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

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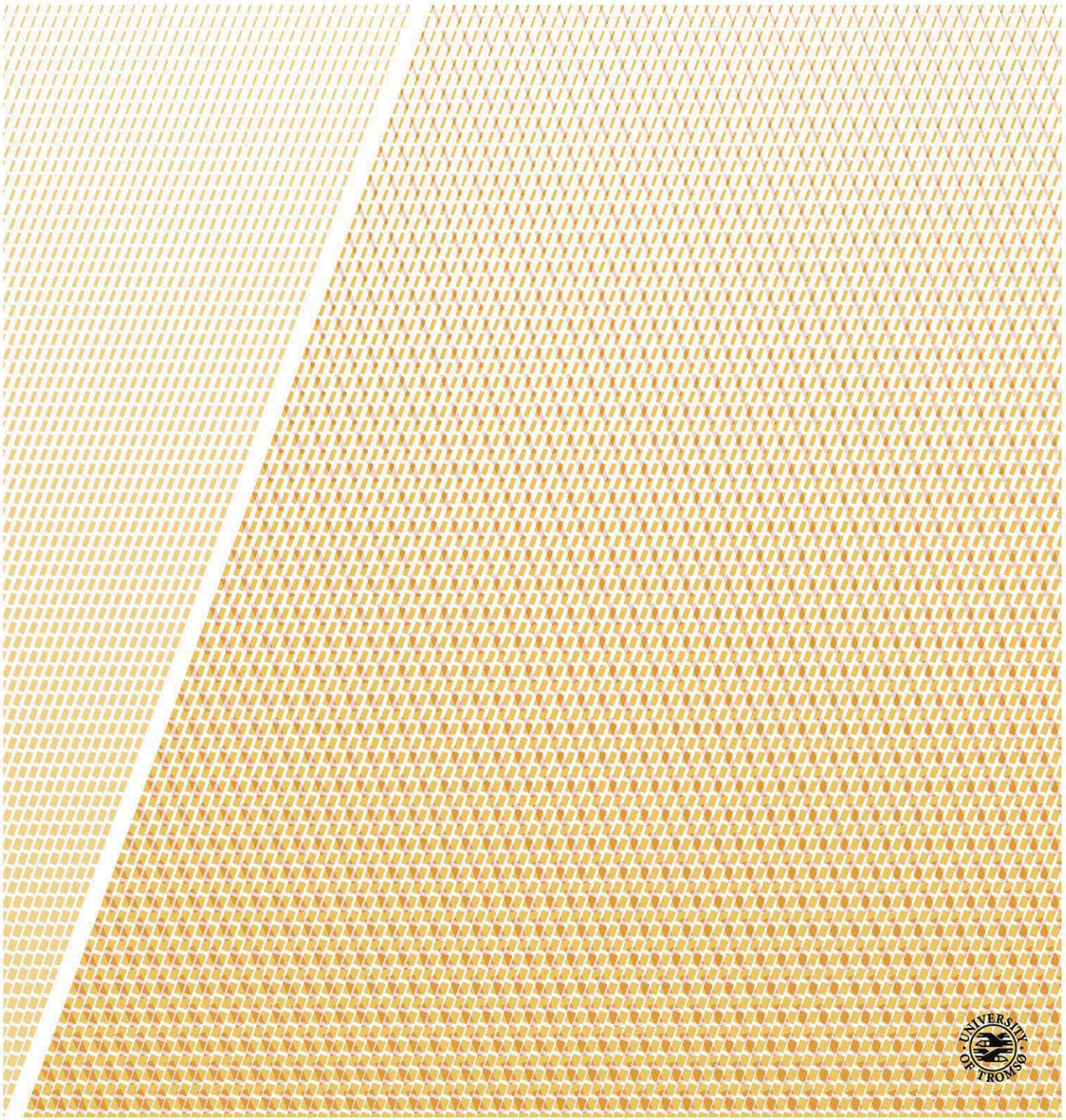
Anne Margrete Gussgard

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).

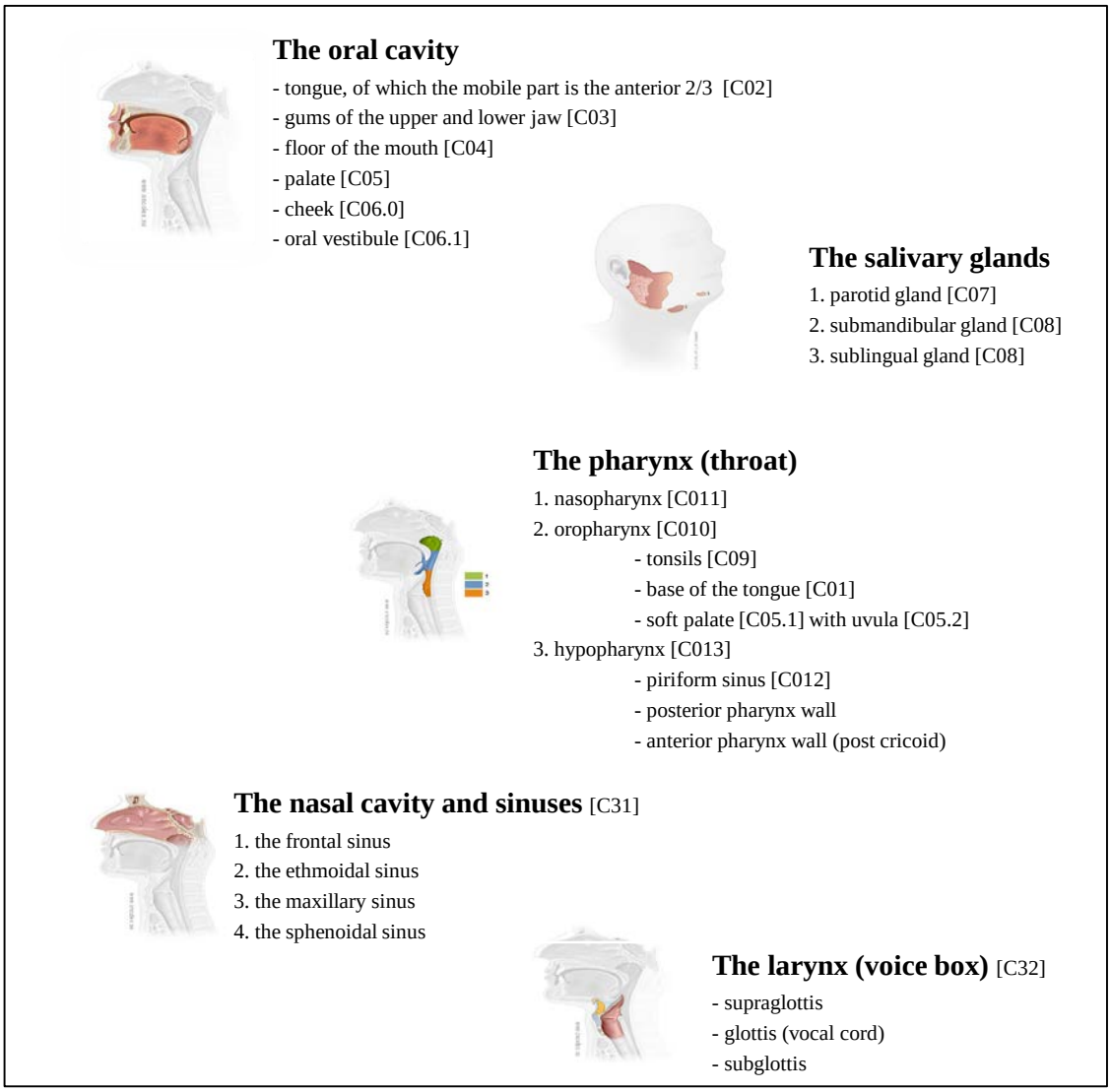

Figure 1: Anatomical location of Head and Neck Cancers. Adopted from: Oncolex Norway www.oncolex.no. (Permission for use obtained from editor).
[ICD-10- Diagnosis Codes] (www.who.int/classifications/icd/)

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).

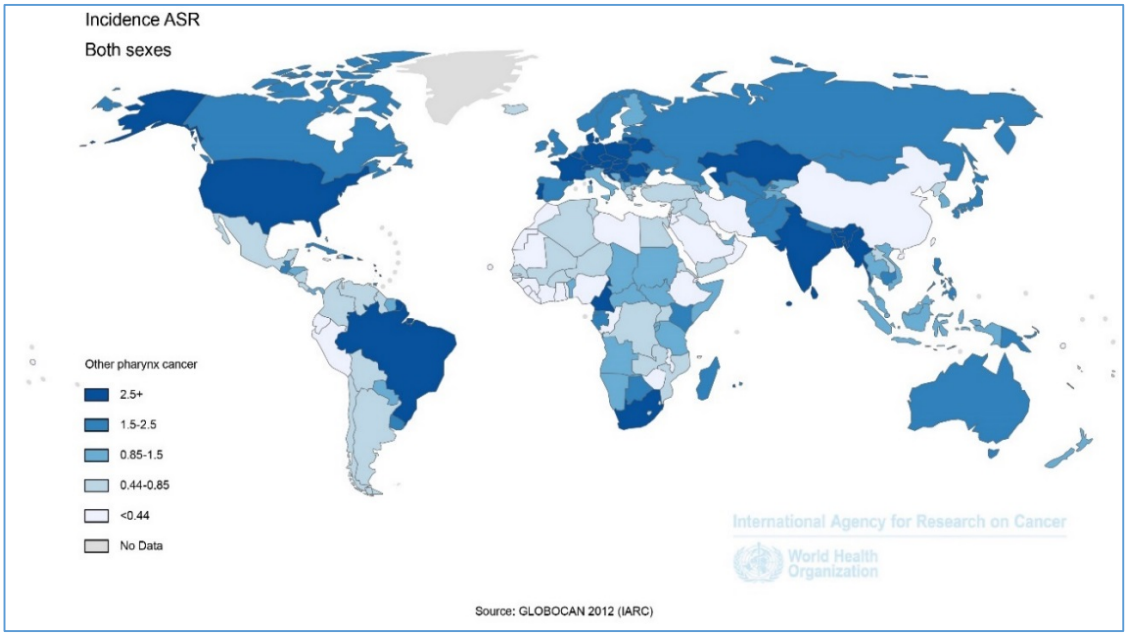

Figure 3a. Cancer of the pharynx other than nasopharynx

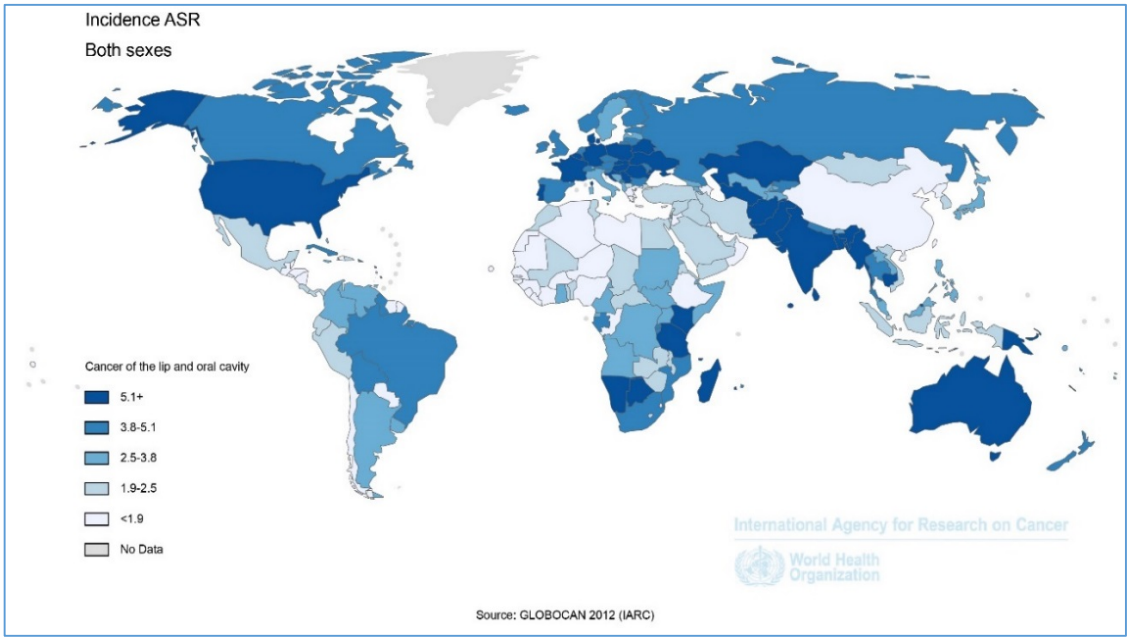

Figure 3b. Cancer of the lip and oral cavity

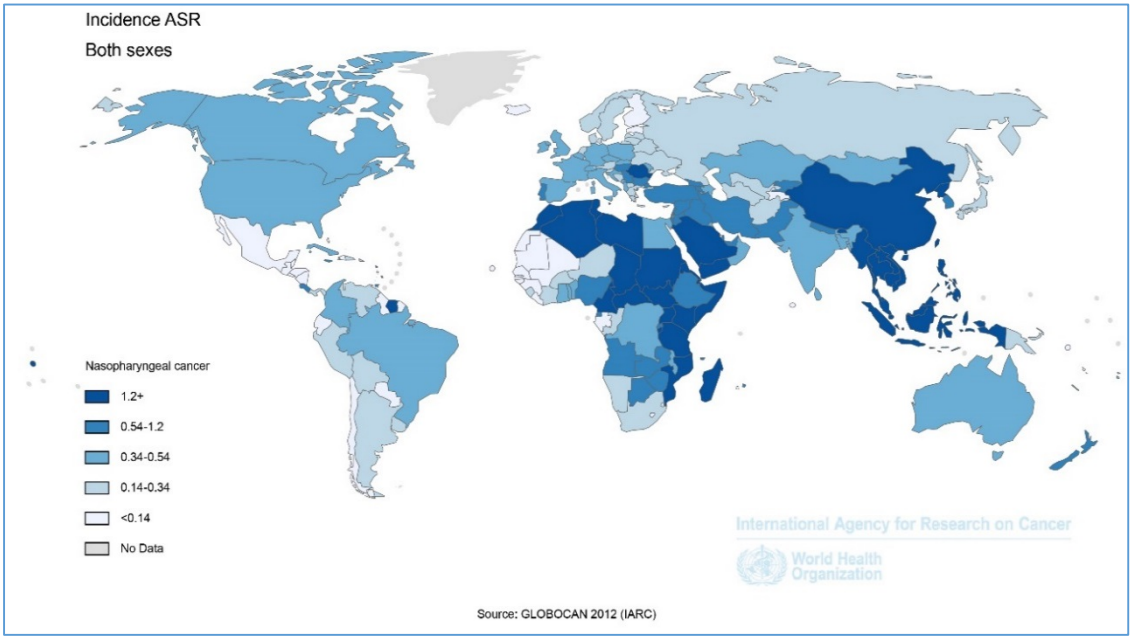

Figure 3c. Cancer of the nasopharynx

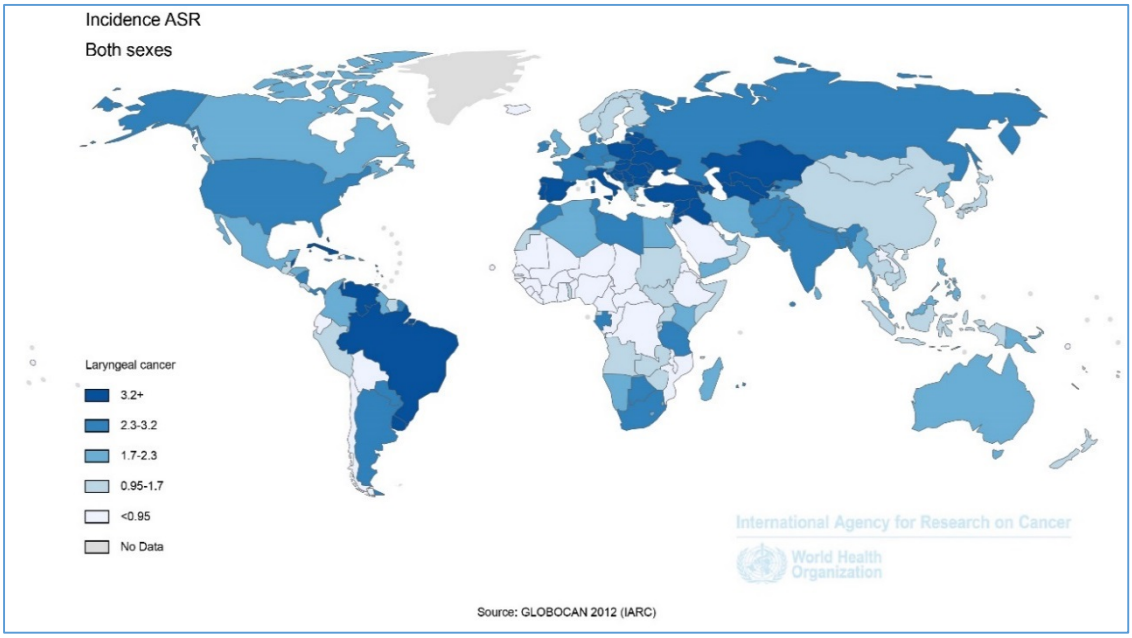

Figure 3d. Cancer of the larynx

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].

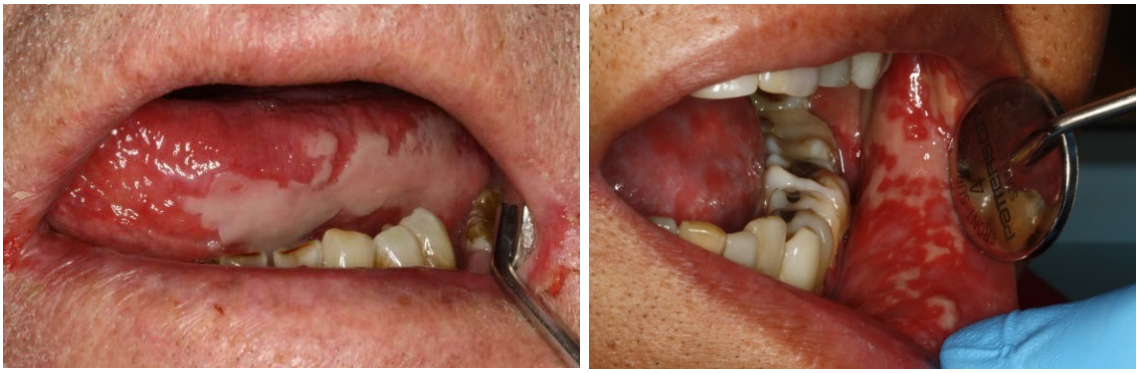

Figure 4: Oral mucositis is a side effect of radiation treatment that leads to pain and limitations of mouth opening and numerous oral functions. Photographs: AM Gussgard

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).

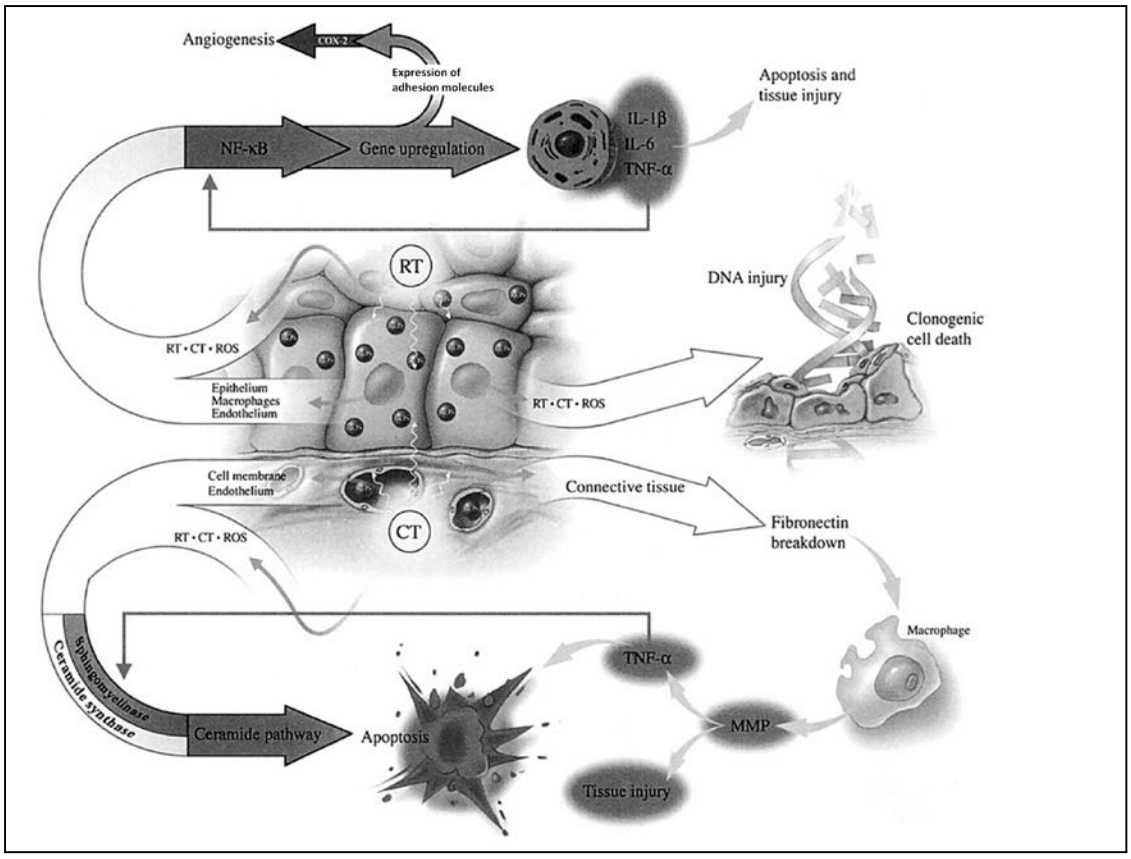

Figure 5a: Signaling and amplification phase. Illustration from [45] (Permission obtained from publisher). RT: radiotherapy, CT: chemotherapy, IL: interleukin, TNF: tumour necrosis factor, NF-kB: Nuclear Factor-kappaB, MMP: Matrix Metalloproteinases, ROS: Reactive Oxygen Species

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).

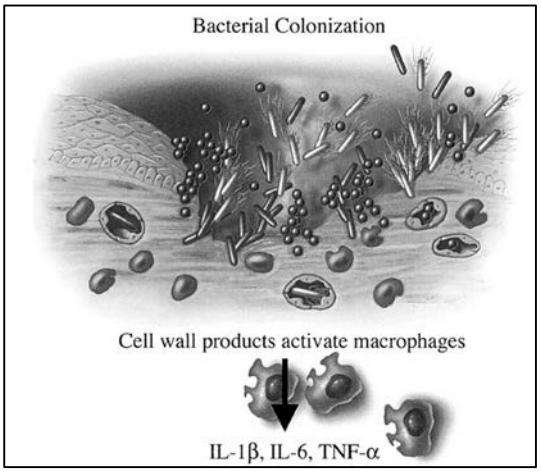

Figure 5b; Ulceration. Cell wall products from bacteria stimulate macrophages to release proinflammatory cytokines

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.

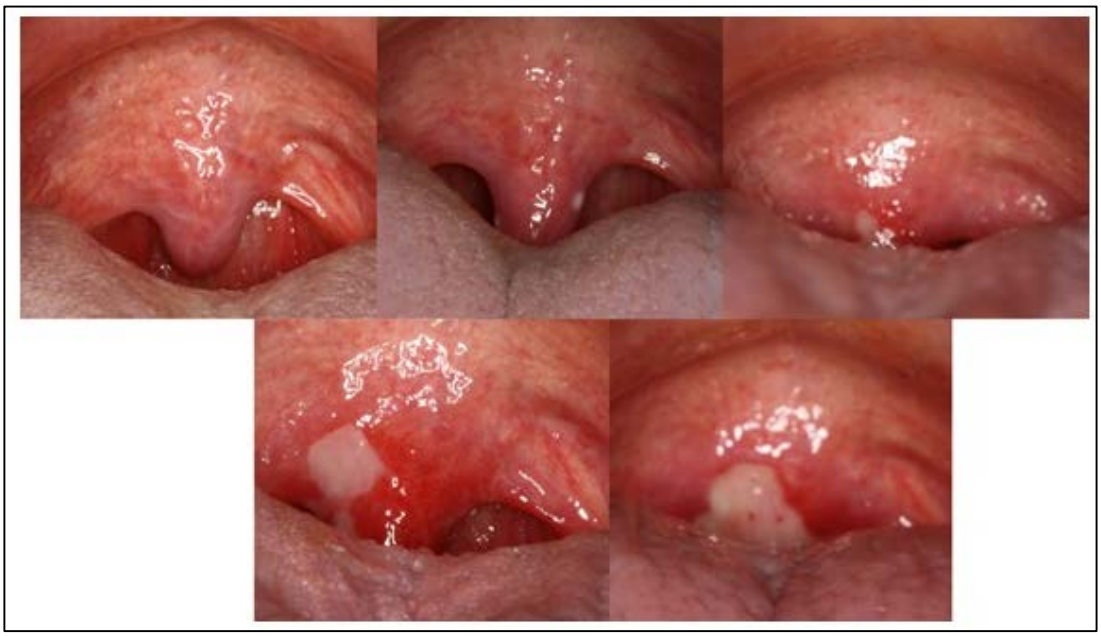

Figure 6: Development of OM in the soft palate. In this participant, the first clinical sign of ulceration developed in the midst of an erythematous area on the uvula (upper centre picture) during the 3rd week of radiotherapy. The size of the ulceration increased over the subsequent weeks 4 (upper right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

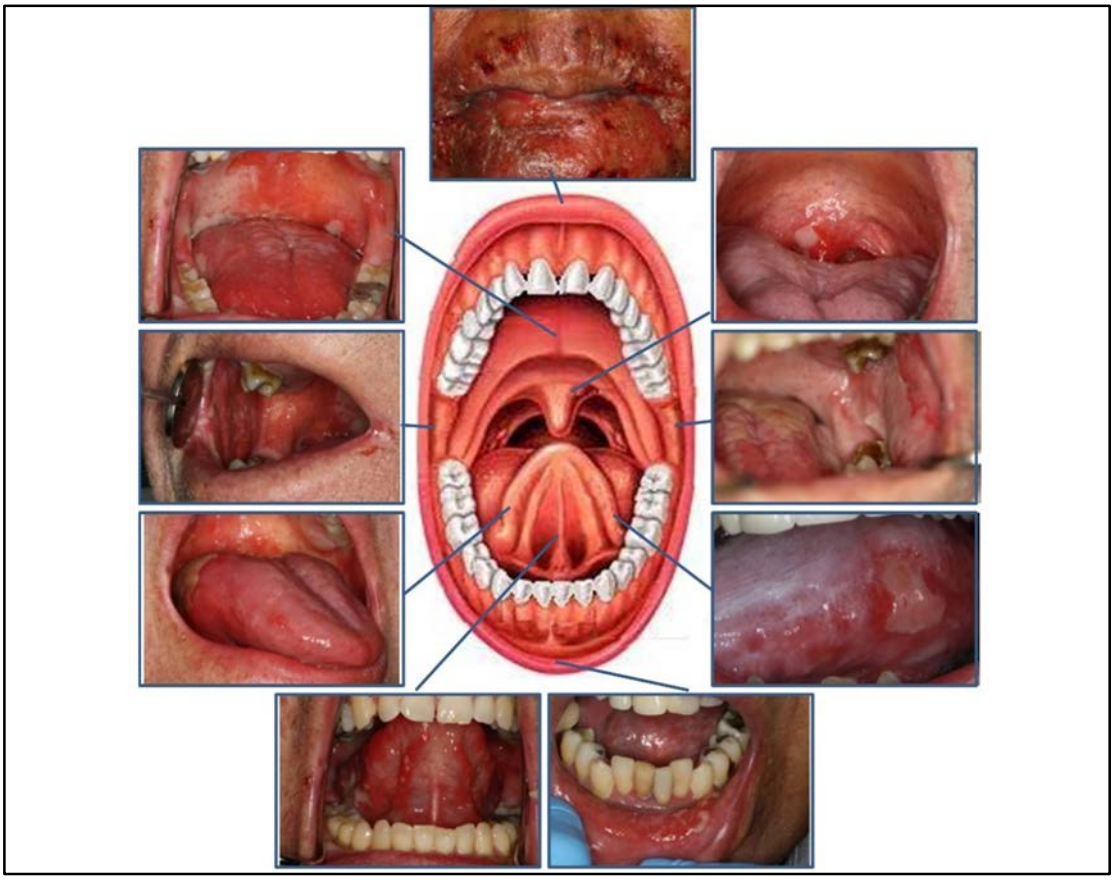

Figure 7: Clinical manifestations of OM in the nine anatomical sites according to the OMAS [67]. Photographs: AM Gussgard

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).

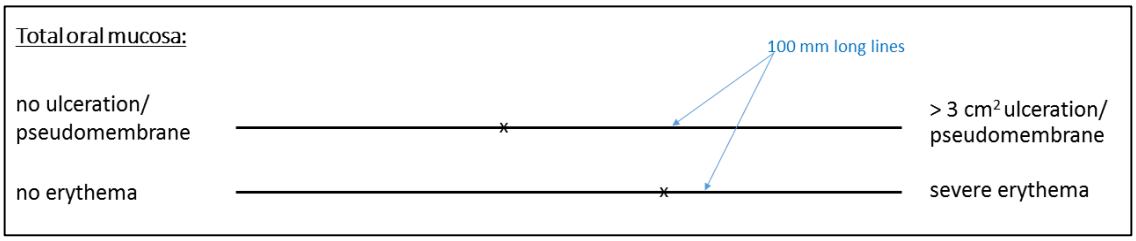

Figure 8. The "Total VAS-OMAS" concept. The "x"-marks set for illustration represent scores of 40 for ulceration and 65 for erythema, respectively.

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.

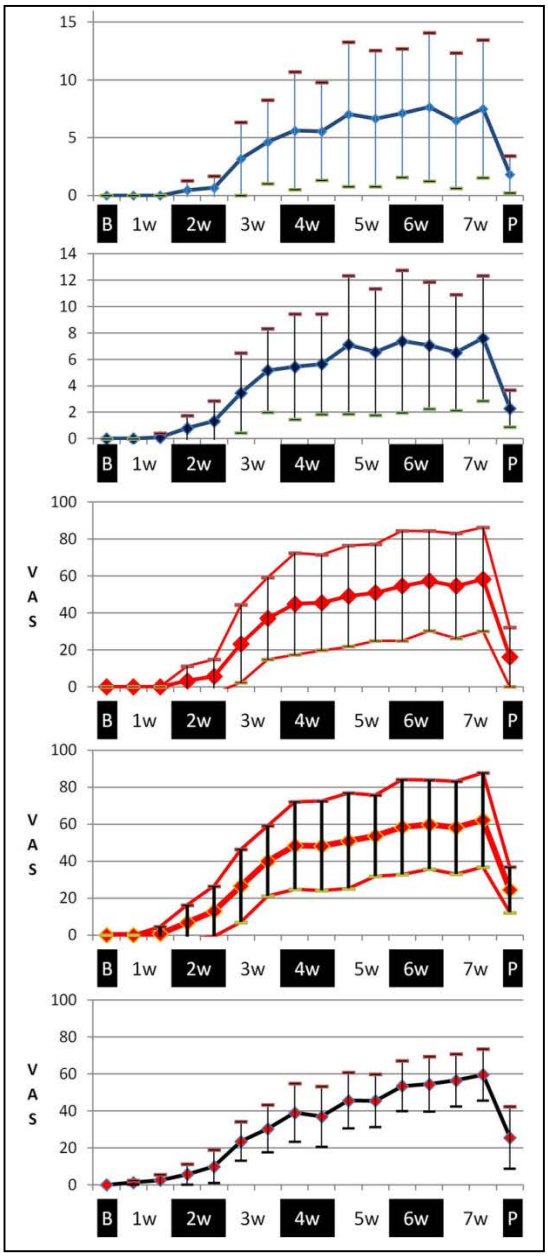

Figure 11. Clinical signs and patient symptoms recorded over the observation period (7 weeks) and at the 4-6 week post-therapy examination ("P").

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.

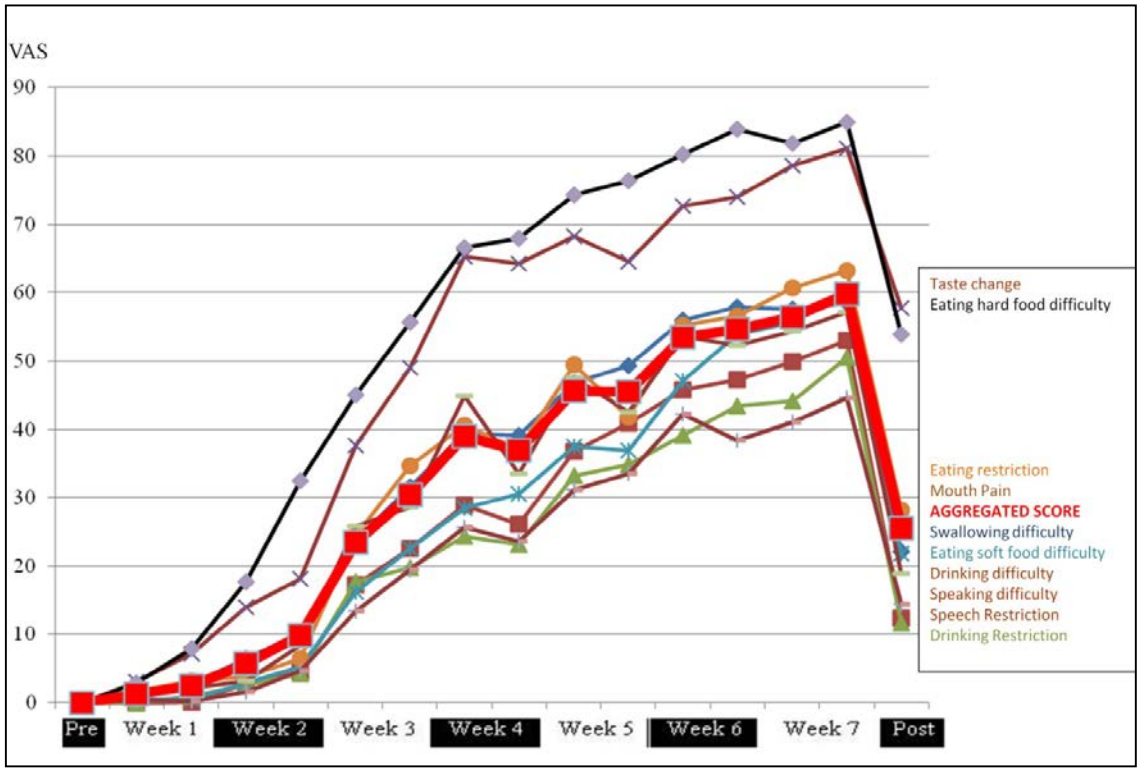

Figure 12. Patient-reported PROMS scale VAS-values experienced over the full course of the 7 weeks cancer therapy period. Left side indicate the mean PROMS scale VAS-values at baseline "Pre" before commencing therapy. Right side show the mean PROMS scale VAS-values at the post-therapy examination 4-6 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)

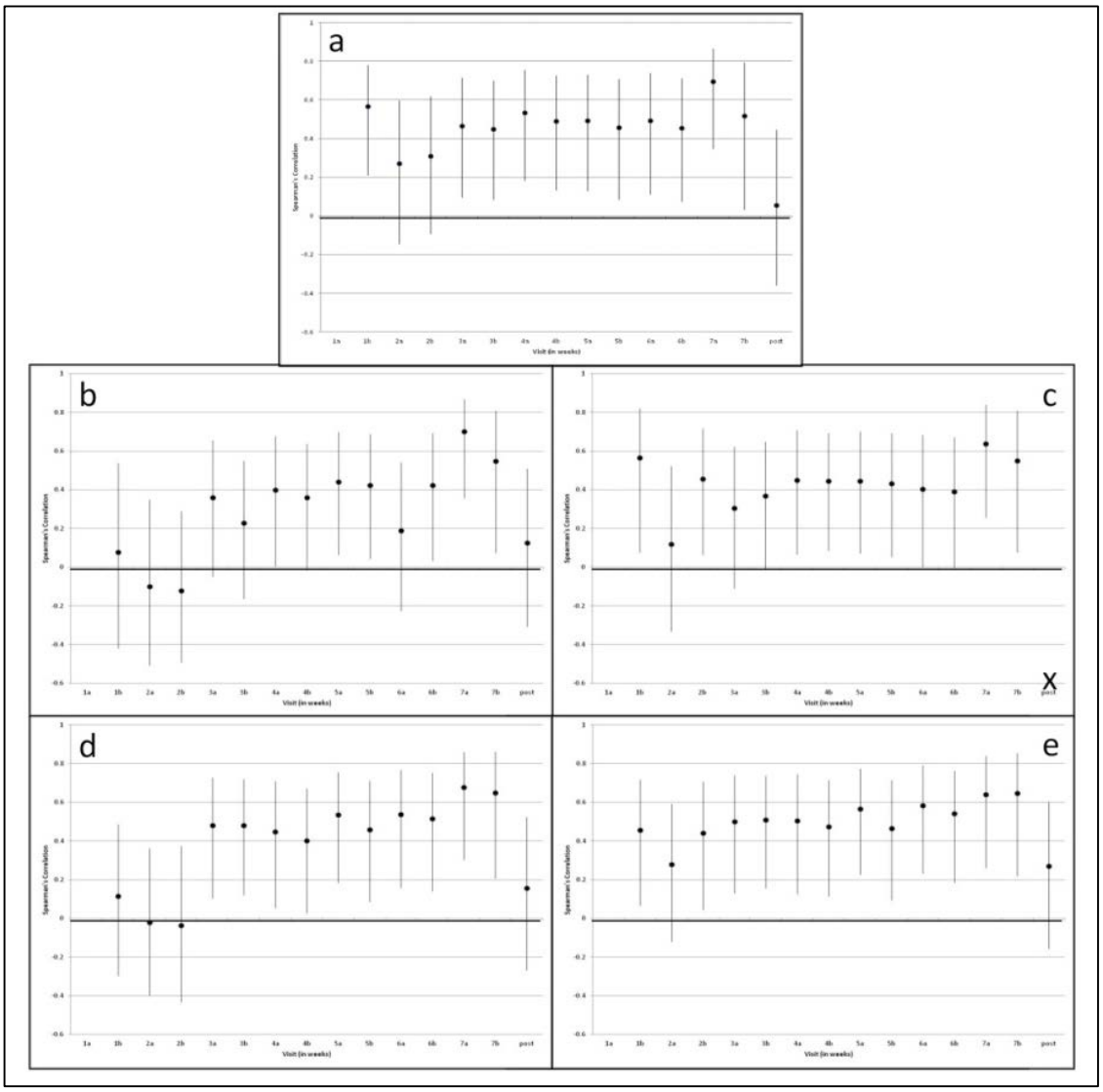

Figure 13. Spearman rho correlation coefficients over the observation period (6 or 7 weeks) and at the 4-6 week post-therapy examination between clinical signs of oral mucositis, as reported by different clinician-based scoring tools and the experience of oral mucositis by the participants, as reported 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).

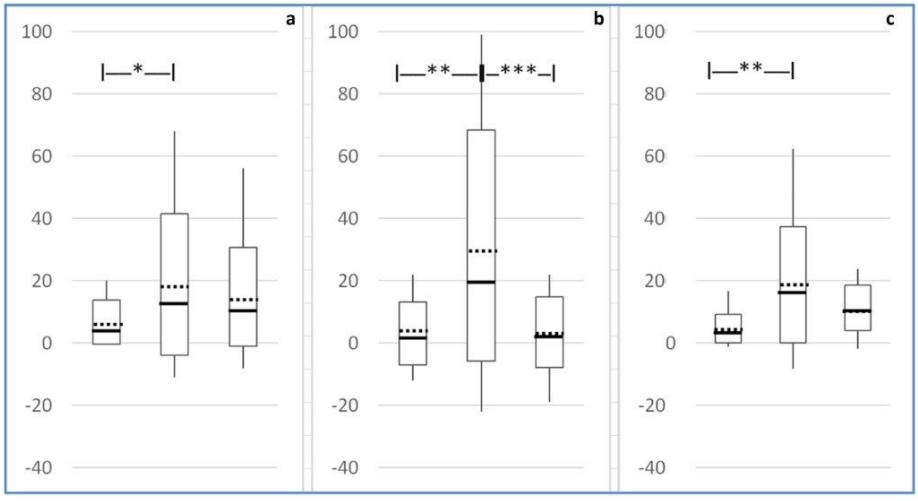

Figure 14. Change of patient-reported PROMS scale VAS-values upon transitions between OMAS scores 0 to 1, 1 to 2 and 2 to 3 anywhere in the mouth. The three boxplots within each graph show the dispersion of changes in VAS-values of mouth pain (a, left), difficulties eating hard food (b, centre) and aggregated 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.

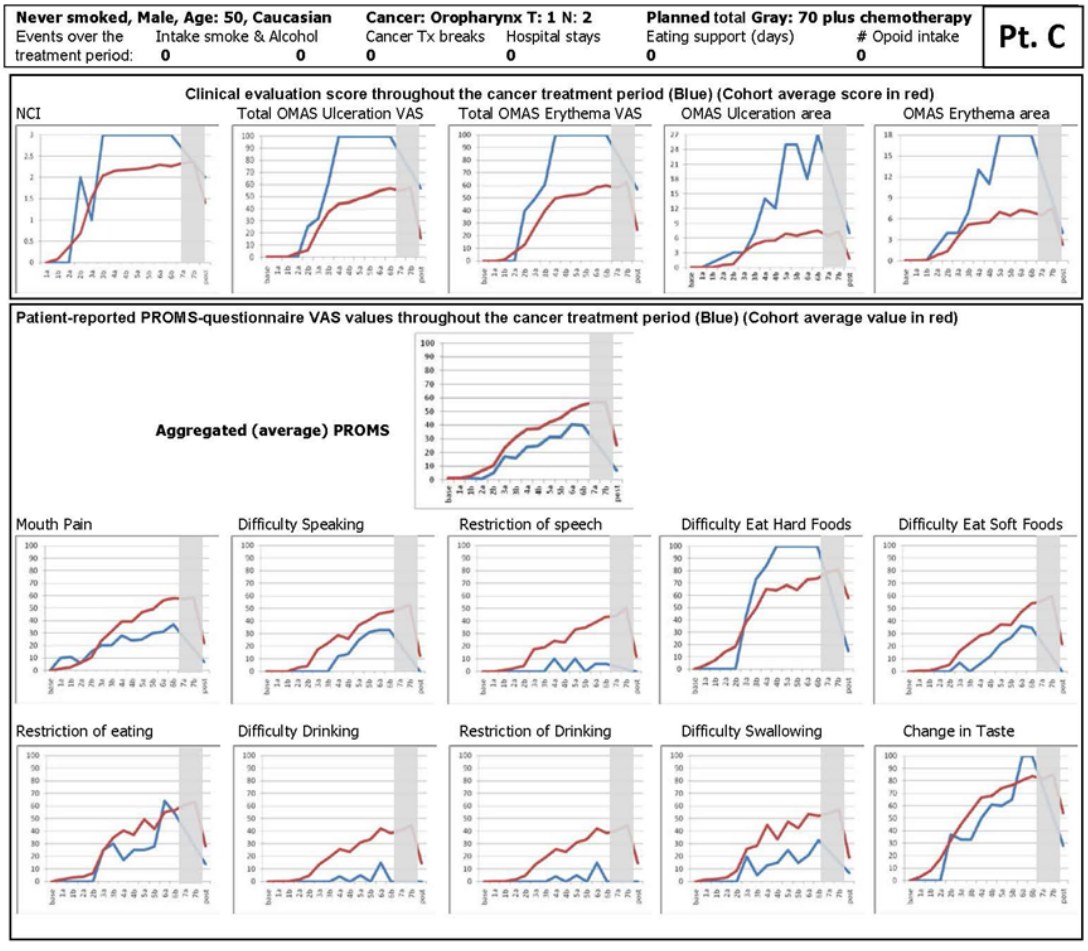

Figure 15: Representative stoical sufferer with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions. The graphs in the top row represent the five different clinical scores of OM. The patient reported OM values are shown in the 11 graphs below. All horizontal lines 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

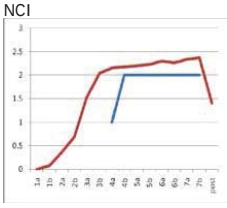
14.2 OM experience of individual study participants

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

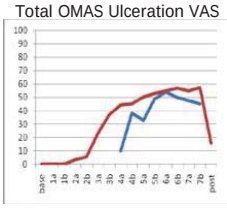
Smoker, Male, Age: 61, Caucasian		Cancer: Other T: 0 N: 2		Planned total Gray: 70 plus chemotherapy		2
Events over the treatment period:	Intake smoke & Alcohol 35 25	Cancer Tx breaks 0	Hospital stays 0	Eating support (days) 6	# Opoid intake 7	

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

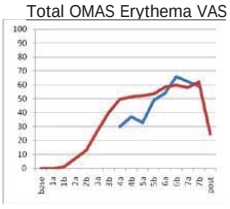
NCI



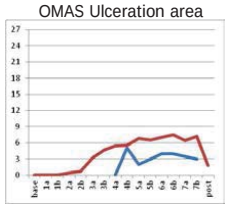
Total OMAS Ulceration VAS



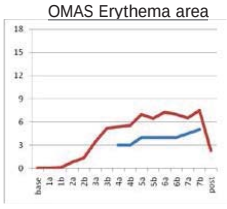
Total OMAS Erythema VAS



OMAS Ulceration area

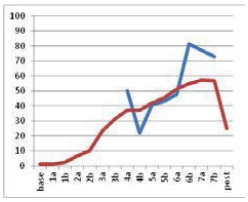


OMAS Erythema area

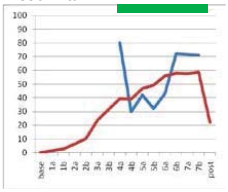


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

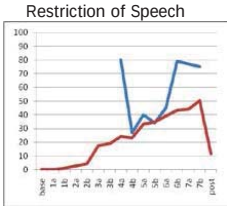


Mouth Pain

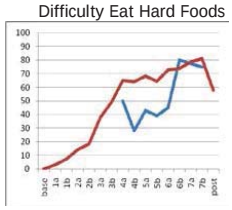


Difficulty Speaking

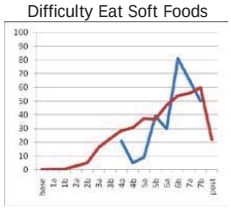
Restriction of Speech



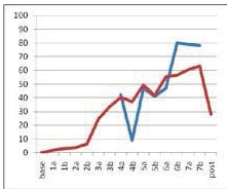
Difficulty Eat Hard Foods



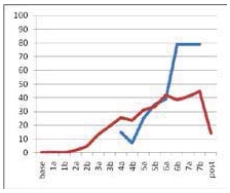
Difficulty Eat Soft Foods



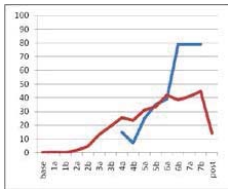
Restriction of eating



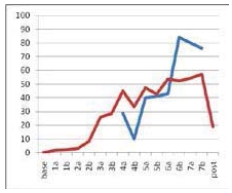
Difficulty Drinking



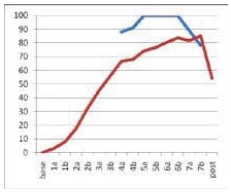
Restriction of Drinking



Difficulty Swallowing



Change in Taste



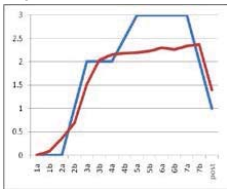
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

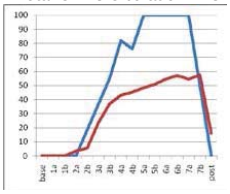
Smoker, Male, Age: 48, Caucasian		**Cancer: Other T: 4 N: 0**		**Planned total Gray: 70 plus chemotherapy**		**4**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	160 **2**	**0**	**0**	**6**	**13**	

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

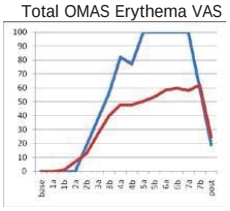
NCI



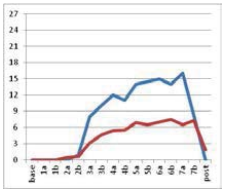
Total OMAS Ulceration VAS



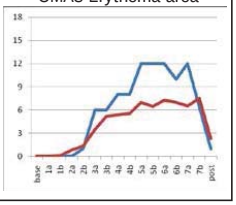
Total OMAS Erythema VAS



OMAS Ulceration area

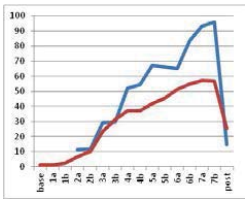


OMAS Erythema area

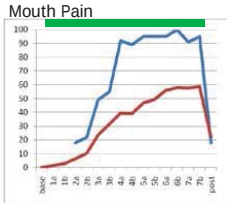


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

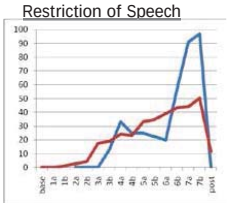


Mouth Pain

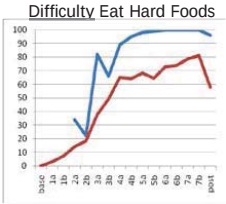


Difficulty Speaking

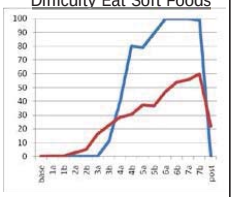
Restriction of Speech



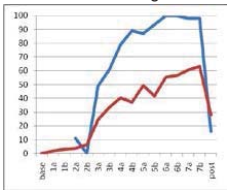
Difficulty Eat Hard Foods



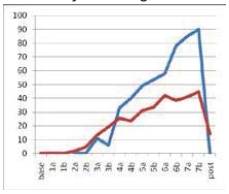
Difficulty Eat Soft Foods



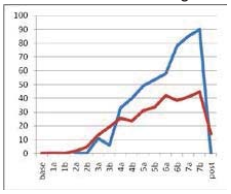
Restriction of eating



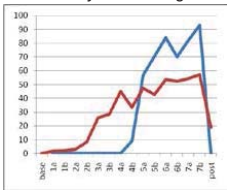
Difficulty Drinking



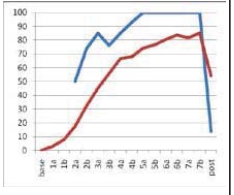
Restriction of Drinking



Difficulty Swallowing



Change in Taste



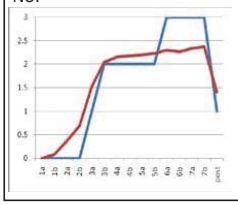
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

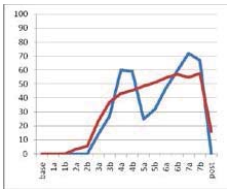
Ex-Smoker, Female, Age: 38, Asian		Cancer: Salivary T: 2 N: 0		Planned total Gray: 66		5
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	0	0	

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

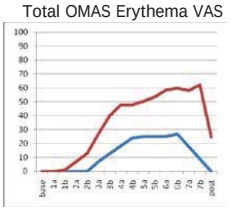
NCI



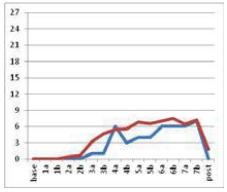
Total OMAS Ulceration VAS



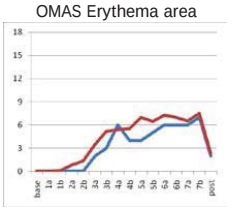
Total OMAS Erythema VAS



OMAS Ulceration area

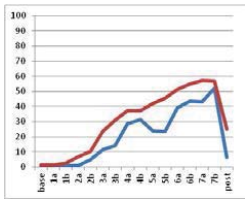


OMAS Erythema area

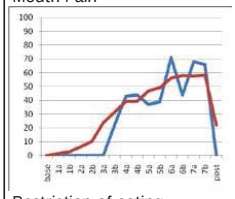


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

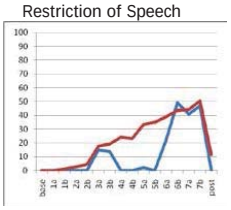


Mouth Pain

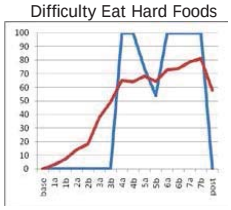


Difficulty Speaking

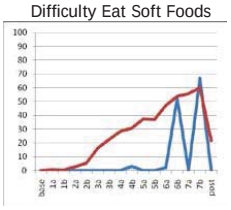
Restriction of Speech



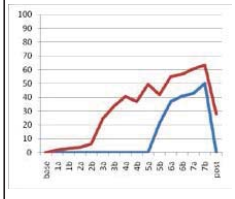
Difficulty Eat Hard Foods



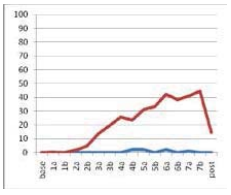
Difficulty Eat Soft Foods



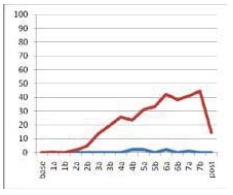
Restriction of eating



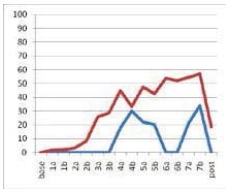
Difficulty Drinking



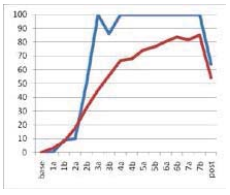
Restriction of Drinking



Difficulty Swallowing



Change in Taste



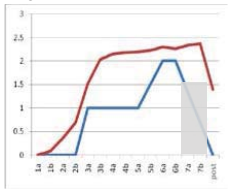
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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**	

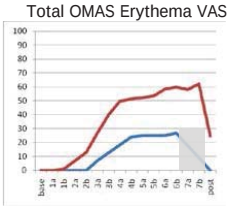
Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)

NCI

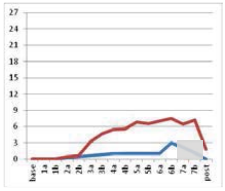


Total OMAS Ulceration VAS

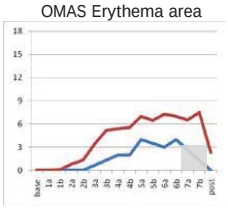
Total OMAS Erythema VAS



OMAS Ulceration area

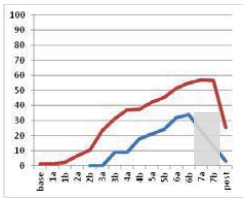


OMAS Erythema area

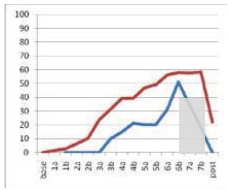


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

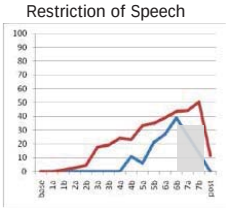


Mouth Pain

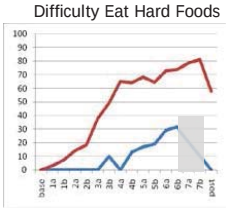


Difficulty Speaking

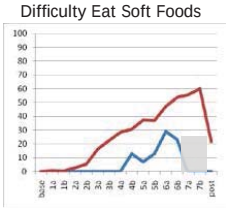
Restriction of Speech



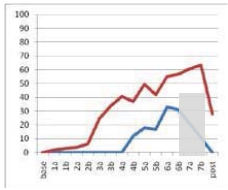
Difficulty Eat Hard Foods



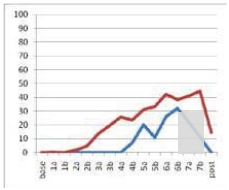
Difficulty Eat Soft Foods



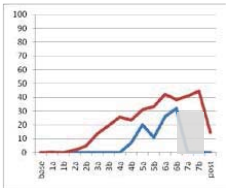
Restriction of eating



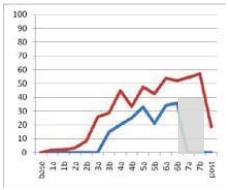
Difficulty Drinking



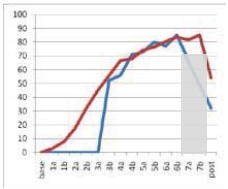
Restriction of Drinking



Difficulty Swallowing



Change in Taste



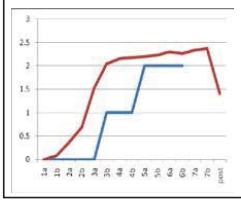
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

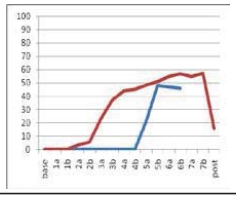
Smoker, Male, Age: 63, Caucasian		Cancer: Oropharynx T: 3 N: 2		Planned total Gray: 70		Pt. D
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	32 0	0	0	5	3	

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

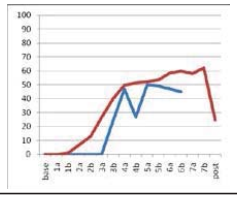
NCI



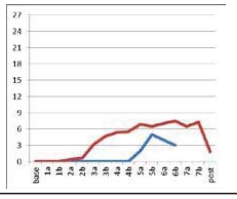
Total OMAS Ulceration VAS



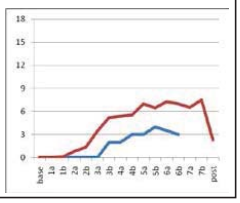
Total OMAS Erythema VAS



OMAS Ulceration area

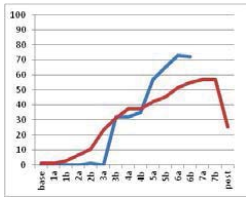


OMAS Erythema area



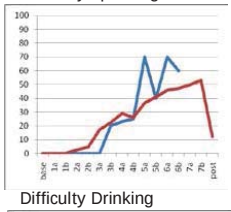
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS



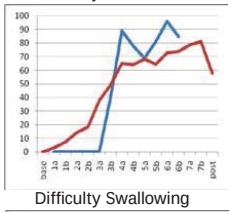
Mouth Pain

Difficulty Speaking

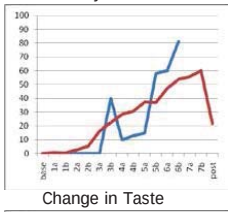


Restriction of Speech

Difficulty Eat Hard Foods

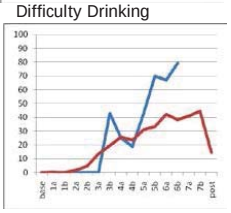


Difficulty Eat Soft Foods

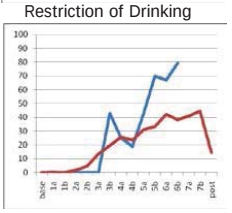


Restriction of eating

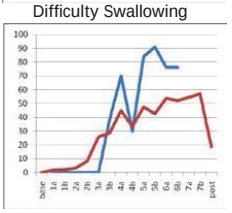
Difficulty Drinking



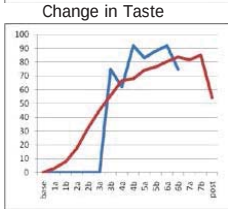
Restriction of Drinking



Difficulty Swallowing



Change in Taste



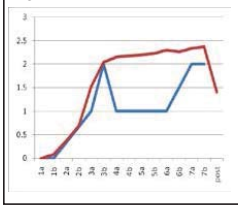
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

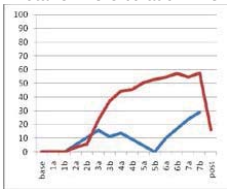
Ex-Smoker, Male, Age: 46, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**8**
Events over the treatment period:	Intake smoke & Alcohol **0** **0**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake 2	

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

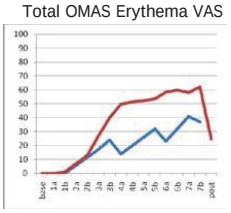
NCI



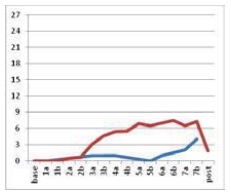
Total OMAS Ulceration VAS



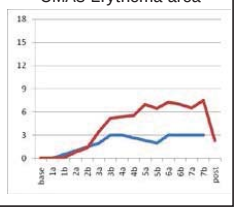
Total OMAS Erythema VAS



OMAS Ulceration area

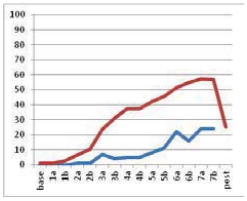


OMAS Erythema area

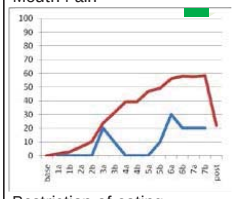


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

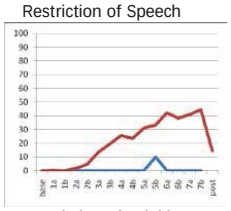


Mouth Pain

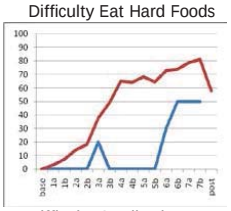


Difficulty Speaking

Restriction of Speech

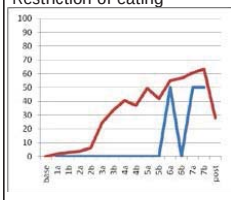


Difficulty Eat Hard Foods

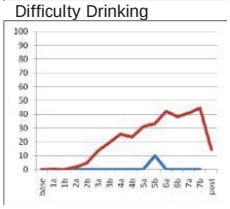


Difficulty Eat Soft Foods

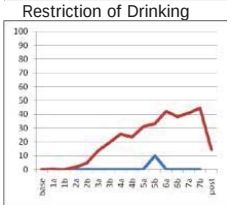
Restriction of eating



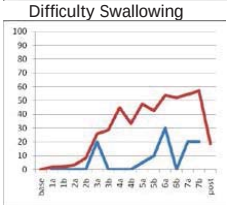
Difficulty Drinking



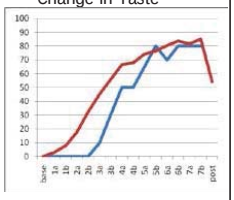
Restriction of Drinking



Difficulty Swallowing



Change in Taste

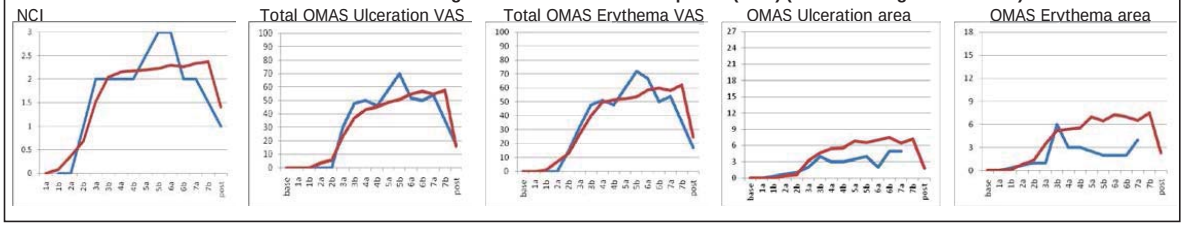


Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

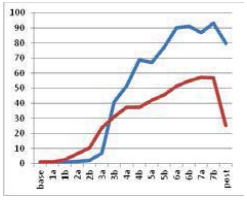
Ex-Smoker, Female, Age: 62, Caucasian		Cancer: Other T: 0 N: 0		Planned total Gray: 70 plus chemotherapy		9
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 22	0	1	9	10	

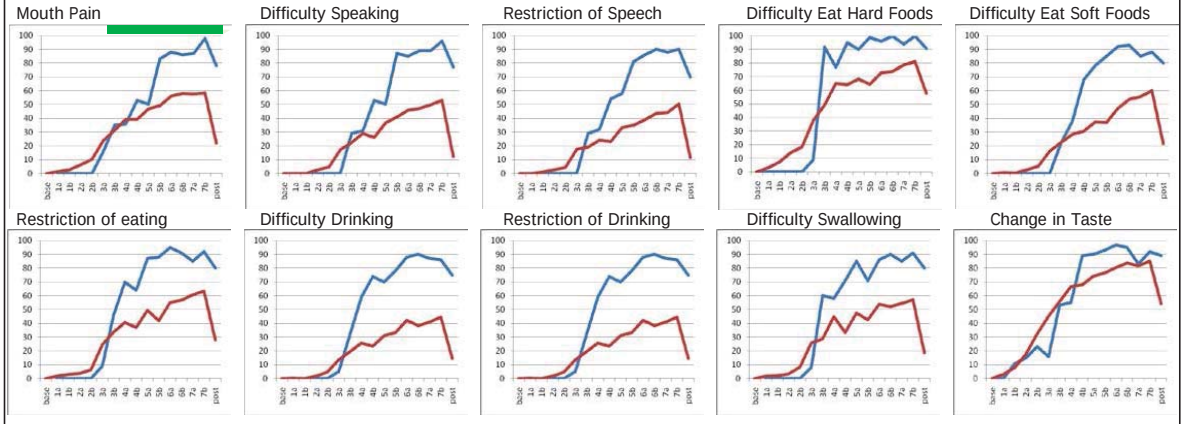
Clinical evaluation score throughout the cancer treatment period (Blue) (Cohort average score in red)



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

Aggregated (average) PROMS





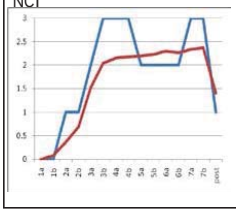
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

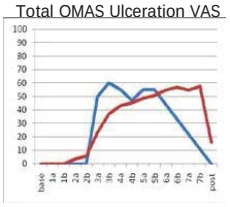
Ex-Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 2 N: 0**		**Planned total Gray: 66 plus chemotherapy**		**11**
Events over the treatment period:	Intake smoke & Alcohol **0** **21**	Cancer Tx breaks **1**	Hospital stays **9**	Eating support (days) **12**	# Opoid intake **10**	

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

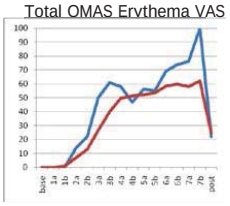
NCI



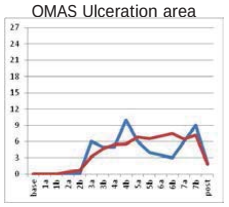
Total OMAS Ulceration VAS



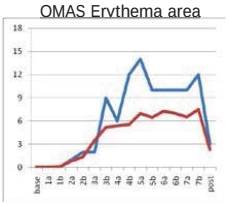
Total OMAS Erythema VAS



OMAS Ulceration area

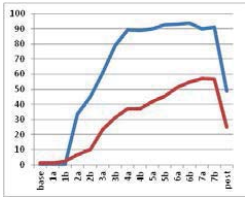


OMAS Erythema area

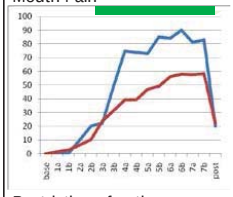


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

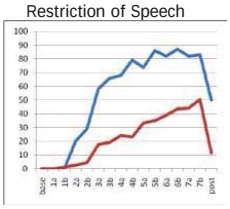


Mouth Pain



Difficulty Speaking

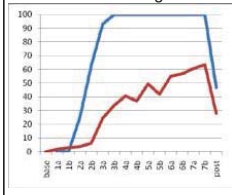
Restriction of Speech



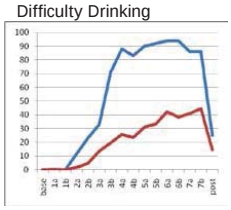
Difficulty Eat Hard Foods

Difficulty Eat Soft Foods

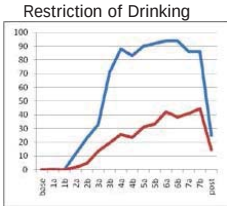
Restriction of eating



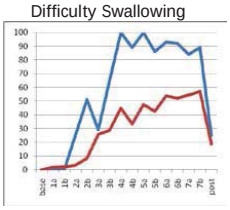
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

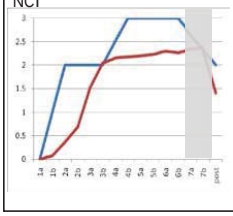
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

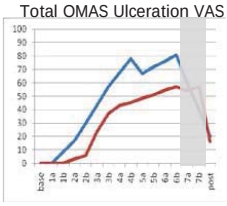
Never smoked, Male, Age: 65, Asian		Cancer: Oral Cavity T: 1 N: 0		Planned total Gray: 60		12
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	1	0	0	5	

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

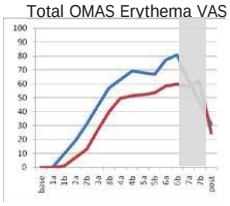
NCI



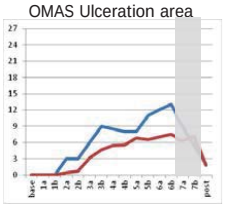
Total OMAS Ulceration VAS



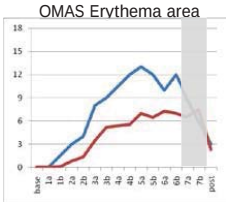
Total OMAS Erythema VAS



OMAS Ulceration area

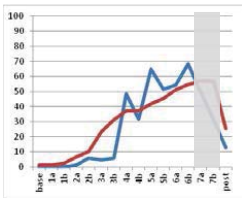


OMAS Erythema area

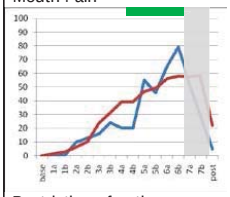


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

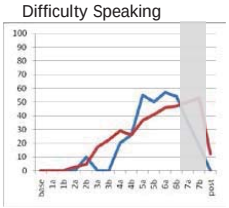
Aggregated (average) PROMS



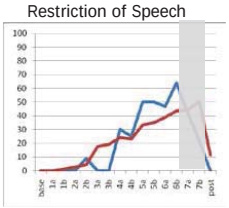
Mouth Pain



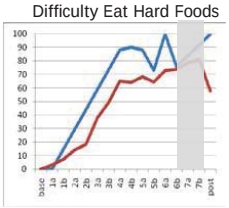
Difficulty Speaking



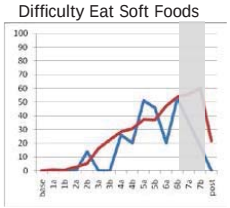
Restriction of Speech



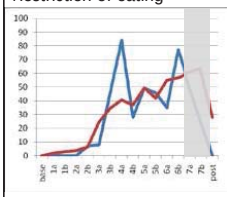
Difficulty Eat Hard Foods



Difficulty Eat Soft Foods



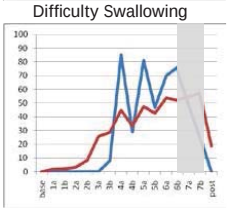
Restriction of eating



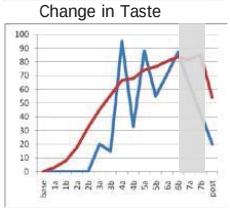
Difficulty Drinking

Restriction of Drinking

Difficulty Swallowing



Change in Taste



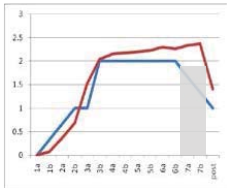
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

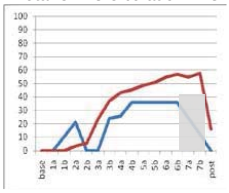
Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 2 N: 2**		**Planned total Gray: 70**		**15**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	18 **160**	**0**	**0**	**1**	**0**	

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

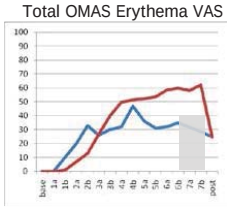
NCI



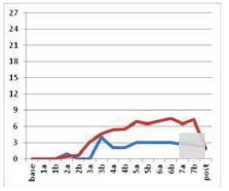
Total OMAS Ulceration VAS



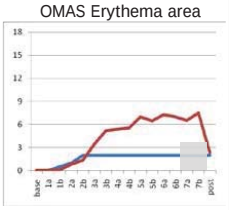
Total OMAS Erythema VAS



OMAS Ulceration area

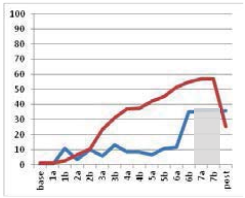


OMAS Erythema area

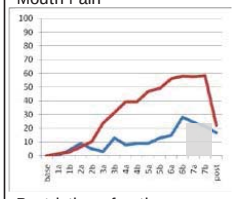


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in in red)

Aggregated (average) PROMS



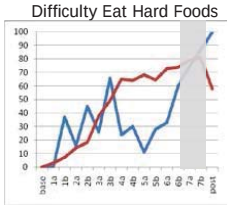
Mouth Pain



Difficulty Speaking

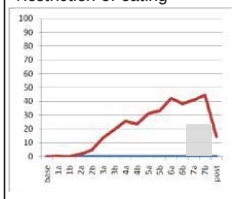
Restriction of Speech

Difficulty Eat Hard Foods



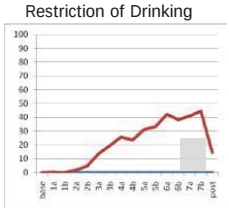
Difficulty Eat Soft Foods

Restriction of eating

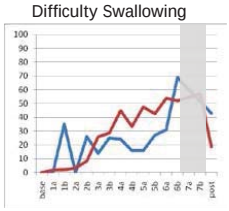


Difficulty Drinking

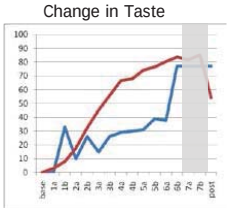
Restriction of Drinking



Difficulty Swallowing



Change in Taste



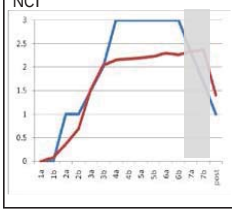
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

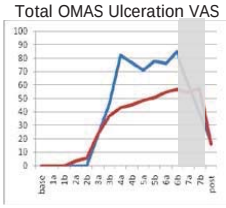
Smoking unknown, Male, Age: 60, Caucasian	**Cancer: Other T: 0 N: 2**			**Planned total Gray: 70**		**16**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0	**0**	**0**	**7**	**3**	

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

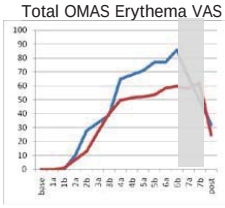
NCI



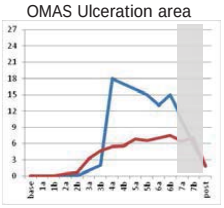
Total OMAS Ulceration VAS



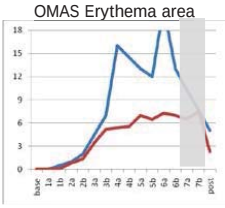
Total OMAS Erythema VAS



OMAS Ulceration area

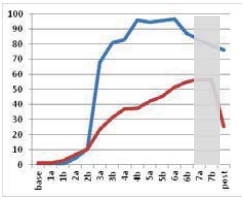


OMAS Erythema area

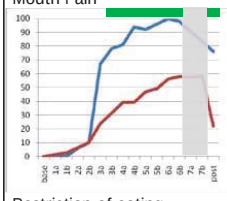


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

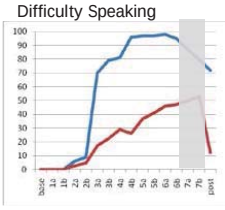
Aggregated (average) PROMS



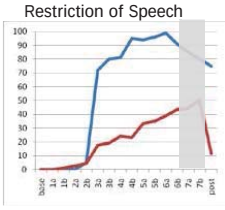
Mouth Pain



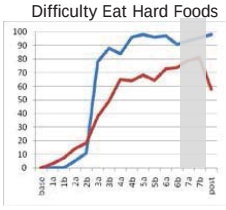
Difficulty Speaking



Restriction of Speech

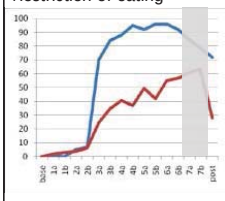


Difficulty Eat Hard Foods

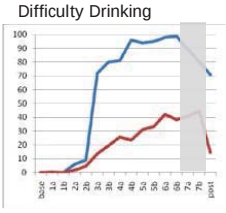


Difficulty Eat Soft Foods

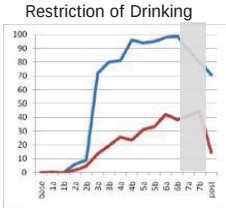
Restriction of eating



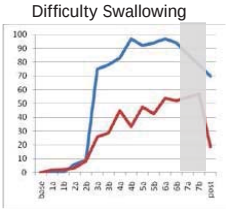
Difficulty Drinking



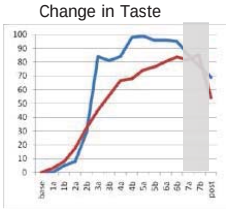
Restriction of Drinking



Difficulty Swallowing



Change in Taste



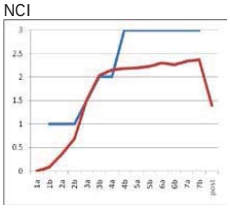
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

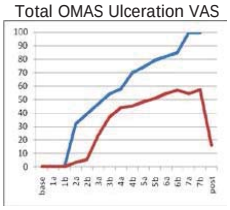
Never smoked, Female, Age: 80, Asian		**Cancer: Oral Cavity T: 2 N: 0**		**Planned total Gray: 70**		**19**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**11**	3	

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

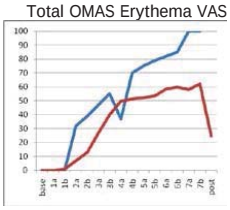
NCI



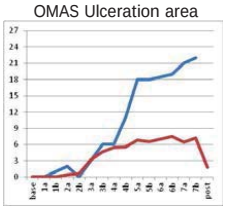
Total OMAS Ulceration VAS



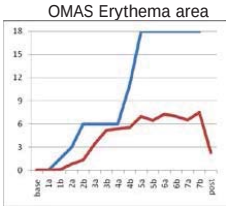
Total OMAS Erythema VAS



OMAS Ulceration area

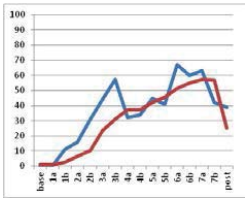


OMAS Erythema area



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

Aggregated (average) PROMS

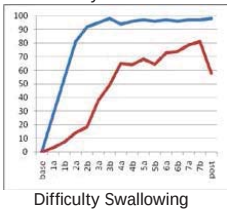


Mouth Pain

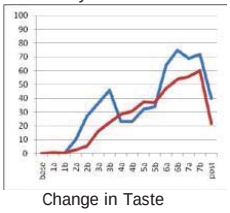
Difficulty Speaking

Restriction of Speech

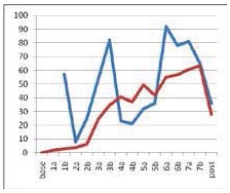
Difficulty Eat Hard Foods



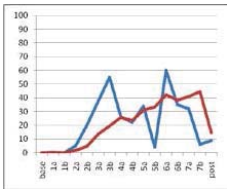
Difficulty Eat Soft Foods



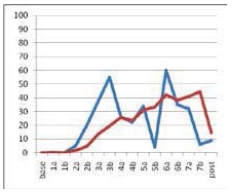
Restriction of eating



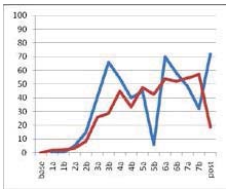
Difficulty Drinking



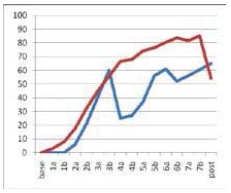
Restriction of Drinking



Difficulty Swallowing



Change in Taste



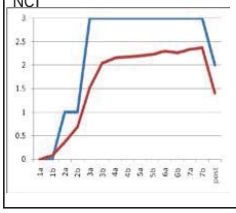
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

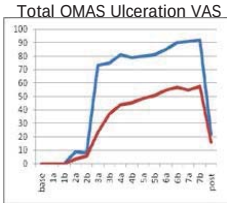
Smoker, Male, Age: 61, Caucasian		Cancer: Oral Cavity T: 3 N: 2		Planned total Gray: 66		21
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	127 184	0	0	0	14	

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

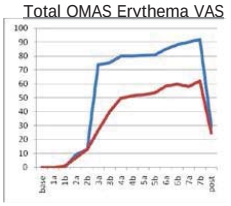
NCI



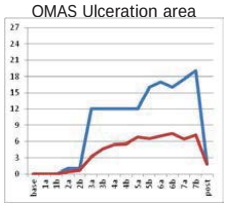
Total OMAS Ulceration VAS



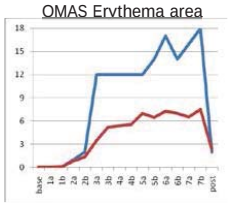
Total OMAS Erythema VAS



OMAS Ulceration area

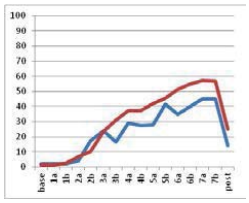


OMAS Erythema area

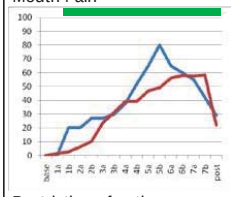


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

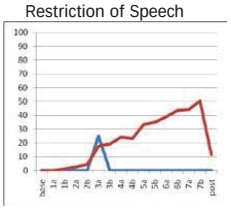


Mouth Pain

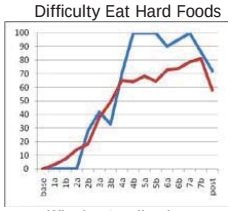


Difficulty Speaking

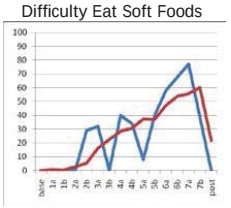
Restriction of Speech



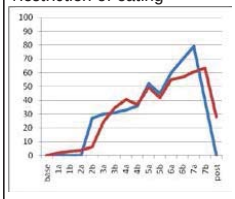
Difficulty Eat Hard Foods



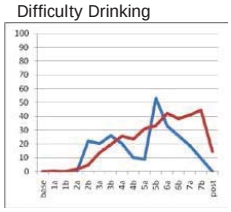
Difficulty Eat Soft Foods



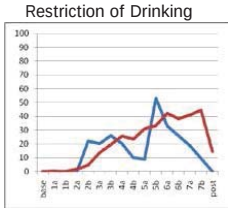
Restriction of eating



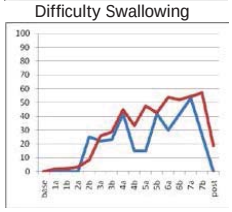
Difficulty Drinking



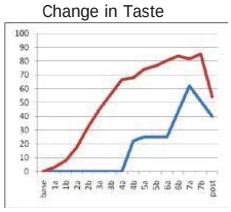
Restriction of Drinking



Difficulty Swallowing



Change in Taste



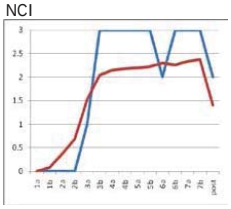
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

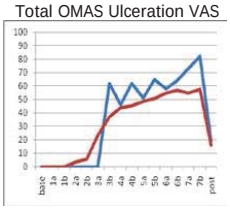
Ex-Smoker, Male, Age: 69, Caucasian		Cancer: Oropharynx T: 3 N: 0		Planned total Gray: 70		22
Events over the treatment period:	Intake smoke & Alcohol: 0	Cancer Tx breaks: 0	Hospital stays: 0	Eating support (days): 0	# Opoid intake: 11	

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

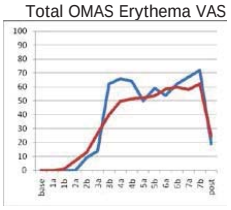
NCI



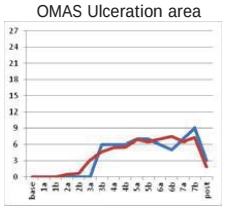
Total OMAS Ulceration VAS



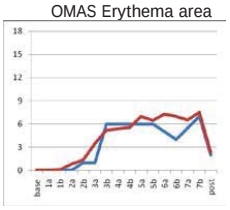
Total OMAS Erythema VAS



OMAS Ulceration area

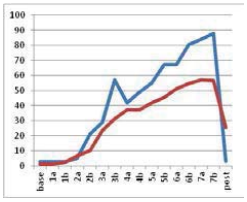


OMAS Erythema area

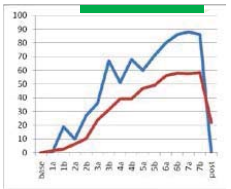


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

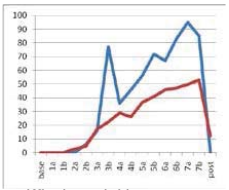
Aggregated (average) PROMS



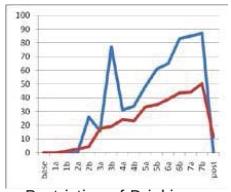
Mouth Pain



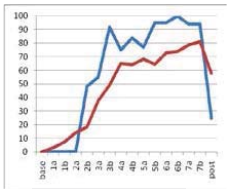
Difficulty Speaking



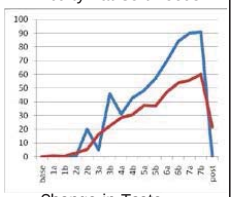
Restriction of Speech



Difficulty Eat Hard Foods

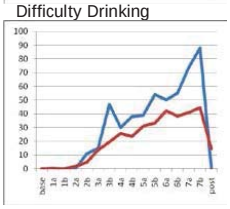


Difficulty Eat Soft Foods

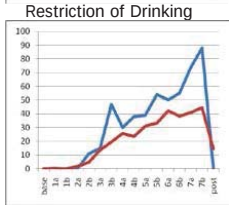


Restriction of eating

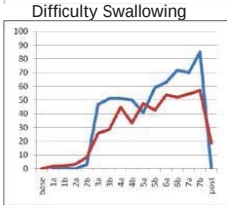
Difficulty Drinking



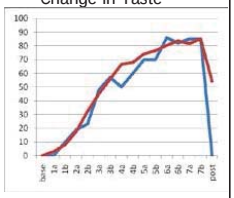
Restriction of Drinking



Difficulty Swallowing



Change in Taste



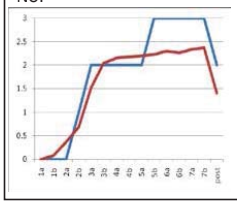
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

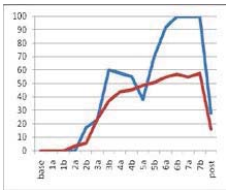
Never smoked, Male, Age: 69, Caucasian		Cancer: Oral cavity T: 4 N: 0		Planned total Gray: 66		**Pt. B**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	0 **29**	**0**	**0**	**0**	**9**	

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

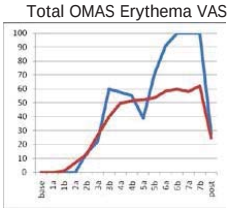
NCI



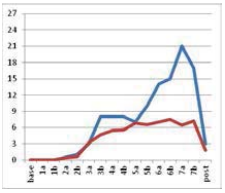
Total OMAS Ulceration VAS



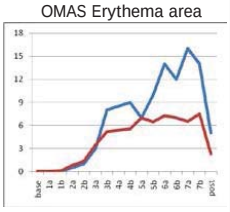
Total OMAS Erythema VAS



OMAS Ulceration area

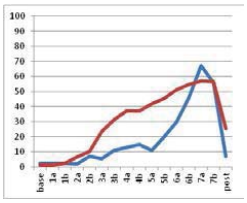


OMAS Erythema area

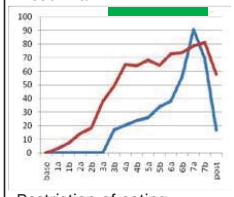


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

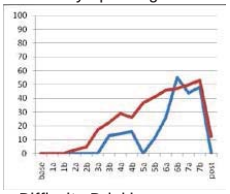
Aggregated (average) PROMS



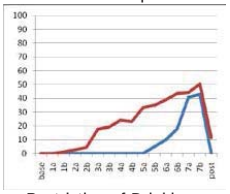
Mouth Pain



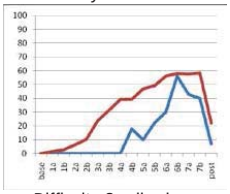
Difficulty Speaking



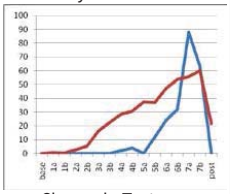
Restriction of Speech



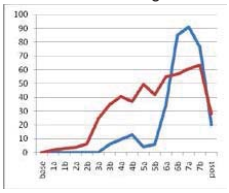
Difficulty Eat Hard Foods



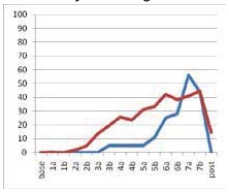
Difficulty Eat Soft Foods



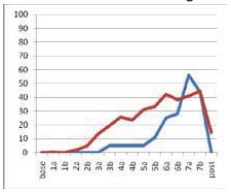
Restriction of eating



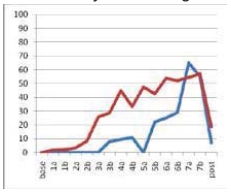
Difficulty Drinking



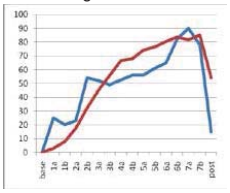
Restriction of Drinking



Difficulty Swallowing



Change in Taste



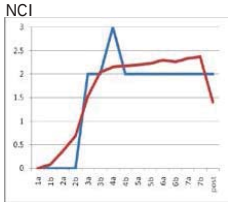
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

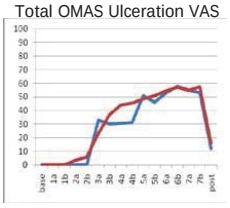
Ex-Smoker, Female, Age: 63, Caucasian		Cancer: Salivary T: 3 N: 0		Planned total Gray: 66		24
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	1	0	0	12	

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

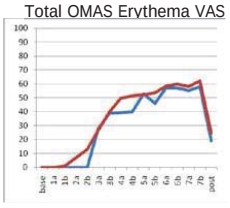
NCI



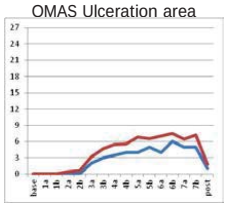
Total OMAS Ulceration VAS



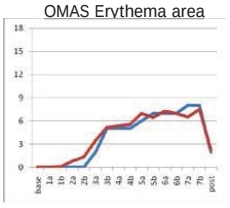
Total OMAS Erythema VAS



OMAS Ulceration area

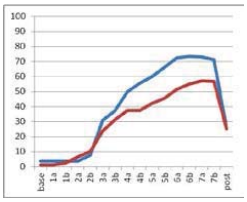


OMAS Erythema area



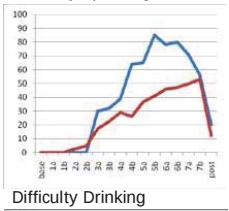
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS



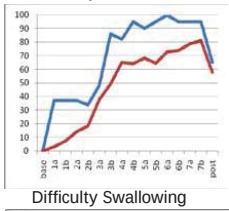
Mouth Pain

Difficulty Speaking

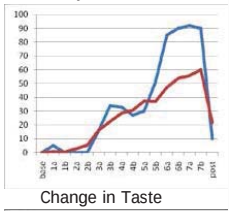


Restriction of Speech

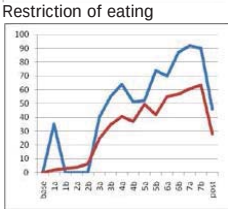
Difficulty Eat Hard Foods



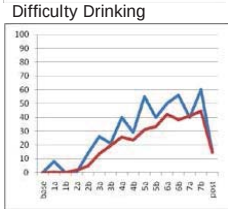
Difficulty Eat Soft Foods



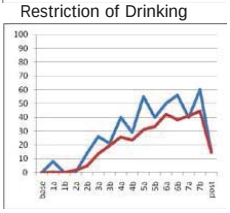
Restriction of eating



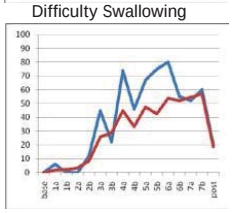
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

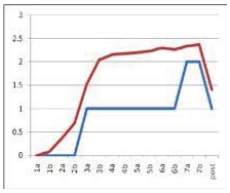
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

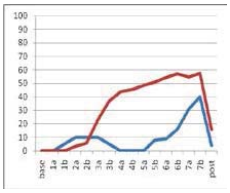
Smoker, Female, Age: 69, Caucasian		**Cancer: Oropharynx T: 0 N: 0**		**Planned total Gray: 66**		**Pt. A**
Events over the treatment period:	Intake smoke & Alcohol **60** **72**	Cancer Tx breaks **1**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake **0**	

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

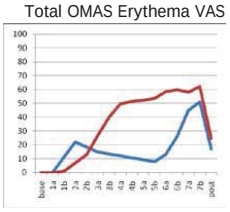
NCI



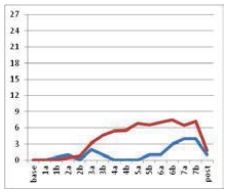
Total OMAS Ulceration VAS



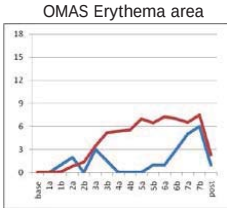
Total OMAS Erythema VAS



OMAS Ulceration area

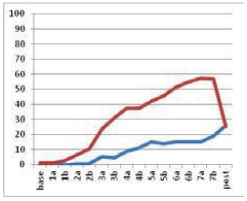


OMAS Erythema area

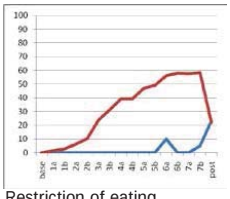


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

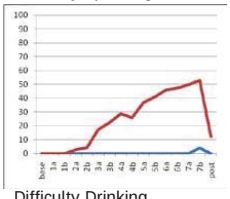
Aggregated (average) PROMS



Mouth Pain

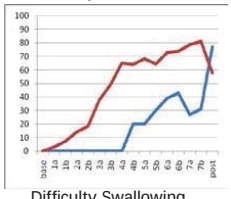


Difficulty Speaking

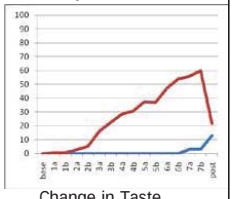


Restriction of Speech

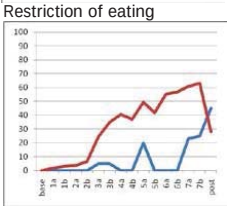
Difficulty Eat Hard Foods



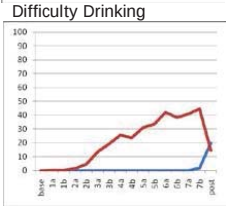
Difficulty Eat Soft Foods



Restriction of eating

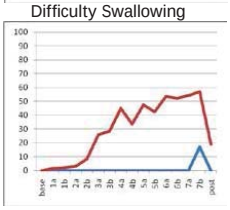


Difficulty Drinking

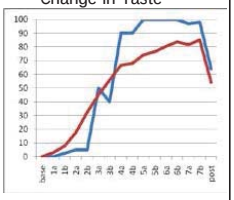


Restriction of Drinking

Difficulty Swallowing



Change in Taste



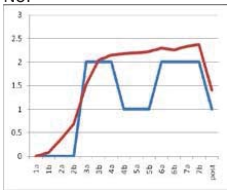
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

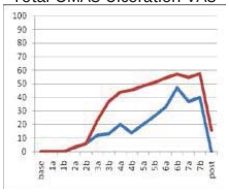
Never smoked, Male, Age: 42, Caucasian		**Cancer: Salivary T: 4 N: 0**		**Planned total Gray: 66**		**26**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**4**	**0**	**0**	**5**	

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

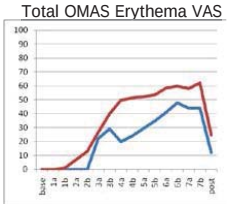
NCI



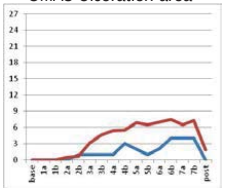
Total OMAS Ulceration VAS



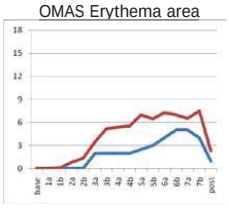
Total OMAS Erythema VAS



OMAS Ulceration area

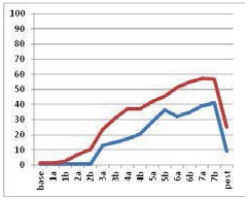


OMAS Erythema area

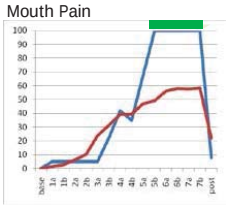


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

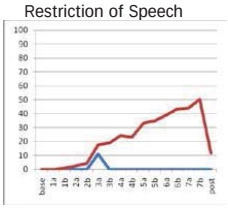


Mouth Pain

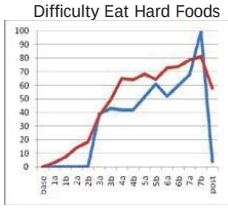


Difficulty Speaking

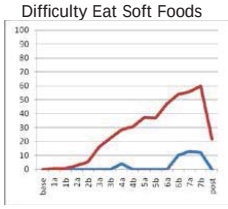
Restriction of Speech



Difficulty Eat Hard Foods

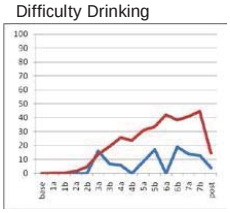


Difficulty Eat Soft Foods

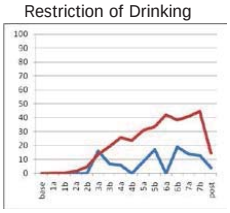


Restriction of eating

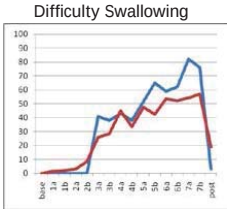
Difficulty Drinking



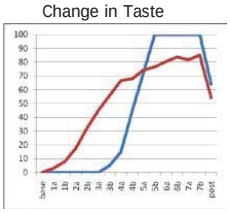
Restriction of Drinking



Difficulty Swallowing



Change in Taste



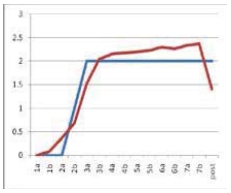
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

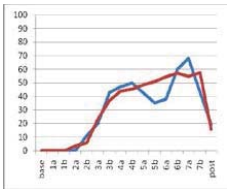
Never smoked, Male, Age: 45, Caucasian		**Cancer: Oropharynx T: 2 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**27**
Events over the treatment period:	Intake smoke & Alcohol **0** **2**	Cancer Tx breaks **0**	Hospital stays **1**	Eating support (days) **0**	# Opoid intake **0**	

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

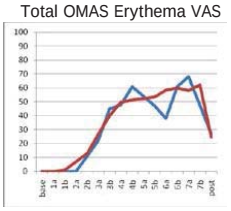
NCI



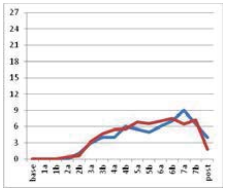
Total OMAS Ulceration VAS



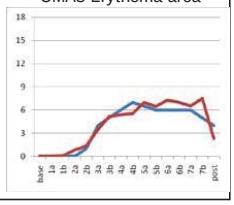
Total OMAS Erythema VAS



OMAS Ulceration area

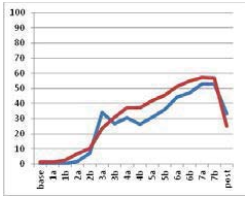


OMAS Erythema area

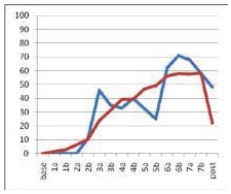


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

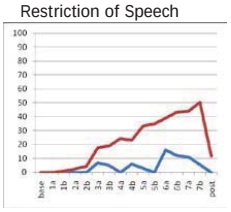


Mouth Pain

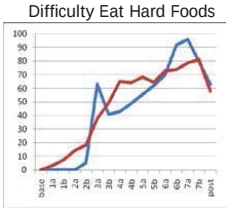


Difficulty Speaking

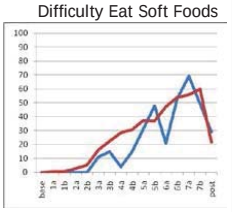
Restriction of Speech



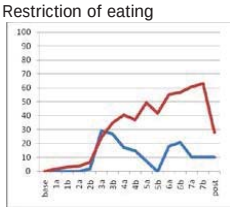
Difficulty Eat Hard Foods



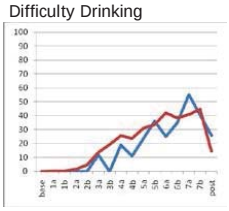
Difficulty Eat Soft Foods



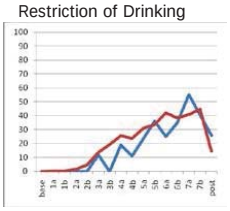
Restriction of eating



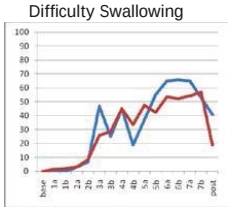
Difficulty Drinking



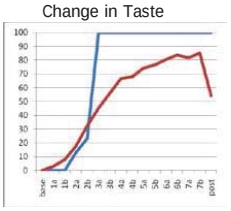
Restriction of Drinking



Difficulty Swallowing



Change in Taste



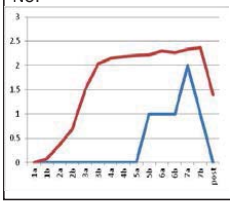
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

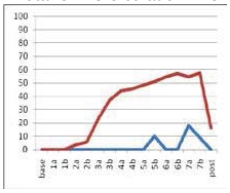
Ex-Smoker, Male, Age: 49, Black		Cancer: Other T: 2 N: 1		Planned total Gray: 70 plus chemotherapy		29
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	3	0	

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

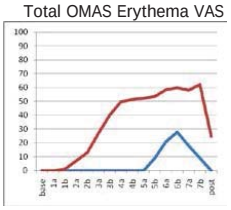
NCI



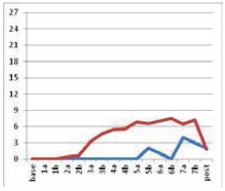
Total OMAS Ulceration VAS



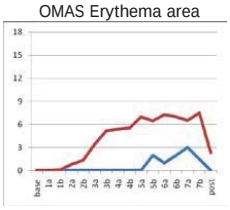
Total OMAS Erythema VAS



OMAS Ulceration area

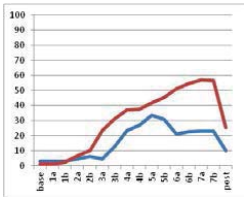


OMAS Erythema area

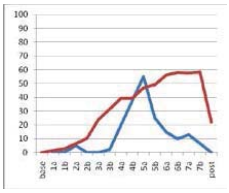


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

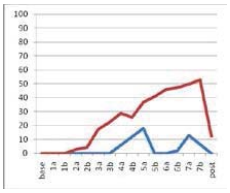
Aggregated (average) PROMS



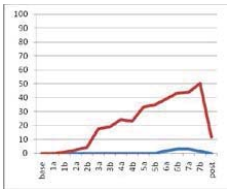
Mouth Pain



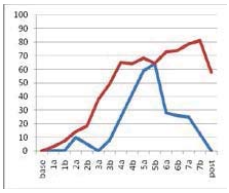
Difficulty Speaking



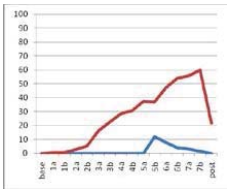
Restriction of Speech



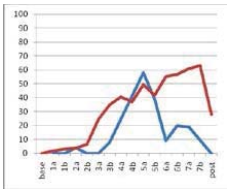
Difficulty Eat Hard Foods



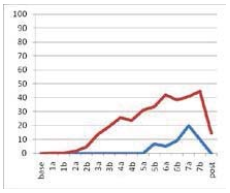
Difficulty Eat Soft Foods



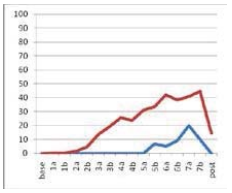
Restriction of eating



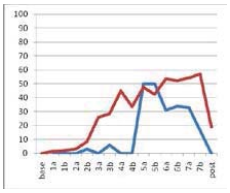
Difficulty Drinking



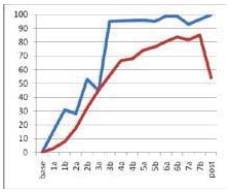
Restriction of Drinking



Difficulty Swallowing



Change in Taste



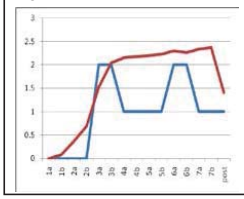
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

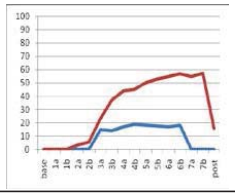
Ex-Smoker, Male, Age: 77, Caucasian		**Cancer: Salivary T: 3 N: 0**		**Planned total Gray: 69**		**35**
Events over the treatment period:	Intake smoke & Alcohol **0** **4**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **0**	# Opoid intake **0**	

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

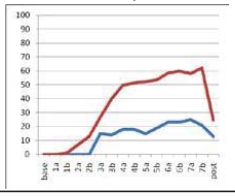
NCI



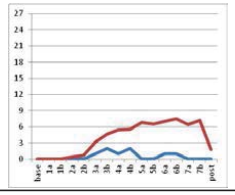
Total OMAS Ulceration VAS



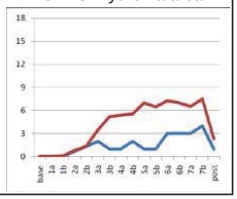
Total OMAS Erythema VAS



OMAS Ulceration area

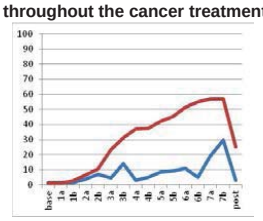


OMAS Erythema area

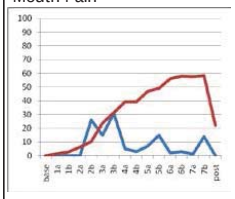


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

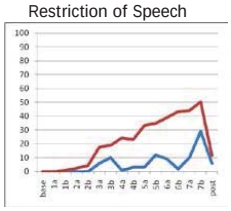


Mouth Pain

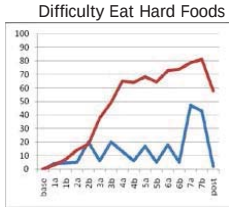


Difficulty Speaking

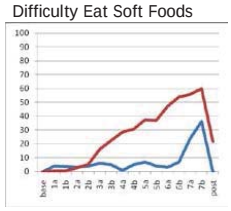
Restriction of Speech



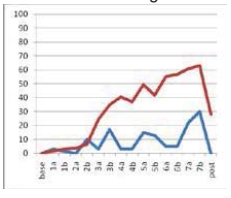
Difficulty Eat Hard Foods



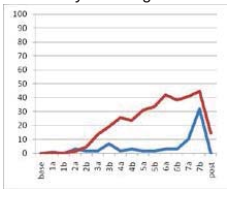
Difficulty Eat Soft Foods



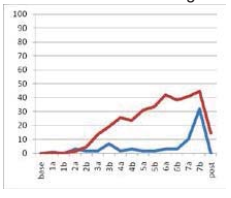
Restriction of eating



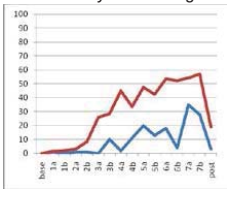
Difficulty Drinking



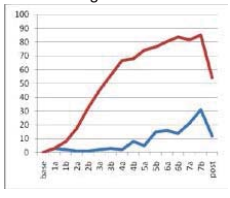
Restriction of Drinking



Difficulty Swallowing



Change in Taste



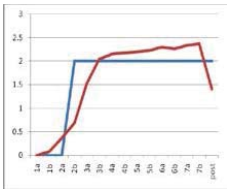
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

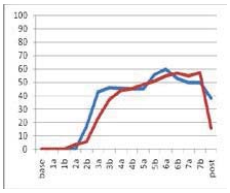
Ex-Smoker, Female, Age: 63, Caucasian		**Cancer: Oropharynx T: 3 N: 1**		**Planned total Gray: 70 plus chemotherapy**		**36**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**1**	**16**	**4**	**10**	

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

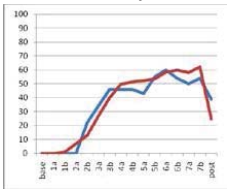
NCI



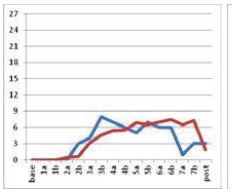
Total OMAS Ulceration VAS



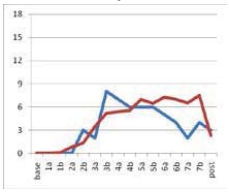
Total OMAS Erythema VAS



OMAS Ulceration area

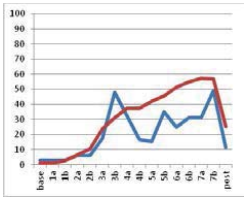


OMAS Erythema area

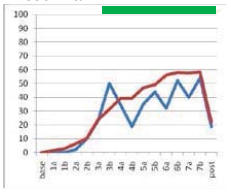


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

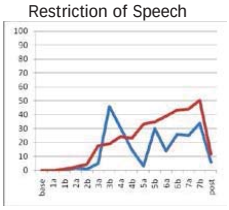


Mouth Pain

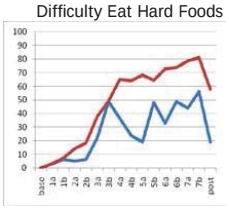


Difficulty Speaking

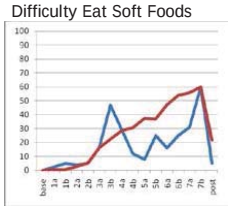
Restriction of Speech



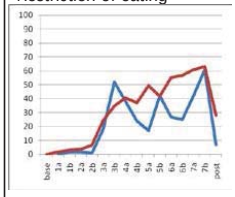
Difficulty Eat Hard Foods



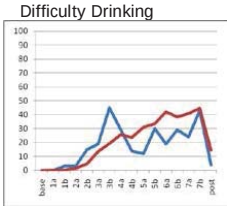
Difficulty Eat Soft Foods



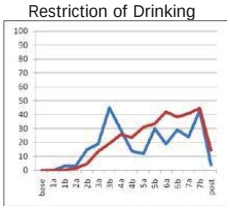
Restriction of eating



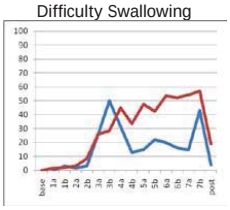
Difficulty Drinking



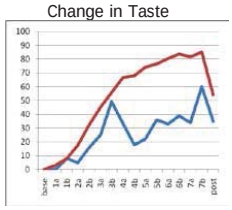
Restriction of Drinking



Difficulty Swallowing



Change in Taste



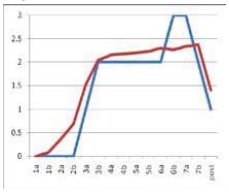
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

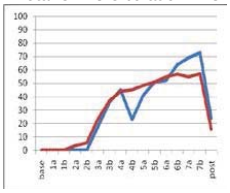
Ex-Smoker, Male, Age: 60, Asian		Cancer: Oral Cavity T: 0 N: 1		Planned total Gray: 66 plus chemotherapy		38
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	1	8	10	

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

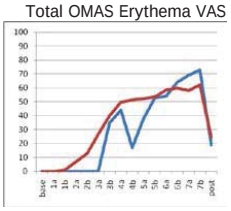
NCI



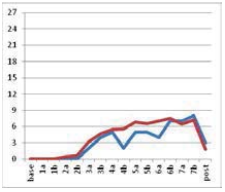
Total OMAS Ulceration VAS



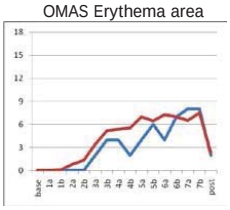
Total OMAS Erythema VAS



OMAS Ulceration area

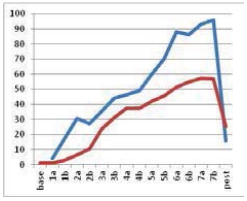


OMAS Erythema area

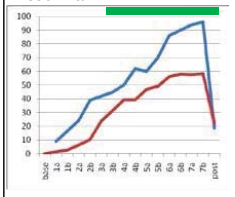


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

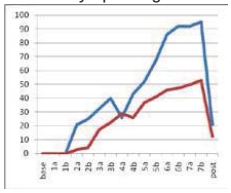
Aggregated (average) PROMS



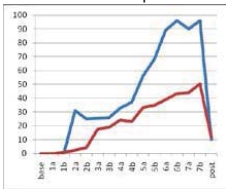
Mouth Pain



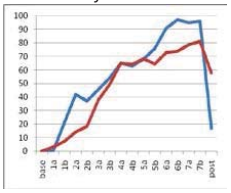
Difficulty Speaking



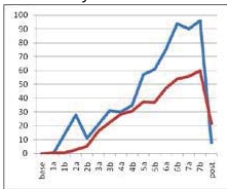
Restriction of Speech



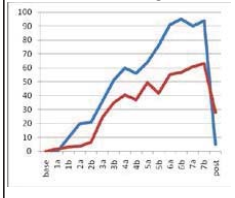
Difficulty Eat Hard Foods



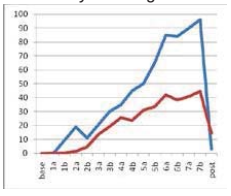
Difficulty Eat Soft Foods



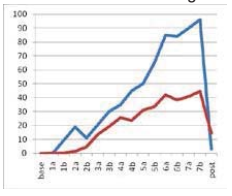
Restriction of eating



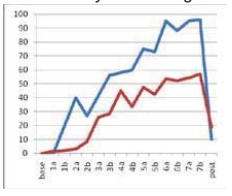
Difficulty Drinking



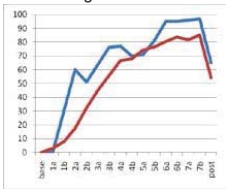
Restriction of Drinking



Difficulty Swallowing



Change in Taste



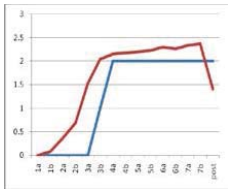
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

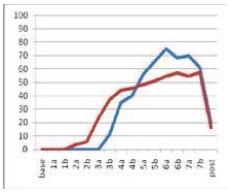
Never smoked, Male, Age: 77, Caucasian		**Cancer: Other T: 2 N: 1**		**Planned total Gray: 70**		**39**
Events over the treatment period:	Intake smoke & Alcohol **0** **0**	Cancer Tx breaks **0**	Hospital stays **0**	Eating support (days) **14**	# Opoid intake 6	

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

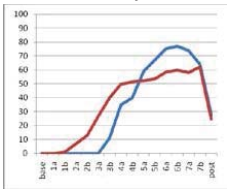
NCI



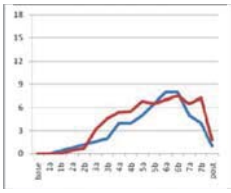
Total OMAS Ulceration VAS



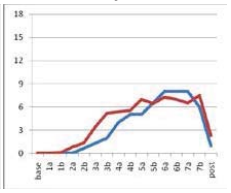
Total OMAS Erythema VAS



OMAS Ulceration area

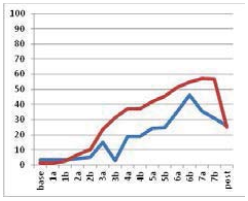


OMAS Erythema area

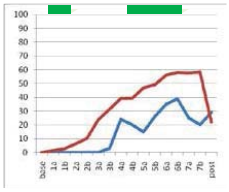


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

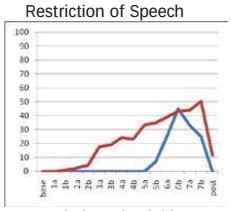


Mouth Pain



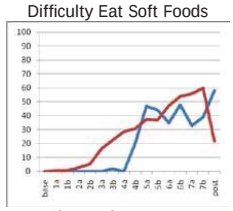
Difficulty Speaking

Restriction of Speech

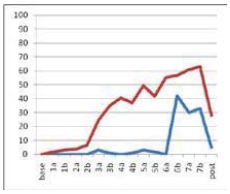


Difficulty Eat Hard Foods

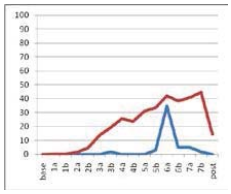
Difficulty Eat Soft Foods



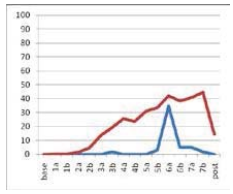
Restriction of eating



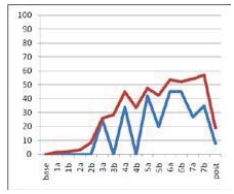
Difficulty Drinking



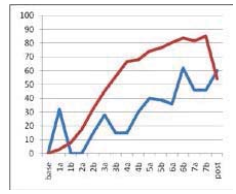
Restriction of Drinking



Difficulty Swallowing



Change in Taste



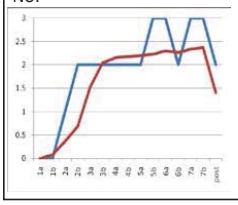
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

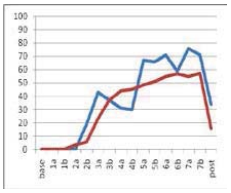
Ex-Smoker, Male, Age: 65, Caucasian		Cancer: Other T: 0 N: 2		Planned total Gray: 70 plus chemotherapy		40
Events over the treatment period:	Intake smoke & Alcohol 0 6	Cancer Tx breaks 0	Hospital stays 4	Eating support (days) 9	# Opoid intake 11	

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

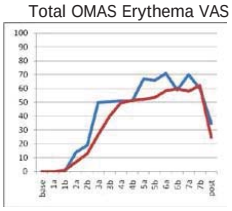
NCI



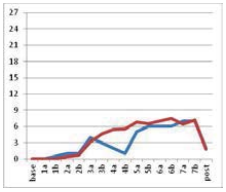
Total OMAS Ulceration VAS



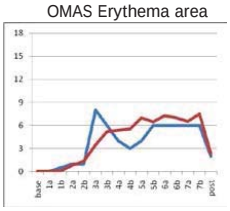
Total OMAS Erythema VAS



OMAS Ulceration area

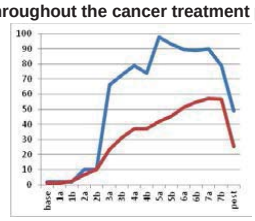


OMAS Erythema area

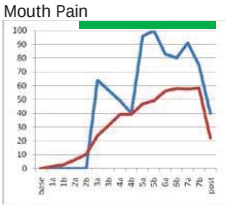


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

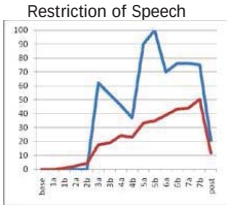


Mouth Pain

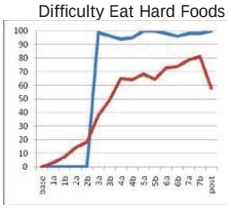


Difficulty Speaking

Restriction of Speech

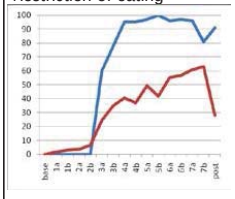


Difficulty Eat Hard Foods

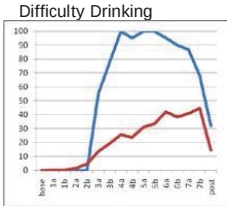


Difficulty Eat Soft Foods

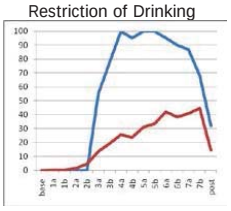
Restriction of eating



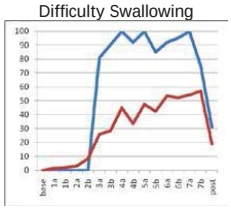
Difficulty Drinking



Restriction of Drinking



Difficulty Swallowing



Change in Taste

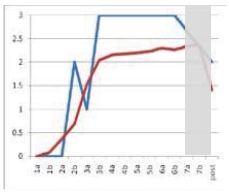
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

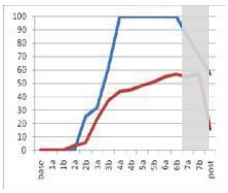
Never smoked, Male, Age: 50, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**Pt. C**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**0**	**0**	

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

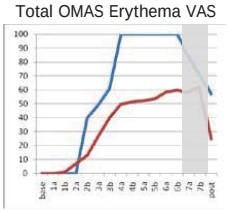
NCI



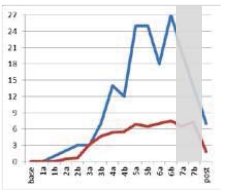
Total OMAS Ulceration VAS



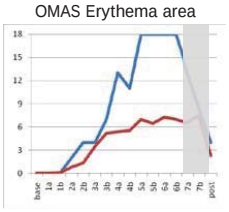
Total OMAS Erythema VAS



OMAS Ulceration area

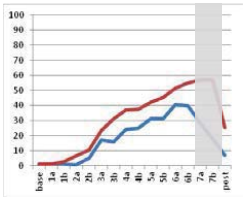


OMAS Erythema area

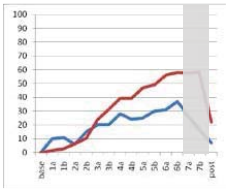


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

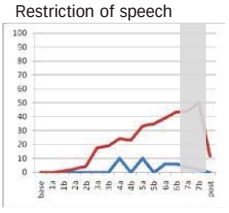


Mouth Pain

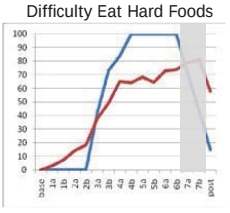


Difficulty Speaking

Restriction of speech

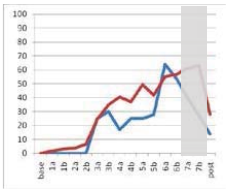


Difficulty Eat Hard Foods

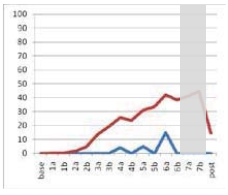


Difficulty Eat Soft Foods

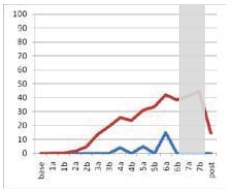
Restriction of eating



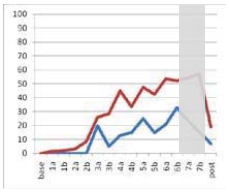
Difficulty Drinking



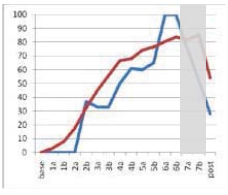
Restriction of Drinking



Difficulty Swallowing



Change in Taste



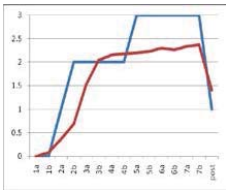
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

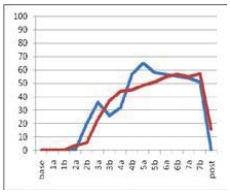
Ex-Smoker, Male, Age: 62, Asian		Cancer: Other T: 3 N: 1		Planned total Gray: 70 plus chemotherapy		43
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 0	0	0	8	3	

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

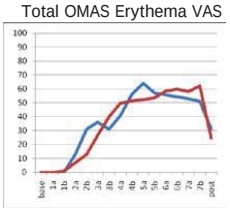
NCI



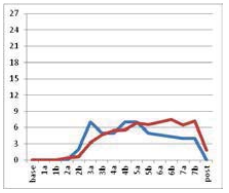
Total OMAS Ulceration VAS



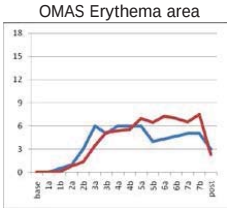
Total OMAS Erythema VAS



OMAS Ulceration area

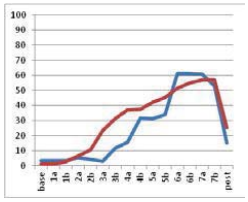


OMAS Erythema area



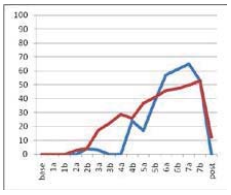
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

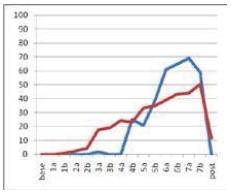


Mouth Pain

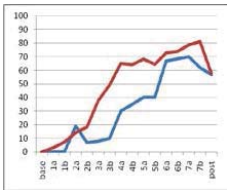
Difficulty Speaking



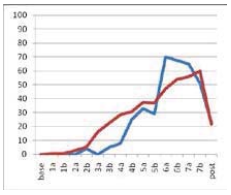
Restriction of Speech



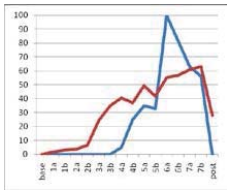
Difficulty Eat Hard Foods



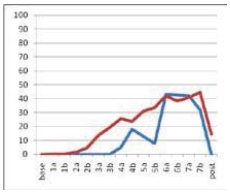
Difficulty Eat Soft Foods



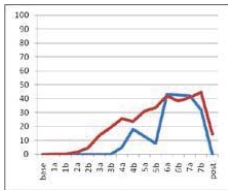
Restriction of eating



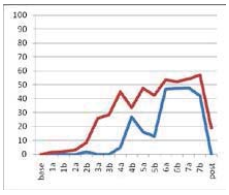
Difficulty Drinking



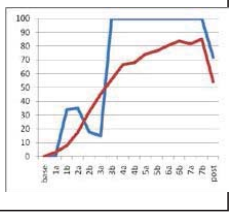
Restriction of Drinking



Difficulty Swallowing



Change in Taste



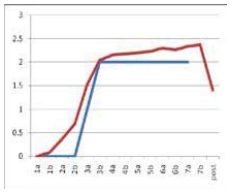
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

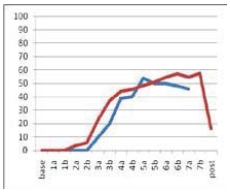
Ex-Smoker, Male, Age: 63, Caucasian		Cancer: Other T: 4 N: 0		Planned total Gray: 66		44
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support	# Opoid intake	
	0 0	0	0	0	10	

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

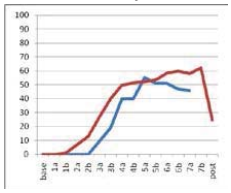
NCI



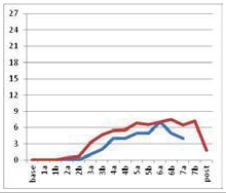
Total OMAS Ulceration VAS



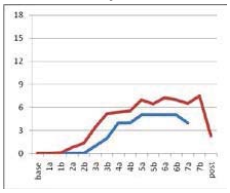
Total OMAS Erythema VAS



OMAS Ulceration area

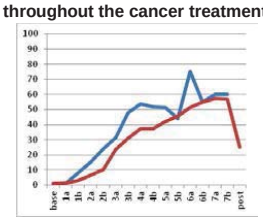


OMAS Erythema area



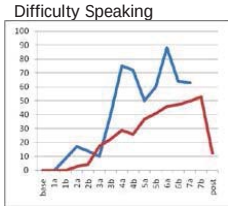
Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

Aggregated (average) PROMS

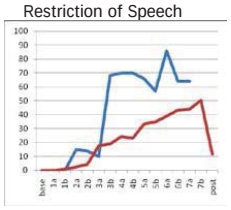


Mouth Pain

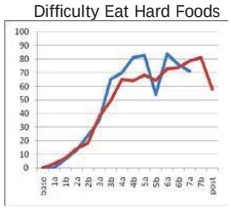
Difficulty Speaking



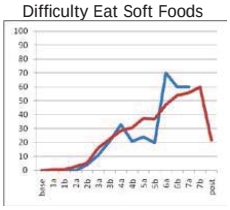
Restriction of Speech



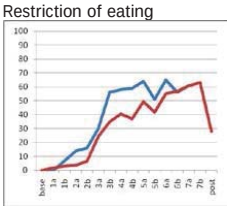
Difficulty Eat Hard Foods



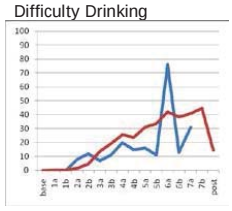
Difficulty Eat Soft Foods



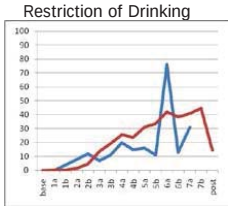
Restriction of eating



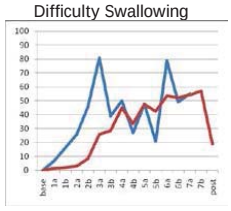
Difficulty Drinking



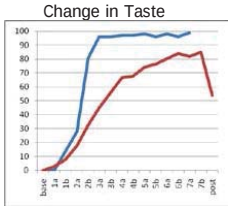
Restriction of Drinking



Difficulty Swallowing



Change in Taste



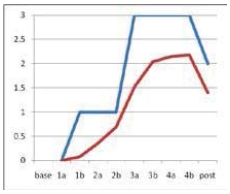
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

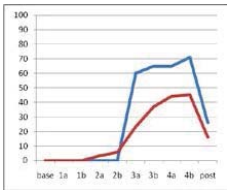
Never smoked, Male, Age: 56, Caucasian		**Cancer: Oropharynx T: 1 N: 2**		**Planned total Gray: 64**		**45**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**5**	6	

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

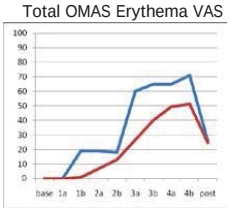
NCI



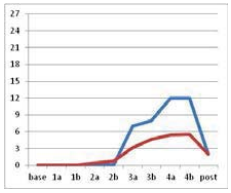
Total OMAS Ulceration VAS



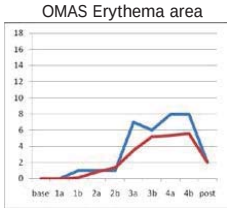
Total OMAS Erythema VAS



OMAS Ulceration area

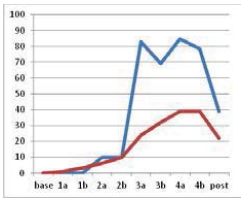


OMAS Erythema area

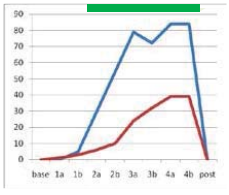


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

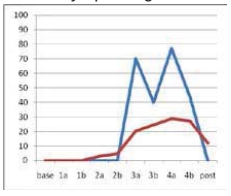
Aggregated (average) PROMS



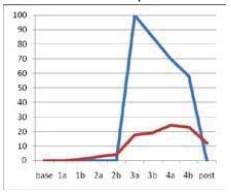
Mouth Pain



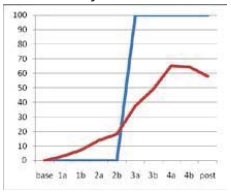
Difficulty Speaking



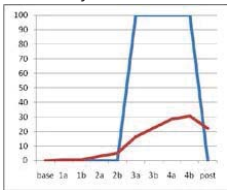
Restriction of Speech



Difficulty Eat Hard Foods



Difficulty Eat Soft Foods

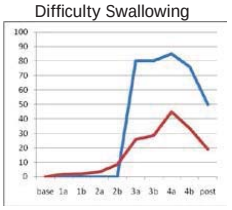


Restriction of eating

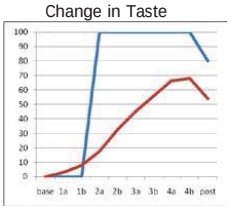
Difficulty Drinking

Restriction of Drinking

Difficulty Swallowing



Change in Taste



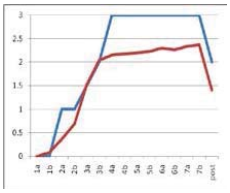
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

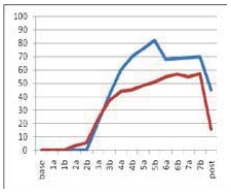
Ex-Smoker, Male, Age: 48, Caucasian		Cancer: Oropharynx T: 2 N: 3		Planned total Gray: 70 plus chemotherapy		47
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**1**	**6**	**3**	

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

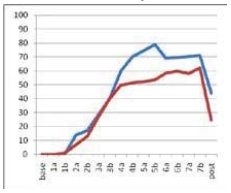
NCI



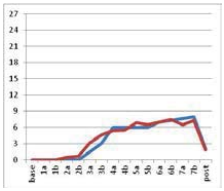
Total OMAS Ulceration VAS



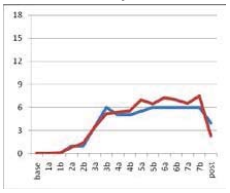
Total OMAS Erythema VAS



OMAS Ulceration area

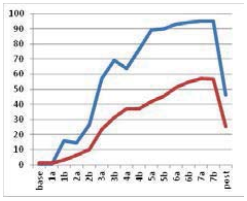


OMAS Erythema area

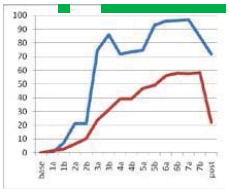


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

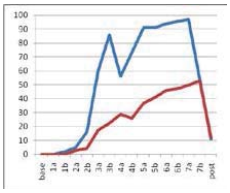
Aggregated (average) PROMS



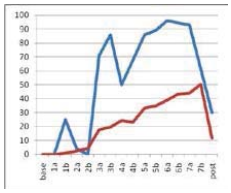
Mouth Pain



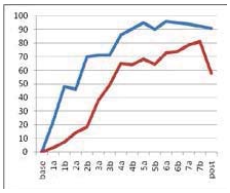
Difficulty Speaking



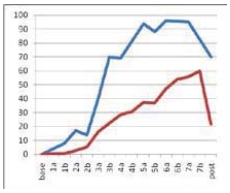
Restriction of Speech



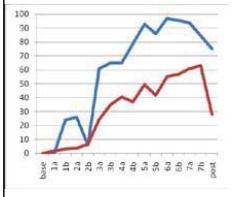
Difficulty Eat Hard Foods



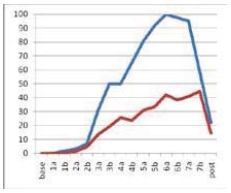
Difficulty Eat Soft Foods



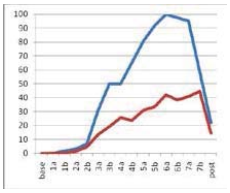
Restriction of eating



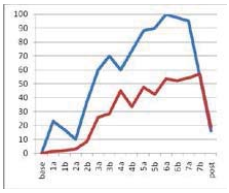
Difficulty Drinking



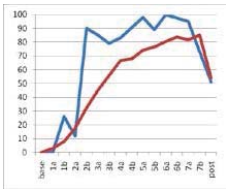
Restriction of Drinking



Difficulty Swallowing



Change in Taste



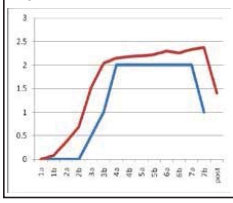
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

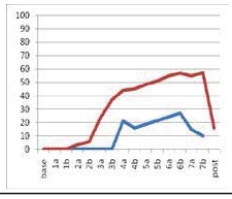
Never smoked, Female, Age: 64, Caucasian		**Cancer: Salivary T: 2 N: 0**		**Planned total Gray: 66**		**48**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**0**	6	

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

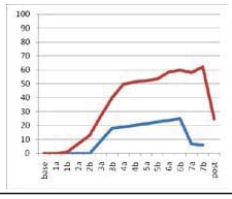
NCI



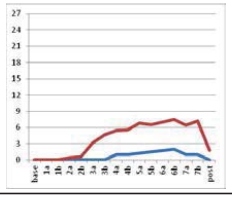
Total OMAS Ulceration VAS



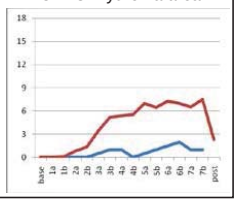
Total OMAS Erythema VAS



OMAS Ulceration area

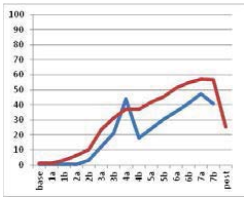


OMAS Erythema area

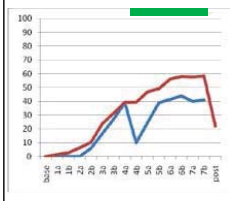


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

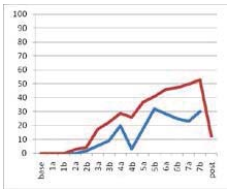
Aggregated (average) PROMS



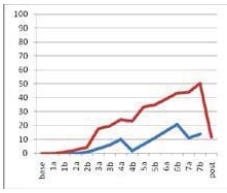
Mouth Pain



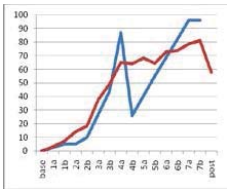
Difficulty Speaking



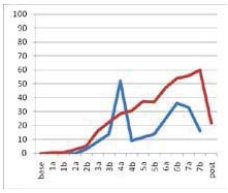
Restriction of Speech



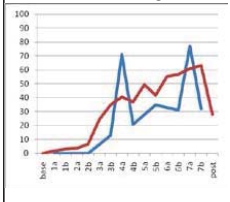
Difficulty Eat Hard Foods



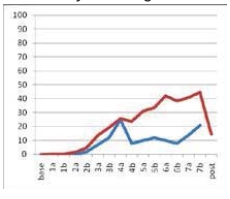
Difficulty Eat Soft Foods



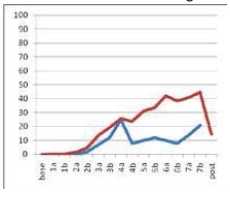
Restriction of eating



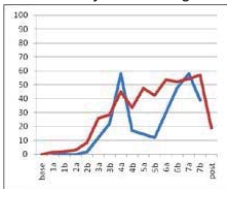
Difficulty Drinking



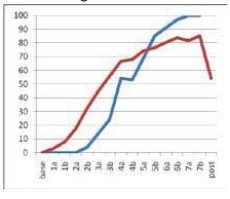
Restriction of Drinking



Difficulty Swallowing



Change in Taste



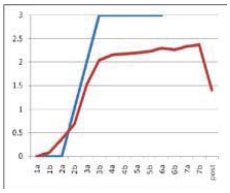
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

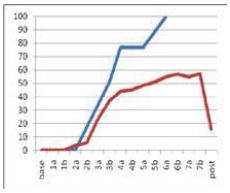
Smoker, Male, Age: 66, Caucasian		**Cancer: Oropharynx T: 4 N: 0**		**Planned total Gray: 70 plus chemotherapy**		**49**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	145 **0**	**0**	**0**	**2**	**2**	

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

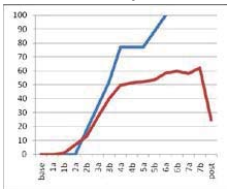
NCI



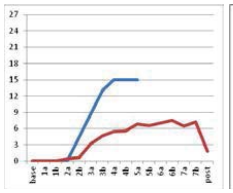
Total OMAS Ulceration VAS



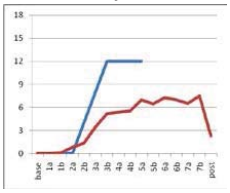
Total OMAS Erythema VAS



OMAS Ulceration area

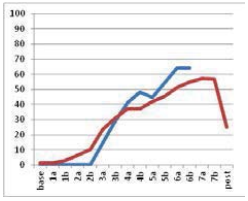


OMAS Erythema area

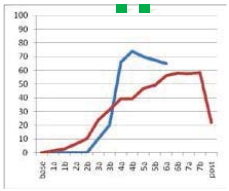


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

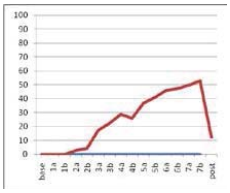
Aggregated (average) PROMS



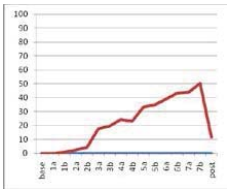
Mouth Pain



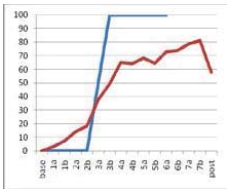
Difficulty Speaking



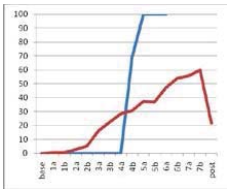
Restriction of Speech



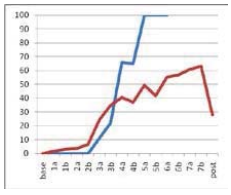
Difficulty Eat Hard Foods



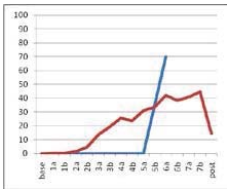
Difficulty Eat Soft Foods



Restriction of eating



Difficulty Drinking



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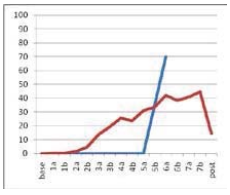
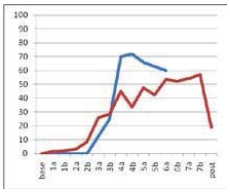
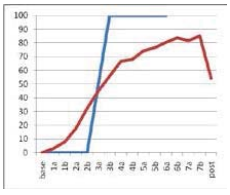


Difficulty Swallowing



Change in Taste



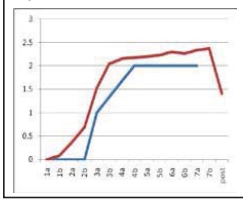
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

	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

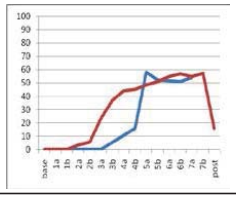
Ex-Smoker, Male, Age: 49, Caucasian		**Cancer: Oropharynx T: 4 N: 2**		**Planned total Gray: 70 plus chemotherapy**		**50**
Events over the treatment period:	Intake smoke & Alcohol	Cancer Tx breaks	Hospital stays	Eating support (days)	# Opoid intake	
	0 **0**	**0**	**0**	**4**	**10**	

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

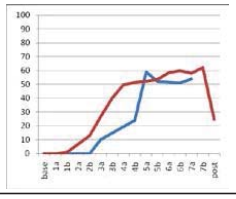
NCI



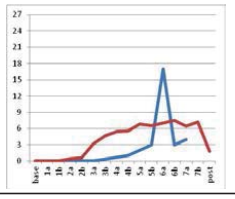
Total OMAS Ulceration VAS



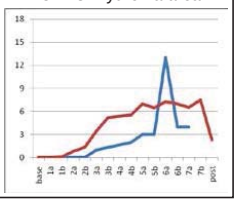
Total OMAS Erythema VAS



OMAS Ulceration area

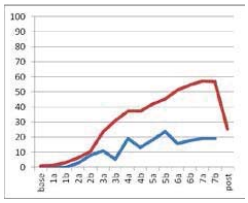


OMAS Erythema area

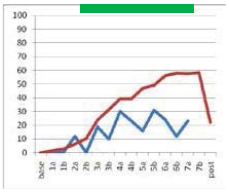


Patient-reported PROMS-questionnaire VAS values throughout the cancer treatment period (Blue) (Cohort average value in red)

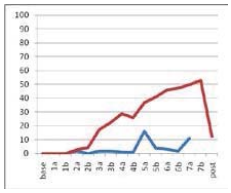
Aggregated (average) PROMS



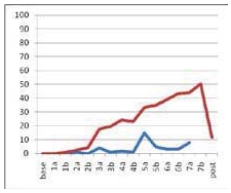
Mouth Pain



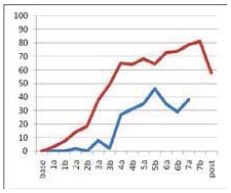
Difficulty Speaking



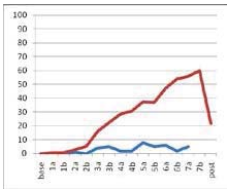
Restriction of Speech



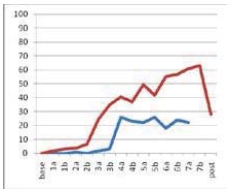
Difficulty Eat Hard Foods



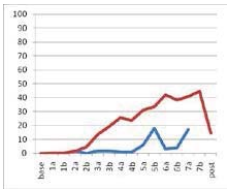
Difficulty Eat Soft Foods



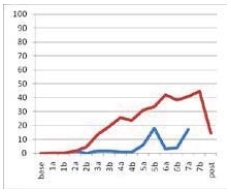
Restriction of eating



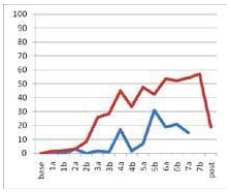
Difficulty Drinking



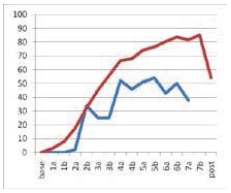
Restriction of Drinking



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

Paper #1

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PLOS ONE

Assessment of Cancer Therapy-Induced Oral Mucositis Using a Patient-Reported Oral Mucositis Experience Questionnaire

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Abstract

Objectives: Treatment of oral mucositis (OM) is challenging. In order to develop and test useful treatment approaches, the development of reliable, reproducible and simpler methods than are currently available for assessment of OM is important. A Patient-Reported Oral Mucositis Symptom (PROMS) scale was assessed in patients with head and neck cancer to determine if the patient-reported OM experience, as determined by using the PROMS scale, correlate with OM assessed by clinician-based scoring tools.

Materials and Methods: Fifty patients with head and neck cancer and undergoing radiotherapy consented to participate. They were examined before cancer treatment and twice weekly during 6–7 weeks of therapy and once 4–6 weeks after therapy. Signs of OM were evaluated using the 3 clinician-based scoring tools; NCI-CTCAE v.3, the OMAS criteria and the Total VAS-OMAS. The participants' OM experiences were recorded using PROMS-questionnaires consisting of 10 questions on a visual analogue scale. Spearman rank correlation test were applied between the PROMS scale values and the clinician-determined scores. Repeated measures mixed linear models were applied to appraise the strengths of correlation at the different time points throughout the observation period.

Results: Thirty-three participants completed all stages of the study. The participant experience of OM using the PROMS scale demonstrates 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. When mouth opening was problematic, i.e. during the 6th and 7th week after commencing cancer treatment, the Spearman's Rho varied between 0.19 and 0.70 ($p<0.001$).

Conclusion: Patient experience of OM, as reported by the PROMS scale may be a feasible substitute for clinical assessment in situations where patients cannot endure oral examinations.

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Introduction

Numerous clinical studies have focused on mucosal toxicity associated with cancer therapy, which is a common acute toxic effect of radiotherapy in head and neck (H&N) cancer patients [1–3]. Oral mucositis occurs in near all patients who receive H&N radiotherapy to the oral cavity or oropharynx and is exacerbated with concurrent chemotherapy [2,4]. Severe oral mucositis can be very painful leading to decreased intake of food and drink and clinically significant weight loss or dehydration (Fig. 1). Moreover, the psychosocial consequences of debilitating oral mucositis can be considerable since the additional morbidity and pain while undergoing the cancer therapy may cause anxiety and depression [5–8]. When severe oral mucositis develops, cancer treatment may be modified or even halted which can limit the efficacy of treatment, and this is estimated to occur in about 10–25% of all patients [9–11], although interruption rates as high as 47% have been reported [12]. Severe oral mucositis can lead to increased use of healthcare resources, additional supportive care and even hospitalization. The direct economic consequences of oral mucositis induced by cancer therapies may be significant and require allocation of considerable resources [13–15]. Unfortunately, preventing and treating oral mucositis is difficult at best [16,17]. It is critically important to develop and validate methods that can be used to quantify the oral mucositis experienced by patients in order to develop targeted interventions that efficiently reduce this particular adverse effect of cancer treatment [18].

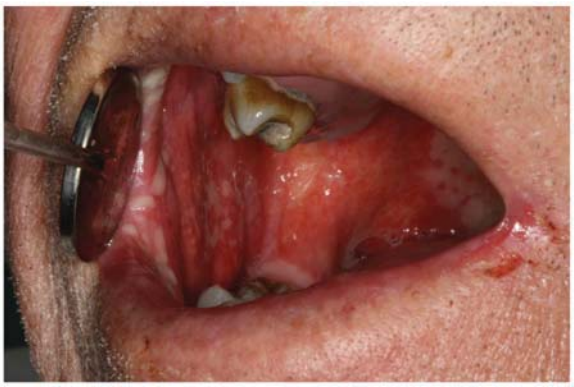

Figure 1. Oral mucositis is a side-effect of radiation treatment that leads to pain and limitations of mouth opening and numerous oral functions.
doi:10.1371/journal.pone.0091733.g001

Extensive resources have been used to find meaningful tools that can be used for accurate assessment of the extent and severity of oral mucositis and/or the burden of oral mucositis for individual patients. Pain associated with oral mucositis is assumed to result from visible ulcerations and from such a perspective it might make sense to use ulceration surface area as a proxy for pain. However, the relationship between size and/or extent of oral lesions and pain is not straightforward and in this regard, other mechanisms of pain experienced by patients with oral mucositis, including neurobiological mechanisms cannot be ruled out [19]. There is a newly emerging body of evidence suggesting that assessments of oral mucositis should include a standardized instrument or a combination of instruments that measure both physical and functional factors, as well as patient-perception [20].

In addition to issues pertaining to assessment of oral mucositis from a clinical perspective (e.g. when and/or if a patient must be provided with less aggressive treatment due to the development of oral mucositis), it has been difficult to assess the efficacy of any particular management protocol for oral mucositis due to the lack of a universally validated and clinically-relevant measurement tool for oral mucositis. Even more importantly, when oral mucositis severity is at its peak, the patient may be unable or unwilling to open his or her mouth to permit a comprehensive clinical assessment of the severity of oral mucositis [21]; a problem that again would interfere with the ability to monitor the condition and also assess the efficacy of various clinical interventions. Hence, in this critical phase of cancer treatment, where a patient may renounce further care, it is critically important to develop other means for assessment of oral mucositis and for confirming the efficaciousness of various treatment interventions for this condition.

Appraising subjective measures that demonstrate a close correlation with intraoral clinical measures may be one strategy. Two promising tools that rely on subjective measurement include the Oral Mucositis Weekly Questionnaire – Head and Neck patients (OMWQ-HN) scale, used in a cohort of head and neck patients [22], and the Patient-Reported Oral Mucositis Symptom (PROMS) scale in a cohort of patients undergoing bone marrow transplantation [23]. The latter measurement tool should be possible for use amongst patients receiving radiotherapy for head and neck malignancy. Hence, a study was designed to evaluate the feasibility of using the PROMS scale to (i) complement common clinician-determined assessments of oral mucositis and (ii) possibly substitute the common clinician-determined assessments of oral mucositis in situations where patients with H&N cancer undergoing treatment have difficulties in opening their mouths for a complete clinical assessment. The hypothesis of this investigation is that the relative magnitude of oral mucositis assessed by clinician-based scoring tools correlates with patient- reported oral mucositis experience as determined by using the PROMS scale.

Materials and Methods

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 oral mucositis 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), and written informed consent was obtained from all study participants. The study was conducted at the Princess Margaret Hospital/Ontario Cancer Institute (PMH) in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (http://www.pre.ethics.gc.ca/eng/archives/tcps-eptc/Default/).

Participants

Potentially eligible participants were informed by the dental department staff about the ongoing study. Eligible participants were identified by being 18 years of age or greater and willing and able to provide informed consent. Participation meant a commitment to bi-weekly clinical examination during cancer treatment, and at one postoperative examination. Patients with carcinoma of the oral cavity, nasopharynx, oropharynx, salivary glands or the maxillary sinus scheduled to receive radiotherapy for their cancer with a minimum prescription radiation dose of 54Gy, with or without concurrent chemotherapy were invited to participate in the study. Patients also had a minimum Karnofsky score performance status of 60% and no indications of active significant acute or chronic diseases that might compromise the ability to carry out intraoral assessment of mucositis. Potential participants were advised that at the outset of the study there should be no visible signs of ulcerations. Dental status was appraised as good at the screening visit (no need for dental treatment), fair/poor (dental treatment required before start of cancer treatment) or edentulous. The study recruitment period ended when 50 participants had been enrolled.

Measures

Participants were scheduled for appointments at baseline, twice weekly over the course of their 6 to 7-week cancer treatment and once more 4 to 6 weeks after completion of treatment. At each appointment participants had an oral examination by a previously-calibrated investigator with the help of mouth mirrors and the use of a high-power head-lamp as a light source. Participants reported how oral mucositis which developed during the radiotherapy period impacted on selected oral functions using the PROMS-questionnaire. Analgesic use, need for hospital admission, or the addition of nutritional support since the previous examination was recorded based on self-reports provided by the participants.

Clinical oral examination

Clinical signs of oral mucositis were recorded using three different clinician-based scoring tools, two of which are probably the most common tools used by clinicians worldwide, i.e., the clinical component of the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (NCI-CTCAE

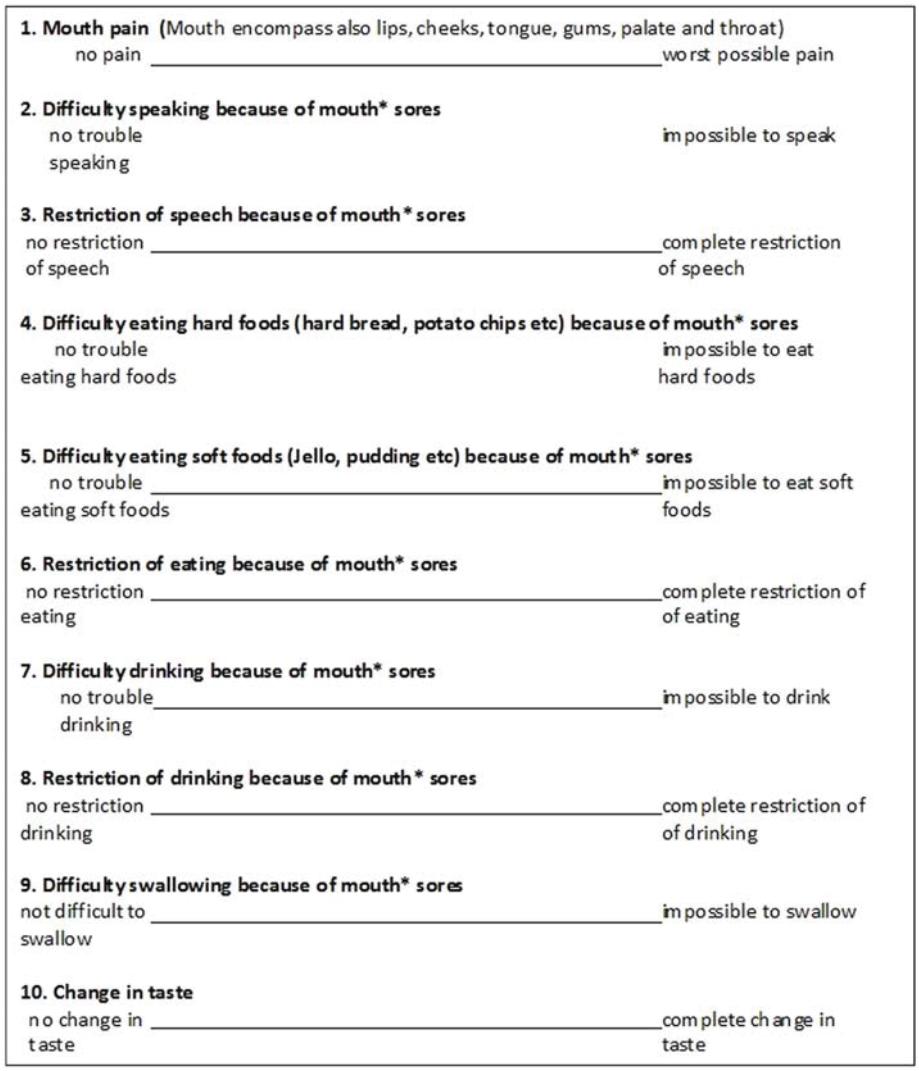

Figure 2. PROMS scale questionnaire with the ten components each detailing two extremes of a functional characteristic within a 100 mm horizontal line or Visual Analogue Scale (VAS) (23).
doi:10.1371/journal.pone.0091733.g002

v. 3) [24], and the clinical component of the Oral Mucositis Assessment Scale (OMAS) [21]. The third tool has been developed locally and is termed "TOTAL-VAS-OMAS" [23]. In the NCI-CTCAE v. 3 the occurrence and severity of oral mucositis is graded using an ordinal score ranging between 0 (none) and 4 (most) as observed at any site within the oral cavity. The OMAS tool was used as described previously whereby a score of 0 (none) and 3 (ulceration) or 2 (erythema) is assessed in nine specific intra-oral locations. 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 experience. Hence, the maximum sum score of ulceration was 27 (9 sites x3) and of erythema 18 (9×2). The "TOTAL-VAS-OMAS" tool consists of two visual analogue scales ranging between 0 to 100 mm for full mouth assessments of erythema and ulceration respectively. The first author (A.M.G.) undertook training and calibration in oral mucositis assessment prior to initiation of the study until Kappa = 1.0, by the use of a photographic set developed for such purposes for the OMAS tool, kindly provided by Dr. Monique Stokman at the University Medical Center Groningen, The Netherlands. Additionally, a laminated booklet containing these images was used during the study to maintain reliability. Most participants made strong efforts to allow complete assessment of their oral conditions, despite the presence, for example, of severe oral mucositis. This suggested that the participants were motivated and dedicated to the completion of this investigation. The oral examinations were done independent of the patient-reported measures.

Table 1. Baseline Demographic and Clinical Characteristics of the participants who completed the full study (n = 33).

Characteristic	Subcategory	No. (%)
Sex	Male	25 (76)
	Female	8 (24)
Race	Caucasian	27 (82)
	Black	1 (3)
	Asian	5 (15)
Age (years) Mean (Standard deviation, Range)		61 (10, 38–78)
Dental status	Good	15 (45)
	Fair/Poor	16 (49)
	Edentulous	2 (6)
Smoking *	Never	9 (29)
	Present smoker	7 (22)
	Ex-smoker	16 (50)
Alcohol*	No	12 (38)
	Yes	20 (62)
Primary tumour location	Oral cavity/oropharynx	18 (55)
	Salivary glands	6 (18)
	Other	9 (27)
T stage	T0/TX	6 (18)
	T1	5 (15)
	T2	9 (27)
	T3	7 (21)
	T4	6 (18)
N stage	N0	15 (45)
	N1	5 (15)
	N2	12 (36)
	N3	1 (3)
Chemotherapy	No	18 (55)
	Yes	15 (45)
Therapy length	4 weeks	1 (3)
	6 weeks	7 (21)
	7 weeks	25 (76)

*1 unknown.

doi:10.1371/journal.pone.0091733.t001

Reporting of symptoms

The oral mucositis experience of the participants was assessed by using the PROMS scale [23]. The PROMS scale consists of 10, 100-mm horizontal visual analogue scales addressing oral functions affected by oral mucositis. Participants were asked to mark on the 100 mm line what best represented their present intra-oral condition (Fig. 2). During the baseline examination and prior to their completion of the actual PROMS scale questionnaire, participants were subjected to a few test-visual analogue scale questions focused on simple everyday topics to familiarize them with the concept of visual analogue scale assisted measurements. The participants completed a PROMS questionnaire at each clinical study appointment; baseline, twice per week during their radiotherapy period and at the post-operative visit, prior to and independently of the actual clinical oral examination.

Data management and statistical analyses

A power analysis was done *a priori* to establish a rank correlation of rho = 0.90 between the PROMS scale and the NCI-CTCAE v.3 and/or OMAS scores and yielded a sample estimated size of 20 participants (Alpha level 0.05% and power of 80%, 2-tailed correlations) (Sample power, SPSS Inc. Chicago, USA). Since patients with H&N cancer may experience relatively high study dropout rates [25], it was considered prudent to recruit 50 participants into the study.

All recordings were documented using de-identified case report forms. The information from the case report forms was transferred into a relational 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 and the NCI-CTCAE v.3 as well as OMAS & TOTAL-VAS-OMAS scores using the statistical procedure "PROC CORR" in the SAS System Version 9.2 software (SAS

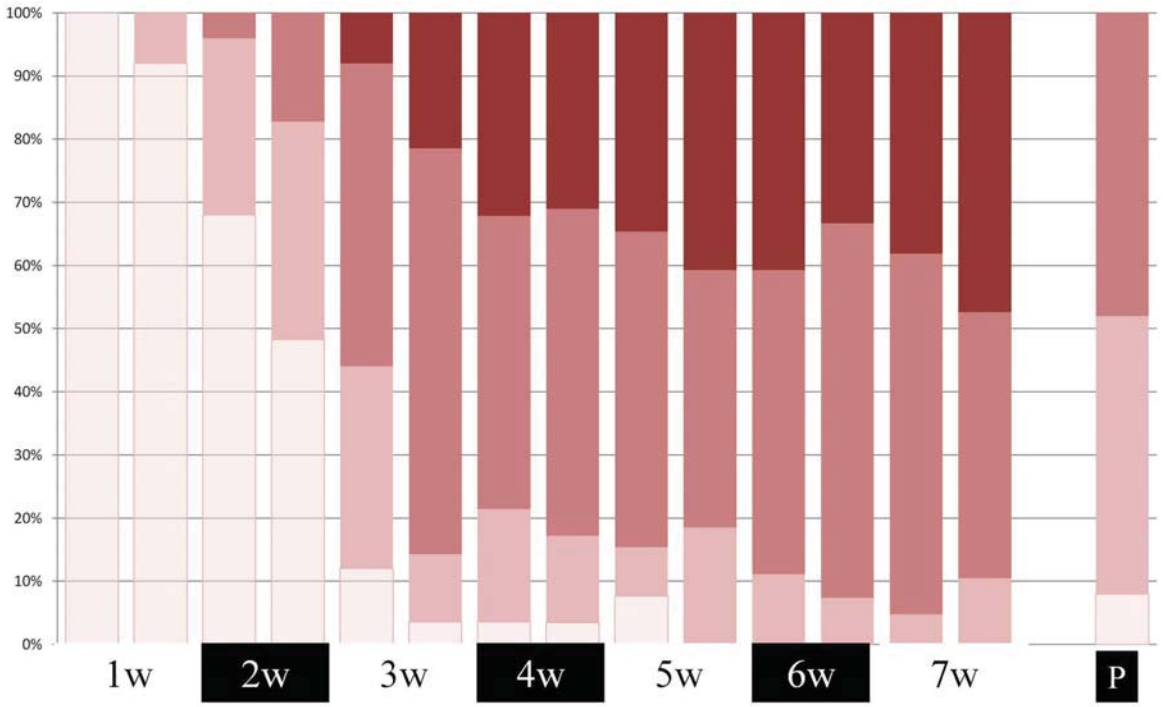

Figure 3. NCI-CTCAE v.3 (Cumulative %) (No color = Score 0, Dark = Score 3) recorded over the cancer treatment period (7 weeks) and at the 4–6 week post-therapy examination.
doi:10.1371/journal.pone.0091733.g003

Institute, Cary, NC, USA). 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 showing a Spearman's Rho 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 [26].

Results

Fifty patients were recruited and followed throughout radiation treatment between August 17, 2009 and July 19, 2010. During this time 520 clinical examinations were undertaken, of which 500 were undertaken by the first author (A.M.G.). Thirty-three participants completed the study, while 7 discontinued due to exhaustion. Ten participants either did not start or had stopped their cancer treatment (n = 7). Others were excluded because the prescribed radiation dose was below 54 Gray (n = 3). Most participants received radiation once daily for six (n = 7) or seven weeks (n = 25), while one participant received radiation twice daily for 4 weeks. Demographic information on participants who completed the study can be seen in (Table 1).

Clinical signs and symptoms of oral mucositis

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. The prevalence of the score "3" was close to 50% by the end of the cancer treatment period (Fig. 3). This may be an underestimate as intra-oral scoring was not possible in some participants due to their inability or unwillingness to open their mouth for a complete clinical assessment. At the post treatment examination about 50% of the participants still demonstrated a NCI-CTCAE v.3 score of "2". 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 fractionated radiotherapy period. At the post-treatment examination the average scores were approximately a third of the maximal scores reported during radiotherapy. The PROMS-aggregated scores increased gradually during cancer treatment period culminating with a visual analogue scale value of 60 by the end of treatment. Hence, all measurements displayed similar patterns of increasing oral mucositis scores 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 (Fig. 4).

Statistical correlations

The dataset used for statistical analyses was based on the 33 participants who completed the full study. The scorings of the 7 participants who discontinued the study did not appear to differ from the remaining up to the point of their drop-out. The normality of the data distribution of the measurement variables was checked for skewness before applying the Spearman rank correlation tests. Minimal skewness was observed, which enabled correlation analyses without log-transformation. Very good correlations (Spearman's rho 0.86–0.96) were observed between the different clinician-based scoring tools. Participant experience of oral mucositis using the PROMS scale demonstrated good

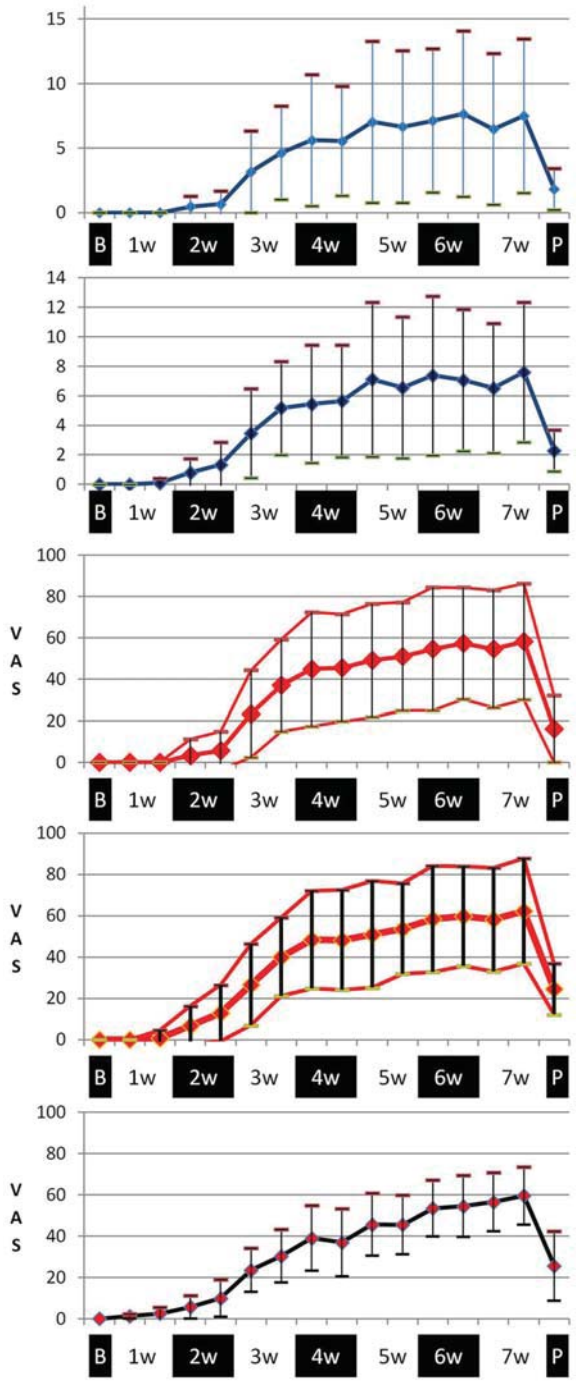

Figure 4. Clinical signs and patient symptoms recorded over the observation period (7 weeks) and at the 4–6 week post-therapy examination ("P"). From top to bottom: OMAS Scores for Ulceration (Means +/− SDs; maximum score = 27), OMAS Scores for Erythema (Means +/− SDs; maximum score = 18), TOTAL-VAS-OMAS 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).
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correlations on the group level with clinician-determined scores over all the time points (Spearman's Rho 0.65–0.78, $p<0.001$). (Table 2). These correlations were performed over all time points using a statistical model that accounted for the repeated nature of the data assessment for calculation of p-values. PROMS scores for participant experience of oral mucositis demonstrated poor to good correlations on the group level at different time points with the clinician-determined scores. (Spearman's Rho -0.12–0.70, $p<0.001$). The correlations between PROMS scales and the scores obtained by measurement of clinical indices changed over time, but specific trends could not be established. At the critical phase where mouth opening was problematic, i.e., during the 6th and 7th week after commencing cancer treatment, the Spearman's Rho varied between 0.19 and 0.70 ($p< 0.001$) (Fig. 5).

Discussion

Oncology patients that undergo cancer treatment needs supporting care in time of extreme psychological duress [16–18]. Preventing and managing oral mucositis as a side-effect of the therapy is an important contribution to increase the patient endurance so he or she can tolerate and ultimately benefit from the cancer therapy. The combination of clinician-observed signs of oral mucositis and patient-reported experience of the symptoms of oral mucositis appears to be the best approach to assess the severity of oral mucositis, rather than relying exclusively on either one or the other. The current study shows that the PROMS scale can complement common clinician-determined assessments of oral mucositis. Moreover, the PROMS can also substitute the common clinician-determined assessments of oral mucositis in patients where these can't open their mouth or endure a comprehensive clinical oral examination or simply can't come to the treatment centre. There are several occasions when comprehensive clinical assessments of oral mucositis may be impossible, while data based on PROMS assessment can almost always be obtained. In these situations the PROMS score might be used to replace missing clinical data on an individual patient level. If needed, the PROMS questions can potentially be completed via telecommunications equipment (e.g. Internet) to substitute a clinical oral mucositis assessment during the cancer treatment.

It should be emphasized that the PROMS is not a measure of quality of life and does not address psychological duress, but is developed with an objective to elucidate the possible effectiveness of any therapeutic interventions against oral mucositis. To facilitate user-friendliness, only a limited number of questions are asked, and these focus on simple everyday daily functions that empirically are noted as side effects of radiotherapy. Including more questions is not necessarily advantageous, since completing the questionnaire will become more cumbersome for the patient. Admittedly, some questions may be redundant, which will be the focus of future studies. Moreover, including questions that would rely on adequate cognitive function such as enquiry about periodicity of burning sensations and incidence of bleeding would be unreliable due to the patients' extraordinary emotional circumstances [6].

A general impression was that few participants had any problems understanding the questions on the PROMS questionnaire relatively quickly. Moreover, completing the questionnaire was perceived by most as quick and easy and not felt as burdensome while they received their cancer treatments. If a patient-reporting instrument, such as the PROMS scale is implemented in routine care or as an outcome in a clinical trial it should be stressed to the patients in an early stage of their cancer treatment that the data generated from the PROMS may possibly

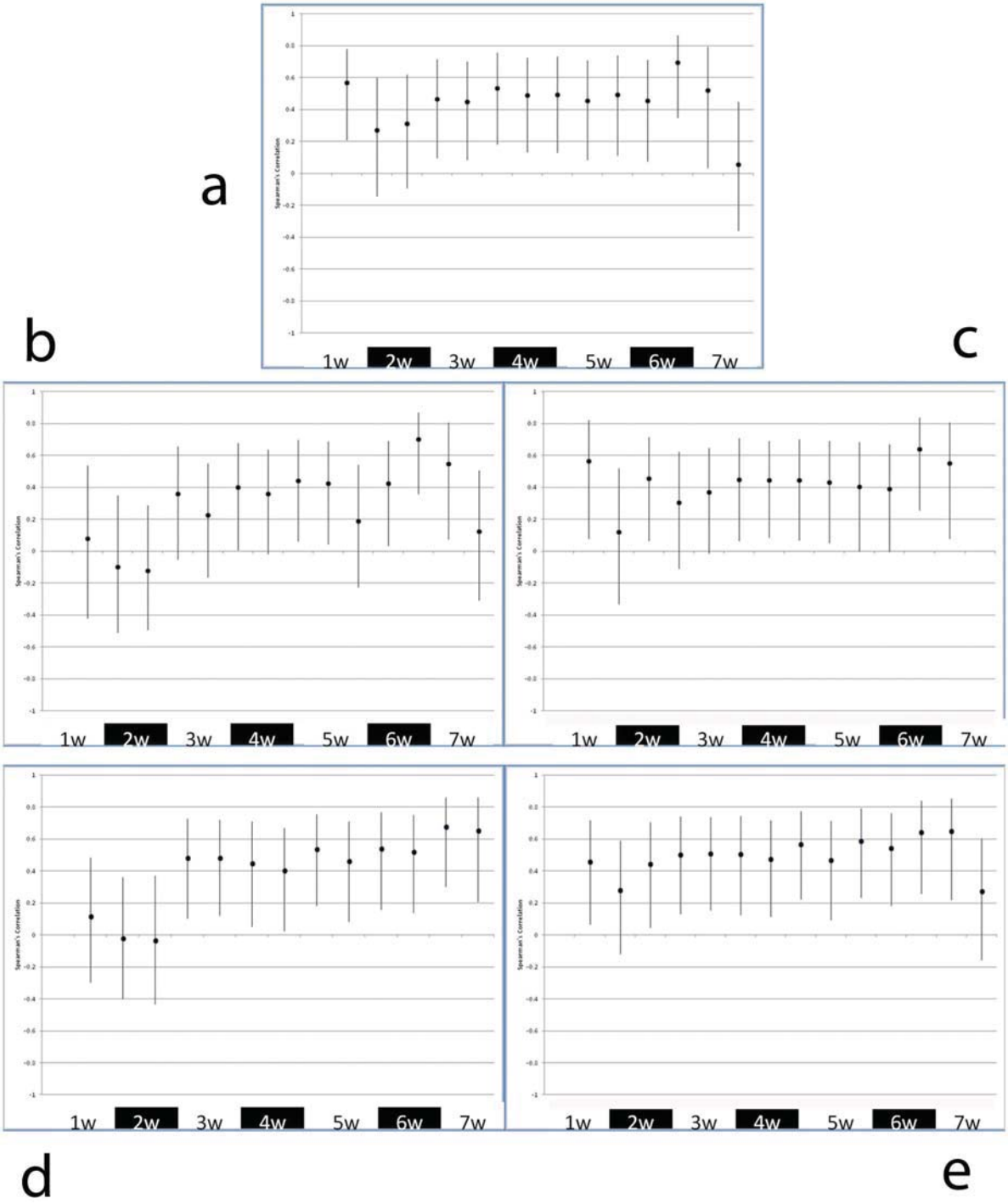

Figure 5. Spearman rho correlation coefficients over the observation period (7 weeks) and at the 4–6 week post-therapy examination between clinical signs of oral mucositis, as reported by different clinician-based scoring tools and the experience of oral mucositis by the participants, as reported by 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).
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Table 2. Spearman rho correlation coefficients over the full cancer treatment 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 values.

	OMAS-U	OMAS-E	TOTAL-VAS-OMAS-U	TOTAL-VAS-OMAS- E	PROMS
NCI- CTCAE v. 3	0.89	0.86	0.92	0.91	0.75
OMAS Ulcerate Area	-	0.92	0.95	0.90	0.65
OMAS Erythema Area	-	-	0.91	0.92	0.69
TOTAL-VAS-OMAS Ulceration	-	-	-	0.96	0.75
TOTAL-VAS-OMAS Erythema	-	-	-	-	0.78

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become the only manner their intraoral oral mucositis status can be assessed at later stages in the cancer treatment period.

The correlation between the data using the PROMS and the clinician-based scoring tools were fairly similar over all the time periods as well as during the critical 6^{th} and 7^{th} weeks period during cancer treatment when the oral mucositis is at its worst. The extent of ulceration was not a sufficient indicator of the patient burdens experienced during the onset and development of oral mucositis. Yet, should not the patient burden direct changes in cancer treatment (ranging from reduction in the intensity of treatment to total cessation of treatment) as opposed to what might be less meaningful clinical assessments of lesion appearance and size? As with management of other chronic conditions characterized by pain, including 'chronic pain' itself, it is the patient burden that should ideally be used as the endpoint or outcome measure for making decisions regarding further treatment of the condition, in this case, oral mucositis. Thus, assessment of the extent of ulceration as the most important and in some cases sole outcome measure, while interesting and important from a mechanistic and pathophysiological point of view is important, it would seem much more critical to understand how a patient is functioning during cancer treatment, and the patient's relative extent of duress while undergoing the treatment so that appropriate measures can be taken. After all, a patient with 'small' areas of ulceration, but who is demonstrating severe levels of suffering, may require intervention, whereas a patient with larger ulcerations but minimal symptoms may not. This is something that simply cannot be measured by determining the size and/or extent of ulceration, particularly since the pain associated with this condition is considered complex and likely neuropathological in origin [19].

There was a large degree of heterogeneity in the participants of the study, particularly in relation to the location of their malignancy, tumour stage, sex and choice of radiotherapy procedure. (Table 1). Since the study was designed to test for the hypothesis that the patients' self-reported experience of oral mucositis correlated with other currently available measures of oral mucositis, the impact of this heterogeneity was considered to be of minor importance. There were no attempts to relate the oral mucositis data to any specific demographic, clinical or other extrinsic and intrinsic factors due to a high risk of spurious associations.

The three clinician-based scoring tools have different characteristics that need to be recognized. The clinical scoring of oral mucositis with the use of the ordinal NCI-CTCAE v.3 tool is in general straightforward, but borderline cases may be challenging to differentiate using this tool. In particular, the distinction between grades '2' and '3' can occasionally be challenging; a characteristic that reinforces subjectivity in making assessments. The challenge has apparently been recognized, since the NCI tools have undergone several modifications over the years in order to facilitate their use [24,27–29].

Using the clinical component of the OMAS scale is also generally straightforward albeit more time consuming than using the NCI-CTCAE v. 3 tool [24]. A calibration booklet such as the one used in the current study facilitates scoring by visual comparison with photographs. A characteristic of the OMAS tool is that if severe oral mucositis is present in only one or two areas in the oral cavity but minimal or absent elsewhere, the total score for the severity of oral mucositis will be low, no matter how severely ulcerated those one or two areas are. The authors of the original paper outlined various ways of handling the sum-scores statistically, but ended up with more than one recommendation [21]. In light of the experiences of patients suffering from oral mucositis, it is uncertain whether having one area with severe erythema and/or ulcerations is worse than having multiple areas that on their own might be less severely involved. Moreover, it is not entirely clear why one large ulcer should affect the patient more (or not) than several small ulcerations.

The TOTAL-VAS-OMAS tool has so far only been tested by the developers in one patient population [23], and there are no published guideline documents regarding its use, challenges and interpretations. In the lack of pictorial guides or descriptors there is a possibility that observers, including the one in the current study may create skewed data since relatively high scores can be given in the early phases during cancer treatment before the really severe cases of oral mucositis become observable. Regardless of which clinician-based scoring tools is used, it is important that all sites of the oral cavity are examined, which can be difficult or uncomfortable at later stages of cancer treatment.

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. Moreover, the number and strength of narcotic and non-narcotic analgesics could also affect self-reported experiences of mouth pain resulting from oral mucositis. Conversely, some participants continued to report significant mouth pain in spite of the use of high amounts of analgesic medication [30].

Many consider correlations between patients'-recorded subjective measures and clinically recorded measures obtained by health professionals as biased with high levels of variability. Attempts to minimize bias in the current study were done by undertaking calibration *a priori*, consistent use of a booklet/poster with clinical photographs while appraising the participants and use of mainly one single clinical examiner throughout the study. The great majority of the clinical examinations were completed by one investigator (A.M.G.), since one important factor for negative

experiences in cancer trial participation is involving many physicians at check-up appointments [31]. Moreover, this assured that measurements were done mainly by one calibrated investigator which would tend to lead to less variability.Although there appears to be a statistical correlation between clinical signs and patient-reported symptoms on group level, multiple individuals deviated from this pattern in this study. Consequently, there is a possibility that subtle intra-individual improvements (or deteriorations) can be masked if the effectiveness of new therapeutic and preventive interventions targeted towards oral mucositis is determined on group level point estimates rather than on intra-individual levels.

Conclusions

The current findings indicate good correlations between assessment of the oral mucositis experience obtained from the PROMS scale and currently available instruments used commonly to assess oral mucositis in patients with head and neck cancer. Hence, patient-based experiences of oral mucositis, as reported by the PROMS scale, may be a useful tool to augment clinical assessment of oral mucositis or as a substitute assessment in situations where patients cannot endure oral examinations.

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Author Contributions

Conceived and designed the experiments: AMG AJH AJ HT RW. Performed the experiments: AMG RW. Analyzed the data: AMG AJ. Contributed reagents/materials/analysis tools: AMG AJH AJ HT RW. Wrote the paper: AMG AJH AJ HT RW.

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Paper #2

Symptoms reported by head and neck cancer patients during radiotherapy and association with mucosal ulceration site and size: an observational study

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Abstract

Background: Self reported pain and impairment of oral functions varies markedly and often in spite of extensive oral mucositis (OM). The aim of the current study was to appraise how patient-reported debilitation caused by OM is influenced by the extent and possibly location of the OM lesions.

Methods: Patients with head and neck cancer undergoing radiotherapy were examined before treatment, twice weekly during 6-7 weeks of therapy, and 3-4 weeks after therapy completion. OM signs of 33 participants were evaluated using the Oral Mucositis Assessment Scale (OMAS), while OM symptoms were recorded using Patient-Reported Oral Mucositis Symptom (PROMS)-questionnaires. Changes in OM experience as a function of OM signs was undertaken by comparing the aggregated and individual PROMS scale values at the point of transition of OMAS ulceration scores between 0 to 1, 1 to 2 and 2 to 3, respectively in the nine intra-oral locations designated in the OMAS. ANOVA with pairwise contrasts using the LSD procedure was applied for comparisons of mean changes of PROMS scale values for the participants who experienced an OMAS score of 2 or more during therapy (n=24).

Results: Impairment of eating hard foods was more when the OMAS score for ulceration anywhere in the mouth or in the soft palate changed from 1 to 2, compared to between score 0 and 1 (p=.002 and p=.05) or between score 2 and 3 (p=.001 and p=.02). Mouth pain increased more upon transition of OMAS score anywhere in the mouth from 1 to 2 compared to 0 to 1 (p=.05).

Conclusion: The relationship between patient-reported impairment of oral function and pain caused by OM ulceration is not linear, but rather curvilinear. Our findings should prompt investigators of future interventional trials to consider using a less severe outcome than maximum OM scores as the primary study outcome.

Keywords: oral mucositis; oral ulcer; pain; head and neck cancer; oral cancer; radiotherapy; patient outcome assessment; adverse effects

Introduction

Head and neck (H&N) cancer patients often experience mouth pain. The mouth pain may be due to the spread of the original tumour, due to surgery, or by the development of oral mucositis (OM) as a toxic side effect of radiotherapy or chemotherapy [1]. Patients with cancer have numerous questions about pain and whether and how pain can be managed during their treatment [2,3]. The patient's experience of pain is modulated by intrinsic dimensions such as adaptive coping style, co-morbidity, subjective need of analgesics, psychological duress or depression, e.g., due to fear of permanent disfigurement and likely, previous experiences of severe pain [4]. A range of extraneous factors can also influence the patient experience of pain, ranging from the positive effects of emotional support from professionals, family or social network [5], to the negative effects of social isolation.

Mouth pain associated with the H&N cancer therapy is a significant contribution to emotional duress and often leads to lower food intake potentially resulting in undernourishment and weight loss [6]. The level of suffering caused by the mouth pain can extend to such level that the patient may request a lowering of the intensity of the radiotherapy or even renounce further cancer therapy. Many regard the extent of visual manifestation of OM as a proxy for the degree of mouth pain, although perhaps somewhat surprisingly, the scientific evidence for this presumption does not seem entirely justified (Table 1), [7-13]. Patients with extensive OM often report significant mouth pain, despite use of analgesic medication [14]. The OM-derived pain appears to be associated with neurobiological etiological mechanisms [15,16], although the exact details remain unknown. The type of pain in H&N cancer patients appears to be predominantly

nociceptive or mixed nociceptive and neuropathic pain [17]. Clarifying the principal pain in H&N cancer patients through detailed description of how the patients report the history and presence of neurological dysfunction may provide indications that can have implications for clinical practice and research. Moreover, it is essential to understand how the H&N cancer patient experiences his or her mouth pain during cancer therapy, to institute possible interventions that could decrease their levels of suffering. Reducing or at least explaining to the patient how pain will affect their daily activities may lower patient anxiety, bolster the compliance with cancer therapy [18] and likely make it easier for the patient to endure comprehensive intraoral examinations. Since the OM-associated pain contributes to total mouth pain (i.e. in addition, say, to pain associated with surgical resection of the tumour) it is imperative to identify interventions that may prevent or reduce the development of OM.

The current investigator group recently appraised the merits of adopting a new patient-reported oral mucositis experience instrument named PROMS (Patient-Reported Oral Mucositis Symptom) [19] in a cohort of H&N cancer patients [20]. The main purpose of this observational study was to elucidate whether the OM that affected the study participants during the course of their radiotherapy correlated with signs of OM. The investigators undertook detailed intra-oral examinations that included clinical scoring of OM according to the Oral Mucositis Assessment Scale (OMAS) protocol [21] twice per week while the participants underwent radiotherapy (Fig. 1). Upon applying Spearman rank correlation tests in repeated-measures mixed linear models between the PROMS scale values and three different clinician-based scores at various time points while the patients underwent radiotherapy it was apparent that the patient experiences of OM correlated well with the scoring tools on a group basis [20]. However an intriguing observation in the investigation was that some participants reported hardly any mouth pain, in spite of visual manifestation of large and often confluent areas of ulcerations of the intraoral mucosa, and vice versa. These observations led the current investigator team to explore how the

participants' self-reported mouth pain was associated with the intraoral location and extent of OM lesions. The working hypothesis was that the advent of patient-reported debilitation due to OM was influenced by the extent and possibly location of the OM lesions.

Materials and Methods

The materials and methods have been described in detail elsewhere [20], and the data presented in this paper are based on secondary analyses of the main study.

Main study

In brief, a prospective single cohort study was undertaken at the Princess Margaret Hospital/Ontario Cancer Institute (PMH). The objective was to appraise the merits of supplementing clinical assessments of OM with the PROMS instrument amongst H&N cancer patients undergoing radiotherapy with or without concurrent chemotherapy. Study approval was obtained from the Research Ethics Boards of the Toronto University Health Network in 2009 (ref. #09-0231-CE) and written informed consent was obtained from all study participants. Twenty participants were required to obtain 80% power of the study, based on estimation of 90% correlation between self-reported and observed data. In expectation of a high participant dropout, the investigators recruited more participants than strictly required.

Eligible participants were identified by being 18 years of age or greater and diagnosed with carcinoma in the head and neck region and a minimum Karnofsky score performance status of 60%. The 60% lower threshold was chosen for logistical as well as ethical reasons, as patients below this score require considerable assistance that would introduce a disproportionate burden for the participant and the hospital support staff. All participants were scheduled to receive radiotherapy for their H&N cancer with a minimum prescription radiation dose of 54Gy, with or without concurrent chemotherapy.

Fifty consenting participants underwent an oral examination at baseline prior to the commencement of cancer therapy. Seven participants did not complete the cancer therapy and three received less than the 54 Gray radiation dose while 7 discontinued their participation in the current study, primarily due to fatigue. The remaining 33 participants were examined clinically twice-weekly over their course of seven (n=25), six (n=7) and four (n=1) weeks of radiotherapy, and then one more time four to six weeks after the completion of the cancer therapy.

The visual manifestation of OM was appraised clinically in accordance with the OMAS-instrument as described by its developers [21]. An assessment of ulceration or erythema was made in nine different intra-oral locations (upper lip, lower lip, right and left cheek, right and left ventrolateral tongue, floor of mouth, soft palate and hard palate). Scores were assigned values of 0, or 1 to 3 according to the extent of mucositis. For ulceration, scores 1 and 2 denote an ulcerated area, respectively of less than, and more than 1 cm^2, and a score of 3 denotes an area of more than 3 cm^2. The clinical examiners were calibrated prior to the study initiation by using photographs developed for such purposes, and laminated photographs were used during the study to avoid drifting of the intra-rater assessments.

At each clinical examination, the participants completed a PROMS questionnaire [18] to appraise how OM affected common daily oral functions. The PROMS scale consists of 10 questions that are answered on a visual analog scale (VAS), by setting a mark on each horizontal line measuring 100 mm. Two questions focused on mouth pain and change in taste ranging from none to worst possible and complete change in taste, respectively. The other 8 questions focused on how much their mouth sores impaired different oral functions on the day of the clinical examination. Memory of pain or other dysfunction was not requested, on grounds of being deemed unreliable. Impaired oral functions included difficulty with speaking, swallowing, drinking or eating hard or soft foods as well as restriction of eating, drinking or speech. The

participants were also solicited about any intake of analgesic medication or necessary in-hospital stay, with or without required nutritional support through tube feeding in-between the clinical examinations. The participants were consistently asked at every visit whether they felt a need to discuss with the investigator any issues regarding oral dysfunction, including mouth pain and pain management during the course of their radiotherapy.

Secondary analyses

The secondary analyses aimed to determine whether there was an association between oral mucositis symptoms and any specific extent or location(s) of visually manifest OM. In this perspective, the changes of the aggregated and individual PROMS scale values were measured when changes were identified 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 [21]. Prior to being subjected to parametric or non-parametric statistical tests for comparative purposes, the mean changes of 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 0 to 1, 1 to 2 and 2 to 3, with the hypothesis that the PROMS changes are equal to each other (IBM SPSS ver. 22, IBM Corporation, Somers, NY).

Results

Demographics

Twenty-four of the 33 participants provided data that enabled the appraisal of change of the PROMS scale value changes as a function of OMAS score changes. Six participants did not experience oral mucositis beyond an OMAS score of “1”. Two participants had missing clinical

scores or self-reported PROMS scale data, and one participant received radiotherapy over four weeks only. Of the 24 participants, half received concurrent chemotherapy (n=12, 50%). The cohort was predominantly Caucasian (n=20, 83%), and consisted of 19 males (79%). The average age was 60 years (range 38-78 years). The proportion of never-smokers was 25% (n=6), ex-smokers 50% (n=12) and smokers 25% (n=6). The participants were diagnosed with either carcinoma of the oral cavity or oropharynx (n=14, 54%), or in the salivary glands, nasopharynx, maxillary sinus or primary site unknown.

Twenty-two of the 24 reported that they self-administrated analgesic medication more or less constantly during the course of the cancer therapy. The type of medication varied, but often included opioids. Despite this medication, the participants reported consistently on the PROMS VAS-forms that they experienced mouth pain throughout the entire period of cancer therapy.

OMAS and PROMS measurements

The OMAS scores in this study cohort increased progressively towards the end of the cancer therapy period and for some patients ulcerations were visually manifest as early as the 2nd week of radiotherapy. The predominant intra-oral locations of the ulcerations were the soft palate, cheeks and right and left ventral and lateral tongue. The upper and lower lips were involved less frequently, and OM in the floor of the mouth was reported only to a small extent (Fig. 2).

The VAS values for all the ten components of PROMS, as well as the aggregated average, increased gradually during the cancer treatment period. “Change of Taste” and “Difficulty eating hard foods”, were considerably more affected by OM than the other 8 components of the PROMS (Fig. 3).

PROMS and OMAS association

The changes in extent and severity of intra-oral visually manifest erythema seemed to have little influence on the change of patient-reported PROMS scale values amongst the 24 participants (data not shown). The changes in visually manifest ulceration on the other hand, appeared to closely relate to changes in the PROMS scale values .

Upon transition between OMAS ulceration scores 0 to 1, 1 to 2 and 2 to 3 anywhere in the mouth, the PROMS scale values changed more between the shift from scores 1 to 2, than between the shift from scores 0 to 1 or between the shift from scores 2 to 3 ($p=0.009$). Patient reported difficulties with eating hard food due to mouth sores anywhere in the mouth changed also more between the shift from scores 1 to 2, than between the shift from scores 0 to 1 or between the shift from scores 2 to 3 ($p=0.001$). In general, upon transition of ulcerations from scores 1 to 2 anywhere in the mouth, there was a tendency that the relative increase of mouth pain, and eating hard foods and the aggregated PROMS scale values appeared to be higher compared to the shift from scores 2 to 3 (Fig. 4).

The majority of participants experienced visually manifest ulceration in two to four sites (Fig. 5). One participant had OMAS score 3, i.e., more than 3 cm^2 in one site, while two participants suffered from OM in all 9 intra-oral sites and of these two, one had the maximum OMAS score of 3 in all nine sites (i.e., OMAS score 27, Fig. 5). Both reported relatively medium mouth pain and average PROMS scale values (VAS 37-55), but severe (VAS = 100) impairment of eating hard foods.

Discussion

The study cohort can be characterized as heterogeneous, in terms of participant age, dental status, smoking and alcohol intake, primary tumour location, TNM cancer stage, surgery

excision or not, use of supplementary chemotherapy, therapy length and severity of OM. To clarify to what extent these factors individually or in concert affect patient-experienced 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. The size of the current sample is small and was not originally designed to test correlation between size and/or location of oral mucositis ulcerations and patients' experiences of OM. The risk of potential bias introduced by conducting post-hoc analyses is acknowledged. Still, to the authors' knowledge, the assumed linear correlation between mouth pain and extent and location of OM has not been addressed before by any investigators. Moreover, while the size of OM might not have the expected impact on pain as ordinarily expected, it could still impair functions that are equally, if not more important to the patient, than pain alone.

The participants in this study did not report mouth pain during their first week of radiation therapy, which is at odds with other studies suggesting that about 50% of H&N cancer patients have pain prior to cancer therapy [22,23]. One possible explanation of the apparent discrepancy may be that PROMS-questionnaire focus on effects of actual mouth sores (i.e. oral mucositis) and the question about mouth pain was also considered within this context [19]. 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, which would likely reduce underreporting of pain. Participants were not requested to describe the qualities or intensity of their pain as modulated by functions. This does not negate that other strategies should also be attempted to hopefully elucidate which factors that aggravate pain in H&N cancer patients [24].

Best practice to deal with oral mucositis and associated mouth pain is unfortunately not obvious, which is reflected by the most updated evidence-based guidelines recently developed by the Multinational Association of Supportive Care in Cancer (MASCC) and The International Society of Oral Oncology (ISOO) [25]. Part of the conundrum is our incomplete understanding of how radiotherapy-induced OM affects the cancer patient. In this context, our findings that patients report relatively more problems upon transitions from small to medium size visually manifest OM rather than between medium to larger confluent ulcerations or between none to minor size OM is of high clinical relevance.

Our current understanding of pain associated with cancer is inadequate and attempts to elucidate the etiopathogenesis is tempered by both patient expectations of pain and symptom reporting, as well as clinician perceived perceptions of effectiveness [26-28]. The patient-reported high intake of analgesics and impression of poor effects noted in the current study corroborates observations made in other clinical studies. Poor analgesic control may indicate that the pain mechanisms involved during the radiotherapy of H&N cancer patients may have a neuropathic rather than a strictly nociceptive component. Neuropathic cancer pain is associated with a negative impact on activities of daily living and greater requirements for analgesics than nociceptive cancer pain [29].

In the current investigation, the participants had a Karnofsky performance status of minimum 60%. To what extent this affects the external validity of the results to more disabled patients is uncertain. The current consensus is that pain symptoms and associated psychological distress does not appear to be influenced by Karnofsky scores [30,31]. Most of the patients developed mucosal ulcerations on their soft palate and/or tongue although the variability was great. The combination of large variability and small study sample cautions against making any strong inferences, but it appears that the location of a lesion could be more important insofar as oral

functions are concerned than merely size of the lesion. 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 (Fig. 4). 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 ulceration 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.

When there is extensive OM there are likely several ongoing transitions between OMAS scores 0 to 1, or 1 to 2, alternatively from 2 to 3 simultaneously in several areas intra-orally. The sum of these mouth sores influence the patient when he or she reports the level of suffering by marking on the VAS scale in the PROMS questionnaire. The soft palate was more affected by OM than the other locations during the early stages of the radiotherapy. It is therefore important to realize that pain experienced upon OMAS transition from score 0 to 1 is less in the soft palate compared to when the transition occurs in other intra-oral sites.

An element that was not measured in the current study, but needs to be considered is whether the depth of the OM lesions is associated with the extent of pain or functional debilitation. Optical Coherence Tomography is a technique that may be used for detecting OM before visual manifestation, but with the current state of the technology contrasts become blurred when the OM develops [32].

The association between the individuals' PROMS-scale values with the OMAS scores (Fig. 5) did not demonstrate any clear patterns. The small study sample precludes the possibility to draw too 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 in terms of amount of intra-oral ulcerations reported only modest mouth pain, as defined by a VAS-values between 37 mm and 65 mm, while some of the individuals with ulcerations limited

to two or three sites reported VAS values above the 80's (Fig. 5). The size of the ulceration itself is important, but Fig. 5 shows that an increased number of ulcerations may not necessarily contribute to more pain than having just one ulceration. 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"* [21].

Clinical studies that select as primary outcome the most severe visually manifest OM scores select a clinically relevant outcome. However, measurements of a less severe level of visually manifest OM appear to be more patient relevant. The current study showing that patients report pain and significant impairment of oral functions even when scores are lower than e.g. OMAS score 3 or WHO (World Health Organization) score 3 or NCI-CTCAE score 3 is obviously clinically relevant.

The current observations that the major change in PROMS scale values occurs upon transition from small to medium, rather than from medium to large visually manifest ulcerations corroborate observations findings reported by Elting et al. [10]. 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.

Conclusion

The development of one or more ulcerations with surface areas of less than approximately 1 cm^2 does not impair oral functions much, as measured with the PROMS questionnaire. However, an increase of any ulceration surface area to more than 1 cm^2 cause a relatively large change of reported impairment and mouth pain, which was larger than the relative change upon transition

of any ulceration area 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 is not linear, but rather more curvilinear.

Clinical trials that select the maximum visual manifest OM score as primary outcome, such as OMAS score 3, NCI scores 3 and 4, WHO score 3 to assess intervention efficacy, select a clinically relevant outcome. However, the observations made in the current study would suggest that a less severe primary outcome may be more patient-relevant. Further and larger clinical studies are needed to appraise the association between severity of OM and patient-experienced pain and dysfunction.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

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Authors' contributions

AMG, AJ, RW, AJH and HT conceived and designed the study. AMG and RW performed the patient screening, informed consent and the clinical assessments. AMG and AJ analyzed and interpreted the data. AMG drafted the manuscript and AJ, RW, AJH, and HT critically revised the manuscript.

All authors have given final approval of the final version and agree to be accountable for all aspects of the work.

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Table 1. Prevalence of severe oral mucositis during radiotherapy of H&N cancer patients and patient-reported mouth pain

Lead author	N	UICC-cancer stage*	Radiotherapy	Prevalence (OM Grade)	Clinical OM assessment	Pain reporting during therapy
Nutting CM et al. 2011 [7]	94	T1-4/N0-3/M0	60-65Gy CRT vs. IMRT	61% vs. 63% (Gr. 3+4)	NCICTCAE v3	Likert scale; Grade 0-4
Murphy BA et al. 2009 [8]	75	T1-4	n.r.Gy CRT vs. IMRT +/- chemo	95% vs. 66% (Gr. 3+4)	OMWQ-HN	Likert scale; Grade 0-4 (MTS)
Palazzi M et al. 2008 [9]	149	T1-4	66-74 Gy IMRT/CRT/3d CRT	28% (Gr. 3+4)	NCICTCAE -v3	Likert scale; Grade 0-4
Elting LS et al. 2007 [10]	204	T1-4/N0-3	64-70Gy IMRT/CRT +/- chemo	66% (Gr. 3+4)	NCI-CTCv.2	Likert scale; Grade 0-4
Urbano TG et al. 2007 [11]	30	T2-4/N0-3	63Gy vs. 67Gy (All + Chemo)	67% vs. 40% (Gr. 3)	NCI-CTCv.2	Pain Y/N
Wendt TG et al.2006 [12]	38	T2-4/N0-3	60-70Gy 3D-cIMRT	11% (Gr. 3)	RTOG	Likert scale; Grade 0-6
Bentzen SM et al. 2001 [13]	918	T2-4/N1-3	54Gy CHART vs. 66Gy CRT	60% vs. 44% (Gr. 4)	EMS(Dische -89)	Likert scale; Grade 0-3

* UICC = International Union against Cancer, (http://www.uicc.org/resources/tnm/publications)

Other acronyms used in table 1:

Gr.: Grade
CRT: ChemoRadiotherapy
IMRT: Intensity-modulated radiation therapy
RT: Radiotherapy
CHART: Continuous Hyperfractionated Accelerated Radiotherapy
NCICTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
OMWQ-HN: Oral Mucositis Weekly Questionnaire-Head and Neck cancer
RTOG: Radiation Therapy Oncology Group
EMS: Elements of Morbidity System
MTS: mouth and throat soreness

Figure titles and legends

Fig. 1. Development of oral mucositis ulceration in the soft palate. In this participant, the first sign of ulceration developed during the 3rd week of radiotherapy on the uvula (upper centre picture). The size of the ulceration increased over the subsequent weeks 4 (upper right picture), 5 (bottom left picture) and 6 (bottom right picture). A common challenge in the clinic examination is that pain and impaired control of pharyngeal and extrinsic tongue muscles caused by the oral mucositis often counteracts a clear visual examination of the back of the mouth and throat.

Fig. 2. Development of oral mucositis ulceration from week 2 of the 7 weeks cancer therapy period. Nine locations shown, in accordance with the OMAS scoring system (Sonis et al. 1999). From top is shown the ulceration status of the: upper lip, hard palate, soft palate, right and left cheek, right and left ventrolateral tongue, floor of mouth and lower lip. Percentage of OMAS score 0 (no mucositis) = white; Percentages of OMAS scores 1,2 and 3 = increasing shading.

Fig. 3. 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).

Fig. 4. 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 difference of PROMS change (ANOVA with LSD pairwise contrasts (*= P< 0.05, **= p<0.01, ***=p<0.001)).

Fig. 5. Oral mucositis ulceration score and PROMS scale VAS values recorded on the last radiotherapy session of the 7 weeks cancer therapy period. The horizontal axis shows the observed number of intra-oral sites with ulceration (max = 9). The vertical axis indicates the accumulated OMAS score of the ulcerations (max = 27). The boxes show the individual participants' PROMS scale VAS values for: Pain - Difficulty eating hard food - Aggregated PROMS average. Higher VAS-values denote more impairment of oral functions (max VAS=100).

Supporting Information

S1 File. Raw Data matrix. The supporting information file "S1_Dataset.xls" is a Microsoft Excel file containing all raw data. Three separate sheets contain data from the Case Report Forms, OMAS clinical scores and PROMS scores respectively. Column #1 is the case identifier number of the 50 participants. The top row contain the names of the variables. Further details about this data matrix can be addressed to: anne.m.gussgard@uit.no.

Figure 1

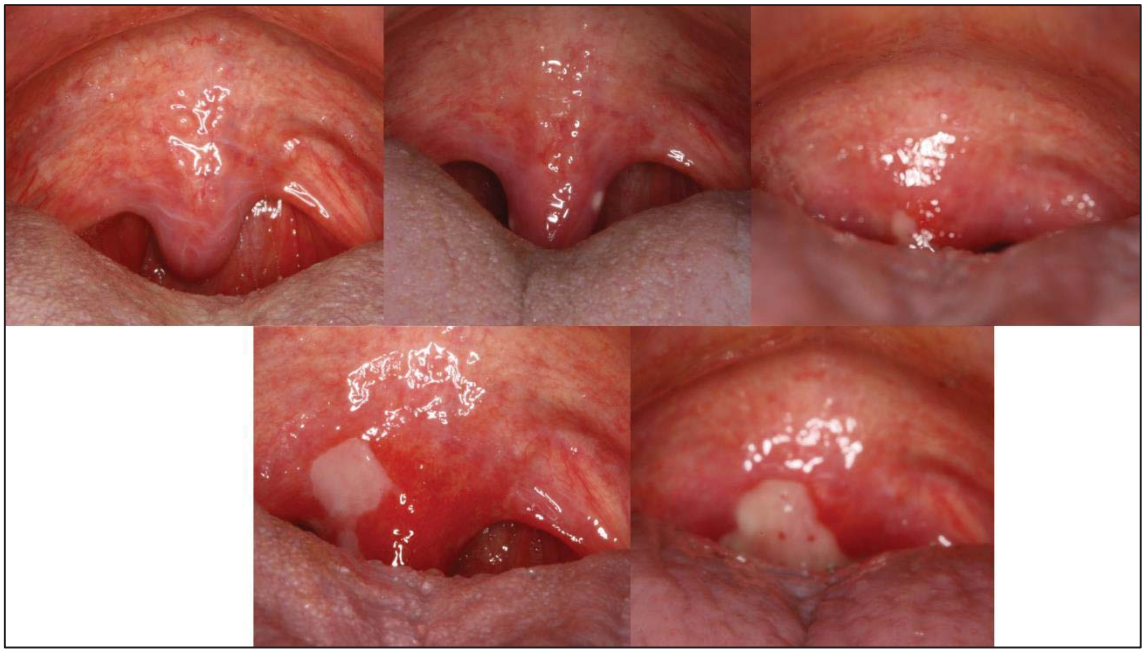


Figure 2

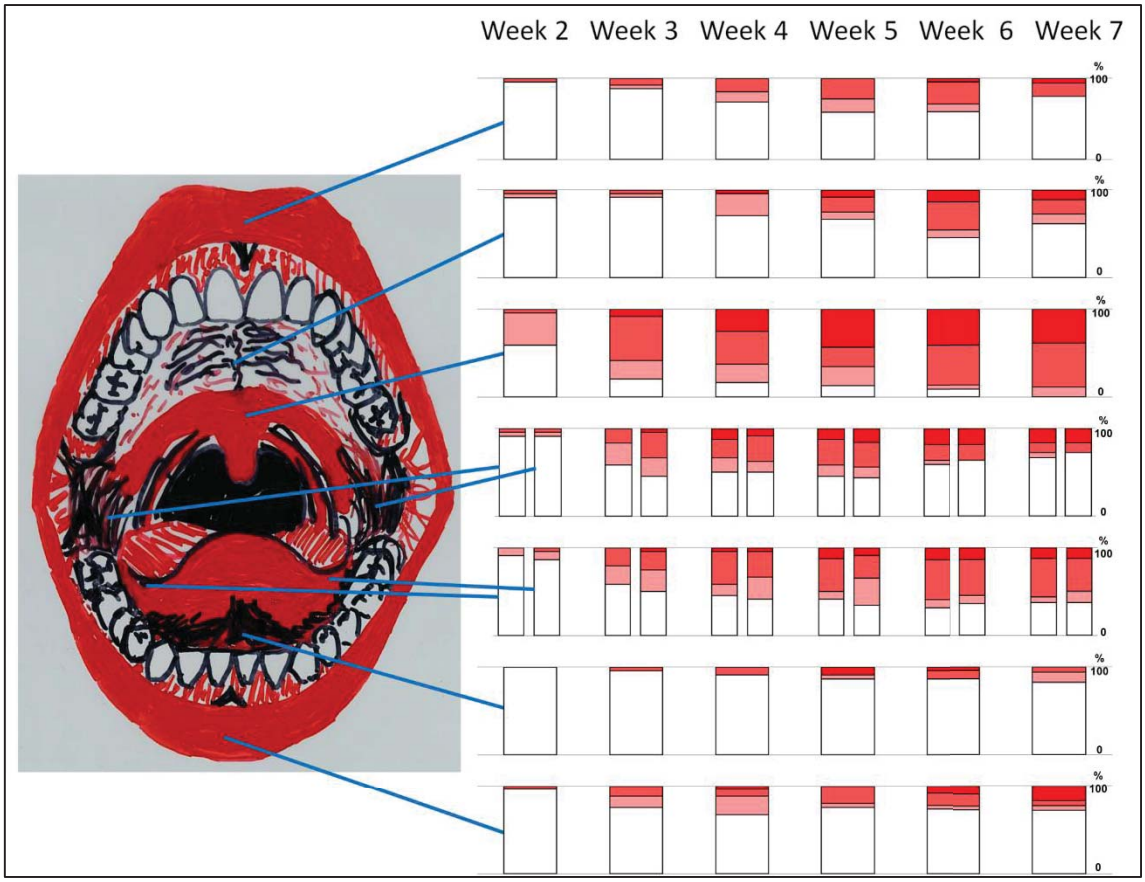


Figure 3

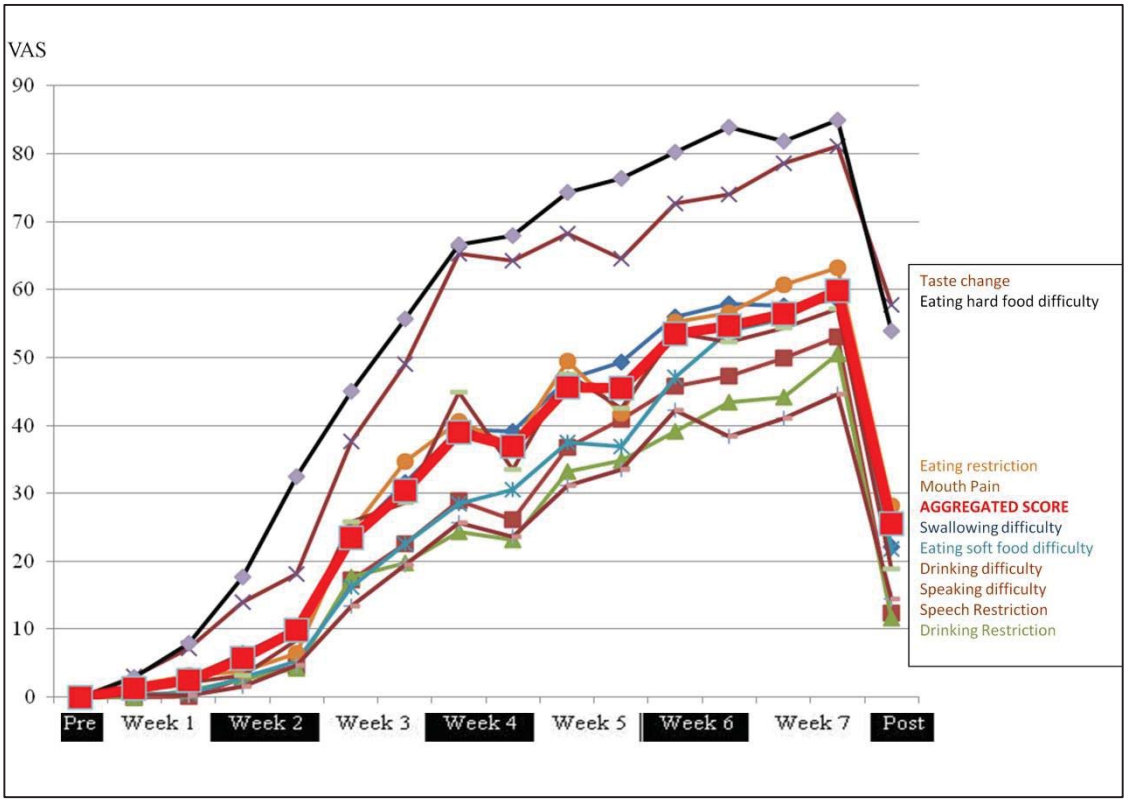


Figure 4

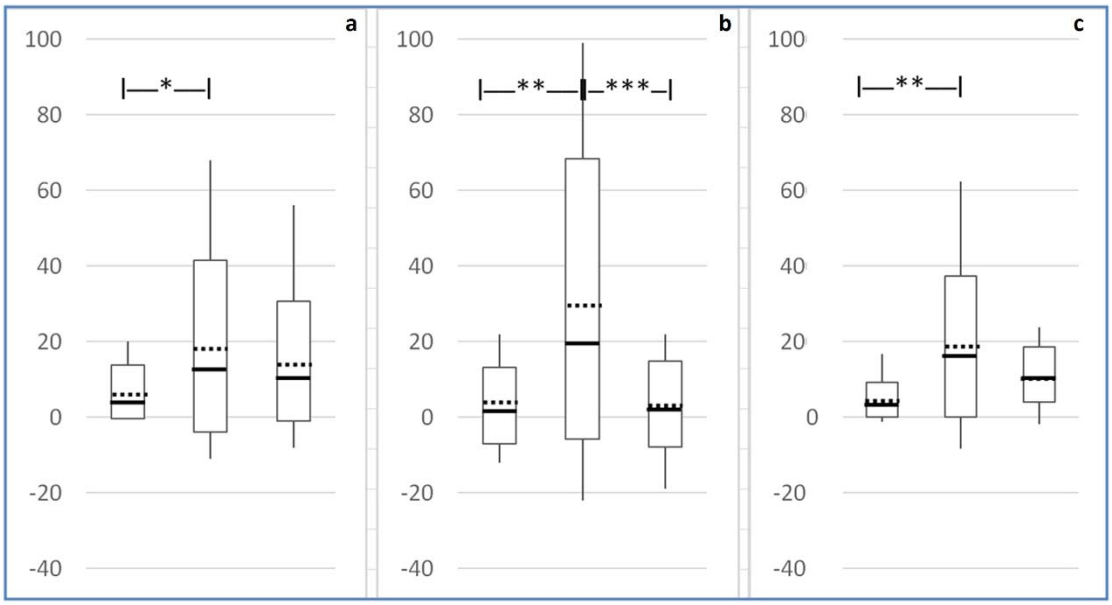
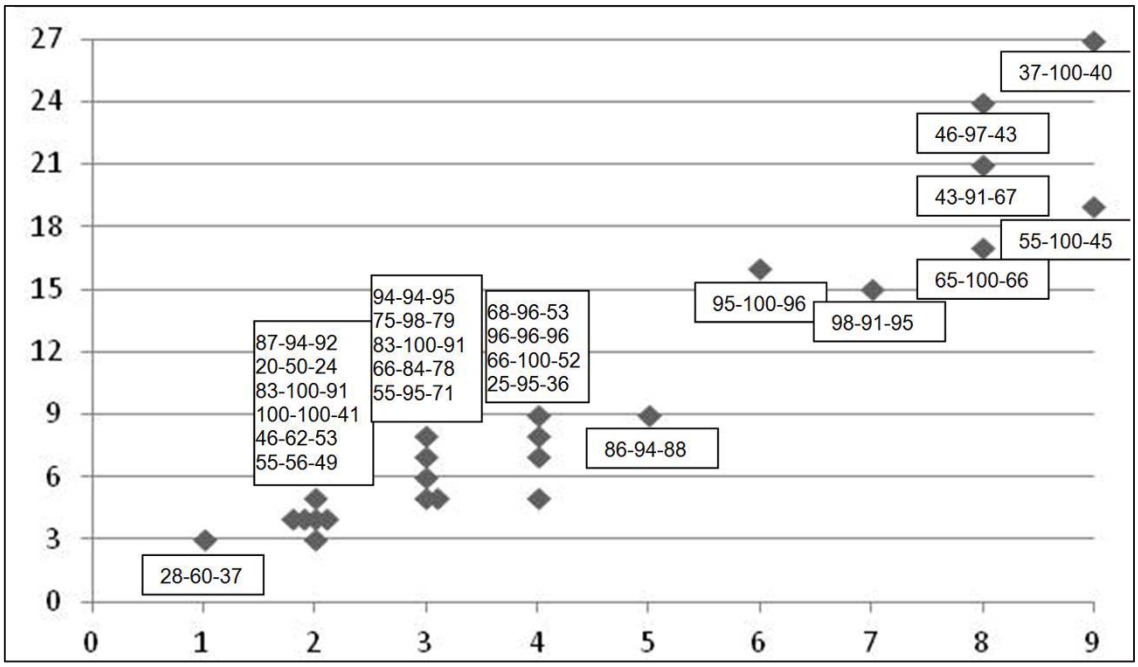


Figure 5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Paper #3

Title Page

Head and neck cancer patients experiencing radiation-induced mucositis - should the signs or the symptoms be measured?

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Abstract

Objective: To improve our understanding of how patient reported outcomes (PROs) in head and neck (H&N) cancer patients who undergo cancer treatment may possibly be influenced by factors beyond local effects of radiotherapy.

Methods: Initially 50 H&N cancer patients scheduled to receive radiation therapy consented to participate in a prospective observational study. The participants underwent an oral examination prior to the commencement of therapy and twice weekly over the course of the therapy period. The 33 participants who finished the therapy underwent one more examination four to six weeks after its completion. At each clinical session, clinical signs of oral mucositis (OM) were recorded using clinician-based scoring tools and the participants completed a VAS-questionnaire recording the degree of impairment caused by OM with regard to common oral functions. The strengths of correlation between signs and symptoms at the different time points throughout the study period was appraised using a linear mixed model with robust repeated measures. 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). As well, the study participants with moderate correlations between signs and symptoms (n=5) were contrasted with the ones with very good correlations (n=10). Simple bivariate tests were used for these comparisons.

Results: 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). 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.

Conclusion: H&N cancer patients often report different adverse impacts on daily oral functions caused by OM that are discordant with objective clinical findings. PROs should be incorporated as outcomes in any interventional studies regarding OM. If outcomes are to be used in interventional studies, the changes of PROs values should be measured on the intra-individual rather than on any inter-individual levels.

Keywords: oral mucositis, oral ulcer, pain, head and neck cancer, oral cancer, radiotherapy; patient outcome assessment, adverse effects

Background

Patient-reported outcomes (PROs) and experiences can augment clinical data and may help assess effectiveness of interventions in cancer care [1-4]. PROs in cancer clinical research have been recommended in patients with e.g., prostate [5], ovarian [6], gynaecological [7], oesophageal [8] or head and neck (H&N) cancer [9]. In cancer patients, PROs monitor symptoms such as oral pain, skin changes, dental health, dry mouth, taste, saliva quality and quantity, swallowing and mouth opening difficulties, shoulder disability/motion, voice/hoarseness, social domains, and functional domains [9]. One symptom that develops during radiotherapy treatment is oral mucositis (OM), which can interfere with cancer treatment [10], initiate weight loss due to non-intake of food [11] and even cessation of treatment [12]. A novel PRO tool named PROMS (Patient Reported Oral Mucositis Symptom) addresses the extent that OM impairs oral functions, including dysphagia and dysgeusia [13].

Many challenges remain with regard to establishing acceptable methodological qualities of PROs, and how PROs may be implemented optimally in cancer clinical research [14,15]. A primary challenge is to define the most relevant PROs [16]. A second challenge is that PRO and clinician reported outcomes are often incongruous. [17]. Hence, demonstrating a strong correlation between PRO and relevant clinical outcomes remains important, to strengthen the justification for including the subjective experiences reported by study participants in prospective clinical cancer research.

In a recent cohort study of patients with head and cancer patients, the authors observed that all participants in the study developed oral and pharyngeal mucositis of varying degrees of severity during the course of the 6 or 7 weeks treatment period [18]. The study participants were monitored closely twice weekly throughout the full treatment period by an investigator who conducted intraoral examinations applying different clinician-based assessment tools,

and in addition collected questionnaire information. On a group level, the OM signs as appraised by the clinician using the NCI [19] and OMAS [20] tools, correlated well with the patient-reported experience of OM, when appraised by the PROMS tool [13]. On an individual level, however, large variations of reported adverse impact on oral functions attributed to OM were recognized. These findings prompted the current investigation to explore potential explanations of these phenomena.

The objective of this investigation was to improve our understanding of how PROs in H&N cancer patients who undergo cancer treatment may possibly be influenced by factors beyond local effects of radiotherapy as well as the clinically assessed degree of lesion-severity, by contrasting the characteristics of the study participants who reported high PROMS scores, but had relatively low clinical reported finding and *vice versa*. Also of interest were the characteristics of the study participants who demonstrated very low correlations between the observed signs of OM versus the patient-reported experience of OM.

Methods

Main Study

The materials and methods have been described in detail elsewhere [18]. In brief, a prospective single cohort study was undertaken at the Princess Margaret Cancer Centre, Toronto, Canada. The objective was to appraise the merits of supplementing clinical assessments of OM with the PROMS instrument amongst H&N cancer patients undergoing radiotherapy with or without concurrent chemotherapy. Study approval was obtained from the Research Ethics Boards of the Toronto University Health Network in 2009 (ref. #09-0231-CE). Twenty participants were required to obtain 80% power of the study, based on estimation of 90% correlation between patient-reported and observed data. In expectation of a

high participant dropout, the investigators recruited more participants than strictly required (i.e. 50 participants).

For inclusion in this study, participants had to be at least 18 years of age and diagnosed with carcinoma in the H&N region and with a minimum Karnofsky score performance status of 60%. All participants were scheduled to receive radiotherapy for their H&N cancer with a minimum prescription radiation dose of 54 Gray (Gy), with or without concurrent chemotherapy.

The fifty consenting participants underwent an oral examination at baseline prior to the commencement of cancer therapy. Seven participants did not complete the cancer therapy and three received less than the 54 Gy of radiation while 7 discontinued their participation in the current study, primarily due to fatigue. The remaining 33 participants were examined clinically twice-weekly over their course of seven (n=25), six (n=7) and four (n=1) weeks of radiotherapy, and then one more time four to six weeks after the completion of the cancer therapy. The prevailing diagnosis amongst the 33 study participants who completed the whole study follow-up was cancer in the oropharynx, T-stages 1 and 2 (Table 1).

All study participants received intensity-modulated radiation therapy (IMRT). The most common dose was fractions of 2 Gy over 33 and 35 visits over 6 or 7 weeks, respectively. The field of radiation and volume of radiated tissue varied depending on tumor location and TNM cancer stage. About half of the study participants received concurrent chemotherapy (n=15, 45%).

Clinical examination

Three different clinician-based scoring tools were used to record clinical signs of OM. These were (i) the clinical component of the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (NCI-CTCAE v. 3) [19], (ii) the clinical component of

the Oral Mucositis Assessment Scale (OMAS) [20] and (iii) a tool locally developed in Toronto and termed “TOTAL-VAS-OMAS” [13]. In the NCI-CTCAE v. 3 the occurrence and severity of OM is graded using an ordinal score ranging between 0 (none) and 4 (most) as observed at any site within the oral cavity. The OMAS concept is based on scoring between 0 (none) and 3 (ulceration) or 2 (erythema) in nine specific intra-oral locations. Hence, the maximum sum scores are 27 (9 sites x3) for ulceration and 18 (9×2) for erythema. The “TOTAL-VAS-OMAS” tool consists of two visual analogue scales (VASs) ranging between 0 to 100 mm for full mouth assessments of erythema and ulceration respectively. Prior to commencing the study the clinical examiners were calibrated by using clinical laminated photographs for scoring of OM of various degrees of severity. These photographs were also used during the study period to prevent drifting of the intra-rater assessments (i.e. periodic re-calibration).

Patient Questionnaire

At each clinical examination, the participants completed a PROMS questionnaire [13] to appraise the degree of impairment caused by OM with regard to common oral functions. The PROMS scale consists of 10 questions that are answered using VAS, by setting a mark on each horizontal line measuring 100 mm. One question focused on mouth pain caused by the OM, ranging from none to worst possible. A second question was directed towards dysgeusia, ranging from hypogeusia to complete loss of taste. The remaining 8 questions dealt with how much the pain was being caused by OM on the day of the clinical examination as well as its impact on different oral functions, including dysphagia.

Statistical analyses

Spearman rank correlation was applied between the PROMS scale values versus respectively, the NCI-CTCAE v.3, the OMAS and the TOTAL-VAS-OMAS scores. A linear mixed model

with robust repeated measures was used to appraise the strengths of correlation at the different time points throughout the observation period, while taking into account the repeated nature of the measurements. A Bonferroni correction was applied to all statistical tests to account for multiple testing of the same measures. All the multivariate statistical tests were done by an independent professional statistician using the statistical procedures ‘‘PROC CORR’’ and ‘‘PROC MIXED’’ in the SAS System Version 9.2 software (SAS Institute, Cary, NC, USA). Correlations showing a Spearman’s *Rho* of less than 0.20 were considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and more than 0.80 very good [21].

The characteristics of the study participants with the most extensive manifestations of OM, but reporting minor pain and adverse impact on oral functions (n=6 “stoical sufferers”) were contrasted with the ones with the most minor manifestations of OM, but reporting extensive pain and adverse impact on oral functions (n=7, “complaining sufferers”). Moreover, the study participants characterized with moderate correlations between clinical signs and patient-reported OM (n=5) were contrasted with the ones with very good correlations (n=10). As the number of study participants was small in light of the many identifiable variables, it was considered inappropriate to apply multivariate statistical analyses. 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.

Results

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 Gray 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. The correlations measured, over all time points, between the clinician-determined scores versus the patient experience of OM ranged between 0.65 and .75 (Spearman’s *Rho).*

The correlations were fairly consistent in the early, middle and late stage of the radiotherapy, except for correlations between OMAS Ulceration scores and the PROMS scale values at early time points. (Table 2). On the individual level, however, the Spearman's *Rho* varied markedly, from moderate to very good correlations, exemplified by study participants "A" and "B". (Figures 1-2). The characteristics of the study participants in the two sub-cohorts defined by high and low correlations are comparable, except perhaps with regard to age ($p < 0.05$, t-test) (table 3).

The study participants in the two sub-cohorts defined by high manifestation and minor complaints and *vice versa* did not differ with regard to the recorded variables (Table 4). The group of "stoical sufferers" is exemplified in particular by study participant "C" (Figure 3). In order to understand this issue more clearly an example of the findings obtained from one particular patient is presented here. A 50 year old Caucasian non-smoker male experienced maximum clinical scores of OM yet, except for reporting "difficulties eating hard food" and "change in taste", his PROMS-values were low during the full 6-week treatment period. Moreover, he reported no intake of opioid analgesics. The correlation between the individual components of the PROMS assessment tool with the clinician-determined scales was good to very good (Spearman's *Rho* 0.70– 0.96) except for difficulties and restriction of drinking and speech.

As an example of a "complaining sufferer", study participant "D" (Figure 4) is presented as well. This patient had modest manifestations of OM and yet reported almost maximum scores using the PROMS. This 63 year old Caucasian male reported high pain levels despite use of opioids. He was a smoker and he continued to smoke during the course of his 6-weeks treatment period, although the number of cigarettes was reduced to one or two cigarettes per day. The correlation between the individual components of the PROMS assessment tool with

the clinician-determined scales was high, (Spearman's *Rho* 0.76– 0.99) *except* for difficulties eating hard foods and change of taste.

Discussion

In this study, it is clear that clinical observations of oral ulceration can vary substantially from individual patient OM experiences. Thus, 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. In this small study, particular patient characteristics were not clearly associated with discrepancies between the clinician observed signs and the patient-reported symptoms. Only age was identified as different between the groups. It is possible that the younger patients (likely to be HPV+) have a different type of response to treatment. 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 other factors. Firstly, the diagnostic abilities and perception of the examiners under the given examination settings may have been inadequate. Secondly, there may be a possibility that the subepithelial tissue damage with manifestation of OM may have differed in the current study sample due to variations in treatment regimes. A third possibility is that patients differ with regard to responsiveness to a given tissue damage, pain or dysfunction. A mixed model analysis on a larger study sample may provide better indications relating to this issue.

Examiner diagnostic abilities

The calibrated clinical examiners used two dental mouth mirrors and a high-power head lamp as the light source for clinical assessment of OM. Although the standard routine was to undertake a structured examination of all intraoral and upper pharyngeal areas, it cannot be ruled out that pharyngeal OM might have been underdiagnosed due to the study participant's

inability to fully open their mouth because of pain or trismus. However, participants with oropharyngeal cancer did not appear to be over- or under-represented in any of the sub-cohorts (Table 3, 4). The illustrated study participant "D" with an oropharyngeal cancer (Figure 4), could have had OM that was undetected since an endoscope was not used by the examiner. Regardless, it bears repeating that mere clinical assessment of ulcers (e.g. measuring ulcer size) may be an inadequate mean to measure the actual clinical impact of OM on any particular patient. This is not only important in relation to management of cancer treatment itself but also in the evaluation of potentially helpful therapeutic agents designed to prevent or ameliorate the severity of OM.

Treatment regime

A possible effect of radiation dose and concurrent chemotherapy did not explain the variance of reported adverse impact or poor correlations (Table 3, 4). All study participants received the same radiation modality (IMRT), even though the targets and consequently the fields of radiation differed. Analysis of these doseimetric factors will be the subject of future work. While there is some information regarding relationship with tissue and dosage [22], the authors have failed to identify any papers that have studied a possible inter-dependency between tissue dosages and patient-reported pain. Some studies [23,24] 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.

Patient responsiveness

Individuals differ with regard to responsiveness to a given amount of tissue damage, pain or dysfunction, and a reaction to oropharyngeal pain is likely linked to the local intraoral

condition, general medical condition, and personality traits boosted by support from family or close community. Certainly it is well-known that personality traits and even levels of cognitive function can alter pain perception, reactions and responses to treatments for pain [25].

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 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 [20,26], but so far no consensus has been reached.

A range of cofactors linked to life-style and medical comorbidity have been identified as risk factors for increased OM. Smoking has not been linked consistently with any particular presentation of OM since it's been demonstrated to be a risk factor for higher [27], lower [28] or no effects [29], on levels of OM, but with no elaboration of whether the OM-caused pain and adverse impact on oral functions is amplified or diminished. The same applies to oral hygiene [30-33]. It has been suggested that some individuals may be more susceptible to mucosal damage due to genotypic variation [34]. 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 [35]. This factor may be partially responsible for the identification of age as a significant difference between the groups.

The current study aimed primarily to monitor closely the development of OM both clinically and experientially by study participants in order to describe the extent of any adverse impacts that OM might have on various oral functions. In this regard it was noted that

several keywords could be applied to characterize the experiences of patients who have developed OM, which might include anxiety, distress, pain, exhaustion, fatigue and nausea. At the time the study was conceived, questionnaire burden was a concern and it was therefore considered counter-productive to burden the participants with more questionnaires that would address other functional issues (e.g., coping styles, level of distress, personality indices, comorbidity status or health related quality-of-life inventories).

General Findings

Earlier pain experience and different coping mechanisms may also have influenced the way they answered the PROMS-questionnaire. An example is the study participant C (Figure 3) who stated to the investigator that he "was sure he was going to be fine" and continued to show a very optimistic attitude at all study appointments. In general, dispositional pessimists tend to report more pain than optimists [36,37]. Moreover, for some of the participants, the early experiences with debilitating acute OM caused anxiety and may have led to embellished reports of discomfort, while as the therapy progressed, the perception of pain and adverse impact on oral functions became more tempered.

Individuals, whether they are study participants in a trial or not, are influenced by mood and psychological status on the day they are asked to complete questionnaires [38,39]. We observed frequently that the participants' psychological status on the particular examination day appeared to influence their PROMS-reporting. More than once, study participants expressed, particularly towards the end of the treatment period, that they were so happy to know that their radiotherapy sessions were coming to an end and accordingly, we noted but did not quantify (not large enough sample) that these subjects tended to enter lower VAS-values regarding the impact of their OM during the last few study visits.

Many patients with newly diagnosed H&N cancer develop high levels of mental distress and psychiatric morbidity during the treatment process [40,41]. One estimate suggests that about

one-third of all patients appear to have a probable case of a major mood disorder, with predominantly females appearing more anxious than males at diagnosis, and patients under 65 years of age more than those over 65 [42]. It has been also noted that patients who experience OM demonstrate a significant increase in mood disturbance [43].

Finally, different coping mechanisms [44] may influence the way patients feel how they are affected by OM and also the way they report their symptoms on the PROMS questionnaire. Because there appears to be a relationship between anxiety and the use of negative coping styles [45] all reported PROs should be viewed with caution. Yet, it is the PROs that should dictate how one manages a patient who has developed OM as opposed to merely basing management on the size, location or extent of lesions.

Study participants with different ethnicity [46] or cultural differences [47,48] may have a different way of both reporting and coping with pain. The possible impact of cultural background was not studied in the current investigation. Most of our study participants were Caucasian (82%), however their cultural background may not have been the same.

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 [18]. 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 is advised when appraising quality of life improvements [49]. It is this type of approach that could optimize individual management of patients as alluded to above. What remains to be resolved is to identify the relative intra-individual changes in patient-reported VAS-values to categorize whether the individual cancer patient's condition is improving or worsening *versus* no change. An advantage of using an intra-participant approach is that relative, intra-individual changes may provide a good indication of

meaningful changes for individual patients rather than absolute changes. However, it is still reasonable to infer that this relative change of VAS-scoring is also subjective, as well as influenced by the factors described above. Observations made in other research domains is that a ≥ 20% intra-individual VAS-improvement in performance-based physical functioning is a minimal clinically important difference that may be used to categorize ankylosing spondylitis patients as improvers or non-improvers [50].

Conclusion

H&N cancer patients often report different adverse impacts on daily oral functions caused by OM that are discordant with objective clinical findings. Especially in the low dose range, the correlation is low between patient reported and clinical manifestations of OM. PROs should be incorporated to augment clinical observations, as either primary or secondary outcomes in any interventional studies regarding OM. If outcomes are to be used in interventional studies, 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.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors have given final approval of the final version and agree to be accountable for all aspects of the work.

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Table 1: Patient diagnosis and T-stage, number of patients in each category (n=33).

	Total No (%)	T0/Tx	T1	T2	T3	T4
Oral cavity	5 (15)	1	1	1	1	1
Oropharynx	13 (39)	1	3	4	3	2
Salivary glands	6 (18)	-	1	2	2	1
Other	9 (27)	4	-	2	1	2

Table 2. Correlations (Spearman's *rho*) between the aggregate PROMS scale values versus the other measurements measured at different stages of the radiotherapy

Aggregate PROMS versus:	**NCI-CTCAE v3**	**TOTAL-VAS-OMAS Ulcerate**	**TOTAL - VAS-OMAS Erythema**	**OMAS Ulcer Area**	**OMAS Erythema Area**
Radiotherapy < 20 Gray	0.51	0.25	0.54	0.24	0.54
Radiotherapy 20 - 60 Gray	0.54	0.57	0.60	0.41	0.47
Radiotherapy > 60 Gray	0.52	0.48	0.47	0.45	0.44
Across all values	**0.75**	**0.75**	**0.78**	**0.65**	**0.69**

Table 3. 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

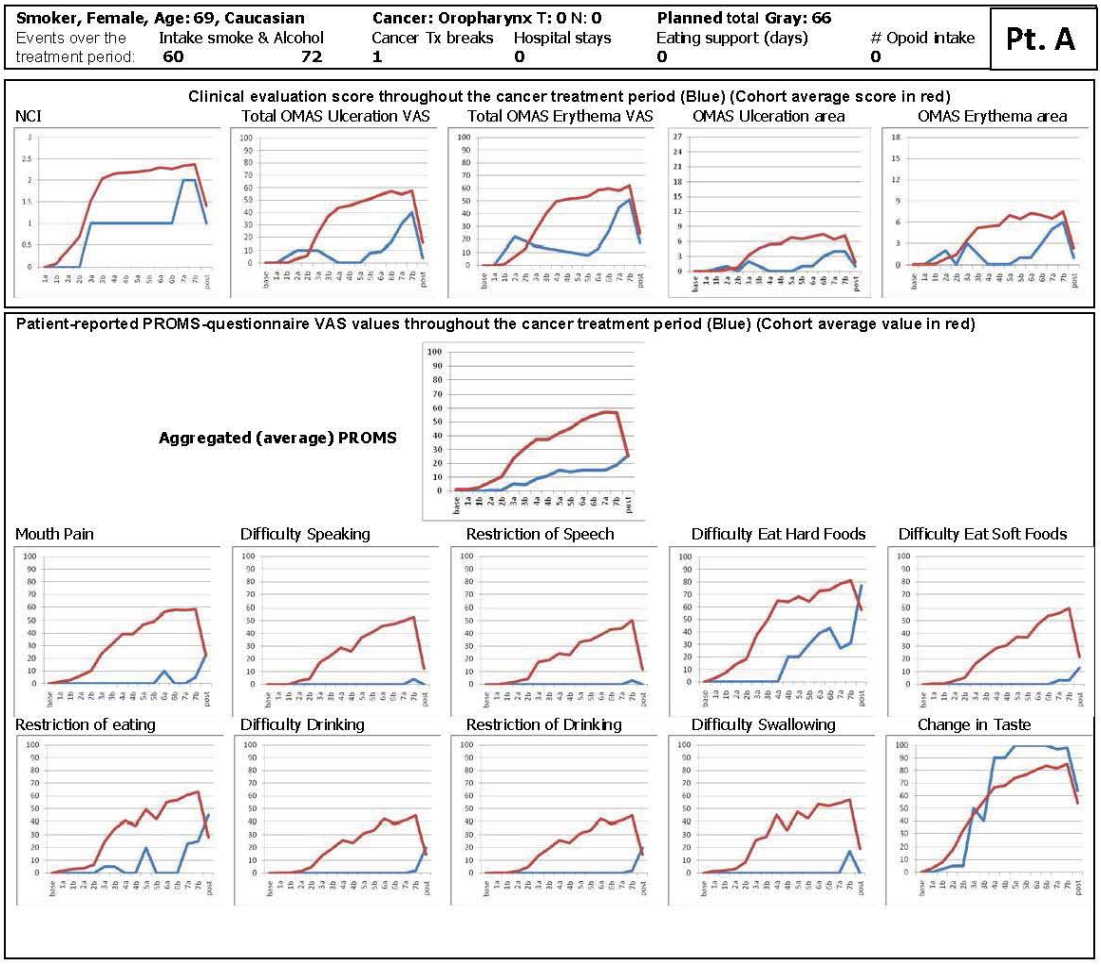
Table 4. Characteristics of the study participants with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions (left column, n=6), the study participants with minor manifestation of OM, but reporting extensive pain and adverse impact on oral functions (center column, 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

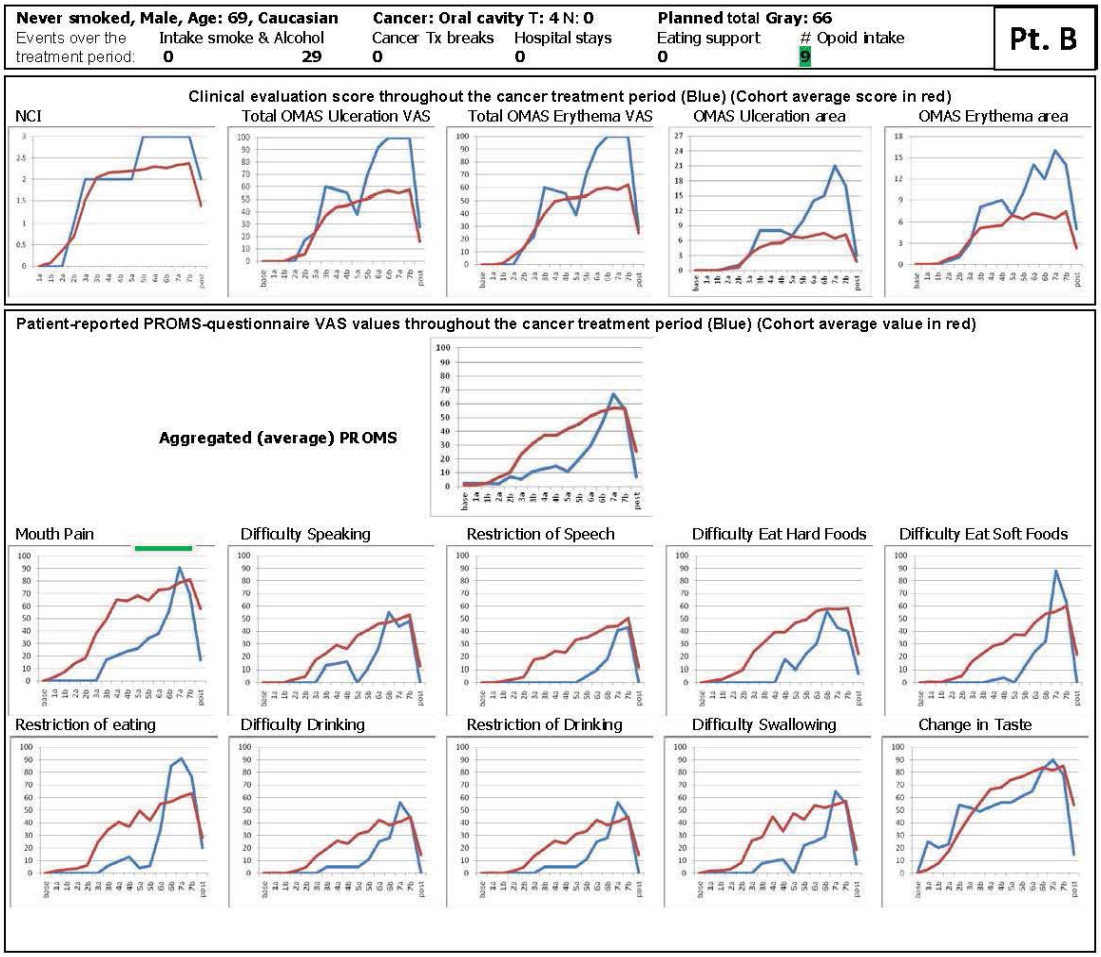
Figure 1. Representative study participant with moderate correlations between clinical signs and self-reported OM experience represented by the individual components of the PROMS tool, (Spearman's *rho* .0.16-0.70).



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

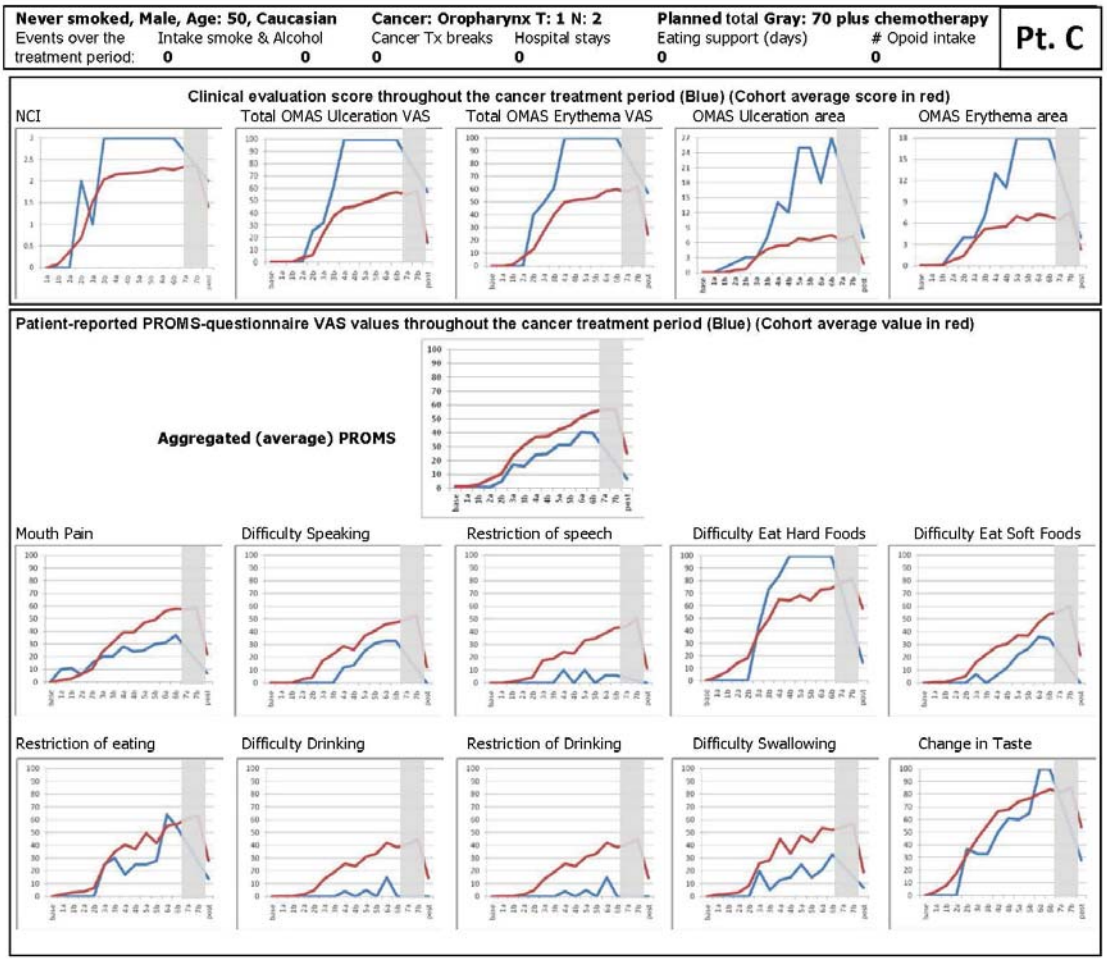
Figure 2. Representative study participant with very good correlation between clinical signs and self-reported OM experience, represented by the individual components of the PROMS tool (Spearman's *rho* .0.83-0.98).



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

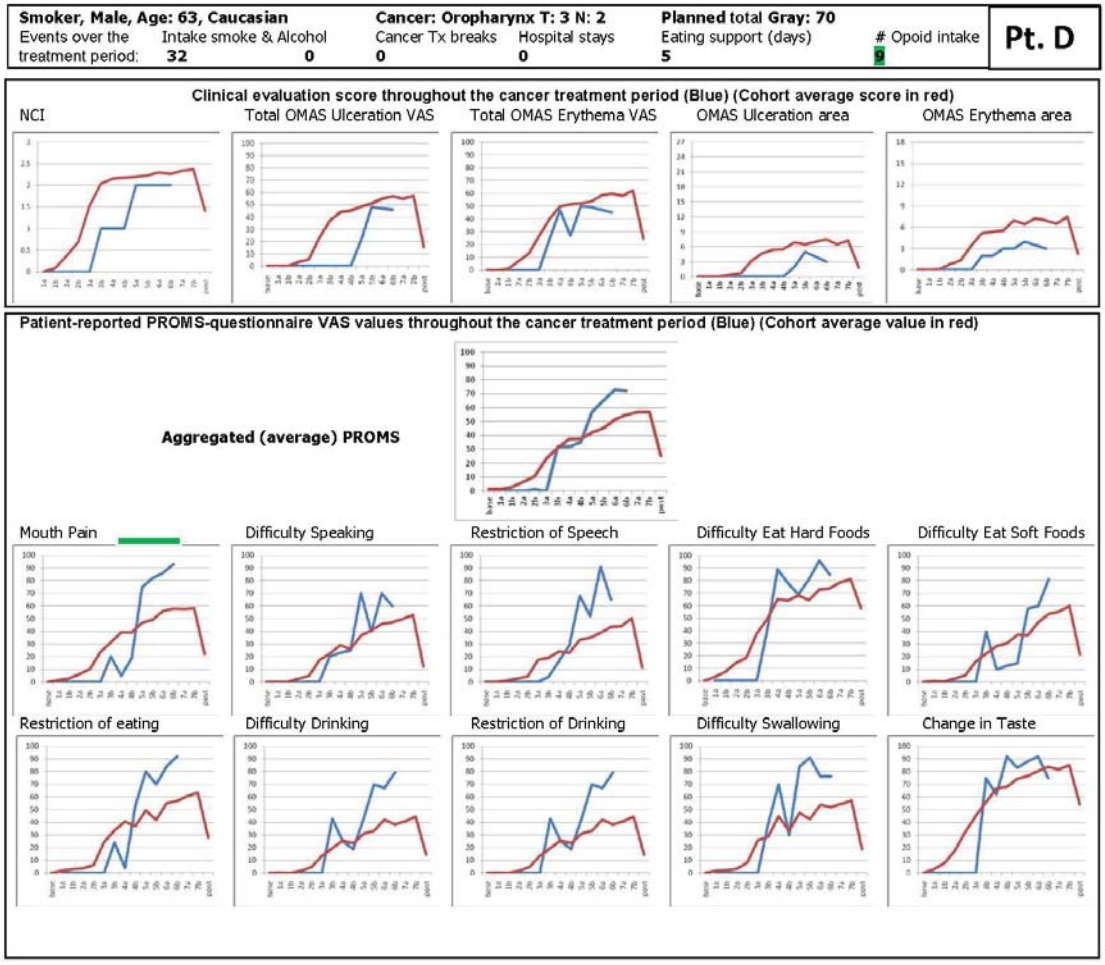
Figure 3. Representative stoical sufferer with extensive manifestation of OM, but reporting minor pain and adverse impact on oral functions.



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

Figure 4. Representative complaining sufferer with minor manifestation of OM, but reporting extensive pain and adverse impact on oral functions.



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