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Original article

Development and external validation of a prediction model for tube feeding dependency for at least four weeks during chemoradiotherapy for head and neck cancer

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SUMMARY

Background & aims: Patients who receive chemoradiotherapy or bioradiotherapy (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often experience high toxicity rates interfering with oral intake, causing tube feeding (TF) dependency. International guidelines recommend gastrostomy insertion when the expected use of TF exceeds 4 weeks. We aimed to develop and externally validate a prediction model to identify patients who need TF $\geq$ 4 weeks and would benefit from prophylactic gastrostomy insertion.

Methods: A retrospective multicenter cohort study was performed in four tertiary head and neck cancer centers in the Netherlands. The prediction model was developed using data from University Medical Center Utrecht and the Netherlands Cancer Institute and externally validated using data from Maastricht University Medical Center and Radboud University Medical Center. The primary endpoint was TF dependency $\geq$4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. Potential predictors were extracted from electronic health records and radiotherapy dose–volume parameters were calculated.

Results: The developmental and validation cohort included 409 and 334 patients respectively. Multivariable analysis showed predictive value for pretreatment weight change, texture modified diet at baseline, ECOG performance status, tumor site, N classification, mean radiation dose to the contralateral parotid gland and oral cavity. The area under the receiver operating characteristics curve for this model was 0.73 and after external validation 0.62. Positive and negative predictive value for a risk of 90% or higher for TF dependency $\geq$4 weeks were 81.8% and 42.3% respectively.

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Conclusions: We developed and externally validated a prediction model to estimate TF-dependency ≥4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

1. Introduction

Side effects of concurrent chemoradiotherapy or bioradiotherapy (CRT/BRT) often impair oral intake in patients with locally advanced (stage III/IV) head and neck squamous cell carcinoma (LAHNSCC), which may contribute to involuntary weight loss [1]. Weight loss has a detrimental effect on the risk of side effects, therapy tolerance, response rate, and survival [2–6]. In order to maintain sufficient nutritional intake, tube feeding (TF) has to be initiated in 37–74% of LAHNSCC patients undergoing CRT/BRT [7–9]. TF can be administered using a nasogastric tube (NGT) or a percutaneous gastrostomy, either placed radiologically (PRG) or endoscopically (PEG). The advantages of a gastrostomy compared to a NGT are increased physical mobility, less cosmetic disadvantage, and better quality of life. Patients fed via NGT experience more dislodgement and weight loss compared to patients with a gastrostomy tube [10].

Previously, prophylactic gastrostomy insertion (before onset of side effects impairing oral intake) in all LAHNSCC patients undergoing CRT/BRT, used to be common in the majority of the clinical settings [11–13]. However, gastrostomy insertion is not a risk-free procedure; tube-related and infectious complications occur in 6–16% [14]. Therefore, new guidelines recommend that a prophylactic gastrostomy should only be inserted upon indication in LAHNSCC patients treated with CRT/BRT [15]. It is generally agreed that when the expected use of TF exceeds four weeks, gastrostomy insertion should be considered [16–20]. Ideally, patients at risk of TF $\geq$ 4 weeks are identified prior to treatment, so they can be provided with a gastrostomy before the onset of side effects potentially complicating insertion, e.g. mucositis (painful insertion), neutropenia (infection risk), and ongoing weight loss (higher complication risk) [21].

Until recently it remained challenging to predict for which patient prophylactic gastrostomy insertion would be appropriate. In a previously published study, we developed and internally validated a prediction model for calculating a patients' individual probability of TF dependency ≥4weeks [22]. New normal tissue complication probability (NTCP) models shed light on the potential additional value of RT doses on the pharyngeal constrictor muscles (PCM) and oral cavity (OC) in predicting swallowing outcomes [23–25]. Therefore, we considered it worth investigating whether these RT parameters could increase the performance of the new model. The present study describes the development and external validation of a prediction model to identify patients at risk for TF dependency ≥4 weeks who would benefit from prophylactic gastrostomy insertion.

2. Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. We reported this study in accordance with Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [26].

2.1. Source of data

The electronic health records of patients treated in four Dutch cancer centers were retrospectively reviewed to compile the development and validation dataset. For every center, data was collected by different independent researchers, in consultation with the executive researchers about the methods of data extraction and any uncertainties about the way of reporting.

2.2. Populations

The developmental dataset consisted of LAHNSCC patients treated between 2013 and 2016 in University Medical Center Utrecht (UMCU) and patients treated between 2014 and 2017 in Netherlands Cancer Institute (NCI). The external validation of the model was performed on data from patients treated between 2013 and 2016 in Maastricht University Medical Center + (MUMC+) and Radboud University Medical Center (RUMC).

LAHNSCC patients were included when they were treated with primary or adjuvant concurrent CRT or BRT. Patients were excluded from the study in case of histology other than squamous cell carcinoma, esophageal tumor location, bilateral neck dissection with removal of submandibular glands (RT dose calculation on contralateral gland not possible), refusing TF despite the physician's strong recommendation, premature discontinuation of RT, switch to palliative treatment, or death during oncological treatment.

Oncological treatment was previously described in detail [22,27,28]. In brief, patients treated with CRT received cisplatin (100 mg/m^2 three weekly or 40 mg/m^2 weekly) or carboplatin (1.5 AUC weekly) combined with RT. BRT treatment consisted of a loading dose of cetuximab (400 mg/m^2), followed by a weekly dose of cetuximab (250 mg/m^2) combined with RT. RT was given in 33–35 daily fractions of 2 Gy (CRT) or 30 to 34 fractions of 2 Gy (BRT). All patients were counseled by a dietitian.

2.3. Outcome

The primary endpoint of this study was the use of TF $\geq$ 4 weeks initiated during CRT/BRT or within 30 days after CRT/BRT completion. TF was initiated when oral nutritional intake was insufficient in meeting nutritional requirements according to the Dutch guideline on malnutrition [29] as described earlier [22].

2.4. Predictors

The potential predictors of TF dependency were based on existing literature and included: age [30], gender [31,32], tobacco use [33], alcohol use, Body Mass Index (BMI) at baseline [34,35], pretreatment weight change [36], texture modified diet at baseline (e.g. ground, minced or liquid) [31], Eastern Cooperative Oncology Group performance status (ECOG PS) [37], tumor site [31,35], T classification [9,31], N classification [31,35] (AJCC 7th edition TNM staging system [38]), disease stage, p16 status [39] (immunohistochemically as a surrogate marker for human papillomavirus

(HPV), treatment setting (primary or adjuvant) [35], type of systemic therapy (platinum based or cetuximab) [33] and neck irradiation (non or unilateral versus bilateral) [9]. The dosimetric parameters extracted from electronic health records were: mean RT dose (in Gy) to the contralateral submandibular and parotid gland, swallowing muscles (PCM), and oral cavity (OC). The contours for the PCM and the OC were not available in all cases in the radiation treatment planning system and were delineated for the purpose of this study. All organs at risk were contoured according to Brouwer et al. [40] and added to the database.

2.5. Sample size

As a rule of thumb, at least ten events should be included for each candidate predictor to minimize the risk of overfitting [41]. The least frequent outcome is defined as an event. In our study, receiving TF < 4 weeks was the least frequent outcome and was therefore defined as an event. For the external validation set, at least 100 events and 100 non-events are recommended [42].

2.6. Missing data

Missing data were imputed using stochastic regression imputation with full conditional specification, while considering the following covariates: age, gender, tobacco use, alcohol use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, systemic therapy, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, mean RT dose to the OC, and TF $\geq$ 4 weeks. Values to be imputed were drawn using predictive mean matching.

2.7. Statistical analysis methods

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p < 0.30$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. Stepwise backward elimination was used to omit all predictors from the model that did not contribute substantially, using a p-value for selection of 0.10. Model performance was quantified as the model's ability to correctly discriminate between those who will and those who will not develop TF dependency $\geq$4 weeks using the area under the receiver operating characteristic curve (AUC).

For external validation, we applied the model to our validation dataset. For evaluating the performance, the AUC was computed. The Hosmer and Lemeshow goodness-of-fit test was used to assess the agreement between predicted and observed probabilities. A significant p-value would denote significant deviation from a good model [43].

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, NY) [44].

3. Results

3.1. Patient sample

The development cohort consisted of 409 patients. The validation cohort included 334 patients. Characteristics of both datasets are displayed in Table 1. Of note is the difference between the cancer centers with regard to the tube insertion protocol: In both UMCU and MUMC + gastrostomies were placed prophylactically in the majority of patients, NCI placed reactive gastrostomies and the RUMC prefers insertion of a NGT, instead of a gastrostomy tube. Details on tube insertion and TF use per cancer center are shown in Supplemental Table 1.

In the development cohort, 261 out of 409 patients (64%) required TF $\geq$ 4 weeks, whereas in the validation cohort, 176 out of 334 (53%) required TF $\geq$ 4 weeks, $p = 0.003$.

In the development cohort, 36% (n = 148) remained on a total oral diet or used TF < 4 weeks. The risk of overfitting is minimized if no more than fourteen predictors are included in the model. Regarding the 36% without TF or TF < 4 weeks, we aimed to compile an external validation set of at least 278 subjects (100/36*100%). With 158 patients (47%) receiving TF < 4 weeks and 176 patients (53%) receiving TF $\geq$ 4 weeks, our validation dataset meets the criteria of at least 100 events and 100 non-events.

3.2. Model development

Univariable regression analysis revealed $p < 0.30$ for the following variables in the development cohort: tobacco use, BMI at baseline, pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, T classification, N classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and parotid gland, mean RT dose to the PCM, and mean RT dose to the OC (Table 2).

3.3. Model specification

In the multivariable regression analysis tobacco use, BMI at baseline, T classification, disease stage, p16 status, treatment setting, neck irradiation, mean RT dose to the contralateral submandibular and PCM did not yield a p-value <0.10 and were therefore eliminated from the model. Pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, mean RT dose to the contralateral parotid gland and OC were significant predictors of risk of TF use $\geq$4 weeks. Table 3 shows the regression coefficients for all predictors included in the final multivariable regression model.

The individual probability for TF $\geq$ 4 weeks can be calculated as: $P(TF \geq 4 \text{ weeks}) = 1/(1 + e^{-LP})$, in which LP is the linear sum of all predictor values multiplied by the regression coefficients, as shown in Fig. 1.

The formula is accessible via the online supplemental material (Supplemental File 1) and invites the reader to use the prediction model in clinical practice, as suggested in Fig. 1.

3.4. Model performance

Figure 2a–2d and 3 show the performance of the prediction model. The receiver operating characteristic (ROC) curve of the model yielded an AUC of 72.8% before external validation. The Hosmer–Lemeshow test statistics showed a p-value of 0.46, indicating a good model calibration. External validation in the combined MUMC+ and RUMC sample showed an AUC of 62.4%. External validation in the MUMC + sample only showed a considerably higher AUC of 70.8%, whereas external validation in the RUMC sample only showed an AUC of 55.3%. The calibration plot shows a good agreement between predicted probability and the observed use of TF $\geq$ 4 weeks.

3.5. Sensitivity and specificity

The positive and negative predictive value for a risk of 90% or more of TF dependency $\geq$4 weeks were 81.8% and 42.3%, respectively. Specifications of sensitivity and specificity at different cut-off values are shown in Supplemental Table 2.

Table 1
Frequency distribution of patient, tumor, and treatment characteristics of the developmental and validation cohort.

	Development cohort UMCU and NCI, n = 409[a] (%)	Validation cohort MUMC+ and RUMC, n = 334[a] (%)	p-value
Patient characteristics			
Age (mean ± SD)	60.2 ± 8.1	58.5 ± 8.1	**0.003**
Male	274 (67.0)	222 (66.5)	0.880
Female	135 (33.0)	112 (33.5)	
History of tobacco use	220 (53.8)	292 (87.4)	0.383
No history of tobacco use	39 (9.5)	42 (12.6)	
Missing	150 (36.7)	0 (0.0)	
Alcohol consumption ≥1/ day	145 (35.5)	196 (58.7)	0.510
No alcohol consumption	114 (27.9)	138 (41.3)	
Missing	150 (36.7)	0 (0.0)	
BMI at baseline (kg/m^2) (mean ± SD)	24.4 ± 4.6	24.9 ± 4.9	0.120
Weight change baseline (%) (mean ± SD)	−4.4 ± 7.0	−2.9 ± 5.5	**0.003**
No modified diet at baseline	246 (60.1)	230 (68.9)	**0.014**
Texture modified diet[b] at baseline	163 (39.9)	104 (31.1)	
ECOG PS 0	142 (34.7)	85 (25.4)	**<0.001**
ECOG PS 1	180 (44.0)	224 (67.1)	
ECOG PS 2	32 (7.8)	24 (7.2)	
ECOG PS 3	2 (0.5)	1 (0.3)	
Missing	53 (13.0)	0 (0.0)	
Tumor characteristics			
Oral cavity	85 (20.8)	41 (12.3)	**<0.001**
Nasopharynx/sinus	35 (8.6)	29 (8.7)	
Oropharynx	174 (42.5)	156 (46.7)	
Hypopharynx	56 (13.7)	49 (14.7)	
Larynx	29 (7.1)	54 (16.2)	
Unknown primary	13 (3.2)	5 (1.5)	
Synchronous tumors	9 (2.2)	0 (0.0)	
Neck recurrence	9 (2.0)	0 (0.0)	
T classification (TNM)			
T0	20 (4.9)	8 (2.4)	0.233
T1	32 (7.8)	38 (11.4)	
T2	78 (19.1)	64 (19.2)	
T3	101 (24.7)	83 (24.9)	
T4	178 (43.5)	141 (42.2)	
N classification(TNM)			
N0	69 (16.9)	77 (23.1)	0.106
N1	53 (13.0)	35 (10.5)	
N2	269 (65.8)	213 (63.8)	
N3	18 (4.4)	9 (2.7)	
Disease stage			
Stage I	0 (0.0)	1 (0.3)	
Stage II	12 (2.9)	6 (1.8)	
Stage III	47 (11.5)	49 (14.7)	
Stage IV	350 (85.6)	278 (83.2)	
p16 expression in oropharynx only			
p16+	74 (42.5)	87 (55.8)	**0.017**
p16-	92 (52.9)	74 (47.4)	
Missing	8 (4.6)	5 (3.2)	
Treatment characteristics			
Primary treatment	324 (79.2)	291 (87.1.)	**0.005**
Adjuvant	85 (20.8)	43 (12.9)	
Systemic therapy			
Platinum-based	313 (76.5)	264 (79.0)	0.413
Cetuximab	96 (23.5)	70 (21.0)	
Neck irradiation			
Unilateral	47 (11.5)	22 (6.6)	**0.040**
Bilateral	333 (81.4)	308 (92.2)	
No neck RT	29 (7.1)	4 (1.2)	
Mean RT dose to contralateral submandibular gland (Gy) (mean ± SD)	44.4 ± 17.4	46.6 ± 15.4	0.060
Missing	4 (1.0)	0 (0.0)	
Mean RT dose to contralateral parotid salivary gland (Gy) (mean ± SD)	20.6 ± 9.9	21.3 ± 10.7	0.279
Missing	5 (1.2)	0 (0.0)	
Mean RT dose to PCM (Gy) (mean ± SD)	52.6 ± 15.0	53.1 ± 11.4	0.480
Missing	7 (1.8)	0 (0.0)	
Mean RT dose to OC (Gy) (mean ± SD)	42.6 ± 16.1	39.1 ± 16.3	**0.010**
Missing	6 (1.5)	0 (0.0)	
Tube type			
Gastrostomy	256 (62.6)	132 (39.5)	**<0.001**
Nasogastric tube	38 (9.3)	86 (25.7)	
No feeding tube	115 (28.1)	116 (34.7)	
Missing	0 (0.0)	0 (0.0)	
Tube feeding use	274 (67.0)	200 (59.9)	**0.040**
No tube feeding use	135 (33.0)	134 (40.1)	
Tube feeding use ≥4 weeks	261 (63.8)	176 (52.7)	**0.003**
No tube feeding use ≥4 weeks	148 (36.2)	158 (47.3)	

Abbreviations: BMI, body mass index; OC, oral cavity; PCM, pharyngeal constrictor muscles; RT, radiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM-classification, tumor, node, metastasis classification according to the 7th edition; Gy, Gray. Bold values denote statistical significance at the level of $p<0.05$.
[1]Independent samples t-test. [2]Pearson's chi-square test.
[a] Original data (not imputed) presented as mean ± SD for continuous variables or absolute n (%) for categorical variables.
[b] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

4. Discussion

In the current study we developed and externally validated a prediction model to identify LAHNSCC patients who are expected to use TF ≥ 4weeks and thus would benefit from prophylactic gastrostomy insertion. According to our knowledge, this is the first external validation study in a large multicenter retrospective cohort (n = 409 and n = 334). The model includes the following predictors: pretreatment weight change, texture modified diet at baseline, ECOG PS, tumor site, N classification, and mean RT dose to the contralateral parotid gland and OC.

Remarkably, RT dose to the PCM was not a significant predictor of TF dependency in the model. Previous studies described a significant relationship between increasing RT dose to the PCM and the rising incidence and duration of TF dependency and long-term dysphagia [24,25,45]. An explanation for these different outcomes might be that we used total RT dose to all PCM, while other studies often used RT dose per PCM subtype; superior, middle, and inferior PCM, with dose to the superior PCM being highly predictive for dysphagia [25]. Although dose to the PCM is not a predictor in our multivariable model, it does not mean that minimizing dose to the PCM in radiotherapy planning is not useful. Indeed our univariable results indicate that dose to the PCM is associated with the risk of TF ≥ 4 weeks. The association between OC dose and TF dependency may be explained by the fact that the OC has an important function in salivation, taste, chewing, and bolus transport. In a recent study by Van de Bosch et al. on the dosimetric effects of organs at risk, the oral cavity was involved in several toxicity-related effects including dysphagia [46].

Previous studies have also shown that dosimetric variables were statistically dependent, particularly dose to the PCM and OC, the latter being a predictor in our model. Inclusion of such a dependent variable might make the other variable non-significant following correction in the statistical model [45].

In addition, dysphagia, toxicity-related nausea and severe taste alterations (dysgeusia) causing food aversion can also negatively

Table 2
Results of univariable logistic regression analysis of potential predictors for tube feeding for at least four weeks.

	OR	CI-95%		p value
		lower	upper	
Age (years)	0.988	0.963	1.013	0.341
Male gender	0.947	0.617	1.452	0.801
Tobacco use	1.523	0.751	3.091	0.244
Alcohol consumption one or more per day	0.944	0.554	1.610	0.834
BMI at baseline (kg/m^2)	0.950	0.909	0.993	**0.023**
Baseline weight change (%)	0.943	0.911	0.976	**0.001**
Texture modified diet[a] at baseline	1.981	1.291	3.040	**0.002**
ECOG PS $\geq$ 1	2.124	1.400	3.223	**<0.001**
Oral cavity, oropharynx, and hypopharynx	0.689	0.419	1.133	0.143
T classification $\geq$ T2 (TNM)	1.472	0.817	2.652	0.198
N classification $\geq$ N2 (TNM)	1.984	1.285	3.062	**0.002**
Disease Stage IV	2.205	1.263	3.849	0.005
p16 + oropharynx	0.699	0.424	1.151	0.159
Primary treatment setting	0.765	0.469	1.247	0.283
Cetuximab	0.985	0.612	1.584	0.949
Bilateral neck irradiation	2.315	1.397	3.837	**0.001**
RT dose to contralateral submandibular glands (Gy)	1.022	1.010	1.034	**<0.001**
RT dose to contralateral parotid glands (Gy)	1.046	1.022	1.070	**<0.001**
RT dose to PCM (Gy)	1.027	1.013	1.041	**<0.001**
RT dose to OC (Gy)	1.028	1.015	1.041	**<0.001**

Abbreviations: BMI, body mass index; CI, confidence interval; Gy, Gray; OC, oral cavity; OR, Odds ratio; PCM, pharyngeal constrictor muscles; RT, radiotherapy; TNM-classification, tumor, node, metastasis classification according to the 7th edition; ECOG PS, Eastern Cooperative Oncology Group performance status. Bold values denote statistical significance at the level of $p<0.05$.
[a] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

affect oral intake leading to TF requirement. Up to now, it remains difficult to predict which patients will experience dysgeusia during CRT/BRT.

In contrast to our previously published model, BMI at baseline, disease stage, type of systemic therapy and mean dose to the contralateral submandibular gland were not included into this new model as they did not yield a p < 0.10 in the multivariable analysis. We included RT dose to the contralateral salivary glands as potential predictors as the remaining saliva production will correlate with the dose on the spared gland [47]. Although one study previously reported mean RT dose to the contralateral submandibular gland to have a predictive value for TF at six months [48], this was not a significant predictor in our model. This could be explained by the different endpoints of both studies: TF initiation during CRT/BRT versus TF dependency at six months. Mean dose to the parotid gland was a significant predictor in accordance with our previously published model [22].

It should also be noted that potential predictors not included in our final model could still have predictive value. However, the current combination of predictors presented the strongest prediction model.

4.1. Performance of the model

The model has good accuracy (AUC on internal validation 0.73 and after external validation 0.62 and 0.71 depending on the composition of the validation cohort), but there was a remarkable difference between the two cancer centers participating in the external validation process. While the AUC did not differ much in the MUMC + validation cohort, a marked decrease of AUC was seen in the pooled cohort of MUMC+ and RUMC together. Despite adherence to national guidelines on when to initiate TF, individual and institutional preferences in feeding tube insertion policy might have affected the external validity outcome. RUMC had fewer patients receiving TF $\geq$ 4 weeks compared to the three other centers

Table 3
Regression coefficients in the model for predicting tube feeding use for at least four weeks.

	Regression coefficients	S.E.	p-value	OR (95%CI)
Model intercept	−1.419		0.001	
Pretreatment weight change(%)	−0.038	0.020	0.054	0.963 (0.926–1.001)
Texture modified diet at baseline				
No modified diet (reference)	0.448	0.247	0.070	1.565 (0.965–2.538)
Texture modified diet[a]				
ECOG PS				
0 (reference)	0.674	0.232	0.004	1.963 (1.246–3.092)
>0				
Tumor site				
Others (reference)	−0.793	0.286	0.006	0.452 (0.258–0.792)
Oral cavity, oropharynx, and hypopharynx				
N classification (TNM)				
N0, N1 (reference)	0.646	0.246	0.009	1.908 (1.179–3.088)
N2, N3				
Mean RT dose to contralateral parotid gland (Gy)	0.027	0.008	0.038	1.027 (1.001–1.054)
Mean RT dose to the OC (Gy)	0.022	0.013	0.004	1.022 (1.007–1.037)

Abbreviations: BMI, body mass index; CI, confidence interval; Gy, Gray; OC, oral cavity; OR, Odds ratio; RT, radiotherapy; S.E. standard error; TNM-classification, tumor, node, metastasis classification according to the 7th edition [37]; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

(43% versus 70%, 61% and 54% for RUMC and UMCU, MUMC+ and NCI respectively). This difference might be explained by the variations in patient characteristics. Also the effect of the cisplatin administration protocol, weekly in RUMC versus three weekly in all other cancer centers, cannot be ruled out as additional explanation for the differences in TF prevalence. High level evidence for best treatment regimen in primary setting in terms of toxicity and survival is lacking [49,50]. Another remarkable difference that should be highlighted is the significantly lower number of gastrostomy insertions in the validation cohort versus the developmental cohort (39.5% and 62.6%). This is the result of a different policy in the RUMC regarding prophylactic gastrostomy insertion where reactive NGT insertion is preferred with only 5% of the RUMC patient sample receiving a gastrostomy.

To our clinical experience, prophylactic gastrostomy insertion could lower the threshold for TF initiation. Studies have shown that reactive NGT insertion is associated with a shorter duration of TF use [10,51,52]. This was also reflected in our study population, as the median TF duration in RUMC (reactive NGT) was 23 days versus 85 and 82 days in UMCU and MUMC + respectively (prophylactic gastrostomy). It has been argued that (prophylactic) gastrostomies might be related to long term swallowing dysfunction based on the 'use-it-or-lose-it' paradigm of dysphagia rehabilitation, but the literature remains controversial on this side effect [53–56]. The present study did not evaluate long-term swallowing function after CRT/BRT with or without gastrostomy insertion. Differences in feeding tube policy between the cancer centers, as shown by our nationwide survey [57], could be considered a limitation of the

Formula

$P(TF \geq 4 \text{ weeks}) = 1/(1 + e^{-LP})$

LP = -1.419 - 0.038 * pretreatment weight change + 0.448 * texture modified diet at baseline + 0.674 * ECOG PS – 0.793 * tumor site + 0.646 * N classification + 0.027 contralateral parotid gland dose + 0.022 oral cavity dose

Variable explanation

Pretreatment weight change: "-5" is 5% weight loss
Texture modified diet at baseline: yes =1, no = 0
ECOG PS: ECOG PS ≥ 1 = 1, ECOG PS 0 = 0
Tumor site: oral cavity, oropharynx or hypopharynx = 1, others = 0
N classification: N2-3 = 1, N0-1 = 0
Parotid gland dose: mean dose in Gy
Oral cavity dose: mean dose in Gy

Example calculation

A patient with a cT4aN3bM0 hypopharynx tumor will receive locoregional CRT. She had 8% weight loss at baseline, only used mashed meals, had an ECOG PS score of 1, and will receive a mean RT dose to the contralateral parotid gland and oral cavity of 29 Gy and 36 Gy respectively:

LP = -1.419 - 0.038 * -8 + 0.448 * 1 + 0.674 * 1 – 0.793 * 1 + 0.646 * 1 + 0.027 * 29 + 0.022 * 36 = 1.435

$P(TF \geq 4 \text{ weeks}) = 1 / (1+e^{-1.435}) = 0.81$.
This patient has a probability of 81% that she will require TF for a period of four weeks or longer.

Flow chart for use in clinical practice

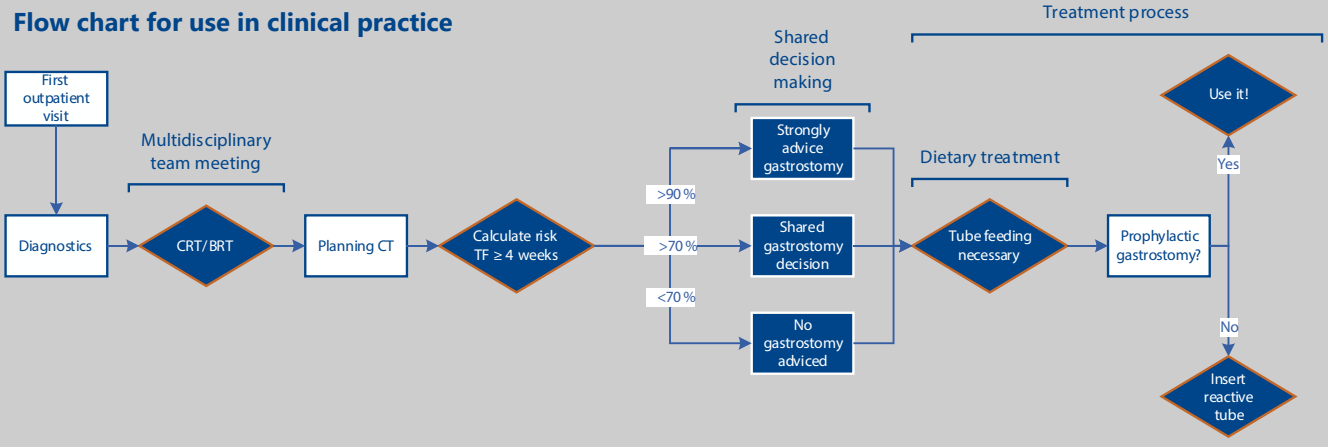

Fig. 1. Example calculation and flow chart for the use of the model in clinical practice.

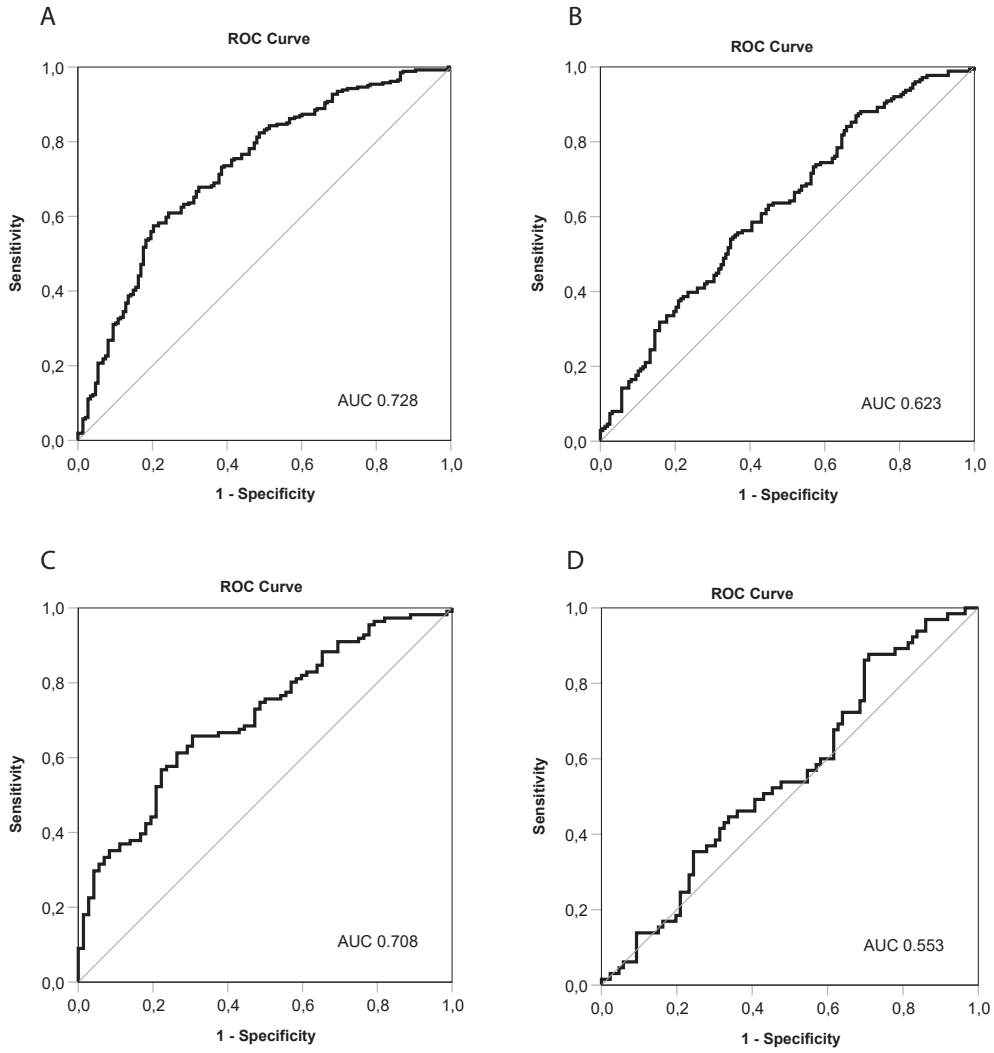

Fig. 2. Receiver operating characteristic curve of the prediction model before external validation (A); after external validation in MUMC+ and RUMC combined (B); after external validation in MUMC + only (C); and after external validation in RUMC only (D).

current study. However, we decided to accept this heterogeneity in patient populations to validate our model, since this reflects real world inter-center heterogeneity. An explanation for the diverse policies is the existence of regional differences in hospital logistics, but also differences in the sociocultural background of patients and health professionals and the lack of high-quality evidence in the literature regarding the indication for prophylactic gastrostomy insertion. These findings emphasize the challenge of standardizing gastrostomy insertion management nationwide. This study was not designed to investigate the best approach for TF initiation and feeding tube insertion. Differences in the effect of reactive versus prophylactic feeding tube insertions on oncological therapy outcome, weight loss and quality of life cannot be evaluated here.

4.2. Generalizability of the model (external validity)

We suggest that in case the model estimates a probability >90% for TF dependency, a prophylactic gastrostomy insertion should be recommended. In case of a probability >70%, a prophylactic gastrostomy insertion should be discussed with the patient. For patients' comfort and to reduce the risk of side effects, we recommend prophylactic gastrostomy insertion in high-risk patients before or within the first two weeks of oncological treatment when mucositis and neutropenia have not developed yet [58,59]. This data-driven model indicates that in case of a probability >90%, approximately 18.2% of the patients with a prophylactic gastrostomy insertion will not develop TF dependency ≥4 weeks. However, that does not mean that these 18.2% patients do not benefit from a gastrostomy. They may still need TF but for a period <4 weeks or they may use

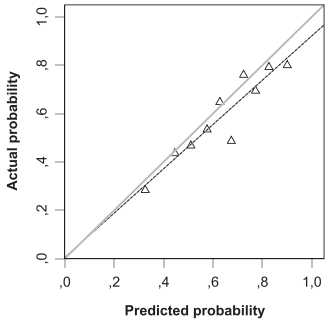

Fig. 3. Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.

their gastrostomy for supplemental fluid administration to prevent nephrotoxicity. In 57.7% of the patients with a probability <90%, a reactive feeding tube insertion will be necessary.

5. Conclusion

We developed and externally validated a prediction model to estimate TF-dependency ≥4 weeks in LAHNSCC patients treated with CRT/BRT. This model can be used to guide personalized decision-making on prophylactic gastrostomy insertion in clinical practice.

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Author contribution

Anna C.H. Willemsen: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Visualization, Funding acquisition. **Annemieke Kok:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Visualization. **Laura W.J. Baijens:** Writing – Review & Editing**,** Supervision. **Jan Paul de Boer:** Writing – Review & Editing**. Remco de Bree:** Conceptualization, Writing – Review & Editing**,** Supervision. **Lot A. Devriese:** Writing – Review & Editing**. Chantal M. L. Driessen:** Writing – Review & Editing**. Carla M. L. van Herpen:** Writing – Review & Editing**. Frank J.P. Hoebers:** Conceptualization, Methodology, Resources, Writing – Review & Editing**. Johannes H.A.M. Kaanders:** Resources, Writing – Review & Editing**. Rebecca T. Karsten:** Investigation, Writing – Review & Editing**. Sander M.J. van Kuijk:** Conceptualization, Methodology, Formal analysis, Writing – Review & Editing. **Roy I. Lalisang:** Conceptualization, Writing – Review & Editing. **Arash Navran:** Investigation, Resources, Writing – Review & Editing**. Susanne R. Pereboom:** Investigation, Writing – Review & Editing**. Annemie M.W.J. Schols**: Writing – Review & Editing, Supervision. **Chris H.J. Terhaard:** Conceptualization, Methodology, Resources, Writing – Review & Editing. **Ann Hoeben:** Conceptualization, Writing – Review & Editing, Supervision.

Disclaimers

The views expressed in this article are our own and is not an official position of the institution or funder. This study has been performed with great care. However, the authors do not take any responsibility and are not liable for any damage caused by the use of the prediction model.

Conflict of interest

Anna C.H. Willemsen, Annemieke Kok, Jan Paul de Boer, Remco de Bree, Chantal M.L. Driessen, Johannes H.A.M. Kaanders, Rebecca T. Karsten, Sander M.J. van Kuijk, Roy I. Lalisang, Arash Navran, Susanne R. Pereboom, Annemie M.W.J. Schols, Chris H.J. Terhaard, and Ann Hoeben declare that they have no conflict of interest.

Laura W.J. Baijens.

Consulting or advisory role: Phagenesis Limited, member of the Independent FEES Review Committee for the PhINEST study.

Lot A. Devriese.

Consulting or advisory role: MSD, Bristol Myers Squibb.

Frank J.P. Hoebers.

Consulting or advisory role: Bristol Myers Squibb.

Carla M.L. van Herpen.

Consulting or advisory role: Bayer, Bristol Myers Squibb, MSD, Regeneron, TRK Fusion Cancer Medical.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.11.019.

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