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Original Research Article

Identifying organs at risk for radiation-induced late dysphagia in head and neck cancer patients

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ABSTRACT

Background and purpose: Dysphagia is a common, severe and dose-limiting toxicity after oncological treatment of head and neck cancer (HNC). This study aims to investigate relationships between radiation doses to structures involved in normal swallowing and patient-reported as well as clinically measured swallowing function in HNC patients after curative (chemo-) radiation therapy (RT) with focus on late effects.

Materials and methods: Patients (n = 90) with HNC curatively treated with RT ± chemotherapy in 2007–2015 were assessed for dysphagia post-treatment by telephone interview and videofluoroscopy (VFS). A study-specific symptom score was used to determine patient-reported dysphagia. The Penetration-Aspiration Scale (PAS) was applied to determine swallowing function by VFS (PAS $\geq$ 4/ $\geq$ 6 = moderate/severe dysphagia). Thirteen anatomical structures involved in normal swallowing were individually delineated on the patients' original planning CT scans and associated dose-volume histograms (DVHs) retrieved. Relationships between structure doses and late toxicity were investigated through univariable and multivariable logistic regression analysis (UVA/MVA) accounting for effects by relevant clinical factors.

Results: Median assessment time was 7 months post-RT (range: 5–34 months). Mean dose to the contralateral parotid gland and supraglottic larynx as well as maximum dose to the contralateral anterior digastric muscle predicted patient-reported dysphagia (AUC = 0.64–0.67). Mean dose to the pharyngeal constrictor muscle, the larynx, the supraglottic larynx and the epiglottis, as well as maximum dose to the contralateral submandibular gland predicted moderate and severe dysphagia by VFS (AUC = 0.71–0.80).

Conclusion: The patients in this cohort were consecutively identified pre-treatment, and were structurally approached and assessed for dysphagia after treatment at a specific time point. In addition to established dysphagia organs-at-risk (OARs), our data suggest that epiglottic and submandibular gland

Abbreviations: AAA, Anisotropic Analytical Algorithm; ACE-27, Adult Comorbidity Evaluation 27; AUC, area under the Receiver Operating Characteristic (ROC) curve; BMI, body mass index; Cc, cubic centimeter; CI, confidence interval; CT, computed tomography; DARS, dysphagia-aspiration-related structures; DESdC, Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking; DVH, dose-volume histogram; EBRT, external beam radiation therapy; EQD2, equivalent dose in 2Gy fractions; Gy, Gray; HNC, head and neck cancer; ICRU, International Commission on Radiation Units and Measurements; IMRT, intensity-modulated radiation therapy; MVA, multivariable logistic regression; N.A, non applicable; OAR, organ-at-risk; OR, odds ratio; PAS, penetration-aspiration scale; PCM, pharyngeal constrictor muscle; PRO, patient-reported outcome; QoL, quality of life; ROC, Receiver Operating Characteristic curve; RT, radiation therapy; SD, standard deviation; SEM, standard error of the mean; SLP, speech-language pathologist; TNM, Tumor location, Nodular engagement, Metastasis; UES, upper esophageal sphincter; UVA, univariable logistic regression; VFS, videofluoroscopy; VMAT, volumetric-modulated radiation therapy; V_x, the volume (%) of a structure receiving $\geq$xGy.; 3D-CRT, Three Dimensional Conformal Radiation Therapy; ρ, Spearman's Correlation Coefficient.

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doses are important for swallowing function post-RT. Keeping DVH thresholds below V60 = 60% and V60 = 17%, respectively, may increase chances to reduce occurrence of severe late dysphagia. The results need to be externally validated in future studies.

1. Introduction

Identifying and refining tolerance doses for organs-at-risk (OARs) involved in radiation-induced dysphagia is of great importance since the occurrence can be decreased by reducing the dose below safe dose thresholds to involved structures during radiation therapy (RT) [1–3]. Dysphagia is a common and severe dose-limiting toxicity after RT for head and neck cancer (HNC) [4–9], where the patients' general health as well as quality of life (QoL) is affected [10,11]. Besides malnutrition and dehydration, one of the most serious consequences of dysphagia is aspiration pneumonia, which occurs in up to one in four HNC patients following concurrent (chemo)-RT [12,13] and is reported to cause one fifth of the non-cancer related mortality in overall HNC [14]. Increased knowledge of normal tissue responses and late effects in this context would further improve our understanding of how to design radiation therapy regimens where critical structures for dysphagia can be protected while conditions for tumor control can be improved.

Using modern RT techniques and favorable anatomical conditions, treatments can be optimised to decrease the dose to OARs and thereby decrease the risk of radiation-induced lesions in non-tumorous tissue without jeopardizing tumor control. The relationship between radiation dose to different specific components of the swallowing apparatus, dysphagia-aspiration-related structures (DARS), and dysphagia has previously been studied. Both the pharyngeal constrictor muscle (PCM) and the larynx, as a whole or subdivided, correlate with dysphagia evaluated by videofluoroscopy (VFS) [4,15–20] as well as with patient-reported dysphagia [6,16,18,21]. Specifically, doses above 60 Gy to the PCM and the larynx are reported to predict severe dysphagia [3,22,23]. Furthermore, doses to the upper esophageal sphincter (UES), the floor of mouth and the genioglossus muscle have also been reported to predict various aspects of swallowing impairment [16,20,24].

The purpose of this work was to further investigate the relationships between radiation dose to a wide selection of anatomical structures involved in normal swallowing, and late effects quantified by both patient-reported as well as by clinically measured swallowing function in an HNC patient cohort curatively treated with RT.

2. Subjects and methods

2.1. Subjects

Patients with newly diagnosed HNC, presented at the weekly multidisciplinary tumor board meeting at Sahlgrenska University Hospital Gothenburg Sweden, were identified as potential study participants. The patients were treated in 2007–2015 with external beam radiation therapy (EBRT), with or without chemotherapy, but not with surgery, and were recruited to this study by telephone between November 2010 and June 2016, at least 6 months after oncological treatment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Gothenburg, Sweden. All participants gave their written informed consent before inclusion in the study.

The inclusion criteria were for patients to be diagnosed with cancers of the tonsil, base of tongue, hypopharynx or larynx, treated with curative intent, and agreeing to undergo VFS 6–36 months post oncological treatment. In addition, they were not to have experienced dysphagia prior to treatment due to other causes than their cancer. Exclusion criteria were brachytherapy and patients with non-restorable RT treatment plans were also excluded. Tumors were staged according to the TNM classification of malignant tumors [25].

The study subjects were evaluated regarding dysphagia six months post-RT or later, time point chosen to avoid the capturing of acute toxicity that will recover spontaneously [26]. The follow-up involved patient-reported information on dysphagia (questions regarding drinking, eating, swallowing and coughing when eating/drinking, which were turned into a study-specific symptom score [DESdC = Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking] ranging from 0 to 4, i.e. 0/1/2/3/4 = no/1/2/3/4 symptom(s) [27]), as well as VFS examination to evaluate clinical swallowing function, where the degree of swallowing impairment was quantified by the Penetration-Aspiration Scale (PAS) [28,29]. Comorbidity was evaluated according to the Adult Comorbidity Evaluation 27 (ACE-27) [30].

2.2. Treatment information, delineations of OARs, and dysphagia assessments

Details on given oncological treatment, delineation of potential OARs and dysphagia assessments are given in the Supplementary material. In short, EBRT was delivered as intensity-modulated/volumetric-modulated radiation therapy (IMRT/VMAT) with specified dose constraints to the parotid glands. Prescribed doses were typically in the range of 65–68 Gy with 1.9–2.0 Gy/fraction once daily, five days a week. Contouring of OARs was performed on the patients' original CT scans used for treatment planning, where the main structures involved in normal swallowing and potentially radiation-induced dysphagia, were contoured. These included the soft palate, the base of tongue, the genioglossus muscle, the PCM (superior, middle and inferior), the mylohyoid muscle, the geniohyoid muscle, the hyoglossus muscles, the digastric muscles, the parotid glands, the submandibular glands, the epiglottis, the larynx, the supraglottic larynx, and the UES. A delineation manual ensured contour reproducibility (Supplementary Table S1; Fig. 1). Structure-specific dose-volume histograms (DVH) with a dose bin size of 0.5 Gy were exported for further analysis.

Patient-reported information was collected by semi-structured telephone interviews following written guidelines. Clinical scoring of swallowing ability using VFS were performed with the patients examined seated upright in the lateral position. Six boluses with two swallowing attempts per bolus were observed and the worst overall PAS score for each patient, regardless of bolus consistency or swallowing attempt, was used as an outcome variable in the statistical analysis.

2.3. Statistical analysis

Descriptive statistics were used to summarise the demographical and clinical characteristics of the study participants. The distribution of the variables was given as mean and standard deviation

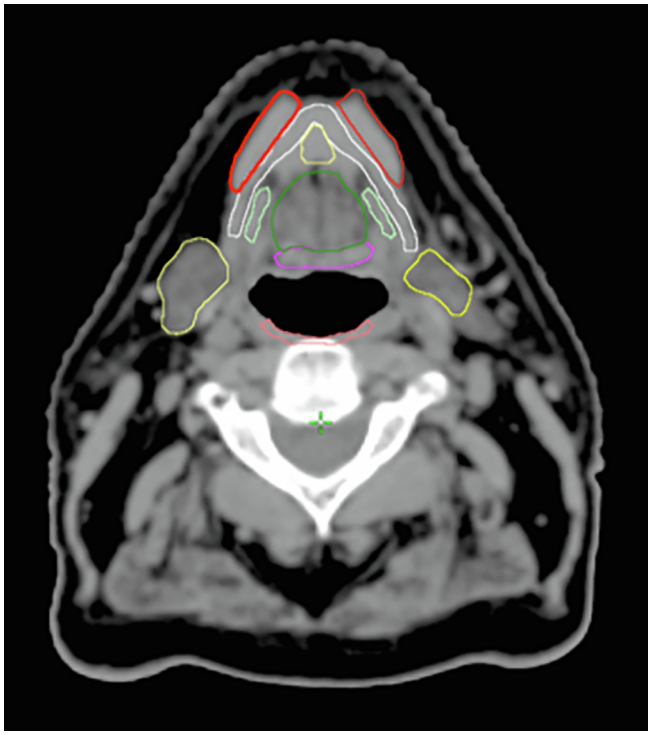

Fig. 1. Delineation of organs-at-risk. One representative cross-section of a pre-treatment planning CT with OARs delineated. Dark green = Genioglossus muscle/Tongue; Dark yellow = Submandibular gland; Light green = Hyoglossus muscle; Light yellow = Geniohyoid muscle; Pink = Superior pharyngeal constrictor muscle; Purple = Base of tongue; Red = Anterior digastric muscle; White = Mylohyoid muscle. For definition of anatomical boundaries, see Supplementary Table S1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(SD) or median and range for continuous variables and as numbers and percentages for categorical variables.

All bilateral OARs were analysed as ipsi-, contra- and bilateral structures with corresponding volumes, and mean and maximum absorbed RT doses. Correlations between absorbed doses to the different OARs, and dysphagia, were calculated using Spearman's correlation coefficients (ρ). Correlations in the range $\rho \leq 0.39$ were regarded as weak; $\rho = 0.4–0.59$ as moderate and $\rho \geq 0.6$ as strong [31].

Univariable logistic regression analysis (UVA) was performed with the mean and maximum absorbed doses to the OARs as predictors for dysphagia, as defined by the two assessment methods (DESdC and PAS). The cut-off levels for clinically significant dysphagia were taken as DESdC ≥ 3 (three or more dysphagia specific symptoms), PAS ≥ 4 (material enters airway, contacts the vocal folds, and is ejected from airway) and PAS ≥ 6 (material enters airway, passes below the vocal folds and is ejected into larynx or out of the airway [27–29]). Potential effects by relevant clinical factors (ACE-27 [ranging from 0 (no comorbidity) to 3 (severe comorbidity)], age, smoking and body mass index) were also assessed. To investigate the inter-relationship between dose to different risk structures, multivariable logistic regression analyses (MVA) with forward and backward selections and the abovementioned significant clinical factors were performed, with the limitation that 8–10 events per variable would be allowed for a final model. Effect size was described by odds ratios (OR) and 95% confidence intervals (CI). The discrimination power of each model was assessed by the area under the Receiver Operating Characteristic (ROC) curve (AUC). For the strongest dose predictor, averaged DVHs were calculated for patients with/without dysphagia as defined by investigated endpoints and compared differences between groups in steps of 10 Gy intervals using the Student's *t*-test (relative volumes receiving 10/20/30/40/50/60/70 Gy [$V_{10/20/30/40/50/60/70}$]). Statistically significant dose levels were converted into fractionation-corrected doses using the standard Linear-quadratic model with an $\alpha/\beta = 3$ Gy for late effects ($EQD2_3$) [26].

All tests were two-tailed and conducted at a 5% significance level ($p < 0.05$; Bonferroni-corrected for multiple DVH cutpoint comparisons; inclusion criteria for MVA at $p < 0.1$). Statistical analyses were performed using the statistical software SAS® System version 9.4 (SAS Institute Inc., Cary, NC, USA) or MATLAB v. R2017b (The MathWorks, Inc., Natick, Massachusetts, USA).

3. Results

3.1. Patient characteristics

Of 130 eligible patients, one patient was excluded due to clinically manifest dysphagia prior to HNC diagnosis, nine due to non-restorable RT treatment plans, and 30 patients due to having received brachytherapy. In total, 90 HNC patients (median age: 62 years) were included in the study (Table 1), 60 men (67%) and 30 women (33%), and assessed seven months after completed oncological treatment (range 5–34 months; mean ± SD 10 ± 6 months). The tonsil was the most common tumor location (67%), followed by the larynx (21%). A majority of the patients had stage four disease at the time of diagnosis (57%), 71% had nodular engagement, and 23% had moderate-severe comorbidity according to ACE-27.

The median total radiation dose was 68 Gy (range 46–72 Gy), and the most common fractionation schedule was 2 Gy times 34 fractions. Four of five patients were treated with intensity-modulated RT (IMRT: 62% or VMAT: 19%; all 6MV photons). The majority of the patients received chemo-RT (n = 64), 31/64 (48%) concomitant chemotherapy with Cisplatin and 18/64 (28%) induction chemotherapy with Cisplatin + 5-FU.

3.2. Dysphagia endpoints

At the study assessment point, 78/90 (87%) patients presented with DESdC ≥ 1 and 44/90 (49%) with PAS ≥ 2; Table 1. DESdC = 3 was the most commonly reported score (27/90; 30%). Among the patients with DESdC ≥ 3 (n = 36), 28/36 (78%) had swallowing difficulties according to the PAS criteria (PAS ≥ 2); 17/28 (61%) had PAS ≥ 4 and 14/28 (50%) had PAS ≥ 6.

3.3. Risk structure doses and volumes

Mean doses for the 17 analysed structures were between 22 and 63 Gy and maximum doses between 49 and 71 Gy (Table 2). For bilateral structures, dose to the ipsilateral structure was, on average, 11 Gy higher than dose to the contralateral structure. Structure volumes were in the range 0.7–53.0 cc, smallest for the middle PCM and largest for the total larynx. The structures receiving the highest/lowest radiation doses were the ipsilateral submandibular gland (mean dose: 63 Gy) and the contralateral parotid gland (mean dose: 22 Gy).

3.4. Relationships between risk structure doses and dysphagia endpoints

The results from the regression analyses are described in Table 3 and Supplementary Table S2. Of the ipsilateral structure doses, the

Table 1
Patient characteristics, treatment information and swallowing outcomes.

Variable	N = 90
Age in years at RT start (median/range)	62 (37–88)
BMI at RT start (mean/SD)	26 (4.4)
Assessment time in months (median/range)	7 (5–34)
	n (%)
Gender	
Male	60 (67)
Female	30 (33)
Smoking	
Never smoked	27 (30)
Current smoker	28 (31)
Former smoker, stopped > 12 months before RT	35 (39)
Comorbidity according to ACE-27 at RT start	
None (grade 0)	38 (43)
Mild (grade 1)	31 (34)
Moderate (grade 2)	12 (13)
Severe (grade 3)	9 (10)
Tumor location (tumor code)	
Tonsil (C09)	60 (67)
Base of tongue (C01.9)	5 (5)
Larynx (C32.0, C32.1)	19 (21)
Hypopharynx (C12, C13)	6 (7)
Overall tumor stage	
1	12 (13)
2	10 (11)
3	17 (19)
4	51 (57)
TNM-T-stage	
I	24 (27)
II	39 (43)
III	17 (19)
IV	10 (11)
Nodular engagement	
Yes	64 (71)
No	26 (29)
Oncological treatment	
EBRT	26 (29)
EBRT + chemotherapy	64 (71)
EBRT technique	
3D-CRT	14 (16)
3D-CRT + IMRT/VMAT	3 (3)
IMRT	56 (62)
VMAT	17 (19)
DESdC total score	
0	12 (13)
1	18 (20)
2	24 (27)
3	27 (30)
4	9 (10)
Patient reported DESdC	**Yes (%)**
Drinking	15 (17)
Eating	58 (64)
Swallowing	65 (72)
Coughing when eating/drinking	45 (50)
PAS	**n (%)**
1	46 (51)
2	18 (20)
3	3 (3)
4	5 (6)
5	2 (2)
6	2 (2)
7	9 (10)
8	5 (6)

Note: Among patients with DESdC = 3 (n = 27), 15/27 (56%) had swallowing difficulties according to the PAS criteria (PAS $\geq$ 2); 13/15 (87%) had PAS $\geq$ 4 and 10/15 (67%) had PAS $\geq$ 6.
Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27; BMI = body mass index; DESdC = Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; PAS = Penetration-Aspiration Scale; SD = Standard deviation; TNM = Tumor location, Nodular engagement, Metastasis; VMAT = Volumetric Modulated Arc Therapy; 3D-CRT = Three Dimensional Conformal Radiation Therapy.

submandibular gland predicted one dysphagia endpoint, whilst among the contralateral structures, the submandibular gland predicted all dysphagia endpoints and the parotid gland as well as the anterior digastric muscle predicted one endpoint. For bilateral structures, the submandibular gland predicted two dysphagia endpoints. Smoking status (current versus never smoked) predicted one dysphagia endpoint in UVA (PAS $\geq$ 4), but its inclusion in the corresponding MVA models did not affect the overall results.

3.5. UVA and MVA results

In UVA, mean/maximum dose of nine/two structures predicted DESdC $\geq$ 3, but none of these resulted in models with an AUC $\geq$ 0.70; mean doses of the contralateral parotid gland as well as supraglottic larynx and contralateral digastric muscle maximum dose resulted in the models with the best discrimination ability ($p \leq 0.049$; AUC = 0.64–0.67). Mean/maximum dose of five/two structures predicted PAS $\geq$ 4; larynx mean dose and contralateral submandibular gland maximum dose resulted in the models with the best discrimination power ($p < 0.001$; AUC = 0.76 for both). Last, mean/maximum dose of seven/five structures each predicted PAS $\geq$ 6; mean dose to the epiglottis as well as the maximum dose to the contralateral submandibular gland resulted in the models with the best discrimination power ($\leq$0.006; AUC = 0.80 and AUC = 0.76, respectively; Fig. 2). Mean dose of the inferior PCM, the epiglottis and the larynx predicted all dysphagia endpoints. No maximum structure dose predicted all three dysphagia endpoints.

In MVA with forward selection, each of the best-performing dose predictors in UVA remained as single strongest predictors for the investigated endpoints, i.e. there were no MVA models including combinations of neither mean nor maximum structure doses. However, in MVA with backward selection, a combination of mean doses of the contralateral parotid gland and supraglottic larynx resulted in a model with an improved discrimination power for DESdC $\geq$ 3 (OR [95% CI] = 1.38–1.58 [1.09–2.11]; p = 0.007/0.002; AUC = 0.73) than each of the two dose predictors considered separately (OR [95% CI] = 1.23–1.37 [1.00–1.75]; p = 0.049/0.013; AUC $\leq$ 0.67). The ROC curve for epiglottis mean dose, the model with the best discrimination power, is presented in Supplementary Fig. 1.

3.6. DVH comparisons

Relationships between predictive structure radiation doses and swallowing outcomes are presented as averaged DVHs for the dysphagia and non-dysphagia groups in Supplementary Table S3 and in Fig. 2. For DESdC $\geq$ 3, the contralateral submandibular gland $V_{60/70}$ as well as the contralateral digastric muscle $V_{40/50}$ differed between the two groups ($p \leq 0.006$; $EQD2_3$ = 57/71 Gy and $p \leq 0.007$; $EQD2_3$ = 33/45 Gy, respectively). Associated statistically most significant thresholds were 60 Gy/14% for the submandibular gland (p = 0.003) and 40 Gy/36% for the digastric muscle (p = 0.006). For PAS $\geq$ 4, larynx $V_{40/50/60/70}$ and the contralateral submandibular gland $V_{60/70}$ differed between the two groups ($p \leq 0.006$; $EQD2_3$ = 33/45/57/71 Gy and $p \leq 0.001$; $EQD2_3$ = 57/71 Gy, respectively) with thresholds at 50 Gy/46% for larynx ($p < 0.001$) and at 70 Gy/1% for the submandibular gland ($p < 0.001$). Finally, for PAS $\geq$ 6, corresponding structure doses concerned the epiglottis and the contralateral submandibular gland $V_{60/70}$ ($p \leq 0.003$; $EQD2_3$ = 57/71 Gy) with thresholds at 70 Gy/8% for epiglottis (p = 0.001) and 70 Gy/2% for the submandibular gland (p = 0.001).

Table 2
Absorbed dose and absolute volume characteristics for potential dysphagia risk structures.

Structure	Ipsilateral mean dose ± SD (Gy) max dose ± SD (Gy) Volume ± SD (cc)	Contralateral mean dose ± SD (Gy) max dose ± SD (Gy) Volume ± SD (cc)	Bilateral or single structure mean dose ± SD (Gy) max dose ± SD (Gy) Volume ± SD (cc)
Soft palate	N.A	N.A	49.0 ± 25.0 57.8 ± 23.5 2.0 ± 0.7
Genioglossus muscle	N.A	N.A	40.5 ± 18.6 60.9 ± 21.7 36.1 ± 7.6
Base of tongue	N.A	N.A	52.8 ± 21.9 62.0 ± 21.5 15.0 ± 3.6
Hyoglossus muscle	56.8 ± 20.8 62.3 ± 18.9 0.8 ± 0.3	46.2 ± 18.6 52.9 ± 17.9 0.8 ± 0.3	51.9 ± 19.5 62.3 ± 18.9 1.6 ± 0.6
Mylohyoid muscle	N.A	N.A	48.8 ± 17.7 65.9 ± 12.4 4.6 ± 1.7
Geniohyoid muscle	N.A	N.A	41.7 ± 16.2 56.4 ± 13.8 1.4 ± 0.6
Digastric muscle	43.0 ± 15.7 63.4 ± 14.3 2.7 ± 0.8	36.7 ± 14.4 51.8 ± 15.5 2.8 ± 1.0	40.3 ± 15.1 63.4 ± 14.3 5.5 ± 1.7
Submandibular glands	62.6 ± 12.2 69.9 ± 3.3 7.3 ± 2.9	49.9 ± 13.2 60.0 ± 9.6 7.6 ± 2.4	57.6 ± 12.4 69.9 ± 3.3 14.9 ± 5.1
PCM total	N.A	N.A	54.1 ± 6.9 70.2 ± 3.1 6.4 ± 1.5
Superior PCM	N.A	N.A	53.2 ± 22.7 61.4 ± 20.7 1.9 ± 0.6
Middle PCM	N.A	N.A	58.9 ± 14.1 67.0 ± 9.3 0.7 ± 0.2
Inferior PCM	N.A	N.A	52.7 ± 10.4 68.0 ± 4.9 3.7 ± 1.1
Parotid glands	35.8 ± 18.0 61.3 ± 20.3 23.1 ± 8.4	22.2 ± 11.4 49.1 ± 19.3 23.7 ± 8.4	29.3 ± 14.3 61.3 ± 20.3 46.8 ± 16.5
Epiglottis	N.A	N.A	60.2 ± 9.6 68.3 ± 3.9 0.9 ± 0.4
Larynx, total	N.A	N.A	52.9 ± 9.6 70.5 ± 3.7 53.0 ± 16.8
Supraglottic larynx	N.A	N.A	54.7 ± 9.1 70.4 ± 3.6 38.8 ± 13.7
Upper esophageal sphincter	N.A	N.A	45.6 ± 11.4 58.1 ± 9.2 1.6 ± 0.4

Abbreviations: cc = cubic centimeter; Gy = Gray; N.A = non applicable; PCM = Pharyngeal constrictor muscle; SD = Standard deviation.

3.7. Dose correlations between different swallowing structures

Correlations between doses of all investigated swallowing structures are presented in Supplementary Table S4 (unilateral and contralateral structure representations only, data for bilateral and ipsilateral representations not shown). Among the final MVA model predictors, the epiglottis mean dose was strongly correlated with six other non-subdivided structures (ρ = 0.61–0.76; highest ρ for the contralateral submandibular gland). The larynx mean dose correlated strongly with two structures (ρ = 0.62–0.91; strongest correlation for the inferior PCM). For the contralateral submandibular gland mean dose, strong correlations were shown with six structures (ρ = 0.63–0.82; strongest correlation for the mylohyoid muscle). The contralateral submandibular gland maximum dose and the contralateral digastric muscle maximum dose showed strong correlations with two and three structures (ρ = 0.62–0.71 and ρ = 0.62–0.79, respectively) with strongest correlations for the larynx and the contralateral hyoglossus muscle, respectively.

4. Discussion

In this study, we explored the relationship between radiation dose to a wide selection of anatomical structures involved in normal swallowing, and both patient-reported as well as clinically measured swallowing function. We found that dose to three of 14 potential risk structures for radiation-induced dysphagia were strongly associated with VFS-determined swallowing impairment in 90 HNC patients treated with modern parotid-sparing EBRT in

Table 3
Univariable logistic regression and ROC analysis of potential risk structures' mean and maximum absorbed doses as predictors for dysphagia in HNC patients (unilateral, contralateral structure representation).

	DESdC ≥ 3			PAS ≥ 4			PAS ≥ 6		
Organ-at-risk contralateral representation	OR (95% CI) mean/max	p-value mean/max	AUC mean/max	OR (95% CI) mean/max	p-value mean/max	AUC mean/max	OR (95% CI) mean/max	p-value mean/max	AUC mean/max
Soft palate	1.02 (0.94–1.11)/ 1.00 (0.93–1.14)	0.620/1.0	0.56/0.44	0.94 (0.86–1.03)/ 0.93 (0.85–1.02)	0.186/ 0.120	0.47/0.49	0.99 (0.89–1.10)/ 0.98 (0.88–1.10)	0.811/ 0.750	0.39/0.42
Genioglossus muscle	1.06 (0.94–1.19)/ 1.03 (0.93–1.14)	0.349/ 0.530	0.57/0.51	0.95 (0.84–1.07)/ 0.93 (0.84–1.03)	0.417/ 0.140	0.47/0.48	1.05 (0.90–1.23)/ 1.00 (0.88–1.14)	0.554/ 0.950	0.62/0.61
Base of tongue	1.03 (0.93–1.14)/ 1.04 (0.93–1.15)	0.550/ 0.490	0.55/0.54	0.93 (0.84–1.03)/ 0.92 (0.83–1.02)	0.150/ 0.100	0.49/0.53	1.00 (0.88–1.13)/ 0.99 (0.88–1.12)	0.949/ 0.920	0.41/0.44
Hyoglossus muscle*	1.11 (0.98–1.26)/ 1.14 (0.99–1.31)	0.110/ 0.074	0.61/0.62	0.99 (0.87–1.12)/ 1.01 (0.88–1.15)	0.860/ 0.900	0.45/0.60	1.10 (0.92–1.30)/ 1.20 (0.95–1.50)	0.290/ 0.130	0.61/0.67
Mylohyoid muscle	1.09 (0.96–1.24)/ 1.16 (0.91–1.48)	0.196/ 0.220	0.60/0.51	0.99 (0.86–1.13)/ 1.05 (0.84–1.31)	0.850/ 0.650	0.40/0.52	1.10 (0.91–1.33)/ 1.19 (0.80–1.78)	0.317/ 0.390	0.66/0.59
Geniohyoid muscle	1.14 (0.98–1.32)/ 1.21 (1.00–1.47)	0.079/ 0.047	0.61/0.60	1.02 (0.88–1.18)/ 1.25 (0.98–1.58)	0.812/ 0.068	0.57/0.64	1.19 (0.97–1.47)/ 1.45 (1.03–2.03)	0.098/ **0.031**	0.66/0.71
Digastric muscle*	1.20 (1.02–1.43)/ 1.24 (1.04–1.47)	**0.032**/ **0.018**	0.64/0.66	1.05 (0.89–1.25)/ 1.16 (0.96–1.39)	0.570/ 0.130	0.59/0.67	1.26 (0.99–1.59)/ 1.21 (0.96–1.53)	0.057/ 0.110	0.68/0.68
Submandibular gland*	1.35 (1.09–1.68)/ 1.23 (0.96–1.56)	**0.006**/ 0.097	0.65/0.58	1.15 (0.93–1.41)/ 1.80 (1.27–2.55)	0.19/ **<0.001**	0.61/0.76	1.47 (1.02–2.14)/ 1.76 (1.18–2.62)	**0.016**/ **0.006**	0.69/0.76
PCM total	1.70 (1.16–2.50)/ 1.38 (0.60–3.19)	**0.007**/0.45	0.67/0.57	1.44 (0.97–2.13)/ 2.38 (0.62–9.08)	0.210/ 0.067	0.61/0.66	2.07 (1.23–3.46)/ 9.78 (1.36–70.53)	**0.006**/ **0.024**	0.74/0.70
Superior PCM	1.00 (0.91–1.10)/ 1.02 (0.92–1.14)	1.0/0.660	0.51/0.47	0.93 (0.84–1.02)/ 0.93 (0.84–1.04)	0.138/ 0.200	0.49/0.52	0.98 (0.87–1.10)/ 1.03 (0.89–1.19)	0.738/ 0.670	0.39/0.59
Middle PCM	1.23 (1.00–1.52)/ 1.23 (0.89–1.71)	0.055/ 0.210	0.65/0.52	1.03 (0.86–1.23)/ 1.01 (0.78–1.31)	0.765/ 0.950	0.62/0.56	1.63 (0.98–2.69)/ 2.61 (0.76–8.99)	0.058/ 0.130	0.75/0.67
Inferior PCM	1.24 (1.01–1.53)/ 1.10 (0.70–1.71)	**0.044**/ 0.680	0.64/0.58	1.55 (1.21–2.00)/ 2.15 (0.98–4.74)	**<0.001**/ 0.057	0.76/0.66	1.45 (1.11–1.91)/ 2.48 (0.91–6.79)	**0.007**/ 0.076	0.73/0.68
Parotid gland*	1.23 (1.00–1.51)/ 1.09 (0.96–1.23)	**0.049**/ 0.170	0.67/0.55	1.01 (0.82–1.25)/ 1.00 (0.88–1.13)	0.910/ 0.990	0.58/0.59	1.19 (0.91–1.55)/ 1.14 (0.94–1.37)	0.200/ 0.190	0.67/0.66
Epiglottis	1.46 (1.09–1.97)/ 1.03 (0.60–1.79)	**0.012**/ 0.910	0.68/0.51	1.42 (1.01–2.01)/ 2.05 (0.82–5.10)	**0.045**/0.12	0.71/0.62	2.92 (1.45–5.91)/ 3.28 (0.90–11.94)	**0.003**/ 0.071	0.80/0.68
Larynx, total	1.26 (1.00–1.58)/ 0.98 (0.55–1.74)	**0.046**/ 0.940	0.61/0.47	1.68 (1.27–2.23)/ 2.59 (0.86–7.77)	**<0.001**/ 0.090	0.76/0.66	1.64 (1.20–2.23)/ 3.32 (0.81–13.61)	**0.002**/ 0.095	0.76/0.66
Supraglottic larynx	1.37 (1.07–1.75)/ 0.99 (0.55–1.77)	**0.013**/ 0.970	0.64/0.46	1.75 (1.28–2.38)/ 2.67 (0.86–8.30)	**<0.001**/ 0.09	0.76/0.67	1.73 (1.22–2.46)/ 3.31 (0.79–13.99)	**0.002**/ 0.100	0.76/0.66
Upper esophageal sphincter	1.09 (0.90–1.31)/ 1.03 (0.82–1.30)	0.390/ 0.810	0.55/0.51	1.24 (1.00–1.53)/ 1.38 (1.04–1.85)	**0.048**/ **0.028**	0.66/0.65	1.26 (1.00–1.59)/ 1.33 (0.96–1.85)	0.054/ 0.084	0.68/0.64

$p \leq 0.05$ marked in bold.
Abbreviations: AUC = area under the ROC-curve; CI 95%=Confidence Interval 95%; DESdC = Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking; HNC = Head and Neck Cancer; N.A = non applicable; OR = Odds ratio; PAS = Penetration-Aspiration Scale; PCM = Pharyngeal constrictor muscle; ROC = Receiver Operating Characteristic. * = contralateral structures.

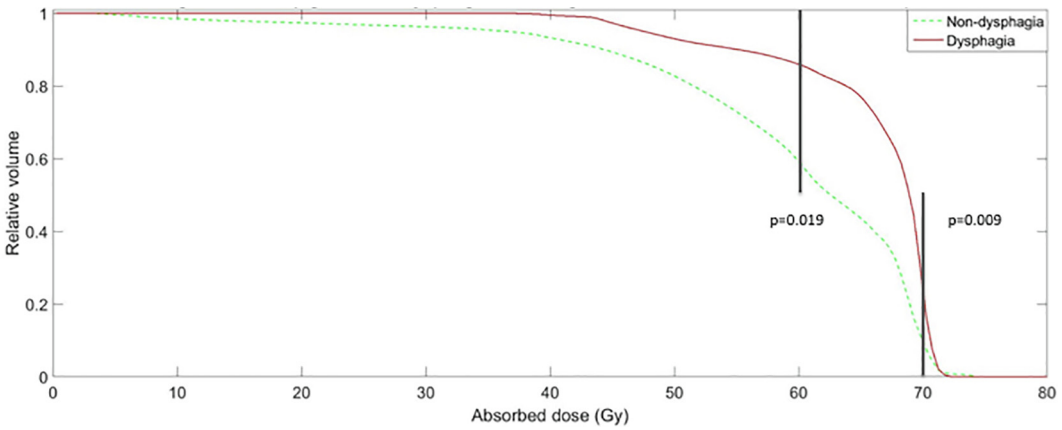

Fig. 2. Averaged dose-volume histograms for epiglottis, the structure with the best discrimination power for dysphagia according to UVA and associated statistically significant volume differences between dysphagia and non-dysphagia patients (dysphagia defined as PAS ≥ 6). Additional dose/volume comparisons between groups for other statistically significant dose predictors in Supplementary Table S3.

2007–2015. Mean dose of the epiglottis and maximum dose of the contralateral submandibular gland were the statistically strongest predictors for severe dysphagia (PAS ≥ 6) with DVH thresholds at 60 Gy and 70 Gy to either of them separating patients with and without dysphagia. However, correlations between investigated dose predictors were strong, as were correlations with dose to other previously reported OARs. Models for patient-reported dysphagia, as determined by a study-specific scale, were inferior to models based on the clinical measure (AUC ≤ 0.73 vs. AUC = 0.65–0.80).

Among previous studies reporting on dysphagia OARs in RT for HNC, radiation doses to the PCM [4,15–23,32–35], the larynx [6,15,16,18,20,22,32], and the UES [6,16,36] have been shown to relate to different aspects of swallowing impairment. For the PCM, whole and subdivided, mean doses have specifically been reported to predict both clinically determined dysphagia by VFS [4,16–20,35] as well as patient-reported dysphagia in terms of specific items of the swallowing scale in European Organization of Research and Treatment of Cancer, Quality of Life Questionnaire, Head and Neck 35 (EORTC H&N35) [21] and the University of Washington Head and Neck-related QOL questionnaire (UWQOL) [35]. Corresponding relationships have been established between mean (supraglottic) larynx doses and aspiration by VFS [16,32,35] as well as by patient-reported swallowing [6,16,18]. Importance of identified substructures for either of these OARs typically depend on which diagnosis is investigated [35]. Dose to the superior PCM is a stronger candidate for determining dysphagia when patient series is limited to oropharyngeal cancer only whilst the dose to the inferior PCM or dose to the larynx determines dysphagia when patient series include all cancer sites. Even though our patient series are more in line with the latter, and mean doses of the inferior PCM as well as both larynx representations predicted all dysphagia endpoints in UVA, only mean dose of the supraglottic larynx was included in a final MVA model for patient-reported dysphagia [DESdC $\geq$ 3].

Our strongest model included mean epiglottis dose as a predictor for severe dysphagia. However, multiple correlations between the investigated structure doses existed. Correlations between doses to the epiglottis and the larynx were moderate (mean doses: $\rho < 0.6$) whilst doses between the epiglottis and the submandibular glands/PCM were strongly correlated (mean doses: $\rho = 0.8/0.7$). There were also strong correlations between dose to the PCM and the larynx/submandibular glands (mean doses: $\rho = 0.9/0.8$). Correlations between doses to the contralateral parotid gland and the PCM were moderate (mean doses: $\rho < 0.51$). These findings suggest that the interplay between dose to the previously established dysphagia OARs, in particular the PCM and the larynx, and dose to other less investigated DARS may be more complex than previously reported. Our results on submandibular gland doses and radiation-induced dysphagia also add to previous data. Since dysphagia is reported to worsen with xerostomia [37–39] our findings suggest an indirect dysphagia-worsening effect by reduced salivary production as a result of injured submandibular glands. Several studies have demonstrated correlation between dose to the submandibular gland and xerostomia [40–42] and submandibular doses exceeding 35 Gy have been identified as critical in this context [43]. Although, this is a lower threshold than what we identified as critical for separating patients with and without dysphagia at submandibular gland doses of $\geq$ 60 Gy, our data clearly suggests that this OAR is of importance also for this endpoint.

Strengths of this study are that we included dose data by several tumor locations and investigated all possible structure representations. The majority of the patients were treated with IMRT and we also excluded patients with non-cancer associated swallowing difficulties prior to treatment. Together, this allowed for an exhaustive exploratory investigation designed to identify OARs for modern EBRT with parotid-sparing technique, and to contribute to current knowledge about OARs for radiation-induced dysphagia. Based on the fact that it is known that clinically measured swallowing ability often underestimate patient-reported dysphagia [44–46] we used both a study-specific PRO and VFS-determined scale for clinical evaluation of the swallowing function. However, models based on clinically verified dysphagia provided better ability to distinguish between patients with and without dysphagia, compared with models based on PRO. The study is based on detailed dose data with 14 risk structures systematically delineated according to written guidelines and, when applicable, assessed as ipsi-, contra-, and bilateral in the analyses. The study is also based on a relatively large cohort of consecutively-recruited patients, when comparing to previous studies. One limitation is that we did not use a validated PRO instrument to evaluate patient-reported dysphagia. On the other hand, we used PAS to quantify VFS-determined dysphagia [28,29], which has been found to successfully differentiate between normal and abnormal airway protection in healthy and dysphagia patients in multiple studies [29,47–50]. Another aspect is that when several health care professionals are involved in interviews this can influence the patients' responses to some extent. However, for our data collection of patient-reported information, the five SLPs followed a strict protocol with 19 defined questions on presence, handling and treatment of dysphagia, and we found no indication of uneven response quality. Finally, it must be kept in mind that there was no systematic baseline assessment of tumor-related dysphagia in this cohort and thus we could not provide any information on potential temporal effects for dysphagia.

In conclusion, in this study we investigated doses to the vast majority of the structures involved in the swallowing apparatus and their interactions. We found two OARs previously not emphasized to be critical for VFS-determined severe radiation-induced dysphagia in HNC, the epiglottis and the contralateral submandibular gland. If radiation dose is kept below $V_{60} = 60\%$ and $V_{60} = 17\%$, respectively, chances to reduce the occurrence of this burdensome condition may increase. Patients, for whom the OAR radiation dose exceed these thresholds, are at risk of toxicity and may need swallowing rehabilitation both during and after completed RT. We also provide evidence showing that doses to these structures are strongly correlated to each other as well as to other OARs involved in dysphagia symptomology. The patients in this cohort were consecutively identified pre-treatment, were prescribed and underwent treatment according to the clinical routine exercised in Sweden, and were structurally approached and assessed for dysphagia after treatment at a specific time point. In the absence of a validation cohort, our results need to be externally validated to fully understand these complex multi-organ effects and dependencies, but our data indicate that in addition to the established dysphagia OARs, dose to the submandibular gland can be a key player given that xerostomia may be as important for the swallowing function post-RT as dose to the swallowing apparatus itself. Future research should also evaluate the xerostomia status before start of RT among HNC patients to further investigate the parotid and submandibular glands as OARs for radiation-induced dysphagia.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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