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Radiation-Associated Chronic Dysphagia Assessment by Flexible Endoscopic Evaluation of Swallowing (FEES) in Head and Neck Cancer Patients: Swallowing-Related Structures and Radiation Dose-Volume Effect

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Abstract

Purpose: We aimed to restore dose-volume parameters of swallowing-related structures (SRSs) by evaluating long-term swallowing dysfunctions after radiotherapy (RT) in head and neck cancer patients (HNCPs).

Materials and Methods: Head and neck cancer patients whose pharyngeal region was involved in RT portal and treated with definitive RT/chemoradiotherapy (CRT) were included in the analyses. Patients underwent objective swallowing assessment by flexible endoscopic evaluation of swallowing (FEES). Volumes of SRSs that received 55 Gy (V_{55}) (mean dose [D_{mean}]) were evaluated according to the dose-volume histograms of each patient. For every SRS, optimal dose-volume cut-off values were determined by receiver operating characteristic curve analysis.

Results: Fifty-five patients at a median 20 months (range, 12-26 months) after their treatments were evaluated. There was a strong negative correlation between FEES scores and dose-volume parameters of SRS ($r \leqslant -0.5$, $P < .0001$). According to our results, middle pharyngeal constrictor (MPC) and inferior pharyngeal constrictor (IPC) had a $D_{mean} > 57$ Gy, base of tongue (BOT) $D_{mean} > 50$ Gy, supraglottic larynx (SGL) and glottic larynx (GL) $D_{mean} > 55$ Gy, and cervical esophagus (CE) $D_{mean} > 45$ Gy. MPC $V_{55} > 70\%$, IPC $V_{55} > 50\%$, BOT $V_{55} > 65\%$, CE $V_{55} > 40\%$, and SGL and GL $V_{55} > 50\%$ were significant predictors for dysphagia.

Conclusion: It was found that dysphagia correlates strongly with dose-volume parameters of SRSs. IPC, SGL, and CE were found to be structures significantly associated with dysphagia.

Keywords

dysphagia, FEES, head and neck cancer, radiation dose-volume effects, swallowing-related structures

Introduction

The aim of organ-sparing strategies in cancer patients is to preserve organ function while treating cancer.[1] In locally advanced head and neck cancer patients (HNCPs), efficient tumor control can be achieved by definitive radiotherapy (RT) and/or concomitant chemotherapy (CT), which are the main alternative treatment modalities to surgery.[2,3] Unfortunately, after RT, 40% of HNCPs develop dysphagia symptoms, with 4% of cases having daily life adversely affected.[4] Radiation-induced dysphagia occurs as a result of acute inflammation, edema, and fibrosis that might also result in neuronal and muscular injury.[5,6] In the posttreatment setting, there may be consecutive changes in anatomical and functional structures, such as impaired motility of the base of tongue (BOT) or pharyngeal muscles, prolonged oropharyngeal transit time, decreased laryngeal

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elevation, and incomplete closure of vestibules and vocal cords compared with the normal swallowing process.[7,8] As a result, swallowing becomes labored, eating duration prolongs, and feeding becomes harder and decreases in amount, leading to disruption in social relations and decreased quality of life (QoL).[9] Further, aspiration pneumonia risk may increase significantly.[10] In patients treated with intensive chemoradiotherapy (CRT), treatment-induced chronic dysphagia and aspiration have quite complicated mechanisms. This toxicity might be prevented by sparing the swallowing-related structures (SRSs) with advanced RT planning techniques, sculpting the dose precisely toward the target but away from critical structures.[11-16] But there are scarce data about the SRS-specific dose-volume parameters that predispose to swallowing dysfunction. There also have been limited studies concerning videofluoroscopic (VF) evaluation of dysphagia and dose-volume relations.[15-18] On the other hand, flexible endoscopic evaluation of swallowing (FEES) is more comfortable and tolerable for patients compared with VF without radiation exposure. Furthermore, this technique is significantly sensitive in terms of evaluation of residue, premature spillage, laryngeal penetration, and aspiration. Also, it provides the opportunity to evaluate pharyngeal and vocal cord dysfunction and changes in mucosal and intraluminal structures.[19,20] To our knowledge, there has been no study evaluating the relation between FEES and SRS-related dose-volume parameters. In the present study, we aimed to restore dose-volume parameters of each SRS related to radiation-associated dysphagia after definitive RT/CRT in the long term with an objective method.

Materials and Methods

Patient and Treatment Characteristics

Head and neck cancer patients treated with definitive RT or CRT between January 2010 and December 2014 were included in the study. Inclusion criteria were pathologically confirmed diagnosis of HNCPs, pharyngeal region involved in RT portal, minimum follow-up of at least 12 months since treatment, and physically and mentally capable of participation. Patients with distant metastasis, who had previous RT and/or operation in the head and neck region, or who had unilateral RT were excluded. Among 64 patients who met the criteria described above, 6 patients did not want to participate and 3 patients did not come to the appointment, leaving a total of 55 patients for the evaluation. The median age was 52 years (range, 19-70 years); 67% of the patients were male.

In the first 26 patients (47%), 3-dimensional conformal radiotherapy (3D-CRT) planning at 6 megavoltage (MV) energy was carried out using the precise treatment planning system (TPS). By the end of 2011, volumetric arc therapy (VMAT) had been adapted at our institution, and the rest of the plans were done using the Monoco TPS; since then, patients have been treated with the VMAT technique at 6 MV energy.

The prescribed dose was 70 Gy in 33 fractions to the primary tumor and involved lymph nodes, 58 to 62 Gy to high-risk regions, and 50 to 56 Gy to low-risk regions. The prescribed dose was the isodose surface that encompasses at least 95% of the planning target volume (PTV). No more than 20% of PTV_{70} (volume of PTV receiving 70 Gy) received $\geqslant$110% of the prescribed dose, and no more than 1% of PTV_{70} received $\leqslant$93% of the prescribed dose.

Of the 55 patients, 20 underwent 3 cycles of induction CT followed by concurrent CRT. The induction regimen was cisplatin (75 mg/m^2) and docetaxel (75 mg/m^2) given every 3 weeks. Twenty-nine patients receieved only concurrent CRT, and 6 underwent RT alone. Concurrent CT schedule was either cisplatin (75 mg/m^2) at 3-week intervals or weekly cisplatin (40 mg/m^2). Patient and treatment characteristics are presented in Table 1. Before enrollment, all patients were informed about the study and signed a study-specific consent form. This study was approved by the Ethics Committee of Ege University (No. 13-1/4).

Dosimetric Factors

Radiotherapy plans and dosimetric data of 55 patients were restored and evaluated retrospectively. For each patient, the following SRSs were delineated according to guidelines previously described by Christianen at al[21]: inferior, middle, and superior pharyngeal constrictor muscles (PCM), BOT, supraglottic larynx, glottic larynx, cricopharyngeal inlet, and cervical esophagus. Dose-volume histograms (DVHs) were generated for each SRS. The mean doses (D_{mean}) of each SRS and partial volumes receiving specific doses (V_d) (eg, V_{55} defines the volume of structure that receieves 55 Gy) were recorded.

Evaluation of Dysphagia

Study Procedure

Before the procedure, sociodemographic and clinical data were obtained from patients' files and patient-reported information was assessed during face-to-face conversations. Clinical variables included age, gender, tumor subsite, stage, type of RT planning, and RT dose. During their follow-up visits, patients went through clinical and instrumental evaluation.

Table 1. Patient Characteristics.

Characteristic	n (%)
Median age (range)	52 (19-70)
Gender	
Female	18 (33)
Male	37 (67)
Primary site	
Nasopharynx	22 (40)
Larynx, hypopharynx	20 (36)
Oral cavity, oropharynx	9 (17)
Cervical esophagus	4 (7)
Stage	
I	5 (9)
II	18 (33)
III	20 (36)
IV	12 (22)
Chemotherapy	
None	6 (11)
Concurrent chemoradiotherapy	29 (53)
Induction chemotherapy followed by concurrent chemoradiotherapy	20 (36)
Swallowing-Related Structures	**D_{mean}, Gy**
Superior pharyngeal constrictor muscles (PCM)	53
Middle PCM	57
Inferior PCM	52
Base of tongue	43.8
Supraglottic larynx	53.6
Glottic larynx	49.6
Cricopharyngeal inlet	47.9
Cervical esophagus	41.9

Abbreviation: D_{mean}, mean dose.

Clinical Evaluation

The clinical patient-reported swallowing function was assesed via a case report file composed of several questions that were asked to the patients before FEES concerning the following: difficulty in swallowing, dysphagia related to consistency of diet (liquid, semisolid, solid), grade of dysphagia according to a Likert scale (normal, mild-moderate, severe), difficulty in bolus control, need to clear the throat after swallowing, feeling of having food stuck in the throat, and sense of choking and coughing during meals. The answers were analyzed and interpreted using a Likert scale.

Instrumental Evaluation by FEES

An ear, nose, and throat (ENT) specialist and physical therapy and rehabilitation specialist (physiatrist) were present during each procedure, and all procedures were monitored and videorecorded. All tests were assessed by the same physiatrist, specialized and experienced on FEES, and the same ENT specialist, who were blinded to the primary location of the tumor, by using a flexible fiber-optic nasopharyngoscope (KAY PENTAX Ltd, Montvale, New Jersey, USA). Each patient had an intravenous line and pulse oximeter for monitoring and safety. The procedure was carried out while the patient was sitting in an upright position and without topical anesthesia into the nasal cavity. The patients were asked to swallow the liquid (3-5-10 mL water), semisolid food (5 mL yogurt), and solid food (fish cracker) materials (colored with green food coloring) consecutively. For evaluation of the swallowing function by FEES, the endoscope was first placed in the high position above the epiglottis before and during swallowing, to evaluate premature spillage (the bolus in the oral cavity, BOT, valleculae(s) or further down, without swallowing being triggered) and after swallowing to evaluate residue/secretion (the presence of bolus material or secretion residue in the pharynx). If residue was detected during the test, cleaning of the material was provided by asking the patient to drink some water. Then, the endoscope was advanced for about 10 seconds to a lower position just above the vocal folds in order to evaluate penetration (any material entering the laryngeal vestibule but remaining at or above the level of the vocal cords) or aspiration (any material entering the airway below the vocal cords). If penetration or aspiration had occurred, the presence of protective reflexes was noted. Premature spillage, residue/secretion, and penetration/aspiration findings were scored according to the grading scale of FEES built by Topaloglu et al[22] (Table 2).

Each test was repeated twice for each bolus material. The examinations were monitored and recorded in all patients, and the average of the 2 scores was taken. Each FEES was evaluated and rated by the same professor of physical therapy and rehabilitation who has specialized in dysphagia and FEES and worked in the Swallowing Lab at Ege University since 2004.

Statistical Analysis

The relationships between the dose-volume parameters of SRS and FEES scores for premature spillage, residue/secretion, and penetration/aspiration and between patient-reported swallowing function and FEES scores were assessed using Spearman's correlation coefficient. Optimal sensitive and specific predictive values for dose-volume parameters of SRS were calculated by receiver operating characteristic (ROC) curve analysis. The upper and lower dose-volume thresholds for SRS in patients with and without dysphagia were compared using the Pearson's chi-square or Fisher exact test. The FEES scores were compared for upper and lower dose-volume thresholds using an independent-samples t test. Statistical analysis was performed using SPSS version 18.0. Statistical significance was determined at $P \leqslant .05$ (2-tailed).

Table 2. Early Spillage, Residue/Secretion, and Penetration/Aspiration Scale by FEES.

Points	Early Spillage	Residue/Secretion	Penetration/Aspiration
1	Severe	Severe congestion	Material enters the trachea, cannot be discharged from airway
2	Significant	Moderate congestion residue/secretion	Material enters the trachea, is discharged from airway
3	Moderate	Mild congestion residue/secretion	Material enters the larynx, cannot be discharged from airway
4	Mild	Surface-staining residue/secretion	Material enters the larynx, is discharged from airway
5	None	No residue/secretion	Material does not enter the airway

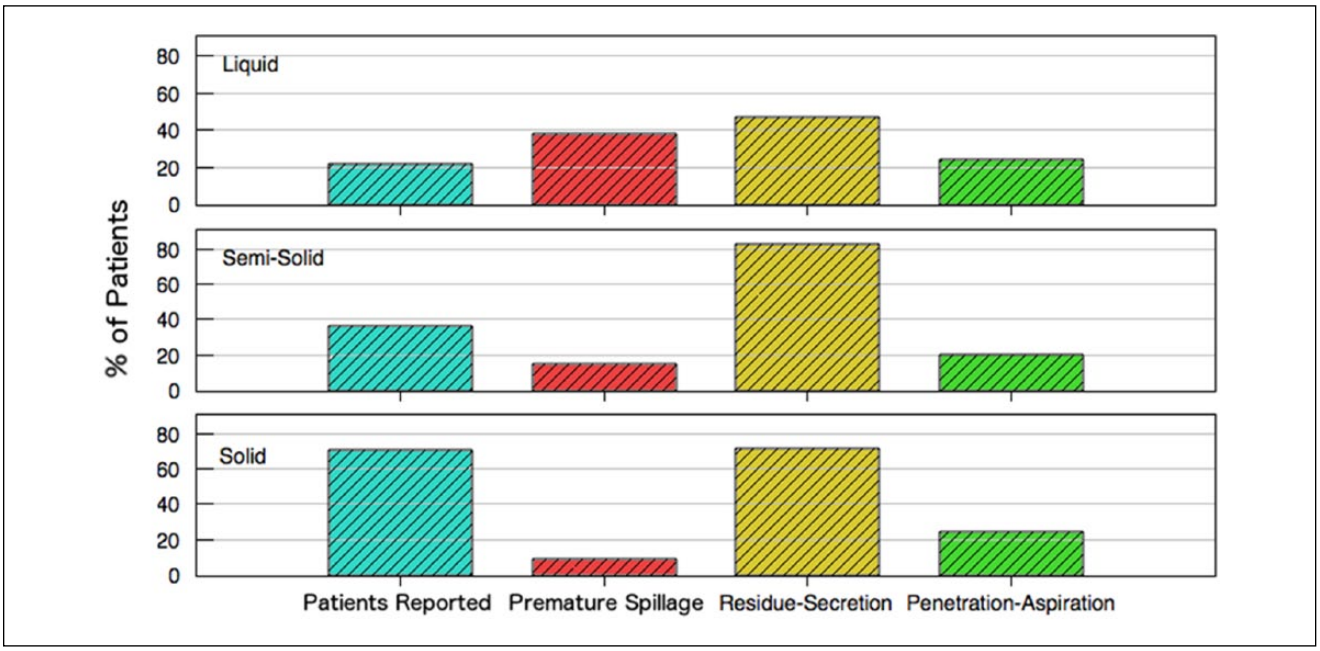

Figure 1. Evaluation of subjective patient-reported data and objective FEES findings (premature spillage, residue/secretion, aspiration/penetration).
Abbreviation: FEES, fiber-optic endoscopic evaluation of swallowing.

Results

The Correlation between Subjective Patient-Reported Swallowing Function and Objective FEES Findings

The medical records of 55 consecutive patients were assessed. Clinical data and FEES evaluations were carried out at a median 20 months (range, 12-26 months) after completion of their treatments. When the patients were asked if they had any swallowing difficulties, 79% declared that they had difficulty with solid food. When patient-reported results were compared with the FEES findings, it was found that the results had a low negative correlation considering solid food and penetration/aspiration ($r = -0.389$, $P = .023$), but they were inconsistent considering semisolid food ($r = -0.145$, $P = .343$) or liquids ($r = -0.175$, $P = .255$). In addition, 40% of patients who rated themselves as having no difficulty in swallowing with semisolid food or liquids had abnormal FEES findings in terms of residue/secretion scores (Figure 1).

SRS Dose-Volume Parameters and Dysphagia

In 5 patients (2 hypopharynx, 1 oropharynx, 1 oral cavity, 1 cervical esophagus) who showed clinical signs of severe aspiration with the 3 mL water test, other tests (5-10 mL water, semisolid and solid food) could not be carried out further. With FEES, it was found that patients with residue and aspiration had lower scores with semisolid and solid food compared with liquids ($P < .01$).

There was a moderate negative correlation between FEES scores and dose-volume parameters of SRS (middle and inferior PCM, BOT, supraglottic larynx, glottic larynx, cricopharyngeal constrictors, and cervical esophagus) ($r \leqslant -0.5$, $P \leqslant .0001$). The details are presented in Table 3. The data showing correlation underwent ROC curve analysis to assess the most sensitive and specific dose-volume thresholds for D_{mean} and $V_{55.}$ Optimal predictive values for dysphagia of dose-volume thresholds for SRS were as follows: for middle PCM, $D_{mean} > 57$ Gy and $V_{55} > 70\%$; for inferior PCM, $D_{mean} > 57$ Gy and $V_{55} > 50\%$; for BOT, $D_{mean} > 50$ Gy and $V_{55} > 65\%$; for supraglottic and glottic larynx,

Table 3. The Correlation between the Dose-Volume Parameters of SRS and Swallowing Dysfunction by FEES for Premature Spillage, Residue/Secretion, and Penetration/Aspiration (Spearman's correlation coefficient by *rs*).

		Liquid			Semisolid			Solid		
		Premature Spillage	Residue/ Secretion	Penetration/ Aspiration	Premature Spillage	Residue/ Secretion	Penetration/ Aspiration	Premature Spillage	Residue/ Secretion	Penetration/ Aspiration
Superior PCM	**V55**	−0.12	−0.18	−0.23	−0.21	−0.27	−0.25	−0.18	−0.29	−0.26
	D_{mean}	−0.17	−0.24	−0.29	−0.19	−0.29	−0.28	−0.19	−0.26	−0.23
Middle PCM	**V55**	−0.21	−0.29	−0.21	−0.21	−0.55[b]	−0.23	−0.26	−0.53[b]	−0.28
	D_{mean}	−0.19	−0.27	−0.24	−0.19	−0.43[a]	−0.29	−0.23	−0.54[b]	−0.51[b]
Inferior PCM	**V55**	−0.23	−0.51[b]	−0.43[a]	−0.29	−0.57[b]	−0.56[b]	−0.26	−0.55[b]	−0.52[b]
	D_{mean}	−0.29	−0.46[a]	−0.44[a]	−0.31	−0.51[b]	−0.53[b]	−0.23	−0.53[b]	−0.63[b]
Base of tongue	**V55**	−0.17	−0.21	−0.24	−0.29	−0.45[a]	−0.26	−0.25	−0.56[b]	−0.29
	D_{mean}	−0.21	−0.29	−0.29	−0.27	−0.55[b]	−0.23	−0.28	−0.51[b]	−0.27
Supraglottic larynx	**V55**	−0.23	−0.39	−0.45[a]	−0.23	−0.60[b]	−0.42[a]	−0.29	−0.68[b]	−0.55[b]
	D_{mean}	−0.28	−0.36	−0.44[a]	−0.31	−0.65[b]	−0.56	−0.31	−0.50[b]	−0.49[a]
Glottic larynx	**V55**	−0.21	−0.33	−0.26	−0.29	−0.50[b]	−0.46[a]	−0.21	−0.26	−0.29
	D_{mean}	−0.19	−0.37	−0.27	−0.24	−0.23	−0.46[a]	−0.29	−0.49[a]	−0.45[a]
Cricopharyngeal inlet	**V55**	−0.28	−0.49[a]	−0.39	−0.26	−0.36	−0.45[a]	−0.25	−0.33	−0.38
	D_{mean}	−0.23	−0.30	−0.46[a]	−0.23	−0.51[b]	−0.47[a]	−0.28	−0.37	−0.40[a]
Cervical esophagus	**V55**	−0.29	−0.41[a]	−0.34	−0.33	−0.55[b]	−0.54[b]	−0.24	−0.56[b]	−0.51[b]
	D_{mean}	−0.27	−0.35	−0.38	−0.29	−0.55[b]	−0.59[b]	−0.29	−0.51[b]	−0.51[b]

[a] $P < .01$.
[b] $P < .001$.
Abbreviations: D_{mean}, mean dose; FEES, fiber-optic endoscopic evaluation of swallowing; PCM, pharyngeal constrictor muscles; V_{55}, volume of structure receiving ⩾55 Gy.

$D_{mean} > 55$ Gy and $V_{55} > 50\%$. Inferiorly located SRS had less tolerance to radiation; for cricopharyngeal inlet, $D_{mean} > 50$ Gy and $V_{55} > 40\%$ were predictive for dysphagia; for cervical esophagus, $D_{mean} > 45$ Gy and $V_{55} > 40\%$ were predictive for dysphagia.

In the second part of the analysis, the pathologic FEES findings were compared with upper and lower dose-volume thresholds of each SRS for liquid, semisolid, and solid food, as explained below.

SRS and Premature Spillage

Premature spillage was associated with doses higher than 57 Gy for inferior PCM, 55 Gy for supraglottic larynx, and 45 Gy for cervical esophagus by semisolid or solid food. The details are presented in Table 4.

SRS and Residue/Secretion

The residue and secretion were present in patients with damaged PCM, BOT, supraglottic larynx, and cervical esophagus. The residue/secretion scores were associated with doses higher than 57 Gy for inferior PCM, 55 Gy for supraglottic larynx, and 45 Gy for cervical esophagus with liquid. With semisolid and solid food, in addition to these dose-volume thresholds mentioned for liquid, mean doses higher than 57 Gy for middle PCM and 50 Gy for BOT were associated with residue/secretion scores. The details are presented in Table 5.

SRS and Penetration/Aspiration

Penetration/aspiration was detected in patients with damaged inferior PCM and inferiorly located SRS. With liquids, penetration/aspiration was associated with doses higher than 57 Gy for inferior PCM, 50 Gy for cricopharyngeal inlet, and 45 Gy for cervical esophagus. With semisolid and solid food, in addition to these dose-volume thresholds for liquid, penetration/aspiration was associated with doses higher than 55 Gy for supraglottic and glottic larynx. The details are presented in Table 6.

Discussion

In our study, chronic dysphagia results of HNCPs who received definitive RT or CRT were evaluated. Among radiation-induced damaged SRS, the inferior PCM, supraglottic larynx, and cervical esophagus were found to be structures significantly associated with dysphagia by FEES evaluation (Figure 2), and residue/secretion and penetration/aspiration problems were found more often than premature spillage.

In the present study, both relatively subjective patient-reported dysphagia and objective FEES findings were analyzed together. In the analysis of patient-reported symptoms, swallowing difficulties were reported with liquid and semisolid food in only 20% and 40% of patients, respectively. According to objective FEES results, these rates were 50% and 80%, respectively, and they were especially higher in terms of residue scores. Although there were objective

Table 4. Premature Spillage Results According to Dose-Volume Threshold Values of SRS with Liquid, Semisolid, and Solid Food by FEES (Independent-Samples *t* Test).

		Premature Spillage														
		Liquid					Semisolid					Solid				
		n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*P* Value
SPC V_{55} (%)	⩽70	14	4.86 (0.3)	0.468	48	.642	16	4.94 (0.2)	0.813	50	.42	17	4.88 (0.7)	0.623	48	.53
	>70	36	4.78 (0.5)				36	4.81 (0.6)				35	4.81 (0.8)			
SPC D_{mean} (Gy)	⩽60	17	4.59 (0.7)	−1.078	21.9	.125	19	4.79 (0.7)	−0.573	50	.57	19	4.89 (0.9)	−1.603	48	.77
	>60	33	4.91 (0.2)				33	4.88 (0.4)				33	4.90 (0.5)			
MPC V_{55} (%)	⩽70	16	4.81 (0.4)	0.112	48	.911	17	4.94 (0.2)	0.886	50	.38	20	4.92 (0.3)	0.897	48	.39
	>70	34	4.79 (0.5)				35	4.80 (0.6)				32	4.80 (0.6)			
MPC D_{mean} (Gy)	⩽57	14	4.79 (0.4)	−0.117	48	.908	15	4.87 (0.5)	1.733	50	.863	16	4.83 (0.9)	1.762	42.5	.874
	>57	36	4.81 (0.5)				37	4.84 (0.5)				36	4.65 (0.5)			
IPC V_{55} (%)	⩽50	25	4.84 (0.3)	0.525	48	.602	26	4.92 (0.3)	3.031	50	.037	26	4.92 (0.4)	1.131	46	.256
	>50	25	4.76 (0.6)				26	3.67 (0.6)				26	4.77 (0.2)			
IPC D_{mean} (Gy)	⩽57	32	4.88 (0.3)	1.033	26.9	.079	33	4.94 (0.3)	3.446	25.6	.029	30	4.96 (0.2)	1.59	48	.098
	>57	18	4.67 (0.7)				19	3.48 (0.7)				22	4.68 (0.6)			
BOT V_{55} (%)	⩽65	35	4.86 (0.3)	0.815	27.8	.352	37	4.86 (0.4)	0.391	50	.698	32	4.86 (0.4)	0.091	36.8	.798
	>65	15	4.67 (0.8)				15	4.80 (0.7)				20	4.83 (0.5)			
BOT D_{mean} (Gy)	⩽50	25	4.88 (0.3)	1.06	48	.295	26	4.96 (0.1)	1.568	32.2	.123	26	4.88 (0.8)	1.518	45.9	.253
	>50	25	4.72 (0.6)				26	4.73 (0.7)				26	4.73 (0.4)			
SGL V_{55} (%)	⩽50	24	4.88 (0.3)	0.952	48	.336	25	4.92 (0.4)	2.351	50	.046	25	4.92 (0.3)	0.943	48	.321
	>50	26	4.73 (0.6)				27	4.28 (0.6)				27	4.77 (0.7)			
SGL D_{mean} (Gy)	⩽55	28	4.86 (0.3)	0.85	48	.399	29	4.93 (0.3)	3.28	32.5	.032	28	4.93 (0.5)	2.182	35.2	.042
	>55	22	4.73 (0.7)				23	3.84 (0.6)				24	4.14 (0.7)			
GL V_{55} (%)	⩽45	28	4.79 (0.6)	−0.211	48	.834	28	4.79 (0.6)	−0.873	50	.387	28	4.79 (0.4)	0.673	36	.357
	>45	22	4.82 (0.3)				24	4.92 (0.2)				24	4.72 (0.6)			
GL D_{mean} (Gy)	⩽55	28	4.79 (0.6)	−0.211	48	.834	28	4.79 (0.6)	−0.873	50	.387	27	4.79 (1.1)	−0.473	44.9	.493
	>55	22	4.82 (0.3)				24	4.92 (0.2)				25	4.82 (1.2)			
CPI V_{55} (%)	⩽40	28	4.79 (0.6)	−0.211	48	.834	28	4.82 (0.6)	−0.355	50	.724	28	4.82 (1.3)	2.235	39.4	.04
	>40	22	4.82 (0.3)				24	4.88 (0.3)				24	3.99 (0.9)			
CPI D_{mean} (Gy)	⩽50	27	4.75 (0.6)	−0.847	48	.401	27	4.81 (0.6)	−0.433	50	.667	27	4.81 (1.1)	0.033	43.8	.867
	>50	23	4.87 (0.3)				25	4.88 (0.3)				25	4.80 (1.2)			
CE V_{55} (%)	⩽40	29	4.89 (0.3)	2.426	27.3	.047	36	4.92 (0.3)	2.183	25.6	.046	30	4.92 (0.8)	3.183	48	.031
	>40	21	4.20 (0.9)				16	4.02 (0.8)				22	3.68 (0.4)			
CE D_{mean} (Gy)	⩽45	25	4.88 (0.3)	1.062	34.6	.295	25	4.92 (0.4)	0.951	50	.346	25	4.92 (1.1)	2.351	48	.039
	>45	25	4.72 (0.6)				27	4.78 (0.6)				27	4.01 (0.9)			

Abbreviations: BOT, base of tongue; CE, cervical esophagus; CPI, cricopharyngeal inlet; D_{mean}, mean dose; FEES, fiber-optic endoscopic evaluation of swallowing; GL, glottic larynx; IPC, inferior pharyngeal constrictor; MPC, middle pharyngeal constrictor; SG, supraglottic larynx; SPC, superior pharyngeal constrictor; V_{55}, volume of structure receiving ⩾55 Gy.

Table 5. Residue/Secretion Results According to Dose-Volume Threshold Values of SRS with Liquid, Semisolid, and Solid Food by FEES (Independent-Samples *t* Test).

		Residue/Secretion														
		Liquid					Semisolid					Solid				
		n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*P* Value
SPC V_{55} (%)	⩽70	17	4.21 (0.9)	−0.6	48	.551	16	4.94 (1.4)	0.813	50	.42	17	3.71 (1.3)	1.223	48	.227
	>70	33	4.39 (0.9)				36	4.81 (1.2)				33	3.14 (0.9)			
SPC D_{mean} (Gy)	⩽60	17	4.18 (0.9)	−0.903	48	.371	19	4.79 (1.2)	−0.573	50	.57	17	0.376 (1.5)	1.595	48	.117
	>60	33	4.42 (0.9)				33	4.88 (1.3)				33	3.306 (1.4)			
MPC V_{55} (%)	⩽70	20	4.50 (0.7)	0.844	48	.403	17	4.94 (0.9)	0.886	50	.38	16	4.13 (1.2)	3.497	48	.006
	>70	30	4.26 (0.9)				35	4.80 (1.2)				34	2.91 (1.1)			
MPC D_{mean} (Gy)	⩽57	19	4.71 (0.4)	3.179	46.2	.017	15	4.87 (0.5)	5.378	42.5	<.001	14	4.79 (0.5)	7.58	47.3	<.0001
	>57	31	3.72 (1.0)				37	3.54 (0.5)				36	2.72 (1.3)			
IPC V_{55} (%)	⩽50	25	4.76 (0.4)	3.615	31.6	.001	26	4.92 (0.9)	5.047	46.6	<.001	25	4.12 (1.0)	4.582	44.6	.001
	>50	25	3.62 (1.0)				26	3.77 (1.2)				25	2.48 (1.4)			
IPC D_{mean} (Gy)	⩽57	28	4.58 (0.7)	2.027	48	.048	33	4.94 (1.0)	4.19	50	<.001	30	3.99 (1.2)	2.597	48	.013
	>57	22	4.00 (1.0)				19	3.88 (1.2)				20	2.61 (0.9)			
BOT V_{55} (%)	⩽65	30	4.43 (0.8)	1.044	48	.302	37	4.86 (1.3)	0.191	50	.091	32	3.80 (1.2)	4.149	48	.001
	>65	19	4.13 (0.9)				15	4.80 (1.1)				18	2.13 (1.3)			
BOT D_{mean} (Gy)	⩽50	25	4.52 (0.8)	1.401	48	.168	26	4.96 (1.1)	3.368	50	.007	25	3.88 (1.2)	3.136	48	.005
	>50	25	4.16 (0.9)				26	3.73 (1.3)				25	2.72 (1.2)			
SGL V_{55} (%)	⩽50	24	4.67 (0.5)	3.152	38.9	.014	25	4.92 (0.0)	3.829	45.7	<.001	24	3.92 (1.1)	3.143	46.8	.004
	>50	26	3.67 (1.0)				27	3.78 (1.2)				26	2.77 (1.3)			
SGL D_{mean} (Gy)	⩽55	28	4.86 (0.7)	2.08	48	.043	29	4.93 (1.0)	3.545	50	.001	28	3.86 (1.2)	3.239	48	.002
	>55	22	3.83 (1.0)				23	3.74 (1.1)				22	2.59 (1.3)			
GL V_{55} (%)	⩽45	28	4.54 (0.7)	1.73	48	.089	28	4.79 (1.2)	1.273	50	.214	28	3.50 (1.2)	1.062	48	.293
	>45	22	4.09 (1.0)				24	4.52 (1.3)				22	3.05 (1.3)			
GL D_{mean} (Gy)	⩽55	28	4.54 (0.7)	1.63	36.1	.089	28	4.79 (1.1)	−0.873	50	.387	28	3.50 (1.2)	1.062	48	.293
	>55	22	4.09 (1.0)				24	4.92 (1.0)				22	3.05 (1.1)			
CPI V_{55} (%)	⩽40	28	4.79 (0.7)	−0.211	48	.089	28	4.82 (1.11)	−0.355	50	.724	28	3.50 (1.4)	1.062	48	.293
	>40	22	4.82 (1.0)				24	4.88 (1.3)				22	3.05 (1.6)			
CPI D_{mean} (Gy)	⩽50	27	4.59 (0.6)	2.19	38.7	.041	27	4.81 (1.2)	−0.433	50	.667	27	3.67 (1.2)	1.921	48	.061
	>50	23	4.04 (1.0)				25	4.88 (1.1)				23	2.87 (1.1)			
CE V_{55} (%)	⩽40	30	4.42 (0.8)	1.156	48	.271	36	4.92 (1.1)	1.683	50	.015	32	3.45 (1.1)	1.248	48	.224
	>40	20	4.08 (1.0)				16	4.04 (0.9)				18	2.83 (1.2)			
CE D_{mean} (Gy)	⩽45	25	4.64 (0.7)	3.125	42.9	.019	25	4.92 (1.0)	3.951	50	.001	25	3.92 (1.4)	2.045	48	.047
	>45	25	3.94 (1.0)				27	3.78 (1.2)				25	2.88 (1.2)			

Abbreviations: BOT, base of tongue; CE, cervical esophagus; CPI, cricopharyngeal inlet; D_{mean}, mean dose; FEES, fiber-optic endoscopic evaluation of swallowing; GL, glottic larynx; IPC, inferior pharyngeal constrictor; MPC, middle pharyngeal constrictor; SG, supraglottic larynx; SPC, superior pharyngeal constrictor; V_{55}, volume of structure receiving ⩾55 Gy.

Table 6. Penetration/Aspiration Results According to Dose-Volume Threshold Values of SRS with Liquid, Semisolid, and Solid Food by FEES (Independent-Samples *t* Test).

		Penetration/Aspiration													
		Liquid					Semisolid Food					Solid Food				
		n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*P* Value	n	Test Score Mean (SD)	*t* Value	*df*	*p* Value
SPC V_{55} (%)	⩽70	17	4.50 (1.0)	−1.546	48	.129	16	4.31 (1.3)	−1.62	50	.111	17	4.64 (0.9)	−0.529	48	.599
	>70	33	4.83 (0.4)				36	4.78 (0.7)				33	4.78 (0.7)			
SPC D_{mean} (Gy)	⩽60	17	4.59 (1.0)	−0.888	22.7	.371	19	4.32 (1.2)	−1.639	25.1	.121	17	4.59 (0.9)	−0.958	48	.343
	>60	33	4.82 (0.4)				33	4.82 (0.7)				33	4.82 (0.7)			
MPC V_{55} (%)	⩽70	20	5.00 (0.0)	2.729	33	.01	20	4.65 (0.7)	0.064	50	.949	18	4.75 (0.6)	0.884	48	.953
	>70	30	4.12 (0.8)				32	4.63 (1.0)				32	4.74 (0.8)			
MPC D_{mean} (Gy)	⩽57	16	5.00 (0.0)	2.714	35	.01	20	4.87 (0.5)	1.456	48.6	.152	18	5.00 (0.0)	2.328	35	.026
	>57	34	4.14 (0.7)				32	3.54 (1.0)				32	4.21 (0.9)			
IPC V_{55} (%)	⩽50	25	4.92 (0.2)	1.98	29.4	.05	26	4.92 (0.3)	2.824	33.6	.034	25	5.00 (0.0)	2.627	28.9	.025
	>50	25	4.26 (0.9)				26	3.77 (1.2)				25	3.41 (1.0)			
IPC D_{mean} (Gy)	⩽57	28	4.94 (0.2)	2.273	24.3	.041	28	4.94 (0.3)	3.122	23.6	.021	30	5.00 (0.0)	2.656	27.4	.023
	>57	22	3.99 (1.0)				24	3.18 (1.1)				20	3.28 (1.2)			
BOT V_{55} (%)	⩽65	30	4.71 (0.7)	−0.397	48	.671	35	4.65 (0.9)	0.162	50	.878	32	4.80 (0.8)	0.804	48	.425
	>65	20	4.80 (0.5)				15	4.60 (1.1)				18	4.60 (0.6)			
BOT D_{mean} (Gy)	⩽50	25	4.80 (0.6)	1.607	48	.542	26	4.54 (0.7)	0.711	50	.482	25	4.88 (0.7)	0.524	48	.603
	>50	25	4.66 (0.7)				26	4.73 (0.9)				25	4.68 (0.9)			
SGL V_{55} (%)	⩽50	24	4.92 (0.2)	1.86	32.7	.084	25	4.92 (0.4)	2.658	38.6	.04	24	5.00 (0.0)	2.394	29	.025
	>50	26	4.58 (0.9)				27	3.78 (1.1)				26	3.57 (1.0)			
SGL D_{mean} (Gy)	⩽55	28	4.89 (0.2)	2.08	36.4	.044	29	4.93 (0.3)	3.019	34.8	.027	28	5.00 (0.0)	2.445	27	.023
	>55	22	4.00 (0.9)				23	3.37 (1.1)				22	3.21 (0.2)			
GL V_{55} (%)	⩽45	28	4.89 (0.3)	1.793	32.1	.079	28	4.96 (0.1)	3.423	27	.007	28	4.96 (0.1)	2.029	24.7	.05
	>45	22	4.55 (0.9)				24	3.05 (1.1)				22	3.08 (1.1)			
GL D_{mean} (Gy)	⩽55	28	4.89 (0.3)	1.693	28.3	.117	28	4.96 (0.1)	3.123	31.9	.015	28	4.96 (0.1)	2.329	29.8	.047
	>55	22	4.55 (0.9)				24	3.15 (1.2)				22	3.08 (1.1)			
CPI V_{55} (%)	⩽40	28	4.93 (0.2)	2.028	28.6	.049	28	5.00 (0.0)	3.342	32.9	.007	28	5.00 (0.0)	2.448	27.1	.024
	>40	22	4.23 (0.9)				24	3.21 (0.1)				22	3.11 (1.1)			
CPI D_{mean} (Gy)	⩽50	27	4.52 (0.2)	2.92	29.3	.007	27	5.00 (0.0)	3.74	50	.004	27	5.00 (0.0)	1.98	29.8	.024
	>50	23	3.74 (0.9)				25	3.28 (0.9)				23	3.39 (1.1)			
CE V_{55} (%)	⩽40	30	4.42 (0.7)	1.156	48	.071	34	4.89 (0.5)	2.525	31.5	.032	32	4.89 (0.5)	2.292	23.9	.046
	>40	20	4.08 (0.6)				18	3.32 (1.2)				18	3.35 (1.1)			
CE D_{mean} (Gy)	⩽45	25	4.64 (0.3)	2.825	28.9	.009	25	5.00 (0.0)	2.877	26.4	.008	25	5.00 (0.0)	2.397	29.9	.025
	>45	25	3.84 (0.9)				27	3.55 (1.2)				25	3.28 (0.2)			

Abbreviations: BOT, base of tongue; CE, cervical esophagus; CPI, cricopharyngeal inlet; D_{mean}, mean dose; FEES, fiber-optic endoscopic evaluation of swallowing; GL, glottic larynx; IPC, inferior pharyngeal constrictor; MPC, middle pharyngeal constrictor; SG, supraglottic larynx; SPC, superior pharyngeal constrictor; V_{55}, volume of structure receiving ⩾55 Gy.

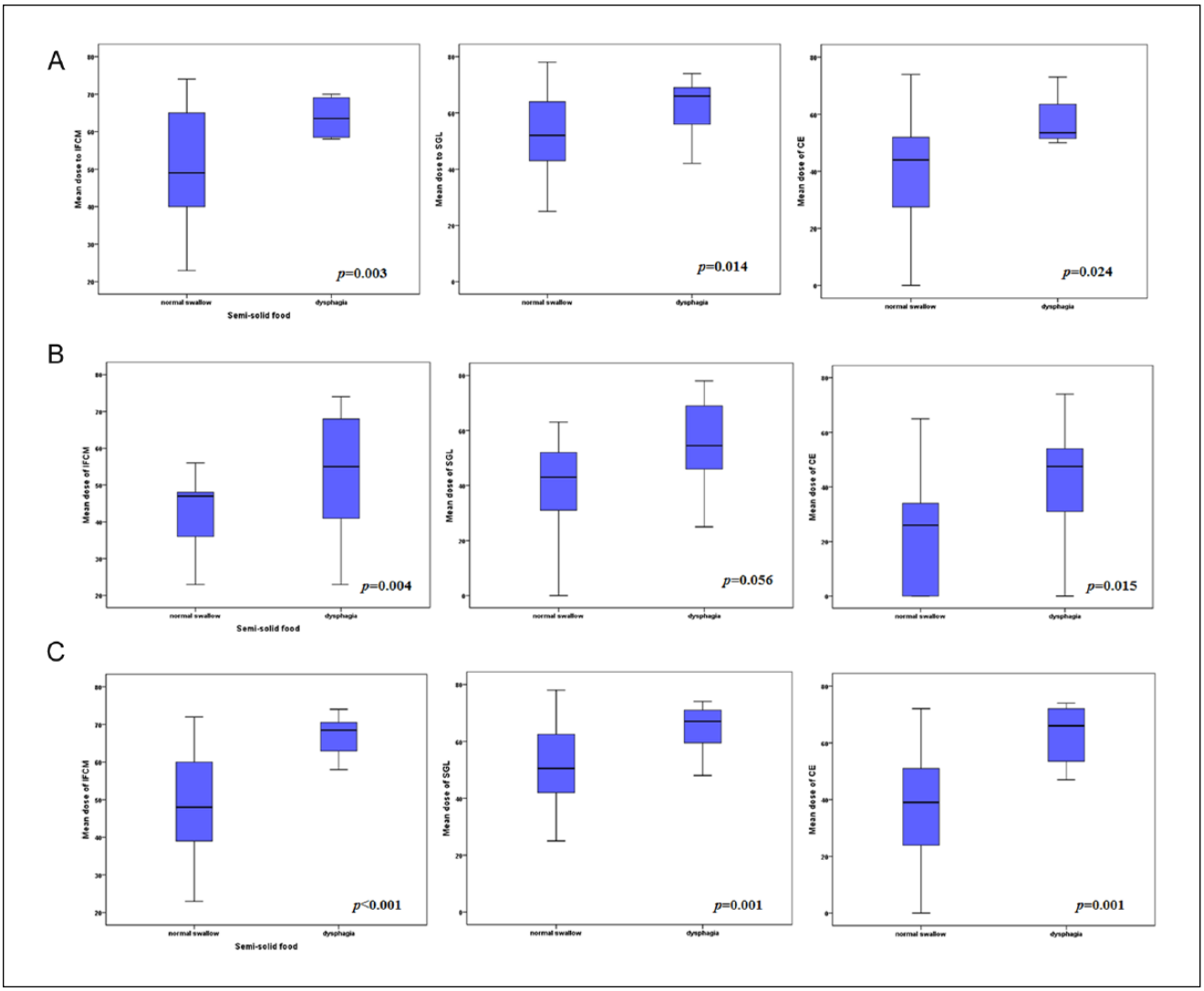

Figure 2. Comparison of mean doses (D_{mean}) of IPC, SGL, and CE in patients with normal swallowing and dysphagia by FEES according to (A) premature spillage, (B) residue/secretion, and (C) penetration/aspiration. Independent-samples *t* test, boxplot graphs. Abbreviations: CE, cervical esophagus; FEES, flexible endoscopic evaluation of swallowing; IPC, inferior pharyngeal constrictor; SGL, supraglottic larynx; VF, videofluoroscopic evaluation.

dysphagia findings in 50% by FEES, in clinical evaluation, these patients claimed that they did not have any dysphagia. Similarly, in a study evaluating post-RT swallowing dysfunction in nasopharyngeal carcinoma, despite some patients reporting no swallowing difficulty, it was found that they had nasal regurgitation during swallowing, oral retention of food bolus, and even choking symptoms.[23] In another study, there wasn't any correlation between subjective patient reports and objective VF findings.[24]

We found a significant correlation between dose-volume parameters of SRS and FEES findings. Also, D_{mean} and V_{55} values for each SRS were assessed. In a study by Feng et al[14] evaluating SRS dose-volume parameters before and 3 months after therapy, dysphagia was assessed by VF. The mean superior, middle, and inferior PCM; supraglottic larynx; and cervical esophagus doses were compared in aspirator and nonaspirators. It was reported that patients who received superior PCM $D_{mean} > 70$ Gy, middle PCM $D_{mean} > 66$ Gy, inferior PCM $D_{mean} > 56$ Gy, and supraglottic larynx $D_{mean} > 61$ Gy developed aspiration.[14] Aspiration was detected with PCM doses of $V_{60} > 83\%$ and $V_{65} > 73\%$. In another study, 294 patients were evaluated with a QoL questionnaire, and 65 patients had further evaluation by VF. QoL endpoints correlated with supraglottic and glottic larynx dose-volume parameters, and VF findings correlated with PCM dose.[25] Using VF, Caglar et al[15] retrospectively evaluated early swallowing impairment in 96 HNCPs. The inferior and superior PCM $D_{mean} > 54$ Gy, middle PCM $D_{mean} >$

63 Gy, and larynx $D_{mean} > 48$ Gy doses were associated with aspiration.[15] To evaluate dysphagia in our study, SRS dose-volume thresholds were defined by ROC curve analysis. According to our results, upper threshold values that were significant predictors of dysphagia were as follows: inferior PCM, $D_{mean} > 57$ Gy; supraglottic and glottic larynx, $D_{mean} > 55$ Gy; cervical esophagus, $D_{mean} > 45$ Gy. Although we did not find any correlation between superior PCM dose-volume parameters and dysphagia, in other studies there was a statistically significant difference at doses >70 Gy,[14-16] and lower aspiration risk was reported at doses <60 Gy.[25] In another study, inferior PCM was the main structure responsible for persistent dysphagia that may result in percutaneous endoscopic gastrostomy usage in the long term.[26] For dysphagia assessment in our study, all SRSs from the beginning of PCM to the end of the cervical esophagus were evaluated prospectively and objectively in the long term after RT; it was found that the inferior PCM, supraglottic larynx, and cervical esophagus were the main structures associated with dysphagia.

Our patient cohort was composed mostly of CRT patients. This might be a confounding factor and might have an effect on the results, as the literature shows that CRT significantly increases toxicity, including swallowing complications.[27] In subset analysis, we did not show any difference between the CRT and RT-only groups in terms of dysphagia, which might be the result of the small RT-only group. In addition, the strength of dose-volume effects of RT might have minimized other clinical factors.

In a study in which magnetic resonance imaging–based changes of PCM were evaluated before and at 3 months after CRT, it was declared that PCM receiving >50 Gy showed decreased T1-weighted and increased T2-weighted signals and increased thickness that were statistically significant.[28] During the acute phase of RT, there could be severe mucositis, inflammation, and edema in SRSs. There have been some studies that have evaluated the relation between SRS dose-volume parameters and dysphagia in the acute phase of RT.[14,15] But during the chronic phase, submucosal damage and fibrosis might develop, resulting in vascular changes that worsen sensory and motor innervation disturbances. As a result, in the chronic phase, permanent sequelae become prominent.[29-31] In our study, since dysphagia was evaluated in the long term after treatment, we believe that our results may represent the correlation of FEES results and SRS dose-volume parameters more realistically.

There are some major pitfalls of our study. First, we didn't exclude patients with laryngeal or hypopharyngeal primaries, where the tumor-related effects might have had an influence on swallowing dysfunction since the primary site of disease might have overlapped with SRS in these patients. Second, although it's known that xerostomia has a major impact on dysphagia, mainly with solid food, it was not evaluated in an objecive manner, and dose-volume parameters of parotid and submandibular glands were not assessed. Similar to our study, in some other studies, xerostomia was also not evaluated.[14-16] Third, it would have been better if we had evaluated post-RT swallowing in the acute phase and the long term instead of in the long term only. Nevertheless, we think that long-term findings might be more important in the clinical management of patients. Further, it would have been better if we could make a comparison in terms of superiority between FEES and VF methods. Finally, history of smoking was lacking in our patient cohort, which is a well-known clinical predictor of swallowing toxicity after RT.[15]

Despite inherent limitations, the objective evaluation of dysphagia in the long term after RT by FEES in all symptomatic and asymptomatic patients, the use of different consistencies of food, and the evaluation of dose-volume thresholds for very detailed and numerous SRSs can be viewed as the strengths of our study. To our knowledge, our study is the first to evaluate the relation between FEES findings and SRS dose-volume parameters. In addition, SRS dose-volume parameters of each structure to predict dysphagia were evaluated by ROC curve analysis to find the most specific and sensitive cutoff values.

In conclusion, in this study, radiation-induced changes in the chronic phase of RT resulting in SRS dysfunction were investigated using an objective and reliable method. It was found that dysphagia correlates strongly with SRS dose-volume parameters, and for every swallowing-related substructure, optimal dose-volume cutoff levels were described. In our findings, patient-reported subjective results did not realistically define dysphagia with liquid or semisolid food, although swallowing dysfunction was documented by these patients with objective FEES findings. This is especially important in terms of presence of silent aspiration when considering its life-threatening complications. Among SRSs, the inferior PCM, supraglottic larynx, and cervical esophagus were found to be significantly associated with dysphagia. According to FEES results, residue, penetration, and aspiration pathologies were detected more often than was premature spillage. Our data suggest that, by delineating and improving dose-volume parameters of substructures important for swallowing, patients' QoL might be improved. Further, our study might be a guide for swallowing rehabilitation and exercise programs.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Conflicting Interests

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