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	4	0	11	15 (45)
Fair-Poor	5	4	7	16 (49)
Edentulous	1	1	0	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	3	4	8	15 (45)
Fair-Poor	2	2	12	16 (49)
Edentulous	1	1	0	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).
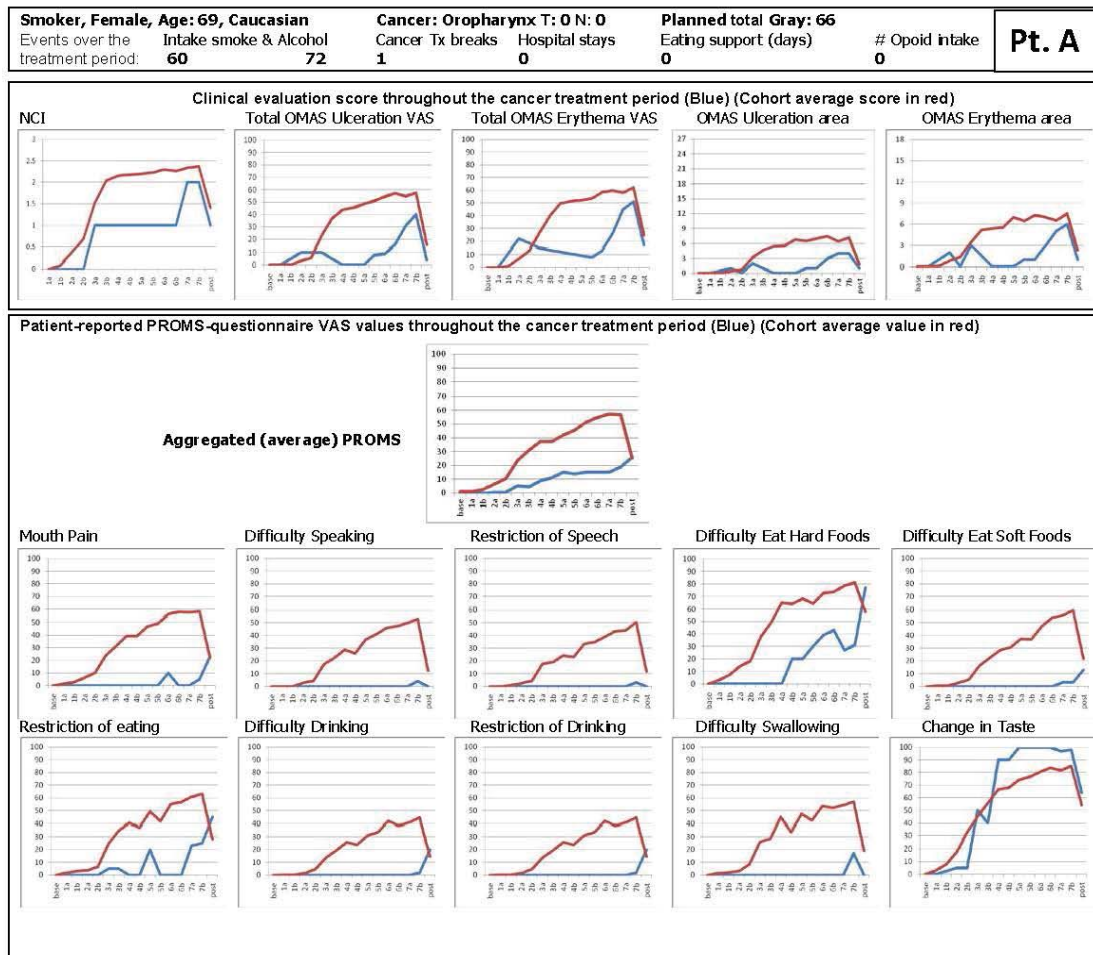
	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.43	0.35	0.35	0.35	0.34
Difficulty Speaking	0.47	0.51	0.51	0.46	0.50
Restriction of Speech	0.47	0.51	0.51	0.46	0.50
Difficulty Eat Hard Foods	0.55	0.47	0.47	0.56	0.48
Difficulty Eat Soft Foods	0.70	0.69	0.69	0.68	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

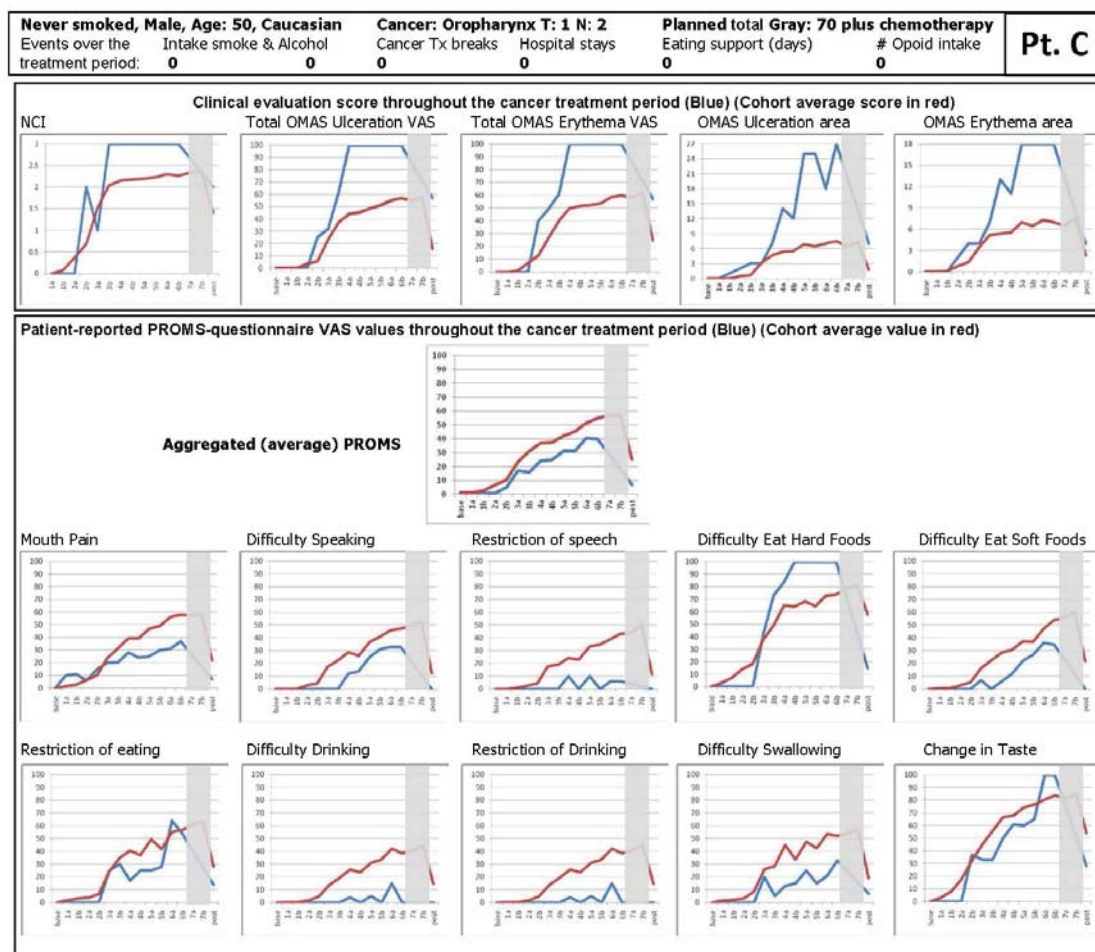Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

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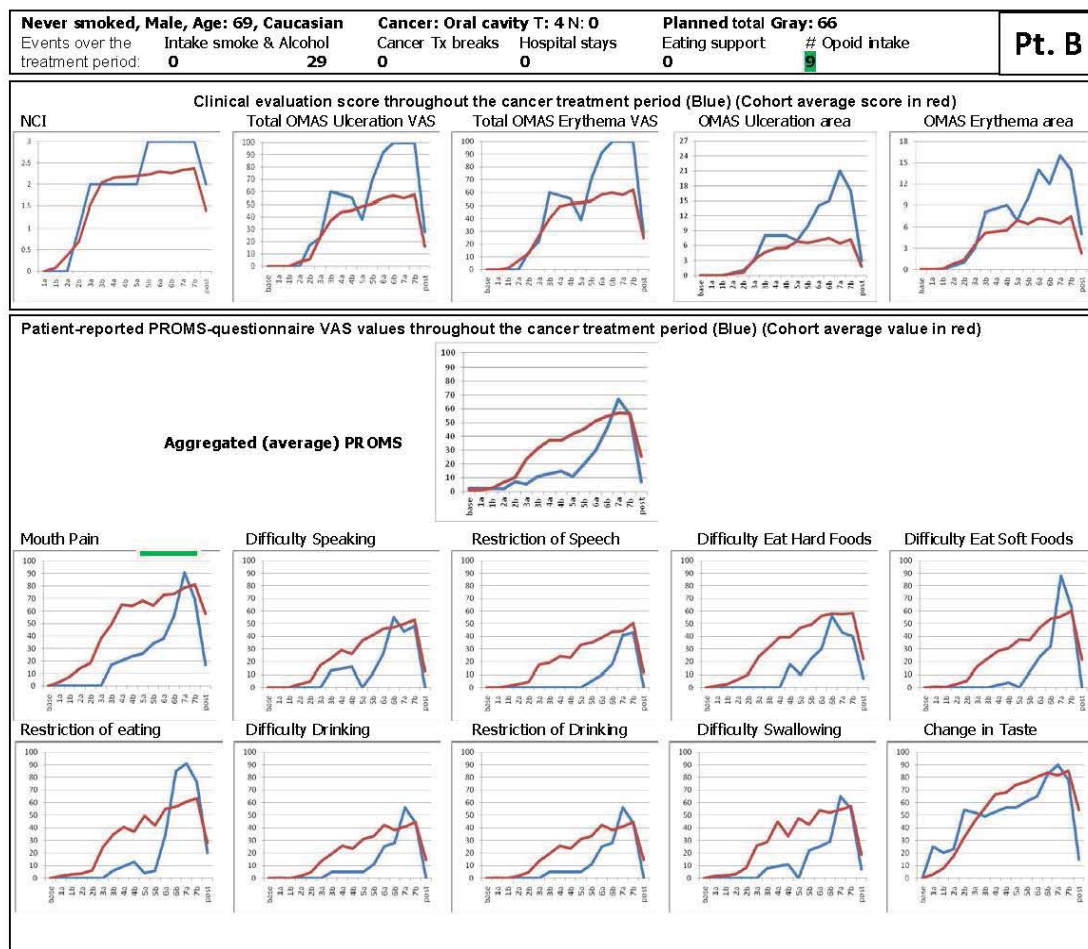
Correlations between patient-VAS values (individual components of the PROMS) and clinical scores

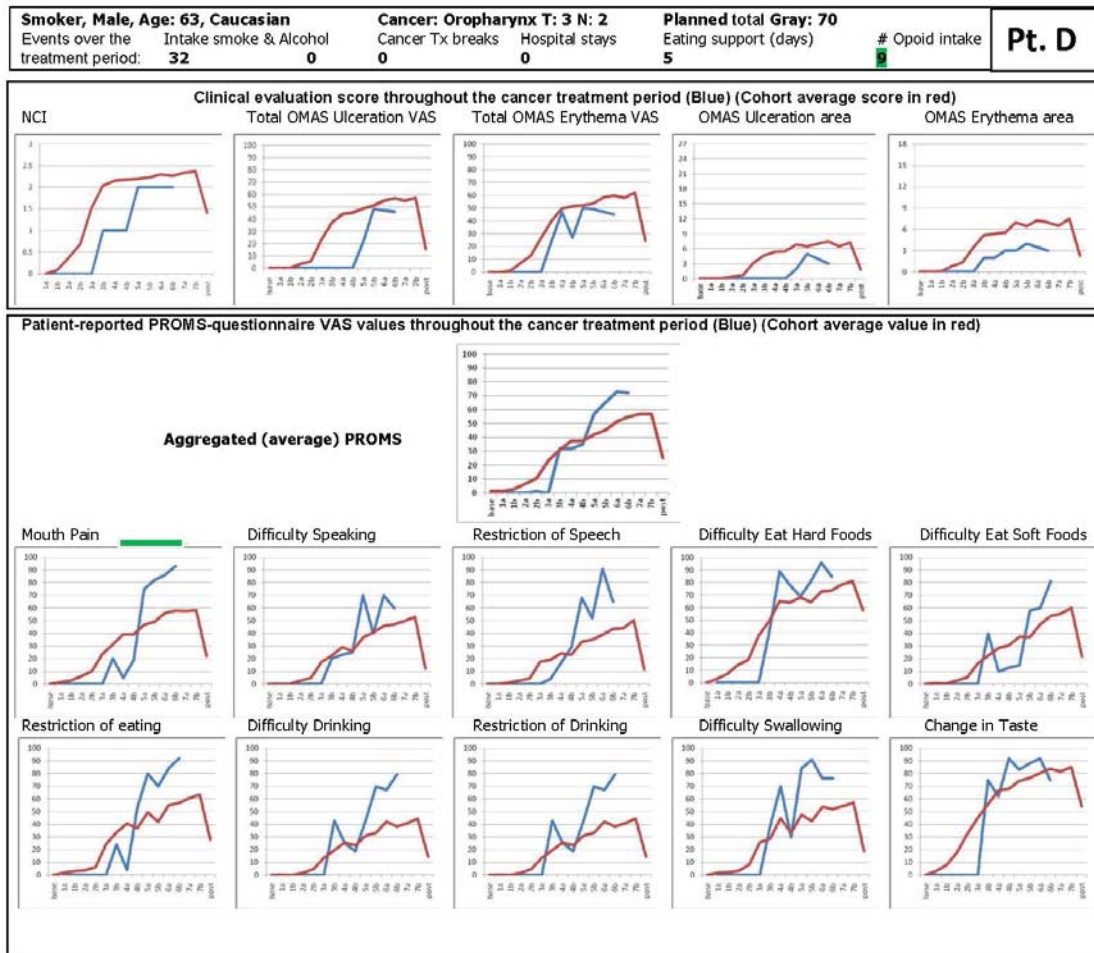|	NCI-v3	Total OMAS Ulceration	Total OMAS Erythema	OMAS Ulcer Area	OMAS Erythema
Mouth Pain	0.89	0.90	0.90	0.91	0.90
Difficulty Speaking	0.83	0.93	0.93	0.91	0.88
Restriction of Speech	0.86	0.87	0.87	0.91	0.88
Difficulty Eat Hard Foods	0.91	0.95	0.95	0.96	0.95
Difficulty Eat Soft Foods	0.87	0.89	0.89	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.