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FULL PAPER

Clinical factors impacting on late dysphagia following radiotherapy in patients with head and neck cancer

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Objective: Patient and treatment characteristics of patients with head and neck cancer (HNSCC) were correlated with dysphagia scored on swallowing-videofluoroscopy (VFS) and with patient- and physician-scored dysphagia.

Methods: 63 HNSCC patients treated with radiotherapy (RT) were evaluated at baseline, and 6 and 12 months post-RT. VFS was scored with Penetration Aspiration Scale (PAS) and Swallowing Performance Scale (SPS). Physician- and patient-scored dysphagia were prospectively recorded according to Common Terminology Criteria for Adverse Events scoring system, Radiation Therapy Oncology Group/EORTC scoring system and European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ H&N35).

Results: Univariable analysis revealed a significant association between tumour-subsite and higher SPS ($p = 0.02$) and patient-scored dysphagia ($p = 0.02$) at baseline. At 12 months, tumour-subsite was significantly associated with higher PAS and SPS. Multivariable analysis and pairwise comparison showed that hypopharyngeal

cancer and carcinoma of unknown primary were associated with higher SPS at baseline and at 12 months, respectively ($p = 0.03$ and $p = 0.01$). Upfront neck dissection (UFND) was significantly associated with higher SPS and physician-scored dysphagia in univariable analysis at all timepoints. At 12 months, there was also a significant association with higher PAS ($p < 0.01$) and patient-scored dysphagia ($p < 0.01$). After multivariable analysis, the association between UFND and higher PAS ($p < 0.01$) and SPS ($p < 0.01$) remained significant at 12 months.

Conclusion: Hypopharyngeal tumours and carcinoma of unknown primary were related to more dysphagia at baseline and at 12 months, respectively. Furthermore, UFND was associated with more severe dysphagia scored by physicians and patients and on VFS at 12 months.

Advances in knowledge: This is the first paper reporting a significant link between UFND and late dysphagia scored with VFS. We advocate abandoning UFND and preserving neck dissection as a salvage option post-RT.

INTRODUCTION

Radiotherapy (RT), alone or in combination with chemotherapy, has emerged as one of the most used treatment modalities in head and neck squamous cell carcinoma (HNSCC).¹ Treatment with RT can cause severe acute and late toxicity, in particular xerostomia and dysphagia, influencing the quality of life (QoL) of patients with HNSCC.² Many research projects have focused on diminishing the toxicity without compromising the oncological outcome in HNSCC. The incidence of xerostomia is reduced by the introduction of parotid-sparing intensity-

modulated radiotherapy, but late dysphagia remains a major problem.^{3–5} Swallowing is a complex interaction involving multiple muscles and nerves, and radiotherapy-induced changes, such as fibrosis in one or multiple swallowing-related muscles, can cause dysphagia.⁶ It is well established that the dose to the pharyngeal constrictor muscles, glottis and supraglottic larynx, plays a crucial role in the development of severe late dysphagia.^{7–11} These anatomical structures related to swallowing and swallowing dysfunction are called swallowing organs at risk (SW-OAR). The radiation oncologist delineates

these SW-OAR on the RT planning-CT in daily clinical practice.¹² They strive to keep the dose on these SW-OAR as low as possible. Nonetheless, reducing the dose on the SW-OAR is often troublesome because of their close proximity to the elective nodal volume and to the tumour.

To this end, our research group included 200 patients in a randomized controlled trial reducing the dose on the elective nodal volume from an equivalent dose in 2 Gy fractions (EQD2Gy) of 50 Gy to an EQD2Gy of 40 Gy without compromising the therapeutic coverage. The hypothesis was that the reduction in dose on the elective nodal volume would result in a reduction of the acute and late side effects.^{13,14}

3 months post-RT, the elective dose de-escalated group showed significantly less severe acute dysphagia ($\geq$ Grade 3).¹⁴ At 6 months, however, only a trend towards less dysphagia was observed and this trend could not be observed at later time-points. In this prospective randomized study, reduction of the dose to the elective nodal volume did not result in a clear benefit in terms of decrease in late dysphagia.¹³ Other factors, specific to the patient or the treatment, may contribute to the development of severe dysphagia.

The aim of this study was therefore to evaluate the role of patient and treatment characteristics on dysphagia in a patient population treated within a randomized controlled trial. Since dysphagia can be scored by various objective and subjective measuring scales, we chose to use dysphagia scored on swallowing-videofluoroscopies (VFS) as well as patient- and physician-scored dysphagia.

METHODS AND MATERIALS

Patient and treatment characteristics

The current paper is an additional analysis of a prospective randomized controlled trial on dose de-escalation to the elective nodal volume in head and neck cancer.¹⁴ An overview of the inclusion criteria, the different fractionation schedules and Clinical and Planned Target Volume margins can be found in the first analysis of this trial.^{13,14} Treatment plans were planned using intensity-modulated radiotherapy and tumours were classified according to the American Joint Committee on Cancer seventh TNM edition.¹⁵ Upfront neck dissection (UFND) was allowed, as well as concomitant chemoradiotherapy (CRT). CRT consisted of cisplatin 100 mg m⁻² three-weekly or cisplatin 40 mg m⁻² weekly. Local ethics committee approval was obtained before start of the study and all patients gave written informed consent.

In two participating centres, patients received a VFS before the start of the RT, at 6 months and at 12 months following the end of treatment. Patients from the original trial lacking pretreatment VFS were excluded from the current analysis. This resulted in the current study population of 63 patients to be further analysed. None of the included patients had tumour recurrence at the time of post-treatment analysis.

VFS protocol and dysphagia scoring

Dysphagia was rated on VFS, by the patients themselves and by the treating physician before the start of the RT, at 6 months and at 12 months following the end of the therapy. VFS is a radiological evaluation of swallowing during which patients were given first a 5 cc liquid bolus, subsequently a 10 cc liquid bolus and then a more concentrated 10 cc bolus. When feasible, a piece of bread with a contrast agent (Micropaque® Barii Sulfas Guebert, France) was administered as well. In those patients considered at risk for aspiration, a low osmotic iodine agent was used (Ultravist®). Pulse and frame rate were 15 s. The images were digitalised and scored blindly by two trained supervisors with at least 20 years of experience in the evaluation of VFS (coauthors AG and ED). Severity of dysphagia on VFS was quantified by each observer using the Swallowing Performance Scale (SPS), ranging from 1 to 7, and the Penetration Aspiration Scale (PAS), ranging from 1 to 8, in accordance with the criteria shown in the [Supplementary Material 1](#). SPS provides an accurate assessment of the presence and severity of dysphagia and aspiration risk by combining clinical and radiographic data.¹⁶ PAS describes penetration and aspiration events. The scores are primarily determined by the depth through which the bolus passes in the airway and by whether or not the bolus entering the airway is expelled.¹⁷

Afterwards we calculated the inter-rater agreement between the two observers and made a consensus scoring for the PAS and SPS based on the highest score of the two observers for every patient at every timepoint (baseline, 6 months, 12 months).

Data on patient-scored dysphagia was collected with the EORTC-QLQ H&N35 quality of life swallowing questionnaire, consisting of four questions.¹⁸ All scores were analysed at the start of RT, at 6 months and at 12 months. The answers were scaled and scored using the recommended EORTC Quality of Life Group procedures. Raw scores were transformed into a linear scale ranging from 0 to 100. We compared the baseline mean scores to reference data as suggested by EORTC.^{19,20}

In addition, the treating physician prospectively scored dysphagia using the Common Terminology Criteria for Adverse Events version 3 toxicity scoring pre-RT and the Radiation Therapy Oncology Group (RTOG)/EORTC late radiation morbidity scoring post-RT.²¹

STATISTICS

To determine the inter-rater agreement between both observers, the intraclass correlation coefficient (ICC), according to the Shrout and Fleiss convention, was calculated.²² The ICC takes values between 0 and 1 with higher values indicating higher levels of agreement.

Proportional odds models for ordinal variables were used to look at the link between the different patient or treatment characteristics and dysphagia scored by the physician. Linear regression models were used for patient-scored dysphagia, PAS and SPS. Random effects were modelled to deal with longitudinal measurements. For all associations, the interaction with time was tested. A significant interaction with time means that the association between

the variables is different between the three timepoints (baseline, 6 months, 12 months). In such a case, results are reported per time-point. In the absence of an interaction effect, the main effect is presented. Pairwise tests were done in case of a significant global effect. Multivariable analysis was performed to correct for specific confounders. All tests were two sided, and a 5% significance level was assumed for all tests. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows). No correction for multiple testing has been done.

RESULTS

Patient characteristics

Patient characteristics are listed in [Table 1](#). 63 patients received a baseline VFS, 54 of those patients received an additional VFS at 6 months of follow-up and 39 patients received an additional VFS at 12 months. All patients answered the EORTC-QLQ H&N35 swallowing questionnaire, and dysphagia was scored by their treating physician before RT and during follow-up.

Table 1. Patient and treatment characteristics at baseline, at 6 months and at 12 months

Patient and treatment characteristics			
	Baseline	6 months	12 months
Gender			
Female	12/63 (19.05%)	10/54 (18.52%)	10/39 (25.64%)
Male	51/63 (80.95%)	44/54 (81.48%)	29/39 (74.36%)
Age			
Mean (Range)	61.4 (38; 80)	61.6 (38; 80)	61.3 (38; 80)
Dose to the elective neck			
40 Gy	46/63 (73.02%)	42/54 (77.78%)	29/39 (74.36%)
50 Gy	17/63 (26.98%)	12/54 (22.22%)	10/39 (25.64%)
Upfront neck dissection			
No	42/63 (66.67%)	33/54 (61.11%)	29/39 (74.36%)
Yes	21/63 (33.33%)	21/54 (38.89%)	10/39 (25.64%)
Tumour-subsite			
CUP	4/63 (6.35%)	4/54 (7.41%)	3/39 (7.69%)
Hypopharynx	15/63 (23.81%)	14/54 (25.93%)	7/39 (17.95%)
Larynx	11/63 (17.46%)	8/54 (14.81%)	8/39 (20.51%)
Oropharynx	33/63 (52.38%)	28/54 (51.85%)	21/39 (53.85%)
T			
CUP	4/63 (6.35%)	4/54 (7.41%)	3/39 (7.69%)
1	4/63 (6.35%)	4/54 (7.41%)	4/39 (10.26%)
2	24/63 (38.10%)	18/54 (33.33%)	15/39 (38.46%)
3	19/63 (30.16%)	18/54 (33.33%)	11/39 (28.21%)
4	12/63 (19.05%)	10/54 (18.52%)	6/39 (15.38%)
N			
0	10/63 (15.87%)	9/54 (16.67%)	8/39 (20.51%)
1	10/63 (15.87%)	9/54 (16.67%)	7/39 (17.95%)
2a	3/63 (4.76%)	3/54 (5.56%)	2/39 (5.13%)
2b	22/63 (34.92%)	18/54 (33.33%)	11/39 (28.21%)
2c	18/63 (28.57%)	15/54 (27.78%)	11/39 (28.21%)
Concomitant chemotherapy			
No	25/63 (39.68%)	21/54 (38.89%)	18/39 (46.15%)
Yes	38/63 (60.32%)	33/54 (61.11%)	21/39 (53.85%)

CUP, cancer of unknown primary; Gy, Gray.

All staging is per American Joint Committee on Cancer seventh edition

Table 2. Univariable analysis: Correlation of Penetration Aspiration Scale (PAS) with clinical factors

PAS		Baseline	6 months	12 months	
				<i>p</i> -value	Estimate (95% CI)
Tumour-subsite	Global effect	NS	NS	0.043	
	CUP <i>vs</i> hypopharynx			0.025	3.00 (0.34;5.60)
	CUP <i>vs</i> oropharynx			0.0144	2.95 (0.63;5.28)
	CUP <i>vs</i> larynx			0.0052	3.75 (1.20;6.30)
UFND	Yes <i>vs</i> No	NS	NS	0.0003	2.56 (1.27;3.90)

95% CI, 95% confidence interval; CUP, carcinoma of unknown primary; NS, not significant; UFND, Upfront neck dissection.

p-value is given in case of a significant association. Pairwise test for tumour-subsite is given in case of a significant global effect. Risk estimate > (<) 0 means higher (lower) score for the first written element.

Bold values represents statistical significant results.

Dysphagia scoring

The ICC values for the agreement regarding the PAS and SPS scoring between both observers demonstrated a fair level of inter-rater agreement for SPS (range 0.56–0.75) and a good level of agreement for PAS (range 0.64–0.94). Agreement seemed to be better for pretherapy measurements than at 6 or 12 months (Supplementary Material 1). For further analysis we used the consensus scoring.

The mean EORTC-QLQ H&N35 baseline swallowing score was 23.4 with a standard deviation of 7.17. This incidence of patient-scored dysphagia was comparable to the data regarding QoL in the EORTC reference group containing 2235 patients with all stages of head and neck cancer.^{19,20} At baseline, half of the patients had grade 0 physician-scored dysphagia, and 28.6 and 22.2% were scored Grade 1 and Grade 2 dysphagia, respectively. The incidence of patient- and physician-scored dysphagia at the three timepoints is presented in Supplementary Material 1.

Correlation of patient and treatment-related factors with dysphagia

Association with swallowing-videofluoroscopy

Concerning patient-related factors, we observed a significant interaction with time in the correlation of tumour-subsite with PAS and SPS scores. This means that the association of tumour-subsite with PAS and SPS was different between the three timepoints (Tables 2–3). At 12 months, patients with carcinoma of unknown primary (CUP) had higher mean PAS scores compared to patients with the primary tumour located in the oropharynx, hypopharynx or larynx. SPS scores were significantly different depending on tumour-subsite at baseline ($p = 0.02$) and at 12 months ($p < 0.01$). Specifically, tumours in the hypopharynx were associated with higher mean SPS scores at baseline while patients with CUP had higher mean SPS scores at 12 months. Higher N-classification according to the TNM stage was significantly associated with higher SPS scores ($p = 0.03$). Other patient-related factors, such as

Table 3. Univariable analysis: Correlation of Swallowing Performance Scale (SPS) with clinical factors

SPS		Baseline		6 months		12 months	
		<i>p</i> -value	Estimate (95% CI)	<i>p</i> -value	Estimate (95% CI)	<i>p</i> -value	Estimate (95% CI)
Tumour-subsite	Global effect	0.020		NS		0.001	
	Hypopharynx <i>vs</i> oropharynx	0.0022	1.47 (0.56;2.40)			NS	
	Hypopharynx <i>vs</i> larynx	0.0352	1.26 (0.09;2.43)			NS	
	CUP <i>vs</i> hypopharynx	NS				0.0183	2.19 (0.34;3.99)
	CUP <i>vs</i> oropharynx	NS				0.0019	2.67 (1.06;4.27)
	CUP <i>vs</i> larynx	NS				<0.0001	3.83 (2.07;5.60)
N-classification		0.029	0.29 (0.02;0.43)	0.029	0.29 (0.02;0.43)	0.029	0.29 (0.02;0.43)
UFND	Yes <i>vs</i> No	0.022	0.86 (0.13;1.59)	0.035	0.82 (0.13;1.59)	<0.0001	2.17 (1.21;3.13)

95% CI, 95% confidence interval; CUP, carcinoma of unknown primary; NS, not significant; UFND, Upfront neck dissection.

p-value is given in case of a significant association. Pairwise test for tumour-subsite is given in case of a significant global effect. Risk estimate > (<) 0 means higher (lower) score for the first written element or for a higher N-level. For the N-classification the association was identical at the three timepoints.

Bold values represents statistical significant results.

Table 4. Multivariable analysis: Correlation of Penetration Aspiration Scale (PAS) with clinical factors

PAS		baseline	6 months	12 months	
				<i>p</i> -value	Estimate (95% CI)
Tumour-subsite	Global effect	NS	NS	NS	
UFND	Yes vs No	NS	NS	0.0003	2.61 (1.24;3.99)

95% CI, 95% confidence interval; NS, not significant; UFND, Upfront neck dissection.

p-value is given in case of a significant association. Risk estimate > (<) 0 means higher (lower) score for the first written element.

Bold values represents statistical significant results.

gender, age and T-classification were not significantly associated.

Next, we analysed the effect on dysphagia of two treatment-related factors, UFND and treatment with concomitant chemotherapy. Patients with UFND had higher mean PAS scores than patients without UFND but the difference in PAS scores between both groups was only significant at 12 months ($p < 0.01$). Moreover, patients with UFND had significantly higher mean SPS scores at all three timepoints (baseline $p = 0.02$; 6 months $p = 0.04$, 12 months $p < 0.01$). Treatment with concomitant chemotherapy was not significantly associated with the development of late dysphagia scored on VFS.

In case a significant effect was found in the univariable analysis, we redid the analysis with correction for possible confounders (Tables 4–5). First, we analysed in multivariable analysis the influence of UFND on the association between tumour-subsite and PAS or SPS. There was no longer a significant interaction between tumour-subsite and PAS score although tumour-subsite and SPS scores remained significantly associated at baseline and at 12 months ($p = 0.04$ and 0.01 , respectively). After pairwise comparison, hypopharyngeal cancer was associated with higher mean SPS scores compared to oropharyngeal cancer at baseline. At 12 months, CUP was associated with higher mean SPS scores compared to oropharyngeal and laryngeal cancer.

Second, the effect of UFND on the PAS and SPS scores was corrected for tumour-subsite in multivariable analysis. UFND

remained significantly associated with higher PAS scores ($p < 0.01$) and SPS scores ($p < 0.01$) at 12 months. The association between UFND and higher SPS scores at baseline and at 6 months was no longer significant after correction for tumour-subsite.

Association with patient scored dysphagia

Tumour-subsite was only significantly associated with patient-scored dysphagia at baseline ($p = 0.02$). Pairwise test revealed that especially hypopharynx tumours result in more baseline dysphagia compared to oropharynx tumours and CUP. UFND was significantly associated with patient-scored dysphagia but only at 12 months ($p < 0.01$). (Supplementary Material 1).

Association with physician-scored dysphagia

UFND and higher N-classification were significantly associated with higher physician-scored dysphagia ($p < 0.01$ and $p = 0.02$, respectively). The association was similar at the three timepoints. There was no significant correlation between tumour-subsite and physician-scored dysphagia (Supplementary Material 1).

In our analysis, gender, age, higher T-classification and the use of concomitant chemotherapy were never significantly associated with higher dysphagia scores independent of the measuring method.

DISCUSSION

The aim of this study was to evaluate if patient and treatment characteristics of patients with head and neck cancer were

Table 5. Multivariable analysis: Correlation of Swallowing Performance Scale (SPS) with clinical factors.

SPS		Baseline		6 months	12 months	
		<i>p</i> -value	Estimate (95% CI)		<i>p</i> -value	Estimate (95% CI)
Tumour-subsite	Global effect	0.0351		NS	0.0111	
	Hypopharynx vs oropharynx	0.0041	1.36 (0.45;2.26)		NS	
	Hypopharynx vs larynx	NS			NS	
	CUP vs hypopharynx	NS			NS	
	CUP vs oropharynx	NS			0.0054	1.95 (0.62;3.28)
	CUP vs larynx	NS			0.0016	2.58 (1.05;4.10)
UFND	Yes vs No	NS		NS	<0.0001	2.02 (1.05;2.98)

95% CI, 95% confidence interval; CUP, carcinoma of unknown primary; NS, not significant; UFND, Upfront neck dissection.

p-value is given in case of a significant association. Pairwise test for tumour-subsite is given in case of a significant global effect. Risk estimate > (<) 0 means higher (lower) score for the first written element.

Bold values represents statistical significant results.

correlated with dysphagia scored on VFS and with patient- and physician-scored dysphagia.

Dysphagia remains a very common complaint before and after treatment of HNSCC. It is well known to compromise the health-related QoL of patients.²³ Dysphagia leads to nutritional deficiency, weight loss and prolonged use of feeding tube and can cause potential life-threatening events in case of aspiration.²⁴

Swallowing problems are quantified in the literature by different objective or subjective scales and measurements. For this study, we chose two objective scales (PAS and SPS) and two subjective scales (patient- and physician-scored dysphagia) based on a recent review regarding this subject.²⁵

VFS is one of the most frequently used techniques for swallowing evaluation.²⁶ Two validated scales were used to evaluate the VFS by two experienced observers in a standardized manner.^{16,17,25,27,28} Levels of agreement between both observers were fair to excellent for both scales, when we take into account that values over 0.75 are considered as being excellent, 0.40 to 0.75 as fair to good and below 0.40 as poor.²⁹ Although many studies only rate physician-scored dysphagia,³⁰ we chose to include patient-scored dysphagia as well, since this is highly correlated with the impact on the QoL.²³

In general, patients with hypopharyngeal cancer had more severe dysphagia at baseline while CUP was associated with more severe dysphagia at 12 months. UFND was associated with higher dysphagia independent of the measuring method 12 months after CRT.

Hypopharyngeal tumours were associated with higher baseline dysphagia scored with SPS and EORTC-QLQ H&N35. At 12 months post-treatment, particularly CUP was associated with higher late dysphagia seen on VFS. In literature contradictory results are published. In Langendijk *et al*³⁰ oropharyngeal and nasopharyngeal tumour-sites were independent prognostic factors in the total dysphagia risk score for Grade 2 or higher RTOG swallowing dysfunction at 6 months, while others reported hypopharyngeal and laryngeal primary tumour-sites as independent risk factors for late dysphagia at 3 years.³¹ CUP is often treated with UFND followed by RT or CRT ([Supplementary Material 1](#)). To look at the impact of UFND on the association between CUP and late dysphagia, we performed multivariable analysis. The association between SPS scores and CUP remained significant at 12 months. Considering the small number of patients with CUP, we must be careful to draw conclusions. In both participating centres, the radiotherapy target volume for CUP includes the bilateral neck and elective mucosal irradiation. This large volume of radiotherapy may explain the association between CUP and more late dysphagia. The same reasoning can be applied to why higher N-classification is associated with more late dysphagia scored by SPS or by the physician. Higher N-classification usually results in larger volumes of the neck treated with high-dose radiotherapy.

UFND was associated with more late dysphagia. In univariable analysis we also observed a significant association between UFND and both baseline SPS scores and physician-scored dysphagia. The small time interval between the surgery and the baseline assessment could be the main reason. During UFND, patients are intubated and the tissue surrounding the SW-OAR is manipulated, which could explain this baseline observation. However, the significant association disappeared in multivariable analysis after correction for tumour-subsite at baseline. Tumour-subsite, on the other hand, remained significant after correction for UFND. Therefore tumour-subsite seems to be more influential than UFND for dysphagia at the start of the RT.

At 12 months, UFND remained significantly associated with more dysphagia in multivariable analysis independent of tumour-subsite. Different authors previously investigated the role of adjuvant neck dissection and the development of late dysphagia, but toxicity data regarding UFND is rather scarce.^{31–33} Allal *et al* and Al-Mamgani *et al* looked at the relationship between UFND and late toxicity, but neither studies could observe a difference in late dysphagia measured with the Common Terminology Criteria for Adverse Events, RTOG toxicity score or EORTC-QLQ H&N35 swallowing questionnaire, in contrast to our results.^{34,35} However, none of these papers looked at the relationship between UFND and late dysphagia on VFS. The stronger correlation between UFND and dysphagia at later timepoints suggests an important influence of fibrosis. Fibrosis after RT is a well-known late reaction induced by damage to the soft tissue by means of oxidative stress.²⁴ The additional influence of UFND is less explored, although recent research could establish the relationship between UFND and fibrosis grade ≥ 2 at 6, 12, 18 and 24 months after CRT.³⁶ In addition, there are, to our knowledge, no prospective randomized controlled trials, conducted with the current radiotherapy techniques, showing a benefit in oncological outcome for UFND compared with CRT followed by salvage neck dissection in case of persistent nodal disease.^{36–38} Although salvage neck dissection also contains a surgical risk and increases the late toxicity, only a small fraction of the patients treated with primary CRT will be exposed to this risk and extra toxicity.^{36,38} Abandoning UFND and preserving neck dissection as a salvage option could therefore diminish the late swallowing problems as fewer patients will receive both surgery and CRT.

In our analysis, the use of concomitant chemotherapy did not affect the reported or observed late dysphagia. In the literature conflicting results are published. CRT did not appear to affect severe late RT-related toxicity in a randomized controlled trial of Ghadjjar *et al*³⁹ and Machtay *et al* saw also no significant association between chemotherapy dose received and late dysphagia.³¹ On the other hand, in a large prospective study of Langendijk *et al* including 529 HNSCC patients, concomitant chemotherapy was an independent risk factor in a multivariate model for swallowing dysfunction at 6 months.³⁰ A larger study population may be needed to confirm or refute the influence of chemotherapy on late dysphagia.

We would like to draw attention to the fact that in this study, patients with baseline physician-scored dysphagia Grade 2 were included, while numerous studies exclude these patients.^{30,31} We are aware that in the follow-up it is very difficult to distinguish between treatment-related toxicity and dysfunctions caused by tumour destruction of critical normal structures. Nevertheless, by excluding Grade 2 dysphagia or higher, a considerable part of the HNSCC population would be excluded, with the potential risk of bias.

The strength of this paper is that all data were prospectively scored. We included both objective and subjective scores for swallowing dysfunction. It is, to our knowledge, the first paper looking at the relationship with UFND and radiographic symptoms of swallowing dysfunction.

The main limitation of this paper is the small and relatively heterogeneous study population. Unfortunately, only 63 of the initial 200 patients had VFS at baseline. Presumably, there are more patient and treatment-related factors, such as smoking and human papillomavirus status, influencing the baseline and late dysphagia that were not included in our analysis. Correction on the statistics for multiple testing was not performed as this subgroup analysis was considered exploratory and hypothesis generating. Another limitation is the lack of correction for RT dose to the SW-OAR, even though previous research has shown a relationship between dysphagia and the dose to the pharyngeal constrictor muscles and larynx.^{40,41} Further analysis of the dose on the SW-OAR is ongoing and is beyond the scope of this paper. Correcting for RT dose to SW-OAR, however, is very difficult as swallowing is affected by more than only muscle action. It is additionally influenced, for example, by mucositis and xerostomia, and other radiotherapy-induced side effects.

Although the main focus in the treatment of HNSCC remains cure and overall survival, it is important for physicians as well as patients to have knowledge of the toxicity profile of the proposed treatment. Selecting the patients at risk for developing late dysphagia makes it possible to intervene in time, e.g. with a prophylactic swallowing exercise program,⁴² or to select an alternative treatment, e.g. proton therapy.⁴³

CONCLUSION

UFND was associated with higher dysphagia 12 months after the treatment independent of the evaluation method. Patients with hypopharyngeal cancer had more baseline dysphagia while CUP was more often associated with dysphagia at 12 months.

To our knowledge, this is the first paper reporting on a significant link between UFND and higher late dysphagia scored with VFS as well as with physician- and patient-scored toxicity scales. We advocate abandoning UFND and preserving neck dissection as a salvage option after primary radiotherapy.

ETHICAL STATEMENT

All procedures performed in the 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.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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