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ORIGINAL ARTICLE

Evolution of self-perceived swallowing function, tongue strength and swallow-related quality of life during radiotherapy in head and neck cancer patients

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Abstract

Background: Radiation-associated-dysphagia is a serious side effect of radiotherapy (RT) for head and neck cancer (HNC).

Methods: Seventy-six patients had a weekly prospective follow-up from baseline until one week post-RT. Combined mixed model analysis ($n = 43$) determined the evolution of self-perceived swallowing function, isometric tongue strength (MIP), tongue strength (TS) during swallowing (Pswal), and quality of life (QoL) in these patients during RT.

Results: Swallowing deteriorated from the third week on, resulting in an increase of tube dependency from 10% at baseline toward 31% post-RT. Both MIP and Pswal are reduced, with anterior MIP decreasing in 29% of patients and posterior MIP in 17%. Pswal decreases for saliva and a bolus swallow. All QoL subscales except "sleep" were affected during RT.

Conclusions: *Self-perceived s*wallowing function, TS and QoL decrease during RT for HNC. Current findings highlight the need for early monitoring of these parameters.

KEYWORDS

head and neck cancer, quality of life, radiotherapy, swallowing, tongue strength

1 | INTRODUCTION

Treatment intensification for head and neck cancer (HNC) with high doses of radiotherapy (RT), often in combination with concurrent chemotherapy (CCRT) improves survival, but this intensive treatment comes with an important acute and late toxicity of which xerostomia and swallowing disorders are the most invalidating.[1–8] Organ preservation rarely translates into function preservation and may result in radiation-associated dysphagia (RAD).[2,8] RAD refers to impaired swallowing efficiency and safety, a long-term or even permanent iatrogenic sequel that negatively impacts the patients' quality of life (QoL) and ability to function in society.[9,10]

The pathophysiological characteristics of RAD are muscle weakness and limited range of motion at different levels such as the base of the tongue, pharynx, epiglottis, and larynx.[3,11–13] This results in impaired nutrition, aspiration, oral and pharyngeal residue, and impaired QoL in 20%-50% of all patients, thereby making RAD an important contributor to noncancer-related mortality.[2–4,12–19]

Patients differ in their sensitivity to RT due to genetic factors.[20,21] Patients who are more susceptible to RT-induced side effects are more prone to develop both acute and late toxicity.[22] A large proportion of previous research focuses on the different variables contributing to or correlating with RAD.[2,3,8,11,16,17,19,22–27] This resulted in the development of predictive models for RAD[28,29] and guidelines for swallowing sparing RT in an effort to maximize both organ and function preservation.[29–31] Van der Laan et al.[22] determined acute dysphagia and xerostomia in weeks 3-6 during RT, as prognostic factors for dysphagia 6 months after completing RT and as biomarkers for late toxicities.

Eisbruch et al.[11] described weakness of the base of the tongue as a cause of RAD. Tongue strength (TS) is the main driving force behind food propulsion from the oral cavity to the esophagus, contributing to and necessary for efficient and safe swallowing.[32–34] As the tongue consists of type I and II muscle fibers,[35–37] with type II muscle fibers being sensitive to early RT injury,[1] it can be hypothesized that TS will be affected by RT. Measuring TS is a feasible practice in research during[37] and after RT for HNC.[33,38–41] Research on the evolution of TS after RT, however, is inconclusive with the majority of research finding no significant differences between baseline and different time points after RT.[33,38,39,41] In humans, only two studies describe significant decreases in TS between baseline, the third and the sixth month after RT.[40,42] In rats also, radiation was associated with a significant decrease in TS at 12 weeks post-RT.[43] Other research has demonstrated a decrease in TS, the severity of dysphagia and QoL in HNC between baseline and after treatment, with meaningful correlations between those parameters.[18,40] Since patients with HNC often experience unintentional weight loss during treatment,[44] associated with significant impairments in general physical performance,[45] a possible local strength decrease needs to be distinguished from a general strength decrease. Grip strength is recommended as a reliable clinical measure of muscle strength.[46]

To our knowledge, almost all research focuses on symptoms and consequences of chronic dysphagia (>6 months post-RT) while no data are available on the evolution of TS during and immediately after the end of RT.[1] Early injuries already begin to develop within the first minutes after RT in irradiated epidermis and mucosa and permanent muscle fibrosis may occur, especially in muscle fibers with high glycolytic capacity, as type II fibers, such as the tongue and swallowing musculature.[1,5] Progressive mylohyoid muscle changes with atrophy and fatty replacement immediately following the end of RT have been described.[47] Besides radiation effects, decreased use of swallowing muscles during periods of nil per os or dietary modifications can result in muscle atrophy and loss of function.[4,5] All reported data are based on changes in anterior tongue strength (MIP_A), or observations of tongue movement during videofluorographic studies, but the evolution of posterior tongue strength (MIP_P) has not been reported on yet.

HNC RAD is prevalent and causes impaired QoL but functional data on swallowing function, evolution of TS and QoL during RT or CCRT are lacking. Measuring swallowing function and TS in HNC patients during and shortly after RT treatment will increase insight into the described process of muscle deterioration.[37] This knowledge of the evolution of TS is necessary to develop therapeutic interventions for the prevention and rehabilitation of RAD.[37] The purpose of the current study is to analyze the evolution of the self-perceived swallowing function, the anterior and posterior isometric TS, TS during swallowing, grip strength, and the QoL in patients with HNC while treated with RT or CCRT.

2 | PATIENTS AND METHODS

2.1 | Study population and treatment

This multicenter prospective study presents data collected between August 2012 and April 2015 at three different centers (XX, YY, and ZZ) in the context of the Belgian Federal Cancer Plan (CP) project (KPC29_033). During this period, all patients with a newly diagnosed locally advanced squamous cell carcinoma of the head and neck region (including oral cavity, oropharynx, hypopharynx, and larynx) meeting the inclusion criteria were referred to participate in the CP study. Inclusion criteria were the presence of sufficient cognitive and language abilities and the indication of RT with curative intent. A history of prior carcinoma and/or cancer surgery or RT in the head and neck region and the presence of metastases were exclusion criteria.

2.2 | Material and procedure

Measurements of self-perceived swallowing function, TS and QoL were performed prior to RT (baseline, BL), at the first, second, third, fourth, fifth, and sixth week of RT (RT1, RT2, RT3, RT4, RT5, and RT6) and 1 week after treatment (post-RT).

Self-perceived swallowing function was assessed by measuring both the patient's perception of swallowing and his functional oral intake, corresponding to the patients functional eating abilities.[48] For the first, patients scored a 100 mm visual analog scale (VAS) ranging from "I'm not able to swallow" (0) to "I swallow normally" (100). For the latter, the Functional Oral Intake Scale (FOIS[48]) was completed by the researcher based on a short interview with the patient. The FOIS is an ordinal scale, consisting of seven different levels between nil per os (FOIS 1) and a total oral diet without restrictions (FOIS 7). FOIS scores 1, 2, and 3 correspond to tube dependency while scores 4, 5, and 6 refer to an impaired intake without tube dependency.

FIGURE 1 The Iowa Oral Performane Instrument

TS was measured using the Iowa Oral Performance Instrument version 2.3 (IOPI; IOPI Medical LCC, Redmond, Washington, Figure 1). Isometric TS was quantified by measuring maximal isometric pressure (MIP) as described in previous research.[37,49–51] The location for anterior MIP (MIP_A) was determined by placing the part of the bulb closest to the connecting tube in contact with the posterior face of the upper incisors, thereby positioning the bulb against the hard palate just posterior to the alveolar ridge. The location for posterior MIP (MIP_P) was determined by placing the tip of the bulb at the level of the transition of the hard to soft palate. A permanent mark on the connecting tube just anterior to the incisors assured accurate placement for each measurement of MIP_P. These two positions of the bulb were also used to measure TS while swallowing. Boluses used were saliva ($Pswal_A$_sal and $Pswal_P$_sal) and 5 mL yogurt ($Pswal_A$_yogh and $Pswal_P$_yogh). Participants were instructed to execute an effortful swallow for both boluses. The LCD screen of the IOPI displayed the exerted pressure in kPa. The instruction to perform an effortful swallow instead of a natural one was preferred because of the clinically observed variability in outcome when patients were asked to perform "naturally" with an IOPI bulb in their mouth. Moreover, the instruction to swallow forceful is often given to these patients to increase oropharyngeal pressure and decrease pharyngeal residue.[52]

As a proxy for general physical strength, *grip strength* was measured by a handheld JAMAR dynamometer.[46]

For all strength measurements, the instruction was given to press, swallow or squeeze as hard as possible, with the greatest value of three attempts used for further analysis.[33,38,41,46,50]

QoL was assessed with the Dutch Version of the Swallowing Quality-of-Life Questionnaire (DSWAL-QOL[53]). The DSWAL-QoL samples 11 domains at how they are impacted by dysphagia: general burden, eating duration, eating desire, symptoms, food selection, communication, fear of eating, mental health, social functioning, sleep, and fatigue. Each area is scored between 0 (lowest QoL) and 100 (no impact on QoL).

2.3 | Statistical analysis

All cases with missing baseline data or more than 50% missing values for MIP_A or MIP_P for the whole study duration were excluded. Tables, figures, described statistics, and correlations were performed in SPSS v21. Concerning subsequent analyses regarding the evolution of the different parameters during RT, remaining missing values were adjusted by applying multiple

imputation.[28,54,55] The analysis in the imputed data set (five imputations) was combined by the combined mixed model analysis with post hoc analyses to describe the differences between baseline and different time points. This General Linear Model with fixed and random effects was chosen because the data used are permitted to exhibit correlation and nonconstant variability. Bonferroni correction for multiple testing was applied. Multiple imputation and subsequent analyses were performed in SAS v9.4. Analyses were based on nongrouped data, and the graph representing FOIS scores was constructed with grouped data to improve comprehensibility. Power analysis by G*power[56,57] revealed that the current study would require 47 participants to achieve a 95% power to detect changes in MIP.

2.4 | Ethical approvals

This study was independently reviewed and approved by the Ethical Committee of XXX (B300201318333). All subjects agreed voluntarily to participate in this study and signed an informed consent in full accordance with ethical principles including the World Medical Association Declaration of Helsinki (version 2002) and additional requirements.

3 | RESULTS

3.1 | Patient characteristics

Seventy-six patients were referred to the study for baseline measurements. Fifty-five (72%) of them continued until the post-RT phase and ultimately, data of 43 subjects (57%) was used for statistical analysis (Figure 2). Table 1 describes patient characteristics. Patients were treated with RT, CCRT, or induction chemotherapy followed by RT. Induction chemotherapy was TPF-based (Docetaxel, Cisplatin, 5-Fluorouracil). Chemotherapy during RT consisted of cisplatin, cetuximab or gemcitabine.[58] The mean dose of RT was 69 Gy (range 69-70 Gy). Median age was 62.5 year (range 38-85). The majority of tumors was located in the oropharynx (65%) and classified (TNM7) as T2 (35%). CCRT was the most common treatment (49%) and a comparable number of patients were treated by intensity-modulated RT using helical tomotherapy or classic linear accelerator.

3.2 | Evolution of self-perceived swallowing function

Based on the analysis of the VAS (Figure 3), there is an important decrease in self-perceived swallowing function during RT in comparison with baseline ($P < 0.001$) with a significant decline from RT3 on ($P < 0.001$ at RT3, $P = 0.004$ at RT4, and $P < 0.01$ at RT5, RT6, and post-RT). Regarding FOIS, significant decreases in functional oral intake ($P < 0.0001$) with significant drops are also registered from RT3 on (Figure 4 and table; $P = 0.002$ at RT3, $P < 0.0001$ at RT4, RT5, RT6, and post-RT). At baseline, the majority of patients (76%) obtained FOIS 7 and only 10% needed tube feeding (FOIS 1, 2, and 3). However, post-RT, tube dependency (FOIS 1-2-3) increased toward 31%.

3.3 | Evolution of TS

Regarding isometric TS, the majority of subjects (72% for MIP_A and 65% for MIP_P) obtains baseline MIP values

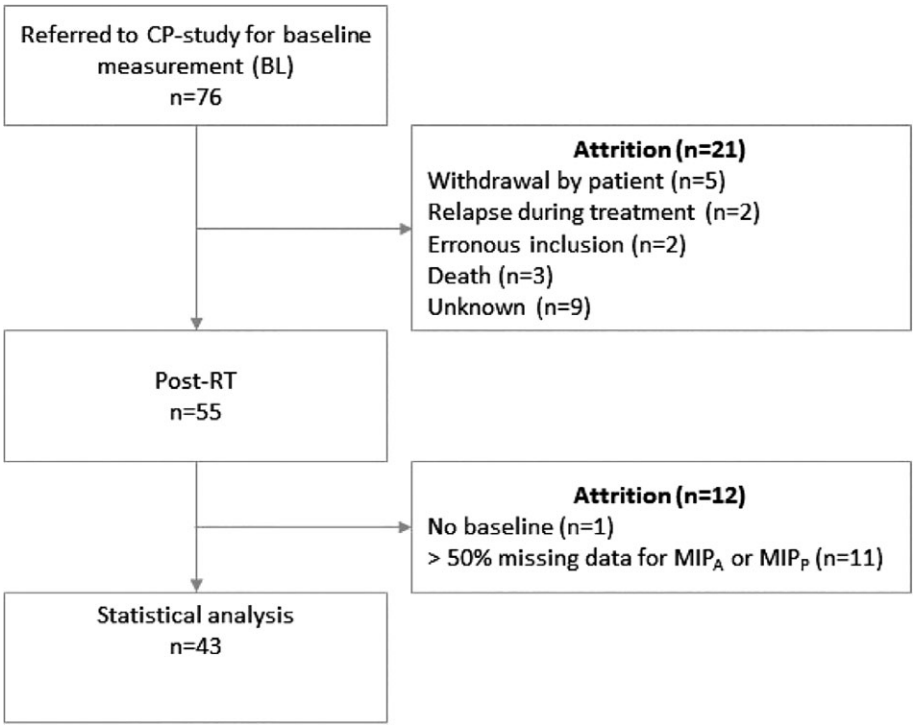

FIGURE 2 Patient attrition from baseline to statistical analysis

TABLE 1 Characteristics of 43 patients included for statistical analysis

Characteristic	No. of patients	No. of patients (%)
Sex		
Male	33	77
Female	10	23
Tumor site		
Oropharynx	28	65
Hypopharynx	10	23
Larynx	5	12
Tumor classification[a]		
I	7	16
II	15	35
III	11	26
IV	7	16
Not specified	3	7
Node classification[a]		
0	10	23
I	9	21
IIa	4	9
IIb	11	26
IIc	5	12
III	3	7
Not specified	1	2
Stage[a]		
I	1	2
II	4	9
III	12	28
IVA	21	49
IVB	2	5
IVC	1	2
Not specified	1	2
Treatment		
CCRT	21	49
RT	13	30
ICT→ CRT	8	19
Not specified	1	2
Radiation type		
TOMO	22	51
LINAC	21	49

Abbreviations: CCRT, concurrent chemoRT; ICT, induction chemotherapy; RT, radiotherapy.
[a] TNM7 classification.

within the sex and age specific 95% prediction interval.[50] One week post-RT, only 43% of MIP_A values and 48% of MIP_P values remain within the normal values.[50] MIP_A decreases nonsignificantly ($P = 0.39$) and the decrease of MIP_P is significant ($P = 0.003$), with significant differences at time points BL-RT5 ($P = 0.001$) and BL-post-RT ($P = 0.03$) (Table 2).

TS during swallowing saliva decreases significantly anteriorly as well as posteriorly ($Pswal_A$_sal, $P = 0.002$; $Pswal_P$_sal, $P < 0.001$). Regarding TS during a bolus swallow of 5 mL yogurt (Pswal_yog), a significant overall decrease in anterior ($Pswal_A$_yog, $P = 0.006$) as well as posterior TS ($Pswal_P$_yog, $P < 0.001$) is also measured. Post hoc analyses show a major decrease in $Pswal_A$_sal (18% from baseline to post-RT) and $Pswal_A$_yog (16% from baseline to post-RT), with the highest decrease (21%) measured at RT5.

3.4 | Evolution of grip strength

Grip strength changes significantly during RT ($P < 0.001$), with post hoc significantly decreasing at RT5 ($P = 0.02$), RT6 ($P = 0.02$), and post-RT ($P < 0.001$). Maximal decrease from baseline is 5%. Moderate correlations ($0.50 < r > 0.70$[59]) between grip strength and other strength parameters are observed at RT1 and RT2 (Table 3).

3.5 | Evolution of QoL

Baseline values for all subscales except "sleep" are situated within normative values (ie, >pc 25 on DSWAL-QoL[53]). The only subscale not decreasing during RT is "sleep" (Table 4). Scores on the sleep subscale are situated below normative values at all time points.[53] "Eating desire," "food selection," "mental health," and "fatigue" show significant decreases leading all to QoL scores below normative values from RT3 until post-RT.

4 | DISCUSSION

Current treatment in HNC is characterized by a high degree of acute and late toxicity,[1–8] of which RAD is the most invalidating together with xerostomia.[2,8,10] Since acute symptoms during RT are correlated with late toxicities, acute dysphagia is known as a prognostic factor and biomarker for RAD.[22] RAD is an important contributor to noncancer-related mortality and decreased QoL.[2–4,9,12–19] Therefore, it is important to avoid or minimize RAD and its consequences.

Whereas several studies mentioned RAD as a long-term consequence after RT,[2,8–10] literature reveals limited data on the evolution of the swallowing function during a course RT.[22,31] In the current study, the subjective swallowing function decreased from the third week of RT on which is similar to Van der Laan et al[22]. After chemoradiation, 86% of our patients experienced swallowing difficulties, and 31% were tube dependent. The latter is consistent with data of previous studies on tube dependency following RT.[22,31] It has to be acknowledged that described swallowing difficulties are based on patient-reported outcomes, and therefore cannot be considered as an objective measurement. Future research concerning the evolution of swallowing measured by objective instruments is necessary.

The current study reveals the first data on the evolution of TS during CCRT. For MIP_A no significant changes were found, although there is a decrease in TS for 30% of patients. These findings are consistent with previous studies showing no significant differences from baseline to 1,[39] 2,[33,38] or

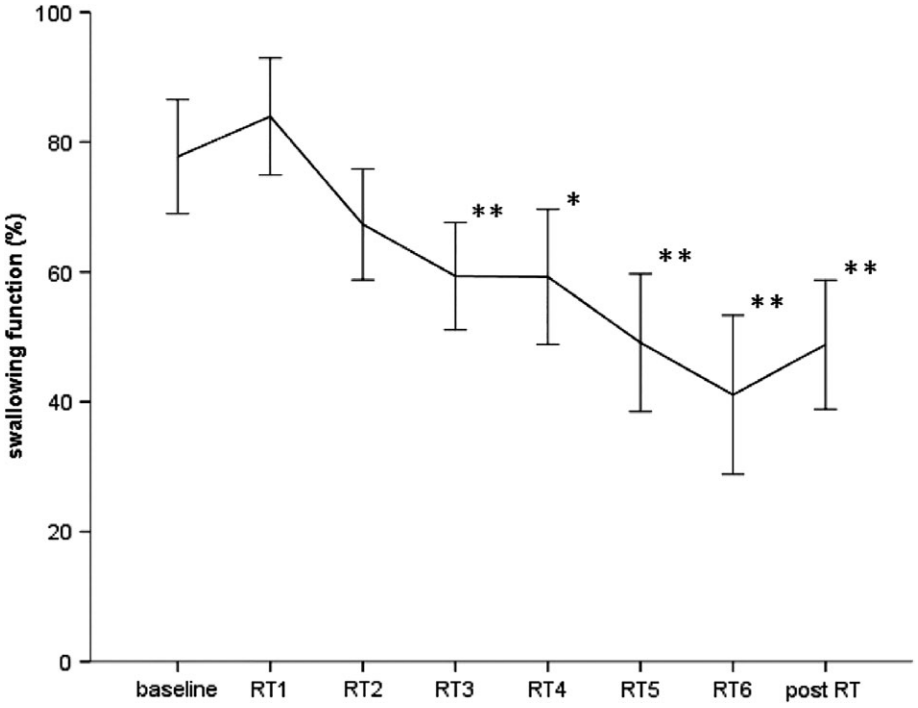

FIGURE 3 Evolution of self-perceived swallowing function (VAS, %) during RT in comparison to baseline reporting (nonimputed dataset); error bars: 95% CI; $*P < 0.05$; $**P < 0.001$

3[41] months post-RT. In contrast, our data show a significant decrease in MIP_P, from the fifth week of RT on. These unique findings suggest RT to has a higher negative impact on MIP_P than on MIP_A in patients with oropharyngeal, hypopharyngeal or laryngeal carcinoma. Local differences in muscle composition do not explain this MIP_p decrease, since the anterior part of the tongue consists of relatively more type II fibers compared to the posterior part and as these type II fibers are prone for acute toxicity.[1,36] Additional analysis of our data will show whether this dissimilarity between MIP_A and MIP_P might be related to regional differences in dosimetric parameters since high doses to the base of tongue and superior pharyngeal constrictor muscle are associated with an increasing risk to develop dysphagia and increased functional impact.[25,28] Although no statistically significant decrease in MIP_A was observed, MIP_A from 57% of all patients is situated below normative values, indicating a clinically relevant decrease in TS. Since more than 50% of all patients showed reduced MIP_A or MIP_P (52% of all patients), we may conclude a clinical important drop in TS following RT.

A possible explanation for this early decline in swallowing and TS is multifactorial. Firstly, the early deterioration in the self-perceived swallowing function may be explained by

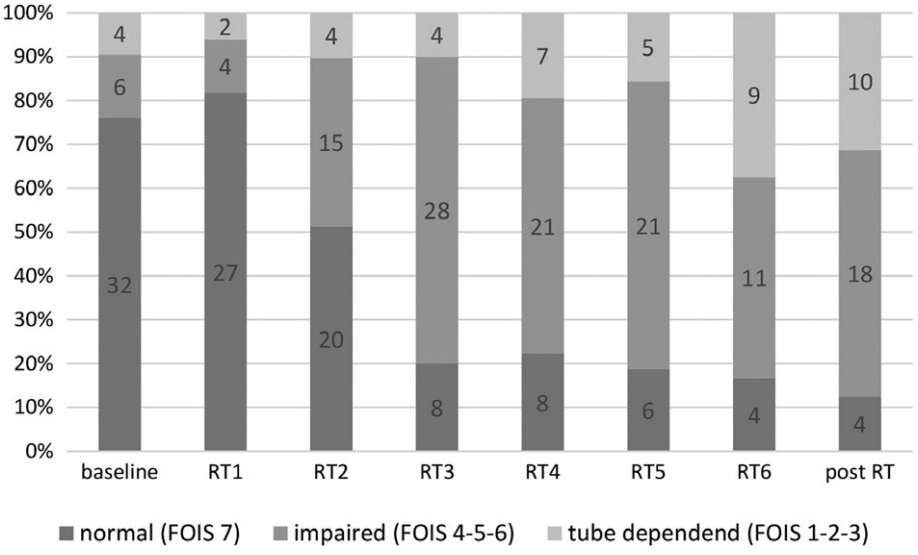

FIGURE 4 Evolution of functional oral intake during CRT (nonimputed dataset), *n* per subgroup displayed in stacked column

TABLE 2 Evolution of tongue strength during radiotherapy compared to baseline measurements

Parameter	Time point	Baseline	RT1	RT2	RT3	RT4	RT5	RT6	Post-RT
MIP_A	Mean ± SD (kPa)	45 ± 13	48 ± 15	46 ± 13	45 ± 11	46 ± 13	43 ± 11	42 ± 11	42 ± 12
	P		NA	NA	NA	NA	NA	NA	NA
	Estimate (SE)		NA	NA	NA	NA	NA	NA	NA
MIP_P	M ± SD (kPa)	42 ± 13	43 ± 14	40 ± 12	42 ± 12	40 ± 14	38 ± 12	36 ± 13	38 ± 13
	P		0.94	0.71	0.86	0.13	**0.001**	0.33	**0.03**
	Estimate (SE)		0.19 (1.58)	1.87 (1.58)	1.23 (1.56)	3.74 (1.66)	5.75 (1.55)	3.96 (2.15)	5.95 (1.96)
$Pswal_A$_sal	Mean ± SD (kPa)	39 ± 15	40 ± 13	36 ± 14	36 ± 14	34 ± 14	31 ± 11	35 ± 15	32 ± 11
	P		0.64	0.17	0.24	0.23	**0.003**	0.17	**0.03**
	Estimate (SE)		1.08 (2.27)	4.97 (2.34)	3.59 (2.31)	4.05 (2.29)	8.83 (2.46)	4.75 (2.35)	8.83 (2.91)
$Pswal_P$_sal	Mean ± SD (kPa)	36 ± 14	37 ± 16	31 ± 12	34 ± 13	32 ± 12	29 ± 9	30 ± 12	32 ± 12
	P		0.54	**0.002**	0.21	0.09	**0.003**	0.07	0.09
	Estimate (SE)		−1.23 (2.00)	7.24 (2.00)	3.21 (1.98)	4.34 (1.99)	7.10 (2.02)	5.57 (2.21)	5.12 (2.21)
$Pswal_A$_yog	Mean ± SD (kPa)	38 ± 15	36 ± 13	35 ± 14	33 ± 12	33 ± 12	30 ± 12	31 ± 12	32 ± 13
	P		0.94	0.94	0.36	0.12	**0.04**	**0.02**	**0.04**
	Estimate (SE)		1.42 (1.98)	0.92 (2.17)	3.12 (2.01)	4.74 (2.16)	6.29 (2.26)	6.63 (2.12)	6.06 (2.18)
$Pswal_P$_yog	Mean ± SD (kPa)	34 ± 13	36 ± 11	30 ± 10	31 ± 12	30 ± 11	28 ± 9	25 ± 10	30 ± 11
	P		0.72	0.72	0.72	**0.04**	**0.0007**	0.72	0.22
	Estimate (SE)		−1.88 (1.56)	2.54 (1.85)	1.77 (1.56)	5.47 (1.89)	7.36 (1.76)	0.92 (2.10)	4.93 (2.22)

Abbreviations: estimate: estimate of the difference vs baseline based on combined mixed model analysis; MIP_A, anterior maximal isometric pressure; MIP_P, posterior maximal isometric pressure; NA: post hoc analysis not applicable since overall time-effect in combined mixed model analysis is not significant; RT, radiotherapy; $SWAL_A$_sal, saliva swallow with anterior measurement; $SWAL_P$_sal, saliva swallow with posterior measurement; $SWAL_A$_yog, yogurt swallow with anterior measurement; $SWAL_P$_yog, yogurt swallow with posterior measurement; *P* and estimate values based on combined mixed models analysis with multiple imputations; Mean ± SD based on nonimputed dataset. Bold values are significance-levels (*P*-values).

the treatment itself. RT creates muscular damage already during treatment[1,5,47] and the addition of CCRT is known as a predictive factor for the development of acute toxicities and dysphagia after CCRT.[29] Secondly, early changes in functional oral intake with associated dietary modifications can result in periods of decreased loading of the system with possible disuse of the swallowing musculature and ultimately promote further loss of function.[4,5] Thirdly, as moderate correlations between grip and TS are only measured at RT1 and RT2, when no significant decreases in any other parameter are observed yet, reported declines in MIP cannot sufficiently be explained by a general decrease in muscle strength. Finally, xerostomia and mucositis add to the deterioration of the oral phase of swallowing,[22,39,60] leading to difficulties with bolus formation and bolus transport and possibly influencing TS measurement. However, the precise impact of these acute toxicities may lead to decreased functional oral intake, also resulting in periods of decreased loading of the swallowing system. In conclusion, a vicious cycle may appear combining acute muscular damage and loss of function, increasing the likelihood of developing RAD.

Swallowing pressures are more closely related to a patient's actual swallowing function than MIP measurements,[39] because swallowing is a submaximal strength activity.[61,62] The current study is the first one measuring swallowing pressures in patients with HNC. All Pswal parameters were significantly reduced during RT, with the most striking declines in $Pswal_A$_sal and $Pswal_A$_yogh, that decrease by 21% at the fifth week of RT compared to the baseline measurements. Decreased values of Pswal do not occur with age,[61,63] and have—as yet—been only described in patients with neuromuscular disorders.[64,65] Since the impact of pain and mucositis on swallowing pressure is not analyzed in this article, it is unknown if the decrease in strength was related to less effort to pain.

TABLE 3 Correlations between grip strength and tongue strength

Time point	BL	RT1	RT2	RT3	RT4	RT5	RT6	Post-RT
Parameter								
MIP_A	0.111	0.659	0.734	0.464	0.488	0.459	0.542	0.369
MIP_P	0.347	0.540	0.694	0.430	0.484	0.428	0.510	0.343
$Pswal_A$_sal	0.362	0.582	0.610	0.395	0.580	0.382	0.443	0.344
$Pswal_P$_sal	0.111	0.513	0.548	0.366	0.467	0.364	0.360	0.273
$Pswal_A$_yogh	0.308	0.592	0.641	0.518	0.491	0.356	0.471	0.228
$Pswal_P$_yog	0.219	0.540	0.593	0.418	0.442	0.353	0.385	0.196

Abbreviations: MIP_A, anterior maximal isometric pressure; MIP_P, posterior maximal isometric pressure; RT, radiotherapy; $SWAL_A$_sal, saliva swallow with anterior measurement; $SWAL_P$_sal, saliva swallow with posterior measurement; $SWAL_A$_yog, yogurt swallow with anterior measurement; $SWAL_P$_yog, yogurt swallow with posterior measurement.

TABLE 4 Evolution of swallow-related QoL during RT compared to baseline measurements

Time point	Baseline	RT1	RT2	RT3	RT4	RT5	RT6	Post-RT
Subscale								
General burden								
Mean ± SD (kPa)	71 ± 35	87 ± 23	55 ± 32	47 ± 31	49 ± 31	41 ± 28	32 ± 28	41 ± 30
P		0.12	0.02	**0.007**	**0.0000**	**0.0007**	**0.0000**	**0.001**
Estimate (SE)		−7.28 (4.52)	14.45 (5.07)	22.05 (5.77)	26.40 (4.46)	33.89 (5.97)	36.10 (5.39)	35.58 (6.38)
Eating duration								
Mean ± SD (kPa)	66 ± 38	72 ± 37	52 ± 37	39 ± 31	32 ± 29	32 ± 34	29 ± 28	26 ± 30
P		0.83	**0.001**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**
Estimate (SE)		1.23 (5.68)	19.04 (5.56)	34.38 (5.55)	43.53 (5.61)	46.08 (6.25)	46.39 (6.90)	50.95 (5.79)
Eating desire								
Mean ± SD (kPa)	70 ± 30	69 ± 34	55 ± 29	46 ± 30	35 ± 25	33 ± 28	29 ± 28	35 ± 26
P		0.76	**0.005**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**
Estimate (SE)		−2.12 (6.74)	16.14 (5.22)	23.92 (5.30)	35.12 (5.74)	40.26 (5.16)	41.92 (5.52)	42.96 (5.23)
Symptoms								
Mean ± SD (kPa)	82 ± 14	87 ± 12	80 ± 17	76 ± 17	73 ± 19	70 ± 16	68 ± 22	70 ± 17
P		0.62	0.81	0.12	**0.009**	**0.01**	**0.0004**	**0.003**
Estimate (SE)		−3.66 (3.61)	1.13 (4.64)	7.37 (3.55)	10.82 (3.46)	13.59 (4.20)	19.67 (4.21)	17.21 (4.35)
Food selection								
Mean ± SD (kPa)	82 ± 29	87 ± 23	66 ± 32	50 ± 38	44 ± 32	42 ± 32	33 ± 26	40 ± 25
P		0.40	**0.02**	**0.002**	**0.0000**	**0.0000**	**0.002**	**0.0002**
Estimate (SE)		−5.33 (6.34)	15.88 (5.94)	31.41 (7.88)	38.77 (6.39)	39.15 (6.78)	46.12 (9.28)	48.95 (8.37)
Communication								
Mean ± SD (kPa)	73 ± 33	86 ± 20	74 ± 31	72 ± 29	64 ± 32	61 ± 33	54 ± 34	55 ± 27
P		0.13	0.74	0.74	0.13	**0.003**	**0.0000**	**0.0002**
Estimate (SE)		−10.31 (5.03)	2.03 (4.87)	4.33 (4.85)	10.58 (4.92)	17.29 (5.00)	26.00 (4.87)	23.26 (5.33)
Fear of eating								
Mean ± SD (kPa)	88 ± 17	93 ± 18	85 ± 24	80 ± 27	79 ± 34	74 ± 32	72 ± 30	80 ± 26
P		0.79	0.36	0.12	**0.003**	**0.02**	**0.0000**	**0.0000**
Estimate (SE)		0.97 (3.70)	6.65(4.66)	9.64 (4.28)	17.46 (4.16)	17.29 (4.16)	25.66 (3.70)	21.33 (3.25)
Mental health								
Mean ± SD (kPa)	82 ± 27	88 ± 21	74 ± 30	55 ± 34	58 ± 34	48 ± 35	44 ± 36	46 ± 32
P		0.24	0.24	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**
Estimate (SE)		−7.00 (5.78)	10.72 (6.62)	27.12 (5.61)	26.20 (5.27)	37.76 (5.55)	43.71 (7.08)	42.77 (5.59)
Social functioning								
Mean ± SD (kPa)	76 ± 29	91 ± 21	78 ± 26	71 ± 30	66 ± 29	52 ± 36	53 ± 35	51 ± 32
P		0.03	0.90	0.59	0.06	**0.0000**	**0.002**	**0.004**
Estimate (SE)		−11.75 (4.51)	−0.61 (4.64)	5.17 (4.89)	14.51 (5.12)	23.80 (4.58)	22.89 (5.57)	28.42 (6.47)
Sleep								
Mean ± SD (kPa)	55 ± 32	57 ± 32	52 ± 30	50 ± 34	53 ± 36	39 ± 33	49 ± 35	44 ± 36
P		NA	NA	NA	NA	NA	NA	NA
Estimate (SE)		NA	NA	NA	NA	NA	NA	NA
Fatigue								
Mean ± SD (kPa)	66 ± 28	59 ± 25	56 ± 25	50 ± 27	47 ± 28	43 ± 30	40 ± 31	43 ± 30
P		0.07	0.07	**0.0001**	**0.0000**	**0.0000**	**0.0002**	**0.0000**
Estimate (SE)		8.03 (3.82)	9.98 (5.06)	18.72 (4.24)	22.25 (4.00)	26.83 (4.00)	30.07 (5.46)	26.97 (4.24)

Abbreviations: estimate, estimate of the difference vs baseline based on Combined Mixed Model analysis; NA, post hoc analysis not applicable since overall time-effect in Combined Mixed Model analysis is not significant; RT, radiotherapy; *P* and estimate values based on Combined Mixed Model analysis with multiple imputations; Mean ± SD based on nonimputed dataset. Bold values are significance-levels (*P*-values)

Impact on QoL is another important aspect of RAD highlighted in this study. The consequences of dysphagia following RT are socially debilitating, hence, increasing social isolation.[18,66] To the best of our knowledge, this is the first study reporting QoL during and directly after completion of RT. A decline in QoL can already be detected in the second week of RT for most domains, further lowering until completion of RT, with eating duration, food selection and

eating desire showing the steepest decreases. Remarkable are the slight increases in QoL scores the first week of RT, possibly biased by positive expectations patients have by starting their treatment. Literature reports increasing QoL between 3 and 6 months after treatment, but normalization of QoL scores is rarely described,[18,19,40] with appetite, speech, and swallowing often remaining severely affected.[19] Gillespie et al.[66] stated that patients with depressed mental health are more prone to long-term dysphagia. Furthermore, patients with a decreased swallow-related QoL might avoid eating with others because of the discomfort during mealtime,[18] indirectly resulting in a changed or decreased oral intake.[4,5] Consequently, decreased QoL implies a loss of function and might, therefore, be included in the vicious cycle between acute muscular damage and loss of function, increasing the likelihood to develop RAD.

Like other prospective HNC research, dropout has been a common problem in the current study.[15,39] Although the actual attrition rate of 43% is situated between 41% and 47%, described as common in prospective cancer,[67] an increase in participants could reveal additional relationships. Thus, although these exploratory results show interesting patterns, expanding sample size in future research is necessary before generalization. Nevertheless, this is the first prospective data set in HNC patients consisting of data on self-perceived swallowing function, TS and QoL during radical (C)RT and therefore unique and meaningful.

A limitation of this study is the heterogeneous population consisting of patients with different tumor locations and the inclusion of patients with RT as well as CCRT. Nevertheless, clustering different patient groups is analogous to other publications[22,41,42] to increase power. Furthermore, to limit heterogeneity, stringent criteria have been set out conserving only including patients with a newly diagnosed carcinoma, starting curative treatment, and excluding patients with any history of HNC.

The findings of this prospective exploratory study add considerably to the knowledge of the development of RAD in HNC patients. The results revealed self-perceived swallowing function, functional oral intake, TS and QoL to decrease already during RT or concurrent chemoradiotherapy. Regardless of etiology, these early deteriorations may result in loss of function, contributing to RAD. Close monitoring, early treatment and research on prevention of swallowing dysfunction seem therefore warranted in this population.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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