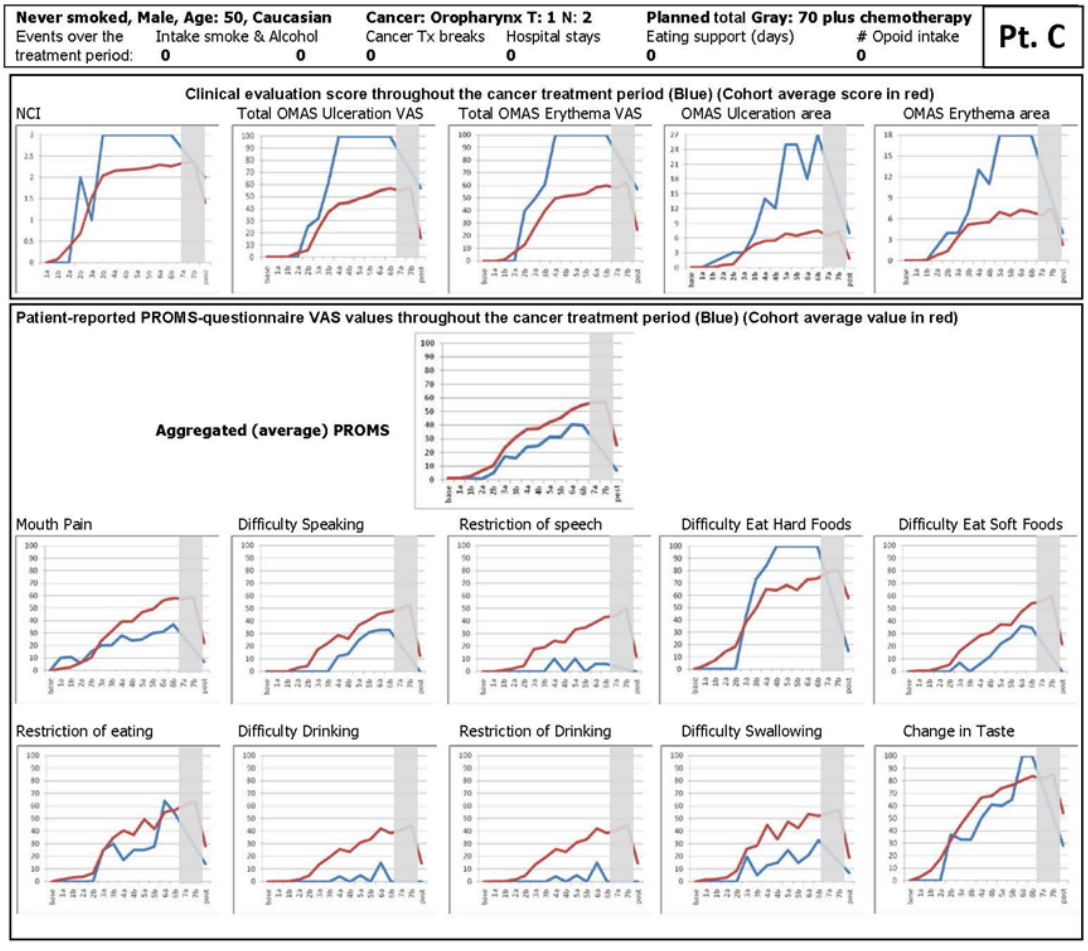

Figure 15: Representative stoical sufferer with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions. The graphs in the top row represent the five different clinical scores of OM. The patient reported OM values are shown in the 11 graphs below. All horizontal lines represent study visits from baseline (to the left) to the end of 6 or 7 weeks treatment, and finally post-treatment visit (to the right). The blue lines represent the actual study participant whereas the red lines represent cohort average.

Table 7a. Characteristics of the study participants with very good correlation (Spearman's rho > 0.85) between clinical manifestation of OM versus patient-reported pain and adverse impact on oral functions (left column, n=10), versus the study participants with moderate correlation (Spearman's rho < 0.60) between clinical signs and reported symptoms (center column, n=5). Status of the remaining participants in the right column (n=18).

	Very good correlation N=10	Moderate correlation N=5	Remaining participants N=18	Total n (%)
Sex				
Male /Female	9/1	4/1	12/6	25 (76) /8 (24)
Race				
Caucasian / Other	9/2	5/0	14/4	27 (82) /6 (18)
Age (years)				
Mean (SD, Range)	59 (8, 49-70)	68 (6, 62-78)	60 (12, 39-80)	61 (9, 39-80)
Dental status				
Good Fair-Poor Edentulous	4 5 1	0 4 1	11 7 0	15 (45) 16 (49) 2 (6)
Smoking				
Never /Ex-smoker /Present smoker	3/4/2*	0/2/3	6/10/2	9 (29) /16 (50) /7 (22)*
Alcohol				
No / Yes	3/6*	0/5	8/9*	11 (38) /20 (62)**
Primary tumor location				
Oral cavity/ oropharynx /Salivary glands /Other	3/4/1/2	0/2/1/2	2/7/4/5	5 (15) /13 (38) /6 (18) /9 (27)
T stage				
T0-T1 / T2 / T3-T4	4/1/5	2/1/2	5/7/6	11 (33) /9 (27) /13 (39)
N stage				
N0-N1 / N2 / N3	5/4/1	3/2/0	13/5/0	20 (60) /12 (36) /1 (3)
Planned Gray				
70 / 66 / <66	5/3/2	3/2/0	13/5/0	21 (64) /10 (30) /2 (6) [#]
Planned chemotherapy				
No / Yes	6/4	4/1	8/10	18 (55) /15 (45)

(*) = Unknown

[#] 64 & 60 Gray planned

Table 7b. Characteristics of the study participants with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions (left column, n=6), the study participants with minor manifestation of OM, but reporting extensive pain and adverse impact on oral functions (center column, n=7). Status of the remaining participants in the right column (n=20).

	Major OM Minor impact N=6	Minor OM Major impact N=7	Remaining participants N=20	Total n (%)
Sex				
Male / Female	6/0	5/2	14/6	25 (76) /8 (24)
Race				
Caucasian / Other	5/1	5/1	17/4	27 (82) /6 (18)
Age (years)				
Mean (SD, Range)	63 (11, 50-78)	61 (9, 42-67)	61 (11, 39-80)	61 (9, 39-80)
Dental status				
Good Fair-Poor Edentulous	3 2 1	4 2 1	8 12 0	15 (45) 16 (49) 2 (6)
Smoking				
Never /Ex-smoker /Present smoker	3/2/1	1/5/1	5/9/5*	9 (29) /16 (50) /7 (22)*
Alcohol				
No / Yes	1/5	4/3	6/12**	11 (38) /20 (62)**
Primary tumor location				
Oral cavity/ oropharynx /Salivary glands /Other	1/3/0/2	1/2/2/2	3/8/4/5	5 (15)/ 13 (38) / 6 (18) / 9 (27)
T stage				
T0-T1 / T2 / T3-T4	1/2/3	3/1/3	7/6/7	11 (33) /9 (27) /13 (39)
N stage				
N0-N1 / N2 / N3	3/3/0	5/2/0	13/7/1	20 (60) /12 (36) /1 (3)
Planned Gray				
70 / 66 / <66	5/1/0	3/4/0	13/5/2	21 (64) /10 (30) /2 (6)[#]
Planned chemotherapy				
No / Yes	3/3	3/4	12/8	18 (55) /15 (45)

(*) = Unknown

[#]64 & 60 Gray planned

10 Discussion

10.1 Critique of study methodology

10.1.1 Study design

This study was purely observational, with no intention to appraise the effect of a new preventive, or interventional procedure. The study participants were therefore not exposed to any particular risks, but they were made aware of the burden of being examined twice per week and subjected to a more thorough than usual intra-oral examination as well as having to complete a questionnaire. In this regard, an additional visit in a specific room of the hospital for an additional examination meant to last 10 minutes could be interpreted as a burden for someone who is tired, fearful, and uncertain. Obviously, all participants were informed prior to the study that they could withdraw at any time, without any need to explain why and without any consequences whatsoever for future cancer care.

10.1.2 Study power

The a priori power calculation indicated that only 20 study participants were required to establish a rank correlation between the objective and subjective measurements of OM with 80% study power. Nonetheless, more study participants were included for various reasons. The problems recruiting, enrolling and maintaining participation in cancer trials have been recognized in general [88, 90] and locally at PMCC [91]. A primary reason for high study attrition in this patient group is rapid health deterioration or early deaths, and difficulties of collecting data from patients who are exhausted or have experienced extensive therapy-related adverse events [92, 93]. Whether H&N cancer patients in particular are less reliable in research studies compared to other cancer patients remains uncertain [94-96]. However, the compliance of H&N cancer patients with follow-up treatment after therapy completion is poor for dental care [97] as well as speech and swallow therapy [98]. Dentists recognize H&N cancer patients in general as being challenging because of poor oral health behaviours and compliance problems [99, 100]. The lower than expected withdrawal rate carried both logistical challenges as well as interpretative considerations. The logistical challenge was that as many one as 520

clinical examinations had to be completed, mostly by the main examiner (A.M.G.).

10.1.3 Study participants and dropouts

The cohort of study participants can be characterized as heterogeneous from the perspective of their age, dental status, smoking and alcohol habits, primary tumour location, TNM cancer stage, surgery procedure, use of supplementary chemotherapy and therapy length. From the perspective of correlating subjective symptoms versus the objective signs the heterogeneity shouldn't really matter. In contrast, a study planned to clarify to what extent these factors individually or in concert affect patient-experienced OM-associated mouth pain during cancer therapy can only be determined in a far larger study. The logistical, ethical and practical challenges upon conducting studies that necessarily will require multivariate, multilevel statistical analyses of a large sample size to address such issues are likely reasons why these potential associations to a little extent have been elucidated in the research literature. The author was fully aware of the potential to draw erroneous conclusions caused by spurious statistical observation when re-analyzing the data in Papers #2 and #3.

It was perplexing that fewer study participants dropped out of the study than anticipated. Other studies of H&N cancer patients operate with as high as 66% drop-out rates [101], while in the current study only 7 participants dropped out of the 40 (i.e. about 17%) who continued their cancer therapy and received radiotherapy of more than 54 Gy.
An interpretative consideration is whether the participants who completed the full study can be regarded as H&N cancer patients undergoing cancer therapy in general. True or not, there is little reason to suspect that the actual subjective and objective correlations on the group level can be challenged. However, one should not rule out the possibility of a Hawthorne effect (i.e., participants alter their responses because they take part in research) from some of the participants, especially the participants who felt a strong urge to talk with a health care provider and had their needs realized [102].

Several reports have proposed that altruism [103] is an important drive when patients decide whether to partake in clinical research [104, 105]. In the information package provided to all potential study participants, several incentives for partaking were listed.

Although the reason for partaking was not recorded, the majority of participants frequently voiced during the therapy period that they hoped and expected that their study participation would potentially benefit future patients. Also, one should not rule out that patients undergoing exhausting cancer care experience a "psychological boost" by knowing that they form part of a research project.

10.1.4 Clinical measurement error

The examiner who carried out the great majority of clinical examinations (A.M.G) had extensive experience with patient management and care but, at the outset, had less clinical experience of appraising and scoring radiation-induced OM. In order to improve the primary investigator's diagnostic skills related to OM assessment, A.M.G. frequently attended the dental clinic at PMCC as an observer prior to beginning the study. Dr. Stokman in The Netherlands wrote an article in where she described in detail the training of future evaluators of OM based on clinical pictures used as guide for the OMAS scoring system [106]. Dr. Stokman kindly granted permission to use her clinical pictures in a calibration booklet, which was used in the dental clinic at PMCC during the study period.

Obviously, the study participants prioritized their actual cancer therapy sessions. When these were delayed, much time was spent on searching for study participants who were occasionally located in the radiotherapy waiting room or elsewhere in the hospital. If required by the circumstance, the clinical assessment of OM was done *ad hoc* in the waiting room or in an adjacent room. In some situations, the measurements were done while the study participant was in bed receiving chemotherapy or other intravenous treatment. These study participants always gave their permission to be examined under these circumstances and the intra-oral examinations were completed by using a high-power head-lamp as a light source. The potential for measurement error under these circumstances was considered unlikely, since a head-lamp was also used in the dental clinic setting.

As reported in other clinical studies [67], the possibility to score OM in the pharynx became very difficult if the patient was no longer able to open his or her mouth. The risk of under-reporting clinical manifestation of OM in these sites is recognized.

10.1.5 Error in study participant reporting

PROs described in the literature can often consist of multiple questions and sometimes with complex wordings. Sometimes there is a mixture of VAS-scales and Likert-type categories on the questionnaires that is perhaps statistically rational, but creates confusion for individuals completing the questionnaires. Moreover, sometimes the scales are not necessarily in the same direction, which permits incorrect reporting by the stressed or fatigued responder. The PROMS scale incorporates many of these considerations in that the questionnaire consist of single questions for 10 items. The wordings of the questions are kept deliberately simple. The same horizontally linear VAS-scale is used for all 10 items and the minimum positive score is always on the left side and the maximum worst to the right, i.e. there is the same visual direction for all questions. Following the exercise with the dummy questions prior to study commencement, none of the study participants had issues understanding and completing the questionnaires (Figure 9).

Pain is common in patients with H&N cancer. Estimates suggest that about 50% of patients prior to the cancer therapy, 81% during therapy, 70% at the end of therapy, and by 36% at 6 months after treatment have pain. Importantly, approximately one third of patients still report pain up to 6 months post-therapy [107]. These estimates are higher than observed in the current study where the incidence was 0% at start, 50% at the end of the therapy period and approximately 25% post-therapy.

The observation that the participants did not report mouth pain during their first week of radiation therapy is especially intriguing. Other studies suggest that about 50% of H&N cancer patients have pain prior to cancer therapy [107, 108]. One possible explanation of the apparent discrepancy may be that PROMS-questionnaire focuses on effects of actual mouth sores (i.e. oral mucositis) and the question about mouth pain was also considered within this context [73]. To emphasize this element further, the information that *"the mouth encompasses also lips, cheeks, tongue, gums, palate and throat"* was added to the pertinent question on the PROMS questionnaire for clarification.

Study participants who missed occasional clinical examinations (Figure 10), did so because (i) they simply forgot, (ii) they were receiving chemotherapy that day and were

in bed, (iii) they had become in-patients on short notice for intravenous treatment, or (iv) they simply felt too ill or inconvenienced to come by their own means to the dental clinic in the hospital. The effect of these occasional missing data were not considered important and had minimal to no impact on the overall findings reported here.

10.2 Ethical reflections

H&N cancer patients should be considered as a particularly vulnerable patient group. Not only do these malignancies have a high mortality risk, but the cancer is also located in a part of the body that is important in the context of social relationships. The patients are uncertain what to expect during the cancer therapy, as well as the outcome of the actual therapy. “Will I become healthy or will the cancer kill me”, is one dimension of the anxiety. Another is the apprehension about the likely physical or psychological debilitation that will follow. Sometimes, portions of the craniofacial complex need to be surgically removed, or altered, salivary glands are negatively affected, which increases dramatically the risk of intraoral diseases and there is even a danger of trismus. Even though some of the damage can be restored with prostheses or grafting of lost hard and soft tissues, the patients will usually perceive themselves as altered. Some patients unfortunately become socially handicapped because of, e.g., a «monstrous» appearance or because of persistent speech difficulties.

A common observation was that “someone to talk with” was of major importance for several of the study participants to endure the cancer treatment. At PMCC all cancer patients are offered consultations with e.g., doctors, nurses, psychologists, faith-based social service providers and others, while they undergo therapy. Yet, many of the study participants expressed relief of having someone to talk with, without having to undertake a proactive initiative to book such appointments in advance. As the participants experienced a gradual worsening OM with debilitating effects, anxiety frequently crept in about a possible return of the cancer or manifestation of some form of new cancer. It appears apparent that cancer patients in therapy need access to a person that is readily available to respond to distresses and to explain that the adverse toxic effects of radiotherapy are typical. The ten minutes set aside for each study participants was more often than not prolonged, some times for an hour because the

participant had a need for a dialogue beyond the pure research aspects, a shoulder to cry on, or a hand to hold.

When the investigator is also a doctor, where does one draw the line between the research endeavor and the role as a health care provider? Our main role as a doctor is to cure sometimes, to relieve often, to comfort always. It follows that time is required to console, also when one undertakes the role as researcher. In a busy everyday clinical practice, time is unfortunately a luxury. However, the legal and moral requirements in Norway, Canada and many other countries is that the safeguarding of the integrity and welfare of the study participant shall precede the interest of science and society [109, 110]. Attention to the welfare of my study participants required that I prioritized my time to answer questions and counsel when the situation, in my opinion, so required. Obviously, my presence beyond the pure research-related activities stole time from other commitments. The time and efforts were considerable, but the reward was the gratefulness received from the participants and their close relatives. A common theme in many textbooks on medical ethics is cost-utility and cost-benefit discussions, but always on the public health macro-level [111]. Undertaking this study has persuaded me that this issue should also be considered on the micro-level, i.e., all doctors that conduct clinical research on vulnerable patients should reflect on what benefit the single patient there and then versus the possible indirect benefit that other patients may benefit from a future research publication.

10.3 Critique of findings

10.3.1 General

Objective signs

Given that a single ulceration site may cause just as much suffering as multiple and/or confluent areas it is debatable as to what is the most meaningful approach to interpret the scores originating from different scales that measure only clinical visual manifestations of OM. Moreover, sum scores and averages have the potential to be misleading if a few high scores are neutralized by sum scores from multiple intra-oral sites. This statistical dilemma has been discussed by several developers of scoring systems [67, 112], but so far no consensus has been reached.

Subjective symptoms

That the most common patient-reported acute and late problem was alteration in taste is consistent with findings reported in previous studies [113-118]. One can question whether a change in taste indirectly may affect eating and drinking. Patients may not feel a need for food if "everything taste like cardboard" (actual comment from some patients). Even though the questions regarding eating and drinking in the PROMS-scale questionnaire where specified "because of mouth sores", there is a possibility that participants may have reported problems with eating or drinking due to change alterations of taste.

The study participants reported swallowing difficulties often, but not to the magnitude of these problems representing their chief problem as has been reported in other patient cohorts [119]. The discrepancy may be explained by differences in xerostomia incidence as well as distribution of tumour sites in different study cohorts. Swallowing is substantially affected if there is concurrent xerostomia, a factor that was not considered in the current study. The location of the cancer would likely also influence the risk of swallowing problems. Patients with a cancer located in the oropharynx will likely experience swallowing problems as a combined effect of tumour location as well as the radiation-induced OM [120].

Correlations

The combination of large variability and small study sample cautions against making any strong inferences, but it appears that the location of an ulceration could be more important insofar as oral functions are concerned than merely size. Ulceration in the soft palate caused a major increase in problems eating hard food as well as reported pain, when the OMAS score for ulceration changed from score 1 to 2 (Table 6). This change could be due to increased swallowing sensitivity resulting from soft palate ulceration. Patients may be able to more or less ignore an OM ulcer that is less than 1cm^2 (OMAS score 1) in this location, but that when exceeding 1cm^2, they certainly are affected and their PROMS scale values increase.

The association between the individuals' PROMS-scale values with the OMAS scores (Paper #2) did not demonstrate any clear patterns. The small study sample precludes the possibility of drawing many conclusions in this regard. Severe impairment of oral functions was reported by some participants with ulcerations limited to two or three sites. Alternatively, six of the worst affected study participants in terms of amount of intra-oral ulcerations reported only modest mouth pain, as defined by VAS-values between 37 mm and 65 mm, while some of the individuals with ulcerations limited to two or three sites reported VAS values for mouth pain above the 80 mm range (Paper #2). The size of the ulceration itself is important, but the number of ulcerations may not necessarily contribute to more pain than having just one ulcer. The observation that a single ulceration above a certain size may cause major discomfort for a patient is consistent with the statement made in the original OMAS-study paper that: *"...worst site and extent of severe mucositis appeared to be more responsive to change [in mucosal health] than mean mucositis score"* [67].

That patients report significant impairment of oral functions even when scores are lower than e.g. OMAS score 3 or WHO score 3 or NCI-CTCAE score 3 is both clinically relevant and important when planning for clinical research. Using the most severe OM scores as the primary outcome in a clinical study is of course very relevant from a research perspective. However, measurements of lower levels of OM appear to be more patient relevant.

That the major change in PROMS scale values occurs upon transition from small to medium, rather than from medium to large corroborate observations findings reported by Elting et al. [22]. Although these investigators worded that *"oral pain scores peaked earlier than the maximum grade of OM"* the essential interpretation is that the size of OM ulceration above a certain level does not necessarily lead to more pain.

10.3.2 Individual level

Smoking has not been linked consistently with any particular presentation of OM since it's been demonstrated to be a risk factor for higher [121], lower [122] or no effects [123]. The same applies to oral hygiene [124-126]. It has been suggested that some individuals may be more susceptible to mucosal damage due to genotypic variation [37]. The sub-category of oropharyngeal cancers that is linked to human papillomavirus rather than to the traditional etiological factors may potentially also present with different symptomatology during the cancer treatment [127]. This factor may be partially responsible for the identification of age as a significant difference between the groups.

We failed to identify particular patient-characteristics that were associated with discrepancies between the patient-reported symptoms and the clinician observed signs (Paper #3). Only age was identified as different between the groups, which may be a spurious statistical finding. On the other hand, it is also possible that the younger study participants more likely were HPV-positive and further that such patients respond differently to radiotherapy compared to patients with other likely etiology. Given that this conclusion can be a type 2 error, the observed discrepancy between the observed OM and the reported pain and adverse impact on oral functions may be the result of clinical measurement errors or errors in study participants reporting, described in sections 10.1.3 and 10.1.4.

A possible effect of radiation dose and concurrent chemotherapy did not explain the variance of reported adverse impact or poor correlations (Paper #3). All study participants received the same radiation modality (IMRT), even though the targets and consequently the fields of radiation differed. While there is some information regarding relationship with tissue and dosage [128], the authors have failed to identify any papers that have studied a possible inter-dependency between tissue dosages and patient-

reported pain. Some studies [20, 22] report that chemotherapy together with radiation treatment makes patients more susceptible to OM. In the current study, 45% of the study participants received chemotherapy, but under the conditions used here, it was not apparent that concomitant chemotherapy resulted in more or less pain and/or better or worse correlations between objective signs and subjective symptoms.

It is often tempting to interpret patient symptom data on inter-individual rather than on intra-individual levels. Self-assessed patients may enter a higher score than other patients depending on several factors including, but not limited to, previous experiences regarding illness or pain [129]. However, one conclusion from the current study, is that the most appropriate data for comparison may be measures of within-participant pre- and post-intervention change, as it is also advised when appraising quality of life improvements [130]. After all, it is the experiences of the individual patient that should dictate how he or she should be managed. What remains to be resolved is to identify the relative intra-individual changes in patient-reported VAS-values to judge whether the individual cancer patient's condition is improving or worsening *versus* no change.

11 Conclusions

- There is good correlation between the radiation-induced OM experience of the study participants with H&N cancer on the group level, as reported by the PROMS scale questionnaires, and common clinical instruments for assessment of OM.
- The development of one or more ulcerations less than approximately 1 cm^2 does not impair oral functions much, as measured with the PROMS scale questionnaire. The increase of an ulceration to more than 1 cm^2 cause a relatively larger change of reported impairment and mouth pain, in comparison with the relative change upon transition from less than to more than 3 cm^2. Hence, the relationship between patient-reported impairment of oral function and mouth pain caused by OM ulceration and clinical manifestation of OM is not linear, but rather more curvilinear (Paper #2).
- H&N cancer patients report different adverse impacts on daily oral functions caused by OM that occasionally are discordant with the objective clinical findings. The causes are likely multifactorial, and no clear patient-, diagnosis- or intervention-characteristics could be associated with the participants that under- or over-reported adverse symptoms, or the participants with medium-to-poor correlation between the objective signs and the subjective symptoms (Paper #3).

12 Significance of results

Reliance upon clinical measures of oral ulceration/mucositis alone to gauge patient symptoms (with regard to OM) following radiotherapy and/or chemotherapy must be reconsidered.

Combining clinician-observed signs of OM with patient-reported experience of symptoms of OM appear to be a better approach for assessing the severity of OM, rather than relying exclusively on either one or the other. The current study shows that the information provided by the patient by way of the PROMS scale questionnaire can complement common clinician-determined assessments of OM. Moreover, the information provided by the patient in the PROMS scale questionnaire can also substitute for common clinician-determined assessments of OM in patients who cannot open their mouth, endure a comprehensive clinical oral examination or simply can't come to the treatment centre.

Clinical trials that implement the maximum OM score as primary outcome, such as OMAS score 3 or NCI scores 3 and 4 or WHO score 3 to assess intervention efficacy are common. Less severe primary outcomes appear to be more patient-relevant. Further and larger clinical studies are needed to appraise the complex correlations between severity of OM and patient-experienced pain and dysfunction.

PROs should be incorporated to augment clinical observations, as either primary or secondary outcomes in any interventional studies regarding OM. H&N cancer patients often report different adverse impacts on daily oral functions caused by OM that are discordant with objective clinical findings. Consequently, the changes of PROs values should be measured on the intra-individual rather than on any inter-individual levels. If average point or variability estimates on the patient group level are used, subtle but important positive effects on some, but not necessarily all patients, may become masked.

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14 Appendices

14.1 REB approval

14.2 OM experience of individual study participants

University Health Network
Toronto General Toronto Western Princess Margaret

University Health Network
Research Ethics Board
8th Floor South, Room 8-23
700 University Ave
Toronto, Ontario, M5G 1Z5
Phone: (416)946-4438

Notification of REB Initial Approval

Date: May 5th, 2009

To: Dr. Robert Wood
Surgical Oncology, Dentistry
2nd floor, Room 2-933
Princess Margaret Hospital
610 University Ave
Toronto, ON M5G 2M9

Re: 09-0231-CE
Development of a Novel Psycho-Biological Tool for the Measurement of Oral Mucositis in Head and Neck Cancer Patients Undergoing Radiation Therapy and Concomitant Chemotherapy

REB Review Type:	Expedited
REB Initial Approval Date:	May 5th, 2009
REB Expiry Date:	May 5th, 2010
Documents Approved:	
Protocol	Version date: March 10th, 2009
Consent Form	Version date: April 29th, 2009
Case Report Form	Received on: March 27th, 2009

The above named study has been reviewed and approved by the University Health Network Research Ethics Board. If, during the course of the research, there are any serious adverse events, confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation - Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information.

Please be aware that it is UHN policy that research-related activities involving an external party require a research agreement. An 'external party' refers to a corporation other than UHN or an individual who is not UHN personnel. Should a research agreement be required in this case, the study may not begin at UHN until the agreement has been signed by all parties. Should the negotiation process raise concerns, the REB reserves the right to reconsider its approval.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must be notified of the completion or termination of this study and a final report provided. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH/GCP

Sincerely,

Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

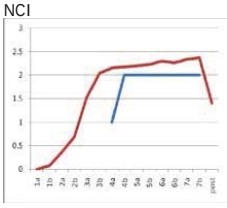
14.2 OM experience of individual study participants

For figure legends, please see Figure 15 in main thesis.

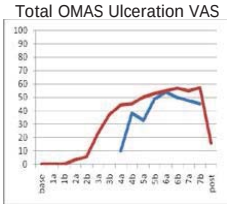
Smoker, Male, Age: 61, Caucasian		Cancer: Other T: 0 N: 2		Planned total Gray: 70 plus chemotherapy		2
Events over the treatment period:	Intake smoke & Alcohol 35 25	Cancer Tx breaks 0	Hospital stays 0	Eating support (days) 6	# Opoid intake 7	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

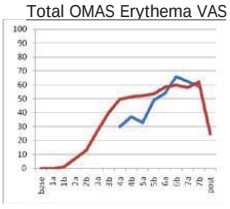
NCI



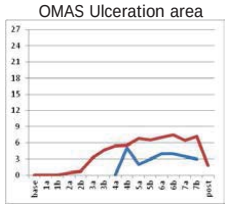
Total OMAS Ulceration VAS



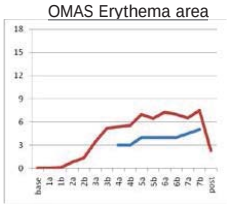
Total OMAS Erythema VAS



OMAS Ulceration area

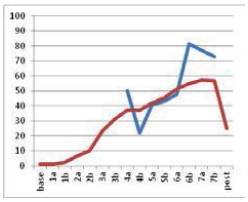


OMAS Erythema area

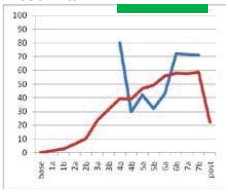


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

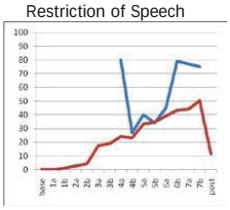


Mouth Pain

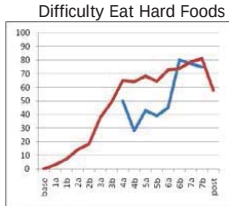


Difficulty Speaking

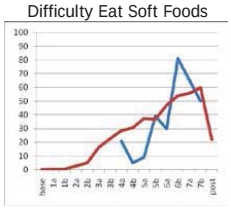
Restriction of Speech



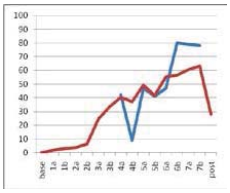
Difficulty Eat Hard Foods



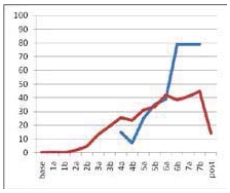
Difficulty Eat Soft Foods



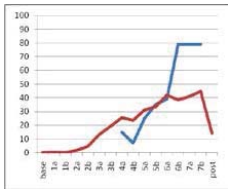
Restriction of eating



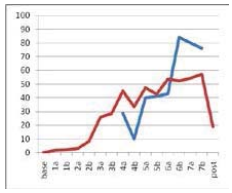
Difficulty Drinking



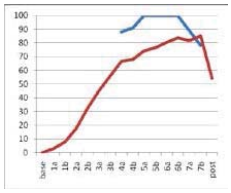
Restriction of Drinking



Difficulty Swallowing



Change in Taste



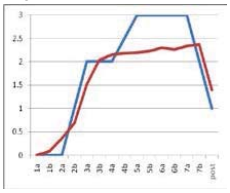
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.61	0.07	0.14	0.45	0.10
Difficulty Speaking	0.61	0.07	0.14	0.45	0.10
Restriction of Speech	0.61	0.07	0.14	0.45	0.10
Difficulty Eat Hard Foods	0.20	0.21	0.54	0.20	0.44
Difficulty Eat Soft Foods	0.20	0.61	0.82	0.04	0.68
Restriction of eating	0.21	0.38	0.67	0.06	0.68
Difficulty Drinking	0.41	0.68	0.88	0.11	0.85
Restriction of Drinking	0.41	0.71	0.89	0.15	0.80
Difficulty Swallowing	0.41	0.71	0.89	0.15	0.80
Change in Taste	0.45	0.51	0.16	0.21	0.07

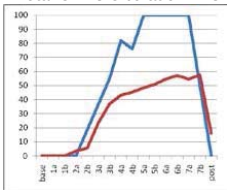
Smoker, Male, Age: 48, Caucasian		**Cancer: Other T: 4 N: 0**		**Planned total Gray: 70 plus chemotherapy**		**4**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	160 **2**	**0**	**0**	**6**	**13**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

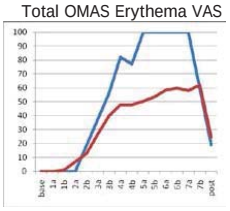
NCI



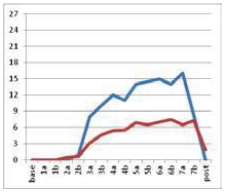
Total OMAS Ulceration VAS



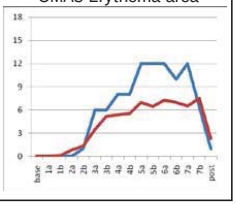
Total OMAS Erythema VAS



OMAS Ulceration area

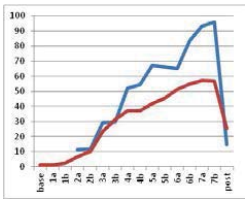


OMAS Erythema area

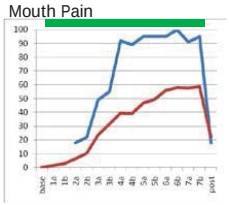


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

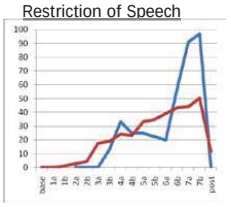


Mouth Pain

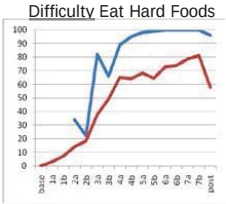


Difficulty Speaking

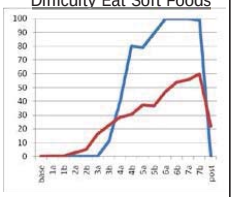
Restriction of Speech



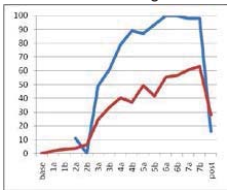
Difficulty Eat Hard Foods



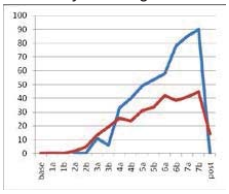
Difficulty Eat Soft Foods



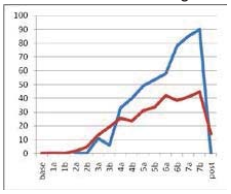
Restriction of eating



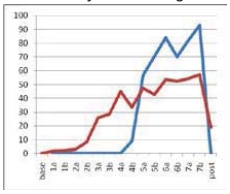
Difficulty Drinking



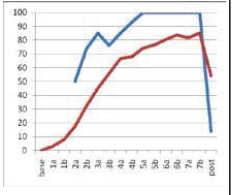
Restriction of Drinking



Difficulty Swallowing



Change in Taste



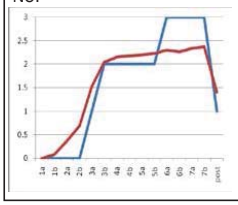
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.83	0.88	0.88	0.85	0.87
Difficulty Speaking	0.64	0.75	0.75	0.89	0.82
Restriction of Speech	0.71	0.79	0.79	0.88	0.80
Difficulty Eat Hard Foods	0.94	0.94	0.94	0.94	0.93
Difficulty Eat Soft Foods	0.91	0.84	0.84	0.92	0.88
Restriction of eating	0.92	0.83	0.83	0.89	0.87
Difficulty Drinking	0.91	0.91	0.91	0.95	0.93
Restriction of Drinking	0.88	0.82	0.82	0.87	0.86
Difficulty Swallowing	0.89	0.77	0.77	0.80	0.81
Change in Taste	0.98	0.97	0.97	0.93	0.96

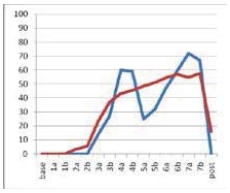
Ex-Smoker, Female, Age: 38, Asian		Cancer: Salivary T: 2 N: 0		Planned total Gray: 66		5
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	0	0	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

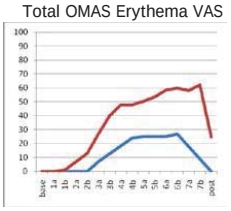
NCI



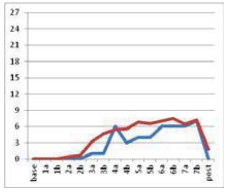
Total OMAS Ulceration VAS



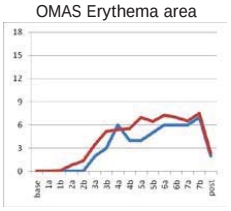
Total OMAS Erythema VAS



OMAS Ulceration area

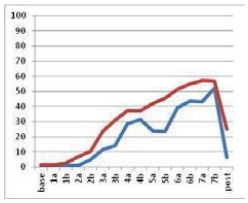


OMAS Erythema area

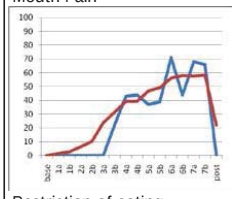


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

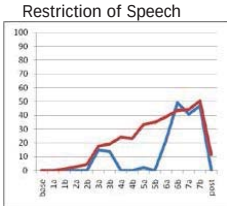


Mouth Pain

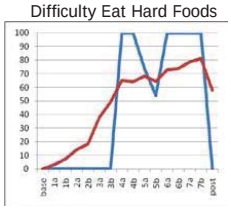


Difficulty Speaking

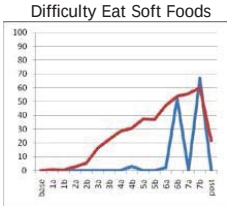
Restriction of Speech



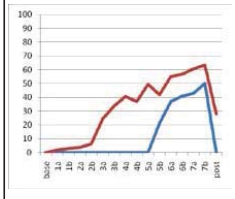
Difficulty Eat Hard Foods



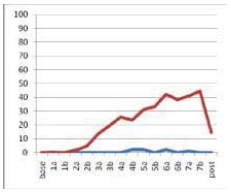
Difficulty Eat Soft Foods



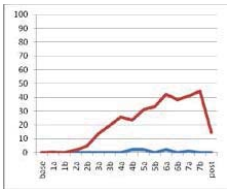
Restriction of eating



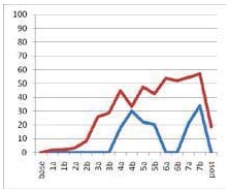
Difficulty Drinking



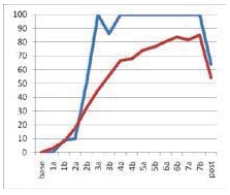
Restriction of Drinking



Difficulty Swallowing



Change in Taste



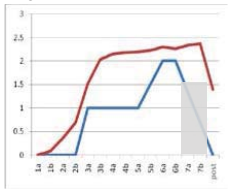
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.95	0.92	0.89	0.91	0.92
Difficulty Speaking	0.85	0.84	0.78	0.77	0.79
Restriction of Speech	0.73	0.55	0.51	0.63	0.57
Difficulty Eat Hard Foods	0.85	0.90	0.88	0.90	0.89
Difficulty Eat Soft Foods	0.56	0.51	0.47	0.51	0.52
Restriction of eating	0.78	0.67	0.67	0.74	0.76
Difficulty Drinking	0.53	0.40	0.35	0.40	0.33
Restriction of Drinking	0.38	0.32	0.32	0.33	0.25
Difficulty Swallowing	0.62	0.72	0.75	0.68	0.64
Change in Taste	0.80	0.80	0.80	0.85	0.80

Ex-Smoker, Female, Age: 65, Caucasian		Cancer: Salivary T: 1 N: 0		Planned total Gray: 70		6
Events over the treatment period:	Intake smoke & Alcohol **0** **0**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake **0**	

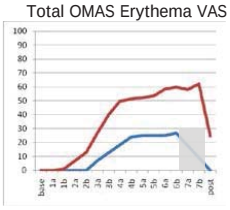
Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

NCI

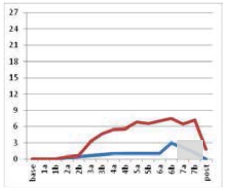


Total OMAS Ulceration VAS

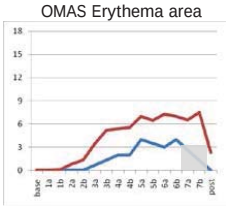
Total OMAS Erythema VAS



OMAS Ulceration area

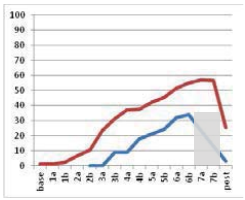


OMAS Erythema area

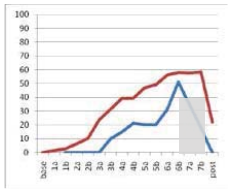


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

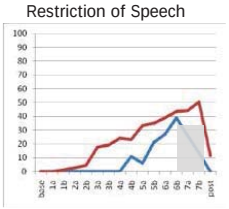


Mouth Pain

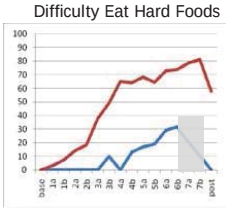


Difficulty Speaking

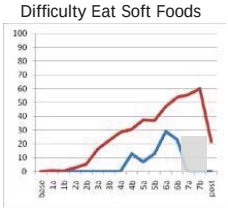
Restriction of Speech



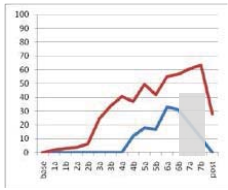
Difficulty Eat Hard Foods



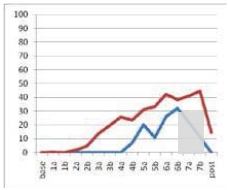
Difficulty Eat Soft Foods



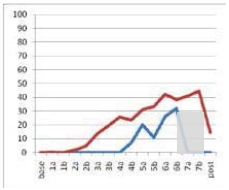
Restriction of eating



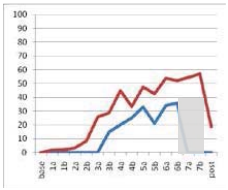
Difficulty Drinking



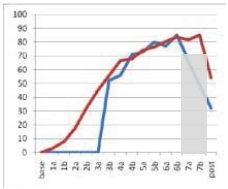
Restriction of Drinking



Difficulty Swallowing



Change in Taste



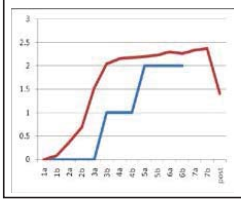
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.83	0.46	0.82	0.71	0.47
Difficulty Speaking	0.84	0.10	0.67	0.35	0.32
Restriction of Speech	0.84	0.46	0.82	0.71	0.47
Difficulty Eat Hard Foods	0.84	0.56	0.97	0.71	0.79
Difficulty Eat Soft Foods	0.84	0.10	0.67	0.35	0.32
Restriction of eating	0.84	0.21	0.82	0.35	0.63
Difficulty Drinking	0.84	0.56	0.97	0.71	0.79
Restriction of Drinking	0.63	0.10	0.67	0.00	0.63
Difficulty Swallowing	0.83	0.56	0.97	0.71	0.79
Change in Taste	0.83	0.56	0.97	0.71	0.79

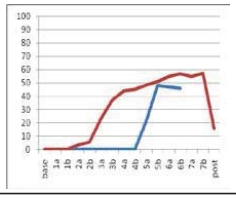
Smoker, Male, Age: 63, Caucasian		Cancer: Oropharynx T: 3 N: 2		Planned total Gray: 70		Pt. D
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	32 0	0	0	5	3	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

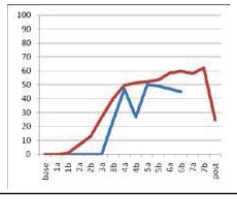
NCI



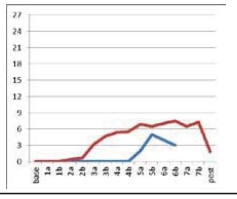
Total OMAS Ulceration VAS



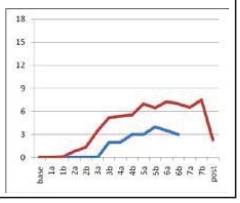
Total OMAS Erythema VAS



OMAS Ulceration area

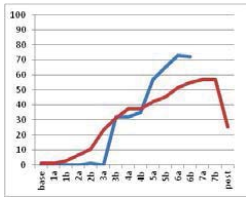


OMAS Erythema area



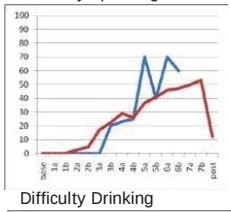
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS



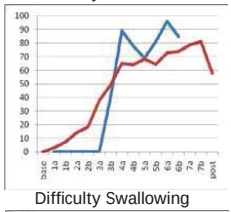
Mouth Pain

Difficulty Speaking

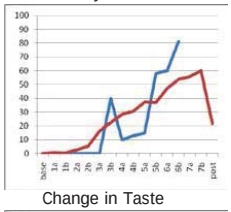


Restriction of Speech

Difficulty Eat Hard Foods

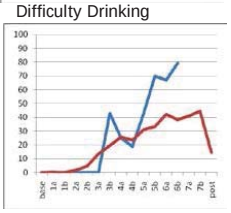


Difficulty Eat Soft Foods

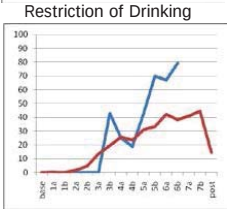


Restriction of eating

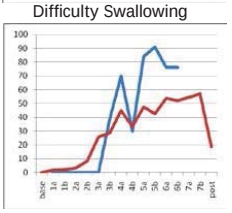
Difficulty Drinking



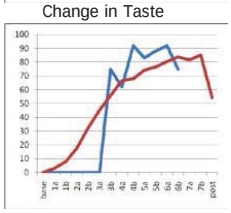
Restriction of Drinking



Difficulty Swallowing



Change in Taste



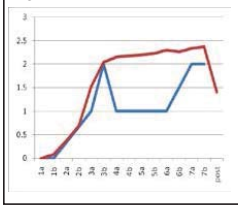
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.97	0.82	0.83	0.85	0.86
Difficulty Speaking	0.97	0.78	0.94	0.77	0.87
Restriction of Speech	0.98	0.80	0.98	0.76	0.81
Difficulty Eat Hard Foods	0.81	0.53	0.83	0.44	0.62
Difficulty Eat Soft Foods	0.93	0.76	0.77	0.77	0.80
Restriction of eating	0.97	0.79	0.86	0.80	0.87
Difficulty Drinking	0.96	0.79	0.83	0.81	0.77
Restriction of Drinking	0.93	0.76	0.77	0.77	0.80
Difficulty Swallowing	0.97	0.82	0.96	0.85	0.85
Change in Taste	0.84	0.56	0.80	0.47	0.89

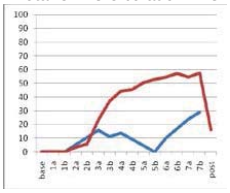
Ex-Smoker, Male, Age: 46, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**8**
Events over the treatment period:	Intake smoke & Alcohol **0** **0**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake 2	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

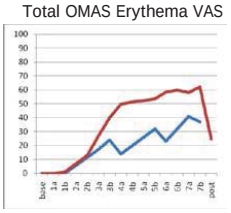
NCI



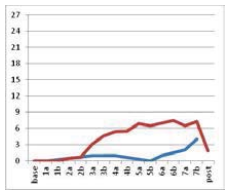
Total OMAS Ulceration VAS



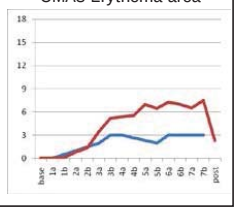
Total OMAS Erythema VAS



OMAS Ulceration area

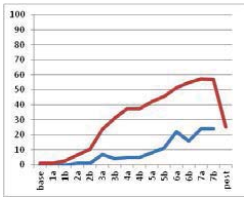


OMAS Erythema area

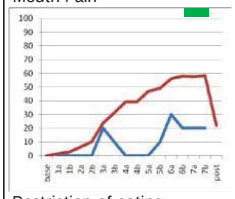


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

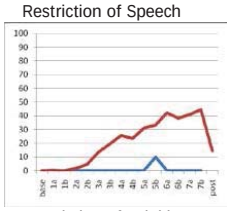


Mouth Pain

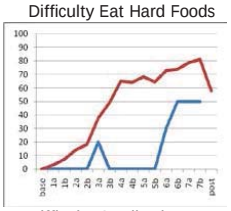


Difficulty Speaking

Restriction of Speech

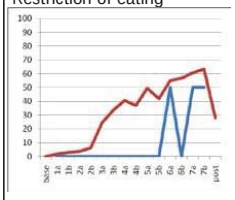


Difficulty Eat Hard Foods

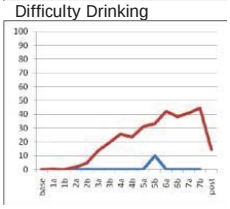


Difficulty Eat Soft Foods

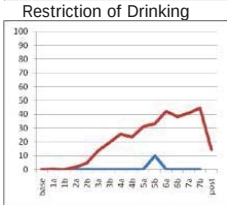
Restriction of eating



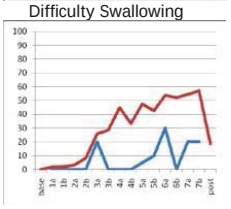
Difficulty Drinking



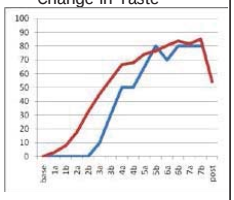
Restriction of Drinking



Difficulty Swallowing



Change in Taste

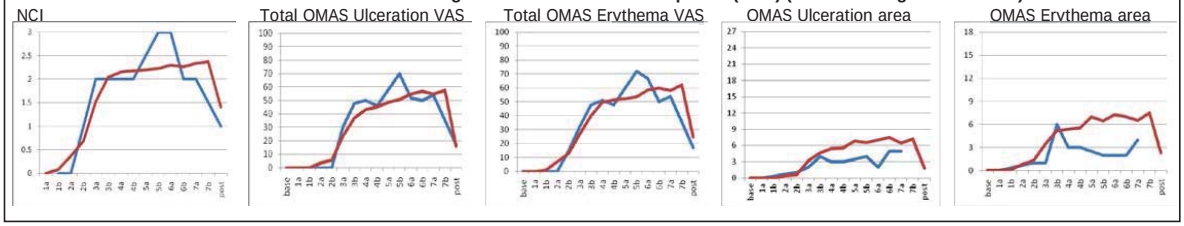


Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.39	0.42	0.52	0.40	0.08
Difficulty Speaking	.	.	.	.	.
Restriction of Speech	.	.	.	.	.
Difficulty Eat Hard Foods	0.53	0.73	0.63	0.83	0.33
Difficulty Eat Soft Foods	0.69	0.76	0.76	0.87	0.40
Restriction of eating	0.49	0.51	0.62	0.72	0.55
Difficulty Drinking	0.18	0.50	0.25	0.68	0.65
Restriction of Drinking	.	.	.	.	.
Difficulty Swallowing	0.22	0.38	0.45	0.35	0.00
Change in Taste	0.56	0.34	0.85	0.29	0.16

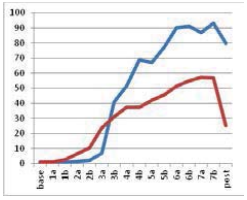
Ex-Smoker, Female, Age: 62, Caucasian		Cancer: Other T: 0 N: 0		Planned total Gray: 70 plus chemotherapy		9
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 22	0	1	9	10	

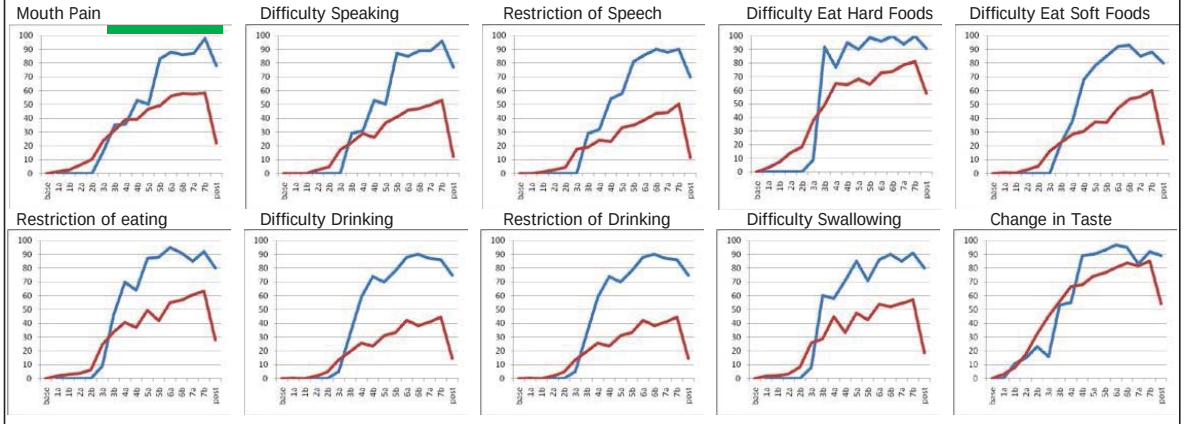
Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)



Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS





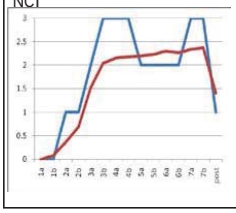
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.82	0.90	0.89	0.51	0.29
Difficulty Speaking	0.69	0.88	0.84	0.77	0.33
Restriction of Speech	0.69	0.85	0.82	0.70	0.29
Difficulty Eat Hard Foods	0.82	0.83	0.82	0.61	0.17
Difficulty Eat Soft Foods	0.75	0.85	0.84	0.59	0.19
Restriction of eating	0.87	0.90	0.92	0.47	0.15
Difficulty Drinking	0.78	0.86	0.85	0.61	0.22
Restriction of Drinking	0.78	0.85	0.83	0.64	0.31
Difficulty Swallowing	0.77	0.82	0.80	0.63	0.29
Change in Taste	0.84	0.81	0.86	0.38	0.13

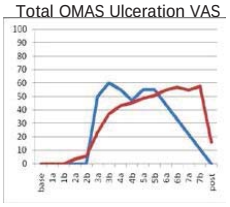
Ex-Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 2 N: 0**		**Planned total Gray: 66 plus chemotherapy**		**11**
Events over the treatment period:	Intake smoke & Alcohol **0** **21**	Cancer Tx breaks **1**	Hospital stays **9**	Eating support (days) **12**	# Opoid intake **10**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

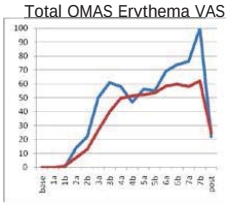
NCI



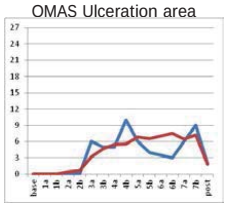
Total OMAS Ulceration VAS



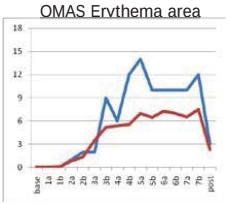
Total OMAS Erythema VAS



OMAS Ulceration area

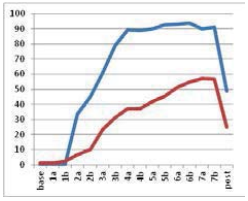


OMAS Erythema area

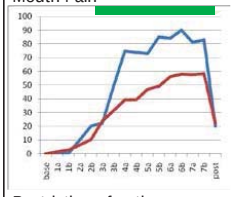


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

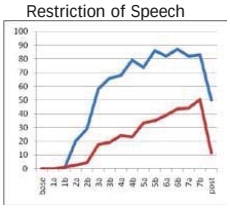


Mouth Pain



Difficulty Speaking

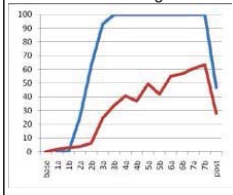
Restriction of Speech



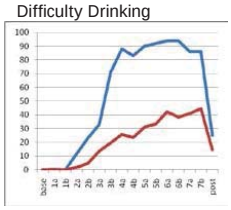
Difficulty Eat Hard Foods

Difficulty Eat Soft Foods

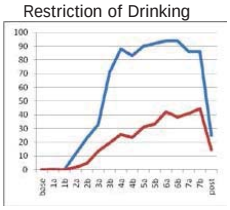
Restriction of eating



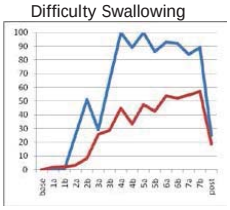
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

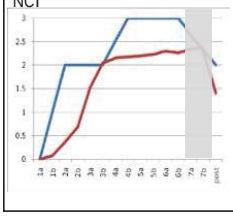
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.58	0.77	0.81	0.35	0.73
Difficulty Speaking	0.56	0.73	0.76	0.38	0.78
Restriction of Speech	0.60	0.73	0.81	0.45	0.81
Difficulty Eat Hard Foods	0.64	0.55	0.61	0.47	0.62
Difficulty Eat Soft Foods	0.84	0.87	0.83	0.62	0.86
Restriction of eating	0.84	0.87	0.83	0.62	0.87
Difficulty Drinking	0.36	0.76	0.68	0.15	0.69
Restriction of Drinking	0.42	0.76	0.77	0.27	0.79
Difficulty Swallowing	0.50	0.66	0.58	0.33	0.74
Change in Taste	0.67	0.64	0.63	0.52	0.64

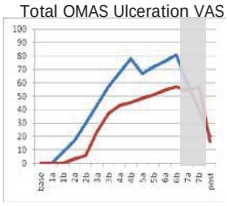
Never smoked, Male, Age: 65, Asian		Cancer: Oral Cavity T: 1 N: 0		Planned total Gray: 60		12
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	1	0	0	5	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

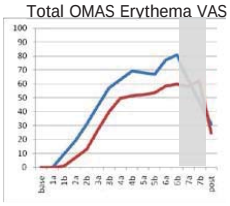
NCI



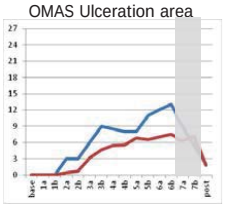
Total OMAS Ulceration VAS



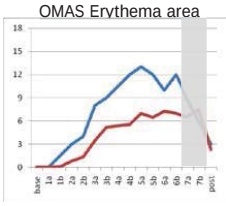
Total OMAS Erythema VAS



OMAS Ulceration area

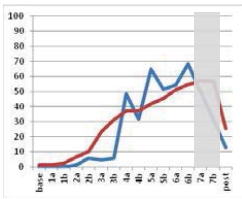


OMAS Erythema area

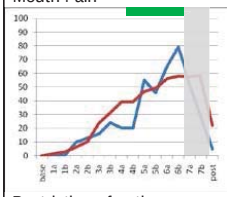


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

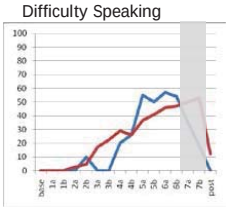
Aggregated (average) PROMS



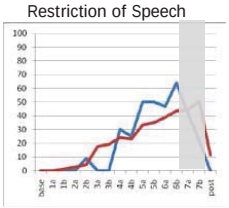
Mouth Pain



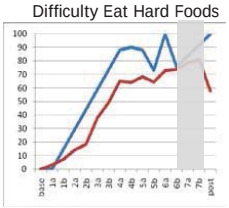
Difficulty Speaking



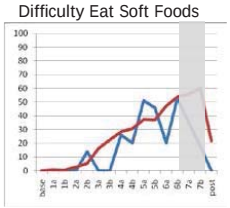
Restriction of Speech



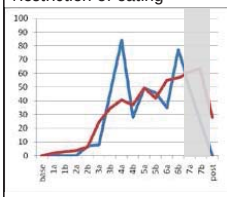
Difficulty Eat Hard Foods



Difficulty Eat Soft Foods



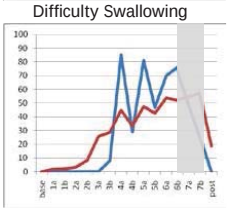
Restriction of eating



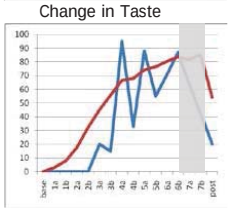
Difficulty Drinking

Restriction of Drinking

Difficulty Swallowing



Change in Taste



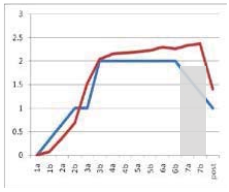
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.84	0.87	0.93	0.95	0.83
Difficulty Speaking	0.88	0.74	0.82	0.69	0.77
Restriction of Speech	0.88	0.79	0.80	0.72	0.83
Difficulty Eat Hard Foods	0.65	0.49	0.66	0.35	0.21
Difficulty Eat Soft Foods	0.88	0.79	0.80	0.68	0.86
Restriction of eating	0.88	0.80	0.83	0.72	0.86
Difficulty Drinking	0.90	0.80	0.80	0.78	0.85
Restriction of Drinking	0.88	0.79	0.83	0.79	0.93
Difficulty Swallowing	0.88	0.81	0.87	0.80	0.91
Change in Taste	0.88	0.82	0.88	0.78	0.91

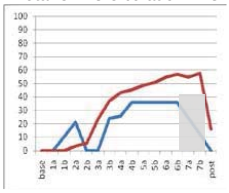
Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 2 N: 2**		**Planned total Gray: 70**		**15**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	18 **160**	**0**	**0**	**1**	**0**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

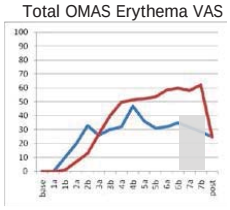
NCI



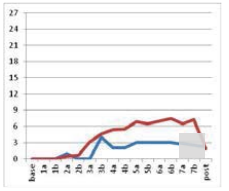
Total OMAS Ulceration VAS



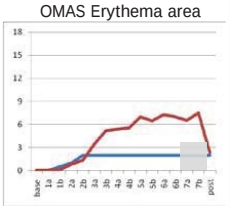
Total OMAS Erythema VAS



OMAS Ulceration area

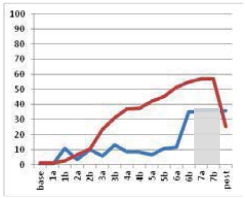


OMAS Erythema area

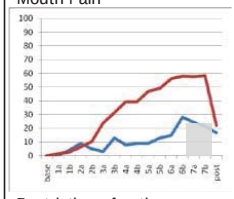


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in in red)

Aggregated (average) PROMS



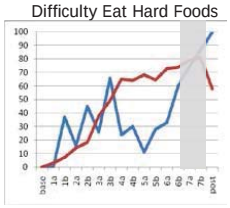
Mouth Pain



Difficulty Speaking

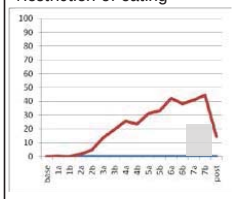
Restriction of Speech

Difficulty Eat Hard Foods



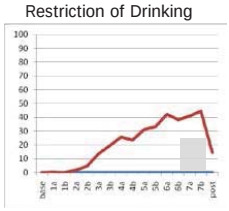
Difficulty Eat Soft Foods

Restriction of eating

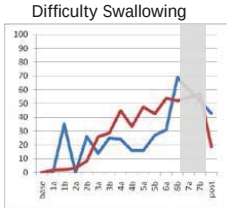


Difficulty Drinking

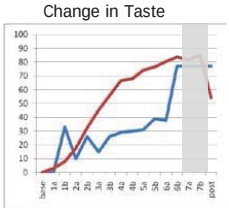
Restriction of Drinking



Difficulty Swallowing



Change in Taste



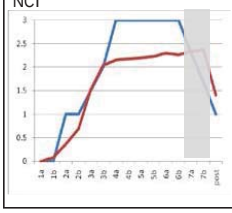
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.73	0.71	0.15	0.82	0.06
Difficulty Speaking	0.19	0.19	0.29	0.54	0.11
Restriction of Speech	.	.	.	.	.
Difficulty Eat Hard Foods	0.00	0.01	0.12	0.34	0.41
Difficulty Eat Soft Foods	0.19	0.31	0.29	0.24	0.11
Restriction of eating	0.19	0.31	0.29	0.24	0.11
Difficulty Drinking	.	.	.	.	.
Restriction of Drinking	.	.	.	.	.
Difficulty Swallowing	0.31	0.46	0.30	0.52	0.52
Change in Taste	0.68	0.88	0.59	0.61	0.52

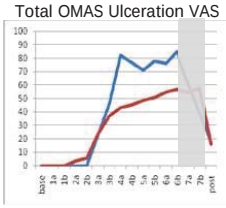
Smoking unknown, Male, Age: 60, Caucasian	**Cancer: Other T: 0 N: 2**			**Planned total Gray: 70**		**16**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0	**0**	**0**	**7**	**3**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

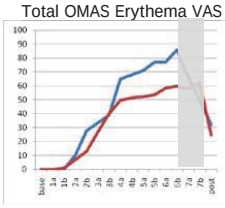
NCI



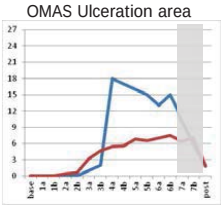
Total OMAS Ulceration VAS



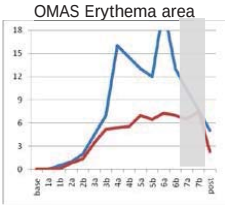
Total OMAS Erythema VAS



OMAS Ulceration area

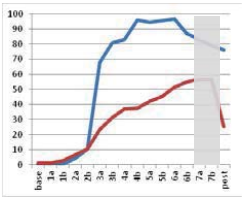


OMAS Erythema area

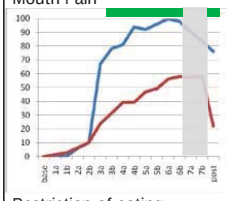


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

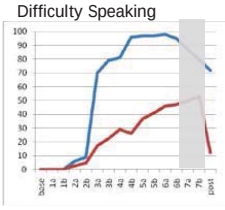
Aggregated (average) PROMS



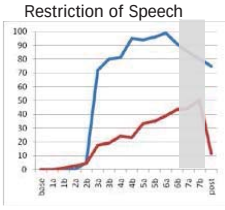
Mouth Pain



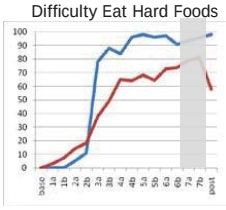
Difficulty Speaking



Restriction of Speech

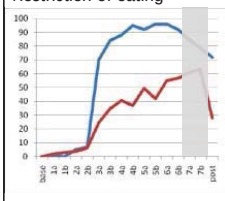


Difficulty Eat Hard Foods

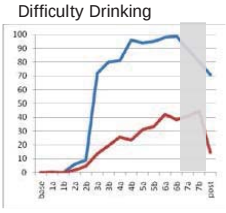


Difficulty Eat Soft Foods

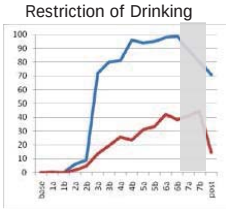
Restriction of eating



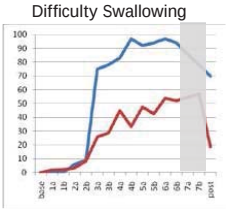
Difficulty Drinking



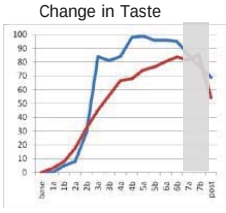
Restriction of Drinking



Difficulty Swallowing



Change in Taste



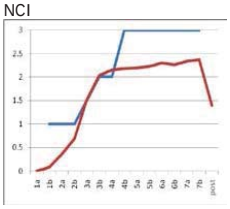
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.93	0.85	0.98	0.66	0.87
Difficulty Speaking	0.94	0.76	0.92	0.70	0.86
Restriction of Speech	0.92	0.78	0.91	0.68	0.84
Difficulty Eat Hard Foods	0.89	0.68	0.87	0.67	0.76
Difficulty Eat Soft Foods	0.92	0.82	0.91	0.79	0.69
Restriction of eating	0.94	0.81	0.95	0.69	0.82
Difficulty Drinking	0.93	0.88	1.00	0.68	0.83
Restriction of Drinking	0.92	0.91	0.99	0.71	0.76
Difficulty Swallowing	0.94	0.84	0.97	0.66	0.86
Change in Taste	0.93	0.74	0.89	0.77	0.80

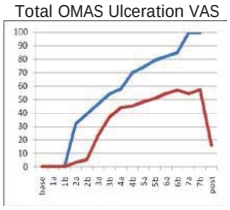
Never smoked, Female, Age: 80, Asian		**Cancer: Oral Cavity T: 2 N: 0**		**Planned total Gray: 70**		**19**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**11**	3	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

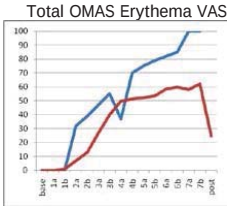
NCI



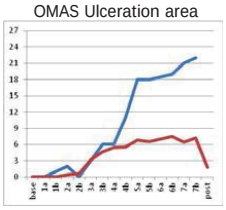
Total OMAS Ulceration VAS



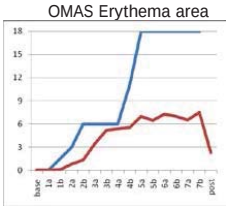
Total OMAS Erythema VAS



OMAS Ulceration area

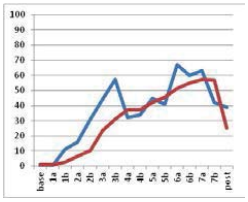


OMAS Erythema area



Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

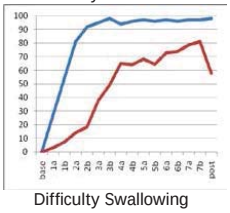


Mouth Pain

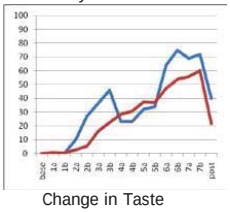
Difficulty Speaking

Restriction of Speech

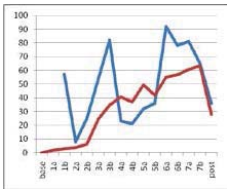
Difficulty Eat Hard Foods



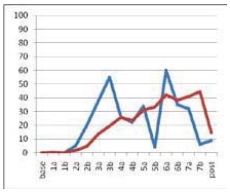
Difficulty Eat Soft Foods



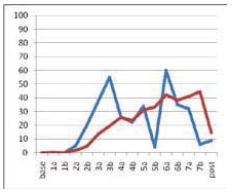
Restriction of eating



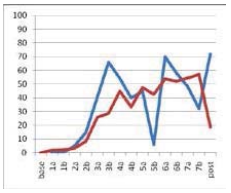
Difficulty Drinking



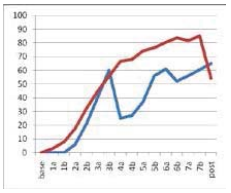
Restriction of Drinking



Difficulty Swallowing



Change in Taste



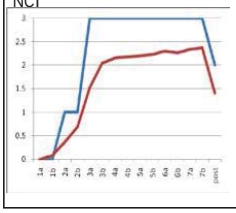
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.69	0.82	0.87	0.72	0.75
Difficulty Speaking	0.72	0.92	0.92	0.78	0.85
Restriction of Speech	0.72	0.92	0.92	0.79	0.87
Difficulty Eat Hard Foods	0.56	0.64	0.72	0.61	0.54
Difficulty Eat Soft Foods	0.58	0.88	0.89	0.77	0.73
Restriction of eating	0.11	0.48	0.53	0.55	0.52
Difficulty Drinking	0.22	0.32	0.35	0.12	0.11
Restriction of Drinking	0.14	0.29	0.30	0.02	0.01
Difficulty Swallowing	0.19	0.30	0.39	0.21	0.14
Change in Taste	0.37	0.35	0.42	0.19	0.31

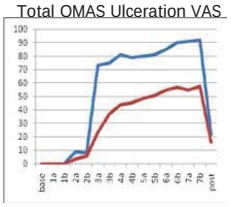
Smoker, Male, Age: 61, Caucasian		**Cancer: Oral Cavity T: 3 N: 2**		**Planned total Gray: 66**		**21**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	127 **184**	**0**	**0**	**0**	**14**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

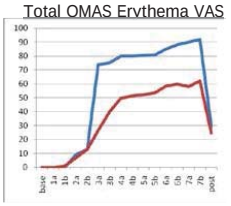
NCI



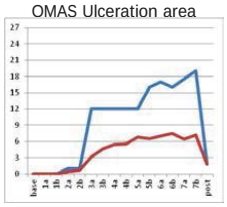
Total OMAS Ulceration VAS



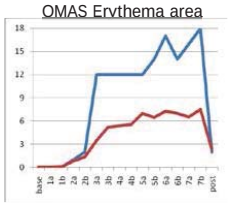
Total OMAS Erythema VAS



OMAS Ulceration area

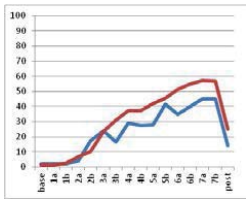


OMAS Erythema area

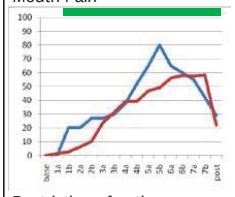


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

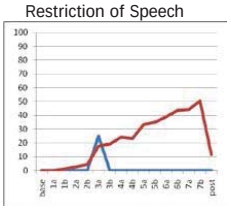


Mouth Pain

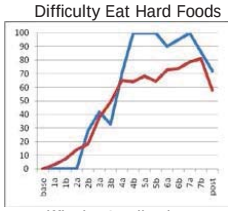


Difficulty Speaking

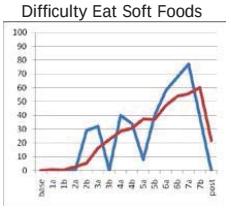
Restriction of Speech



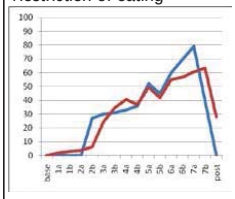
Difficulty Eat Hard Foods



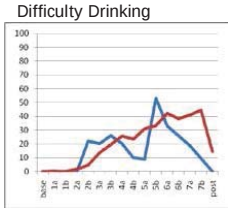
Difficulty Eat Soft Foods



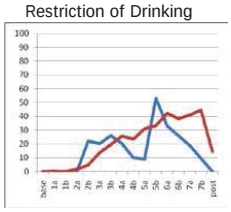
Restriction of eating



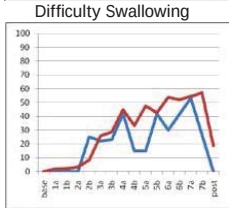
Difficulty Drinking



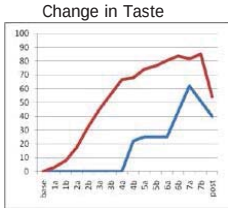
Restriction of Drinking



Difficulty Swallowing



Change in Taste



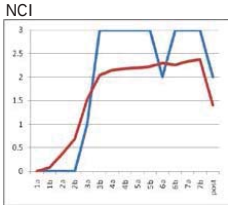
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.77	0.90	0.97	0.87	0.88
Difficulty Speaking	0.32	0.19	0.08	0.09	0.09
Restriction of Speech	0.22	0.14	0.14	0.06	0.06
Difficulty Eat Hard Foods	0.81	0.84	0.91	0.78	0.79
Difficulty Eat Soft Foods	0.59	0.86	0.88	0.77	0.79
Restriction of eating	0.80	0.94	0.99	0.89	0.89
Difficulty Drinking	0.53	0.63	0.73	0.73	0.77
Restriction of Drinking	0.50	0.32	0.42	0.50	0.54
Difficulty Swallowing	0.53	0.72	0.75	0.66	0.70
Change in Taste	0.51	0.72	0.81	0.72	0.72

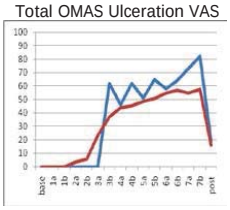
Ex-Smoker, Male, Age: 69, Caucasian		Cancer: Oropharynx T: 3 N: 0		Planned total Gray: 70		22
Events over the treatment period:	Intake smoke & Alcohol: 0	Cancer Tx breaks: 0	Hospital stays: 0	Eating support (days): 0	# Opoid intake: 11	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

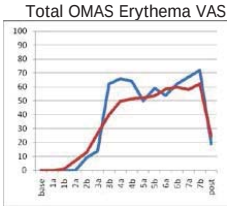
NCI



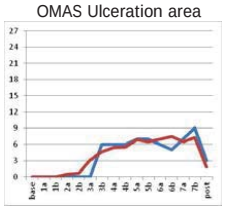
Total OMAS Ulceration VAS



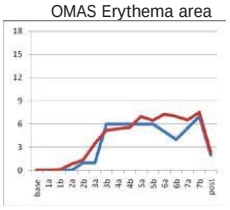
Total OMAS Erythema VAS



OMAS Ulceration area

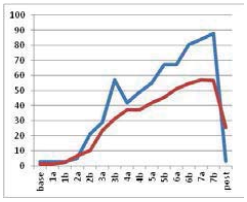


OMAS Erythema area

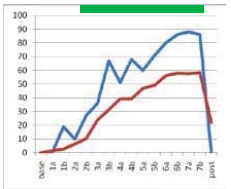


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

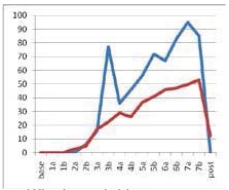
Aggregated (average) PROMS



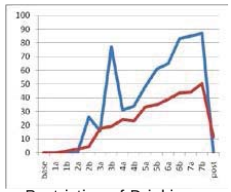
Mouth Pain



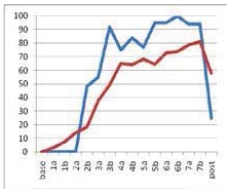
Difficulty Speaking



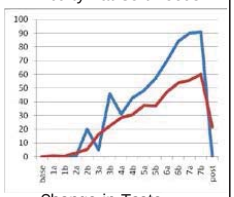
Restriction of Speech



Difficulty Eat Hard Foods

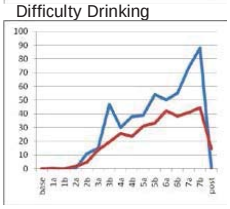


Difficulty Eat Soft Foods

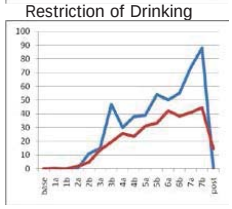


Restriction of eating

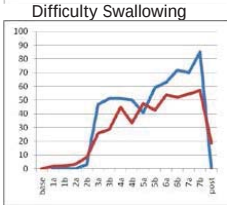
Difficulty Drinking



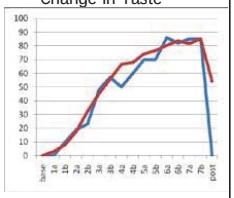
Restriction of Drinking



Difficulty Swallowing



Change in Taste



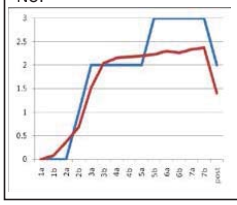
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.65	0.91	0.67	0.62	0.57
Difficulty Speaking	0.73	0.92	0.67	0.68	0.66
Restriction of Speech	0.68	0.88	0.65	0.65	0.64
Difficulty Eat Hard Foods	0.63	0.86	0.54	0.55	0.47
Difficulty Eat Soft Foods	0.63	0.87	0.58	0.71	0.61
Restriction of eating	0.55	0.78	0.50	0.57	0.47
Difficulty Drinking	0.69	0.93	0.63	0.71	0.64
Restriction of Drinking	0.56	0.75	0.67	0.56	0.53
Difficulty Swallowing	0.60	0.83	0.74	0.56	0.56
Change in Taste	0.57	0.77	0.52	0.69	0.56

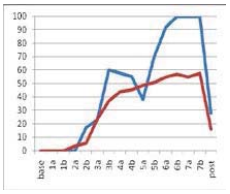
Never smoked, Male, Age: 69, Caucasian		Cancer: Oral cavity T: 4 N: 0		Planned total Gray: 66		**Pt. B**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	0 **29**	**0**	**0**	**0**	**9**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

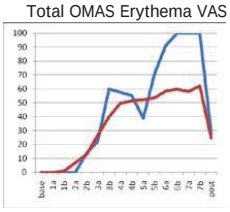
NCI



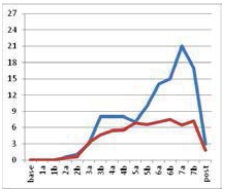
Total OMAS Ulceration VAS



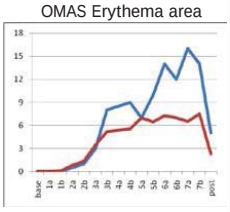
Total OMAS Erythema VAS



OMAS Ulceration area

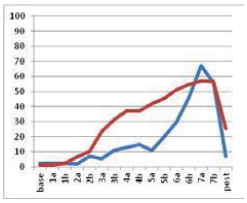


OMAS Erythema area

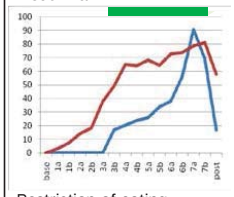


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

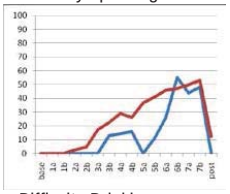
Aggregated (average) PROMS



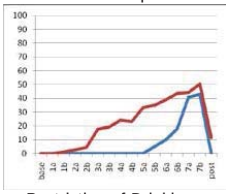
Mouth Pain



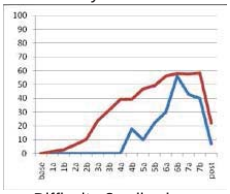
Difficulty Speaking



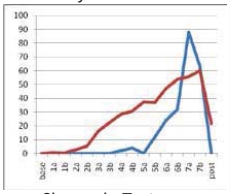
Restriction of Speech



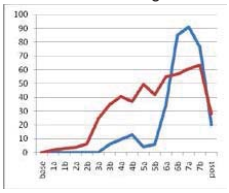
Difficulty Eat Hard Foods



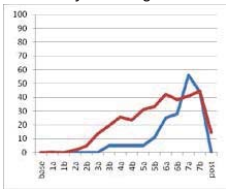
Difficulty Eat Soft Foods



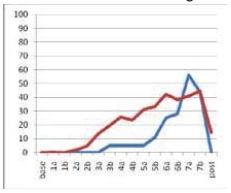
Restriction of eating



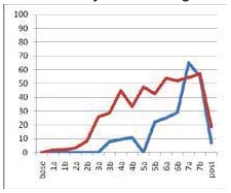
Difficulty Drinking



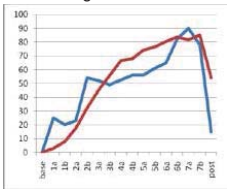
Restriction of Drinking



Difficulty Swallowing



Change in Taste



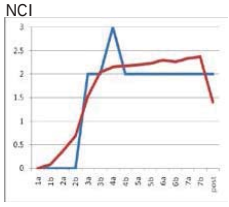
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.89	0.90	0.90	0.91	0.90
Difficulty Speaking	0.83	0.93	0.93	0.91	0.88
Restriction of Speech	0.86	0.87	0.87	0.91	0.88
Difficulty Eat Hard Foods	0.91	0.95	0.95	0.96	0.95
Difficulty Eat Soft Foods	0.87	0.89	0.89	0.94	0.94
Restriction of eating	0.88	0.95	0.95	0.96	0.94
Difficulty Drinking	0.92	0.97	0.97	0.98	0.97
Restriction of Drinking	0.86	0.86	0.86	0.91	0.91
Difficulty Swallowing	0.89	0.94	0.94	0.97	0.96
Change in Taste	0.92	0.93	0.93	0.91	0.90

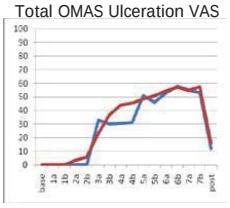
Ex-Smoker, Female, Age: 63, Caucasian		Cancer: Salivary T: 3 N: 0		Planned total Gray: 66		24
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	1	0	0	12	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

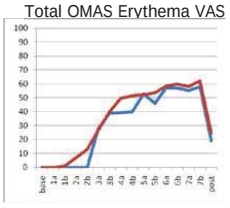
NCI



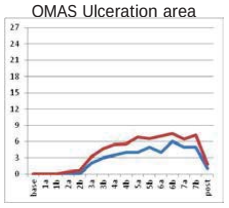
Total OMAS Ulceration VAS



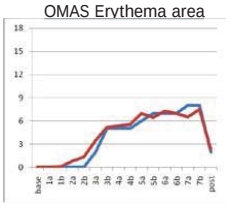
Total OMAS Erythema VAS



OMAS Ulceration area

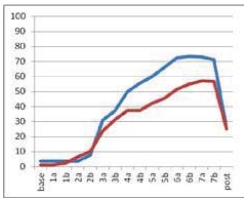


OMAS Erythema area



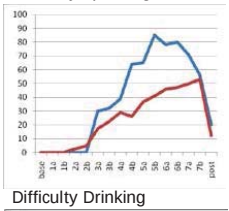
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS



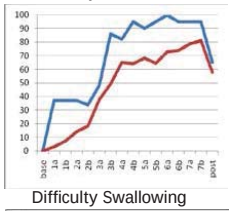
Mouth Pain

Difficulty Speaking

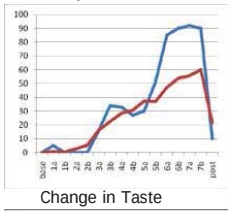


Restriction of Speech

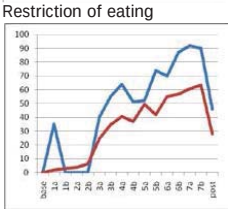
Difficulty Eat Hard Foods



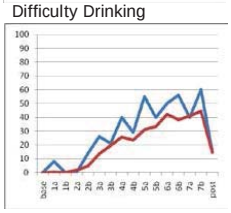
Difficulty Eat Soft Foods



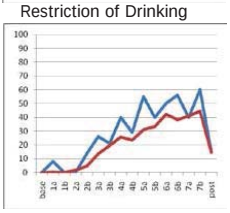
Restriction of eating



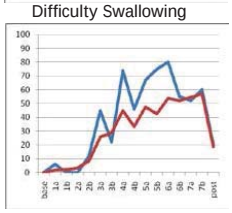
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

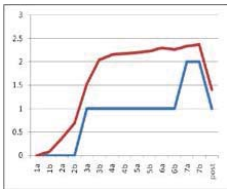
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.64	0.70	0.70	0.79	0.75
Difficulty Speaking	0.67	0.85	0.82	0.88	0.81
Restriction of Speech	0.67	0.87	0.79	0.89	0.83
Difficulty Eat Hard Foods	0.65	0.85	0.90	0.84	0.87
Difficulty Eat Soft Foods	0.69	0.93	0.93	0.91	0.97
Restriction of eating	0.72	0.91	0.91	0.92	0.97
Difficulty Drinking	0.72	0.91	0.96	0.87	0.87
Restriction of Drinking	0.69	0.89	0.95	0.84	0.86
Difficulty Swallowing	0.79	0.82	0.87	0.76	0.80
Change in Taste	0.70	0.96	0.96	0.91	0.95

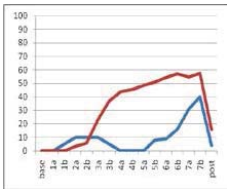
Smoker, Female, Age: 69, Caucasian		**Cancer: Oropharynx T: 0 N: 0**		**Planned total Gray: 66**		**Pt. A**
Events over the treatment period:	Intake smoke & Alcohol **60** **72**	Cancer Tx breaks **1**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake **0**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

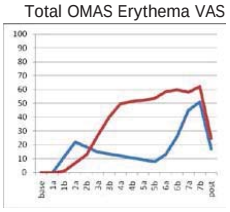
NCI



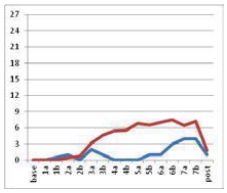
Total OMAS Ulceration VAS



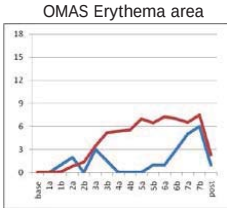
Total OMAS Erythema VAS



OMAS Ulceration area

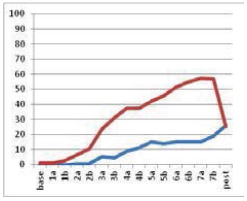


OMAS Erythema area

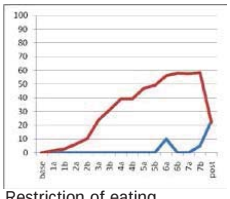


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

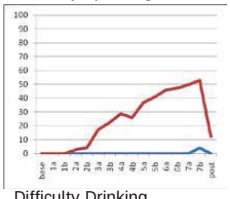
Aggregated (average) PROMS



Mouth Pain

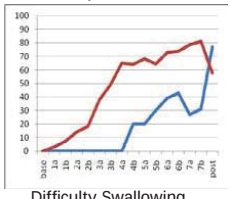


Difficulty Speaking

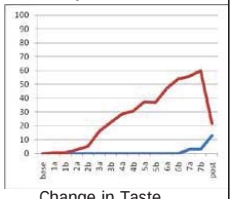


Restriction of Speech

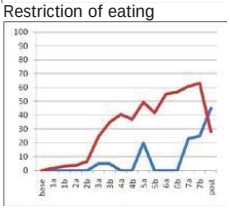
Difficulty Eat Hard Foods



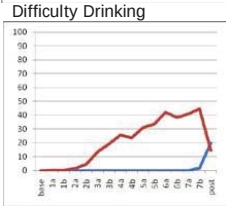
Difficulty Eat Soft Foods



Restriction of eating

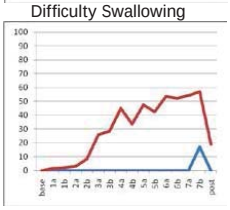


Difficulty Drinking

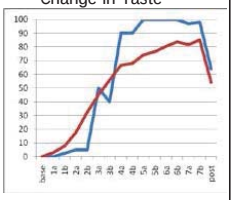


Restriction of Drinking

Difficulty Swallowing



Change in Taste



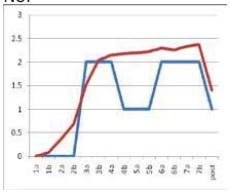
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	**Total OMAS Ulceration**	**Total OMAS Erythema**	**OMAS Ulcer Area**	**OMAS Erythema**
Mouth Pain	0.43	0.35	0.35	0.35	0.34
Difficulty Speaking	0.47	0.51	0.51	0.46	0.50
Restriction of Speech	0.47	0.51	0.51	0.46	0.50
Difficulty Eat Hard Foods	0.55	0.47	0.47	0.56	0.48
Difficulty Eat Soft Foods	0.70	0.69	0.69	0.68	0.67
Restriction of eating	0.52	0.51	0.49	0.54	0.56
Difficulty Drinking	0.47	0.51	0.51	0.46	0.50
Restriction of Drinking	0.47	0.51	0.51	0.46	0.50
Difficulty Swallowing	0.47	0.51	0.51	0.46	0.50
Change in Taste	0.34	0.17	0.16	0.34	0.26

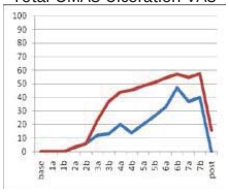
Never smoked, Male, Age: 42, Caucasian		**Cancer: Salivary T: 4 N: 0**		**Planned total Gray: 66**		**26**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**4**	**0**	**0**	**5**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

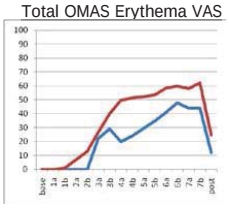
NCI



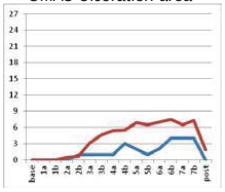
Total OMAS Ulceration VAS



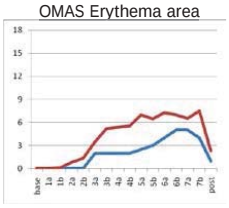
Total OMAS Erythema VAS



OMAS Ulceration area

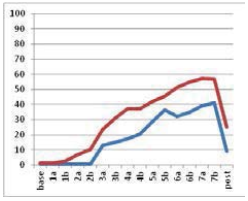


OMAS Erythema area

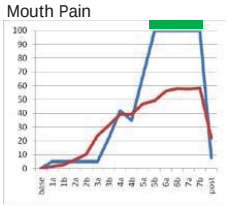


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

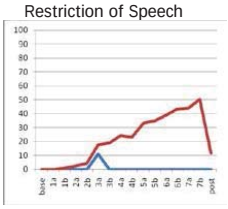


Mouth Pain

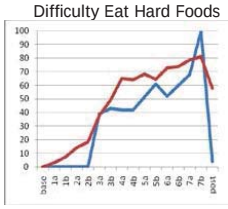


Difficulty Speaking

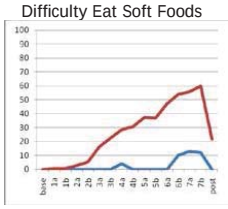
Restriction of Speech



Difficulty Eat Hard Foods

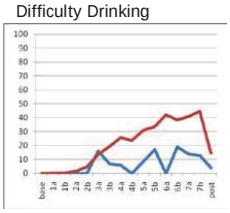


Difficulty Eat Soft Foods

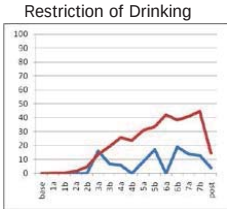


Restriction of eating

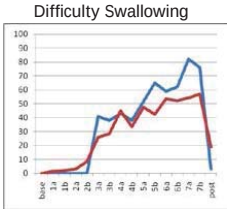
Difficulty Drinking



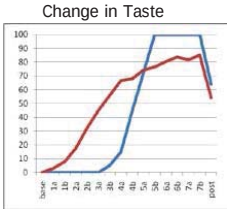
Restriction of Drinking



Difficulty Swallowing



Change in Taste



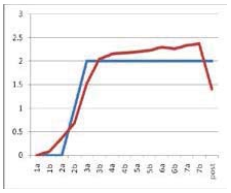
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.59	0.95	0.89	0.77	0.92
Difficulty Speaking	0.39	0.66	0.55	0.57	0.59
Restriction of Speech	0.25	0.22	0.13	0.14	0.09
Difficulty Eat Hard Foods	0.66	0.92	0.93	0.79	0.91
Difficulty Eat Soft Foods	0.56	0.73	0.63	0.71	0.69
Restriction of eating	0.06	0.13	0.01	0.05	0.13
Difficulty Drinking	0.56	0.60	0.65	0.43	0.66
Restriction of Drinking	0.25	0.13	0.04	0.14	0.09
Difficulty Swallowing	0.70	0.91	0.88	0.76	0.93
Change in Taste	0.55	0.94	0.91	0.80	0.92

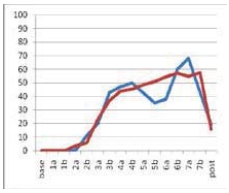
Never smoked, Male, Age: 45, Caucasian		**Cancer: Oropharynx T: 2 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**27**
Events over the treatment period:	Intake smoke & Alcohol **0** **2**	Cancer Tx breaks **0**	Hospital stays **1**	Eating support (days) **0**	# Opoid intake **0**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

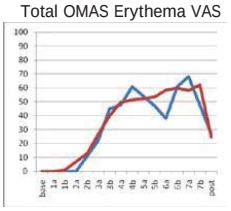
NCI



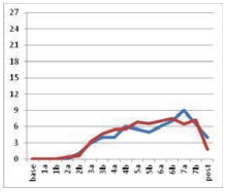
Total OMAS Ulceration VAS



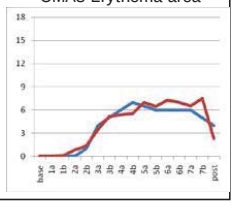
Total OMAS Erythema VAS



OMAS Ulceration area

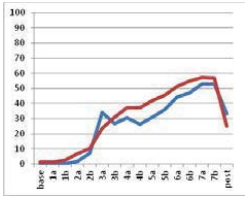


OMAS Erythema area

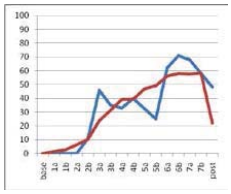


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

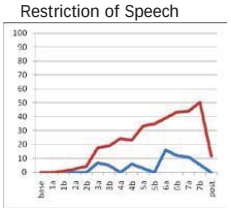


Mouth Pain

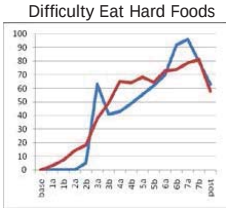


Difficulty Speaking

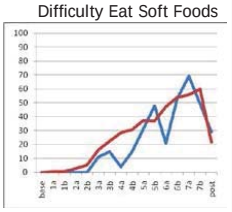
Restriction of Speech



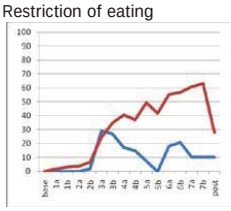
Difficulty Eat Hard Foods



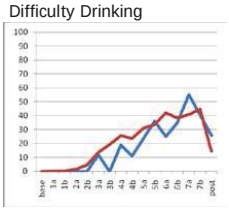
Difficulty Eat Soft Foods



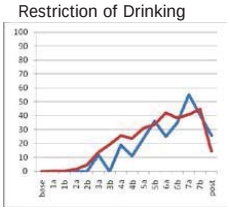
Restriction of eating



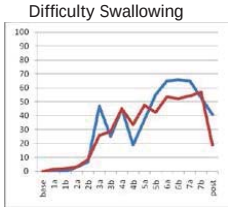
Difficulty Drinking



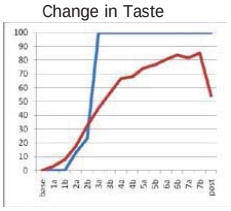
Restriction of Drinking



Difficulty Swallowing



Change in Taste



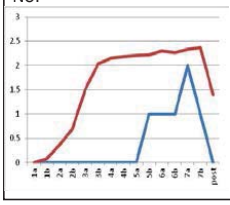
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.84	0.85	0.79	0.89	0.74
Difficulty Speaking	0.82	0.70	0.67	0.83	0.68
Restriction of Speech	0.65	0.65	0.55	0.76	0.55
Difficulty Eat Hard Foods	0.84	0.80	0.80	0.91	0.76
Difficulty Eat Soft Foods	0.82	0.83	0.85	0.94	0.79
Restriction of eating	0.73	0.56	0.44	0.47	0.43
Difficulty Drinking	0.73	0.71	0.77	0.84	0.74
Restriction of Drinking	0.40	0.67	0.64	0.51	0.43
Difficulty Swallowing	0.83	0.76	0.75	0.87	0.72
Change in Taste	0.99	0.83	0.83	0.83	0.86

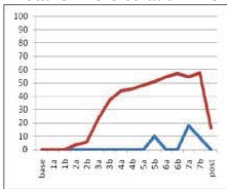
Ex-Smoker, Male, Age: 49, Black		Cancer: Other T: 2 N: 1		Planned total Gray: 70 plus chemotherapy		29
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	3	0	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

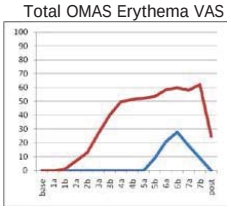
NCI



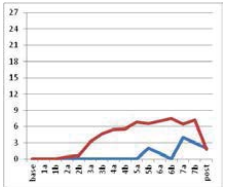
Total OMAS Ulceration VAS



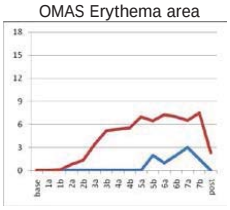
Total OMAS Erythema VAS



OMAS Ulceration area

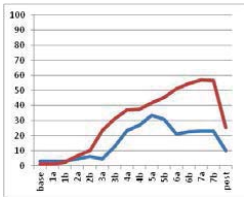


OMAS Erythema area

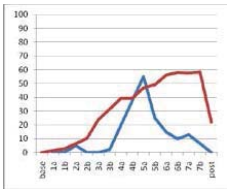


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

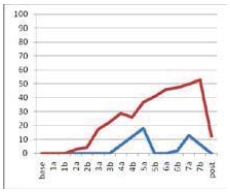
Aggregated (average) PROMS



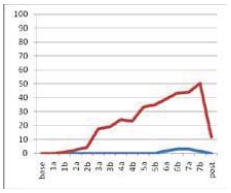
Mouth Pain



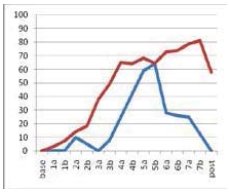
Difficulty Speaking



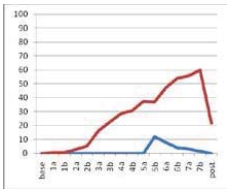
Restriction of Speech



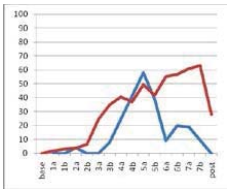
Difficulty Eat Hard Foods



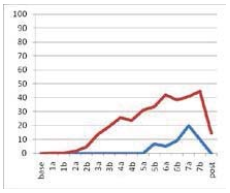
Difficulty Eat Soft Foods



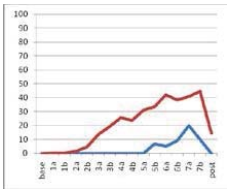
Restriction of eating



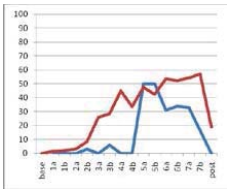
Difficulty Drinking



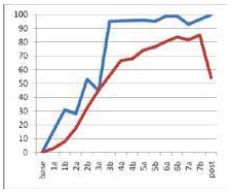
Restriction of Drinking



Difficulty Swallowing



Change in Taste



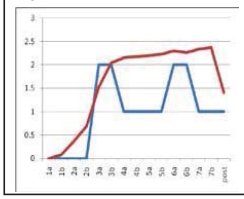
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.55	0.42	0.50	0.55	0.53
Difficulty Speaking	0.35	0.27	0.31	0.14	0.38
Restriction of Speech	0.83	0.33	0.89	0.49	0.80
Difficulty Eat Hard Foods	0.58	0.40	0.57	0.53	0.58
Difficulty Eat Soft Foods	0.89	0.56	0.89	0.76	0.88
Restriction of eating	0.55	0.42	0.53	0.43	0.58
Difficulty Drinking	0.98	0.70	0.92	0.76	1.00
Restriction of Drinking	0.92	0.57	0.94	0.65	0.95
Difficulty Swallowing	0.58	0.46	0.55	0.47	0.61
Change in Taste	0.52	0.03	0.68	0.27	0.49

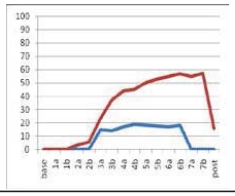
Ex-Smoker, Male, Age: 77, Caucasian		**Cancer: Salivary T: 3 N: 0**		**Planned total Gray: 69**		**35**
Events over the treatment period:	Intake smoke & Alcohol **0** **4**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake **0**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

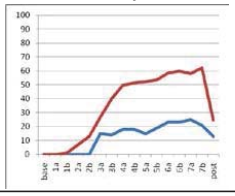
NCI



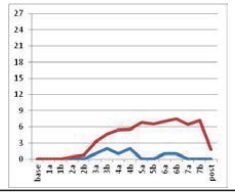
Total OMAS Ulceration VAS



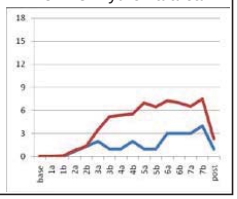
Total OMAS Erythema VAS



OMAS Ulceration area

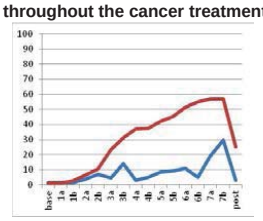


OMAS Erythema area

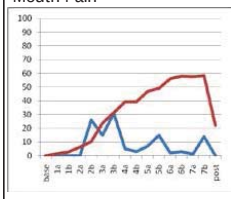


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

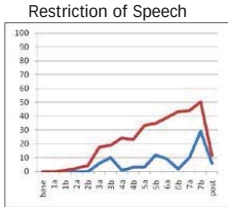


Mouth Pain

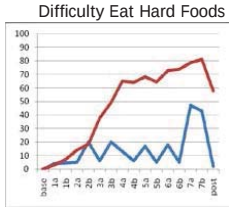


Difficulty Speaking

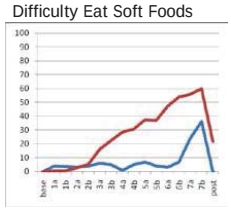
Restriction of Speech



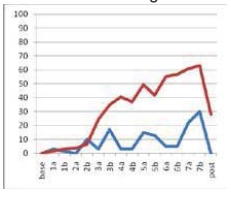
Difficulty Eat Hard Foods



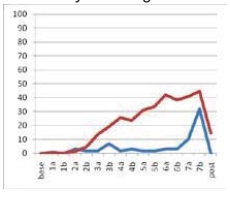
Difficulty Eat Soft Foods



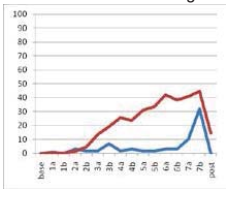
Restriction of eating



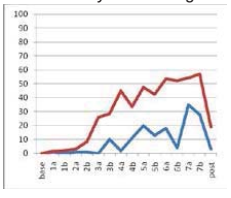
Difficulty Drinking



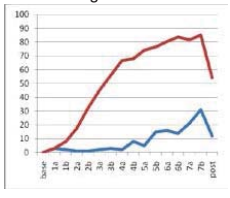
Restriction of Drinking



Difficulty Swallowing



Change in Taste



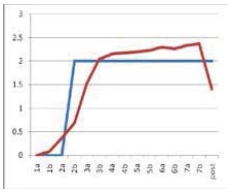
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.31	0.02	0.15	0.21	0.13
Difficulty Speaking	0.17	0.31	0.56	0.45	0.56
Restriction of Speech	0.54	0.05	0.62	0.19	0.46
Difficulty Eat Hard Foods	0.17	0.16	0.31	0.02	0.50
Difficulty Eat Soft Foods	0.27	0.14	0.39	0.32	0.56
Restriction of eating	0.21	0.38	0.42	0.40	0.40
Difficulty Drinking	0.33	0.10	0.52	0.17	0.76
Restriction of Drinking	0.33	0.17	0.61	0.08	0.56
Difficulty Swallowing	0.20	0.14	0.71	0.43	0.49
Change in Taste	0.36	0.03	0.85	0.41	0.70

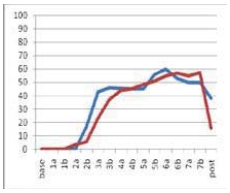
Ex-Smoker, Female, Age: 63, Caucasian		**Cancer: Oropharynx T: 3 N: 1**		**Planned total Gray: 70 plus chemotherapy**		**36**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**1**	**16**	**4**	**10**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

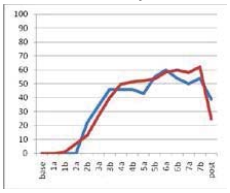
NCI



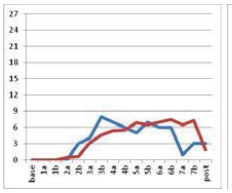
Total OMAS Ulceration VAS



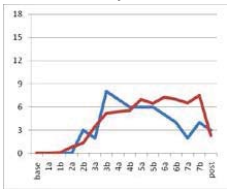
Total OMAS Erythema VAS



OMAS Ulceration area

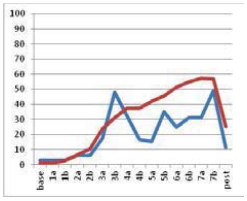


OMAS Erythema area

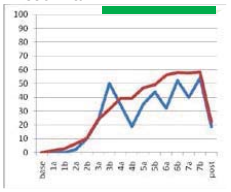


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

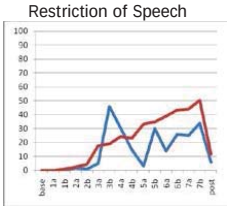


Mouth Pain

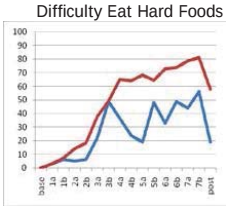


Difficulty Speaking

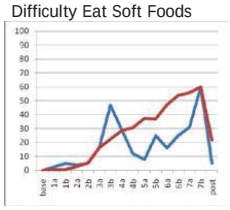
Restriction of Speech



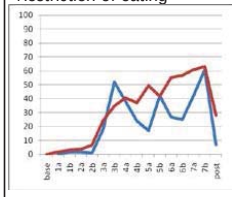
Difficulty Eat Hard Foods



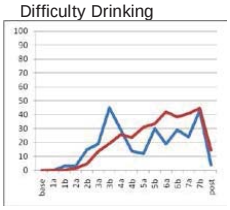
Difficulty Eat Soft Foods



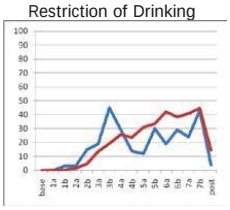
Restriction of eating



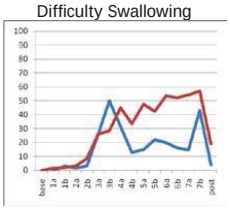
Difficulty Drinking



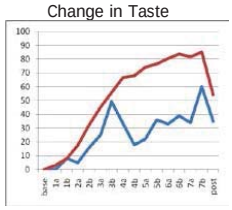
Restriction of Drinking



Difficulty Swallowing



Change in Taste



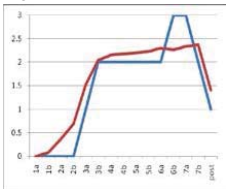
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	**Total OMAS Ulceration**	**Total OMAS Erythema**	**OMAS Ulcer Area**	**OMAS Erythema**
Mouth Pain	0.65	0.76	0.75	0.54	0.53
Difficulty Speaking	0.58	0.79	0.78	0.66	0.65
Restriction of Speech	0.58	0.72	0.73	0.65	0.61
Difficulty Eat Hard Foods	0.62	0.79	0.80	0.58	0.53
Difficulty Eat Soft Foods	0.62	0.72	0.72	0.47	0.43
Restriction of eating	0.52	0.77	0.78	0.50	0.50
Difficulty Drinking	0.65	0.71	0.70	0.59	0.49
Restriction of Drinking	0.55	0.76	0.75	0.57	0.53
Difficulty Swallowing	0.62	0.62	0.62	0.62	0.53
Change in Taste	0.65	0.77	0.77	0.57	0.51

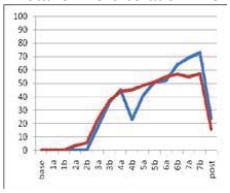
Ex-Smoker, Male, Age: 60, Asian		Cancer: Oral Cavity T: 0 N: 1		Planned total Gray: 66 plus chemotherapy		38
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	1	8	10	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

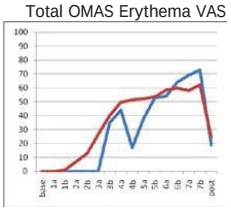
NCI



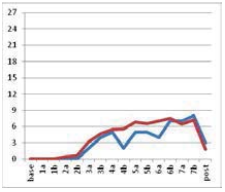
Total OMAS Ulceration VAS



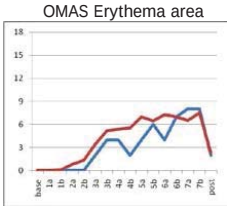
Total OMAS Erythema VAS



OMAS Ulceration area

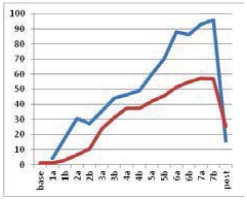


OMAS Erythema area

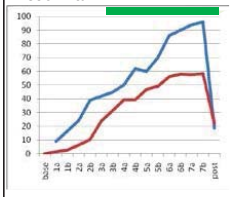


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

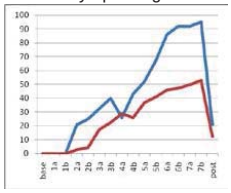
Aggregated (average) PROMS



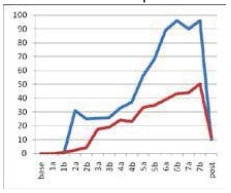
Mouth Pain



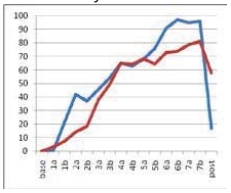
Difficulty Speaking



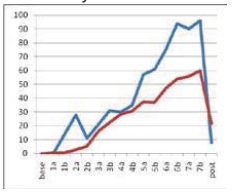
Restriction of Speech



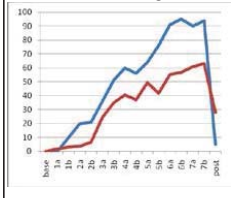
Difficulty Eat Hard Foods



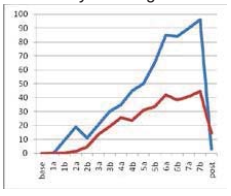
Difficulty Eat Soft Foods



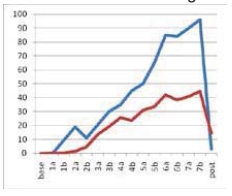
Restriction of eating



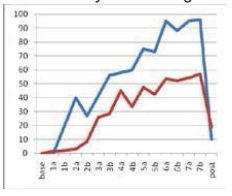
Difficulty Drinking



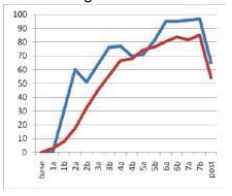
Restriction of Drinking



Difficulty Swallowing



Change in Taste



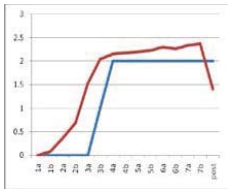
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.82	0.94	0.94	0.86	0.90
Difficulty Speaking	0.82	0.94	0.94	0.87	0.92
Restriction of Speech	0.80	0.92	0.92	0.86	0.87
Difficulty Eat Hard Foods	0.85	0.96	0.96	0.91	0.92
Difficulty Eat Soft Foods	0.82	0.94	0.94	0.87	0.91
Restriction of eating	0.82	0.94	0.94	0.87	0.88
Difficulty Drinking	0.78	0.95	0.95	0.85	0.89
Restriction of Drinking	0.78	0.95	0.95	0.85	0.90
Difficulty Swallowing	0.76	0.93	0.93	0.84	0.86
Change in Taste	0.80	0.98	0.98	0.89	0.94

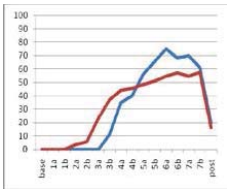
Never smoked, Male, Age: 77, Caucasian		**Cancer: Other T: 2 N: 1**		**Planned total Gray: 70**		**39**
Events over the treatment period:	Intake smoke & Alcohol **0** **0**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **14**	# Opoid intake 6	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

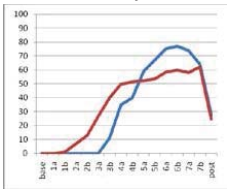
NCI



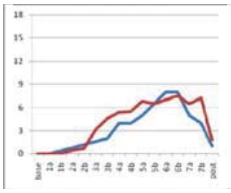
Total OMAS Ulceration VAS



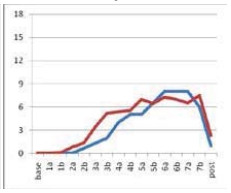
Total OMAS Erythema VAS



OMAS Ulceration area

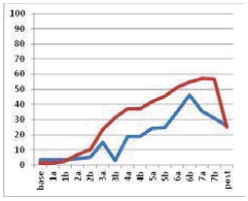


OMAS Erythema area

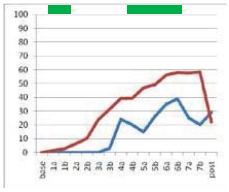


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

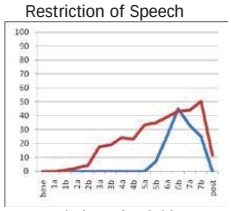


Mouth Pain



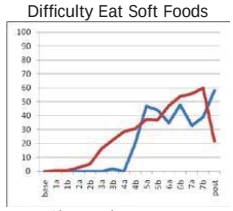
Difficulty Speaking

Restriction of Speech

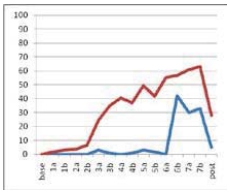


Difficulty Eat Hard Foods

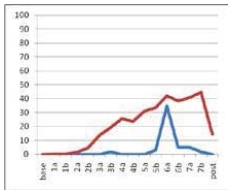
Difficulty Eat Soft Foods



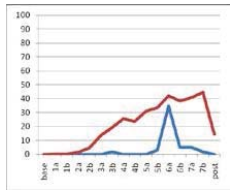
Restriction of eating



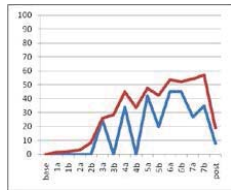
Difficulty Drinking



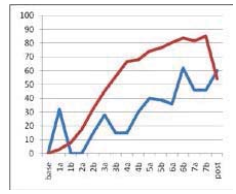
Restriction of Drinking



Difficulty Swallowing



Change in Taste



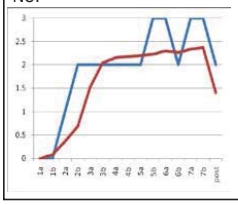
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.89	0.92	0.94	0.89	0.90
Difficulty Speaking	0.57	0.80	0.83	0.68	0.85
Restriction of Speech	0.57	0.81	0.84	0.71	0.87
Difficulty Eat Hard Foods	0.88	0.68	0.68	0.60	0.52
Difficulty Eat Soft Foods	0.77	0.84	0.89	0.81	0.79
Restriction of eating	0.46	0.49	0.57	0.48	0.61
Difficulty Drinking	0.51	0.80	0.79	0.67	0.79
Restriction of Drinking	0.57	0.85	0.85	0.77	0.88
Difficulty Swallowing	0.71	0.78	0.81	0.87	0.76
Change in Taste	0.64	0.76	0.80	0.71	0.80

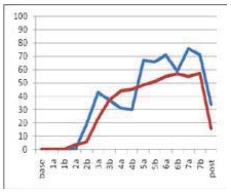
Ex-Smoker, Male, Age: 65, Caucasian		Cancer: Other T: 0 N: 2		Planned total Gray: 70 plus chemotherapy		40
Events over the treatment period:	Intake smoke & Alcohol 0 6	Cancer Tx breaks 0	Hospital stays 4	Eating support (days) 9	# Opoid intake 11	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

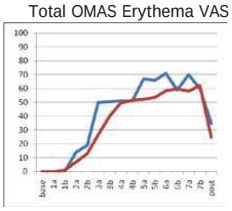
NCI



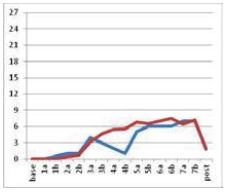
Total OMAS Ulceration VAS



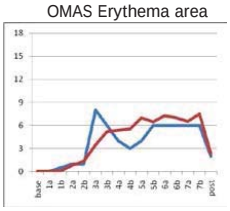
Total OMAS Erythema VAS



OMAS Ulceration area

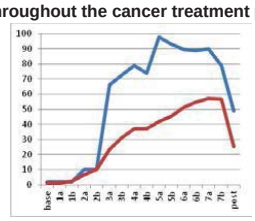


OMAS Erythema area

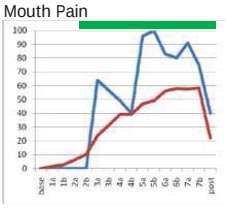


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

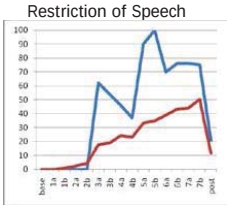


Mouth Pain

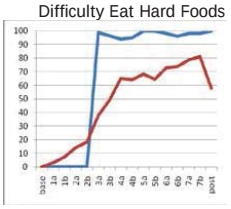


Difficulty Speaking

Restriction of Speech

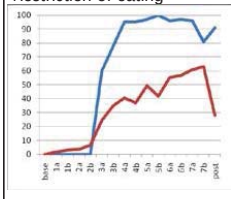


Difficulty Eat Hard Foods

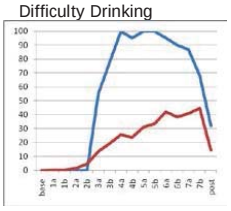


Difficulty Eat Soft Foods

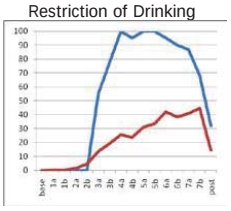
Restriction of eating



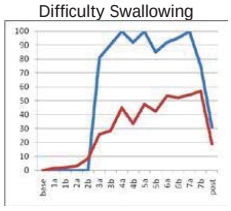
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

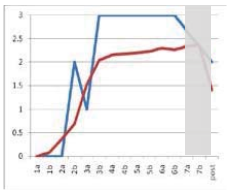
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.78	0.88	0.91	0.81	0.70
Difficulty Speaking	0.74	0.84	0.82	0.82	0.70
Restriction of Speech	0.74	0.85	0.85	0.82	0.70
Difficulty Eat Hard Foods	0.71	0.81	0.78	0.69	0.77
Difficulty Eat Soft Foods	0.66	0.67	0.81	0.56	0.51
Restriction of eating	0.66	0.74	0.84	0.65	0.54
Difficulty Drinking	0.56	0.59	0.73	0.39	0.34
Restriction of Drinking	0.59	0.61	0.76	0.40	0.34
Difficulty Swallowing	0.50	0.67	0.75	0.48	0.40
Change in Taste	0.19	0.05	0.20	0.21	0.13

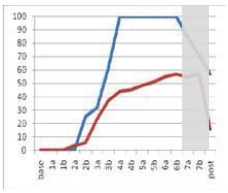
Never smoked, Male, Age: 50, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**Pt. C**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**0**	**0**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

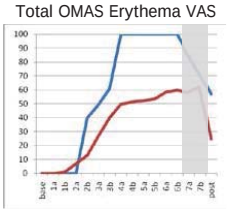
NCI



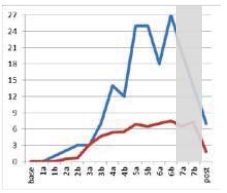
Total OMAS Ulceration VAS



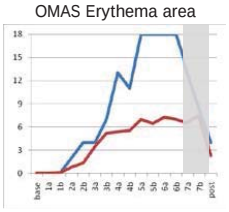
Total OMAS Erythema VAS



OMAS Ulceration area

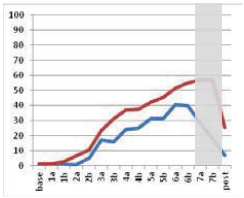


OMAS Erythema area

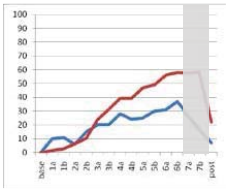


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

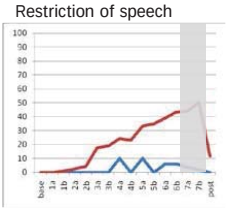


Mouth Pain

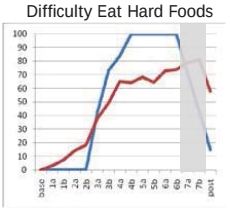


Difficulty Speaking

Restriction of speech

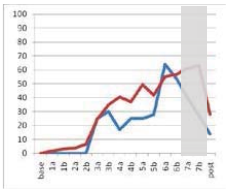


Difficulty Eat Hard Foods

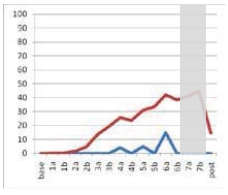


Difficulty Eat Soft Foods

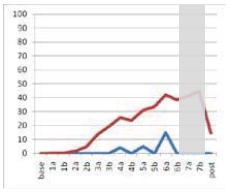
Restriction of eating



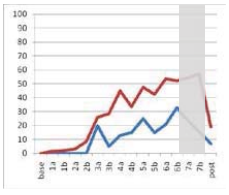
Difficulty Drinking



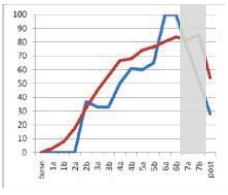
Restriction of Drinking



Difficulty Swallowing



Change in Taste



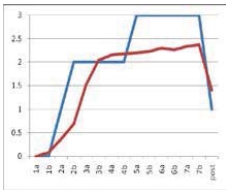
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.86	0.93	0.93	0.92	0.93
Difficulty Speaking	0.76	0.87	0.87	0.90	0.93
Restriction of Speech	0.56	0.65	0.65	0.62	0.64
Difficulty Eat Hard Foods	0.89	0.96	0.96	0.89	0.92
Difficulty Eat Soft Foods	0.69	0.84	0.84	0.82	0.86
Restriction of eating	0.79	0.75	0.75	0.65	0.68
Difficulty Drinking	0.46	0.53	0.53	0.39	0.54
Restriction of Drinking	0.25	0.28	0.28	0.35	0.36
Difficulty Swallowing	0.70	0.81	0.81	0.77	0.76
Change in Taste	0.85	0.91	0.91	0.86	0.89

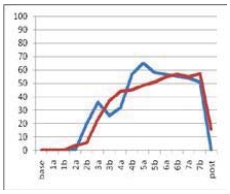
Ex-Smoker, Male, Age: 62, Asian		Cancer: Other T: 3 N: 1		Planned total Gray: 70 plus chemotherapy		43
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	8	3	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

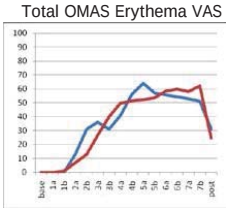
NCI



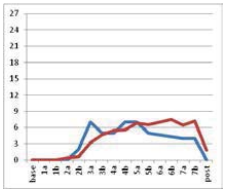
Total OMAS Ulceration VAS



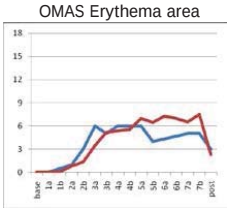
Total OMAS Erythema VAS



OMAS Ulceration area

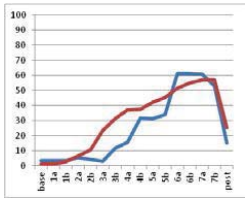


OMAS Erythema area



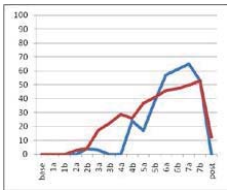
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

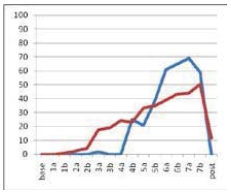


Mouth Pain

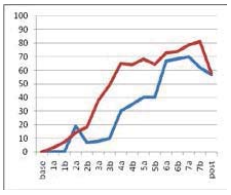
Difficulty Speaking



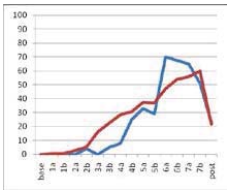
Restriction of Speech



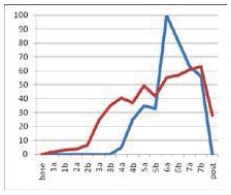
Difficulty Eat Hard Foods



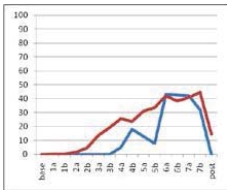
Difficulty Eat Soft Foods



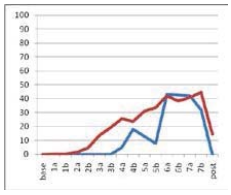
Restriction of eating



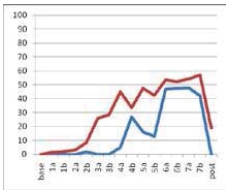
Difficulty Drinking



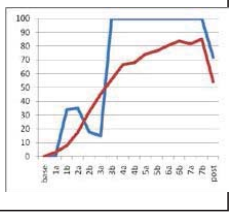
Restriction of Drinking



Difficulty Swallowing



Change in Taste



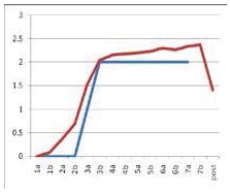
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.84	0.77	0.76	0.35	0.19
Difficulty Speaking	0.84	0.77	0.76	0.35	0.19
Restriction of Speech	0.82	0.81	0.78	0.42	0.30
Difficulty Eat Hard Foods	0.88	0.80	0.84	0.42	0.36
Difficulty Eat Soft Foods	0.90	0.81	0.83	0.41	0.36
Restriction of eating	0.85	0.80	0.83	0.36	0.35
Difficulty Drinking	0.78	0.78	0.81	0.38	0.40
Restriction of Drinking	0.81	0.76	0.80	0.33	0.31
Difficulty Swallowing	0.81	0.77	0.80	0.35	0.36
Change in Taste	0.71	0.69	0.74	0.48	0.49

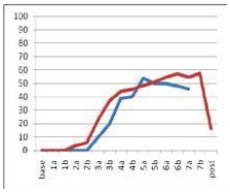
Ex-Smoker, Male, Age: 63, Caucasian		Cancer: Other T: 4 N: 0		Planned total Gray: 66		44
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	0 0	0	0	0	10	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

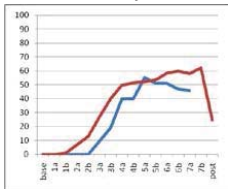
NCI



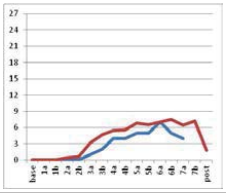
Total OMAS Ulceration VAS



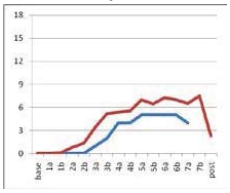
Total OMAS Erythema VAS



OMAS Ulceration area

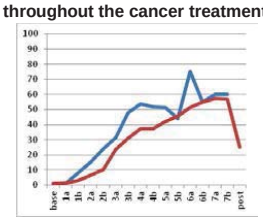


OMAS Erythema area



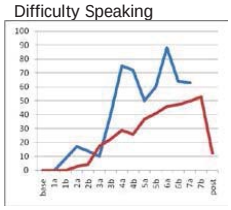
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

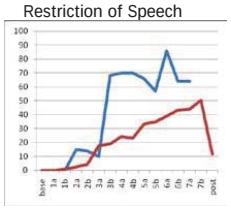


Mouth Pain

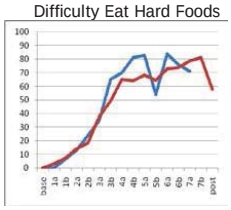
Difficulty Speaking



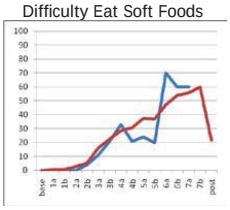
Restriction of Speech



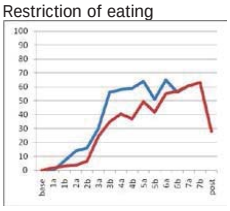
Difficulty Eat Hard Foods



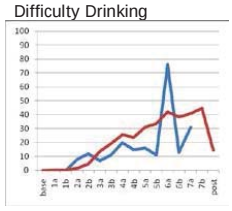
Difficulty Eat Soft Foods



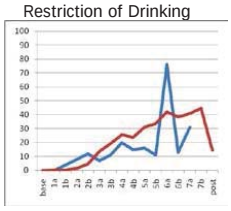
Restriction of eating



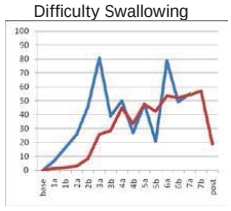
Difficulty Drinking



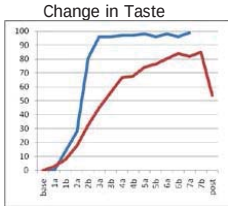
Restriction of Drinking



Difficulty Swallowing



Change in Taste



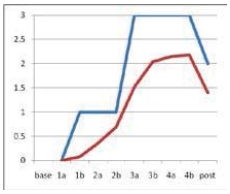
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.55	0.55	0.54	0.66	0.57
Difficulty Speaking	0.55	0.29	0.30	0.55	0.44
Restriction of Speech	0.55	0.11	0.11	0.29	0.15
Difficulty Eat Hard Foods	0.55	0.63	0.61	0.67	0.59
Difficulty Eat Soft Foods	0.55	0.42	0.44	0.58	0.49
Restriction of eating	0.55	0.55	0.54	0.53	0.42
Difficulty Drinking	0.28	0.32	0.33	0.39	0.26
Restriction of Drinking	0.41	0.14	0.13	0.16	0.02
Difficulty Swallowing	0.14	0.17	0.21	0.31	0.19
Change in Taste	0.56	0.51	0.51	0.42	0.35

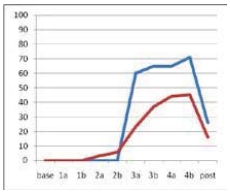
Never smoked, Male, Age: 56, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 64**		**45**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**5**	6	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

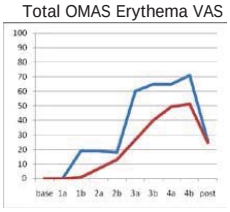
NCI



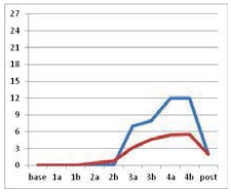
Total OMAS Ulceration VAS



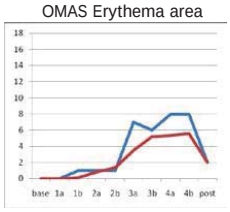
Total OMAS Erythema VAS



OMAS Ulceration area

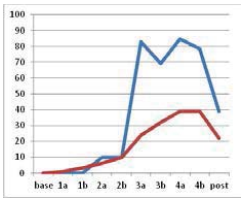


OMAS Erythema area

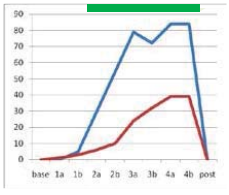


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

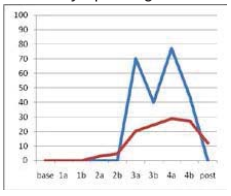
Aggregated (average) PROMS



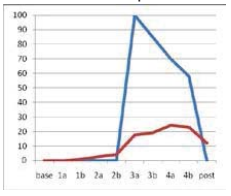
Mouth Pain



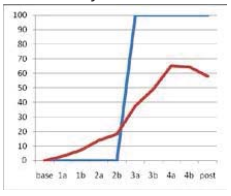
Difficulty Speaking



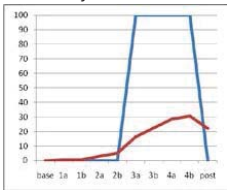
Restriction of Speech



Difficulty Eat Hard Foods



Difficulty Eat Soft Foods

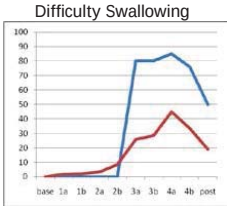


Restriction of eating

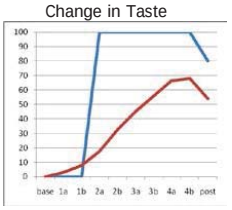
Difficulty Drinking

Restriction of Drinking

Difficulty Swallowing



Change in Taste



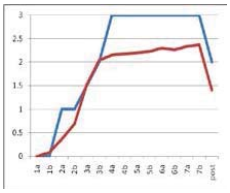
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	**Total OMAS Ulceration**	**Total OMAS Erythema**	**OMAS Ulcer Area**	**OMAS Erythema**
Mouth Pain	0.89	0.90	0.90	0.93	0.95
Difficulty Speaking	0.89	0.83	0.78	0.90	0.92
Restriction of Speech	0.72	0.61	0.58	0.69	0.80
Difficulty Eat Hard Foods	0.96	0.94	0.88	0.94	0.90
Difficulty Eat Soft Foods	0.96	0.94	0.88	0.94	0.90
Restriction of eating	0.96	0.94	0.88	0.94	0.90
Difficulty Drinking	0.90	0.94	0.89	0.99	0.95
Restriction of Drinking	0.90	0.94	0.89	0.99	0.95
Difficulty Swallowing	0.90	0.82	0.77	0.88	0.84
Change in Taste	0.69	0.54	0.57	0.54	0.65

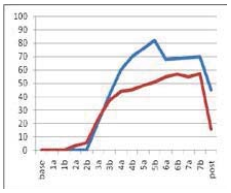
Ex-Smoker, Male, Age: 48, Caucasian		Cancer: Oropharynx T: 2 N: 3		Planned total Gray: 70 plus chemotherapy		47
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**1**	**6**	**3**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

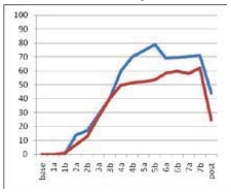
NCI



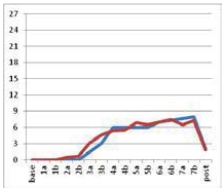
Total OMAS Ulceration VAS



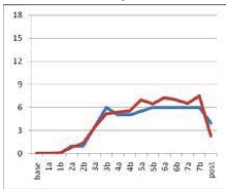
Total OMAS Erythema VAS



OMAS Ulceration area

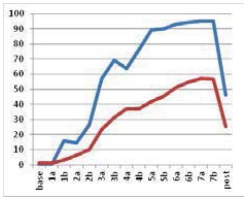


OMAS Erythema area

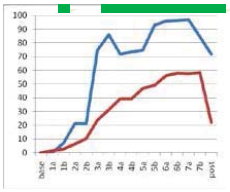


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

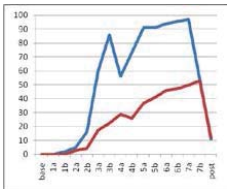
Aggregated (average) PROMS



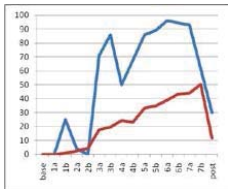
Mouth Pain



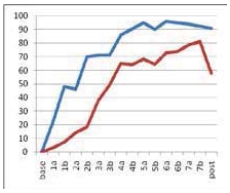
Difficulty Speaking



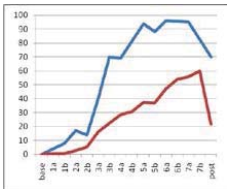
Restriction of Speech



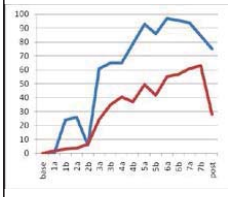
Difficulty Eat Hard Foods



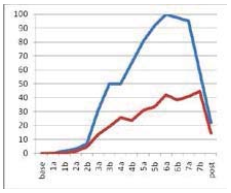
Difficulty Eat Soft Foods



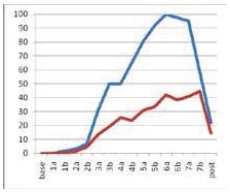
Restriction of eating



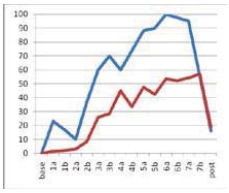
Difficulty Drinking



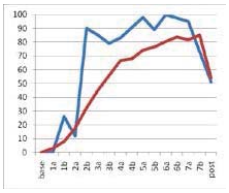
Restriction of Drinking



Difficulty Swallowing



Change in Taste



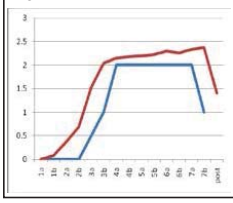
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.89	0.90	0.92	0.91	0.96
Difficulty Speaking	0.88	0.89	0.93	0.90	0.95
Restriction of Speech	0.77	0.89	0.79	0.90	0.84
Difficulty Eat Hard Foods	0.90	0.93	0.93	0.95	0.82
Difficulty Eat Soft Foods	0.88	0.89	0.89	0.90	0.95
Restriction of eating	0.87	0.92	0.85	0.93	0.87
Difficulty Drinking	0.93	0.92	0.95	0.93	0.93
Restriction of Drinking	0.95	0.93	0.96	0.95	0.88
Difficulty Swallowing	0.82	0.89	0.89	0.90	0.90
Change in Taste	0.58	0.56	0.68	0.62	0.51

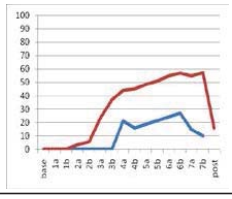
Never smoked, Female, Age: 64, Caucasian		**Cancer: Salivary T: 2 N: 0**		**Planned total Gray: 66**		**48**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**0**	6	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

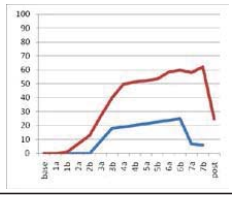
NCI



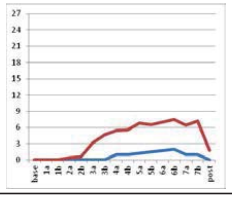
Total OMAS Ulceration VAS



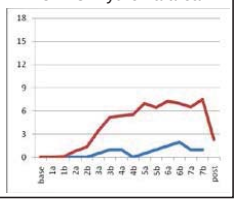
Total OMAS Erythema VAS



OMAS Ulceration area

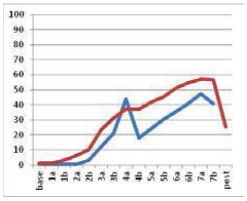


OMAS Erythema area

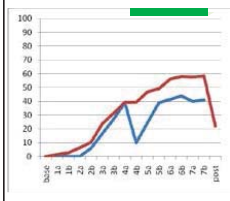


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

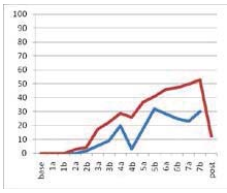
Aggregated (average) PROMS



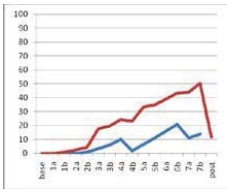
Mouth Pain



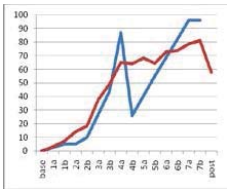
Difficulty Speaking



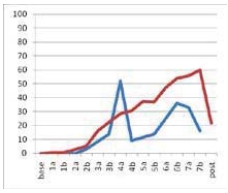
Restriction of Speech



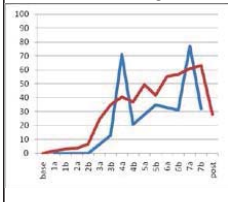
Difficulty Eat Hard Foods



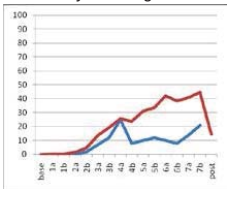
Difficulty Eat Soft Foods



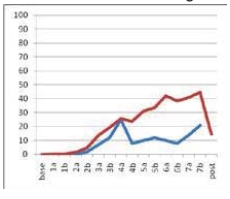
Restriction of eating



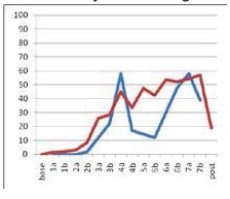
Difficulty Drinking



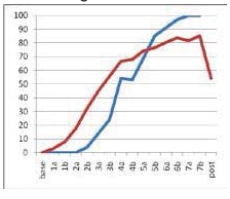
Restriction of Drinking



Difficulty Swallowing



Change in Taste



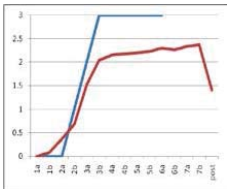
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.62	0.66	0.76	0.82	0.91
Difficulty Speaking	0.54	0.56	0.66	0.76	0.85
Restriction of Speech	0.62	0.66	0.76	0.82	0.91
Difficulty Eat Hard Foods	0.58	0.48	0.58	0.63	0.72
Difficulty Eat Soft Foods	0.77	0.78	0.88	0.76	0.85
Restriction of eating	0.78	0.66	0.56	0.72	0.63
Difficulty Drinking	0.54	0.42	0.56	0.44	0.58
Restriction of Drinking	0.62	0.44	0.64	0.48	0.66
Difficulty Swallowing	0.78	0.69	0.79	0.70	0.79
Change in Taste	0.66	0.60	0.50	0.79	0.70

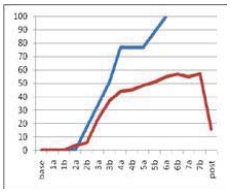
Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 4 N: 0**		**Planned total Gray: 70 plus chemotherapy**		**49**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	145 **0**	**0**	**0**	**2**	**2**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

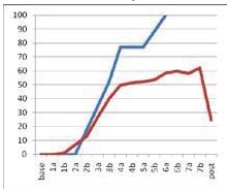
NCI



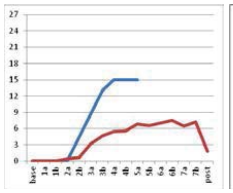
Total OMAS Ulceration VAS



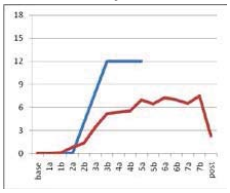
Total OMAS Erythema VAS



OMAS Ulceration area

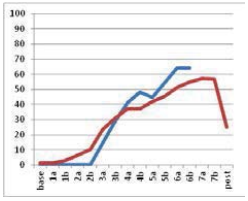


OMAS Erythema area

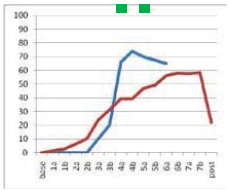


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

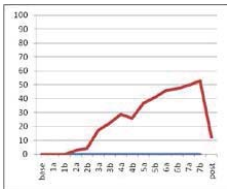
Aggregated (average) PROMS



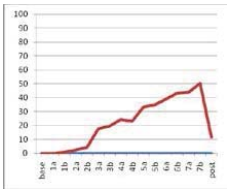
Mouth Pain



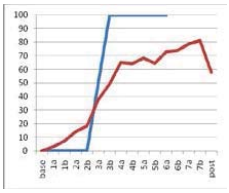
Difficulty Speaking



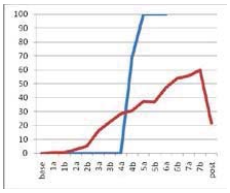
Restriction of Speech



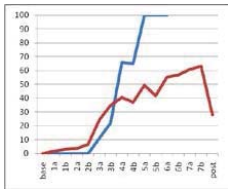
Difficulty Eat Hard Foods



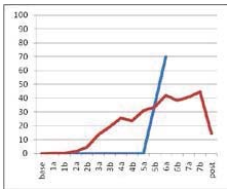
Difficulty Eat Soft Foods



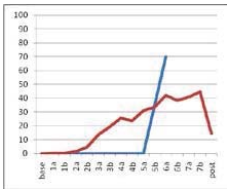
Restriction of eating



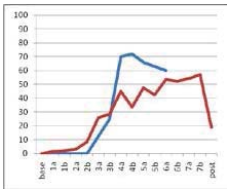
Difficulty Drinking



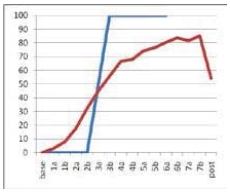
Restriction of Drinking



Difficulty Swallowing



Change in Taste



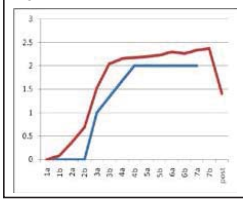
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	**Total OMAS Ulceration**	**Total OMAS Erythema**	**OMAS Ulcer Area**	**OMAS Erythema**
Mouth Pain	0.87	0.82	0.82	0.96	0.90
Difficulty Speaking	.	.	.	.	.
Restriction of Speech	.	.	.	.	.
Difficulty Eat Hard Foods	0.93	0.82	0.82	0.83	0.94
Difficulty Eat Soft Foods	0.59	0.78	0.78	0.67	0.54
Restriction of eating	0.87	0.96	0.96	0.96	0.90
Difficulty Drinking	0.29	0.61	0.61	.	.
Restriction of Drinking	0.29	0.61	0.61	.	.
Difficulty Swallowing	0.87	0.82	0.82	0.96	0.90
Change in Taste	1.00	0.89	0.89	0.94	1.00

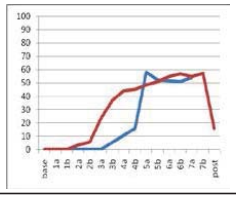
Ex-Smoker, Male, Age: 49, Caucasian		**Cancer: Oropharynx T: 4 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**50**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**4**	**10**	

Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

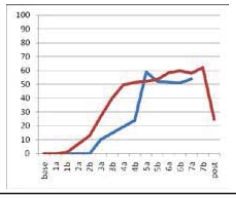
NCI



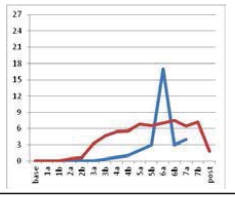
Total OMAS Ulceration VAS



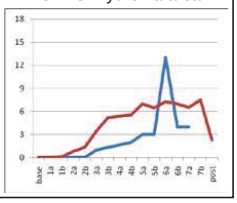
Total OMAS Erythema VAS



OMAS Ulceration area

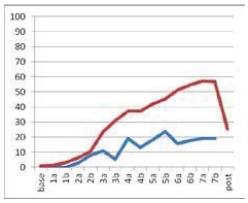


OMAS Erythema area

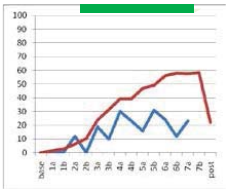


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

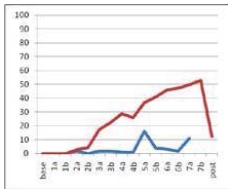
Aggregated (average) PROMS



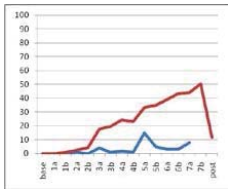
Mouth Pain



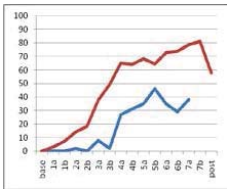
Difficulty Speaking



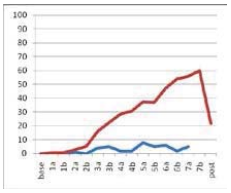
Restriction of Speech



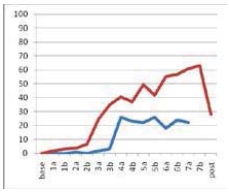
Difficulty Eat Hard Foods



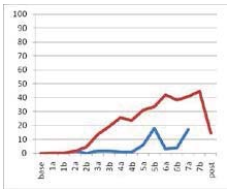
Difficulty Eat Soft Foods



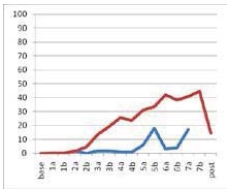
Restriction of eating



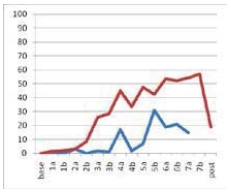
Difficulty Drinking



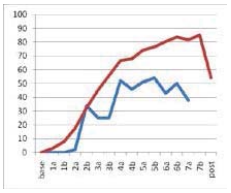
Restriction of Drinking



Difficulty Swallowing



Change in Taste



Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.80	0.65	0.74	0.74	0.73
Difficulty Speaking	0.73	0.83	0.88	0.73	0.74
Restriction of Speech	0.80	0.84	0.92	0.65	0.72
Difficulty Eat Hard Foods	0.92	0.88	0.92	0.86	0.83
Difficulty Eat Soft Foods	0.84	0.85	0.94	0.77	0.82
Restriction of eating	0.92	0.75	0.79	0.73	0.75
Difficulty Drinking	0.79	0.82	0.86	0.78	0.78
Restriction of Drinking	0.84	0.82	0.88	0.80	0.82
Difficulty Swallowing	0.79	0.77	0.79	0.84	0.84
Change in Taste	0.87	0.84	0.84	0.71	0.72