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ORIGINAL ARTICLE

# Dysphagia and Oral Morbidities in Chemoradiation-Treated Head and Neck Cancer Patients

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## Abstract

This study prospectively evaluated relationships between oral morbidities and swallowing ability in head/neck cancer patients following chemoradiation therapy (CRT) and at 3 months following CRT. Thirty patients with confirmed head/neck cancer undergoing chemoradiation were assessed with a battery of swallowing measures and measures of oral morbidities related to chemoradiation (xerostomia, mucositis, pain, taste/smell, oral moisture). All measures were completed at baseline (within the first week of CRT), at 6 weeks (end of treatment), and at 3 months following chemoradiation. Descriptive and univariate statistics were used to depict change over time in swallowing and each oral morbidity. Correlation analyses evaluated relationships between swallowing function and oral morbidities at each time point. Most measures demonstrated significant negative change at 6 weeks with incomplete recovery at 3 months. At 6 weeks, mucositis ratings, xerostomia, and retronasal smell intensity demonstrated significant inverse relationships with swallowing function. In addition, oral moisture levels demonstrated significant positive relationships with swallowing function. At 3 months, mucositis ratings maintained a significant, inverse relationship with swallow function. Taste and both orthonasal and retronasal smell intensity ratings demonstrated inverse relationships with measures of swallow function. Swallow functions and oral morbidities deteriorate significantly following CRT with incomplete recovery at 3 months post treatment. Furthermore, different patterns of relationships between swallow function measures and oral morbidities were obtained at the 6-week versus the 3-month assessment point suggesting that different mechanisms may contribute to the development versus the maintenance of dysphagia over the trajectory of treatment in these patients.

**Keywords** Dysphagia · Head and neck cancer · Oral morbidities · Chemoradiation therapy

## Introduction

External beam radiotherapy and concurrent chemotherapy (CRT) for head/neck cancer (HNC) contribute significantly to oral morbidities [1, 2]. Oral morbidities are often long lasting given that HNC prevalence is increasing in younger patients [3] and survival rates are increasing [4]. Moreover, oral morbidities are expected to change during and following treatment. Acute effects of radiation may persist beyond CRT while additional chronic effects may develop 90 days or more after discontinuation of treatment [5, 6]. Common oral morbidities resulting from CRT include oral pain, oral dryness, and taste and smell deviations. One of the most prevalent and debilitating symptoms resulting from CRT for HNC is swallowing difficulty (dysphagia) [1, 7]. Dysphagia has been reported in over 76% of HNC

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patients treated with CRT and may result from both acute and chronic complications of CRT [8–10]. Prior research has implicated relationships between various oral morbidities and dysphagia in CRT-treated HNC patients, but these observations are primarily from patient surveys with few studies prospectively assessing changing patterns in oral morbidities and swallowing functions [7]. Therefore, the primary aim of this study was to prospectively evaluate a cohort of HNC patients to identify the presence and severity of oral morbidities and dysphagia following treatment and at 3 months post treatment. The secondary aim of this study was to identify potential relationships between dysphagia and oral morbidities immediately following CRT and following 3 months of recovery.

## Materials and Methods

The study was undertaken at a university hospital cancer center. The local institutional review board approved the study protocol and all participants signed an approved informed consent form before inclusion in the study. Patients were examined at baseline (within the first 5 days of CRT initiation), 6 weeks (at the completion of CRT), and 3 months (after completion of CRT).

### Patients

Thirty patients receiving CRT for HNC were included in the study at baseline. Inclusion criteria were (1) HNC of oropharyngeal or adjacent regions, confirmed by clinical history and examination, with positive cross-sectional imaging studies and histopathological biopsy excluding other pathologies; (2) planned CRT; (3) no previous history of dysphagia from cancer-related illness. Exclusion criteria were (1) co-existing neurological or medical disorders known to cause dysphagia; (2) prior radiation therapy or surgery to the head and neck region that could contribute to dysphagia; (3) presence of dysphagia, oral pain, xerostomia, or chemosensory deviations at enrollment. All patients received multiple fractional CRT. Twenty-seven of the 30 patients (27/30) received adjuvant chemotherapy with 21 receiving Cisplatin, 3 receiving Erbitux, 2 receiving Cetuximab, and 1 receiving Carboplatin. Table 1 presents demographic characteristics for age, gender, tumor stage, and total radiation dose in Gy. As noted, the majority of cases presented T2 or T3 tumors and 21 cases presented with nodal involvement. Mean Gy was 71.05 within a range from 60.0 to 74.4. The majority of cases (27/30) received either 70.0 or 74.40 Gy. Table 2 summarizes primary tumor sites. The majority of tumors (19/27: 3 with unknown primary) were located in the oropharyngeal region. An additional 5 tumors involved laryngeal structures.

**Table 1** Patient demographics

| Variable | Total cohort |
|---|---|
| Age (Mean and SD) | 61.23 (12.15) |
| Gender (Male:female) | 27:3 |
| Total dose of Gy (Mean and SD) | 71.05 (4.3) |
| Range of Gy | 60.0–74.4 |
| **Tumor stage** | **Number (%)** |
| T0 N2 | 2 (6.7) |
| T1 N1 | 1 (3.3) |
| T1 N2 | 1 (3.3) |
| T2 N0 | 2 (6.7) |
| T2 N1 | 2 (6.7) |
| T2 N2 | 5 (16.7) |
| T2 N3 | 1 (3.3) |
| T3 N0 | 3 (10.0) |
| T3 N2 | 7 (23.3) |
| T4 N0 | 1 (3.3) |
| T4 N2 | 3 (10.0) |
| T4 N3 | 1 (3.3) |
| T*x* N2 | 1 (3.3) |

**Table 2** Primary tumor location and frequency

| Location | *n* |
|---|---|
| Nasopharynx | 2 |
| Faucial arch | 2 |
| Tonsillar fossa/tonsil | 6 |
| Base of tongue | 10 |
| Pyriform fossa | 1 |
| Supraglottic larynx | 2 |
| Suprahyoid epiglottis | 1 |
| Aryepiglottic fold | 1 |
| Vocal folds | 2 |
| Unknown primary | 3 |

### Swallowing Function Assessments

Swallowing function was evaluated with the Mann assessment of swallowing ability-cancer version (MASA-C) [7]. MASA-C has been validated for use in HNC population and demonstrates strong sensitivity, specificity, and positive predictive value for the identification of dysphagia. The total maximum score that can be obtained from MASA-C is 200 points. A cut-off score of 185 determines the presence of dysphagia in the HNC population.

The Functional Oral Intake Scale (FOIS) was used as a measure of functional eating status [11]. FOIS is a valid and reliable tool used to document functional eating abilities. A 7-point ordinal scale describes the functional oral intake of patients with dysphagia.

Spontaneous swallow frequency (SSF) is a measure of integrity of the swallow mechanism, and has demonstrated potential as a clinical screening protocol to identify dysphagia in at-risk populations [12]. SSF was measured with an acoustic recording obtained via a miniature microphone (VT506; Voice Technologies, Zurich) connected to a digital voice recorder (DS-40, Olympus, Tokyo). The microphone was adhered to the skin of the anterolateral neck just below the lateral cricoid cartilage in the area identified by Takahashi [13] as optimal to record swallow sounds. Recordings were obtained over a 15-min interval with all patients seated quietly. All recordings were analyzed offline using an acoustic software program (TF 32; P. Milenkovic, Madison, WI). An experienced judge blind to patient status reviewed all recordings in 1-min segments to identify swallows. SSF rate was calculated as swallows per minute for each 15-min recording.

### Weight Change

Participant weight was measured at each time point. Change in body weight and percentage of body weight change from baseline were calculated between each time point.

### Oral Pain, Mucositis

A generalized Labeled Magnitude Scale (gLMS) [14] was used to rate each patient's perception of oral pain. Patients were asked to determine a maximum point (100) as the strongest sensation they had ever experienced. Following the identification of their strongest sensation, patients were trained on the scale with several questions comparing intensities of various modalities against their strongest sensation, rated at 100. To assess oral pain, patients were asked to use this scale to rate their "current oral pain." Additionally, the World Health Organization Mucositis Scale (WHOMS) [15] was used to grade the severity of oral inflammation.

### Xerostomia and Oral Moisture

Xerostomia was evaluated using the University of Michigan Xerostomia Scale (UMXS) [16]. UMXS is an 8-item scale with self-reported xerostomia ratings from 0 to 10. Higher scores indicate higher patient-perceived xerostomia. Oral moisture was assessed using the Periotron Model 8000 (Oraflow, New York, NY). The Periotron is an electronic micro-moisture meter designed to assess salivary flow from minor salivary glands [17]. A specialized paper was calibrated for moisture then held against the patient's hard palate for 5 s. The paper was subsequently replaced in the Periotron to detect the difference attributable to oral moisture collected from the hard palate. Three measures were completed and an average reading was obtained.

### Taste and Smell

Taste was evaluated with standard preparations of salt (table salt), sweet (table sugar), sour (citric acid), and bitter (quinine) solutions [18]. Patients were asked to "sip and swallow" or "sip and spit" (if they could not swallow) 10 cc of each solution. Patients rated their self-perceived intensity on the gLMS for each tastant. Between each tastant, patients were asked to sip deionized water to neutralize the taste from the previous taste solution.

Smell was evaluated using strawberry and chocolate [19, 20]. Both orthonasal and retronasal routes were evaluated using these materials. To examine orthonasal olfaction, patients were blindfolded and asked to sniff the odorant then rate its intensity with the gLMS. To assess retronasal olfaction, patients were again blindfolded and a nose clip was used to prevent orthonasal olfaction while the odorant was placed in the mouth. After a brief period of oral manipulation of the stimulus material, the nose clip was removed and retronasal smell intensity (via gLMS) was evaluated.

### Statistical Analysis

At each time point, patients were categorized as dysphagic ($\leq$ 185) or non-dysphagic ($>$ 185) based on a validated cut point from the MASA-C. Groups were then examined for swallowing and oral functions. Univariate analyses of potential associations between oral morbidity and swallow function scores were implemented using t-tests for comparison of scores of dysphagic versus non-dysphagic cases. Bivariate correlation coefficients were used to assess relationships among all variables at 6 weeks and 3 months to evaluate any change in the pattern of variables related to dysphagia at these respective time points. Parametric assumptions were confirmed prior to completion of inferential statistics.

## Results

### Patients

During the study, 162 patients were reviewed for eligibility. Of these, 61 met inclusion criteria and 38 (62%) were

recruited into the study. Patient refusal to participate and relocation of oncology services were the primary reasons for non-enrollment. Subsequent to enrollment but prior to baseline testing, 8 patients withdrew consent to participate resulting in 30 patients at baseline. A single patient was not available for the 6-week assessment resulting in 29 patients at that time point. This patient did return for the 3-month assessment. Between 6 weeks and 3 months, five patients were lost to follow-up, one died, and two withdrew from the study resulting in 22 patients at the 3-month time point. Non-parametric analysis of the eight cases who withdrew from the study revealed no significant difference in demographics (age, gender, tumor stage, tumor site, chemotherapy, or radiation exposure) between cases and withdrawals.

## Swallowing Function Assessments

### Swallowing Function

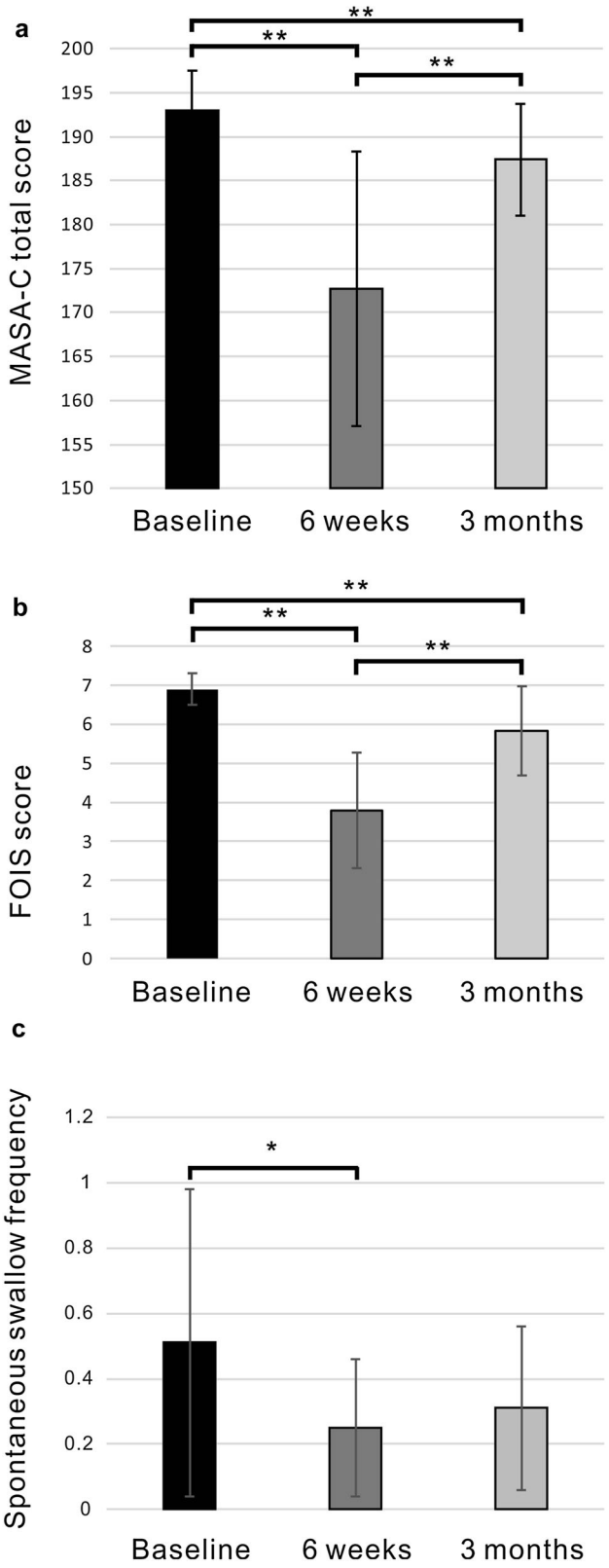
At baseline, the average MASA-C total score for the patient cohort was 192.66 (SD = 4.51). A significant reduction ($t = 6.51$, $p < 0.001$) was observed at 6 weeks ($M = 172.72$, SD = 15.58) with 76% (22/29) of patients demonstrating dysphagia. At 3 months, the average MASA-C score significantly increased ($M = 187.41$, SD = 6.36) compared to 6 weeks ($t = -3.71$, $p = 0.002$) with 27% (6/22) of patients demonstrating persistent dysphagia. Compared to baseline, the average MASA-C score at 3 months remained significantly decreased ($t = 4.22$; $p < 0.001$) (Fig. 1a).

### Functional Oral Intake

At baseline, the mean FOIS score for the patient cohort was 6.90 (SD = 0.40) indicating an unrestricted level of oral intake. No prophylactic feeding tubes were placed in this cohort. At 6 weeks, the mean score of 3.79 (SD = 1.47) decreased significantly ($t = 11.42$, $p < 0.001$). At the 6-week time point, 35% (10/29) of patients were on PEG tube feeding and only 7% (2/29) were on "normal" diets (FOIS > 5). At 3 months, the mean score increased significantly ($M = 5.82$, SD = 1.14) compared to 6 weeks ($t = -4.08$, $p = 0.001$). At 3 months, 9% (2/22) of patients remained on PEG feedings but 73% (16/22) of patients were on "normal" diets (FOIS > 5). Compared to the baseline FOIS score, the mean score at 3 months was decreased significantly ($t = -5.56$, $p < 0.001$) (Fig. 1b).

### Spontaneous Swallow Frequency

At baseline, the mean SSF for the patient cohort was 0.51 (SD = 0.47). SSF decreased significantly ($M = 0.24$,



◀**Fig. 1** Swallow function outcomes. **a** Mean MASA-C scores at baseline, 6 weeks (post-CRT), and at 3 months post CRT. **b** Mean FOIS ratings at baseline, 6 weeks (post-CRT), and at 3 months post CRT. **c** Mean spontaneous swallow frequency (SFF) at baseline, 6 weeks (post-CRT), and at 3 months post CRT

SD = 0.21) at 6 weeks ($t = 2.32$, $p = 0.03$). At 3 months, mean SSF ($M = 0.30$, SD = 0.24) revealed a non-significant ($t = -0.07$, $p = 0.95$) increase compared to 6 weeks. Furthermore, the 3-month mean SSF rate was not significantly different from the baseline value ($t = -1.84$, $p = 0.09$) (Fig. 1c).

## Weight Change

At baseline, the mean body weight was 88.34 kg (SD = 16.15). At 6 weeks, the mean weight decreased significantly compared to baseline ($M = 80.30$, SD = 15.77; $t = 11.77$, $p < 0.001$). At the 6-week assessment, all patients lost weight with a weight loss range from 2 kg to 17 kg and mean percentage of body weight change from baseline was 9.2% (SD = 4.01). Mean weight at 3 months decreased significantly compared to 6 weeks ($M = 77.87$, SD = 11.51; $t = 2.73$, $p = 0.015$). At 3 months, five patients either maintained or gained weight from the 6-week assessment (0–14 kg). All others continue to lose weight beyond the 6-week time point (1–20 kg) and mean percentage of body weight change from baseline was 14.01% (SD = 6.61). Furthermore, the 3-month mean weight was significantly lower than the baseline mean weight ($t = -6.98$, $p < 0.001$).

## Oral Pain, Mucositis

### Oral Pain

At baseline, the mean oral pain rating was 5.52 (SD = 14.96) out of a maximum rating of 100. At 6 weeks, the ratings increased significantly compared to baseline ($M = 29.23$, SD = 29.76; $t = -4.60$, $p < 0.001$). The mean rating at 3 months decreased significantly from the 6-week assessment ($M = 7.65$, SD = 20.09) ($t = -2.36$; $p = 0.035$). Furthermore, the 3-month average rating did not differ significantly from the baseline average ($t = 0.54$, $p = 0.60$) (Fig. 2a).

### Mucositis

At baseline, 20% (6/30) of the patient cohort presented with a mild mucositis (Grade 1: WHO Mucositis Scale). The mean WHOMS score was 0.19 (SD = 0.40). At 6 weeks, 86% (25/29) of the cohort demonstrated mucositis with greater severity than noted at baseline ($M = 1.40$, SD = 0.93; $t = -6.42$, $p < 0.001$). Most cases (72%, 21/29) demonstrated mild-to-moderate mucositis (Grades 1 and 2) while 10% (3/29) demonstrated severe mucositis (Grade 3). The remaining 17% (5/29) of the cohort did not demonstrate clinical evidence of mucositis. At 3 months, 23% (5/22) of the available patient cohort continued to demonstrate mild (Grade 1) mucositis. The mean rating at 3 months significantly decreased from the 6-week time point ($M = 0.23$, SD = .43; $t = -5.51$; $p < 0.001$). Furthermore, the 3-month average rating did not differ significantly from the baseline average ($t = 0.37$, $p = 0.72$) (Fig. 2b).

## Xerostomia and Oral Moisture

### Xerostomia

At baseline, the mean UMXS score was 18.21(SD = 17.14). This value increased significantly ($t = -5.68$, $p < 0.001$) to 43.52 (SD = 14.01) at 6 weeks with no reduction at 3 months ($M = 44.54$, SD = 15.28; $t = -0.604$, $p = 0.555$). The mean UMXS score at 3 months remained elevated from baseline ($t = 5.74$, $p < 0.001$) (Fig. 2c).

### Oral Moisture

Oral moisture measures from minor salivary glands via the Periotron increased significantly from baseline ($M = 93.97$, SD = 47.75) to 6 weeks ($M = 99.87$, SD = 46.01; $t = -3.20$, $p = 0.015$). The mean values at 3 months decreased significantly ($M = 53.62$, SD = 28.10; $t = 2.93$, $p = 0.019$). The mean values at 3 months did not differ significantly from those obtained at baseline ($t = -0.81$, $p = 0.452$) (Fig. 2d).

## Taste and Smell

### Taste Intensity

At 6 weeks, taste intensity ratings of all tastants were significantly decreased from baseline (salt; $t = 2.73$, $p = 0.012$, sweet; $t = 4.21$, $p < 0.001$, sour; $t = 2.15$, $p = 0.043$, bitter; $t = 4.31$, $p < 0.001$) (Table 3). The ratings of salt, sweet, and bitter tastants significantly increased at 3 months (salt; $t = -3.43$, $p = 0.004$, sweet; $t = -5.22$, $p < 0.001$, bitter; $t = -4.42$, $p = 0.001$). Intensity of sour tastant did not increase at 3 months ($t = -1.95$, $p = 0.08$). Non-significant differences were noted between baseline ratings and those obtained at 3 months (salt; $t = 1.04$, $p = 0.315$, sweet; $t = -0.81$,

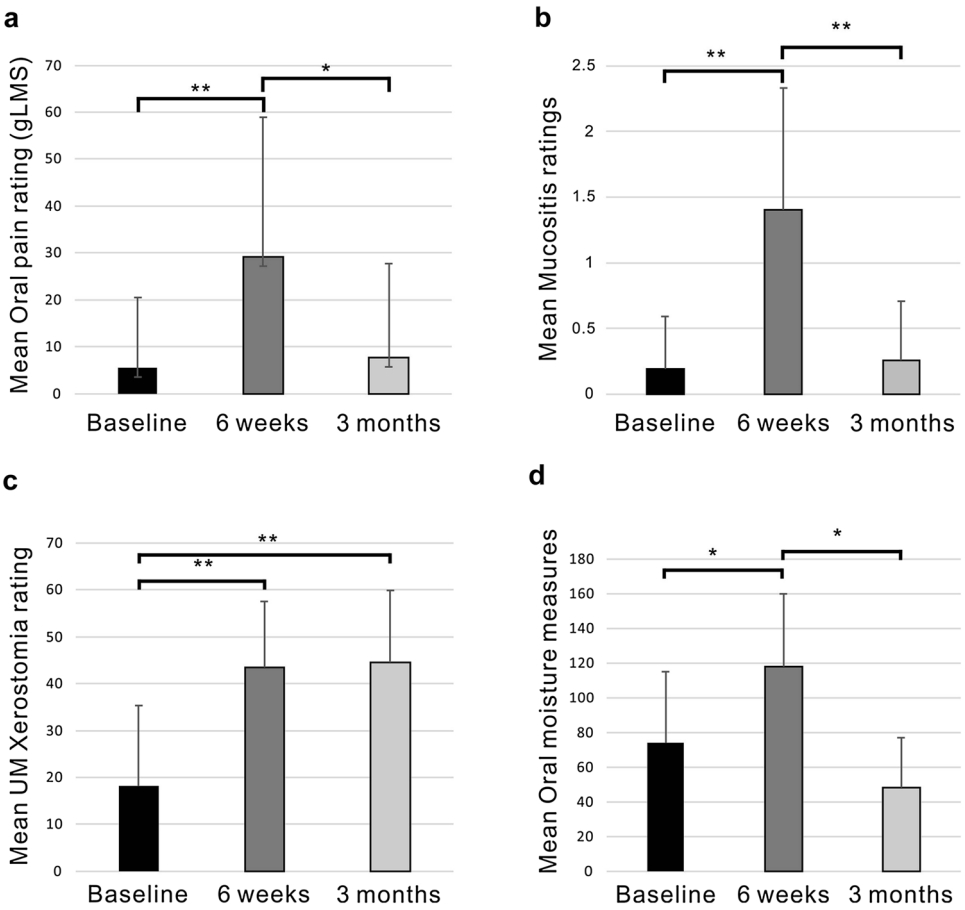



**Fig. 2** Oral morbidities outcomes. **a** Mean oral pain ratings (gLMS) at baseline, 6 weeks (post-CRT), and at 3 months post CRT. **b** Mean mucositis ratings at baseline, 6 weeks (post-CRT), and at 3 months. **c** Mean xerostomia ratings (University of Michigan Xerostomia Scale) at baseline, 6 weeks (post-CRT), and at 3 months. **d** Mean oral moisture measures at baseline, 6 weeks (post-CRT), and at 3 months

**Table 3** Taste and smell intensity means and standard deviations (SD) from patient gLMS ratings

| | Salt | Sweet | Sour | Bitter |
|---|---|---|---|---|
| Taste intensity | | | | |
| Baseline | 46.75 (SD = 30.35) | 45.09 (SD = 26.27) | 53.28 (SD = 28.85) | 58.25 (SD = 29.86) |
| 6 weeks | 25.56 (SD = 33.01) | 19.60 (SD = 30.85) | 35.96 (SD = 33.74) | 23.08 (SD = 35.56) |
| 3 months | 45.71 (SD = 26.32) | 40.12 (SD = 23.00) | 53.06 (SD = 27.17) | 55.06 (SD = 26.77) |
| | Orthonasal smell intensity | | Retronasal smell intensity | |
| | Strawberry odorants | Chocolate odorants | Strawberry odorants | Chocolate odorants |
| Smell intensity | | | | |
| Baseline | 40.54 (SD = 29.40) | 42.21 (SD = 26.02) | 40.44 (SD = 26.94) | 45.87 (SD = 25.94) |
| 6 weeks | 44.74 (SD = 31.45) | 54.82 (SD = 27.53) | 27.50 (SD = 32.51) | 41.40 (SD = 34.63) |
| 3 months | 43.13 (SD = 16.89) | 45.42 (SD = 28.00) | 38.89 (SD = 16.54) | 45.92 (SD = 26.05) |

$p = 0.937$, sour; $t = -0.61$, $p = 0.548$, bitter; $t = 0.17$, $p = 0.867$).

### Orthonasal Smell Intensity

Mean intensity ratings at 6 weeks decreased slightly, but non-significantly from baseline for strawberry ($t = 0.13$, $p = 0.898$) but increased slightly for chocolate ($t = -2.01$, $p = 0.057$) (Table 3). Intensity ratings at 3 months increased slightly, but non-significantly for strawberry ($t = -0.32$, $p = 0.761$) but decreased non-significantly for chocolate ($t = 1.25$, $p = 0.239$) compared to 6 weeks. Compared to baseline, the mean intensity ratings for both odorants were not significantly different at either time point.

### Retronasal Smell Intensity

Mean intensity ratings at 6 weeks decreased non-significantly from baseline for strawberry ($t = 1.77$, $p = 0.092$) and for chocolate ($t = 1.17$, $p = 0.26$) (Table 3). Mean intensity ratings at 3 months increased non-significantly for both odorants when compared to the 6-week assessment (Strawberry; $t = -1.93$, $p = 0.096$, Chocolate; $t = -0.41$, $p = 0.694$). Compared to baseline, the mean intensity ratings for both odorants were not significantly decreased at 3 months.

## Relationships Between Swallow Function and Oral Morbidities

### 6-Week Assessment

At 6 weeks, WHOMS ratings and oral moisture values demonstrated significant relationships with reduced swallowing function, specifically the MASA–C (WHO mucositis: $r = -0.49$, $p = 0.010$) and SSF (oral moisture; $r = 0.58$, $p = 0.038$) (Table 4). Further, UMXS demonstrated a significant, inverse relationship with SSF ($r = -0.412$, $p = 0.05$), and oral moisture ($r = 0.72$, $p = 0.03$) demonstrated a significant, positive relationship with SSF. No other oral morbidity demonstrated a significant relationship with any swallow function measure (Table 4).

### 3-Month Assessment

At 3 months, weight loss demonstrated an inverse relationship with FOIS ($r = -0.48$, $p = 0.05$). WHOMS ratings maintained a significant, inverse relationship MASA-C scores ($r = -0.53$, $p = 0.025$). Taste intensity for salt ($r = -0.69$, $p = 0.009$) and bitter ($r = -0.73$, $p = 0.005$) tastants demonstrated inverse relationships with SSF rate. Both orthonasal ($r = -0.83$, $p = 0.011$) and retronasal ($r = -0.85$, $p = 0.004$) smell intensities for strawberry demonstrated significant, inverse relationships with MASA-C scores at the 3-month assessment. Similarly, both orthonasal ($r = -0.65$, $p = 0.044$) and retronasal ($r = -0.69$, $p = 0.029$) smell intensities for chocolate demonstrated significant inverse relationships with SSF rate (Table 4).

**Table 4** Significant correlations between swallowing measures and measures of oral morbidity at both study time points

| Variable | MASA-C | FOIS | SSF |
|---|---|---|---|
| Weight loss | | | |
| 3-months | | − 0.48* | |
| Mucositis (WHOMS) | | | |
| 6-weeks | − 0.49* | | |
| 3-months | − 0.53* | | |
| Xerostomia (UMXS) | | | |
| 6-weeks | | | − 0.41* |
| Oral moisture (Periotron) | | | |
| 6-weeks | 0.58* | | 0.72* |
| Taste intensity | | | |
| 3-months | | | |
| Salt | | | − 0.69** |
| Bitter | | | − 0.73** |
| Orthonasal smell intensity | | | |
| 3-months | | | |
| Strawberry | − 0.83* | | |
| Chocolate | | | − 0.65* |
| Retronasal smell intensity | | | |
| 6-weeks | | | |
| Strawberry | − 0.46* | | |
| 3-months | | | |
| Strawberry | − 0.85** | | |
| Chocolate | | | − 0.69* |

*MASA-C* Mann assessment of swallowing ability-cancer, *FOIS* Functional Oral Intake Scale, *SSF* spontaneous swallow frequency (*$p < 0.05$, **$p < 0.01$)

## Discussion

Results of this study indicate that swallow functions deteriorate significantly following CRT with incomplete recovery at 3 months post treatment. Similar patterns were noted across the various oral morbidities assessed in this study. Furthermore, different patterns of relationships between swallow function measures and oral morbidities were obtained at the 6-week versus 3-month time points.

Reduction in swallowing function and related oral morbidity following CRT was anticipated and has been documented in prior work [1, 21]. The exception to this pattern in the current study was the intensity of orthonasal smell at 6 weeks. Neither odorant demonstrated a reduction in orthonasal smell intensity post CRT [22]. Likewise, one odorant (chocolate) did not demonstrate any change in retronasal smell intensity following CRT. Conversely, retronasal smell intensity for the other odorant (strawberry) did demonstrate a reduction post CRT without significant recovery at 3 months. This difference between orthonasal and retronasal smell intensity might be related to the position of the respective olfactory cells. Retronasal olfactory cells exist closer to the oropharyngeal region than those for orthonasal olfaction [23]. As a result, retronasal olfaction may be more impacted by CRT to the oropharyngeal region [24].

Relationships between swallow measures and oral morbidity measures differed at 6 weeks versus 3 months. Although preliminary, these results might indicate different mechanisms contributing to the development of dysphagia in CRT-treated HNC patients versus maintenance of dysphagia at least to 3 months post CRT. At 6 weeks, MASA-C scores demonstrated significant relationships with WHOMS ratings, oral moisture, and orthonasal smell intensity for strawberry. Furthermore, SSF was significantly related to oral moisture values and UMXS score at this time point. The inverse relationship between mucositis ratings and clinical swallow performance at 6 weeks may at least partially result from the inclusion of mucositis as an item within the MASA-C or the emphasis on dysphagia in the WHO tool. Conversely, this relationship might also indicate that mucositis contributes to edema, pain, and other sequelae that may negatively impact swallow performance [25, 26]. Of interest is the lack of significant relationships between oral pain ratings and any measure of swallow function. Oral pain ratings increased significantly post CRT but no significant relationships were identified between pain ratings, swallowing or other oral functions. Given this result, the role of pain in post CRT dysphagia in the head/neck population might be reconsidered [27]. The positive relationship between oral moisture and swallow functions (MASA-C and SSF) at 6 weeks may reflect the role of spontaneous swallowing. As the amount of moisture or other material increases in the mouth or pharynx, the frequency of swallowing reportedly increases [28]. Conversely, reduction of swallowing functions (SSF) has been associated with dysphagia in various health conditions [12, 29, 30]. The positive relationship between swallowing function and oral moisture values at the 6 weeks may indicate that individuals with a lesser degree of dysphagia may also demonstrate more preserved oral moisture. Oral moisture, as measured in this study (via Periotron), reflects function of minor salivary glands (primarily in the hard palate). The observed increase in oral moisture at the 6-week assessment was not anticipated. This finding and the observed relationship with swallow function at this time point will require additional investigation with a different focus from the present study. Finally, MASA-C scores at 6 weeks were inversely related to orthonasal smell intensity specific to strawberry. On the surface, this inverse relationship implies that more severe dysphagia may be related to increased smell intensity. However, since only a single smell intensity measure was related to swallowing functions and given that orthonasal smell intensity did not change significantly post CRT, this finding should be viewed as speculative and addressed further in subsequent work. Collectively, the pattern of significant relationships between swallowing functions and oral morbidities following CRT suggests that mucositis and oral moisture may be most related to swallowing performance [31].

At 3 months, a significant inverse relationship between MASA-C scores and WHOMS ratings was maintained. But, as noted only five patients demonstrated any degree of mucositis and these were all rated as grade 1 (mild). As such, we interpret this relationship at 3 months post CRT to reflect the low severity of mucositis in the presence of higher swallow abilities. Of greater interest was the pattern of significant, inverse relationships between smell and taste intensity and swallowing metrics. MASA-C scores at 3 months were inversely related to both orthonasal and retronasal smell intensities for strawberry while SSF was significantly and inversely related to taste intensity for salt and bitter. Collectively, this pattern suggests that enhanced intensity of smell and taste functions might contribute to the maintenance of dysphagia in this population. Enhanced smell and taste intensity might function as an aversive stimulus to swallowing function [24, 32, 33]. Such speculation will require future work as we did not query subjects in the current study regarding their perceptions of smell and taste stimuli as aversive.

## Limitations

This prospective cohort study was limited to a small sample with further reduction in analyzed cases due to subject withdrawal during the study. We experienced loss to follow-up at 6 weeks and 3 months that precluded a more comprehensive analysis of many outcomes. Patient drop out during a prospective HNC study is not unusual [34, 35] but, it may introduce a degree of subject bias into the overall results. We were unable to identify any trends that differentiated patients who dropped out of the study. In addition, we only followed these cases to 3 months post CRT. Furthermore, additional variables such as type, amount, and duration of medications (specifically pain management medications) might provide insight into the observed results. Thus, to better clarify the proposed patterns reported in the current study, future studies should incorporate larger samples, follow patients for a longer post-treatment interval, and consider additional variables that have potential to influence the observed outcomes.

## Conclusion

Swallow functions and oral morbidities deteriorate significantly following CRT with incomplete recovery at 3 months. Furthermore, different patterns of relationships between swallowing function and oral morbidities were obtained at each assessment point suggesting that different

mechanisms may contribute to the development versus the maintenance of dysphagia over the trajectory of treatment in patients treated with CRT.

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## Compliance with Ethical Standards

**Conflicts of interest** The authors declare that they have no conflicts of interest.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the local institutional review board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants including in the study.

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