Impact of Xerostomia on Dysphagia after Chemo-IMRT for Oropharyngeal Cancer: Prospective longitudinal study

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Abstract

Background: To assess how xerostomia affects dysphagia.

Methods: Prospective longitudinal studies of 93 patients with oropharyngeal cancer treated with definitive chemo-IMRT. Observer-rated dysphagia (ORD), patient-reported dysphagia (PRD) and xerostomia (PRX), assessment of the swallowing mechanics by videofluoroscopy (VF score), and salivary flow rates, were prospectively assessed from pre-therapy through 2 years.

Results: ORD grades ≥2 were rare and therefore not modeled. Of patients with no/mild VF abnormalities, a substantial proportion had PRD that peaked 3 months post-therapy and subsequently improved. Through 2 years, highly significant correlations were observed between PRX and PRD scores for all patients, including those with no/mild VF abnormalities. Both PRX and VF scores were highly significantly associated with PRD. On multivariate analysis, PRX score was a stronger predictor of PRD than VF score.

Conclusions: Xerostomia contributes significantly to PRD. Efforts to further decrease xerostomia, in addition to sparing parotid glands, may translate into improvements in PRD.

Introduction:

Patients with oropharyngeal cancer (OPC), the majority of whom have human papillomavirus-related (HPV+) OPC, have excellent oncological outcomes following chemoradiation, which makes the prevention of radiation-related toxicities a priority [1]. Dysphagia is a common sequel of chemoradiation for head and neck cancer (HNC) and a major determinant of patient-reported quality-of-life (PRQOL) [2, 3]. Previous studies have demonstrated that chemoradiation can affect the mechanics of swallowing, resulting in increased bolus transit time, decreased movement of the tongue base toward the posterior pharyngeal wall, reduced laryngeal elevation, and food retention in the oral cavity [4, 5]. These changes are uncomfortable and place patients at risk for aspiration-related complications [6]. Despite aggressive management of dysphagia with rehabilitation and exercise regimens, many patients do not regain their pretreatment swallowing function, and some may require prolonged feeding tubes for nutritional support [4, 7]. Efforts to characterize the functional anatomy of swallowing using videofluoroscopy (VF) have identified organs-at-risk (OARs) for chemoirradiation, including pharyngeal constrictors, glottis, supraglottic larynx and upper esophagus [5, 8, 9]. We have previously reported our institutional experience with definitive organ-sparing chemoirradiation for OPC, demonstrating that dysphagia and its complications are reduced by limiting the dose to the swallowing-related organs using intensity-modulated radiation therapy (IMRT) [3, 8, 10-12].

Despite use of swallowing organ-sparing IMRT, many patients still complain of difficulty swallowing dry foods. There is evidence that patient-reported dysphagia often does not correlate with objective measures of dysphagia; i.e. the *feeling* of difficulty swallowing may not relate to the dysfunction of the swallowing structures [13-15]. This disparity implies that other factors related to eating, not involving dysfunction of the swallowing structures, may be responsible for the sensation of dysphagia. Indeed, xerostomia, another common consequence of head and neck radiotherapy, can

make swallowing, especially dry food, difficult to the point where patients require excessive water or simply avoid such foods [16, 17]. Although parotid gland-sparing with IMRT in recent years has decreased xerostomia rates, approximately 25-50% of patients still report persistent xerostomia after IMRT [18, 19]. In order to clarify the relationships between xerostomia and dysphagia, we sought to evaluate the correlations between patient-reported xerostomia, patient-reported dysphagia, and functional assessments of swallowing (VF) and salivary output (stimulated salivary flow rates [SSF]), in patients who participated in prospective studies of chemo- IMRT for OPC.

Methods and Materials

Patients and Therapy

Between May 2003 and March 2011, 93 patients with newly diagnosed, stage III-IV OPC were treated on two prospective consecutive Institutional Review Board-approved studies of organ-sparing chemo-IMRT for locally advanced OPC. Patient eligibility and treatment have been previously detailed and were similar in both protocols [8, 11, 20]. Seventy-three patients were enrolled on a phase II study of chemo-IMRT aiming to reduce dysphagia by sparing the swallowing–related structures [8, 11], and 20 patients on a subsequent study assessing dose-effect relationships based on cone-beam CT-derived actually delivered organ doses [20]. IMRT prescription doses were 70 Gy to the gross primary and nodal tumor volumes (GTVs), 59-63 Gy to high-risk clinical target volumes (CTVs), and 56-59 Gy to low-risk CTVs, delivered over 35 daily fractions. GTVs and CTVs were uniformly expanded 3-5 mm to create planning target volumes. Bilateral necks were treated in all patients. IMRT treatment planning was performed with intent to minimize dose to the parotid glands, contralateral submandibular gland, non-involved oral cavity, glottic and supraglottic larynx, esophagus, and the pharyngeal constrictor muscles, with dosimetric goals and optimization algorithms as previously detailed [8]. The contralateral submandibular

glands were preferentially spared in the latter years of the study period using an optimization goal of mean dose <39 Gy, based on a previous study [21]. All patients received concurrent weekly carboplatin (AUC=1) and paclitaxel (30 mg/m2).

Patient-Reported Dysphagia and Xerostomia Assessments

Three validated health-related quality-of-life (HRQOL) instruments were administered to enrolled patients at pre-treatment and 3, 6, 12, 18, and 24 months following completion of CRT; these consisted of the Head-and-Neck-Quality-of-Life (HNQOL) questionnaire [22], University of Washington Quality-of-Life (UWQOL) questionnaire [2], and Xerostomia Questionnaire (XQ) [18]. Patient-reported dysphagia was assessed using the swallowing question from the HNQOL instrument (HNQOL-Sw: "As a result of your head and neck condition or treatment, over the past four weeks, how much have you been bothered by problems with swallowing soft foods and/or solids?") and the UWQOL instrument (UWQOL-Sw: Over the past week, I [1] swallow normally, [2] cannot swallow certain solid foods, [3] can only swallow soft foods, [4] can only swallow liquid foods, [5] cannot swallow"). Patient-reported xerostomia was assessed using a summary score of the XQ (XQ score) a validated instrument containing eight questions that assess patients' mouth and throat dryness and difficulty with talking, chewing, swallowing, and sleeping due to dryness [18]. Four questions assess dryness during eating/speaking¡ and four questions assess dryness while not eating. Patients rate each question on the XQ from 0-10 on an 11-point ordinal Likert scale, which higher scores indicating greater dryness or discomfort due to dryness. HRQOL instrument individual question and summary scores were normalized on a linear 100-point scale, with 0 representing no toxicity or negative QOL effects and 100 representing the worst possible QOL [3]. Scores of 0, 25, 50, 75, and 100 approximated responses of "none", "mild/slight", "moderate", "severe", and "extreme", respectively.

Observer-Rated Dysphagia and Xerostomia Assessments

Observer (physician)-rated dysphagia was graded at each follow-up using the RTOG/EORTC scoring system (0=no dysphagia; 1=symptomatic, able to eat regular diet; 2=symptomatic, altered eating/swallowing; 3=symptomatic, severely altered eating/swallowing requiring feeding tube; 4=complete obstruction or perforation) [23]. Observer (physician)-rated xerostomia scores were not included in the present study given our demonstration in prior studies that observer-rating underestimated xerostomia severity compared with patient-reported scores, and did not correlate with the salivary flow (SSF) rates, unlike the significant correlations observed for patient-reported scores [24].

Functional Swallowing Assessments by Modified Barium Swallow Video Fluoroscopy

Functional assessment of dysphagia was performed by modified barium swallow videofluoroscopy (VF), as previously detailed [3, 8]. VF was performed pre-treatment and at 3, 12, and 24 months post-therapy, with results quantified using the Swallowing Performance Status Scale (SPSS) score: 1=normal swallow, 2=within functional limits, 3=mild impairment, 4=mild-moderate impairment, 5=moderate impairment, 6=moderate-severe impairment, 7=severe impairment [25-28], as in our prior studies [3, 8, 11].

Salivary Flow Assessments

Functional assessments of xerostomia were performed by measurements of the salivary output from the major salivary glands, as previously described [18, 21]. Unstimulated and stimulated salivary flow (SSF) rates were measured selectively for each parotid and submandibular gland at the same time points as

HRQOL assessments, as previously [29]. For analysis purposes, the sum of the SSF output (in ml/min) from all glands was used for all analyses.

Statistical Analysis

Descriptive statistics were used to calculate means and standard deviations for salivary flow rates and XQ scores at pre-treatment and at 3, 6, 12, 18, and 24 months post-therapy. The prevalence of swallowing impairment, as measured by SPSS score, of patient-reported dysphagia, as measured by HNQOL-Sw and UWQOL-Sw question scores, and of observer-rated dysphagia was calculated at pre-treatment and 3, 12, and 24 months post-therapy. The prevalence of patient-reported dysphagia by HNQOL-Sw and UWQOL-Sw scores was determined for patients with no or minimal functional swallowing impairment (SPSS score $\leq$3) at pre-treatment and 3, 12, and 24 months post-treatment. Spearman rank correlation (ρ) was used to assess the association between XQ score and salivary flow rates, XQ score and HNQOL-Sw and UWQOL-Sw scores, and SPSS score and salivary flow rates at each time-point for all patients and separately for patients with and without functional swallowing impairment on VF (SPSS score $\geq$4 and $\leq$3, respectively).

We fitted proportional odds models to assess the association between dysphagia and xerostomia, and conducted univariate as well as multivariate analysis with adjustment for covariates. The magnitude of the association was quantified using normalized odds ratios (nORs), calculated as the odds ratio per standard deviation (SD) increase in the predictors. A p-value $\leq$0.05 was accepted as statistically significant. Statistical analysis was conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics for the 93 enrolled patients are shown in Table 1. The majority of patients were male with primary tumors that were HPV+ (93%). HRQOL data was available for 92 patients at pre-treatment, 91 at 3 months, 80 at 12 months, and 70 at 24 months. VF and salivary flow data were available, respectively, for 92 and 87 patients at pre-treatment, 87 and 79 at 3 months, 81 and 73 at 12 months, and 65 and 61 at 24 months.

Salivary Flow Rates and Patient-Reported Xerostomia

Mean SSF rates were 0.87 (± SD 0.72) ml/min pre-therapy, declined to 0.19 (±0.35) ml/min at 3 months, and thereafter improved to 0.29 (±0.38), 0.32 (±0.33), 0.39 (±0.42) and 0.37 (±0.38) ml/min at 6, 12, 18 and 24 months post-therapy, respectively. Mean XQ scores pre-therapy were 6.5 (± SD 13), worsened to 51 (±23) and 46 (±24) at 3 and 6 months, and thereafter improved to 37 (±24) , 34 (±23), and 31 (±22) at 12, 18 and 24 months, respectively.

Assessment of the correlations between SSF rates and the XQ scores revealed no significant correlation pre-therapy, but statistically significant correlations ($p<0.05$) at each time point post-therapy. Spearman's correlation coefficients were only modest, however: -0.37, -0.35, -0.55, -0.38, and -0.35 at 3, 6, 12, 18, and 24 months, respectively (Table 3); the negative coefficients denote increased (worsened) XQ scores as salivary output reduced.

Observer-rated Dysphagia

Observer-rated dysphagia grade ≥2 was infrequent. Grade 2 and 3 dysphagia were observed in 7% and 4% of patients at 6 months, 2.7% and 2% at 12 months, and 1% and 1% at both 18 and 24 months,

respectively. Due to the very low frequency of grades ≥2 observer-rated dysphagia at 12 months and beyond, observer-rated dysphagia was not analyzed further.

Functional Swallowing Assessment by Video Fluoroscopy and Patient-Reported Dysphagia

Functional swallowing impairment by SPSS score and patient-reported dysphagia by HNQOL-Sw and UWQOL-Sw score at each time point are shown in Figure 1. Pre-therapy SPSS scores were mostly within functional limits, while at 3 months most scores showed mild-to-moderate impairment, with 14% showing severe impairment. By 12 and 24 months the rate of patients "within functional limits" increased to 25% and 32%, respectively, and "severe impairment" was rare. A similar pattern over time was observed in the HNQOL-Sw and UWQOL-Sw scores (Fig 1).

Patient-Reported Dysphagia in Patients without Functional Swallowing Impairment

We next sought to evaluate whether patients without functional swallowing impairment on VF may nonetheless perceive the feeling of dysphagia (Table 2). Of 39 patients with either no or mild impairment on VF (SPSS score ≤3) at 3 months, 21% reported at least moderate swallowing-related bother on the HNQOL-Sw assessment. On the UWQOL-Sw assessment, 59% of patients with SPSS score ≤3 reported inability to swallow certain solid foods, and 13% reported swallowing ability limited to only soft foods. At 12 and 24 months, moderate or greater severity swallowing-related bother was reported on HNQOL-Sw by 12% and 5% of patients with SPSS ≤3, respectively. By UWQOL-Sw, 30% of patients with no/mild VF abnormalities at 12 months reported inability to swallow certain solid foods and 3% reported being able to swallow only soft foods; the respective rates at 24 months were similar at 28% and 3%.

Relationship between Patient-Reported and Functional Assessments of Xerostomia and Dysphagia

Given that a substantial proportion of patients reported swallowing problems despite mild or no swallowing abnormalities on VF, we explored whether the perception of dysphagia may be related to, and potentially attributable to, patient-reported xerostomia. At pre-treatment, XQ and HNQOL-Sw scores were moderately correlated (ρ=0.43, p<0.001), reflecting the high proportion of patients (84%) who reported either no or slight/mild symptoms (normalized score $\leq$ 25/100) on both the XQ and HNQOL-Sw assessments, consistent with an absence of dysphagia or xerostomia in most patients pre-therapy. Post-treatment, the strength of the correlation between XQ and HNQOL-Sw scores increased (ρ=0.57, 0.52, and 0.54 at 3-, 12-, and 24 months, respectively; all p<0.001 [Table 3]). Similar magnitude correlations were observed between XQ score and UWQOL-Sw score (ρ=0.33, 0.47, 0.61, and 0.47 at pre-therapy and 3, 12, and 24 months post-treatment, respectively; all p<0.01 [Table 3]).

In comparison, the correlations between SSF rates and both HNQOL-Sw scores (ρ=0.014, p=0.90 at pre-therapy; ρ= -0.28, p=0.01 at 3 months; ρ= -0.30, p=0.01 at 12 months; and ρ= -0.23, p=0.08 at 24 months) and UWQOL-Sw score (ρ= -0.12, p=0.27 at pre-therapy; ρ= -0.19, p=0.10 at 3 months; ρ= -0.27, p=0.03 at 12 months; and ρ= -0.05, p=0.69 at 24 months) showed weaker or non-significant associations than those between the XQ and patient-reported dysphagia scores (Table 3). A comparison of functional assessments of xerostomia and dysphagia, as measured by SSF rates and SPSS score, also showed weaker or non-significant correlations than the correlations between patient-reported assessments (pre-treatment: ρ=0.03, p=0.81; 3 months: ρ= -0.31, p<0.01; 12 months: ρ= -0.07, p=0.58; 24 months; ρ= -0.37, p<0.01 [Table 3]). The negative slopes of these correlations suggested a trend of increasing (worsening) HNQOL-Sw, UWQOL-Sw, and SPSS scores as SSF rates decreased.

Relationship between Patient-Reported Xerostomia and Patient-Reported Dysphagia in Patients Without and With Swallowing Impairment of Video Fluoroscopy

Among patients with no/mild evidence of swallowing impairment on VF (SPSS score $\leq$3), post-treatment XQ summary score remained moderately-to-strongly correlated with HNQOL-Sw score at all time-points (ρ=0.50, 0.60, and 0.41 at 3, 12, and 24 months; $p<0.01$ for all) and with UWQOL-Sw score at 3 and 12 months (ρ=0.55, $p<0.001$ and ρ=0.51, p=0.002, respectively; trend at 24 months: ρ=0.27, p=0.10). Among patients with moderate or greater swallowing impairment on VF (SPSS score $\geq$4), similar significant correlations were observed between XQ summary score and both HNQOL-Sw score (ρ=0.58, 0.32, and 0.48 at 3, 12, and 24 months; $p<0.001$, p=0.04, and p=0.02, respectively) and UWQOL-Sw score (ρ=0.32, 0.53, 0.47 at 3,12, and 24 months; p=0.03, $p<0.001$, and p=0.03, respectively).

Univariate and Multivariate Regression Analyses

Regression analysis was performed to further assess the relative impact of XQ score, salivary flow rates, and SPSS scores on post-treatment HNQOL-Sw and UWQOL-Sw scores. At all post-treatment time points, both XQ score and SPSS scores were significantly positively associated on univariate analysis with patient-reported dysphagia by both HNQOL-Sw and UWQOL-Sw (Table 4). SSF rates were less associated with HNQOL-Sw and UWQOL-SW score than were XQ score, showing significant associations with only HNQOL-Sw at 3 months and 12 months, with trends toward significance at these time points for the UWQOL-Sw endpoint and no association at 24 months with either HNQOL-Sw or UWQOL-Sw. On multivariable analysis (Table 5), XQ score remained independently associated with both HNQOL-Sw and UWQOL-Sw score after adjustment for SPSS score at nearly all time-points. Moreover, XQ score was a stronger predictor of HNQOL-Sw and UWQOL-Sw score than the VF SPSS scores at most time points. By contrast, the association between the stimulated salivary flow rates and patient-rated dysphagia, after

adjustment for VF SPSS score on multivariable analysis, was non-significant for nearly all time points (Table 5).

Discussion

This study demonstrates that in patients receiving chemo-IMRT whose planning objectives included the sparing of both salivary and swallowing-related structures, patient-reported xerostomia was significantly correlated with patient-reported dysphagia. The assessment in the current study of both patient-reported outcomes for dysphagia and xerostomia, as well as the functional assessments of the related physiological dysfunctions (SPSS scores and major salivary gland flow rates), highlights the distinctions in relationships between patient-reported and functional outcome measures, and indirectly suggests potential mechanisms through which xerostomia may affect patient perceptions of dysphagia.

A consistent finding throughout the longitudinal 2-year assessment period was the highly significant relationships of both SPSS scores and XQ score with patient-reported dysphagia. On the other hand, SSF rates, measured from the major salivary glands, had lower correlations with patient-reported dysphagia in the univariate analyses, and were not significant or of only borderline significance in multivariate analysis. Thus, while the functional assessment of swallowing impairment via VF was highly predictive of patient-reported dysphagia, patients' subjective perception of xerostomia was an additional, highly significant factor.

One of the reasons for the discrepancy between the association of XQ score and SSF rates on patient-reported dysphagia is the weak correlation between xerostomia symptoms and the measured SSF. The only modest correlation coefficients of xerostomia symptoms vs. salivary output found in our study post-therapy, despite being statistically significant, suggest that SSF explains only part of the

variability in patient-reported xerostomia. While the majority of stimulated saliva during eating is secreted by the parotid glands, these secretions are predominantly serous, consisting almost entirely of water. In contrast, the secretions from the submandibular glands and especially the minor salivary glands dispersed within the oral cavity, though relatively of small volumes, are rich in salivary mucins, which adhere to mucosal and food particle surfaces to provide lubrication for food passage and mucosal protection. Mucins bind water molecules effectively, and their presence on the mucosal surfaces helps maintain these tissues in a hydrated state and, importantly, provide a sense of hydration to the patient [21]. Reduced salivary mucins after chemoradiation may greatly impact the sensation of dry mouth [30]. The importance of the mucin-containing secretions is highlighted in the relatively weak correlations between SSF rates, dominated by parotid gland secretions, and patient-reported xerostomia in our study. They also explain the failure of randomized studies of parotid-sparing IMRT to demonstrate a clinically meaningful advantage in patient-reported xerostomia, despite improvements in salivary flow rates and observer-rated xerostomia in the IMRT compared with the 2D RT arms (19, 28). For example, Nutting et al reported that through 12 months after treatment, patient-reported benefit of IMRT vs 2D RT was <10 points on a 0-100 scale, regarded not clinically relevant, despite a large advantage in salivary output (19). Thus, the SSF measurements, which are predominantly a measure of the parotid gland secretions, underestimate the contribution of the mucin-producing glands. This is reflected in studies demonstrating that in addition to mean parotid gland dose, doses delivered to the submandibular and minor salivary glands affect patient-reported xerostomia [29]. The results of the current study emphasize that their sparing should be an important goal of IMRT optimization, as further improvement in xerostomia is likely to reduce patient-reported dysphagia.

Few previous studies have been published assessing the association between patient-reported xerostomia and dysphagia in patients with HNC treated with RT. Logemann et al. measured whole mouth saliva in patients with HNC from pre-RT to 3 months after RT, and compared salivary output to

both patient-reported dysphagia and VF results [16]. No significant correlations were found in either this study, nor in a follow-up study through 12 months [17], likely due to very low salivary output in all patients resulting from 2D-radiation techniques, that precluded meaningful analysis. These authors concluded that reduced saliva did not affect the mechanics of swallowing but seemed to change patients' perception of their swallowing ability. Our study, in which the SSF rates and XQ score recovered after IMRT, showed significant correlations between XQ score and SSF and dysphagia symptoms even in patients without VF abnormalities. Further support for a causative, rather than merely correlative, relationship between xerostomia and dysphagia is implied by findings in patients with Sjogren's syndrome, who reported worse dysphagia and had prolonged food transit time on VF compared to healthy controls [31].

The majority of the current literature comparing xerostomia and dysphagia after RT in HNC patients had relied upon observer-rated assessments, yielding conflicting results. Some have reported a significant correlation between these toxicities, [32], while others have reported no apparent correlation [33], rather showing that significant xerostomia persisted long after therapy compared to prompt improvement in dysphagia. Several retrospective studies comparing parotid-sparing IMRT to 3D-RT noted that in parallel to improved xerostomia, swallowing was better in the IMRT treated patients even though no specific effort was made to spare the swallowing-related structures [34-36]. On the other hand, a randomized study of parotid-sparing IMRT vs. 3D-RT found no difference in dysphagia between the arms [19]. The heterogeneous nature of these studies, which included many patients treated without concurrent chemotherapy, and therefore were at a lesser risk of dysphagia, complicates accurate evaluation of their results.

The observer-rated RTOG/EORTC scale for dysphagia, which is very similar to the CTCAE evaluation grading system, disclosed very few patients with grades $\geq$2 at 12 months and beyond, similar

to our prior report in patients treated with swallowing-structure-sparing IMRT [11]. The low frequency of observer-reported dysphagia events precluded statistical evaluation of correlates with this endpoint. In contrast, patient-reported scores showed a wide distribution. We have previously reported the discrepancies between observer-rated and patient-reported dysphagia in assessing the relative severity of dysphagia, showing that VF results were more consistent with patient-reported than observer-rated scoring [37]. We therefore prefer using patient-reported outcomes as the most reliable way to assess dysphagia and other sequelae of treatment.

In conclusion, in this longitudinal study of chemo-IMRT for patients with OPC, patient-reported xerostomia was a significant contributor to patients' perception of dysphagia, irrespective of evidence of functional swallowing impairment and despite the use of organ-sparing IMRT techniques. Efforts to decrease treatment-related xerostomia by increased salivary gland sparing, including the submandibular and minor oral cavity salivary glands in addition to sparing the parotid glands (25), are likely to translate into improvements in patients' perception of dysphagia after CRT for HNC.

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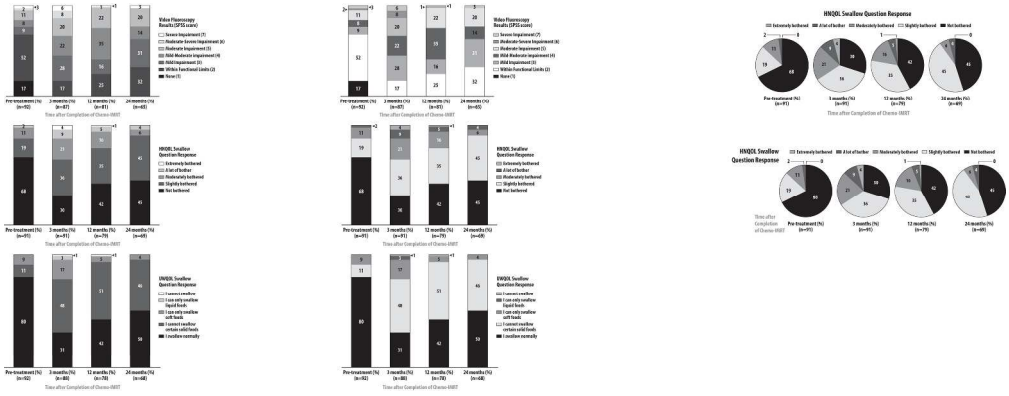
Figure 1. Swallowing impairment pre-treatment and after chemoradiation as rated by (a) video fluoroscopy assessment, (b) patient self-assessment using the Head and Neck Quality of Life Instrument Swallowing Question, and (c) University of Washington Quality of Life Instrument Swallowing Question.



264x102mm (300 x 300 DPI)

Table 1. Patient Characteristics

Characteristic	***Statistic***
Male (N [%])	83 (89%)
Age (years): Median (range)	56 (40 – 78)
Primary Tumor site: N (%)	
Tonsil	45 (48%)
Base of Tongue	48 (52%)
T-classification: N (%)	
T1	12 (13%)
T2	40 (43%)
T3	20 (22%)
T4	21 (23%)
N-classification: N (%)	
N0	5 (5%)
N1	8 (9%)
N2	70 (75%)
N3	10 (11%)
HPV Status: N (%)	
Positive	86 (93%)
Negative	1 (1%)
N/A	6 (7%)
Smoking History: N (%)	
Never smoker	35 (38%)
Former smoker	34 (37%)
Current smoker	24 (26%)
Pack Years: Median (range)	7 (0 – 140)

Table 2: Patient-reported dysphagia in patients without evidence of significant swallowing impairment on video fluoroscopy.

Time after Completion of Chemo-IMRT	No. of pts (%) with no or mild swallowing impairment on VF (SPSS score 1-3)	% reporting ≥moderate bother due to swallowing problems (HNQOL-Sw)	% reporting inability to swallow certain foods (UWQOL-Sw)	% reporting swallowing limited to only soft foods (UWQOL-Sw)
3 months	39 (44%)	21%	59%	13%
12 months	33 (41%)	12%	30%	3%
24 months	39 (60%)	5%	28%	3%

HNQOL-Sw – Head and Neck Quality of Life Instrument Swallowing Question; SPSS – Swallowing Performance Status Scale; UWQOL-SW – University of Washington Quality of Life Instrument Swallowing Question; VF – Video Fluoroscopy

Table 3: Spearman Correlations (ρ) Between Functional and Patient-Reported Assessments of Dysphagia and Xerostomia

		UW QOL-Sw (pre)	UW QOL-Sw (3 mo)	UW QOL-Sw (12 mo)	UW QOL-Sw (24 mo)	SPSS Score (pre)	SPSS Score (3 mo)	SPSS Score (12 mo)	SPSS Score (24 mo)	XQ Score (pre)	XQ Score (3 mo)	XQ Score (12 mo)	XQ Score (24 mo)	SSF (pre)	SSF (3 mo)	SSF (12 mo)	SSF (24 mo)
HNQOL-Sw (pre)	**rho**	0.62				0.27				0.43				0.01			
	p	<0.001				0.01				<0.001				0.90			
HNQOL-Sw (3 mo)	**rho**		0.62				0.37				0.57				-0.28		
	p		<0.001				<0.001				<0.001				0.01		
HNQOL-Sw (12 mo)	**rho**			0.63				0.25				0.52				-0.30	
	p			<0.001				0.03				<0.001				0.01	
HNQOL-Sw (24 mo)	**rho**				0.57				0.50				0.54				-0.23
	p				<0.001				<0.001				<0.001				0.08
UWQOL-Sw (pre)	**rho**					0.36				0.33				-0.12			
	p					<0.001				<0.001				0.27			
UWQOL-Sw (3 mo)	**rho**						0.30				0.47				-0.19		
	p						0.01				<0.001				0.10		
UWQOL-Sw (12 mo)	**rho**							0.47				0.61				-0.27	
	p							<0.001				<0.001				0.03	
UWQOL-Sw (24 mo)	**rho**								0.56				0.47				-0.05
	p								<0.001				<0.001				0.69
SPSS Score (pre)	**rho**									0.31				0.03			
	p									<0.001				0.81			
SPSS Score (3 mo)	**rho**										0.27				-0.31		
	p										0.01				0.01		
SPSS Score (12 mo)	**rho**											0.41				-0.07	
	p											<0.001				0.58	
SPSS Score (24 mo)	**rho**												0.53				-0.37
	p												<0.001				<0.001
XQ Score (pre)	**rho**													-0.15			
	p													0.17			
XQ Score (3 mo)	**rho**														-0.37		
	p														<0.001		
XQ Score (12 mo)	**rho**															-0.55	
	p															<0.001	
XQ Score (24 mo)	**rho**																-0.35
	p																0.01

HNQOL-Sw – Head and Neck Quality of Life Instrument Swallowing Question; SPSS – Swallowing Performance Status Scale; SSF –Stimulated Salivary Flow; UWQOL-SW – University of Washington Quality of Life Instrument Swallowing Question; XQ – Xerostomia Questionnaire

Table ~~34~~: Univariable Analysis of Association of Swallowing Impairment of Video Fluoroscopy, Patient-Reported Xerostomia, and Salivary Flow with Patient-Reported Dysphagia

	Time-Point	Variable	Normalized OR	p-value	Model AUC
HNQOL-Sw	*3 months*	**SPSS Score**	1.91	<0.001	0.652
		XQ Summary Score	4.03	<0.001	0.758
		Stim Salivary Flow	0.54	0.035	0.630
	12 months	**SPSS Score**	1.75	0.021	0.608
		XQ Summary Score	3.77	<0.001	0.750
		Stim Salivary Flow	0.51	0.03	0.649
	24 months	**SPSS Score**	3.39	<0.001	0.754
		XQ Summary Score	3.12	<0.001	0.771
		Stim Salivary Flow	0.80	0.37	0.608
UWQOL-Sw	*3 months*	**SPSS Score**	1.79	0.005	0.643
		XQ Summary Score	2.82	<0.001	0.729
		Stim Salivary Flow	0.58	0.055	0.587
	12 months	**SPSS Score**	3.65	<0.001	0.742
		XQ Summary Score	5.80	<0.001	0.835
		Stim Salivary Flow	0.60	0.081	0.642
	24 months	**SPSS Score**	4.53	<0.001	0.795
		XQ Summary Score	3.10	<0.001	0.755
		Stim Salivary Flow	1.01	0.974	0.536

HNQOL-Sw – Head and Neck Quality of Life Instrument Swallowing Question; SPSS – Swallowing Performance Status Scale; UWQOL-SW – University of Washington Quality of Life Instrument Swallowing Question; XQ – Xerostomia Questionnaire

Table 54: Multivariable Analysis of Impact of Swallowing Dysfunction by Video Fluoroscopy, Patient-Reported Xerostomia, and Salivary Flow with Patient-Reported Dysphagia

Dysphagia Endpoint	Timepoint	Model	Variable	Normalized OR	p-value	Model AUC
HNQOL-Sw	*3 months*	*Model 1*	**SPSS Score**	1.98	0.001	0.795
			XQ Summary Score	3.99	<0.001	
		Model 2	**SPSS Score**	2.31	<0.001	0.708
			Stim Salivary Flow	0.61	0.077	
	12 months	*Model 1*	**SPSS Score**	1.20	0.50	0.754
			XQ Summary Score	3.48	<0.001	
		Model 2	**SPSS Score**	1.64	0.058	0.702
			Stim Salivary Flow	0.48	0.031	
	24 months	*Model 1*	**SPSS Score**	2.83	0.003	0.804
			XQ Summary Score	2.05	0.030	
		Model 2	**SPSS Score**	4.37	<0.001	0.765
			Stim Salivary Flow	1.11	0.69	
UWQOL-Sw	*3 months*	*Model 1*	**SPSS Score**	1.58	0.036	0.740
			XQ Summary Score	2.47	<0.001	
		Model 2	**SPSS Score**	2.16	0.001	0.704
			Stim Salivary Flow	0.62	0.091	
	12 months	*Model 1*	**SPSS Score**	2.56	0.005	0.860
			XQ Summary Score	4.68	<0.001	
		Model 2	**SPSS Score**	3.15	<0.001	0.758
			Stim Salivary Flow	0.59	0.12	
	24 months	*Model 1*	**SPSS Score**	4.20	<0.001	0.821
			XQ Summary Score	1.74	0.12	
		Model 2	**SPSS Score**	7.67	<0.001	0.842
			Stim Salivary Flow	1.57	0.12	

HNQOL-Sw – Head and Neck Quality of Life Instrument Swallowing Question; SPSS – Swallowing Performance Status Scale; UWQOL-SW – University of Washington Quality of Life Instrument Swallowing Question; XQ – Xerostomia Questionnaire