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Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy

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Abstract

Purpose/Objective(s)—We sought to identify swallowing muscle dose-response thresholds associated with chronic radiation-associated dysphagia (RAD) after IMRT for oropharyngeal cancer.

Materials/Methods—T1-4 N0-3 M0 oropharyngeal cancer patients who received definitive IMRT and systemic therapy were examined. Chronic RAD was coded as any of the following ≥ 12 months post-IMRT: videofluoroscopy/endoscopy detected aspiration or stricture, gastrostomy tube and/or aspiration pneumonia. DICOM-RT plan data were autosegmented using a custom region-of-interest (ROI) library and included inferior, middle and superior constrictors (IPC, MPC, and SPC), medial and lateral pterygoids (MPM, LPM), anterior and posterior digastrics (ADM, PDM), intrinsic tongue muscles (ITM), mylo/geniohyoid complex (MHM), genioglossus (GGM),), masseter (MM), Buccinator (BM), palatoglossus (PGM), and cricopharyngeus (CPM), with ROI dose-volume histograms (DVHs) calculated. Recursive partitioning analysis (RPA) was used to identify dose-volume effects associated with chronic-RAD, for use in a multivariate (MV) model.

Results—Of 300 patients, 34 (11%) had chronic-RAD. RPA showed DVH-derived MHM V69 (i.e. the volume receiving ≥69Gy), GGM V35, ADM V60, MPC V49, and SPC V70 were associated with chronic-RAD. A model including age in addition to MHM V69 as continuous variables was optimal among tested MV models (AUC 0.835).

Conclusion—In addition to SPCs, dose to MHM should be monitored and constrained, especially in older patients (>62-years), when feasible.

Keywords

Dysphagia; Intensity-Modulated Radiation Therapy; Oropharyngeal Cancer; Mylohyoid; Geniohyoid; Dose-volume

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Introduction

Dysphagia is a potentially devastating late toxicity of head and neck radiation therapy (RT) [1, 2]. Radiation-associated dysphagia (RAD) is often cited as a dose limiting toxicity in this population[3, 4]. Patients with severe RAD may require lifelong tube feeding[5], or suffer potentially life-threatening aspiration[3, 4]. Population level data suggest 3-fold elevated risk of aspiration pneumonia in head and neck cancer (HNC) patients treated with chemoradiotherapy (CRT) relative to non-cancer controls, and 42% excess mortality among cancer survivors who develop pneumonia[6]. Pooled analysis of Radiation Therapy Oncology Group (RTOG) trials of CRT for HNC reported unacceptably high rates of severe late toxicity (i.e., 43% of patients with adequate baseline function had grade 3–4 late laryngopharyngeal toxicity) suggesting that further dose intensification cannot be safely achieved without new technique(s) to protect against late effects[7]. The therapeutic benefits of aggressive RT for HNC are clear[8–10], but understanding the structure-specific doses predisposing to long-term toxicity is paramount to patient care[11–13].

Swallowing requires complex coordination of numerous structures, and the exact contribution of each is incompletely understood[14]. Intensity-modulated radiation therapy (IMRT), now standard for HNC, substantially reduces normal tissue dose[15]. However, with more beam paths, greater volumes of non-target normal tissue (which may not have been exposed in conventional RT treatments) receive bystander dose[16]. Various studies have concluded that sparing dysphagia-related structures likely improves outcomes[1, 17, 18]. The wide array of candidate dysphagia-associated structures implicated by our group and others in previous studies reflects the complicated nature of RAD and suggests that further insight into its mechanism could be helpful in preparing future treatment regimens. To this end, as part of an ongoing HNC toxicity reduction program[19–33], specific aims of our study include:

- Identify dose-volume parameters of candidate swallowing-related muscular ROI related to chronic-RAD after IMRT.
- Identify candidate single- and multiple-muscle ROI dose-volume response thresholds associated with chronic-RAD
- Identify clinical and dosimetric parameters independently associated with risk of chronic-RAD.

Material and Methods

Study Design and Sampling Method

Patients treated with curative intent IMRT and systemic therapy for oropharyngeal cancer at The University of Texas, MD Anderson Cancer Center between 2002 and 2011 were retrospectively reviewed under an approved Institutional Review Board (IRB) protocol. Eligibility criteria were: Pathologically confirmed diagnosis of oropharyngeal squamous cell carcinoma (OPSCC), IMRT as a definitive treatment, available IMRT plan in the MDACC archive, and a minimum follow-up of ≥12 calendar months after end IMRT. Of 349 patients

identified, 49 were excluded because radiotherapy treatment plans could not be restored to analyze DVHs, leaving a total of 300 patients for analysis.

IMRT

We have previously reported in detail our IMRT approach for oropharyngeal cancer[9]. In brief, IMRT was used to treat the primary tumor and upper neck nodes. IMRT was delivered using “split-field” technique with lower neck below the isocenter treated with an anterior beam, with a larynx midline block. While “whole-field” IMRT used only when tumor might be underdosed using the split-field approach. All patients were treated with definitive bilateral IMRT with systemic therapy.

Data Collection

Chronic-RAD was defined as any of the following criteria occurring ≥12 months post-IMRT: videofluoroscopy/endoscopy detected aspiration or stricture, gastrostomy tube and/or aspiration pneumonia. Gastrostomy tube dependence was coded at 1-year follow-up, 2-year follow-up, and last disease-free follow-up. While, videofluoroscopic studies were conducted for patients referred with post-radiation symptoms of dysphagia (106 patients, 69 of these were ≥12 months post-radiation).

Clinical variables included age, sex, ethnicity, AJCC stage, TNM classification, tumor subsite (tonsil, base of tongue, or other) smoking history (never smoker, former/<10 pack-years, current/>10 pack-years), and chemotherapy regimen. Treatment plan and dosimetric data were restored using Pinnacle 9.6 software (Phillips Medical Systems, Andover, MA). Planning CT DICOM files were exported into a benchmarked [34] commercial deformable registration/segmentation software (Velocity AI 3.0.1, Velocity Medical Solutions, Atlanta, GA). For each patient, dysphagia-related musculature were software autosegmented using an existing atlas dataset [34] and subsequently reviewed by two radiation oncologists (ASR and CDF). DVHs were generated for the following muscle-specific regions of interest (ROIs): inferior, middle and superior constrictors (IPC, MPC, and SPC), medial and lateral pterygoids (MPM, LPM), anterior and posterior digastrics (ADM, PDM), intrinsic tongue muscles (ITM), mylo/geniohyoid complex (MHM), genioglossus (GGM), palatoglossus (PGM), masseter (MM), buccinator (BM), and cricopharyngeus (CPM). Exemplar ROIs are shown in Figure 1; indicative ROIs from 11 selected cases are included as DICOM-RT datasets at http://figshare.com/authors/Abdallah_Mohamed/551961. Prescription dose was as per standard practice, and is detailed in Table 1.

Statistical analysis

ROI summary parameters, including mean dose (D_{mean}) were first investigated non-parametrically. Bivariate plots of cumulative group dose volume histograms (DVH) were dichotomized by the presence or absence of chronic-RAD, with subsequent Wilcoxon rank sum test and p-values plotted via heat map analysis. Multivariate bootstrap resample recursive partitioning analysis (RPA)[35] was conducted to identify and test candidate dose-volume parameters associated with increased probability of chronic-RAD. RPA (also known as classification and regression trees) was selected over other parametric methodologies as it

allows selection of candidate “thresholds” for continuous variables using a binary endpoint (e.g. chronic-RAD).

Sequential random forest/RPA analysis is especially robust when limited priors preclude knowledge-based selection of continuous candidate covariates, and is comparatively unaffected by multi-collinearity and/or potential hyper-dimensional interactions within/between candidate clinical and dosimetric covariates[36], in contrast to standard logistic regression models, and thus require no direct transformation.

Detailed statistical methods are provided in supplementary table S1. RPA and regression models were applied systematically in the following steps to:

1. identify candidate ROI dose-volume parameters using bootstrap resampled RPA for whole ROI D_{mean}, whole ROI D_{max}, and ROI V1-V75 for all patients, with chronic-RAD status as a discriminant variable (step 1),
2. define dose-volume thresholds for chronic-RAD within “best” candidate parameters for each ROI using Receiver Operating Characteristic (ROC) and K-fold cross validation (step 2),
3. identify a predictive model for chronic-RAD by testing “best” dose-volume ROI candidates and clinical variables using stepwise nominal regression with Bayesian Information Criteria (BIC) minimization optimization for model selection and comparison (step 3), and
4. plot population level estimates of continuous toxicity-response profile probabilities using *post hoc* bootstrapped logistic probability models and subsequent unsupervised nonlinear curve fits similar to the methodology of Wedenberg [37] (step 4) as an alternative to NTCP curve assessment that mandates a 0% to 100% probability range for our chronic-RAD outcome of interest that is implausible at standard RT doses for OPSCC and given a non-zero baseline rate of age-/comorbidity-related dysphagia.

For this exploratory analysis and model construction, uncorrected p-values are presented, with a priori α=.05 considered for provisional statistical significance. Bonferroni correction(s), effect sizes, and LogWorth values (wherein Log Worth represents -log10[p-value], such that p=0.01 is equivalent to a LogWorth of 2.0, p=0.001 is denoted by LogWorth of 3.0, etc.) are detailed further for interpretative clarity. All statistical analysis was performed using commercial statistical analysis software (MatLab R2011a, Mathworks, Natick, MA; JMP v12Pro, SAS Institute, Cary, NC, USA; IBM SPSS 22.0, Chicago, IL).

Results

Patient and treatment characteristics

A total of 300 oropharyngeal cancer patient cases were accrued after eligibility screening. The median follow up was 48 months (range 12–110). The majority were male 91% with median age of 56 years. Median IMRT dose was 70 Gy (range 64–75) delivered using

standard fractionation (87%) and split-field technique (95%) in the majority of patients. Detailed demographic, disease, and treatment data are shown in Table 1.

Chronic-RAD

According to the pre-specified criteria, a total of 34 patients (11%) had chronic-RAD (videofluoroscopy detected aspiration n=21 (7%), videofluoroscopy detected stricture n=10 (3%), gastrostomy tube at 12months n=18 (6%), at 24months n=10 (3%), at last disease free follow-up n=12 (4%), and/or aspiration pneumonia n=8 (2.6%)). Of these chronic-RAD patients, only 5 (14.7%) showed clinical evidence of dysphagia prior to radiation therapy (i.e. ≥ grade 2 according to the common terminology criteria of adverse events version 4.0), however, all but one had clear progression of the dysphagia grade following chemoradiation.

Univariate correlates

Age (p=0.0134), T-category (p=0.004), N-category (p=0.03), sex (p=0.008), radiotherapy prescription dose (p=0.003), number of fractions (p=0.0005), and cytotoxic chemotherapy (p=0.03) were significantly associated with differentials in chronic-RAD rates, while smoking status (p=0.4), subsite (p=0.7) and ethnicity (p=0.9) failed to demonstrate an association with chronic-RAD.

Graphical analysis of composite DVHs shows patients with chronic-RAD had numerically higher dose delivery across all DVHs than those without RAD, with some variability of magnitude across ROIs (see Figure 2). After bonferroni correction, significant pairwise dose-volume differences were observed for ADM, GGM, ITM, and MHM (denoted in blue in the heat map for each ROI).

Post-hoc assessment of RPA-derived DVH and clinical parameters revealed that none demonstrated an absolute-value correlation of $|r| > 0.7$ (wherein 1= perfect correlation and 0=no correlation), the canonical threshold (confirmed by Dormann et al.[37]) for data distortion, with maximum of $|r| = 0.68$ observed between ADM V60 and MHM V69. No clinical variables (age, sex, T-category, etc.) showed a collinearity with dosimetric parameters derived from RPA. Consequently, we feel that the resultant stepwise-regression model, while not impervious to collinearity considerations, is unlikely to be inaccurate as a function of ROI dose-parameter covariance.

Assessment of whole ROI D_{mean} is described in Supplementary Figure S1, with significant ($p<0.05$) mean dose differentials between chronic-RAD and no-RAD subgroups for ADM, GGM, MHM, ITM, and SPC ROIs. All but SPC remained significant after Bonferroni correction for multiple comparisons.

Dose-volume thresholds

ROI-specific dose-volume thresholds associated with chronic-RAD were next explored via RPA decision tree analysis, with training and validation ROC AUCs, Again ADM, GGM, ITM, MHM, and SPC (which showed whole ROI mean dose-response signal, *vide supra*) were statistically significant, as well as MPM dose-volume “cutpoints” (Table 2). The resultant statistically significant binary cutpoints were interrogated by confirmatory logistic

regression to establish effect size, communicated as odds ratios and relative risk ratios, for ease of interpretation in Table 2. MHM and SPC dose-volume parameters (specifically MHM V69 and SPC V70) showed lower (superior) substantively BIC values than the other ("Very Strong" evidence grade, consistent with a >99% posterior probability of improved model performance); MHM V69 was only slightly more informative when compared to SPC V70.

Multivariate model

A BIC-minimizing forward stepwise regression model was constructed using the clinical parameters (T- and N-category, chemotherapy, sex, age) and the RPA-derived dose volume thresholds; the resultant model indicated MHM V69 and age as most predictive covariates (AUC=0.835). *Post hoc* RPA comparison of continuous versus binary MHM V69 and age model effects is summarized in Supplementary Table S2. While both models were sound in terms of goodness of fit, significance (i.e. p-value/LogWorth), and detectable effect size, BIC comparison found a continuous model of MHM V69 and age had superior performance (BIC difference 6.28, "Strong" by evidence grade) to a model using binary MHM V69 >79.5% and age of >62 years as model effects. Observed and bootstrapped predicted models for MHM V69 and age are plotted in Figure 3a–b and 3c–d, respectively. Finally, to illustrate interaction, a plot of the observed probability of chronic-RAD as a function of MHM dose, stratified by age over or under 62-years, is shown in Figure 4.

Discussion

Optimizing functional outcomes is a paramount goal in contemporary management of OPSCC. HPV-associated cancers now account for the majority of new OPSCC cases[38]. Clinically-distinct from tobacco related disease, HPV-associated OPSCC is diagnosed in younger patients who have favorable prognosis for long-term survival such that most survivors have potential to live years with effects of therapy. RAD is a priority issue for survivors[39], drives perception of QOL[40], and significantly predicts for aspiration pneumonia[41]. Even in modern practice, up to 60% of patients require feeding tube placement during IMRT[42]. More alarmingly, we previously reported a 7.6% chronic aspiration rate amongst head and neck (primarily oropharyngeal) squamous cell carcinoma patients undergoing chemoradiotherapy[33], and the Michigan group have reported that up to 20% of survivors develop chronic aspiration even with dysphagia-optimized IMRT planned specifically to minimize dose to non-target swallow critical structures including the constrictors and larynx[43–45].

Chronic radiation-associated dysphagia is an exquisitely complex and challenging toxicity. The state of the field is such that there is no effective treatment to reverse chronic-RAD in long-term survivors; intensive and costly therapies are required for incremental gains in functionality. The persistence of refractory RAD in modern practice motivates clinicians to refine preventive efforts through enhanced treatment paradigms. The complexity of swallowing function belies simple definition of dose response to clinical radiotherapy, as in dose-related xerostomia as a function of salivary gland dose. While several groups continue to actively define important benchmarks for RAD[43, 46–57], most investigators study

heterogeneous therapy cohorts (e.g. post-operative and definitive cases) or combine a mélange of organ sites for which beam paths to non-target structures vary widely. Head and neck cancers, owing to anatomical complexities, are far from monolithic. Mixing laryngeal cases, where retropharyngeal (and thus SPC) dose coverage is frequently unnecessary for treatment of subclinical disease, with nasopharyngeal cases, where obligate SPC coverage is the norm, but laryngeal coverage is exempted, is useful given large aggregates of cases, but may obscure systematic dose-response relationships (and achievable constraints) in more homogenous cohorts. Even within oropharyngeal tumors, the obligate muscle coverage when treating base of tongue and tonsillar cancers is quite distinct. The use of a uniform case mix as presented herein overcomes many issues of anatomic heterogeneity, as does the fact that all included patients had comparatively uniform definitive curative-intent IMRT in this non-surgical OPSCC cohort.

Several studies have attempted to link dysphagia to the dose-volume received by specific structures. In particular, Levendag et al found a statistically important correlation between dose to the superior and middle constrictors and dysphagia[5]. Our group likewise found a significant correlation between mean superior pharyngeal constrictor dose and late-onset radiation-associated dysphagia (late-RAD) in a small case-control study[4]. Eisbruch et al. implicated the pharyngeal constrictors and, furthermore, correlated supraglottic and glottic larynx dosage with aspiration[58]. One recent study found that dose to the inferior pharyngeal constrictor best predicted the need for long- term gastrostomy tube[59].

Like others groups, our data points to SPC dose (especially SPC V70) as a strong associate of RAD, consistent with the host of well-documented series above[43, 46–56]. However, in our OPC chemoIMRT-only dataset, MHM dose was a more consistent classifier of chronic-RAD than SPC dose. To our knowledge, our data are the first to specifically characterize mylohyoid/geniohyoid dose-response at a volumetric level in multivariate models as a predictor of RAD. However, recent work by the John Hopkins group shows a similar trend[60], as did a previous work by our group suggesting a more nonspecific anterior oral cavity ROI predictive of long-term modified barium swallow-defined dysphagia[11]. These smaller OPC series which showed trends from floor of mouth muscle ROIs, were limited primarily by sample size (46 patients in the Hopkins series, 31 in our previous MDACC series), but, given the effect size seen in the current study, both pilot series appear to have detected meaningful trends. The correlation of videofluoroscopic kinematics with geniohyoid dose by the Hopkins team points to the importance of these muscle groups, and provides an evidentiary correlate of pathophysiology that may underlie chronic-RAD in our larger cohort.

In our dataset, we characterized the geniohyoid/mylohyoid muscles as a single structural ROI, which raises the necessary caveat in terms of OAR ROI definition for toxicity analyses[61] (*vide infra*). However, the physiologic function of these muscle groups for sensorimotor swallow initiation[62] as well both anterior and superior hyoid lift is well known[63], and serves as potential explanatory rationale for the large observed dose-dependent effect sizes (Supplementary Table S2). While PubMed search for “mylohyoid” and “radiotherapy” resulted in no relevant series, the fact that swallowing tasks have identifiable MRI-demonstrated mylohyoid-related recruitment, also lends credence to our

findings despite their comparative novelty[64]. Suprahyoid muscles are implicated as the anterior sling for airway closure in morphometric analyses of normal swallows. These data point to a need for multi-site functional dose-toxicity validation, and suggest a move to consider dose constraint to the MHM muscles in IMRT planning for OPC primary tumors, in addition to the SPC, when clinically feasible given requisite tumor/nodal coverage.

As part of similar programmatic multi-OAR dose-response assessment/optimization efforts undertaken by the Groningen group[56, 65–69], a recent seminal LASSO-based analysis of a heterogeneous HNC cohort [56] investigated PEG-tube dependence. By way of comparison, we saw some similar associations (e.g. T-category, mean SPC dose), some divergence (IPC and CPM dose were not significant in our cohort), as well as several non-overlapping variables (weight alteration, age). This is likely a factor of demographics (a minority of OPC patients [28%] in the Groningen dataset compared to our exclusively OPSCC cohort) which inform therapy (e.g. with OPC cases we favor a midline block[70, 71], comparatively reducing IPC and CPM dose compared to laryngeal/hypopharyngeal cases where coverage of these structures is normative, which were the majority (53%) in Groningen). Like this series, Wopken et al. [56] used BIC-based classification with resampling, pointing to a growing acceptance of these techniques, for toxicity, and likewise permits assessment of toxicity correlates in cases where model assumptions for parametric methods (such as LKB NTCP models) are either inappropriate or as yet undefined[72].

The finding of age as a substantive correlate of chronic-RAD echoes findings by Beetz et al. [73, 74], showing a distinctive age-related functional recovery differential in the parotid glands of elderly patients. The rationale for these increased age-related radiosensitivity observations are unclear. Fundamentally, our understanding of the biological bases of radiation-associated dysphagia remain opaque, as it is unclear if direct muscle damage (such as late radiation fibrosis[75–77]) and/or denervation effects[78–80] are primary drivers of severe chronic-RAD. Furthermore, identification of mechanistic genomic processes[81–84] which are potentially altered by aging might provide insight into the observed age-dose-toxicity interaction. Since age is strong correlate of pneumonia in HNC chemoradiotherapy patients, as shown by Merlano et al.[85], it may be that preventing incipient dysphagia in the elderly might preclude secondary aspiration pneumonia events, and even reduce mortality in high-risk elderly populations.

Our study has several notable limitations, as with any DVH-based analysis, spatial data is lost in the transition from 3-dimensional dose distributions, precluding sub-ROI volumetric effects, as well as data regarding proximate voxels in distinct structures. Lack of 3D data also precludes incorporation of tumor/node spatial considerations (which themselves are the true driver of systematic OAR ROI dose), and which serves as a general confounder in almost all HNC dose-response models, which tacitly imply dose independence of ROIs from potentially proximate target volumes. Though we used a previously benchmarked OAR segmentation and atlas workflow[34], ROI segmentation variability can substantively alter normal tissue complication assessment and should always be noted as a dependency[61]. Given the longitudinal, retrospective nature of this study, the potential for underreporting is also of concern. However, it should be noted that median follow-up was 48 months, and 94% of patients were followed for more than two years and though videoflouroscopy was

not used routinely creating the potential for missed “silent aspiration,” the 7% rate of chronic aspiration detected by videoflouroscopy in the current study is very close to the 7.6% aspiration rate we previously reported for a group of patients in a prospective institutional organ preservation trial using routine videoflouroscopic dysphagia assessment[33]. Finally, our choice of recursive partitioning analytic methods represents an inherently “greedy” model system, and classification and regression tree approaches often are sensitive to “noise” from random variation within the dataset. In addition to a use of test-training methodology with 20% “holdback” verification and 10-fold cross validation, as suggested by Lemon et al.[86], we used bootstrap resampling with traditional methods such as logistic regression for confirmation/validation whenever possible. The “oversensitivity” of RPA to intrinsic patterns in the extant data (as opposed to conceptual reliance on distributional attributes) provides potential limits to generalizability outside the current dataset, though we have attempted to address this via population risk estimation using bootstrap methods.

Despite inherent limitations, our data represent the largest OPSCC chemo-IMRT study using benchmarked/curated autosegmentation to investigate multivariate clinical and dosimetric correlates from a curated database of patients receiving direct dysphagia-specialist speech pathologist-rated objective swallowing dysfunction for chronic-RAD, and the resultant findings are potentially useful for clinical practice. Our data demonstrate that, in addition to SPC, other OAR ROIs (notably oral cavity/FOM ROIs ADM, GGM, ITM, and MHM) showed a substantive dose-response signal, as did specific clinical/demographic characteristics (T- and N-category, gender, age, and chemotherapy status, prescription dose and fractionation). Our data point to MHM as a strong associate of chronic-RAD in our OPC patients, and point to MHM V69 as a potential target constraint for clinical implementation. Further, the relationship of age confirms observations seen in other head and neck OARs[74] and points to potential risk stratification approach for older head and neck patients.

Moving forward, our goal is to develop multivariate 3D models which incorporate both spatially and hyper-dimensionally covariate data. Our goal is to develop a model that accounts for dose to multiple structures, and gives evidence-based decision tools for therapy, rehabilitation, or supportive care interventions, such as patient/physician/speech pathology for shared decision-making. The identification of high-risk subsets of patients (e.g. older patients with high MHM dose) could drive swallowing exercise, and thus serve as prophylaxis against dysphagia.

Conclusion

Swallowing muscles (SPC, ADM, GGM, ITM, MHM, and MPM) dose-volume parameters were associated with chronic-RAD. A model using age and MHM V69 was the preferred model to identify chronic-RAD. Our data suggest mylohyoid dose and age may be cofactors of interest for reducing or risk-stratifying for dysphagia in future oropharyngeal cancer populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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2. *Drafting the work or revising it critically for important intellectual content;*
3. *Final approval of the version to be published;*
4. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

Specific additional individual cooperative effort contributions to study/manuscript design/ execution/interpretation, in addition to all criteria above are listed as follows:

TD-Drafted initial manuscript, undertook supervised analysis and interpretation of data. KH-Co-primary investigator; with CDF conceived project and interpreted study results, direct and final oversight of toxicity and clinical data collection; direct oversight of trainee personnel (TD).

ASRM-Undertook clinical and imaging data collection; executed and quality assured immobilization, direct oversight of all image registration/segmentation, and data collection workflow; direct oversight of trainee personnel (TD, JM, BW), and participated in data analysis, interpretation, and manuscript drafting and final editing . GBG,JSL,SJF,ASG, SYL, BMB, WHM,JP, HS, NG, RF, RW- Direct patient care provision, direct toxicity assessment and clinical data collection; interpretation and analytic support.

AR- Provided direct statistical support and data interpretation assistance.

JKC- Assisted with project inception; segmentation analysis quality assurance; provided statistical support and data interpretation assistance.

JM, BW- Segmentation workflow and imaging registration execution; supervised data analysis.

DIR- Responsible for data collection, project integrity, manuscript oversight and correspondence, programmatic oversight, toxicity assessment and clinical data collection; direct oversight of trainee personnel (ASRM, CDF).

CDF- Corresponding author; co-primary investigator; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of trainee personnel (TD, JM, BW, ASRM).

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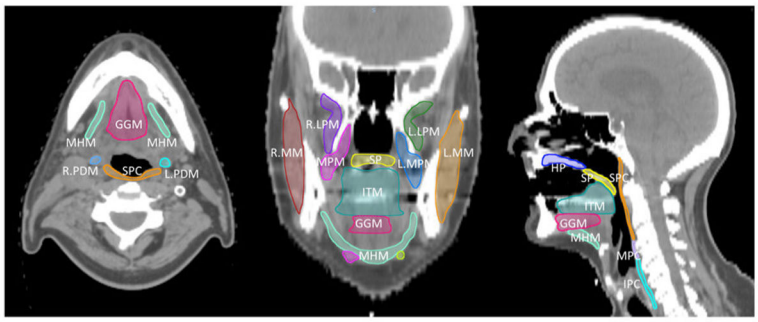

Figure 1. Exemplar swallow-related ROI

Axial, coronal, and sagittal images of the contoured segments.

Abbreviations: GGM – Genioglossus Muscle; HP – Hard Palate; IPC – Inferior Pharyngeal Constrictor; ITM – Intrinsic Tongue Muscles; LPM – Lateral Pterygoid Muscle; MHM – Mylo/geniohyoid Complex; MM – Masseter Muscle; MPM – Medial Pterygoid Muscle; PDM – Posterior Dygastric Muscle; SP – Soft Palate; SPC – Superior Pharyngeal Constrictor, R.-right, L.-left.

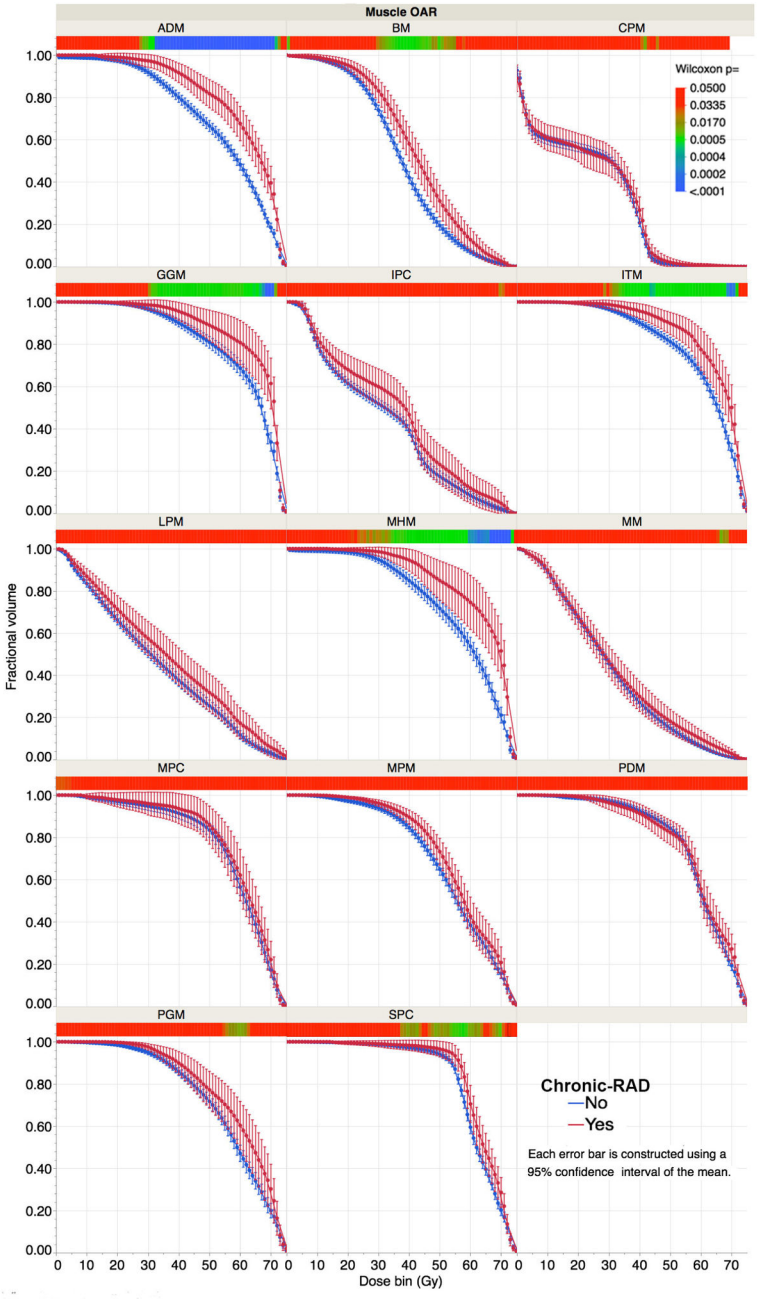

Figure 2. Swallow-related ROI DVH stratified by chronic-RAD

Note non-overlapping confidence intervals of dose in 1-Gy bins visually suggests a magnitude difference of $p<0.05$ using a parametric assessment (i.e. t-test). To account for multiple comparisons and avoid potential error from normal distribution assumptions while illustrating pairwise dose differentials between chronic-RAD and non-RAD subgroups, a heat map is displayed below each ROI DVH to quantify the magnitude of p-values for each 1-Gy bin (per nonparametric Wilcoxon rank sum test for each bin). To account for the comparison across 75 dose levels (0 to 75 Gy), for 14 OARs, a Bonferroni-corrected $p=0.000048$, denoting significance despite large-scale multiple comparison, is indicated on

the heat map by blue shading while red shades denote failure to meet the significance threshold.

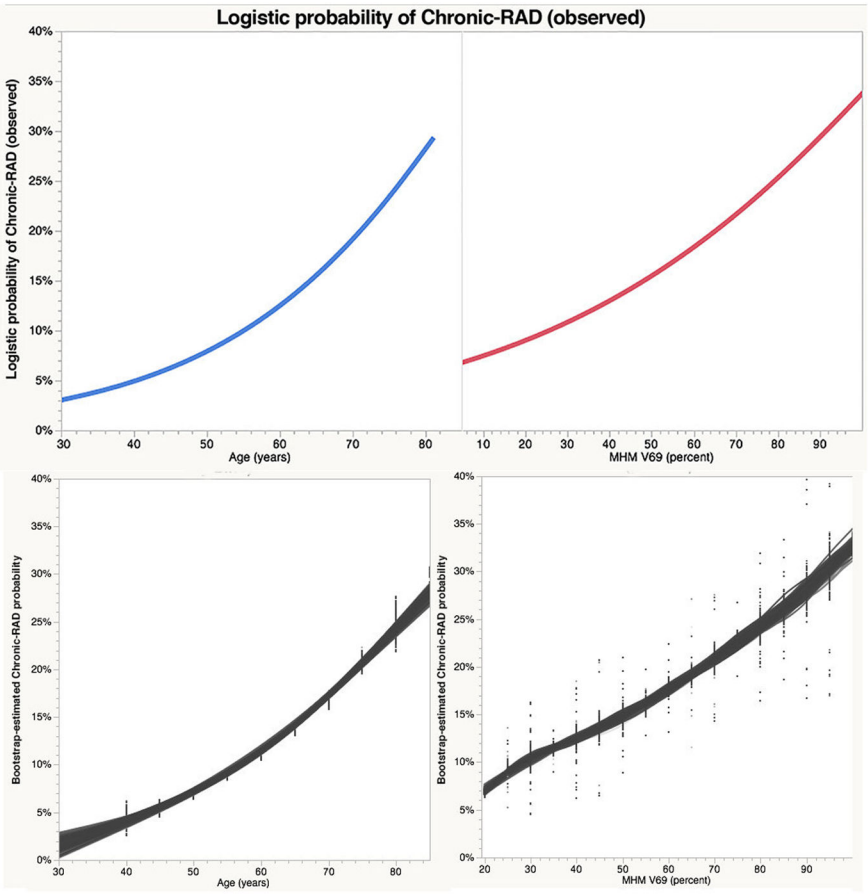

Figure 3. Observed and Predicted probabilities of chronic-RAD by age and MHMV69

Observed nominal logistic continuous variable regressor-response plots for age (3a) and MHM V69 (3b). Bootstrap estimated population probability of Chronic-RAD plots for age (3c) and MHM V69 (3d); points are shown in 5 Gy/5-year "bins" with gray lines representing unsupervised fits across 10^4 resampled distribution, indicative of the expected range of uncertainty attributable to differentials between the observed sample and the parent oropharyngeal cancer patient true population.

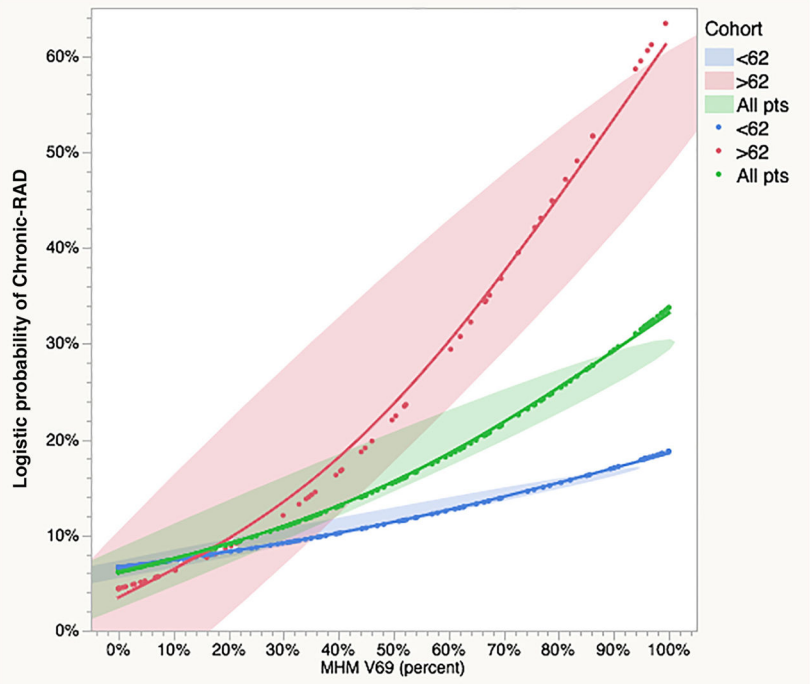

Figure 4. Chronic RAD as a function MHM V69 by Age

Composite plot of MHM V69 (as a continuous variable) and age cohort (green shading denotes the observed whole population; red identifies patients over 62 years of age; blue indicates patients less than 62 years old). Smoothed fits are shown with color-specific ellipses covering 95% of observed values for each cohort as a visual uncertainty estimator.

Table 1

Demographic and clinical data of study patient population.

	All patients (n=300)		Asymptomatic Swallowing (n=266)		Chronic-RAD (n=34)	
T-category	**n.**	**Percent**	**n.**	**Percent**	**n.**	**Percent**
1	53	17.67%	51	19.17%	2	5.88%
2	139	46.33%	128	48.12%	11	32.35%
3	68	22.67%	60	22.56%	8	23.53%
4	40	13.33%	27	10.15%	13	38.24%
N-category						
0	16	5.33%	14	5.26%	2	5.88%
1	12	4.00%	12	4.51%	0	0.00%
2a	21	7.00%	21	7.89%	0	0.00%
2b	167	55.67%	150	56.39%	17	50.00%
2c	71	23.67%	57	21.43%	14	41.18%
3	13	4.33%	12	4.51%	1	2.94%
Site						
Base of tongue	164	54.67%	144	54.14%	20	58.82%
Tonsil	131	43.67%	118	44.36%	15	44.12%
Other	5	1.67%	4	1.50%	1	2.94%
Smoking status						
Never	55	18.33%	46	17.29%	9	26.47%
<10 pack-years	109	36.33%	99	37.22%	10	29.41%
>10 pack-years	136	45.33%	121	45.49%	15	44.12%
Sex						
Male	272	90.67%	238	89.47%	34	100.00%
Female	28	9.33%	28	10.53%	0	0.00%
Ethnicity						
White	283	94.33%	251	94.36%	32	94.12%
Black	7	2.33%	6	2.26%	1	2.94%
Hispanic	9	3.00%	8	3.01%	1	2.94%
Asian/Pacific Islander	1	0.33%	1	0.38%	0	0.00%

	All patients (n=300)		Asymptomatic Swallowing (n=266)		Chronic-RAD (n=34)	
T-category	**n.**	**Percent**	**n.**	**Percent**	**n.**	**Percent**
Chemotherapy						
Cisplatin	195	65.00%	99	37.22%	6	17.65%
Cetuximab	105	35.00%	167	62.78%	28	82.35%
IMRT technique						
Split-field	284	94.6%	253	95%	31	91%
Whole-field	16	5.4%	13	5%	3	9%
IMRT fractionation						
Once-daily	262	87%	233	87.5%	29	85%
Accelerated	38	13%	33	12.5%	5	15%
	Mean±SD	**Median (Range)**	**Mean±SD**	**Median (Range)**	**Mean±SD**	**Median (Range)**
Age (years)	56±9	56 (28–81)	56±8	55 (36–81)	59±10	59 (28–81)
RT dose (Gy)	69±2	70 (64–75)	68±2	70 (64–75)	70±1	70 (66–72)
RT fractions delivered	33±2	33 (29–35)	33±2	33 (29–35)	33±2	33 (30–35)

Table 2

Univariate RPA-derived ROI specific dose-volume thresholds. LogWorth represents the negative logarithm of the p-value.

Recursive partitioning analysis								Confirmatory univariate nominal logistic regression				
Muscle OAR	**V-level**	**Percent-threshold**	**ROC AUC Cohort (test)**	**ROC AUC Holdback (verification)**	**LogWorth**	**P-value**	**SS**	**Odds Ratio (95% CI)**	**Relative risk (95% CI)**	**ΔBIC**	**BIC**	**Evidence Grade §**
ADM	60	79%	0.68	0.60	5.95	<.0001	**	2.88 (1.32–6.12)	2.48 (1.32–4.65)	216.55	12.21	Very Strong
BM	35	65.8%	0.65	0.57	1.09	0.0815	n.s.	-				
CPM	45	0.35%	0.64	0.51	1.00	0.0998	n.s.	-				
GGM	35	98.9%	0.70	0.55	2.74	0.0018	**	3.65 (1.69–8.54)	3.17 (1.53–6.57)	212.08	7.73	Strong
IPC	70	98.2%	0.60	0.51	1.08	0.0831	n.s.					
ITM	47	99.9%	0.67	0.44	2.83	0.0015	*	2.66 (1.13–5.90)	2.30 (1.18–4.48)	218.48	14.14	Very Strong
LPM	66	13.1%	0.53	0.35	1.07	0.0860	n.s.	-				
LRX	63	1%	0.61	0.47	0.89	0.1274	n.s.	-				
MHM	69	17.5%	0.74	0.64	6.77	<.0001	**	4.54 (2.14–10.33)	3.81 (1.89–7.67)	204.34	0.00	$BIC_{minimum}$ (reference)
MM	66	4.4%	0.61	0.53	0.88	0.1314	n.s.	-				
MPC	49	99.9%	0.63	0.54	0.17	0.6825	n.s.	-				
MPM	70	1%	0.59	0.45	3.31	0.0005	*	2.64 (1.27–5.72)	2.37 (1.22–4.60)	216.60	12.25	Very Strong
PDM	69	13.5%	0.60	0.48	0.15	0.7070	n.s.	-				
PGM	65	68.9%	0.62	0.49	0.24	0.5732	n.s.	-				
SPC	70	6.35%	0.68	0.47	5.09	<.0001	**	10.60 (3.12–45.16)	9.00 (2.20–36.83)	205.14	0.80	Weak

* statistically significant at P<0.05;

** statistically significant after Bonferroni correction.