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Analysis of Pharyngeal Edema Post-Chemoradiation for Head and Neck Cancer: Impact on Swallow Function

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Objectives: Edema is a frequent clinical observation following chemoradiation treatment (CRT) of oral/oropharyngeal cancer and is thought to contribute to post-CRT swallowing impairment. Our aims were to reliably quantify pharyngeal edema pre- and post-CRT from videofluoroscopic (VF) swallowing studies and to explore the relationship between edema and swallowing impairment. Swallowing impairment was captured using patient-reported swallowing outcomes (EAT-10) and with VF confirmation of impairment (DIGEST).

Methods: 40 patients (24 M, age 38–76) with oral/oropharyngeal cancer received radiotherapy (70 Gy, 7 weeks) and 3 weekly doses of cisplatin. VF and EAT-10 were completed pre- and 1-month post-CRT. Edema was captured by measuring posterior pharyngeal wall (PPW) thickness, vallecular space, and pharyngeal area (PA) on a single post-swallow rest frame. Wilcoxon sign rank tests and paired t-tests evaluated within-subject changes in impairment and edema respectively. A linear mixed effect regression model explored the influence of time, patient-reported outcomes, and functional impairment on measures of edema.

Results: Swallowing function (EAT-10 and DIGEST) was significantly worse post-CRT. PPW thickness (but not vallecular space and pharyngeal area) was significantly worse post-CRT. PPW thickness was only significantly influenced by time (pre- vs. post-CRT) but not by measures of swallow function.

Conclusion: Our findings establish the use of PPW thickness as a reliable measure of acute edema in post-CRT treatment. In this small, retrospective sample, edema was not significantly correlated with either patient-reported or measured swallow function. Prospective longitudinal work, examining the relationship between objective measures of edema, patient perception of impairment, and swallow function and biomechanics is warranted.

Key Words: Edema, dysphagia, head and neck cancer, chemoradiation, propharyngeal.

Level of Evidence: 4.

INTRODUCTION

In recent decades, researchers have noted an increased prevalence of combined chemotherapy and radiotherapy regimens (CRT) in the treatment of advanced-stage laryngeal cancers.[1] While swallow function has been noted as a top patient-reported priority both before and after organ-preserving head and neck cancer (HNC) treatment,[2] impaired swallow function has frequently been reported following such treatment. In 2010, Francis et al. published a study based on data from 8002 patients with HNC, as identified in the Surveillance Epidemiology and End Results (SEER) registry and Medicare databases. They reported that patients treated with CRT were 2.69 times more likely to experience dysphagia than those treated with surgery alone, and two times more likely to experience dysphagia than those treated with surgery and radiation. CRT resulted in 73% higher odds of dysphagia than radiation alone. Additionally, the odds of developing pneumonia were 44% higher in those treated with CRT compared to treatment with surgery alone. Significantly higher odds of developing pneumonia were noted in comparison to treatment with radiation alone as well.[3]

Radiation treatment of HNC is also known to impact lymphatic function, putting patients at risk for developing lymphedema. A 2012 study noted that 67.9% of patients experienced internal lymphedema (swelling in the mucosa and soft tissue of the pharynx and larynx), that persisted beyond 3 months post-treatment.[4] Acute edema of oropharyngeal and laryngeal structures is also commonly reported in patients receiving radiation-based therapies.[5] Edema increases tissue thickness, which may alter (typically lessen) the dimensions and capacity of dynamic soft structures such as the valleculae, as well as overall openness of the pharyngeal airspace. This has led to speculation regarding the connection between edema and impaired swallow function.

To date, all studies investigating the connection internal edema and dysphagia have utilized the Patterson Scale,[6] a subjective, perceptual rating scale, based on Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

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studies. Intra-rater reliability of this scale is reported to range from "fair" to "good", and the authors suggest that reliability may be improved upon by using a pre-post study design with the patient serving as their own control. Using this subjective scale, Jeans and colleagues noted a correlation between internal edema and qualitative patient reports of swallowing difficulty, including "tightness".[7] Jackson et al.[8] found significant positive correlations between severity of edema of pharyngeal and laryngeal structures and functional swallowing outcomes as indicated by scores on the Dysphagia Outcome and Severity Scale (DOSS)[9] and the National Outcomes Measurement System (NOMS).[10]

These preliminary findings have established a connection between subjective measures of internal edema of pharyngeal and laryngeal structures and both patient reports of swallowing difficulty and impaired functional outcomes. These studies have demonstrated the need for research objectively establishing the connection between edema and dysphagia, using quantitative measures. The goals of this exploratory pre-CRT versus post-CRT design are to reliably and objectively quantify acute pharyngeal edema; to capture change in swallowing function; and to explore the relationship between edema, time, and swallowing impairment. The data for this retrospective study come from 40 patients treated for oral or oropharyngeal cancer with CRT alone. Our specific research questions were:

1. Can change in edema post-CRT be captured objectively on 2D lateral videofluoroscopy (VF)? Our hypothesis is that our proposed objective edema measures taken from VF images will reveal significantly worse values post-CRT.
2. Does swallowing function decline one month post-CRT compared with pre-CRT measures? Our hypothesis is that both patient-reported Eating Assessment Tool (EAT-10)[11] and VF measured Dynamic Imaging Grade of Swallowing Toxicity (DIGEST)[12] scores will be significantly worse post-CRT.
3. Are within-subject measures of edema significantly related to swallowing function? Our hypothesis is that patients with worse edema will have greater perceived impairment reflected by higher EAT-10 scores and will have higher grades on DIGEST rated from VF.

MATERIALS AND METHODS

Participants

This study was approved by the NYU School of Medicine institutional review board. Charts were reviewed between 2014 and 2016 to identify patients who had a newly diagnosed primary oral or oropharyngeal cancer that was treated with CRT only. Data were retrospectively collected from 40 patients (24 male) with newly diagnosed oral (n = 7) and oropharyngeal (n = 33) cancer. The median age was 58, ranging from 38 to 76. Additional patient characteristics, including T classification (extent of primary tumor) and N classification (number of affected lymph nodes), are summarized in Table I. All subjects received radiotherapy (70 Gy, 7 weeks) combined with 3 weekly doses of cisplatin. None of these patients had surgical intervention. Per institution standard of care, all patients were prescribed daily prophylactic swallowing exercises. Adherence to exercise regimen was not tracked in this study. Exclusion criteria included age < 18, prior malignant disease in the head or neck, prior radiotherapy to the head or neck, prior surgery to the head and neck, and preexisting dysphagia or conditions known to cause dysphagia (ie, neurologic conditions).

TABLE I.
Summary of Patient Characteristics.

Sex	Male	24
	Female	16
Age	Median	58
	Range	38–76
T Classification	T1/2	21
	T3	16
	T4	3
N Classification	N0	14
	N1	15
	N2	9
	N3	2
Site	Oral	7
	Oropharyngeal	33

Data Collection

Per standard of care, VF was conducted pre-treatment and again within approximately 4 weeks post-treatment. The standardized VF protocol included two thin liquid boluses of Varibar at 1, 3, 5, 10 ml, and continuous drinking tasks, followed by two 5 ml boluses of Varibar pudding and one-quarter of a cracker coated with Varibar pudding. Protocol deviations were made online by the assessing clinician, based on clinical performance, in order to maximize patient safety and clinical yield of information. All VF recordings and data were assigned a unique alphanumeric code for blinded and randomized analysis in ImageJ (National Institutes of Health, Bethesda, MD, USA) by trained clinicians and graduate student research assistants. Patients completed the EAT-10 on the same day as their VF studies.

Measures

EDEMA. Measurements of edema at each time point were captured from a single post-swallow rest frame, using the first of the two 5 ml thin liquid trials. The post-swallow rest frame was identified as the lowest position of the pyriform sinuses post-swallow with concurrent epiglottic return and pharyngeal relaxation as per previously described operational definitions.[13] In cases of suboptimal video quality or patient positioning, or of termination of VF prior to post-swallow rest, measurements were taken from the second 5 ml thin liquid trial video clip (n = 21), with the 3-ml files used as tertiary selections (n = 2) as needed. All pixel-based measurements were converted to metric units, using a scalar affixed externally to the patient (19 mm coin) for measurement standardization in each video. Three measures proposed to capture edema were collected, and are illustrated in Figure 1:

1. Posterior pharyngeal wall (PPW) thickness: Thickness of the PPW, measured posteriorly to the valleculae at the anterior-inferior corner of C3. This measure has been used to capture post-surgical swelling in anterior cervical discectomy and fusion patients.[14]

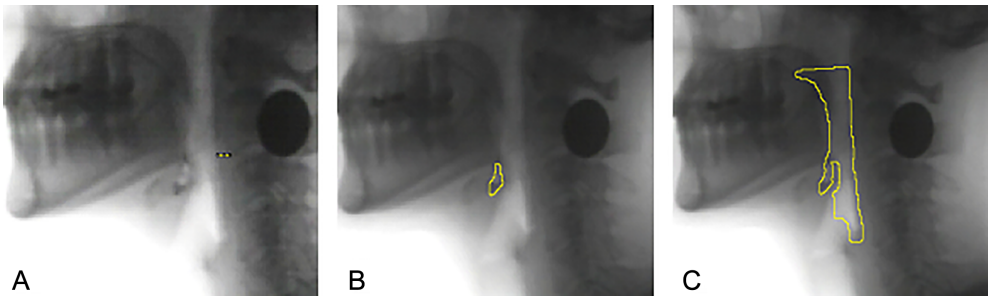

Fig. 1. Measurement of PPW thickness (A), vallecular space (B), and pharyngeal area (C) from a pre-CRT swallow rest frame CRT = chemoradiation therapy; PPW = posterior pharyngeal wall.

2. Pharyngeal area: Unobliterated pharyngeal space, defined superiorly from the anterior-superior corner of C2 to the base of tongue, anteriorly along the base of tongue, the valleculae, and epiglottis to the top of the arytenoid cartilage, inferiorly along the pyriform sinuses, and posteriorly along the entire posterior pharyngeal wall. This measure is routinely captured as a component of the maximum pharyngeal constriction ratio measures.[15,16]
3. Vallecular space: Two-dimensional measure of vallecular space defined by the base of tongue and vallecular border to the tip of the epiglottis. This measure is routinely captured in the normalized residue ratio scale for vallecular residue (NRRSv).[17]

DIGEST. DIGEST is a reliable and valid scale for assessing the toxicity of pharyngeal-stage dysphagia in individuals with HNC. In order to determine a patient's overall DIGEST score, each swallow in a study is rated using the Penetration-Aspiration Scale[18] to assess safety, and an ordinal residue scale to assess efficiency. Aggregate scores are then analyzed, and safety and efficiency scores are assigned. These scores are used to assign a global rating of pharyngeal swallowing function. These scores map onto The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) toxicity framework as follows: 0—none, 1—mild, 2—moderate, 3—severe, 4—life threatening.[12] DIGEST has been found to have increased specificity in the acute phase, when compared to traditional CTCAE ratings of dysphagia.[19] Of note, DIGEST is validated on a VF protocol that includes two trials each of thin liquid Varibar at 5 ml, 10 ml, and uncalibrated cup sips, followed by two Varibar pudding boluses, and a cracker coated in barium paste. This represents a slight deviation from the VF protocol used in the current study.

EAT-10. The EAT-10 is a validated questionnaire consisting of 10 questions related to swallowing function and quality-of-life. Patients are asked to rate perceived impairment on a scale of 0 (no problem) to 4 (severe problem). Total EAT-10 scores can range from 0 to 40. Total scores greater than 2^{11} or 15^{20} have been suggested as cutoffs considered indicative of swallowing impairment. A relationship between EAT-10 scores and impaired swallowing pathophysiology and safety has been established in individuals with HNC both pre-treatment and up to one year post-treatment.[21]

Statistical Analysis

Data were analyzed in IBM SPSS Statistics 24.0 (Armonk, NY, USA). Reliability was assessed using two-way mixed intraclass coefficients for consistency. Wilcoxon sign rank tests were used to assess within-subject change in EAT-10 and DIGEST grade pre- versus post-treatment. Pearson correlations were used to establish a relationship between EAT-10 and DIGEST grade. Descriptive statistics for all three edema measures were completed and subjected to paired samples t-test to assess the overall effect of time (pre-CRT vs. post-CRT) on edema. Measures of edema that were significantly different between pre- and post-CRT time points were then used in linear mixed effect regression models with fixed effects of patient-reported difficulty with swallowing (dichotomized EAT-10), functional impairment (ordinal DIGEST grade), and time (pre-CRT vs. post-CRT). The models employed maximum likelihood estimation and a compound symmetry structure. Two-tailed *P*-values of <.05 were considered significant. Post-hoc comparison of significant between subject main-effects controlled for Type I error via Sidak adjustments.

RESULTS

A random selection of 10% of the data were re-rated by the same rater and repeated by an expert rater for intra- and inter-rater reliability results, respectively. Data were analyzed using mixed two-way intraclass correlation coefficients (ICCs). Results appear in Table II. All measures achieved "excellent" reliability (greater than 0.75) as per Fleiss.[22]

Measures of Impairment

Descriptive data for the measures of impairment appear in Table III. Analysis of the patients' self-reported difficulty swallowing (EAT-10 scores) revealed that one month after the completion of CRT treatment, patients had statistically higher (worse) EAT-10 scores than at baseline ($Z = -5.306$, $P < .001$). Indeed, the median EAT-10 score increased from 1 (pre-treatment) to 12 (post-treatment). Further, the analysis of the patients' objective swallow function (overall DIGEST scores) revealed that one month after the completion of CRT, patients had significantly worse DIGEST scores than at baseline ($Z = -2.201$, $P = .028$). When the DIGEST components were further analyzed only DIGEST safety scores were significantly worse ($Z = -3.83$, $P < .001$) while DIGEST efficiency scores trended towards being significantly worse ($Z = -1.834$, $P = .067$). EAT-10 scores were significantly and positively correlated to overall DIGEST grade ($r = 0.40$, $P < .001$), though more strongly with DIGEST

TABLE II.
Inter- and Intra-Rater Reliability.

	Intra-rater			Inter-rater		
	ICC	Lower CI	Upper CI	ICC	Lower CI	Upper CI
PPW thickness	0.96	0.74	0.99	0.87	0.27	0.98
Vallecular space	0.98	0.88	1.00	0.95	0.64	0.99
Pharyngeal area	0.96	0.78	0.99	1.00	0.98	1.00
DIGEST Grade (overall)	0.96	0.82	0.94	0.75	0.25	0.95
DIGEST Safety score	0.89	0.45	0.98	0.89	0.49	0.98
DIGEST Efficiency score	0.98	0.91	0.99	0.90	0.50	0.98

CI = confidence interval; DIGEST = Dynamic Imaging Grade of Swallowing Toxicity; ICC = intraclass correlation coefficient; PPW = posterior pharyngeal wall.

safety scores (r = 0.49, $P < .001$) than DIGEST efficiency scores (r = 0.29, $P = .009$).

Measures of Edema

Descriptive statistics and paired t-test results for proposed measures of edema appear in Table IV. Only one of the three proposed edema measures extracted from the 2D lateral VF images, PPW thickness, demonstrated significant worsening in a within subject analysis. The PPW was significantly thicker post-CRT compared to pre-CRT. Thus, PPW was chosen as the variable to represent edema in the remaining analyses.

Linear Mixed Effects Regression Model

This analysis was conducted on PPW only, as it was the only edema measure that appeared to robustly capture edema across the two time points. Between-subject fixed effects of sex and age were not found to be significant contributors in the full model and thus were removed. High collinearity between DIGEST scores resulted in the decision to include overall DIGEST grade only in the model. The final model included Time (pre-CRT vs. post-CRT), EAT-10 (over or under 15), and DIGEST grade and controlled for individual variation via random intercepts per participant. Results revealed that time (pre-CRT vs. post-CRT) was the only significant predictor of PPW thickness. Post-hoc pair wise comparisons revealed a significantly greater PPW thickness post-treatment (+1.513 mm, F[1, 56.94] = 11.11, $P = .02$). Alternative model explorations including DIGEST safety and efficiency scores, as well as alternate EAT-10 cut-offs (<3 vs. 3+) did not yield significant results.

Given the retrospective nature of our design, our small sample and our exploratory aims, we opted to plot the data by swallowing impairment (EAT-10, DIGEST) and time (pre-CRT and post-CRT) to visually inspect trends and relationships. These appear in Figures 2 and 3.

DISCUSSION

In this study, we set out to objectively quantify pharyngeal edema in the acute phase post-CRT treatment for oral and/or pharyngeal cancer from 2D lateral VF imaging. We also sought to determine whether there was a relationship between quantitative measures of edema and patient reported outcomes of swallowing (EAT-10 scores) as well as functional ratings of swallowing impairment (DIGEST grade).

The patients in this study certainly appeared to experience negative consequences to swallowing outcomes at one month post-CRT as evidenced by significant worsening of EAT-10 scores and DIGEST grades. With respect to edema, we quantified a significant increase in PPW thickness post-CRT. This finding is consistent with reports of edema of the pharyngeal constrictor muscles secondary to radiation therapy.[23] The location chosen for measurement of PPW thickness, the anterior-inferior corner of C3, corresponds to the approximate position of the middle pharyngeal constrictor muscle,[24] a muscle which has been found to be sensitive to radiation dose.[25] Using magnetic resonance imaging (MRI), Popovetzer et al. found increased pharyngeal constrictor thickness and T2 signal intensity

TABLE III.
Descriptive Variables for Measures of Impairment.

	EAT-10		DIGEST Overall		DIGEST Safety		DIGEST Efficiency	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	3.4	14.95	0.7	1	0.2	0.6	0.7	1
Minimum	0	0	0	0	0	0	0	0
Maximum	17	40	2	3	1	3	3	3
Median	1	12	1	1	0	0	0	1

DIGEST = Dynamic Imaging Grade of Swallowing Toxicity; EAT-10 = Eating Assessment Tool.

TABLE IV.
Descriptive Statistics for Edema Measures.

	Pre-CRT			Post-CRT					
	Mean	SD	N	Mean	SD	N	*t*	df	*P*
PPW thickness (mm)	4.6	1.4	40	6.4	2.0	40	−5.5	39	<.001
Vallecular space (mm^2)	42.7	27.0	39	44.9	27.1	39	−0.3	37	.804
Pharyngeal Area (mm^2)	680.2	205.9	39	617.7	286.1	40	1.4	38	.178

Paired sample t-test to examine main effect of treatment on edema measures.
CRT = chemoradiation therapy; PPW = posterior pharyngeal wall thickness; SD = standard deviation.

post-CRT, both of which were determined to be indicative of edema. A positive correlation was found between dose and both muscle thickness and T2 signal intensity, with significantly greater increases seen in patients receiving radiation doses over 50 Gy.[23] With patients in this study receiving a radiation dose of 70 Gy, increased thickness of the pharyngeal constrictors, representing edema, would be expected, and was adequately captured by measuring the thickness of the posterior pharyngeal wall.

Contrary to our hypothesis, significant differences were not found between pre- and post-CRT measures of pharyngeal area and vallecular space. While pharyngeal area did decrease, as would be expected, this difference did not reach the level of statistical significance. This may be the result of the relatively large area this measure captured, which may not be a sensitive enough measure of edema occurring in individual structures. Further, this could be due to incomplete relaxation of the pharynx post-swallow in the post-CRT condition given that patients were more likely to be executing clearing attempts in the post-CRT condition. Surprisingly, a slight increase in vallecular space was found post-CRT. Previous research has indicated that the frame selected significantly influences the size and shape of the valleculae.[17] It is possible that our data may be susceptible to measurement error, specifically related to the post-swallow rest frame that was selected for measurement. It is also plausible that individuals with base of tongue tumors would reduce the vallecular space available for measurement prior to onset of CRT treatment.

A linear mixed effects regression model revealed that objective measures of edema were not significantly correlated with either patient perceptions of swallowing difficulty (EAT-10), or with measured swallowing function (DIGEST). Time was the only factor found to independently predict edema, with increased edema of the posterior pharyngeal wall noted post-CRT. The lack of significant findings correlating edema with patient perception and swallow function was surprising, given previous studies which have shown such correlations, using subjective measures of internal edema.[7,8] It should be noted, however, that both of these prior studies were conducted on patients >3 months post-CRT; a time when the acute effects of radiation such as mucositis and radiation dermatitis, which cause pain, excessive mucous production, and xerostomia, would have likely subsided.[5] It is plausible that at the early time point (one month post-CRT treatment completion) captured in this study, the etiology of dysphagia is multi-faceted,[26] with factors other than edema alone contributing to increased EAT-10 and DIGEST scores post-treatment. Inspection of the data plotted in Figures 2 and 3 visually confirms the regression results. We see evidence of the main effect of time (pre-CRT vs. post-CRT) but no consistent relationships attributable to patients' perception of swallowing status (Fig. 2) or functional assessment of swallowing (Fig. 3).

This study is not without its limitations. First, this retrospective dataset of 40 individuals may have been underpowered to detect relationships between edema and measures of dysphagia. Second, the VF protocol at the local institution differed slightly from the validated DIGEST protocol. However, the positive, statistically significant relationships between EAT-10 scores and DIGEST scores support the clinical validation of the use

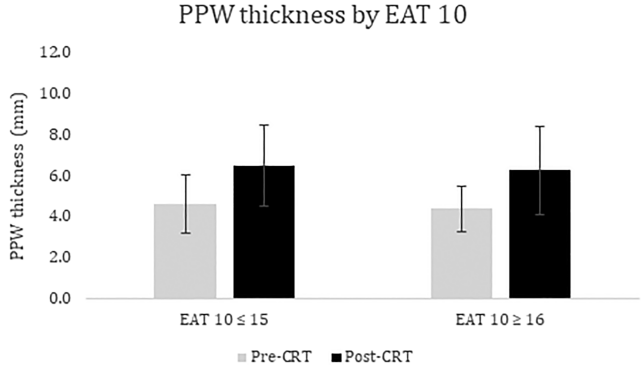

Fig. 2. Measures of PPW thickness by patient-reported outcomes on the EAT-10. CRT = chemoradiation treatment; EAT-10 = Eating Assessment Tool; PPW = posterior pharyngeal wall.

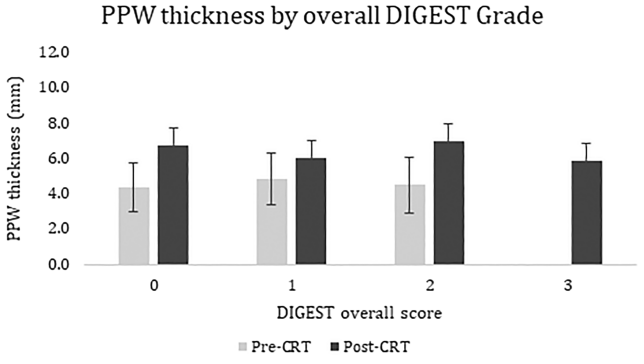

Fig. 3. Measures of PPW thickness by DIGEST grade. CRT = chemoradiation treatment; DIGEST = Dynamic Imaging Grade of Swallowing Toxicity; PPW = posterior pharyngeal wall.

TABLE V.
Linear Mixed Effects Regression Model for PPW.

Source	df	F	Sig.
Intercept	1, 61.02	90.44	<0.001
Pre-CRT vs Post-CRT	1, 40.62	26.55	<0.001
EAT10 (≤15 vs ≥16)	1, 79.27	0.25	0.619
DIGEST Grade (overall)	3, 76.42	0.10	0.619

CRT = chemoradiation treatment; DIGEST = Dynamic Imaging Grade of Swallowing Toxicity; EAT10 = eating assessment tool; PPW = posterior pharyngeal wall thickness.

of DIGEST with this protocol. Further, our retrospective VF studies lacked audio recording, and thus exact bolus identification may have been compromised (required during DIGEST rating). To minimize this limitation, VF studies were compared to clinical reports to confirm suspected protocol deviations (ie, compensatory maneuvers). Another limitation to acknowledge is that all patients in this data set were prescribed prophylactic exercises prior to onset of CRT, although their adherence was not tracked. Completion of swallowing exercises during CRT has been found to have a positive impact on swallowing function, musculature, and physiology, at various time points following treatment.[27–33] Thus, our results may have been influenced without our control over this variable. Finally, as noted above, the post-swallow rest frame selected may have unduly impacted measures of edema.

Going forward, prospective longitudinal work is needed in order to track changes in objective measures of edema over time. Such research should continue to examine the relationship between edema and both patient perceptions and swallow function over time, especially as acute effects of radiation subside. Additionally, future research should examine the relationship between edema and both temporal and biomechanical measures of swallowing, in order to determine the mechanisms by which edema impacts swallow function. Based on the significant edema in the posterior pharyngeal wall observed in this study, potential candidates for future investigation are pharyngeal constriction, pharyngeal stripping wave and epiglottic deflection.

CONCLUSION

Our findings establish the use of posterior pharyngeal wall thickness as a reliable measure of acute edema following concurrent chemotherapy and radiotherapy treatment for head and neck cancer. This study is also the first to demonstrate impaired swallow function following CRT using DIGEST as a functional outcome measure. Using PPW thickness as a proxy for edema, a significant increase in edema was found post-CRT. In this small, retrospective sample, PPW edema was not significantly correlated with either patient-reported or measured swallow function. Based on our findings, prospective longitudinal work examining the relationship between objective measures of edema, patient perception of impairment, and swallow function is warranted.

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