

The Effect of Radiation Dose on Swallowing: Evaluation of Aspiration and Kinematics

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Abstract Radiation oncologists have focused on the pharyngeal constrictors as the primary muscles of concern for dysphagia. However, our prior investigations have demonstrated that radiation dose to the geniohyoid rather than the constrictor muscles was more closely related to penetration aspiration scores (PAS). We examined the relationship between (1) radiation dose and swallowing temporal kinematics, and (2) between PAS and swallowing kinematics in these patients. Videofluoroscopic swallowing studies of 41 patients following radiation therapy for oropharyngeal cancer were analyzed for thin liquid boluses. Timing measures included duration of laryngeal vestibule closure (DLVC), duration to maximum hyoid elevation (DTMHE), duration to cricopharyngeal opening (DTCPO), and pharyngeal transit time (PTT). PAS was extracted for each swallow and considered normal if ≤ 2 . As minimum and mean dose to the geniohyoid increased, DTMHE, DTCPO, and PTT increased. Worse PAS scores were most strongly correlated with radiation dose received by geniohyoid ($r = 0.445, p < 0.0001$). Mean DLVC varied according to PAS group (normal PAS mean = 0.67 s,

abnormal PAS mean = 0.13 s; $p < 0.001$). Similarly, DTCPO was significantly different based upon PAS (normal PAS mean = 0.22 s, abnormal PAS mean = 0.37 s, $p = 0.016$). As PAS increased, DTPCO and PTT increased ($r = 0.208, p = 0.04$; $r = 0.204, p = 0.043$). A negative correlation was noted between PAS and DLVC ($r = -0.375, p = 0.001$). Higher doses of radiation to the geniohyoid muscles are associated with increased severity of dysphagia as measured through both kinematics and PAS. Consideration of dose to the geniohyoid should be considered when planning radiation.

Keywords Deglutition · Deglutition disorders · Dysphagia · Radiation oncology · Head and neck cancer · Swallowing kinematics

Introduction

Non-operative management of head and neck squamous cell carcinoma has become commonplace following the publication of equivalent oncologic outcomes in the VA larynx study and Radiation Therapy Oncology Group (RTOG) 91-11 trials [1, 2]. Despite favorable organ preservation rates, non-surgical modalities have their own set of toxicities both during and following treatment. Radiation and chemoradiation (RT/CRT) are associated with significant treatment-related toxicity, with high-grade mucositis present in nearly all patients [3]. Acute toxicities may influence long-term patient outcomes [4]. Multiple physiologic deficits have been associated with RT/CRT including poor laryngeal elevation, decreased pharyngeal constriction, lack of epiglottic tilt, poor airway protection, and reduced tongue base retraction [5–8]. However, data regarding swallowing temporal kinematics of patients

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following head and neck cancer treatment is lacking. Reduced physiologic function and dysphagia have been associated with poor quality of life (QoL) [4]. Further, long-term follow-up from the RTOG 91-11 trial demonstrated that patients receiving concurrent chemoradiation had an increased risk for non-cancer related deaths, and it has been postulated that this may be related in part to aspiration pneumonia from late radiation-associated dysphagia [9].

The relationship between radiation dose to specific sites of the swallowing apparatus and subsequent dysphagia has received significant attention in recent studies. In 2004, Eisbruch et al. [10] were the first to highlight that radiation dose to the pharyngeal constrictors and larynx played a critical role in the development of RTOG grade 3/4 dysphagia. In a prospective study of 36 patients with Stage III-IV oropharyngeal or nasopharyngeal cancer, Feng et al. found that the mean doses to the pharyngeal constrictors and the supraglottic larynx were significantly higher in patients with aspiration compared to those who did not aspirate (~5 Gy difference) [11]. Additionally, none of the patients who received mean doses ≤ 60 Gy aspirated. Levendag et al. reported a 19 % increase in the probability of dysphagia for every 10 Gy beyond a dose of 55 Gy to the pharyngeal constrictors [12].

Our study team recently published data suggesting that the muscles of the floor of mouth (FoM) responsible for hyo-laryngeal excursion are also implicated in airway protection and aspiration risk [13]. These findings are consistent with the work of Hirano et al. who examined the incidence of postoperative dysphagia and found that removal of the geniohyoid (GH) or mylohyoid muscles was significantly associated with poor swallowing function as measured by diet level and the presence of aspiration [14]. Pearson and colleagues recently reported the results of structural studies modeling the physiologic function of the FoM muscles in laryngeal displacement during swallowing [15]. In their cadaveric studies, they identified that the suprahyoid musculature had greater potential for influencing hyo-laryngeal elevation than did the thyrohyoid or the long pharyngeal muscles. Further, Feng et al. demonstrated that GH atrophy was associated with increased aspiration risk [16]. The underlying impact of radiation to the FoM muscles on swallowing physiology and kinematics is not well understood at this time. As a result, this study examined the relationship between (1) radiation dose and swallowing temporal kinematics, as well as (2) between PAS and swallowing kinematics in patients treated with radiation therapy for HNSCC. We hypothesized that higher radiation doses to the FoM muscles, and particularly to GH, would be correlated with worse penetration and aspiration outcomes as well as disordered airway protection kinematics. We also hypothesized that patients with abnormal PAS would have abnormal swallowing temporal

Table 1 Patient demographics

Sex	
Male	34 (82.93 %)
Female	7 (17.07 %)
Mean age (years)	56.78 years (range 32–69)
Race	
White	36 (87.80 %)
Other	5 (12.20 %)
T stage	
Early (T1–T2)	21 (51.22 %)
Late (T3–T4)	20 (48.78 %)
N stage	
N0	5 (12.20 %)
N1	7 (17.07 %)
N2	24 (58.54 %)
N3	3 (7.32 %)
Unknown	2 (4.88 %)
HPV status	
Positive	32 (78.05 %)
Negative	8 (19.51 %)
Unknown	1 (2.44 %)
Pre-treatment SLP consult	
Yes	34 (82.93 %)
No	7 (17.07 %)

kinematics. The rationale for this hypothesis is based on studies that have reported the importance of FoM muscles in swallowing airway protection [14, 15] and the effect of dose on muscle function [10–12].

Methods

Participants

This study was approved by the Johns Hopkins University Institutional Review Board. We examined 41 patients with oropharyngeal squamous cell carcinoma (OPSCC) who underwent concurrent CRT to the FoM and who had post-radiation swallowing assessment that included videofluoroscopy. All participants completed post-treatment swallowing studies according to standard of care in our institution. Patient demographics can be found in Table 1.

Radiation Contouring

Contouring was performed on the Pinnacle planning software (Philips Healthcare, Andover, MA) version 9.0. The patient's radiation treatment plan was utilized for normal structure delineation. The treatment plan, including treatment beams, dose, and isocenter placement were not

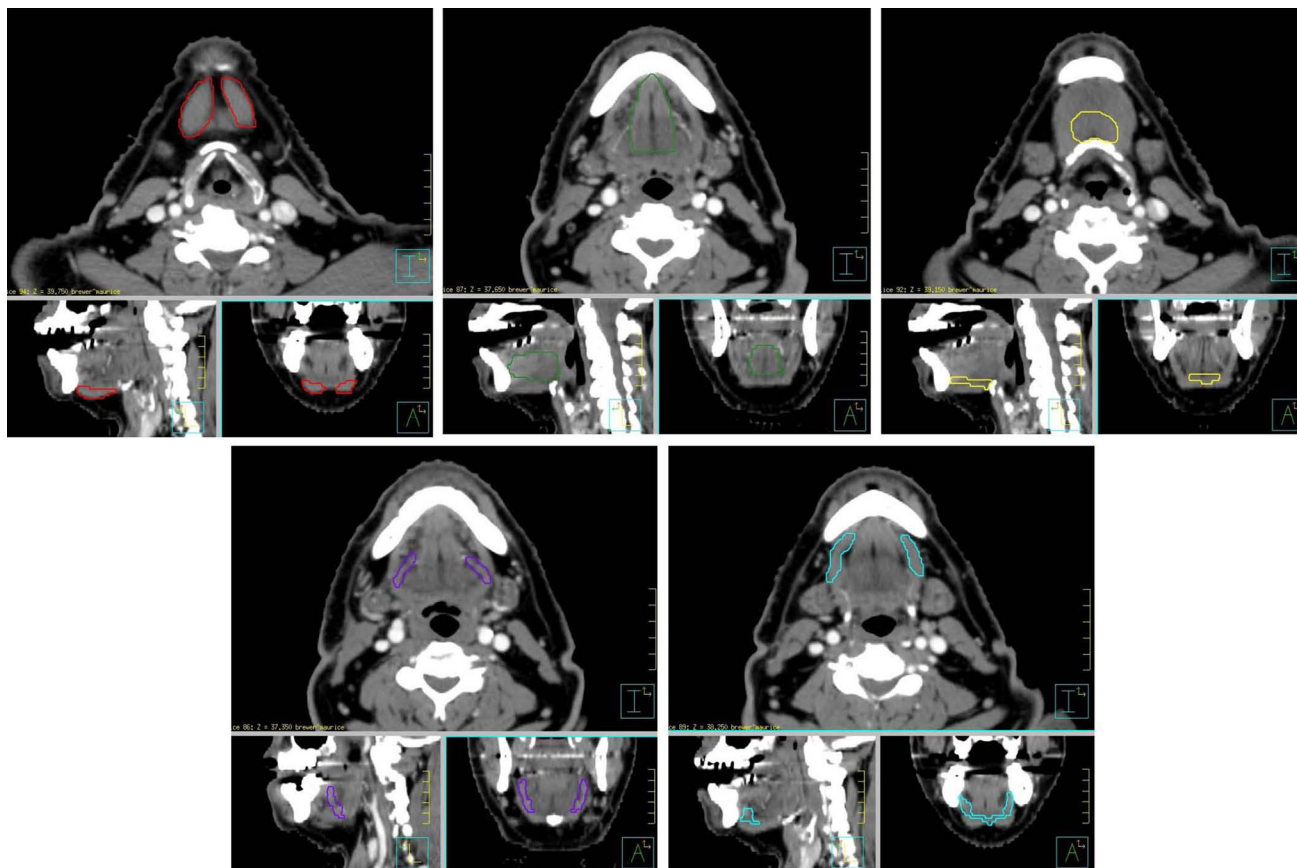


Fig. 1 Representative contours of the muscles of the floor of mouth including (from left to right) anterior digastric, genioglossus, geniohyoid, hyoglossus, and mylohyoid

altered. Standard normal structures including the larynx, pharyngeal constrictors, oral mucosa, and parotid glands were delineated on the patient's planning CT scan as directed by the senior radiation oncologist (HQ). Delineation of the FoM muscles was completed by two independent investigators on the planning CT scan with the oversight of both the senior radiation oncologist (HQ) and expert anatomist (EM), all of whom were blinded to the patient's swallowing outcome (Fig. 1). The radiation treatment plan was re-generated with the additional critical structures [geniohyoid (GH), genioglossus (GG), mylohyoid (MH), anterior belly of digastric (AD), hyoglossus (HG), and composite floor of mouth (FoM)] and the resulting dose was calculated and recorded. The FoM composite contour included the GH, MH, AD, and HG.

Videofluoroscopic Data Collection and Kinematic Analyses

Post-treatment videofluoroscopic swallowing studies (VFSS) were obtained after completion of CRT to assess physiologic outcomes as well as penetration aspiration scores (PAS). We obtained fluoroscopic images real time at

30 frames per second in the lateral view. On average, the VFSS took place approximately 4 months after the end of CRT. At our institution, VFSS are standard of care following treatment regardless of patient complaints of dysphagia. Licensed speech-language pathologists (SLP) specializing in the care of patients with OPSCC conducted the VFSS in conjunction with expert GI radiologists. Patients swallowed puree boluses by teaspoon, 5 cc and 10 cc thin liquid barium, ungraded cup sips of thin liquid barium, and 1/4 graham cracker coated with barium pudding. Varibar barium products were utilized.

All kinematic data analyses were completed by one SLP (HS) who was blinded to the CRT dose. Kinematic analyses were performed on 5 cc swallows of thin liquid barium and ungraded cup sips of thin liquid boluses to evaluate both discrete and sequential swallowing behavior after CRT. These boluses were chosen for analysis as they were consistently present across all VFSS studies. Kinematic measures included duration to laryngeal vestibular closure (DTLVC), duration of laryngeal vestibule closure (DLVC), duration to maximum hyoid elevation (DTMHE), swallow onset delay (STD), and pharyngeal transit time (PTT). We also measured duration to cricopharyngeal

opening in two ways: one being the time interval between hyoid burst and UES opening (DTCPO-H) and the other being the time interval between bolus entry in the pharynx and UES opening (DTCPO-B). Methodology for these measures has been previously described by Kendall [17]. The PAS was used to objectively quantify entrance of material into the laryngeal vestibule and patient response to this material [18]. This is an 8-point ordinal ranking scale that evaluates as follows: normal swallowing (scores 1–2), and abnormal swallows where ingested material enters the larynx at or above the vocal folds and is ejected (scores 3–4) or is not ejected (score 5). As well, the PAS considers more severe dysphagia as abnormal swallows that involve aspiration where ingested material passes the vocal folds and is ejected (score 6), is not ejected despite effort (score 7), or no effort is made to eject the aspirated material (8). Thus, scores of one or two were considered normal and scores of three or greater were considered to be abnormal [19].

Statistical Analysis

Our goal was to examine the relationship between (1) radiation dose and swallowing temporal kinematics, as well as (2) between PAS and swallowing kinematics in these patients. First, to examine radiation dose and swallowing temporal kinematics, we used radiation dose (independent variable) as the predictor for change in swallowing kinematics (dependent variable). Thus, Spearman's rank correlation coefficient was used, given that non-parametric statistics are most appropriate for ordinal data (PAS). For radiation dose, we included minimum and mean dose to GH as well as mean dose to the composite FoM muscles, as these were found most significantly associated with PAS score in our earlier investigation [13]. We interpreted significantly correlated variables ($p < 0.05$) as the following: .00–.19 very weak, .20–.39 weak, .40–.59 moderate, .60–.79 strong, and .80–1.0 very strong. To examine PAS and swallowing kinematics, we compared swallowing kinematics between swallows with normal and abnormal PA scores with a Mixed Models analysis. In the model, fixed factors were group (normal or abnormal PA score) and bolus type (5 cc versus cup sips), and subjects were random factors. When fixed effects were statistically significant ($p < 0.05$), pairwise comparisons were made with Sidak adjustment to correct for multiple comparisons. The DTLVC kinematic measure (duration between hyoid burst and onset of LVC) could not be included in the analysis because several patients with abnormal swallows never achieved LVC. DLVC in these same patients was judged to be zero, meaning that the duration of LVC was zero as closure was never achieved, which has important clinical implications.

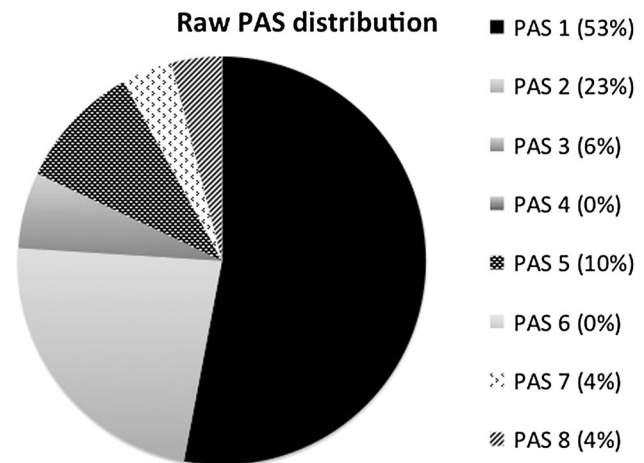


Fig. 2 Raw PAS distribution

Results

Final analysis included forty-one sequential patients with OPSCC treated with concurrent CRT who had post-treatment swallowing studies (Table 1). The majority of the patients were male (83 %) and mean age at diagnosis was 56 years. Patients were balanced in terms of early versus late T-stage, but the majority of patients had advanced nodal stage ($\geq N2$). The majority of patients had HPV-associated OPSCC. Pre-radiation speech-language pathology (SLP) consultation was accomplished in 83 % of patients and included assessment of baseline status as well as provision of prophylactic swallowing exercises. Average time elapsing between end of radiation and videofluoroscopic swallow study was 4 months (range 1–19 months). Eighty-eight percent of patients had a prophylactic PEG placed prior to radiotherapy. All patients underwent once daily fractionated intensity-modulated radiation therapy (IMRT) with concurrent chemotherapy. Mean radiation dose was 69.6 Gy (range 69–72 Gy). Platinum-based chemotherapy was used for 68 % of patients, induction chemotherapy was used in 22 % of patients, and other concurrent chemotherapy regimens were used for 10 % of patients. Induction chemotherapy was employed in patients with T4 and/or advanced nodal disease.

PAS was normal (≤ 2) in 68 % of patients and abnormal (> 2) in 32 % of patients. Raw PA scores are provided in Fig. 2. There were no significant demographic differences between patients with normal and abnormal PAS (Table 2). More patients in the normal PAS group received prophylactic PEG (93 %) in contrast to those in the abnormal PAS group (77 %). Though swallowing studies were completed slightly later in those with abnormal PAS (4.86 vs. 3.69 months), this difference was not statistically significant ($p = 0.17$). Similarly, though a higher proportion

Table 2 Patient demographics by PAS group

	Normal PAS (<i>n</i> = 28)	Abnormal PAS (<i>n</i> = 13)	<i>p</i> value
Mean age	55.54	59.46	0.821
Sex			0.659
Male	24 (85.71 %)	10 (76.92 %)	
Female	4 (14.29 %)	3 (23.08 %)	
Race			1.0
White	24 (85.71 %)	11 (84.62 %)	
Other	4 (14.29 %)	2 (15.38 %)	
T stage			0.098
≤2	19 (67.86 %)	5 (38.46 %)	
>2	9 (32.14 %)	8 (61.54 %)	
N stage			0.719
<2	9 (32.14 %)	3 (23.08 %)	
≥2	19 (67.86 %)	10 (76.92 %)	
HPV status			0.429
Positive	23 (82.14 %)	9 (69.23 %)	
Negative/ unknown	5 (17.86 %)	4 (30.77 %)	
Pre-tx SLP Care			0.18
Yes	25 (89.29 %)	9 (69.23 %)	

Table 3 Correlations between radiation dose and swallowing kinematics

	GH min	GH mean	FoM mean
LVC	<i>r</i> = -0.074 <i>p</i> = 0.27	<i>r</i> = 0.02 <i>p</i> = 0.434	<i>r</i> = -0.054 <i>p</i> = 0.327
DTMHE	<i>r</i> = 0.267 <i>p</i> = 0.014	<i>r</i> = 0.227 <i>p</i> = 0.032	<i>r</i> = 0.064 <i>p</i> = 0.303
DTCPO-B	<i>r</i> = 0.356 <i>p</i> = 0.001	<i>r</i> = 0.327 <i>p</i> = 0.003	<i>r</i> = 0.149 <i>p</i> = 0.106
DTCPO-H	<i>r</i> = -0.329 <i>p</i> = 0.003	<i>r</i> = -0.291 <i>p</i> = 0.008	<i>r</i> = -0.195 <i>p</i> = 0.054
PTT	<i>r</i> = 0.449 <i>p</i> < 0.001	<i>r</i> = 0.383 <i>p</i> < 0.001	<i>r</i> = 0.225 <i>p</i> = 0.029

Bold values indicate *p* < 0.05

of patients in the normal PAS group received pre-tx SLP care, this difference failed to reach statistical significance (*p* = 0.18). We also determined the time of aspiration relative to swallow onset (before, during after), as this provides useful information about how swallowing kinematics and bolus flow are related. No patient aspirated prior to swallow onset. Aspiration occurred during the swallow 27 % of the time. Aspiration was present both during and after the swallow in 9 % of patients. Finally, in most patients, aspiration occurred after the swallow was completed (64 %).

Relationship Between Radiation Dose and Swallowing Kinematics

Significant relationships were found between radiation dose and swallowing kinematics, ranging from weak to moderate (correlations in Table 3). Specifically, weak positive relationships were found between GH mean and all kinematics measured, except DTCPO-H, which had a weak negative relationship. No significant relationship was found between radiation dose and DLVC. For GH min, weak positive relationships with DTMHE and DTCPO-B, and a moderate positive relationship with PTT were observed. A weak negative relationship was noted between GH min and DTCPO-H. For mean dose to the composite FOM muscles, only PTT was significant, which was defined as a weak positive relationship. Higher PAS was moderately correlated with minimum radiation dose received by GH (*r* = 0.445, *p* < 0.0001). Abnormal PA scores were also associated with the mean dose to GH >60 Gy (Fig. 3).

Relationship Between PAS and Swallowing Kinematics

Significant differences in kinematic measures were observed between the patients with normal and abnormal PAS (Fig. 4). Patients with normal PAS had significantly longer DLVC (*p* = 0.001; normal 617 ± 147 ms; abnormal 117 ± 58 ms). Patients with normal PAS also had significantly shorter PTT (*p* = 0.041; normal 678 ± 58 ms; abnormal 818 ± 81 ms) and DTCPO-B (*p* = 0.016; normal 227 ± 46 ms; abnormal 373 ± 80 ms). There were no statistically significant differences between groups for any other swallowing kinematic measure. No differences were found by bolus type/volume and no interaction between patient group or bolus type was found.

Discussion

This manuscript is the first to report a relationship between radiation dose and swallowing kinematics, and between penetration/aspiration and swallowing kinematics in patients treated for head and neck cancer. While previous investigations have demonstrated the relationship between radiation dose to the larynx and pharyngeal constrictors and the development of dysphagia, there is limited understanding of how radiation dose to the hyo-laryngeal elevators impact swallowing kinematics. Our previous report [13] demonstrated that radiation dose to the floor of mouth muscles was associated with elevated risk of laryngeal penetration/aspiration, more so than previously

Fig. 3 Penetration Aspiration Scores (PAS) by mean dose to geniohyoid

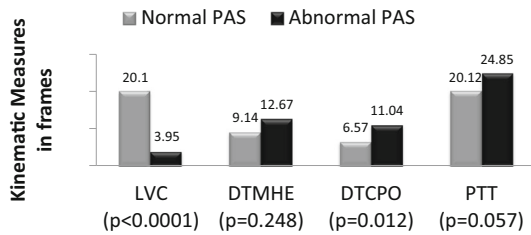
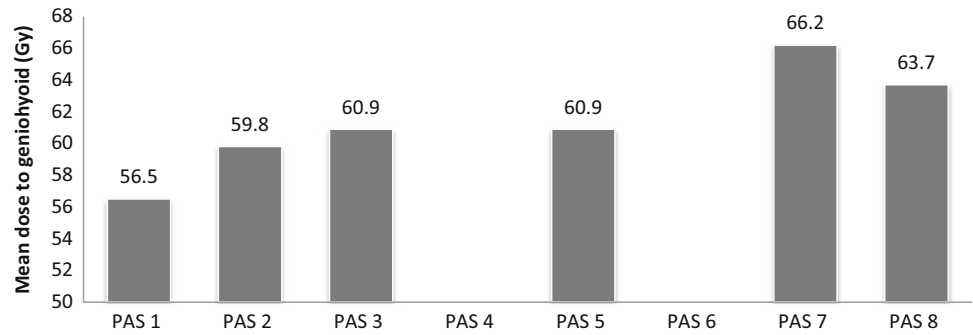


Fig. 4 Penetration Aspiration Scores (PAS) by kinematic measures

recognized organs at risk such as the pharyngeal constrictor muscles.

The time of aspiration must be considered in conjunction with these kinematic data to expand our understanding of the nature of the swallowing impairments in these patients. While dose to GH increased aspiration risk, GH dose was not significantly correlated with DLVC, critical to airway protection during the swallow. It is important to note that penetration/aspiration commonly occurred after the swallow, at a time when the laryngeal vestibule is supposed to be open for respiration, making abnormal DLVC kinematics less detrimental. Thus, one might conclude that the critical connection between GH dose and aspiration in this group of patients may be the impact of GH dose on upper esophageal sphincter (UES) opening. It has been well established that hyo-laryngeal elevation contributes to UES opening, with concurrent cricopharyngeal muscle relaxation [20]. Given the role of suprahyoid (FOM) and thyrohyoid muscles in hyo-laryngeal elevation [21], our results suggest that radiation dose to GH increases the risk of aspiration after the swallow due to impaired bolus clearance through the UES.

Patients receiving higher radiation doses to GH also had prolonged pharyngeal transit times as well as prolonged durations before the hyoid reached its peak elevation position (DTMHE), prolonged durations before the UES opened, and prolonged durations before the bolus cleared the pharynx. While PTT in the abnormal PAS group (818

ms) falls within the previously published range of normal 350–1190 ms [22], wide ranges and confidence intervals makes it difficult to determine the clinical relevance of this difference. However, clearly in those who aspirated in this investigation, the duration of time the bolus remained in the pharynx was notably longer in those patients receiving higher doses to GH at a time when other swallowing events were likely simultaneously disordered.

The duration of laryngeal vestibule closure was significantly shorter in patients with worse penetration aspiration scores. In fact, LVC was only achieved in one of eight episodes when aspiration occurred during the swallow. Patients with abnormal PAS had an average DLVC of 117 ms, which falls below previously reported normal results ranging from 310 ms to 1.07 s [22]. In contrast, the mean DLVC for patients in the normal PAS category was 617 ms, well within the previously aforementioned normal range. This suggests that those with normal PAS scores did not have abnormally prolonged DLVC as a compensation for other deficits.

Aspiration could increase the risk of further health complications due to aspiration pneumonia, possibly leading to serious morbidity or death. Given recent data that late non-cancer deaths are higher in patients receiving chemoradiation, potentially related to aspiration pneumonia, understanding the mechanisms of aspiration in this population is critical to the development of appropriate treatment strategies [23]. It is noteworthy that we were unable to derive enough measures of duration to LVC onset (DTLVC) in the abnormal PAS group, because many did not achieve LVC at all during swallowing. Even though this could not be quantified in our investigation, it stands to reason that this is a further complicating risk factor in this head and neck cancer population. Other studies have shown that when DLVC is frequently too short in duration or delayed, penetration and aspiration are likely to occur [24–26]. Higher radiation exposure to GH was associated with higher PA scores, making this factor critical for radiation treatment planning.

Some limitations of our study design must be acknowledged. Given the limitations of routine clinical practice and the lack of standardization at the time this data was collected, the post-radiotherapy evaluations were not all at the same time relative to treatment. Progressive fibrosis might be expected over time, though there are no data available suggesting specific timelines for development of fibrosis. While the slightly later completion of swallowing studies in the patients with abnormal PAS might reflect another factor which may have influenced swallowing outcomes, the between group differences were small and not statistically significant, therefore we believe that our outcomes are valid. Furthermore, only 3 cc and cup sips of thin liquid were included in our analysis due to inconsistent administration of puree and solid boluses in our swallow studies. Finally, we did not measure range of motion of the hyo-larynx, UES, or pressure changes in the pharynx or UES, which would be of great value when considering the relationship between radiation dose and swallowing outcomes. This is particularly salient given the high proportion of patients in this series demonstrating aspiration after the swallow. It is possible that higher doses of radiation to the floor of mouth muscles also impact the extent of upper esophageal sphincter opening. It must also be acknowledged that the weak and moderate correlations found may be due to under-powering for this investigation. Nonetheless, they appear to be clinically relevant given the number of patients with poor PA scores in our investigation.

We acknowledge that PAS scores and kinematic data do not provide a global measure of the functionality of the swallow. Consideration of other measures such as diet level and patient-perceived handicap would provide additional value in studying this population, however, such measures were unavailable at the time of this publication. As the intention of this manuscript was to explore the relationship between radiation dose, kinematics, and aspiration, we do not believe the exclusion of this complimentary data is critical.

In conclusion, our data demonstrates the importance of the floor of mouth muscles, and the geniohyoid in particular, in the development of dysphagia as characterized by penetration/aspiration and abnormal temporal swallowing kinematics in patients receiving chemoradiation therapy for OPSCC. While our analysis suggests that these muscles are important for airway protection kinematics for the OPSCC patient, prospective validation is still warranted. The findings of our analysis highlight the importance of the floor of mouth musculature for safe swallowing, as well as the need for further attention to the FoM region by the radiation oncology community.

Conflict of interest The authors have no conflict of interest.

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