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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2021.09.017

Radiotherapy and Oncology 164 (2021) 253–260

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Relationship between videofluoroscopic and subjective (physician- and patient- rated) assessment of late swallowing dysfunction after (chemo) radiation: Results of a prospective observational study

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A R T I C L E I N F O

Article history:
Received 19 March 2021
Received in revised form 15 September 2021
Accepted 20 September 2021
Available online 28 September 2021

Keywords:
Head and neck cancer
Dysphagia
Aspiration
(Chemo)radiation
Videofluoroscopy

A B S T R A C T

Background and purpose: Primary (chemo)radiation (CHRT) for HNC may lead to late dysphagia. The purpose of this study was to assess the pattern of swallowing disorders based on prospectively collected objective videofluoroscopic (VF) assessment and to assess the correlations between VF findings and subjective (physician- and patient-rated) swallowing measures.

Material and methods: 189 consecutive HNC patients receiving (CH)RT were included. Swallowing evaluation at baseline and 6 months after treatment (T6) encompassed: CTCAE v.4.0 scores (aspiration/dysphagia), PROMs: SWAL QOL/ EORTC QLQ-H&N35 (swallowing domain) questionnaires and VF evaluation: Penetration Aspiration Scale, semi-quantitative swallowing pathophysiology evaluation, temporal measures and oral/pharyngeal residue quantification. Aspiration specific PROMs (aPROMs) were selected. Correlations between late penetration/aspiration (PA_T6) and: clinical factors, CTCAE and aPROMs were assessed using uni- and multivariable analysis.

Results: Prevalence of PA increased from 20% at baseline to 43% after treatment ($p < 0.001$). The most relevant baseline predictors for PA_T6 were: PA_T0, age, disease stage III–IV, bilateral RT and baseline aPROM 'Choking when drinking' (AUC: 0.84). In general aPROMs correlated better with VF-based PA than CTCAE scores. The most of physiological swallowing components significantly correlated and predictive for PA (i.e. Laryngeal Vestibular Closure, Laryngeal Elevation and Pharyngeal Contraction) were prone to radiation damage.

Conclusion: The risk of RT-induced PA is substantial. Presented prediction models for late penetration/aspiration may support patient selection for baseline and follow-up VF examination. Furthermore, all aspiration related OARs involved in aforementioned swallowing components should be addressed in swallowing sparing strategies. The dose to these structures as well as baseline PROMs should be included in future NTCP models for aspiration.

Swallowing disorders are commonly reported by patients with head and neck cancer (HNC). Some of them, even if asymptomatic, may compromise the safety and efficiency of the sophisticated swallowing process, leading to serious complications varying from swallowing difficulties to (silent) aspiration and subsequent aspiration pneumonia [1]. Definitive radiotherapy (RT) and concurrent chemoradiation (CHRT) are accepted treatment modalities for patients with HNC. However, over the past two decades, it has become clear that widely implemented (CH)RT contributes to further swallowing dysfunction, having detrimental effects on health-related quality of life (HRQoL) [1-3].

Abbreviations: PA, penetration/aspiration; SA, silent aspiration; VF, videofluoroscopy; aPROMs, aspiration specific patient rated outcomes measures; PAS, Penetration Aspiration Scale; OPSE, Oro-Pharyngeal Swallowing Efficiency; MBSImP, Modified Barium Swallowing Impairment Profile; PTT, Pharyngeal Transit Time; OTT, Oral Transit Time; LE, Laryngeal Elevation; LVC, Laryngeal Vestibular Closure; AHE, anterior hyoid excursion; TBR, Tongue Base Retraction; PC, Pharyngeal Contraction; AspPn, aspiration pneumonia; NTCP, Normal Tissue Complication Probability.

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https://doi.org/10.1016/j.radonc.2021.09.017
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VF and flexible 'fiberoptic endoscopic evaluation of swallowing' (FEES) are methods commonly used for an objective dysphagia assessment. The worst-case scenario encountered by patients with dysphagia is aspiration [4-6]. Detection accuracy of aspiration is practically equivalent for VF and FEES, but pathophysiological mechanisms leading to aspiration can only be assessed with VF. Some of these mechanisms are particularly common after (CH) RT, for instance reduction of hyolaryngeal elevation and tongue base retraction [6,7].

VF evaluation may include different standardized scoring tools [8-11]. Also, numerous scoring scales for physician- rated swallowing evaluation are available [12,13]. However, scales with the highest sensitivity for swallowing impairments are composite measures, including an objectively scored VF-based domain [12,14,15]. The question arises, for aspiration in particular, if the non-VF-based physician rated scores (e.g. Common Terminology Criteria for Adverse Events, CTCAE) correlate with/ have any predictive value for VF-based disorders and, hence, can they be used as a substitute for the more invasive, labour intensive VF examination. Despite its simplicity, CTCAE is widely used to classify toxicities across disciplines [16]. However, the performance of CTCAE to detect VF-based objective disorders (especially ≥6 months after treatment) decreases [16]. Similarly, clinical assessment of dysphagia does not reflect an objective outcome, especially for the pharyngeal phase of swallowing [17-19]. On the other hand, patient-rated outcome measures (PROMs) seem to correlate better with objective scores [1,20,21].

The purpose of this analysis was to assess the patterns and prevalence of RT-induced swallowing problems based on prospectively collected VF, CTCAE scores and PROMs. Also, to assess correlations between objective and subjective measures and to determine the extent of any levels of diagnostic consistency. The time point of late dysphagia assessment was chosen based on data showing that (physician-rated) dysphagia 6 months after treatment is highly predictive for persisting swallowing dysfunction thereafter [22]. Moreover, later studies showed that acute VF disorders peak at 3 months and stabilize around 6–12 months after treatment [14].

Table 1
Patients/disease/treatment characteristics.

Characteristics	*N* (%)
Sex	
male	157 (84)
female	29 (16)
Age	
19–65	120 (63)
>65	69 (37)
Tumour staging*	
cTx-T2	130 (69)
cT3-T4	58 (31)
Nodal staging*	
N0	115 (61)
N +	74 (39)
Disease stage*	
I	32 (17)
II	51 (27)
III	39 (21)
IV	67 (35)
Primary site	
pharynx/others	104 (55)
– oropharynx	64 (34)
– hypopharynx	14 (7)
– others	26 (14)
larynx	85 (45)
Treatment	
radiation alone	134 (72)
chemo(bio)radiation	52 (28)
conventional RT	84 (45)
accelerated RT	102 (55)
RT extension	
Local and/or unilateral	69 (37)
Bilateral	116 (63)
RT technic	
IMRT	153 (82)
3D-CRT	33 (18)
Videofluoroscopy ass.	
VF baseline	183
VF 6 mos. after CRT	168
CTCAEdys ass.	
CTCAE baseline	181
CTCAE 6 mos. after CRT	183

* UICC TNM-classification, 7th edition.

Material and methods

Study population

The population of this prospective cohort study included 189 consecutive patients, treated from 2008 to 2012 either at the University Medical Center Groningen (UMCG), Groningen or the VU University Medical Center (VUmc), Amsterdam, The Netherlands. The patient's demographics, treatment and tumour characteristics are summarized in Table 1. All patients were subjected to a standardized follow-up program, including prospective evaluation of toxicity and health related quality of life (HRQoL). Additionally, VF examination was performed in the local Radiology Department. Acute and late toxicity were graded according to CTCAE v.4.0 [23]. HRQoL assessment included: the EORTC QLQ-C30, EORTC QLQ-H&N35 (head and neck cancer module) and SWAL QOL questionnaires [24-28]. All analysed dysphagia measures took place at baseline (T0) and 6 months after treatment (T6). Exclusion criteria included previous surgery and/or (CH)RT, other malignancies and/or distant metastases, CTCAE dysphagia grade ≥2 and age below 18 years.

Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki, and local laws and regulations. Eligible patients were fully informed about the study and requested to participate. All patients were subjected to a prospective data registration program in which complications and treatment results were prospectively assessed (ClinicalTrials.gov, number NCT02435576). Additional assessment, beyond the framework of this routine clinical practice, included VF (an objective X-ray swallowing examination). Informed consent forms were collected from each patient. All data were pseudonymised. The study protocol was approved by the local ethics committees of both the UMCG (2007/302) and VU University Medical Center (2008/70).

Treatment

The treatment consisted of definitive, curative radiotherapy (5 or 6 times/week), either alone or in combination with concomitant chemotherapy or cetuximab. Radiotherapy was delivered using conventional linear accelerators (6MV). Most patients were treated using intensity modulated radiotherapy (IMRT). A simultaneous integrated boost (SIB) was delivered up to a total dose of 70 Gy to the primary tumour and metastatic lymph nodes (fraction dose of 2 Gy) and 54.25 Gy to elective nodal areas. Plans typically consisted of seven equidistant and non-opposing fields. Parotid gland sparing was a standard approach. Various organs at risk were delineated according to previously published delineation guidelines [29,30]. Patients with an early glottic carcinoma were treated up to a total dose of 66 Gy (fraction dose of 2 Gy) to the primary site without elective fields with 3D-CRT only. A detailed description of treatment regimens has been previously published elsewhere [31].

Videofluoroscopic, physician-rated and patient-rated swallowing assessment

VF was performed within one week before and at T6. Videorecorder with frame-by-frame and slow-motion analysis capabilities was used to collect lateral and frontal images of swallowing of 5 ml and 10 ml barium boluses of three consistencies: liquid (barium water), pudding (barium paste) and solid (barium paste with marshmallows) according to the local VF acquisition protocols of the Radiology Departments. All videos were digitally recorded for further analysis. Evaluation of VF images included: 8- point Penetration Aspiration Scale (PAS: 1–2 norm, 3–5 penetration, 6–8 aspiration) [8], quantification of oral/pharyngeal residue, OPSE (an overall swallowing measure describing the interaction between speed of the bolus movement and the efficiency of its clearing from the oropharynx) [9,11] and Modified Barium Swallowing Impairment Profile (MBSImP), a validated method for pathophysiological swallowing assessment [10,14]. Although the VF acquisition method used in this study differed from the MBSImP protocol, 7 selected pharyngeal swallowing components were scored according to the MBSImP scoring guide. Each component, describing motility of specific structures, was rated using a 2- to 4-point scale, assuming 0 as no impairment [10,14].

MBSImP evaluation was done by two MBSImP-certified Speech Language Pathologists. PAS, residue and OPSE were scored by two experienced independent observers, reaching consensus for discrepant outcomes. As the videos were digitally recorded, pseudonymised and retrospectively evaluated, all observers were blinded for the clinical data and the time point of the video.

CTCAE v.0.4 dysphagia and aspiration were scored by radiation oncologists before and 6 months after treatment. SWAL QOL and EORTC QLQ-H&N35 (swallowing domain, HN35-SW) questionnaires, translated to Dutch, were filled in before the consultation. SWAL QOL is a validated questionnaire dedicated specifically to swallowing problems in daily life [24,32,33]. Details of all evaluation scales employed (i.e. VF, CTCAE and PROMs) are summarized in Supplement A (Tables S1/S2/S3).

Statistical methods

Data of all 189 patients was included in the analysis. Analyses described below were used: (1) to compare swallowing findings between T0 and T6 (2) to assess reciprocal correlations between penetration/aspiration (PA) and other VF parameters (3) to assess the associations between PA and subjective scores (CTCAE, PROMs).

The prevalence of penetration/aspiration, silent aspiration, residue and MBSImP measures at T0 and T6 were compared using McNemar's test. For comparison of continuous/discrete measures between two time-points paired-samples T-test was used.

VF and CTCAE parameters were analysed using original ordinal scale as well as dichotomous scale.

Two PAS-based dichotomous endpoints were analysed. First, *penetration/aspiration (PA),* distinguishing between safe and unsafe swallowing (PAS < 3 vs PAS $\geq$ 3). Second, *silent aspiration (SA)*, distinguishing asymptomatic aspiration (PAS = 8) from the norm or penetration/symptomatic aspiration (PAS $\leq$ 7) [8,34].

MBSImP scores (0 to 2–4) were arbitrarily dichotomized in the way that distinguishes moderate/severe from norm/mild impairment. Univariable and stepwise multivariable logistic regression with bootstrapping was used to assess the reciprocal correlations between PA and MBSImP scores (being potential underlying mechanism of PA). All seven MBSImP parameters were the only candidate variables included in the analysis.

Oral/pharyngeal residues were scored with an interval of 5% of the bolus volume (continuous-discrete scale) and dichotomized considering a residue >5% of bolus volume an event [35]. CTCAE measurements were dichotomized, discriminating no/mild from moderate/severe impairments: CTCAEdys (dysphagia grade $\geq$2) and CTCAEasp (aspiration grade $\geq$2).

For the analysis of the relationship between PROMs and PA, aspiration-specific symptoms (aPROMs) were selected. Next to the commonly used EORTC QLQ-H&N35 swallowing domain (HNSW), eight items from the SWAL-QOL (Symptom Frequency) were arbitrary chosen, as they target specific choking complaints or reflect underlying mechanical insufficiencies that may compromise swallowing safety. The scaling of PROMs was modified to scores ranging from 0 to 100 according to the scoring manual, in which higher scores represent more complaints. To investigate the level of association between aPROMs and PA, a multivariate general linear model with correction for baseline covariates (MANCOVA) was used. To validate the statistical significance (p-values), resulting from the analytical F-test in the MANCOVA, an additional numerical permutation test was performed. The correlation of the binary endpoint (PA_T6) with CTCAEasp/ CTCAEdys was analysed using univariable and stepwise multivariable logistic regression with bootstrapping and correction for clinical factors. Stepwise selection procedure resulted in the *basic model* for PA_T6 (i.e. model based on patient/ tumour and treatment characteristics only). aPROMs showing significant associations with PA at any time-point in the MANCOVA were used in subsequent logistic regression analyses (uni-/multivariable with bootstrap and stepwise selection) to investigate their predictive value. First, a *diagnostic model* for PA_T6 was built by adding aPROMs_T6 as candidate predictors to the basic model. Subsequently, to explore if baseline aPROMs have any predictive value for PA_T6, a *baseline prediction model* for PA_T6 was built by adding baseline aPROMs as candidate predictors.

All analyses were performed using SPSS statistics 23 or R software version 3.5.2. For MANCOVA and logistic regressions a multivariate imputation by chained equations (MICE) in R was used to account for missing data (Table S4/S5), as it has been shown that it may reduce the bias [36-38]. The level of statistical significance was determined by 2-tailed p value <0.05 for all analyses.

Results

VF findings are summarized in Table 2. Part A shows the prevalence analysis using dichotomous scale. Part B includes rates of changes (i.e. stable status, deterioration or improvement) from baseline to T6, using ordinal/ discrete scale. Part C includes normalization rates based on ordinal scale, i.e. the percentage of patients with any aberration at baseline (PAS > 2, MBSImP > 0 and residue > 5%) that normalized completely at T6 (assuming normalization as: PAS 1–2, MBSImP = 0 and residue $\leq$ 5%).

All cases of aspiration were scored as silent aspiration (PAS 8), except for one case at baseline and one (other) at T6, having PAS score 7. The baseline prevalence of penetration/aspiration increased significantly after treatment from 20% to 43% (p < 0.001). Of all 133 patients without penetration or aspiration at baseline, any deterioration was seen in 47 (35%) patients (36/47 had stage III-IV disease (TNM v.7) and 40/47 received bilateral RT). Eleven of 15 patients (73%) with aspiration at baseline had persistent aspiration after treatment (10/11 had stage III-IV disease and 6/11 received bilateral RT). Of the 34 patients having penetra-

Table 2
Results of videofluoroscopic swallowing assessment at baseline (T0) and 6 months after treatment (T6). Descriptive analysis.

VF scale	VF parameter	T0 rate [1]	T6 rate[1]	p value"	Impovement[2] (T6 vs T0)	Stable status[2] (T6 vs T0)	Deterioration[2] (T6 vs T0)	% Normalisation rate/ (N normalized T6/N aberrant T0)[2]
PAS	Penetration PEN (PAS 3–5)	12%	18%	0.143	31%	26%	42% (SA)	32% (6/19)
	Silent Aspiration SA (PAS = 8)	8%	25%	^0.000	27%	73%	n.a.	27% (4/15)
	Penetration/Aspiration PA (PAS 3–8)	20%	43%	^0.000	6%	61%	32%	26% (9/34)
MBSImP	Initiation of Pharyngeal Swallow IPS	91%	97%	0.035	8%	79%	13%	0.6% (1/165)
	Laryngeal Elevation LE	37%	57%	^0.000	14%	51%	35%	1.2% (2/164)
	Anterior Hyoid Excursion AHE	4%	12%	^0.003	5%	83%	12%	3.7% (6/166)
	Laryngeal Vestibular Closure LVC	33%	55%	^0.000	8%	63%	29%	18% (11/58)
	Pharyngeal Contraction PC	5%	12%	0.008	5%	77%	18%	4% (6/147)
	Pharyngoesophageal Segment Opening PSO	33%	39%	0.081	15%	61%	24%	2.4% (4/161)
	Tongue Base Retraction TBR	21%	31%	0.033	24%	45%	31%	3.0% (5/166)
RESIDUE	Oral residue ORES	45%	44%	0.892	33%	29%	38%	38% (28/74)
	Pharyngeal residue PRES	64%	79%	0.005	23%	23%	54%	15% (17/110)
			A			**B**		**C**

A: Prevalence of VF disorders: T0 vs T6 with significance levels; B: status of VF parameters at T6 relative to baseline; C: normalization rate (i.e. PAS = 1–2; MBSImP = 0; residue = 0–5%) of VF parameters at T6 relative to baseline. PAS- Penetration Aspiration Scale, MBSImP-Modified Barium Swallowing Impairment Profile.
[1] Dichotomous endpoint; [2] Ordinal/discrete endpoint.
^Significant after Bonferroni correction ($p < 0.00416$).
"McNemar's test.

tion or aspiration at baseline, the majority (74%) remained stable or deteriorated further over time. Normalization was seen in only nine of 34 patients (26%) (Table 2C).

In total, 45% of the patients included had laryngeal cancer, of which the majority (29%) had glottic cancer. Of this group, 26% had PA at baseline and 47% at T6. For pharyngeal tumours, the prevalence of PA was 16% and 41% at T0 and T6, respectively. This difference might suggest a more profound direct impact of the disease itself on PA in laryngeal cancer, especially given the distribution of disease stage III-IV (72% and 39% for pharyngeal and laryngeal tumours respectively) and hence, more aggressive treatment for pharyngeal tumours. However, tumour location was not significantly correlated with PA_T6 in univariable analysis. Also, the multivariable analysis resulted in best performing basic model for PA_T6 (AUC 0.81) with four other clinical factors: PA at baseline, disease stage III-IV, bilateral RT and age (Table 3A).

The prevalence of moderate/severe physiological deterioration increased significantly over time for almost all MBSImP swallowing components. The most profound increase was noted for *Laryngeal Vestibular Closure (LVC), Laryngeal Elevation (LE), Tongue Base Retraction (TBR)* when analysed using dichotomous (Table 2A) as well as original ordinal (0 to 2–4) scale (Table B). In the multivariable analysis, three MBSImP components appeared the most predictive for PA at T6: LVC, LE and PC (*Pharyngeal Contraction*) (AUC: 0.82) with the highest odds ratio for LVC (OR 14) (Table S6).

In general, oral function was relatively well-preserved after treatment. In contrast, pharyngeal function was more prone to radiation damage resulting in excessive pharyngeal residue in more than 60% of cases (Table 2). This difference in deterioration level of oral and pharyngeal function may be a reflection of specific tumour site distribution: larynx/ hypopharynx 53%, oropharynx 32%, oral cavity 4%, others 11%. The majority had the tumour, and subsequently a high dose region, localized in the pharyngeal part of the swallowing tract. Results for OPSE are summarised in Table S7.

The prevalence of the CTCAE scores is summarized in Table 4. When analysed using dichotomous scale, the prevalence of CTCAEasp (symptomatic aspiration) at baseline was 0.6% (1 patient) and remained low at T6 (6 patients, 3.6%). The prevalence of CTCAEdys (grade $\geq$ 2) increased significantly from 7.7% to 19.6% at T6. In univariable analysis, only CTCAEdys significantly correlated with PA_T6. However, after correction for clinical factors (multivariable stepwise selection) it lost its significance and did not enter the diagnostic model (Table 3B).

All but one *(food sticking in throat)* of the aPROMS significantly deteriorated after treatment (Table S8). All aPROMs showed significant associations with VF-based PA in MANCOVA and, hence, some diagnostic consistency with VF (Table S9). In multivariable logistic regression two items (including "*Choking when eating_T6*" and *"Choking when drinking_T6*") entered de *diagnostic model*, improving basic model performance (AUC 0.86 vs. AUC 0.81) (Table 3B). One baseline item: "*Choking when drinking_T0*" entered the *baseline prediction model* and improved basic model performance (AUC 0.84 vs 0.81) (Table 3C).

Discussion

In this study the patterns of swallowing disorders were described from baseline to 6 months after (CH)RT based on prospectively collected data: VF findings (objective evaluation), CTCAE scores and aPROMs (subjective evaluation).

In terms of swallowing safety, our analysis revealed that (chemo)radiation contributes significantly to late penetration/ aspiration in HNC survivors. Substantial percentage of analysed patients developed PA or experienced its worsening after treatment. Subsequently, normalisation rate for PA and especially for all physiological parameters (MBSImP) was consistently low (Table 2C). This is in line with previous suggestions. Moreover, other series indicate not only the occurrence of late RT-induced aspiration (reported range 18–81%) but also its progressive character [21,39-41]. Furthermore, bilateral RT was one of four clinical predictors for late penetration/aspiration. These findings show that the treatment, primarily administered to cure the disease and preserve the organ, may itself jeopardize its function, leading to aspiration. Other clinical predictors were disease stage, age and baseline PA. The correlation with age and T stage was also reported by others [1,40] but baseline PA status is often lacking, what may create a bias [42-44].

Our results confirm that aspiration diagnosed for HNC patients is often silent. As hypothesized by Eisbruch et al., decreased neural

Table 3
Uni- and multivariable logistic regression with stepwise selection resulting models for penetration/aspiration (PA_T6).

A: basic model			B: diagnostic model_T6			C: baseline prediction model		
Variables	Univariable		Variables	Univariable		Variables	Univariable	
	Coeff	*p*-value		Coeff	*p*-value		Coeff	*p*-value
TNM stage (III–IV)	1.692	0.000	**aPROMs_T6**			**aPROMs_T0**		
T stage (T3–4)	1.790	0.000	CHOKING WHEN EATING	0.040	0.000	CHOKING WHEN EATING	0.026	0.000
N stage (N+)	1.088	0.000	CHOKING WHEN DRINKING	0.041	0.001	CHOKING WHEN DRINKING	0.033	0.001
Bilateral RT	1.730	0.000	GAGGING	0.027	0.000	GAGGING	0.027	0.000
PA at baseline	1.513	0.000	HAVING EXCESS SALIVA OR PHLEGM	0.029	0.001	HAVING EXCESS SALIVA OR PHLEGM	0.031	0.001
Chemotherapy	1.268	0.000	HAVING TO CLEAR THROAT	0.024	0.000	HAVING TO CLEAR THROAT	0.044	0.000
Gender (female)	0.491	0.212	FOOD STICKING IN THROAT	0.023	0.001	FOOD STICKING IN THROAT	0.010	0.145
Age	0.024	0.110	FOOD STICKING IN MOUTH	0.016	0.000	FOOD STICKING IN MOUTH	0.012	0.018
Tumor location (larynx)	0.016	0.846	COUGHING FOOD WHEN IT STUCK	0.035	0.000	COUGHING FOOD WHEN IT STUCK	0.037	0.000
			HN35-SW	0.033	0.000	HN35-SW	0.035	0.000
			CTCAEdys	0.782	0.028			
			CTCAEasp	0.947	0.192			
Variables in model	Multivariable		Variables in model	Multivariable		Variables in model	Multivariable	
	Coeff	AUC		Coeff	AUC		Coeff	AUC
PA at baseline	1.584	apparent 0.81	PA at baseline	1.550	apparent 0.86	PA at baseline	1.455	apparent 0.84
TNM stage (III–IV)	1.347		TNM stage (III-IV)	1.439		TNM stage (III-IV)	1.568	
Bilateral RT	1.283		Bilateral RT	1.176		Bilateral RT	1.232	
Age	0.052	corrected 0.77	Age	0.029	corrected 0.82	Age	0.054	corrected 0.79
			CHOKING WHEN DRINKIN_T6	0.022		CHOKING WHEN DRINKING_T0	0.038	
			CHOKING WHEN EATING_T6	0.020				
Intercept	−5.246		Intercept	−4.498		Intercept	−5.840	

A: Correlation between PA_T6 and clinical factors; basic model for PA_T6.
B: Correlation between PA_T6 and both subjective measures: aPROMs_T6 and CTCAE_T6; diagnostic model for PA_T6.
C: Correlation between PA_T6 and baseline aPROMs_T0; baseline prediction model for PA_T6.

transmission/sensibility of pharyngeal mucosa and subsequent suppression of laryngeal closure and coughing reflex may play a role in RT-induced aspiration [45-47]. In our series almost all aspirations noted at baseline were also silent. This may suggest the occurrence of the same phenomenon of sensory loss due to tumour infiltration and accompanying inflammation beside direct damage to other, non-neural tissues. Although without data on baseline status, Jensen et al. demonstrated reduced sensitivity of pharyngeal mucosa in 97% of examined late HNC survivors using FEES [20]. As it might determine the silent nature of aspiration, FEES-based sensory loss could be a useful parameter to guide the clinical practice in HNC population. VF, on the other hand, gives more insights in specific pathophysiological mechanism of aspiration [48,49]. For targeted management of dysphagia it does make a difference in which mechanism the aspiration occurs (e.g. swollen epiglottis, reduction of pharyngeal contraction, tongue base retraction or hyolaryngeal elevation) [35]. Such management would include swallowing rehabilitation as well as swallowing-sparing radiation strategies focused on specific aspiration-related structures (for instance: floor of mouth/ thyrohyoid muscles in case of reduced hyolaryngeal elevation) [40,45,46,50,51]. However, to exploit VF to that level, certain expertise is required. MBSImP is a great tool, but to use it in practice (apply and translate into targeted intervention) a certified Speech Language Pathologist (SLP) must be available, which may be a logistical challenge for some institutions [10]. It is worth mentioning though, that, despite somewhat contradicting data, there are many series suggesting that (prophylactic) exercises and especially targeted swallowing maneuvers applied by SLPs may be beneficial for HNC patients [48,52,53]. Typically, penetration/aspiration still remains the most relevant clinical end-point. Nevertheless, in the framework of this prospective study, MBSImP enabled a deeper exploration of objective findings, including baseline VF. We were able to confirmed previous suggestions [3,7,14] that *laryngeal vestibular closure, hyolaryngeal elevation, tongue base retraction* and *pharyngeal contraction* are the most prone to radiation damage and /or significantly correlated with PA (Table S6). And although the LVC appeared to have the highest predictive value for PA, the role of entire anterior swallowing apparatus should not be underestimated as it extends beyond the larynx itself [47,54-57].

The practical implication for radiation oncology community is that not all structures involved in these swallowing components (i.e. aspiration related OARs) are commonly defined as swallowing-related OARs (SWOARs) [50,58] and therefore potentially at risk of unintentional damage [59]. Moreover, robust NTCP models for VF- aspiration, exploring all aspiration-related-OARs (defined as previously proposed) [60] and including baseline data are lacking [42,43].

Table 4
Prevalence of physician-rated dysphagia and aspiration. CTCAE v.4.0.

CTCAE_DYSPHAGIA *			CTCAE_ASPIRATION		
	T0	T6		T0	T6
Grade 1	92.3%	80.3%	Grade 1	99.4%	96.7%
Grade 2	7.1%	10.9%	Grade 2	0.6%	2.7%
Grade 3	0.6%	8.7%	Grade 3	0.0%	0.6%
Grade 4/5	0.0%	0.0%	Grade 4/5	0.0%	0.0%

*Statistically significant difference T0 vs T6.

Another important implication of presented results is the relevance of analysed aPROMs. Patients with choking complaints 6 months after treatment, especially those with advanced disease stage and older age (diagnostic model, Table 3B), should be referred to SLP for follow-up VF and swallowing intervention. Of note is that these results regard 6 months follow-up time-point, but in general patient-rated symptoms tend to recover partly in the first 2 years whereas aspiration rates tend to increase over time [41,61]. Furthermore, beforehand prediction (baseline prediction model, Table 3C) of late PA could help tailoring more personalized swallowing aftercare as well as referral for baseline VF. Also, future NTCP models for aspiration should consider baseline aPROMs and, certainly, the dose to all aspiration-related-OARs as candidate predictors. Recently Van den Bosch et al. proposed a concept of individually optimized radiation treatment based on comprehensive toxicity risk profiling [62]. Although, consistent, preferably multicenter, prospective data collection and, thus, robust modeling of VF aspiration is challenging, it would make sense to include such models in the modern HNC NTCP set [40,62],

CTCAE scores after treatment were not predictive for late penetration/aspiration. These findings confirm that objective and physician-rated (subjective) evaluation are not interchangeable, which has been supported by other studies [12,14,16,63]. The most likely explanation is the silent nature of almost 60% of PA events and thus, low prevalence of CTCAEasp (symptomatic aspiration). Also, CTCAEdys score, evaluating swallowing problems and subsequent dietary changes, appeared to be not sensitive for PA. In fact, 94% of patients demonstrating PA on VF did not report aspiration complaints (choking) in the consultation room and 80% of them did not report any moderate-to-severe swallowing complaints in anamnesis. The implication of this fact is that these patients, without knowing, may still be at risk of aspiration pneumonia (AspPn), with the mortality rate of up to 20% [1,64]. As our study did not specifically aim to assess aspiration pneumonia (AspPn), the lack of prospective data on this complication is a certain limitation. However, recently published meta-analysis showed that VF aspiration was significantly associated with AspPn [65]. Hunter et al. reported that late aspiration after (CH)RT was an independent predictor of AspPn. The authors concluded that reducing RT-induced aspiration rates is likely to reduce the risk of AspPn, which occurred in 15% and 20% 2 and 3 years after treatment respectively. Finally, they also found that observer-rated CTCAE dysphagia had no predictive value for AspPn in contrast to patient-reported complaints, what, despite different end-point, stays in line with our results [1]. Finally, Shune et al. showed negative impact on survival rates in patients with aspiration after radiotherapy [66].

Conclusion

RT-induced late penetration/aspiration is prevalent. Age, disease stage, baseline PA, bilateral RT and baseline patient-rated choking complaints are the best predictors of late penetration/aspiration. Presented prediction models may contribute to better discrimination of high-risk patients, needing VF and swallowing therapy applied by SLPs. Also, enhanced collaboration between radiation oncologists and SLPs, would result in a higher awareness of each other's scope [67]. This could stimulate proactive rather than reactive multidisciplinary management of dysphagia.

Moreover, as physician-rated CTCAE swallowing evaluation does not cover the entire spectrum of dysphagia in HNC patients, there is an emerging need for VF assessment in the standard follow-up programs. Developing robust prediction tools (e.g. NTCP models) for radiation-induced PA could possibly serve as an equivalent. Inclusion of aspiration specific PROMs as well as the dose to all aspiration-related OARs in NTCP modelling should be considered. The insights into pathology of swallowing mechanics presented in this paper as well as a clear definition of all aspiration-related-OARs proposed previously, support robust and hypothesis driven modelling [50,60].

Funding statement

The study described in the paper was part of a larger project granted by the Dutch Cancer Society (RUG 2008-3983).

Conflict of Interest Statement

A. Gawryszuk:
Grant by the Dutch Cancer Society
I.M. Verdonck-de Leeuw:
Grant by the Dutch Cancer Society.
J.A. Langendijk:
Grant by the Dutch Cancer Society.
The department has research collaboration with IBA, RaySearch, Siemens, Elekta, Leonie and Mirada.
Honoraria from IBA and RaySearch are paid to UMCG Research B.V.
Consultant International Scientific Advisory Committees of IBA and RaySearch.
COI disclosure forms from each author have been submitted separately.

Acknowledgements

The study described in the paper was part of a larger project granted by the Dutch Cancer Society (RUG 2008-3983).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.09.017.

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