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Factors associated with swallowing dysfunction in patients with head and neck cancer

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Abstract

Background: The aim of this prospective cohort study was to investigate swallowing function in relation to personal and clinical factors among patients with head and neck cancer (HNC) from diagnosis up to 2 years after treatment.

Methods: The 100 ml water swallow test was measured before treatment, and 3, 6, 12, and 24 months after treatment. Linear mixed-effects model analysis was conducted to investigate changes over time and the association with personal (sex and age) and clinical (tumor site, tumor stage, and treatment modality) factors.

Results: Among 128 included patients, number of swallows increased from baseline to 3 months after treatment and decreased to baseline again at 6 months after treatment. The number of swallows was associated with age and treatment modality.

Conclusions: In patients with HNC, swallowing (dys)function changes over time with the worst score 3 months after treatment. A higher age and being treated with surgery are factors associated with swallowing dysfunction over time.

KEYWORDS
100 ml water swallowing test, head and neck cancer, linear mixed model, swallowing dysfunction

1 | INTRODUCTION

Head and neck cancer (HNC) is the seventh most common cancer worldwide, most often caused by alcohol and/or tobacco use, or the human papilloma virus (HPV) (Rettig & D'Souza, 2015). Treatment options for HNC include surgery, radiation therapy (RT), and chemoradiation therapy (CRT). The use of high-intensity radiation treatment regimens has resulted in improved survival, but the prevalence of patients suffering from side effects of treatment has increased as well (Langendijk et al., 2009). Patients may suffer from, for example, tissue fibrosis, osteoradionecrosis, xerostomia, or dysphagia. Dysphagia may occur in up to 44% of patients treated with RT and up to 84% of patients treated with surgery (Kreeft et al., 2009; van der Veen & Nuyts, 2017). Swallowing function may be impaired due to a number of normal tissue changes such as edema, neuropathy, fibrosis, and mucositis (Hutcheson et al., 2012). While edema and mucositis disrupt normal swallowing function during treatment, they substantially improve after treatment in the majority of patients. In contrast, neuropathy and fibrosis of the swallowing musculature may develop or persist long after completion of treatment (Hutcheson et al., 2012). Swallowing dysfunction can lead to complications such as malnutrition, aspiration, and subsequent pneumonia, which may depend on tumor stage, sub-site of the tumor, age, and treatment modality (Hutcheson et al., 2019; Riffat et al., 2015). RT may result in a large dose delivery to critical structures necessary for normal deglutition, such as the base of tongue, supraglottic larynx, soft palate, cricopharyngeal muscles, and pharyngeal constrictor muscles (Alterio et al., 2017). Chemotherapy may also have an effect on swallowing function, and it may lead to various side effects such as nausea, vomiting, neutropenia, generalized weakness, and fatigue (Hutcheson et al., 2012). Swallowing problems that occur after surgery vary with tumor site and size of resection, and type of reconstruction (Manikantan et al., 2009).

In order to reduce the risk of swallowing dysfunction before and after curative treatment for HNC, it is important to identify factors associated with swallowing dysfunction. Therefore, the aim of this prospective study was to identify factors associated with swallowing dysfunction in patients with HNC, before, and 3, 6, 12, and 24 months after treatment. It was hypothesized that especially treatment modality, tumor site, and tumor stage will have a significant impact on swallowing function after treatment.

2 | MATERIALS AND METHODS

Patients were included by convenience sampling when they were 18 years or older, were diagnosed with oral, oropharyngeal, hypopharyngeal, or laryngeal HNC, and were treated with a curative intent at the University Medical Center Utrecht (UMCU), the Netherlands between September 2014 and June 2018. Patients with recurrent or residual disease, cognitive impairments, and patients having trouble understanding or reading the Dutch language were excluded. All patients signed written informed consent before participation. The study protocol of this prospective cohort study was approved by the Medical Ethics Committee of the Netherlands (2013.301(A2018.307)-NL45051.029.13), and is part of the NET-QUBIC cohort study (Verdonck-de Leeuw et al., 2019). Patient data about age, sex, tumor stage (Paleri et al., 2010), tumor site, and treatment were used. Patients were assessed before primary treatment (baseline, M0), and 3 (M3), 6 (M6), 12 (M12), and 24 months after treatment (M24). At every assessment, the primary outcome measure in the present study (100 ml water swallow test (WST)) was performed.

2.1 | 100 ml water swallow test

During the WST, a subject is asked to drink 100 ml of water as quickly as is comfortably possible. The time to swallow 100 ml (in seconds) and the number of swallows are counted, both by the subject and the researcher. Timing starts when the water touches the bottom lip and stops when the larynx comes to rest after the last swallow (Patterson et al., 2009). Persons fail the test when they cough or choke post-swallow, have a wet voice quality post-swallow, or are unable to drink the whole 100 ml (Patterson et al., 2011). When a person is unable to drink the 100 ml, the residual water is measured and noted. As shown in previous research, the number of swallows had an excellent reliability (Intraclass correlation coefficient (ICC) = 0.923) when comparing test and retest, while the swallowing duration had a slightly lower reliability (ICC = 0.893). Swallowing duration needed a larger smallest detectable change (SDC%) and standard error of measurement (SEM%) (16.5% versus 52.8%, and 5.9% versus 19.1%, respectively) in comparison with the number of swallows (Vermaire et al., 2021). Therefore, in the current study, the number of swallows was chosen as primary outcome measure. A higher number of swallows indicates more swallowing problems. Data from previous research were used to calculate a cutoff value (Vermaire et al., 2021). A value larger than two standard deviations from the mean value of healthy subjects was used to indicate swallowing problems in patients with HNC (≥8 swallows needed to drink 100 ml of water) (Thomas & Wiles, 1999). Swallowing dysfunction was defined as a failure on the WST and/or a value above the cutoff value of eight number of swallows needed to swallow 100 ml of water (Thomas & Wiles, 1999). Apart from the cutoff value, the SDC found in previous research (0.79 swallows) indicates whether the difference between measurements is a real difference and not a measurement error (Vermaire et al., 2021).

2.2 | Statistical analyses

Descriptive statistics were used to describe the study population. A Kruskal–Wallis H test was performed to examine differences in age between primary treatment groups, and a chi-square test was run to test for differences in sex, tumor site, and tumor stage between primary treatment groups. A linear mixed-effects model

FIGURE 1 Flowchart depicting the number of patients at each time point. X: patients stopped participating; †patients passed away; *missing WST measurement

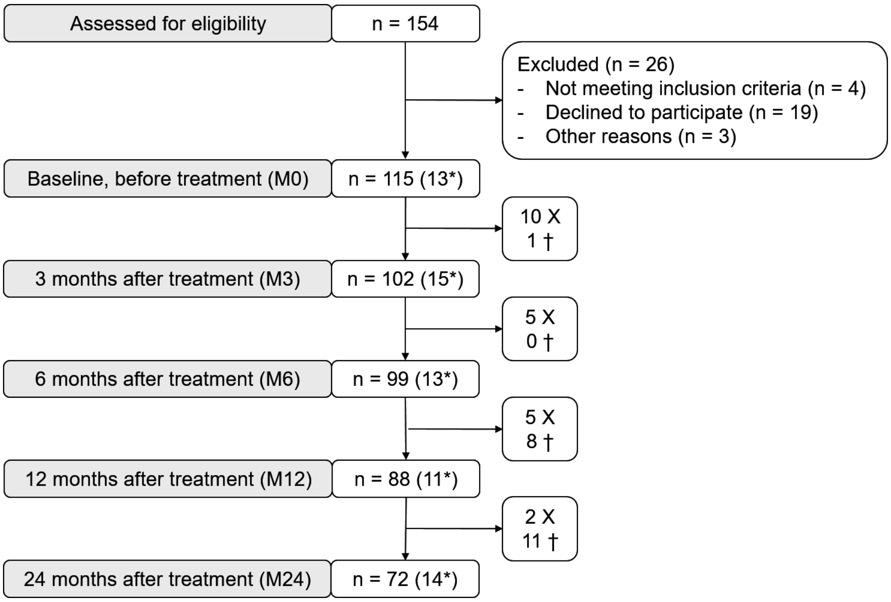

TABLE 1 Baseline characteristics of patients with head and neck cancer that performed the 100 ml water swallow test based on all patients, and sub-groups of patients based on primary treatment

		Primary treatment				
Variable	**All patients ($n = 128$)**	**RT ($n = 54$)**	**CRT ($n = 33$)**	**Surgery ($n = 25$)**	**Surgery with (C)RT ($n = 16$)**	***p*-value**
Age, median (IQR)	61.5 (11.3)	67.0 (15.0)	57.0 (12.5)	64.0 (17.5)	62.5 (16.3)	0.102[a]
Sex	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***N* (%)**	
Male	100 (78.1)	45 (83.3)	26 (78.8)	15 (60.0)	14 (87.5)	0.090[b]
Female	28 (21.9)	9 (16.7)	7 (21.2)	10 (40.0)	2 (12.5)	
Tumor stage						
I	34 (26.6)	16 (29.6)	0	15 (60.0)	3 (18.8)	<0.001*[b]
II	27 (21.1)	17 (31.5)	0	6 (24.0)	4 (25.0)	
III	15 (11.7)	9 (16.7)	3 (9.1)	2 (8.0)	1 (6.2)	
IV	52 (40.6)	12 (22.2)	30 (90.9)	2 (8.0)	8 (50.0)	
Tumor site						
Oropharynx	50 (39.1)	23 (42.6)	26 (78.8)	1 (4.0)	0	<0.001*[b]
Larynx and Hypopharynx	42 (32.8)	31 (57.4)	6 (18.2)	4 (16.0)	1 (6.2)	
Oral cavity	36 (28.1)	0	1 (3.0)	20 (80.0)	15 (93.8)	
Primary treatment						
RT	54 (42.2)					
CRT	33 (25.8)					
Surgery	25 (19.5)					
Surgery with (C)RT	16 (12.5)					

Abbreviations: CRT, chemoradiation therapy; IQR, interquartile range; n, number of patients; RT, radiation therapy. *$p < 0.05$.
[a]Kruskal–Wallis H test.
[b]Chi-square test.

(LMM) analysis was conducted to investigate changes over time in number of swallows, and the association with patient and clinical factors (Bolker et al., 2009). Akaike's Information Criterion (AIC) was used to select the most appropriate covariance structure to fit the data (Burnham & Anderson, 2016). To account for within-patient correlations, a random patient factor was added, and a random intercept was used to account for the different entry levels of patients. The fixed-effect factors tumor site, treatment modality,

TABLE 2 Mean number of swallows for each timing of assessment, and the total swallowing dysfunction as indicated by the number of failed water swallowing tests and/or the number of patients above the cutoff score

	Timing of assessment				
	M0	M3	M6	M12	M24
n patients	115	102	99	88	72
Mean number of swallows (SD)	5.8 (2.6)	6.4 (4.2)	5.8 (3.7)	5.6 (3.4)	5.4 (4.1)
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Swallowing dysfunction[a]	22 (19.1)	22 (21.6)	19 (19.2)	13 (14.8)	10 (13.9)
Number of patients above cutoff score	16 (13.9)	18 (17.6)	14 (14.1)	13 (14.8)	8 (11.1)
Number of WST failures	6 (5.2)	12 (11.8)	9 (9.1)	4 (4.5)	2 (2.8)
Coughing or choking	1/6 (16.7)	9/12 (75)	6/9 (66.7)	4/4 (100)	2/2 (100)
Not able to drink 100 ml	5/6 (83.3)	3/12 (25)	3/9 (33.3)	0	0

Abbreviations: *n*, number of patients; SD, standard deviation; WST, Water swallow test.
[a]Based on number of swallows above cutoff score and/or WST failure.

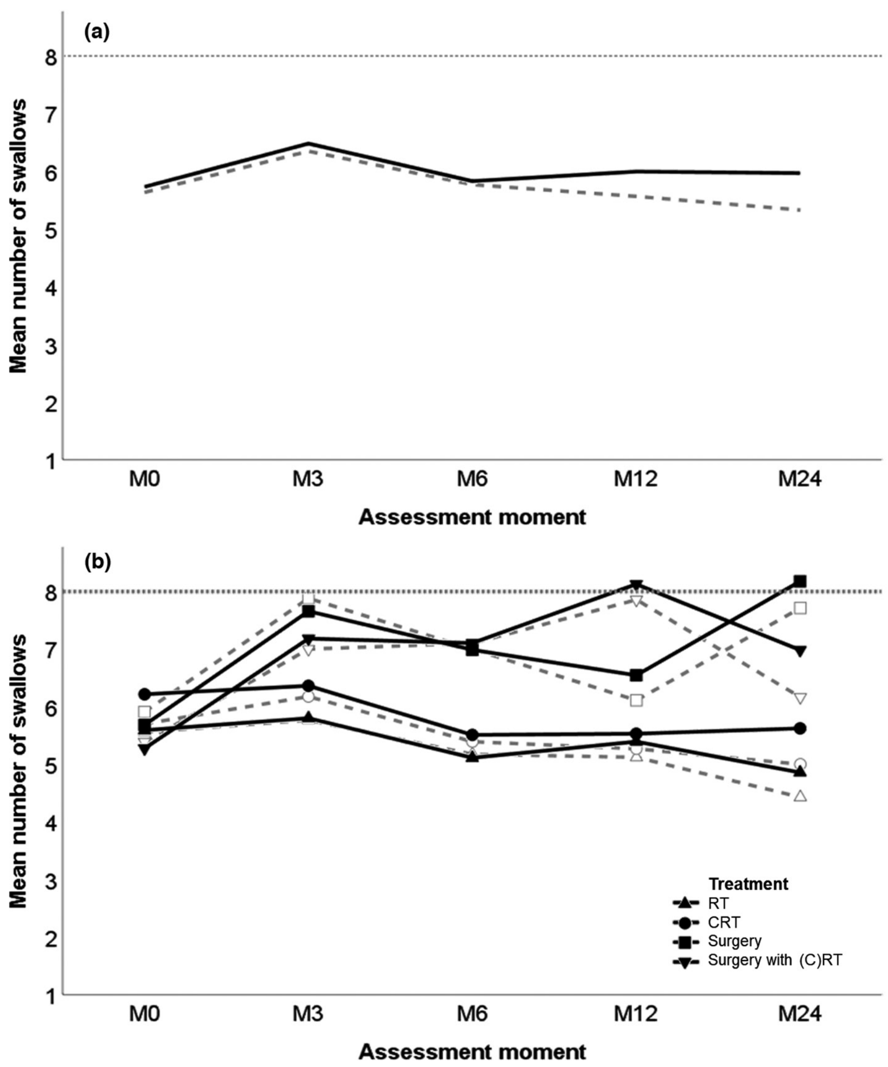

FIGURE 2 Mean number of swallows for all patients (a) and for patients based on treatment modality (b). The black solid lines represent the linear mixed model outcomes of the final model, and the gray striped lines represent the raw data. The mean number of swallows for healthy subjects is 3.68 swallows, and the cutoff value (≥2 times the standard deviation of healthy subjects (8 swallows)) is indicated by the horizontal gray dotted line

tumor stage, timing of assessment, sex, and age, as well as two-way interactions of the factors tumor site, treatment modality, and tumor stage during the assessment period were assessed using the AR(1) method (first-order autoregressive covariance pattern) for parameter estimation. Tumor site consisted of 3 levels: oral cavity, oropharynx, or larynx and hypopharynx. Treatment modality consisted of 4 levels: RT, CRT, surgery, or surgery followed by post-operative (C)RT. Tumor stage consisted of 4 levels (stages

1 to 4), timing of assessment consisted of 5 levels (M0, M3, M6, M12, and M24), sex consisted of 2 levels (male or female), and age was defined as a continuous variable. The model included a stepwise backward selection of factors, in which factors that were not significant at a $p \le 0.10$ level were removed, beginning with the interactions. A hierarchical structure was maintained, meaning that if an interaction was included in the model, the main effects were also represented in the model. Risk factors were reported as estimated unstandardized regression coefficients with 95% confidence intervals (CI) and *p*-values.

Swallowing dysfunction (a score above the cutoff value of 8 number of swallows) was used to create a receiver operating characteristic (ROC) curve, to help facilitate the use of the linear mixed-effects model in identifying factors associated with swallowing problems in patients with HNC.

The coefficients of the significant covariates, together with the value of the intercept of the mixed model analysis, were combined into a formula for the estimated number of swallows. The intercept is the value of the estimated number of swallows when all coefficients remain zero. Addition of the coefficients will lead to an increase or decrease in the estimated number of swallows. For each time point, the formula was filled with average variable values for significant coefficients, as calculated by a restricted maximum likelihood approach (REML). Model assumptions were verified by plotting the residuals versus the fitted values. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A *p*-value <0.10 was considered statistically significant.

3 | RESULTS

3.1 | Recruitment and study population

Of 135 patients that met the inclusion criteria, 128 were included and 115 performed baseline measurements. During the study period with 2 years follow-up, 25 patients were deceased, and 24 patients dropped out. In addition, five measurements at M24 could not be performed because of the COVID-19 situation and were indicated as missing. The flow diagram of the study is shown in Figure 1. Personal and clinical characteristics of the study population are shown in Table 1 for the total patient group, and for sub-groups based on treatment.

Of the 41 patients receiving surgery, reconstruction was performed in 16 patients (39%), and neck dissection was performed in 29 patients (71%), of which 24 were elective neck dissection. Radiotherapy most often consisted of a 35 times 2 Gy schedule: of the 103 patients receiving RT, 55 received conventional RT (53%), 32 received accelerated RT (31%), 6 received hyper fractionated RT (6%), and 10 were classified as other. All patients received either intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). Of the 43 patients receiving chemotherapy, 32 received cisplatin (74%), 6 received carboplatin (14%), and 5 received cetuximab (12%).

3.2 | Swallowing over time

The mean and standard deviation of the number of swallows needed to drink the 100 ml water at the different times of assessment are shown in Table 2. Linear mixed model analysis showed that the number of swallows increased from baseline to 3 months after treatment and decreased to baseline again at 6 months after treatment and beyond (Figure 2a).

The number of patients with swallowing dysfunction per time of assessment is shown in Table 2 as well, either because of WST failure or because a number above the cutoff value was reached. Both a WST failure and a score above the cutoff value were reported in 16 patients. The prevalence of swallowing dysfunction is estimated to be 19.1% at baseline, 21.6% at M3, 19.2% at M6, 14.8% at M12, and 13.9% at M24.

3.3 | Factors associated with number of swallows

Linear mixed model analysis revealed that tumor site, sex, and tumor stage were not associated with the number of swallows, and were therefore removed from the final model. The course of number of swallows was significantly associated with age, and there was a significant interaction between treatment modality and timing of assessment, as shown in Table 3. Higher age was associated with a higher number of swallows (+0.07 more swallows per increasing year). A number of swallows of patients with surgery alone were comparable to number of swallows of patients that received surgery and adjuvant (C)RT: there was an increase in number of swallows from baseline to 3 months after treatment, which remained high up to 24 months after treatment. In contrast, the number of swallows of patients treated with RT or CRT (without surgery) increased from diagnosis to 3 months after treatment, after which the number of number of swallows returned to baseline level (Figure 2b). The cutoff score was used to develop a ROC curve indicating swallowing problems before and after treatment in patients with HNC (Appendix 1). The formula for the estimated number of swallows that are retained in the final model is shown in the footnote of Table 3.

4 | DISCUSSION

Overall, swallowing function as measured by number of swallows needed to drink 100 ml of water, worsened from diagnosis to 3 months after treatment, after which it returned to or below baseline level in patients with head and neck cancer (Table 2). Swallowing dysfunction increased from diagnosis (19%) to 3 months after treatment (22%), after which it returned to or below baseline level (14%). Age and treatment modality were significantly associated with the course of swallowing function. Swallowing function was worse in older patients. Swallowing function of patients receiving surgery as primary treatment in particular was worse 3 months after treatment compared with

TABLE 3 Linear mixed model estimates for the number of swallows

		Estimate (95% CI)	*p*-value	Interactions with timing of assessment								
Intercept		1.46 (−2.40 to 5.32)										
				M0	M3		M6		M12		M24	
				Estimate (95% CI)	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Timing of assessment	M0	Reference										
	M3	1.97 (0.47 to 3.48)	0.011*									
	M6	1.30 (0.04 to 2.56)	0.043*									
	M12	0.86 (−0.49 to 2.22)	0.211									
	M24	2.49 (1.03 to 3.95)	0.001*									
Age		0.07 (0.01 to 0.13)	0.021*									
Treatment	Surgery	Reference		Reference								
	RT	−0.33 (−2.09 to 5.32)	0.711	Reference	−1.77 (−3.55 to 0.02)	0.052*	−1.78 (−3.29 to −0.27)	0.021*	−1.06 (−2.69 to 0.56)	0.200	−3.23 (−4.96 to −1.49)	<0.001*
	CRT	0.84 (−1.09 to 2.77)	0.392	Reference	−1.83 (−3.76 to 0.11)	0.064*	−2.01 (−3.68 to −0.33)	0.019*	−1.55 (−3.32 to 0.23)	0.088*	−3.09 (−5.00 to −1.18)	0.002*
	Surgery with (C) RT	−0.36 (−2.72 to 1.99)	0.761	Reference	−0.07 (−2.53 to 2.39)	0.956	0.53 (−1.62 to 2.67)	0.630	1.99 (−0.46 to 4.44)	0.112	−0.79 (−3.38 to 1.81)	0.552

Note: The following formula for the estimated number of swallows shows the variables and their coefficients. Factors with a positive coefficient will increase the number of swallows and therefore reflect a worse swallowing function: Estimated number of swallows = 1.46 + 1.97M3 + 1.30M6 + 0.86M12 + 2.49M24 + 0.07age − 0.33RT +0.84CRT − 0.36surgery with (C)RT - 1.77RT*M3 − 1.83CRT*M3 - 0.07surgery with (C)RT*M3 − 1.78RT*M6 − 2.01CRT*M6 + 0.53surgery with (C)RT*M6 − 1.06RT*M12 − 1.55CRT*M12 + 1.99surgery with (C)RT*M12 − 3.23RT*M24 − 3.09CRT*M24 − 0.79surgery with (C)RT*M24.

Abbreviations: CI, confidence interval; CRT, chemoradiation therapy; SE, standard error; RT, radiation therapy.

*$p < 0.10$.

baseline and remained worse up to 24 months. Patients treated with (C)RT did not show this worsening after treatment. Instead, their swallowing function improved after treatment.

The clinical relevance of the LMM results can be clarified by taking into account the smallest detectable change (SDC) found in previous research. The SDC for the number of swallows was 0.79 points, indicating that the difference between two measurements has to be at least 0.79 points to be a real difference and not a measurement error (Vermaire et al., 2021). When looking at the estimates in Table 3, all results meet this condition except age; one-year older does not contribute to a worse swallowing function; however, a difference of more than 11 years will.

4.1 | Comparison with literature

In previous research, other factors associated with worse swallowing function were sex (female), tumor stage (T3 and T4), the addition of chemotherapy as treatment modality, and oropharynx tumors (Langendijk et al., 2009; Patterson et al., 2014, 2018). These factors did not contribute to worse swallowing function in our study. In addition, the size of the radiation field, accelerated fractionation, neck irradiation, type of surgery, and normal tissue changes such as edema, neuropathy, fibrosis, and mucositis might influence the WST outcome as well (Hutcheson et al., 2012; Langendijk et al., 2009; Patterson et al., 2014). The sample size of the current study was too small to also include these factors. For example, only 16 patients received surgery followed by (C)RT. It is therefore recommended to repeat this study with a larger sample size and include more factors in the LMM analysis.

This study did not find an effect of RT treatment on swallowing function. This might be explained by the fact that patients treated with RT nowadays often receive IMRT, in order to spare the swallowing muscles (Ursino et al., 2017). The next step should therefore be to investigate the effect of dose to the swallowing organs at risk (OAR) on swallowing function in order to see the effect of OAR sparing.

The number of WST failures increased over time to almost 12% three months after treatment, and the reason for failure changed from "not being able to drink the 100 ml of water," to "coughing or choking post-swallow." Coughing or choking post-swallow was found to have a specificity of up to 91.7% in predicting aspiration, and the WST is therefore a useful tool for early detection of swallowing dysfunction (Wu et al., 2004). Previous research found dysphagia and aspiration rates between 12% and 21%, similar to the results found in this study (Judy et al., 2018; Patterson et al., 2018). Especially, patients that received surgery with adjuvant treatment have a higher prevalence of dysphagia in comparison with patients that receive RT alone, as also seen in this research by the higher number of swallows (Hutcheson et al., 2019). Besides WST failures, between 11% and 18% of patients had a WST score above the cutoff score (>2 standard deviations above the mean of healthy subjects), with the most problems 3 months after treatment.

Previous research showed that the objective WST and subjective patient reported outcomes measuring swallowing function have a low correlation and can therefore not be used interchangeably (Vermaire et al., 2021). A future study might aim at developing a prediction model with subjective questionnaires, to obtain individual risk scores for swallowing problems in patients with HNC, including a larger number of potential predictors. These predictors could then, apart from the predictors used in this study, also include a larger range of treatment modalities and normal tissue changes. This also makes it possible to study whether the factors found in this study are found with subjective outcome measures as well.

4.2 | Strengths and limitations

Strengths of our study were the prospective study design, the use of the linear mixed-effects model checklist with recommendations for reporting multilevel data and analyses (Monsalves et al., 2020), and the use of an objective swallowing test with a high test–retest reliability (Vermaire et al., 2021). Limitations were the relatively low number of patients at follow-up, which limited the number of factors that could be explored, and the relative large drop-out and missing values. These missing data may have influenced the results, because it is unknown how these patients would have performed on the WST. Although linear mixed-effects model analysis is especially designed for repeated measurement analyses, and is better at handling missing values in comparison with other regression analyses (Van der Elst et al., 2013), these regression models do not take into account the number of deaths as competing risk. Additionally, since the study group was relatively small, it was chosen to only look at interactions between timing of assessment and treatment, location, and tumor stage.

Another limitation of this study was the significant differences found between treatment versus tumor stage and tumor site, as seen in Table 1. Patients receiving RT have an oropharynx, hypopharynx, or larynx tumor, while patients receiving surgery most often have a tumor in the oral cavity. In addition, patients receiving CRT have larger tumors (stage III and IV), while patients receiving surgery most often have smaller tumors (stage I and II). Therefore, the association found between the WST outcome and treatment is also caused by tumor site and tumor stage. Unfortunately, because of the low number of patients in this study, no interactions between treatment, tumor stage, and tumor site could be explored in the linear mixed-effects model.

4.3 | Clinical relevance

In order to improve swallowing function, promising results were found using swallowing exercises during the course of radiation treatment (Carroll et al., 2008). These exercises are designed to improve swallowing safety, that is, reduce penetration or aspiration, and increase efficiency of swallowing (Logemann, 1999). The results found in the current study suggest that especially older patients and patients after surgery may benefit from preventive swallowing exercises, because they had a worse swallowing function. It is unknown how many patients received swallowing exercises during or after treatment. Especially in patients treated with surgery, performing swallowing exercises before, during, and/or after (adjuvant) treatment may prevent dysphagia or reduce its severity (Perry et al., 2016). Also in older patients, who are at a higher risk of aspiration due to a decrease in eating and swallowing function, swallowing exercises can help maintain or improve the oral function (Kristensen et al., 2020; Robbins et al., 2005; Sugiyama et al., 2013). In addition to providing swallowing exercises, patients can be informed about expected swallowing difficulties after treatment. It is important to set realistic expectations, so patients can cope with the effects of treatment on daily functioning (Brockbank et al., 2015). Information about expected difficulties can reduce distress and anxiety during treatment, and can increase active patient participation and satisfaction with provided care (Brockbank et al., 2015).

In conclusion, in patients with head and neck cancer swallowing function changes over time from diagnosis up to 2 years after treatment, with the worst scores 3 months after treatment. A higher age and being treated with surgery are factors associated with the course of swallowing function over time. It is estimated that swallowing dysfunction occurs in 14%–22% of patients with head and neck cancer before or after treatment.

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CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

AUTHOR CONTRIBUTIONS

Jorine A. Vermaire: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing – original draft. **Cornelis P. J. Raaijmakers:** Supervision; Visualization; Writing – review & editing. **Evelyn M. Monninkhof:** Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing. **Irma M. Verdonck-de Leeuw:** Investigation; Methodology; Writing – review & editing. **Chris H. J. Terhaard:** Data curation; Supervision; Writing – review & editing. **Caroline M. Speksnijder:** Conceptualization; Formal analysis; Investigation; Methodology; Resources; Supervision; Visualization; Writing – review & editing.

CONSENT TO PARTICIPATE

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

CONSENT FOR PUBLICATION

Patients signed informed consent regarding publishing their data.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.14192.

DATA AVAILABILITY STATEMENT

The collection and integration of large amounts of personal, biological, genetic, and diagnostic information precludes open access to the NET-QUBIC research data. The section Data and sample dissemination (www.kubusproject.nl) described how the data are made available for the research community.

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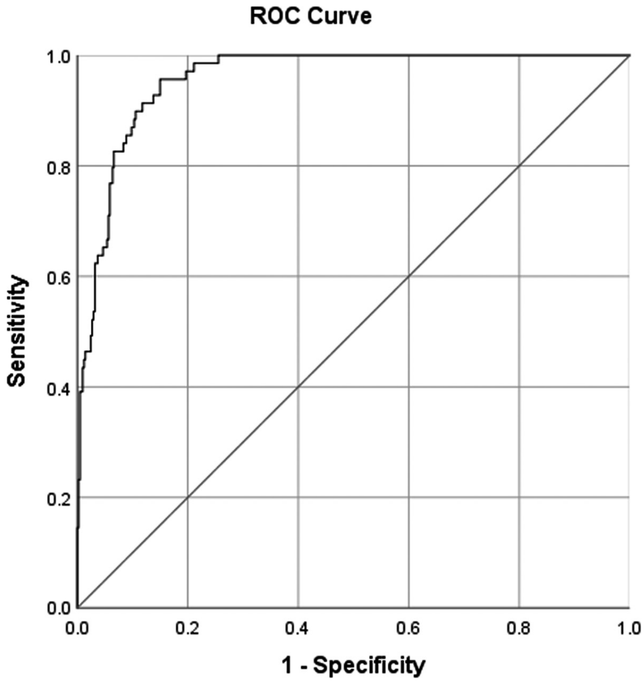
APPENDIX 1

Receiver operating characteristic (ROC) curve for swallowing problems after treatment, using the linear mixed model



The area under the curve (AUC) is 0.957. The AUC for the different timings of assessment is 0.946 (T0), 0.963 (M3), 0.940 (M6), 0.971 (M12), and 0.979 (M24). The AUC can vary between 0 and 1, where a value of 0 indicated that the model has no diagnostic power, and a value of 1 indicates that the model has a perfect diagnostic accuracy