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## RELATION OF MUCOUS MEMBRANE ALTERATIONS TO ORAL INTAKE DURING THE FIRST YEAR AFTER TREATMENT FOR HEAD AND NECK CANCER

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### Abstract

**Background**—Acute oral mucositis is associated with pain and impaired swallowing. Little information is available on the effects of chronic mucositis on swallowing.

**Methods**—Sixty patients treated for cancer of the head and neck were examined during the first year after their cancer treatment. Oral mucosa was rated with the Oral Mucositis Assessment Scale. Stimulated whole-mouth saliva, oral pain rating, percent of oral intake, and 2 subscales of the Performance Status Scale for Head and Neck (PSS-HN) cancer were also collected.

**Results**—Mucositis scores and pain ratings decreased over time while functional measures of eating improved over time. Reduction in chronic mucositis was correlated with improved oral intake and diet.

**Conclusion**—Lack of association with pain was attributed to the absence of ulcerations. Continued impairment of oral intake during the first year posttreatment may be related to oral mucosal changes and other factors.

### Keywords

mucositis; oral intake; diet; head and neck cancer; radiotherapy; chemotherapy

Oral mucositis refers to erythematous and/or ulcerative lesions of the oral mucosa<sup>1,2</sup> and is a frequent and severe consequence of chemotherapy or radiotherapy to the head and neck.<sup>3</sup> The incidence and severity of oral mucositis vary depending upon a number of treatment parameters such as chemotherapy agent, number of cycles of chemotherapy, site of the cancer, amount of radiotherapy, and fractionation schedule.<sup>2,4-6</sup> Reported rates of severe grade 3 or 4 oral mucositis range from 35% to 100% depending upon the fractionation schedule and type of chemotherapy.<sup>3,6-26</sup>

Pain is a common side effect of mucositis, with the ulcerative stage being especially painful.<sup>2,3,14</sup> The correlation between pain and oral mucositis has been reported to range from 0.63 to 0.7.<sup>22,27,28</sup> Ulceration of the oral mucosa and the resulting pain can impair a patient's ability to swallow and eat,<sup>2,3,28,29</sup> with the correlation between mucositis and dysphagia being approximately 0.60.<sup>22,27</sup> In the few studies that report dietary-related outcomes, there is a high and significant correlation between severity of mucositis and the incidence of gastrostomy tube feeding and weight loss.<sup>3</sup>

Oral mucositis peaks near the completion of treatment, approximately 7 to 9 weeks after initiation of radiotherapy<sup>22</sup> and usually resolves between 2 and 10 weeks after the end of treatment.<sup>1,2,9,14,15,30-32</sup> Impaired oral intake, however, often persists long into the first year after cancer treatment<sup>33-39</sup> when the impact of oral mucositis is expected to have dissipated. Few studies have investigated the incidence of oral mucositis after the acute stage and none have examined the relation of potential mucosal change to continued impaired swallowing function. This study reports on a cohort of patients with treated head and neck cancer who were followed for up to 1 year after completion of treatment to determine whether a correlation exists between mucous membrane changes and impaired swallowing function within the first year after cancer treatment.

## MATERIALS AND METHODS

### Patients

Sixty (60) patients with cancer of the head and neck served as subjects; subjects were recruited from 6 participating institutions. Fifty-two of the patients (87%) were men, whereas 8 were women (13%). The patients ranged in age from 23 to 78 years and had an average age of 56 (SD = 11).

Thirty patients (50%) had tumors in the oropharynx. Twelve patients (20%) had laryngeal tumors; 4 patients (7%) had tumors in the oral cavity; 3 patients (5%) had tumors in the hypopharynx. Six patients (10%) had tumors in the nasopharynx and another 5 patients (8%) presented with an unknown primary. Most of the patients (62%) had stage IV disease.

Twelve patients (20%) had stage III disease, 7 patients (12%) had stage II disease, and 4 patients (7%) had stage I disease.

Forty-nine patients (82%) received chemoradiotherapy for treatment of their cancer. Five patients (8%) had primary surgical intervention followed by chemoradiation, and 6 patients (10%) had surgery with postoperative radiotherapy. Patients received an average radiation dose to the primary of 6896 cGy. Fifty-four patients received some form of chemotherapy. Chemotherapy drugs included cisplatin, carboplatin, paclitaxel, and 5-fluorouracil.

### Study Protocol

All procedures were approved by the institutional review board for studies involving human subjects at each participating institution. Subjects were examined at 6 points in time relative to completion of their cancer treatment: 1, 2, 3, 4, 6, and 12 months post-cancer treatment completion. Posttreatment testing times were measured from the completion of primary treatment (ie, after surgery or after completion of all primary chemoradiotherapy).

At each evaluation point, patients completed the tasks described below.

**Xerostomia Assessment (Weight of Stimulated Saliva)**—Stimulated whole-mouth saliva production (from all salivary glands) was quantified by taking the difference of the weight of a 4" × 4" sterile gauze pad before and after chewing for 2 minutes.<sup>40</sup> Weight was reported in grams. Lower saliva weight indicates greater salivary dysfunction.

**Ratings of Oral Mucositis**—Oral mucositis was rated with the Oral Mucositis Assessment Scale (OMAS), a scoring system developed and validated by Sonis et al, 1999.<sup>11</sup> The scale rates ulceration on a 4-point scale (0 = no lesion; 1 = lesion(s) total <1 cm; 2 = lesion(s) total 1–3 cm; 3 = lesion(s) total >3 cm) and erythema on a 3-point scale (0 = none; 1 = not severe; 2 = severe) at 9 locations in the oral cavity (upper labial mucosa, lower labial mucosa, right buccal mucosa, left buccal mucosa, right ventral and lateral tongue, left ventral and lateral tongue, floor of mouth, soft palate, and hard palate). Six mucositis scores were calculated from these measures. Higher values on the mucositis scores indicate greater impairment.

**Patient Rating of Oral Pain**—Patients were asked to rate their pain as the worst mouth pain they had experienced within the last 24 hours on a 10-point scale,<sup>28</sup> with a score of 0 equaling no pain and 10 equaling the worst possible pain.

**Percentage of Nutrition Taken Orally**—Patients were asked to estimate the percentage of their nutrition that they take orally (based upon the number of calories taken orally vs the number of calories taken via tube feedings). A higher percentage of nutrition taken orally indicated better function.

**Performance Status Scale for Patients with Head and Neck Cancer**—The Performance Status Scale for Head and Neck (PSS-HN) cancer<sup>41</sup> is a clinician-rated tool composed of 3 scales defining diet, speech, and eating in public. Two subscales, Normalcy of Diet subscale and the Eating in Public subscale were used in this study. The Normalcy of

Diet subscale assesses the degree to which a patient is able to eat a normal diet. The scale is a ranking of 10 food categories arranged from easy-to-eat at the low end, to hard-to-eat at the high end. Ratings are based on the highest ranking food the patient is able to eat. The Eating in Public subscale assesses the degree to which the patient eats in the presence of others. This scale consists of 5 levels ranging from “always eats alone” at the low end to “no restriction of place, food, or companion” at the high end. Ratings are based on the patient’s report of whom he or she eats with and in what settings. Higher values on these subscales indicate better function.

Assessments were performed by the speech-language pathologist (SLP) at each participating institution. The SLPs were part of the clinical team, working with treating physicians to evaluate swallowing and oropharyngeal function in patients with head and neck cancer. All SLPs were trained in the specific study procedures at a 2-day workshop. Each SLP received extensive instruction and practice in the administration of the OMAS from a representative of the Mucositis Study Group that worked on the development and validation of the scale.<sup>11</sup> The SLPs were not blinded to the patient’s treatment type or time posttreatment.

### Data Reduction and Analysis

Ratings on the OMAS were converted into 6 mucositis scores: mean mucositis ulceration score (MMSU), mean mucositis erythema score (MMSE), mean mucositis score (MMS), weighted mean mucositis score (WMMS), extent of mucositis score (EMS), and worst site score (WSS). Although MMSU and MMSE were not used in the initial validation of the OMAS,<sup>11</sup> they were included in the current study because little has been reported in the literature on the presence of ulceration and erythema between 2 and 12 months post-cancer treatment completion. Although MMS and WMMS are composites of MMSU and MMSE, the investigators were interested in observing which component, ulceration or erythema, or both, were contributing to MMS and WMMS. The scores were calculated as follows:

MMSU: the average of the ulceration ratings over the 9 sites, each on a 0 to 3 scale. MMSU ranges from 0 to 3.

MMSE: the average of the erythema ratings over the 9 sites, each on a 0 to 2 scale. MMSE ranges from 0 to 2.

MMS: the sum of MMSU plus MMSE. MMS ranges from 0 to 5.

WMMS:  $(5/6)MMSU + (5/4)MMSE$ . WMMS ranges from 0 to 5. Because ulceration is based on a 0 to 3 scale and erythema is based on a 0 to 2 scale, MMS weighs ulceration more than erythema in MMS. WMMS weighs ulceration and erythema the same.

EMS: the number of sites with either an ulceration score of 3 or an erythema score of 2. EMS ranges from 0 to 9.

WSS: the maximum erythema score plus the maximum ulceration score across all sites. WSS ranges from 0 to 5.

Using SAS statistical software (SAS Institute, Cary, NC), the following variables were used in the statistical analysis: MMS, MMSU, MMSE, WMMS, EMS, WSS, PSS-HN Normalcy of Diet Scale (PSSD), PSS-HN Public Eating Scale (PSSE), pain rating (PAIN), percent of nutrition taken orally (ORAL), and saliva weight (WEIGHT). Mean values and SDs for each variable were calculated by evaluation point. The independent sample *t* test was used to compare means at the 1-month posttreatment evaluation between patients who did versus those who did not complete the 12-month evaluation. These means were compared over time using repeated measures analysis of variance. For each variable, a linear regression of the variable on follow-up time determined a regression coefficient for each of 60 patients. These coefficients were compared to zero using a 1 sample *t* test. The regression coefficients were then correlated using the Spearman correlation statistic among the 9 measures, with significance determined by the *t* test for zero correlation. Statistical significance was indicated when  $p < .05$ ; no adjustment was made for multiple testing.

## RESULTS

Thirty-five of the 60 patients had 12 months of follow-up, 10 patients had 6 months of follow-up, and 15 patients had follow-up between 2 and 4 months, for a median follow-up time of 6 months (range, 2–12 months). For each measure, means at 1 month did not differ significantly between the 35 subjects with 12 months of follow-up and the 25 subjects without 12 months of follow-up. Means and SDs for each of the measures by evaluation point are summarized in Table 1.

Each variable demonstrated a significant change over time. Mucositis scores decreased over time, indicating a resolution of the symptoms of mucositis with time posttreatment completion. Patient rating of pain also decreased over time. Functional measures related to eating improved over time with Normalcy of Diet, Public Eating, and percent nutrition taken orally all increasing between 1 and 12 months post-cancer treatment. Stimulated saliva production decreased slightly within the first 3 months after cancer treatment but increased slightly by 12 months posttreatment.

Linear regression coefficients were calculated for each measure across the 60 subjects. All mucositis scores, pain rating, and saliva weight were negative, reflecting a decrease over time. EMS demonstrated a significant linear decrease over time (mean regression coefficient =  $-0.09$ ;  $p = .001$ ). All the functional measures of eating (PSSD, PSSE, percent of oral intake) demonstrated significant linear increases over time, indicating an improvement in function. PSSD had a mean regression coefficient of 4.75 ( $p < .0001$ ), PSSE had a mean regression coefficient of 2.97 ( $p = .015$ ), and percent of oral intake had a mean regression coefficient of 5.58 ( $p = .0001$ ).

Table 2 presents the Spearman intercorrelation coefficients and significance levels among the study variables. Correlations represented the relationship between changes over time in 1 variable with change over time in another.

The 6 mucositis scales (MMS, MMSU, MMSE, WMMS, EMS, and WSS) were highly intercorrelated with significant positive correlations ranging from 0.53 to 0.97.

Changes in all mucositis scores except EMS were correlated significantly and negatively with changes in PSSD. Decreases in the mucositis scales over time are associated with increases in the PSSD scale over time.

Three of the mucositis scores (MMS, MMSE, and WMMS) also were significantly and negatively correlated with PSSE. Decreases in the mucositis scales over time were associated with increases in the PSSE scale over time. There was no correlation between MMSU, EMS, or WSS and PSSE.

Changes in all mucositis scores except EMS were correlated significantly negatively with changes in percent of nutrition taken orally. Decreases in the mucositis scales over time were associated with increases in the oral intake scale over time.

Changes in functional measures of eating (PSSD, PSSE, and ORAL) over time were all positively intercorrelated. No variable was significantly correlated with change in pain or change in saliva weight (not included in Table 2).

## DISCUSSION

This study investigated the relation of chronic changes in oral mucosa with pain and oral intake between 1 and 12 months after completion of treatment for head and neck cancer. Very mild mucosal changes persisted after the acute stage, and these changes were correlated with impairment in eating function. As mucosal injury continued to resolve, it was associated with an improvement in oral intake and diet. The change in oral mucositis and pain over time, although statistically significant, was probably not clinically significant given the small degree of mucositis ratings and very low ratings of pain.

Oral mucosal changes during the first year after treatment were characterized more by erythema than ulceration. A comparison of median scores derived from the OMAS indicates that ulceration was essentially absent after 1 month posttreatment completion. Erythema, although very mild in its rating, was the primary characteristic of chronic oral mucositis in this study. Median EMS scores indicated that any existing mucosal injury was not widespread, and that by 6 months posttreatment, the oral mucosa had normalized. In the literature, persistent late mucosal changes such as mild to moderate atrophy have been reported 6 to 12 months after treatment completion.<sup>6,16,22</sup> The OMAS focuses on 2 aspects of mucosal injury, erythema and ulceration, whereas other scales for assessing late mucosal effects of radiotherapy such as the LENT SOMA Scales and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme focus on mucosal dryness, atrophy, telangiectasia, and ulceration. It is possible that the patients in this study had dryness and atrophy which persisted through the first year; however, these mucosal characteristics were not assessed in this study.

There was no correlation between pain ratings and any of the mucositis scores or functional measures of swallowing. Pain during the acute phase is a common side effect of oral mucositis, with the ulcerative stage being especially painful.<sup>2,3,14</sup> The first evaluation point in this study was 1 month posttreatment completion. Based upon the literature, it would be

expected that ulcers are likely to be healed by 4 weeks posttreatment. This expectation was realized in this study, as reflected in the low scores for MMSU. Given the lack of ulceration in these patients, the minimal pain scores would not be unexpected.

None of the mucositis scale scores, oral function variables, or pain were related to change in saliva weight. Saliva weight and oral intake during the first 12 months postchemoradiotherapy also were observed to be unrelated in a separate cohort.<sup>42</sup>

Although this study investigated the relationships between chronic oral mucosal changes and functional measures of eating and swallowing, correlation does not indicate causation. Severe impairments in swallowing function may be observed years after completion of radiotherapy or chemoradiotherapy.<sup>33-39</sup> There is evidence of continued deterioration of swallowing function for years after chemoradiation as a result of progressive fibrosis in irradiated tissues of the head and neck.<sup>37,39</sup> It may well be, therefore, that long-term changes in oral mucosa after treatment for cancer of the head and neck co-occurred with a reduction in functional swallow measures but did not cause the functional impairment.

## CONCLUSION

The purpose of this study was to investigate the relationship between chronic changes in oral mucosa and functional measures of eating and swallowing between 1 and 12 months after treatment for cancer of the head and neck. The results of this study indicate that improvements in the condition of oral mucosa were correlated with improved oral intake and diet, yet not associated with changes in pain. The lack of association with pain was attributed to the absence of ulcerative lesions. Continued impairment of oral intake during the first year posttreatment may be related in part to oral mucosal changes but also the result of progressive fibrosis in irradiated tissues of the head and neck.

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**Table 1**  
Means, medians, SDs, and number of observations across 6 evaluation points for mucositis scale measures and functional measures of eating and swallowing.

	1 mo postcancer treatment	2 mo postcancer treatment	3 mo postcancer treatment	4 mo postcancer treatment	6 mo postcancer treatment	12 mo postcancer treatment
<b>MMSU (<math>p = .003</math>)</b>						
Mean	0.29	0.23	0.20	0.18	0.07	0.05
Median	0.11	0	0	0	0	0
SD	0.46	0.43	0.49	0.44	0.24	0.13
No.	57	57	55	47	42	33
<b>MMSE (<math>p &lt; .0001</math>)</b>						
Mean	0.36	0.26	0.18	0.15	0.10	0.07
Median	0.33	0.11	0.11	0.06	0	0
SD	0.37	0.34	0.30	0.29	0.24	0.14
No.	57	56	55	46	42	33
<b>MMS (<math>p &lt; .0001</math>)</b>						
Mean	0.66	0.48	0.37	0.31	0.16	0.11
Median	0.44	0.22	0.11	0.11	0	0
SD	0.74	0.70	0.74	0.69	0.46	0.23
No.	57	56	55	46	42	33
<b>WMMS (<math>p &lt; .0001</math>)</b>						
Mean	0.70	0.51	0.39	0.32	0.18	0.12
Median	0.56	0.28	0.14	0.14	0	0
SD	0.75	0.72	0.73	0.70	0.48	0.24
No.	57	56	55	46	42	33
<b>EMS (<math>p &lt; .0001</math>)</b>						
Mean	0.55	0.55	0.31	0.34	0.11	0.03
Median	0	0	0	0	0	0
SD	1.2	1.29	1.18	1.32	0.60	0.17
No.	60	58	55	47	46	34
<b>WSS (<math>p &lt; .0001</math>)</b>						
Mean	1.89	1.51	1.16	1.15	0.67	0.52

	1 mo postcancer treatment	2 mo postcancer treatment	3 mo postcancer treatment	4 mo postcancer treatment	6 mo postcancer treatment	12 mo postcancer treatment
Median	1	1	1	1	0	0
SD	1.73	1.62	1.42	1.44	1.10	0.94
No.	57	57	55	47	42	33
PSSD ( $p < .0001$ )						
Mean	27.7	37.1	47.3	57.6	57.7	75
Median	10	40	50	50	50	90
SD	33.7	32.1	30.7	33.2	32.8	25.4
No.	60	58	55	46	44	34
PSSE ( $p < .0001$ )						
Mean	38.0	51.4	57.9	69.3	71.6	74.3
Median	25	50	62.5	75	75	75
SD	32.3	32.0	33.2	32.7	29.3	31.7
No.	52	54	54	44	44	34
ORAL, % ( $p < .0001$ )						
Mean	32.3	41.6	54.8	63.6	71.0	93.1
Median	1	10	50	100	100	100
SD	45.4	45.8	45.8	42.0	40.9	23.8
No.	60	58	55	47	46	34
PAIN ( $p < .0001$ )						
Mean	2.0	1.4	1.8	1.3	1.0	0.9
Median	1	0	0	0	0	0
SD	2.2	2.3	2.7	2.1	1.8	2.1
No.	56	57	55	47	41	33
WEIGHT, gm ( $p < .0001$ )						
Mean	2.99	2.09	1.91	2.00	1.97	2.15
Median	2.19	1.61	1.35	1.35	1.86	1.71
SD	2.95	2.05	2.26	2.00	2.05	1.75
No.	57	57	54	47	46	33

Abbreviations: MMSU, mean mucositis ulceration score; MMSE, mean mucositis erythema score; MMS, mean mucositis score; WMMS, weighted mean mucositis score; EMS, extent of mucositis score; WSS, worst site score; PSSD, Performance Status Scale for Head and Neck Cancer Diet Scale; PSSE, Performance Status Scale for Head and Neck Cancer Public Eating Scale; ORAL, percent nutrition taken orally; PAIN, patient rating of oral pain; WEIGHT, weight of chewed sterile gauze pad.

Table 2

Intercorrelations and significance levels among mucositis scale measures and functional measures of eating and swallowing.

	MMSU	MMSE	WMMS	EMS	WSS	PSSD	PSSE	ORAL
MMS	0.85*	0.89*	0.96*	0.54*	0.89*	-0.47*	-0.36 <sup>†</sup>	-0.39 <sup>†</sup>
MMSU		0.61*	0.76*	0.54*	0.87*	-0.40 <sup>†</sup>	-0.22	-0.43 <sup>†</sup>
MMSE			0.97*	0.53*	0.74*	-0.37 <sup>†</sup>	-0.38 <sup>†</sup>	-0.32 <sup>†</sup>
WMMS				0.58*	0.82*	-0.42 <sup>†</sup>	-0.36 <sup>†</sup>	-0.35 <sup>†</sup>
EMS					0.53*	0.03	-0.07	-0.09
WSS						-0.38 <sup>†</sup>	-0.23	-0.38 <sup>†</sup>
PSSD							.80*	0.63*
PSSE								0.50*

Abbreviations: MMSU, mean mucositis ulceration score; MMSE, mean mucositis erythema score; WMMS, weighted mean mucositis score; EMS, extent of mucositis score; WSS, worst site score; PSSD, Performance Status Scale for Head and Neck Cancer Diet Scale; PSSE, Performance Status Scale for Head and Neck Cancer Public Eating Scale; ORAL, percent nutrition taken orally; MMS, mean mucositis score.

\* Significant at  $p < .0001$ .

<sup>†</sup> Significant at  $p < .01$ .