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Original article

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 ⩾ 69 Gy), 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.

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].

☆ Portions of this dataset were presented at the 2015 American Society for Radiation Oncology Annual Meeting, San Antonio, TX, and the 2016 Multidisciplinary Head and Neck Cancer Symposium, Scottsdale, AZ.

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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 [19–29,11,30–32], 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.

Materials 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 $\geqslant$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 $\geqslant$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 $\geqslant$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 [33] 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 [33] 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 Fig. 1; indicative ROIs from 11 selected cases are included as

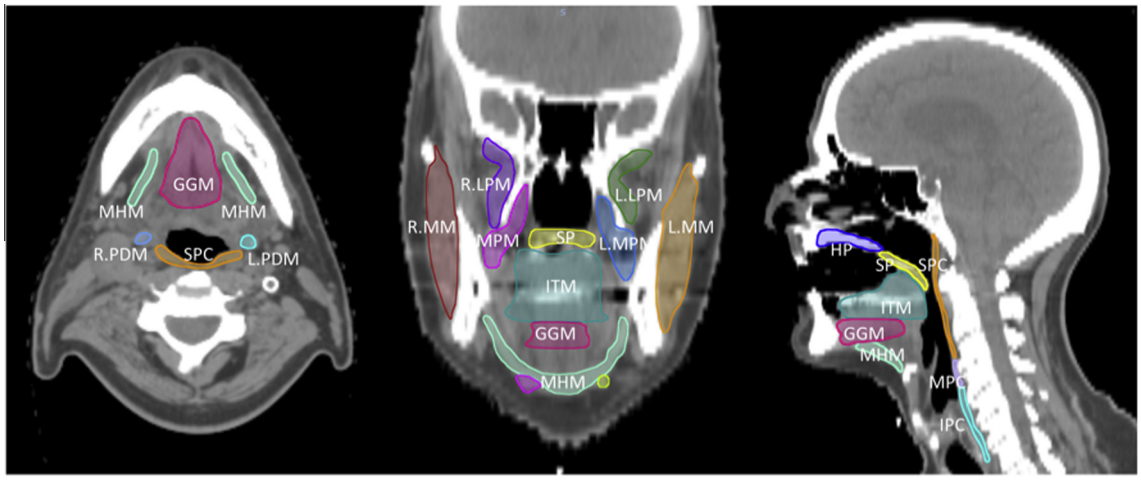

Fig. 1. Exemplar swallow-related ROI. Axial, coronal, and sagittal images of the contoured segments. *Abbreviations:* GGM – genioglossus muscle; HP – hard palate; IPC – inferior pharyngeal constrictor; ITM – intrinsic tongue muscles; LPM – lateral pterygoid muscle; MHM – mylo/geniohyoid complex; MM – masseter muscle; MPM – medial pterygoid muscle; PDM – posterior digastric muscle; SP – soft palate; SPC – superior pharyngeal constrictor, R.-right, L.-left.

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