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ORIGINAL ARTICLE

Predictors of Patient-Reported Dysphagia Following IMRT Plus Chemotherapy in Oropharyngeal Cancer

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Abstract

The aim of this cross-sectional study is to evaluate the factors associated with patient-reported dysphagia in patients affected by locally advanced oropharyngeal cancer (OPC) treated with definitive intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy (CHT), with or without induction CHT. We evaluated 148 OPC patients treated with IMRT and concurrent CHT, without evidence of disease and who had completed their treatment since at least 6 months. At their planned follow-up visit, patients underwent clinical evaluation and completed the M.D. Anderson dysphagia inventory (MDADI) questionnaire. The association between questionnaire composite score (MDADI-CS) and different patients' and tumor's characteristics and treatments (covariates) was investigated by univariable and multivariable analyses, the latter including only covariates significant at univariable analysis. With a median time from treatment end of 30 months [range 6–74 months, interquartile range (IQR) 16–50 months], the median (IQR) MDADI-CS was 72 (63–84). The majority of patients (82.4%) had a MDADI-CS $\geq$ 60. At multivariable analysis, female gender, human papilloma virus (HPV)-negative status, and moderate and severe clinician-rated xerostomia were significantly associated with lower MDADI-CS. Patient-perceived dysphagia was satisfactory or acceptable in the majority of patients. HPV status and xerostomia were confirmed as important predictive factors for swallowing dysfunction after radiochemotherapy. Data regarding female gender are new and deserve further investigation.

Keywords Oropharyngeal carcinoma · Long-term dysphagia · MDADI score · Human papilloma virus · Xerostomia

Introduction

Long-term dysphagia is reported in 30–50% of head and neck cancer (HNC) patients treated with intensive radiochemotherapy (RT-CHT) [1–3]. Although some

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patients completely respond to treatment, up to 50% do not report any improvement after radiotherapy (RT) and continue experiencing dysphagia-associated symptoms [4]. Despite the introduction of modern RT approaches, e.g., intensity-modulated radiation therapy (IMRT), swallowing dysfunction has become the major determinant of quality of life (QoL), potentially superior to xerostomia [4–8]. Over the last decades, significant efforts have been devoted to prevent, predict, and ameliorate swallowing adverse effects resulting from RT.

Some treatment-related predictors of dysphagia after definitive IMRT, such as RT mean dose to the pharyngeal constrictors muscles, have been investigated [9, 10]. Conversely, scant data exist on the impact of different clinical and biological characteristics of patients, such as human papilloma virus (HPV) status, on the development of dysphagia. Tumor p16 expression, a surrogate marker of HPV infection, is a predictor of better baseline and posttreatment overall QoL, compared with p16-negative status and regardless of primary treatment modality [11]. Over the last years, many studies in HNC patients included the assessment of adverse events through patient-reported outcome (PRO) measures, providing invaluable information about QoL [12–14].

At present, tools that measure patient-rated swallowing outcomes are considered easy to administer and sensitive to swallowing changes, especially when nonsurgical strategies are applied [15]. Among them, the M.D. Anderson dysphagia inventory (MDADI) is a practical, disease-specific and short tool, which has been extensively adopted and so far selected as the primary swallowing-related PRO in several ongoing prospective trials [16].

The main objectives of this study were to examine, in an exploratory fashion, the role of different biological and clinical factors, including HPV positivity and physician-reported xerostomia and dysphagia grades, in predicting long-term dysphagia through MDADI in a population of OPC patients treated with curative IMRT and concomitant CHT.

Patients and Methods

We considered consecutive OPC patients treated at three Italian tertiary cancer Centers: the National Cancer Institute in Milan (INT), the European Institute of Oncology in Milan (IEO), and the Santa Croce and Carle Hospital in Cuneo (Cuneo). This study was approved by each Institutional Scientific and Ethical Committee, and patients' informed consent was obtained from all participants. The study included patients with stage III–IV A–B OPC (according to VII AJCC-staging system [17]) who (i) had received conventional, extended-field IMRT or volumetric-modulated arc therapy (VMAT) (total dose of 70 Gy with conventional fractionation, 2–2.12 Gy per fraction), swallowing sparing when clinically feasible and concomitant platinum-based chemotherapy (CHT) at least 6 months before inclusion, and (ii) with disease in complete remission. Induction CHT (i-CHT) with platinum, docetaxel, and 5-fluorouracil (TPF) and/or unilateral neck node dissection before or after treatment were allowed. Patients who had undergone RT to the head and neck area other than OPC curative treatment, patients subjected to total laryngectomy, and those with a concurrent neurological disease were excluded. Percutaneous gastrostomy (PEG) was accepted if prophylactically placed before starting therapy. As per institutional policies, PEG was not placed in a reactive way, but enteral nutrition was applied with nasogastric tube (NGT) during treatment as needed.

Data Collection

All the enrolled patients filled in the MDADI questionnaire at planned follow-up visits. In brief, the MDADI consists of a self-reported questionnaire with 20 questions and 4 subscales about swallowing-related QoL: global assessment, single item-MDADI-G; functional, 5 items-MDADI-F; physical, 8 items-MDADI-P; and emotional, 6 items-MDADI-E. Each question includes a 5-point response scale. A composite score (MDADI-CS) based on 19 items (excluding the global assessment item) was applied to evaluate swallowing-specific QoL. All subscale MDADI scores and CSs were normalized to values ranging from 20 (extremely low-functioning) to 100 (high-functioning) [18]. Higher scores represent better QoL. The Italian version of MDADI has been previously validated [19]. As reported also by Goepfert et al. [16], a MDADI-CS of at least 80 represented "optimal" patient-reported swallowing function, between 60 and 80 was "adequate," and less than 60 was "poor."

Xerostomia and dysphagia, as well as other toxicities, were collected by the physician according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [20] at the routine follow-up visit (at least 6 months after treatment completion); we defined this assessment as "late." The following data were collected: pre-therapy HPV status, time from treatment end, chemotherapy timing, neck dissection (before or after treatment), duration of enteral feeding [nasogastric tube (NGT) or PEG], RT technique, RT overall treatment time (OTT), and interruptions due to toxicity. Baseline physician-reported dysphagia scores, as well as xerostomia and dysphagia measured during the routine follow-up visit, were also recorded. Xerostomia was not considered at baseline because it is not expected to be present at this time point.

Statistical Analysis

The association between categorical variables was tested using the Fisher–Freeman–Halton test [21]. We recorded the MDADI-CS and scores of all subscales for all the patients. The MDADI-CS was selected as primary endpoint, as suggested by other authors [15, 22]. The association between MDADI-CS and subscales and the following covariates was analyzed: patient' gender and age, T and N stage, previous surgery, treatment strategy (with or without i-CHT), HPV status, dysphagia CTCAE grade (at baseline and at follow-up), xerostomia CTCAE grade, enteral nutrition duration/administration, and time from treatment end.

We used the quartiles (1st, median, and 3rd) to summarize MDADI distributions according to the above covariates and the Anderson and Darling (AD) test [23] to test between groups differences (univariable analysis). Multivariable analysis was performed only for MDADI-CS using a quantile regression model, [24] which included only the covariates achieving 5% significance at univariable analysis. The quantile model was applied because it is semiparametric and avoids assumptions about the parametric distribution of dependent variable error. Therefore, when the response is not a Gaussian variable, such as in the case of MDADI score, it presents advantages compared with least squares regression. The model allows estimating and testing groups differences between the quantiles of response variable; we chose to model the three MDADI quartiles (median, 1st and 3rd quartiles).

Since our analysis had an exploratory intent, xerostomia and physician-assessed dysphagia grades (0, 1, 2) were modeled as linear covariates and the corresponding regression coefficient estimated the difference between the MDADI quartiles for every 1-unit increment of the covariate (i.e., G1 vs G0 or G2 vs G1). The model results were shown in terms of quartile differences, together with the corresponding p value at Wald test and, only for the significant covariates, we also graphically represented the quartile differences and their 95% confidence intervals (CI); CIs not including zero correspond to 5% significant differences.

The analyses were performed with SAS (Cary, NC, USA) and R software [25].

Results

Overall, 148 patients were enrolled, 101 (68%) at INT, 36 (24%) at IEO, and 11 (8%) at Cuneo.

Patient and treatment characteristics are shown in Table 1. Seventy-two (48.7%) patients received

Table 1 Baseline patient and treatment characteristics

	N	%
Gender		
Male	112	75.7
Female	36	24.3
Age, years		
Median (IQR)	59 (53–64)	
≤ 55	54	36.5
56–65	55	37.2
> 65	39	26.3
T stage[a]		
T1–T2	83	56.1
T3–T4	65	43.9
N stage[a]		
N0–N1–N2a–N2b	110	74.3
N2c–N3	38	25.7
Surgery		
No	128	86.5
Yes	20	13.5
Treatment combination		
Concurrent RT_CHT	94	63.5
I-CHT > RT-CHT	54	36.5
Pre-therapy HPV status		
Negative	34	23.0
Positive	98	66.2
Not defined	16	10.8
NGT or PEG before i-CHT or RT-CHT		
No	141	95.3
Yes	7	4.7
Time of maintenance of enteral feeding (days)		
No enteral feeding	95	64.2
PEG before treatment	6	4.1
Enteral feeding within 30 days	20	13.5
Enteral feeding beyond 30 days	27	18.2
Median (IQR)	37 (30–59)	
Time from treatment end (months)		
Median (IQR)	30 (16–50)	
≤ 24	61	41.2
> 24	87	58.8
Baseline dysphagia (before i-CHT or RT-CHT)		
G0	121	81.7
G1	22	14.9
G2	5	3.4
Late Physician-assessed dysphagia[b]		
G0	109	73.6
G1	33	22.3
G2	6	4.1
Late Xerostomia assessed dysphagia[b]		
G0	47	32.0
G1	64	43.5

Table 1 (continued)

	N	%
G2	36	24.5

CHT chemotherapy, *IQR* interquartile range, *NGT* nasogastric tube, *PEG* percutaneous endoscopic gastrostomy, *RT* radiotherapy

[a]T and N stage according to AJCC VII edition

[b]According to CTCAE v4.0 scale and recorded during follow-up visit(at least 6 months after RT-CHT)

conventional IMRT (step-and-shoot or sliding window techniques) and 76 patients (51.3%) received VMAT. Median OTT was 49 days (range 47–55 days). All patients received treatment as planned without interruptions due to toxicities.

Treatment consisted of i-CHT followed by RT-CHT in 54 patients (36%), and concomitant platinum-based RT-CHT in 94 patients (64%). Median number of i-CHT cycles was 3, and concurrent cisplatin was administered on a 3-week schedule in most cases (80%). Eight patients received unilateral neck dissection before RT, while 12 patients underwent salvage neck surgery after RT.

PEG was placed in 6 patients (4%) before the initiation of treatment, as it was prophylactically suggested due to the foreseen mucosal toxicity; two of them had it removed immediately at the end of the treatment. The other four maintained it to support a moderately altered swallowing function, and they removed it from 7 to 30 months from treatment end. No patient received reactive PEG during treatment. No patient had PEG in place at the time of the clinical evaluation and questionnaire's completion. Excluding patients with prophylactic PEG, 47 out of 142 patients (33%) had enteral nutrition via NGT during treatment. When performed, median duration of enteral feeding was 37 days (interquartile range, IQR 30–59 days).

Median time from treatment end was 30 months (range 6–74 months; IQR 16–50 months), with 61 patients (41%) having a follow-up of 6–24 months, and 87 (59%) with more than 24 months from treatment end.

At the time of the clinical evaluation and questionnaire's completion, 109 (74%) patients had grade 0 dysphagia, 33 (22%) had grade 1, and 6 (4%) patients had grade 2 dysphagia. As for xerostomia, 47 (32%), 64 (44%), and 36 (24%) patients had grade 0, grade 1, and grade 2, respectively. No patient showed mucositis.

The median (IQR) scores of MDADI-CS and G, F, P, and E subscales were 72 (63–84), 80 (60–80), 80 (68–92), 73 (67–84), and 70 (58–80), respectively. Twenty-six patients had a composite score < 60 (17.6%), and 82.4% had a MDADI-CS ≥ 60. At univariable analysis by Anderson and Darling test, MDADI-CS and the subscales were not significantly associated with age, T and N stages, previous surgery, treatment strategy, and baseline dysphagia grade (data not shown). Moreover, in the T1–2 subset, the HPV-negative and HPV-positive patients had similar MDADI-CS distribution: the median (IQR) was 72 (61–76) versus 72.5 (64.5–88.25) ($p = 0.110$). On the contrary, in the T3–4 subset, the HPV-negative patients had significantly lower MDADI-CS: 64 (56–84) versus 76 (70.3–82.8) ($p = 0.019$).

Table 2 shows the variables significantly associated with at least one MDADI subscale at univariable analysis. Males had significantly higher scores compared with females, both in the CS and in all the subscales. HPV positivity was associated with significantly higher scores compared with negative status in all the subscales except for MDADI-G. An inverse relationship was observed between xerostomia and MDADI score: higher grades were associated with significantly lower scores in the CS and in all the subscales. A similar trend was observed for physician-assessed dysphagia, but it reached significance only for MDADI-F, MDADI-P, and MDADI-CS. Time from treatment end > 24 months was associated with significantly higher MDADI-F, MDADI-P, and MDADI-C scores compared with treatment time ≤ 24 months. The variables significantly associated with MDADI-CS at univariable analysis were investigated in a multivariable model; enteral nutrition administration was not analyzed because it was associated with significantly lower MDADI-F and MDADI-P scores, but significance was not reached for MDADI-CS ($p = 0.0673$; Table 2). The multivariable quantile regression analysis confirmed the trends observed at univariable analysis, with less marked differences (Table S1). In particular, physician-assessed dysphagia and time from RT end were not significant; males had significantly higher median and 3rd quartile compared with females (Fig. 1a). Positive HPV status had significantly higher 1st and 3rd quartiles compared with HPV-negative status (Fig. 1b). For xerostomia, the median and the 3rd quartile reached significance; for instance, high grades had significant lower median scores compared with lower grades (Fig. 1c).

The interaction between T-stage and HPV status highlighted above (i.e., HPV-negative patients having significantly lower MDADI-CS in the T3–4 subset) was confirmed at multivariable quantile regression analysis [median MDADI-CS of HPV-positive vs HPV-negative patients in T3–4 subset: 7 (95% CI 1.56–12.44; $p = 0.012$)] (other data not shown).

Table 2 M.D. Anderson dysphagia inventory score according to patients' and tumor characteristics and treatments

	MDADI-G	MDADI-F	MDADI-P	MDADI-E	MDADI-CS
Gender					
Male	80 (80–80); 76.6 (20.6)	80 (72–96); 81.5 (15.0)	73 (62.3–80); 72.1 (16.5)	77 (67–87); 75.6 (12.8)	76 (67–84.3); 75.6 (13.5)
Female	80 (40–80); 62.2 (28.2)	72 (60–81); 71.3 (15.7)	55 (47.3–68.5); 58.3 (17.7)	70 (59.3–80); 68.8 (17.1)	65 (55–73.5); 65.3 (14.9)
p value	**0.0005**	**0.0004**	**0.0134**	**0.0276**	**0.0001**
Pre-therapy HPV status					
Negative	80 (60–80); 70.6 (24.2)	72 (61–83); 72.9 (15.5)	66.5 (50–75); 63.3 (18.0)	70 (57.8–79.3); 68.9 (12.7)	69 (57–77.8); 67.7 (14.4)
Positive	80 (65–80); 74.3 (23.3)	80 (72–96); 81.1 (15.3)	71.5 (60–80); 71.6 (17.1)	78.5 (70–87); 76.3 (14.7)	76 (67–84.8); 75.6 (14.1)
p value	0.6557	**0.0043**	**0.0379**	**0.0026**	**0.0135**
Late Physician-assessed xerostomia[a]					
G0	80 (80–100); 78.7 (23.4)	88 (74.0–98); 84.6 (15.0)	78 (63–89); 75.4 (17.8)	83 (70–87); 79.5 (12.1)	80 (70–90.5); 79.1 (14.6)
G1	80 (75–80); 74.7 (20.6)	82 (71–92); 80.2 (14.5)	70 (60–80); 69.0 (17.6)	77 (67–83); 74.4 (13.8)	73.5 (66–84); 73.7 (13.3)
G2	80 (40–80); 62.8 (25.8)	72 (60–80); 70.0 (15.4)	60 (49.5–68.5); 60.0 (14.1)	67 (57–77); 66.7 (14.1)	64.5 (57.5–71.3); 64.5 (12.2)
p value	**0.0004**	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
Late Physician-assessed dysphagia[a]					
G0	80 (60–80); 74.1 (23.3)	80 (72–96); 81.2 (15.6)	70 (60–80); 70.7 (17.6)	77 (67–87); 75.4 (13.0)	76 (65.75–84.3); 74.8 (14.5)
G1	80 (80–80); 72.7 (23.4)	72 (60–84); 74.8 (15.2)	65 (53–75); 65.2 (18.1)	77 (67–83); 72.1 (16.9)	69 (64–80); 70.2 (13.8)
G2	60 (40–80); 56.7 (26.6)	68 (61–72); 64.7 (9.6)	55.5 (48–66.8);56.3 (11.3)	61.5 (54.75–70.5); 62.7 (12.3)	59 (55–62.3); 60.2 (7.3)
p value	0.2814	**0.0021**	**< 0.0001**	0.1105	**0.0123**
Enteral nutrition administration					
No	80 (70–80); 75.0 (22.8)	80 (72–96); 81.4 (15.5)	73 (60–80); 71.3 (17.5)	77 (68.5–87); 74.9 (14.2)	76 (66–84.5); 75.2 (14.2)
Yes	80 (50–80); 71.5 (22.7)	76 (64–90); 76.1 (15.4)	65 (51.5–75); 64.6 (18.1)	73 (63–83); 72.7 (14.9)	71 (59.5–80.5); 70.0 (15.0)
p value	0.5070	**0.0358**	**0.0339**	0.2737	0.0673
Time from treatment end (months)					
≤ 24	80 (60–80); 71.2 (24.1)	76 (64–88); 75.5 (14.8)	68 (55–75); 65.3 (16.7)	73 (63–80); 72.6 (12.9)	71 (61.00–78); 70.2 (13.5)
> 24	80 (80–80); 74.5 (23.0)	84 (72–96); 81.4 (16.1)	70 (60–85); 71.1 (18.1)	77 (67–87); 74.9 (15.1)	76 (65.00–86); 75.1 (14.9)
p value	0.5844	**0.0078**	**0.0590**	0.1924	**0.0467**

Significant *p* values or values near to significance are given in bold

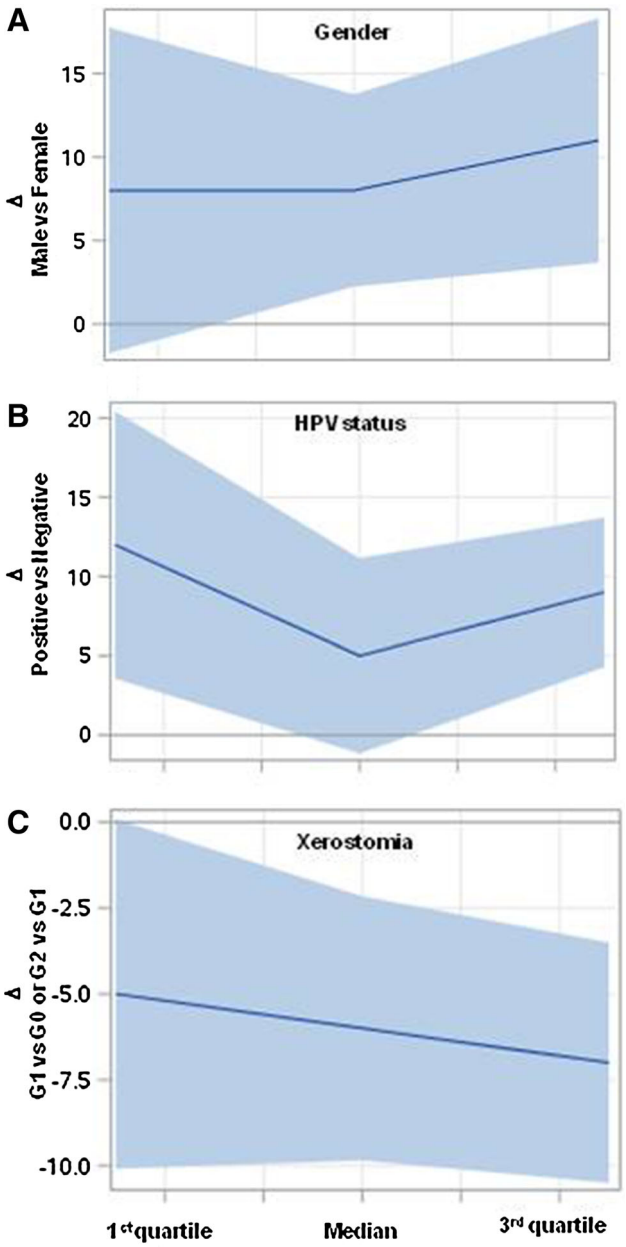
To descriptively represent the MDADI distribution, each cell shows the median and interquartile range in parenthesis (data coherent with the results of the multivariable quantile regression model), the mean, and the standard deviation in parenthesis

MDADI-G MDADI-global assessment, *MDADI-F* MDADI-functional, *MDADI-P* MDADI-physical, *MDADI-E* MDADI-emotional, *MDADI-CS* MDADI-composite score

[a]According to CTCAE v4.0 scale and recorded during follow-up visit (at least 6 months after RT-CHT)

Discussion

Our study suggests that PRO measured by using MDADI questionnaire identified more evident swallowing symptoms compared with physician assessment in a population of OPC patients. With a median time from treatment end of 30 months, about 18% of patients had "poor" MDADI-CSs lower than 60 [16]. However, physicians-assessed dysphagia was recorded as G2 in only 4% of patients. We confirmed that observer-based rating of toxicity



◀**Fig. 1** Results of the multivariable quantile regression model for the three variables significantly associated with MDADI-CS. In the vertical axis, Δ represents the MDADI-CS quartiles difference between two categories estimated by the model. For instance, in panel A, the continuous line joins three points: the 1st one is the estimated difference between the MDADI first quartiles in males versus females, i.e., 8.00 (95% CI − 1.75 to 17.75, Table S1 first row/first column). Such a difference, being estimated according to a multivariable model that takes into account the association between the covariates, is slightly lower than the corresponding observed difference (67–55 = 12, Table 2 first and second rows/last column). The 2nd point is the estimated difference between the MDADI medians in males versus females (8.00 (2.24–13.76), Table S1 first row/second column; observed difference: 76–65 = 11, Table 2). The 3rd point is the estimated difference between the MDADI third quartiles in males versus females (11.00 (3.68–18.32), Table S1 first row/third column; observed difference: 84.3–73.5 = 10.8, Table 2). The shaded area shows the 95% CI of each difference: CIs not including the zero line correspond to 5% significant differences

underestimates the patient-scored side effects, measured by QoL questionnaires [26, 27]. Therefore, even a moderate dysphagia could impact on QoL as reported by Hunter et al. [6] in an OPC population. Similarly, Gluck et al. [28] showed that reporting only grades ≥ 3, the most widespread toxicity criteria in recent trials on HNC therapy, may not be the best way to estimate dysphagia burden.

By evaluating MDADI subscale scores, we observed that emotional and physical scores were the poorest, while functional scores were more favorable. This witnesses, as reported in other papers, that despite physical difficulty in swallowing, patients were able to cope with their condition, achieving acceptable functional outcomes [16, 29]. It should be recognized, however that, psychological and rehabilitative supports should be included in the follow-up program, since dysphagia could strongly affect QoL leading to anxiety and depression [30].

Dysphagia is strongly related to a substantial number of clinical and treatment-related parameters, even if the reported series used different tools to assess dysphagia. Besides PRO questionnaires and physician-assessed scales, endoscopic or radiological examination such as the Fiberoptic Endoscopic Evaluation of Swallowing (FEES), the videofluoroscopic swallow test (VFSS), or the evaluation of presence of NGT or PEG have also been used to assess dysphagia. A recent systematic methodological review about swallowing dysfunction after RT-CHT for HNC found two risk factors supported by robust evidence, namely the use of RT-CHT and the presence of hypopharyngeal carcinoma [31].

In this specific patient series, we also showed that HPV status, xerostomia, and gender were independent predictors for MDADI-CS at multivariable analysis.

The favorable prognostic value of HPV status on dysphagia is another important result. Other works have

suggested a good functional outcome for patients with nonsurgically treated HPV-positive cancers [11, 16, 32]. However, these results were derived from studies with limited samples or lack of patient-reported measures. Our study demonstrated that, based on the evaluation of reported dysphagia in HNC survivors, HPV was one of the most favorable prognostic factor. This fact could reflect an increased tolerance of HPV-related diseases to late effects. On the other hand, HPV-negative cancers, being more frequently associated with chronic insult of genotoxic agents (smoking and alcohol), could be more prone to treatment-related toxicities.

It is interesting to note the double pattern of toxicities in HPV-related diseases: in the acute phase, incidence of mucositis, dysphagia, and opioids use are higher in HPV-positive cancers than in their negative counterpart [33, 34]; in the late period, however, the rate of toxicities changes in these two groups as shown by our results. HPV-positive microenvironment (richer in effector T cells, cytokines and chemokines) may explain the higher level of acute inflammation [35].

Similarly, in the trial by Bonner et al. [36], evaluating RT with or without cetuximab, the analysis of OPC patients revealed that in the acute phase patients with p16-positive cancer had a higher incidence of G3/4 mucositis and dysphagia compared with those with p16-negative OPC. On the other side, at 12 months, the rate of feeding tube dependence was higher for patients with p16-negative cancers [36].

Salivary flow is of paramount importance for an efficient swallowing [36–40]. Moreover, hyposalivation is associated with changes in the perception of swallow ability and changes in diet [41]. Recently, Teguh et al. [42] also found a high correlation between the items of the EORTC H&N35 questionnaire regarding swallowing, dry mouth, and sticky saliva. More recently, a prospective longitudinal study of 93 patients with OPC treated with definitive IMRT-CHT showed that xerostomia significantly contributed to patient-reported dysphagia [43]. Our data confirmed this association, with patients who experienced G0-1 xerostomia (reported by the physician) having significantly higher MDADI-CS at median and 3rd quartile compared to patients with G2 toxicities.

As for gender, to our knowledge it has been never reported that gender independently impacts on dysphagia, with males showing better MDADI-CS compared with females. In the group of patients with higher values of MDADI-CS (median and 3rd quartile), the differences between males and females were significant. Correlation between gender and other domains of QoL has been previously published. Teguh et al. [42] found that gender was a significant factor for late dry mouth. Besides, at multivariate analysis, Leung et al. [44] found that gender was an independent prognostic factor for QLQ-C30. Thus, it is possible that the impact of gender could be related to more interconnected domains of QoL (xerostomia, dysphagia).

Unlike other authors, we found no significant association between swallowing dysfunction and other factors such as age, and advanced T and N stages [1, 45–49], probably because of differences in patients' characteristics and treatment. We found a different association between HPV and MDADI-CS in the two T-stage groups: in the T1–2 subset, HPV-negative and HPV-positive patients had similar MDADI-CS distribution, whereas in the T3–4 subset, HPV-negative patients had significantly lower MDADI-CS. In a recent two-year longitudinal report by Goepfert et al. on 116 locoregionally advanced OPC survivors treated with IMRT, tumor stage was one of the most important predictors of patient-reported swallowing over time, even after assessing for multicollinearity with and potential differences in radiation dose by tumor stage [49]. The majority of patients received accelerated RT (planned schedule was 6 weeks, with 60 Gy in 33 fractions for T1 disease and 72 Gy in 40–42 fractions through concomitant boost regimen) fraction) and split-field IMRT. On the contrary, in our study, all patients received conventional fractionation (fraction size up to 2.2 Gy) and IMRT or VMAT with swallowing sparing when clinically possible. The lack of robust RT dose constraints on all swallowing structures, as deduced from the paper by Goepfert et al. could have a greater impact on dysphagia in patients with extensive tumors, particularly when accelerated RT is employed [49].

We also found no impact of neck dissection, differing from other series [42]. However, Hutcheson et al. [50] showed that postoperative neck surgery did not influence chronic dysphagia rates, justifying the inclusion of patients receiving dissection in the present analysis. Use of enteral nutrition during treatment resulted in worse dysphagia only in the physical and functional subscales. Enteral feeding during the RT course may be associated with long-term tube dependence, leading to prolonged inactivity of swallowing muscles and esophageal constriction [51, 52]. The rate of enteral nutrition need was quite low in our series and most patients adopted a reactive enteral strategy, thus with limited time of inactivity of swallowing structures. Indeed, better swallowing outcomes are evident when reactive feeding tubes are used in preference to prophylactic gastrostomy tubes to supplement enteral nutrition during RT-CHT [53, 54]. Considering altogether patients receiving enteral nutrition, regardless of type of feeding tube, we disclosed no difference in MDADI-CS scores between patients who received placement of feeding tube during treatment and patients who did not. This was likely due to the short duration of enteral feeding, although a trend of better scores was found on a univariable analysis

among patients without enteral nutrition. Differently, in a large retrospective cross-sectional study by Hutcheson et al. [22] conducted on 1386 HNC patients, an average gap of 10 points in MDADI-CS was identified between feeding tube-dependent versus non tube-dependent patients. The most important distinction between our work and that of Hutcheson et al. is that the significant MDADI/tube association observed by Hutcheson et al. was based on current feeding tube use at the time of MDADI collection, whereas in our study we modeled past feeding tube duration as a covariate for MDADI.

We also reported a favorable impact of longer time from treatment end on patient-reported dysphagia, even if only at univariable analysis, with a median CS of 71.5 and 76 in patients evaluated at $\leq$ 24 and $\underline{\geq}$ 24 months from the end of RT, respectively. It is known that the effects of late radiation-induced toxicity on deglutition and QoL are more severe in the first 6–12 months after treatment and gradually decrease after 18–24 months [5, 55, 56]. Caudell et al. [1] showed improvement of swallowing dysfunction over time in patients on RT. However, in the previously cited paper by Goepfert et al., MDADI scores remained depressed at 24 months compared to baseline, suggesting only partial recovery of perceived swallowing function [49]. In a more recent paper by Goepfert et al., which aimed at characterizing long-term MDADI results following IMRT for patients with "low-intermediate risk" OPC included in current trials (e.g., ECOG 3311, NRG HN002, CRUK PATHOS), a poor MDADI CS (< 60) was reported in 4, 11, 15, and 9% of patients at baseline and at 6, 12, and 24 months, respectively [16].

We acknowledge the limitations of our study, primarily the cross-sectional nature of the analysis, the different protocols and standard of management across involved Centers, and the limited number of patients for outcomes other than MDADI. The lack of a longitudinal MDADI scores' assessment makes it difficult to assess the transferability of the results. We were not able to define the changes in swallowing scores from baseline to follow-up, as baseline assessment consisted only in a physician-assessed evaluation. We recognize that the optimal timepoint for dysphagia assessment by PRO is still to be defined; however, the evolution and recovery of swallowing disorders suggest that the baseline, end of treatment, 3, 6, and 12 months from treatment end, and then yearly could constitute an useful timeline for assessment of this toxicity, which should be able to correct and prevent further deterioration.

Another important limitation is that we reported only PRO and physician-assessed dysphagia. However, penetration/aspiration and biomechanical swallowing disorders cannot be reliably judged using questionnaires and self-reports, reinforcing the need for clinical tests of aspiration, i.e., videoendoscopic evaluation of swallowing (VEES). A combination of measures is currently required to comprehensively report on dysphagia.

Moreover, we did not study the potential role of smoking status, due to the absence of complete data. Interestingly, in the paper by Goepfert et al., current smokers had a 9.4-fold lower mean MDADI over time than never smokers [49].

In addition, the correlation between dosimetric results and swallowing organs, as well as the relationship between oropharyngeal acute mucositis and dysphagia, was not assessed. This latter is a crucial point as it has been suggested that inflammation and edema are underlying causes of swallowing organs dysfunctions [57].

Finally, given the cross-sectional nature of the study, we cannot rule out that non-HPV patients had worse pre-therapy scores, thus affecting the observed findings.

Conclusions

MDADI may better describe swallowing symptoms than physician-reported assessment. Overall, most patients had good patient-reported dysphagia with the emotional and physical domains as the most depressed. Our data confirmed the role of HPV and xerostomia as predictive factors in determining dysphagia perception. This underlines the need to better tailor therapy, supportive care, and intervention, especially in HPV-negative patients, with the aim of ameliorating their QoL. However, prospective studies in a larger population are necessary to either confirm or discard these preliminary findings.

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Compliance with Ethical Standards

Conflict of interest The Authors declare that they have no conflict of interest.

Ethical Approval 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.

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

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