Prediction model for tube feeding dependency during chemoradiotherapy for at least four weeks in head and neck cancer patients

Clinical Nutrition 39 (2020) 2600–2608

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prediction model for tube feeding dependency during chemoradiotherapy for at least four weeks in head and neck cancer patients: A tool for prophylactic gastrostomy decision making

Anna C.H. Willemsen [a, b, c, 1], Annemieke Kok [d, *, 1], Sander M.J. van Kuijk [e], Laura W.J. Baijens [b, f], Remco de Bree [g], Lot A. Devriese [h], Frank J.P. Hoebers [b, i], Roy I. Lalisang [a, b], Annemie M.W.J. Schols [c], Chris H.J. Terhaard [j], Ann Hoeben [a, b]

[a] Division of Medical Oncology, Department of Internal Medicine, Maastricht University Medical Center +, the Netherlands
[b] GROW-School of Oncology and Developmental Biology, Maastricht University Medical Center +, the Netherlands
[c] Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center +, the Netherlands
[d] Department of Dietetics, University Medical Center Utrecht, the Netherlands
[e] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center +, the Netherlands
[f] Department of Otorhinolaryngology, Head & Neck Surgery, Maastricht University Medical Center +, the Netherlands
[g] Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, the Netherlands
[h] Department of Medical Oncology, University Medical Center Utrecht, the Netherlands
[i] Department of Radiation Oncology, MAASTRO Clinic, Maastricht, the Netherlands
[j] Department of Radiotherapy, University Medical Center Utrecht, the Netherlands

ARTICLE INFO

Article history:
Received 16 July 2019
Accepted 20 November 2019

Keywords:
Prophylactic gastrostomy
Prediction model
Tube feeding
Predictors
Head neck cancer
Chemoradiotherapy

SUMMARY

Background & aims: Chemoradiation and bioradiation (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often comes with high toxicity rates, interfering with oral intake and leading to temporary tube feeding (TF) dependency. High-quality scientific evidence for indicators of prophylactic gastrostomy insertion is not available. The aim of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks.

Methods: Four-hundred-fifty LAHNSCC patients receiving CRT/BRT with curative intent between 2013 and 2016 were included in the study. Primary outcome was TF-dependency for four weeks or longer. Patient, tumor, and treatment characteristics were extracted from the medical records and their effects on the use of TF were analyzed using univariable and multivariable analysis. The prediction model was internally validated using bootstrapping techniques.

Results: Sixty-five percent (294/450 patients) required TF for four weeks or longer. Variables included in the model were: body mass index and adjusted diet at start of CRT/BRT, percentage weight change at baseline, World Health Organization performance status, tumor subsite, TNM-classification, CRT/BRT, mean radiation dose on the contralateral submandibular and parotid gland. The corrected Area Under the Curve after internal validation was 72.3%, indicating good discriminative properties of the prediction model.

Conclusions: We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as a tool to support personalized decision making on prophylactic gastrostomy insertion.

1. Introduction

The current treatment with curative intent for patients ≤70 years with stage III and IV Locally Advanced Head and Neck

* Corresponding author. P.O. Box 85500, 3508, GA, Utrecht, the Netherlands.
E-mail address: a.kok-4@umcutrecht.nl (A. Kok).
[1] These authors contributed equally.

https://doi.org/10.1016/j.clnu.2019.11.033
0261-5614/

Squamous Cell Carcinoma (LAHNSCC) consists of primary or adjuvant radiotherapy (RT) with concurrent radiosensitizing systemic therapy (cisplatin, carboplatin or cetuximab) [1–4]. Side effects of this chemo or bioradiation therapy (CRT/BRT) protocol include, among others, mucositis [5], xerostomia, sensory changes/taste distortion, pain, dysphagia, and nausea and vomitus [6,7]. These side effects may contribute to reduced oral intake and consequently weight loss during and after CRT/BRT [5–8], resulting in worse functional and oncological outcomes [9–12]. Maintaining body weight leads to improved therapy tolerance, reduced risk of complications and therapy delay, increased response rate [13], and higher survival rate [14]. When oral intake is insufficient to meet protein and energy requirements, tube feeding (TF) is required [15,16]. TF can be administered by means of a nasogastric tube (NGT) or a percutaneous radiologic or endoscopic gastrostomy (PRG or PEG). Current guidelines recommend gastrostomy insertion, not NGT, when TF is expected to be required for at least four weeks [13,17,18].

Currently, there is a lack of consentient directives, leading to various policies for tube insertion in CRT/BRT patients in different institutions. Prophylactic gastrostomy insertion has been the subject of debate, because prophylactic TF in all patients might lead to increased long-term dysphagia, considering the “use it or lose it” principle with respect to swallowing structures [19–21]. Moreover, gastrostomy insertion is not a risk-free procedure with complication rates of about 3.3–19% [22,23] and between 9% and 47% of the prophylactic gastrostomies are never used [24,25]. Therefore, gastrostomies should not be placed prophylactically in every individual, but only upon indication as stated in the Dutch Head and Neck Cancer Society (DHNCS) guidelines [26]. However, this indication has not been described properly due to a lack of scientific evidence.

Previous studies [24,27] identified predictive factors for prophylactic gastrostomy placement and TF during CRT/BRT but failed to develop a strong prediction model. More recently, a prediction model for identifying CRT/BRT patients at risk for long-term (>90 days) tube dependency was presented [28]. By using a model only focusing on long-term TF-dependency, a large proportion of patients requiring TF due to acute toxicities remains unidentified: 68–81% of the patients require TF during CRT/BRT [6,24,28] compared to 20–45% at three months after treatment [20,24,29].

The purpose of this retrospective cohort study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks [26].

2. Patients and methods

2.1. Subjects and study design

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional research ethics boards. Data were collected in patients with LAHNSCC starting CRT/BRT in Maastricht University Medical Center (MUMC+) and the University Medical Center Utrecht (UMCU) between January 1st 2013 and December 31st 2016. Patients received primary or adjuvant RT combined with either cisplatin, carboplatin or cetuximab with curative intent. Exclusion criteria were histology other than squamous cell carcinoma, esophageal tumors, bilateral resection of the submandibular glands because RT dose on submandibular glands cannot be calculated here, early termination of RT, TF-dependency since surgery, patients refusing TF despite significant malnutrition, and age under 18 years. Part of the UMCU cohort has been described previously [24]. Figure 1 shows the inclusion flowchart.

2.2. Oncological treatment

Cisplatin was administered intravenously on days 1, 22, and 43, in doses of 100 mg/m^2 [3,30] to patients without significant cardiovascular or renal disease, neuropathy or hearing impairment. In case of significant side effects during cisplatin treatment, radiosensitizing systemic therapy was either completely ceased or replaced by carboplatin (dose: area under curve (AUC) 5) for the remaining cycles. Cetuximab was indicated in patients having a contraindication for cisplatin. For cetuximab, a loading dose of 400 mg/m^2 was administered intravenously one week before RT initiation, followed by 250 mg/m^2 weekly during RT [2].

RT was administered using intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) and applied five times per week for seven weeks, in 35 daily fractions of 2 Gy to a total dose of 70 Gy. Patients on cetuximab received 30 daily fractions of 2.3 Gy to a total dose of 69 Gy or accelerated fractionated RT twice daily in the final week of IMRT with a total dose of 68 Gy in 34 fractions. Patients undergoing adjuvant CRT received a total dose of 66 Gy in 33 fractions concurrent with cisplatin.

2.3. Primary endpoint and tube feeding policy

The primary endpoint of this study was the use of TF for at least four weeks during CRT/BRT or within 30 days after CRT/BRT completion. The four-week cut off point was based on the Dutch national dietary guidelines, recommending gastrostomy insertion as being superior to NGT when TF is required for a period of four weeks or longer [31,32].

According to the Dutch guideline on malnutrition [33], patients were initially recommended to use oral nutritional supplements or TF in addition to oral intake when 50–75% of the calculated nutritional requirements were met. When oral intake was less than 50% of the calculated nutritional needs, without rapid improvement of oral intake, full TF was indicated, supplemented with any feasible and safe oral intake [33]. Patients were advised to remain on oral intake as much as possible in order to maintain swallowing function.

2.4. Potential predictors

Potential predictors were preselected based on clinical reasoning and evidence of previous research. We preselected patient's age [34–38], gender [29,37], tobacco [39], and alcohol use, body mass index (BMI) [40,41], weight loss [42,43], and texture modified diet at baseline (as indicator for dysphagia) [29,37,42], in which baseline is considered right before treatment initiation, World Health Organization performance status (WHO PS) [44–46], tumor subsite [35,37,41,47,48], tumor stage [35–37,40,42,43,47–51], nodal stage [24,36,37,39,41] (TNM-classification [52]), human papilloma virus (HPV) in situ hybridization (ISH) or P16 expression (surrogate biomarker of HPV infection) of the tumor [34], primary or adjuvant setting [41,44,47], type of radiosensitizing systemic therapy (platinum-based chemotherapy or immunotherapy) [35,39,42–44,47], bilateral neck irradiation [24,49,53], mean RT dose on the contralateral submandibular [44] and parotid gland [43,44].

2.5. Sample size

The inclusion of at least ten events per variable is widely accepted as the sample size rule of thumb for multivariable logistic regression analyses [54]. The least frequent outcome, receiving TF less than four weeks (n = 156), was defined as an event. Thus, a

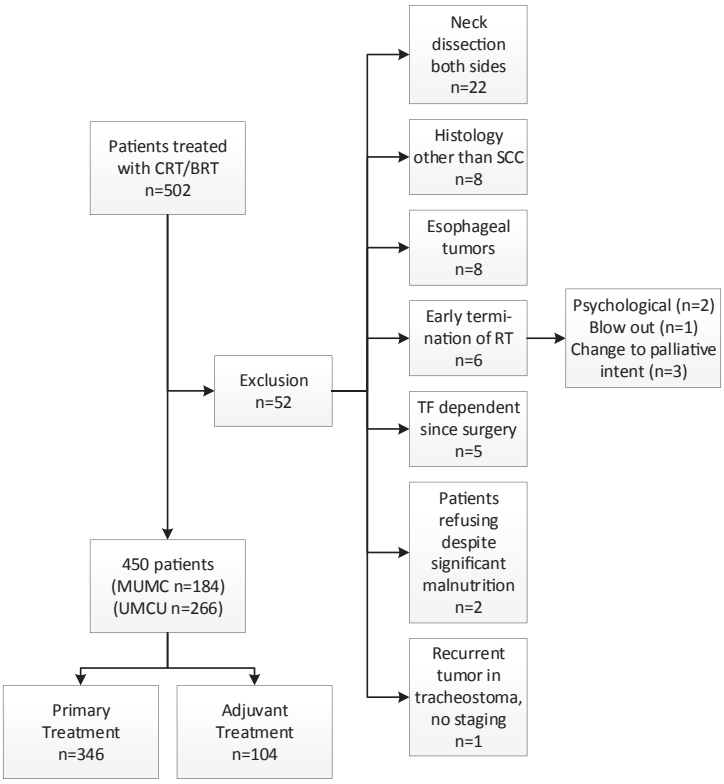

Fig. 1. Flowchart of inclusion.

maximum of fifteen predictors was considered appropriate for developing a model for the cohort in the present study.

2.6. Data collection

Patient data were extracted from electronic medical records. Texture modified diet or the use of tube feeding was used as an indicator for dysphagia. Texture modification includes ground, minced or liquid. This information was collected from questionnaires (e.g. functional oral intake scale) if available or patient reported modifications such as eating bread without crust or mashing food.

2.7. Missing data

Only for the variables mean contralateral submandibular and parotid gland dose, missing data were imputed through stochastic regression imputation, based on the following covariates: BMI and weight change at baseline, tumor subsite, tumor stage, nodal stage, p16 expression/HPV ISH in oropharyngeal tumors, primary or adjuvant setting, CRT/BRT, neck irradiation and mean RT dose on the contralateral submandibular and parotid gland. In case of a midline tumor, the contralateral side was considered the side receiving the lowest mean RT dose.

2.8. Statistical analysis

Descriptive statistics were reported as mean and standard deviation or absolute numbers and percentages. Baseline differences between those who received TF for at least four weeks and those who did not were tested using the independent samples t-test and the chi−squared test. A p-value <0.050 was considered statistically significant.

All potential predictor variables underwent screening through univariable logistic regression. Factors with $p < 0.300$ were selected as potentially relevant predictor variables and were entered in a multivariable logistic regression model. We used stepwise backward elimination to omit all predictors from the model that did not contribute substantially, using a p-value for selection of 0.100. The resulting prediction model was subsequently internally validated using bootstrapping techniques. The bootstrap validation yields a shrinkage factor between 0 and 1. The regression coefficients were multiplied by this shrinkage factor to penalize the coefficients which counteracts effects of overfitting. Additionally, the bootstrap validation provides estimates of model performance corrected for optimism (i.e., it gives estimates of model performance in future patients compared to the patients used to develop the model) [55,56].

Model performance was quantified as the model's ability to discriminate between those who will and those who will not develop the need for TF for at least four weeks using the area under the receiver operating characteristic curve and measures of calibration. Calibration is the agreement between predicted probabilities and observed probabilities and was tested using the Hosmer and Lemeshow goodness-of-fit test [57]. A significant p-value would denote significant deviation from good model calibration. In addition, we visually inspected a calibration plot. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM, Armonk, NY) and R version 3.5.1 [58] (R Core Team, Vienna, Austria).

3. Results

3.1. Patient sample

Data of both MUMC+ and UMCU yielded 502 patients from which 450 patients met the inclusion criteria. Patient, tumor, and

treatment-related characteristics are shown in Table 1. Mean RT dose on contralateral submandibular and parotid gland was missing in 34% (n = 151) and 1% (n = 6) respectively. These were statistically imputed as described earlier. In 72% of our total population (n = 322) a gastrostomy was placed and six percent (n = 26) received a NGT. In total 69% (n = 311) of all patients used TF during or within 30 days after completion of treatment with a median duration of 107 days (Interquartile range (IQR) 129). Sixty-five percent (n = 294) of the patients used TF for four weeks or longer. The median duration of TF use did not significantly differ between subsites oral cavity or oropharynx or hypopharynx on the one hand versus other or remaining subsites on the other hand: 111 (IQR 143) versus 97 (IQR 96) days respectively (p = 0.086).

Univariable regression analysis output (Table 2) yielded a *p*-value <0.300 for the following factors: age, BMI, weight change, texture modified diet, WHO PS, tumor subsite, tumor stage, nodal stage, primary or adjuvant setting, radiosensitizing systemic therapy, neck irradiation and mean RT dose on the contralateral submandibular and parotid gland. In multivariable regression analysis (Table 3), age and adjuvant setting did not yield a *p*-value <0.100 and were therefore eliminated from the final model. Tumor stage was not statistically significant in multivariable analysis but was considered clinically relevant and proven in previous studies [37,41,47,50] and was therefore nevertheless included in the model. Figure 2 shows the receiver operating characteristic (ROC) curve of the crude prediction model. The AUC was 74.8% (95% CI = 70.1–79.6%), which indicates good discriminative ability.

3.2. Internal validation

Internal validation of the model yielded a shrinkage factor of 0.87. The last column of Table 3 shows the shrunken regression coefficients and the model intercept.

Furthermore, internal validation gave a degree of optimism of 2.5%, leading to an AUC corrected for optimism of 72.3%. The calibration plot (Fig. 3) shows a good agreement between predicted probability of TF for at least four weeks and the observed use of TF. The Hosmer and Lemeshow goodness-of-fit test presented a *p*-value of 0.844.

3.3. Formula of the model

The individual probability for TF for at least four weeks can be calculated as:

$LP(TF \geq 4 \text{ weeks}) = 1/(1 + e^{-LP})$, in which LP is the linear sum of all predictor values multiplied by the regression coefficients, or:

−0.506 −0.042 (BMI) −0.030 (pretreatment weight change) +0.452 (modified diet or TF [*yes = 1*]) +0.608 (WHO PS [*WHO>0 = 1*]) −0.510 (tumor location [*oral cavity, oropharynx and hypopharynx = 1*]) +0.311 (T classification [*T2, T3, or T4 = 1*]) +0.561 (N classification [*N2 or N3 = 1*]) −0.655 (systemic therapy [*Cetuximab = 1*]) +0.015 (mean RT dose on contralateral submandibular gland [*Gy*]) +0.042 (mean RT dose on contralateral parotid salivary gland [*Gy*]).

The formula will be available on the following website: www.predictcancer.ai.

For example, a patient with a cT3N2bM0 oropharyngeal tumor will receive locoregional RT including bilateral neck irradiation concurrent with cisplatin. She has a BMI of 19.5 kg/m^2, 8% weight loss at baseline, only eats mashed meals, her WHO PS is 0, and the mean RT dose on the contralateral submandibular and parotid gland will be 36 Gy and 29 Gy respectively.

$LP = -0.506 - 0.042 * \mathbf{19.5} - 0.030 * \mathbf{-8} + 0.452 * \mathbf{1} + 0.608 * \mathbf{0} - 0.510 * \mathbf{1} + 0.311 * \mathbf{1} + 0.561 * \mathbf{1} - 0.655 * \mathbf{0} + 0.015 * \mathbf{36} + 0.042 * \mathbf{29} = 1.487$

$P(TF \geq 4 \text{ weeks}) = 1/(1+e^{-1.487}) = 0.82$. This patient has a probability of 82% that she will require TF for a period of four weeks or longer.

3.4. Sensitivity and specificity

When choosing 90% as cut off value, the model yields a sensitivity of 9%, specificity of 98%, positive predictive value of 90%, and negative predictive value of 64%. In case of 80% as cut off value, the model yields a sensitivity of 31%, specificity of 93%, positive predictive value of 85%, and negative predictive value of 56%.

4. Discussion

The purpose of this study was to develop a prediction model to identify patients who need prophylactic gastrostomy insertion, defined as the expected use of TF for at least four weeks in LAHNSCC patients treated with CRT/BRT. To our knowledge, this is the first study using TF for four weeks or longer as an outcome measure in a large retrospective cohort (n = 450) of LAHNSCC patients receiving CRT/BRT. If the model predicts a high chance of TF for four weeks or longer, prophylactic gastrostomy insertion is advised and preferred over reactive tube insertion, whereby reactive is defined as tube insertion "as required". After internal validation, the model has good accuracy (AUC 72.3%) in discriminating LAHNSCC patients planned for CRT/BRT who will versus will not need TF for at least four weeks and thus would benefit from prophylactic gastrostomy insertion. Our final model includes the following predictors: BMI, weight loss, texture modified diet, WHO PS, tumor subsite, tumor stage, nodal stage, type of radiosensitizing systemic therapy and RT dose on the contralateral submandibular and parotid gland. Previous smaller studies showed largely similar predictors but failed to construct a solid prediction model: BMI <25 [40,41], >10% baseline weight loss [42], tumor-related symptoms at diagnosis (e.g. pain and dysphagia) [29,40,42,45,47,59,60], WHO PS [44,46], tumor located in oropharynx [27,41,44,49], tumor stages T3-T4 [36,40,42,47–49], nodal stage [24,36,39,41], clinical TNM-stage IV [39,49,61], bilateral neck irradiation [24,49], age>60 [61], pack years [39], and surgery prior to CRT/BRT [41,46]. We used texture modified diet as a surrogate marker for dysphagia. Previous studies showed that a higher mean RT dose on the submandibular and parotid glands was associated with dry mouth and sticky saliva, respectively, due to reduced salivary output and a change in salivary composition [62,63]. Remaining salivary production will therefore highly correlate with the RT dose on the spared contralateral salivary glands [64]. To our knowledge, this is the first study including RT dose on the contralateral salivary glands as a possible predictor for TF need combined with other patient and tumor characteristics. Strikingly and unlike other studies, a tumor located in the oral cavity, oropharynx or hypopharynx did not increase the risk of TF for at least 4 weeks as compared to the remaining tumor subsites in the present patient sample [35,37,41,47,48]. This result might be explained by the chosen cut off point of TF for at least four weeks. The median duration of TF use did not significantly differ between the two subgroups (111 versus 97 days, $p = 0.086$), but the

Table 1
Frequency distribution of patient, tumor, and treatment characteristics of the studied population.

Variables	Total oral diet or tube feeding <4 weeks N = 156 (35%)	Tube feeding >4 weeks N = 294 (65%)	p-value
Patient characteristics			
Mean age	59.7 ± 7.2	58.7 ± 8.0	0.223[b]
Gender			
Male	101 (65)	193 (66)	
Female	55 (35)	101 (35)	0.848[c]
Tobacco use			
Yes	138 (89)	256 (87)	
No	18 (12)	38 (13)	0.671[c]
Alcohol consumption one or more per day			
Yes	91 (58)	166 (57)	
No	65 (42)	128 (44)	0.703[c]
BMI at baseline (kg/m[c])	25.4 ± 4.9	23.8 ± 4.6	**0.001**[b]
Weight change at baseline (%)	−2.7 ± 6.0	−5.0 ± 7.4	**0.001**[b]
Diet at baseline			
No modified diet	114 (73)	175 (60)	
Texture modified diet[a]	42 (27)	119 (41)	**0.004**[c]
WHO PS			
0	51 (32)	58 (20)	
1	98 (63)	206 (70)	
2	6 (4)	28 (10)	
3	1 (1)	2 (1)	**0.007**[c]
Tumor characteristics			
Tumor subsite			
Oral cavity	40 (26)	54 (18)	
Nasopharynx/sinus	6 (4)	25 (8)	
Oropharynx	58 (37)	125 (43)	
Hypopharynx	24 (15)	37 (13)	
Larynx	20 (12)	34 (1)	
Unknown primary	5 (3)	5 (2)	
Synchronous tumors	1 (1)	8 (3)	
Neck recurrence	2 (2)	7 (2)	0.151[c]
Tumor stage (TNM)			
Tx	3 (2)	1 (0)	
T0	4 (3)	11 (4)	
T1	20 (13)	23 (8)	
T2	39 (20)	50 (17)	
T3	31 (20)	77 (26)	
T4	59 (38)	132 (45)	**0.033**[c]
Nodal stage (TNM)			
N0	40 (26)	48 (16)	
N1	23 (15)	30 (10)	
N2	87 (56)	205 (70)	
N3	6 (4)	11 (4)	**0.025**[c]
Tumor stage			
Stage II	7 (5)	6 (2)	
Stage III	26 (17)	29 (10)	
Stage IV	123 (79)	259 (88)	**0.030**[c]
P16 expression			
P16+ oropharynx	30 (19)	49 (17)	
Others	126 (81)	245 (83)	0.496[c]
Treatment characteristics			
Primary treatment	112 (72)	230 (78)	0.128[c]
Adjuvant	44 (28)	64 (22)	
Radiosensitizing systemic therapy			
Platinum (carbo-/cis-)	111 (71)	230 (78)	
Cetuximab	45 (29)	64 (22)	0.095[c]
Neck irradiation			
Unilateral	24 (15)	21 (7)	
Bilateral	116 (74)	259 (88)	
No neck RT	16 (10)	14 (5)	**0.001**
RT dose on contralateral submandibular gland (Gy)	34.7 ± 17.2	42.3 ± 14.4	**<0.001**[b]
RT dose on contralateral parotid salivary gland (Gy)	15.8 ± 8.8	20.4 ± 8.4	**<0.001**[b]
Tube type			
PEG	26 (17)	159 (54)	
PRG	20 (13)	114 (39)	
PEJ	0 (0)	2 (1)	
surgical gastrostomy	0 (0)	1 (0)	
NGT	8 (5)	18 (6)	
No feeding tube	102 (65)	0 (0)	**<0.001**[c]

Abbreviations: BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray; PRG, percutaneous radiologic gastrostomy; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; NGT, nasogastric tube. Bold values denote statistical significance at the p<0.050 level.

[a] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

[b] Independent samples t-test.

[c] Pearson's chi-square test.

Table 2
Results of univariable logistic regression analysis of potential predictors presented in odds ratios and *p* values.

	OR	CI-95%		p value
		lower	upper	
Age (years)	0.984	0.959	1.010	0.224
Gender				
Female (ref)				
Male	0.961	0.640	1.444	0.848
Tobacco use				
No (ref)				
Yes	0.879	0.483	1.598	0.672
Alcohol consumption one or more per day				
No (ref)				
Yes	0.926	0.625	1.372	0.703
BMI at baseline (kg/m^2)	0.932	0.894	0.971	**0.001**
Weight change at baseline (%)	0.951	0.921	0.982	**0.002**
Diet at baseline				
No modified diet				
Texture modified diet[a]	1.846	1.208	2.819	**0.005**
WHO PS				
0				
>0	1.976	1.272	3.072	**0.002**
P16 expression				
Others (ref)				
P16 + oropharynx	0.840	0.508	1.389	0.497
Tumor subsite				
Others (ref)				
Oral cavity, oropharynx, and hypopharynx	0.772	0.487	1.222	0.270
T classification (TNM)				
T0, T1, Tx vs higher (ref)				
T2, T3, T4	1.549	0.898	2.670	0.115
N classification (TNM)				
N0, N1 vs higher (ref)				
N2, N3	1.876	1.243	2.831	**0.003**
Treatment setting				
Primary				
Adjuvant	0.725	0.462	1.139	0.163
Radiosensitizing systemic therapy				
Platinum (carbo-/cis-) (ref)				
Cetuximab	0.686	0.441	1.069	0.096
Neck irradiation				
No neck RT + unilateral				
Bilateral	2.552	1.542	4.223	**<0.001**
RT dose on contralateral submandibular glands (Gy)	1.032	1.019	1.046	**<0.001**
RT dose on contralateral parotid salivary glands (Gy)	1.072	1.044	1.102	**<0.001**

Abbreviations: ref, reference; BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance Status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray. Bold values denote statistical significance at the p<0.050 level.
[a] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

IQR of TF use was larger in the oral cavity, oropharynx, hypopharynx subgroup (143 vs 96 days) and more outliers towards longer TF duration were seen in these subsite groups. However, long-term TF-dependency was not our primary endpoint and total TF duration could be studied in more detail in future studies.

Limitations of our study include its retrospective design, although we do not think this greatly affected our outcomes; the small amount of randomly missing data could be compensated using statistical imputation. Our cohort was derived from two different university medical centers, both working according to the Dutch Head and Neck Cancer Society guideline, minimizing the possibility of a local therapist effect on group performance or on treatment outcomes. Thereby, this heterogeneity also enables generalization of applicability of the prediction model. Potentially, TF was started earlier in case of early prophylactic insertion, because there were no additional barriers to initiate TF and a better patient compliance was expected compared to reactive feeding tube placement [65]. However, to our experience patients also frequently report barriers initiating TF when the tube was already inserted and ready to use.

Because of a lack of high quality randomized studies, it remains unclear whether prophylactic gastrostomy insertion is superior to reactive insertion. Considering the effect of gastrostomy insertion and TF on weight loss, dehydration, treatment interruptions or change in treatment schedule [24,66], and post treatment health-related quality of life [67,68], prophylactic gastrostomy insertion might be preferred above reactive placement in well selected cases.

Available literature is inconsistent about whether prophylactic gastrostomy insertion increases the risk of long-term dysphagia [65,67,69–74]. The risk of long-term dysphagia can be reduced using a proactive policy of feeding tube removal, guidance by a speech and language pathologist, and swallowing exercise [75].

The aim of the present prediction model was to support clinicians in obtaining best clinical practice protocols to prevent delayed reactive gastrostomy insertions. Based on the outcome of the prediction model, upfront prediction of TF-dependency can be performed which immediately enables the decision-making on prophylactic tube insertion in patients at risk for TF for four weeks or longer. We are currently working on the external validation of our model, through collaborations with other Dutch head and neck

Table 3
Results of multivariable logistic regression analysis presented in odds ratios and *p* values. The shrunk regression coefficients represent the regression coefficients after internal validation yielded a shrinkage factor of 0.87.

	Crude OR (CI-95%)	p value	Crude regression coefficient	Shrunk regression coefficients
Model intercept			−0.661	−0.506
BMI at baseline (kg/m^2)	0.953 (0.910–0.999)	**0.045**	−0.048	−0.042
Weight change at baseline (%)	0.966 (0.931–1.002)	0.066	−0.035	−0.030
Diet at baseline				
No modified diet (ref)	1	**0.036**	0.520	0.452
Texture modified diet[a]	1.682 (1.034–2.737)			
WHO PS				
0 (ref)	1	**0.005**	0.699	0.608
>0	2.012 (1.235–3.279)			
Tumor subsite				
Others (ref)	1	**0.028**	−0.586	−0.510
Oral cavity, oropharynx, and hypopharynx	0.556 (0.329–0.940)			
T classification (TNM)				
T0, T1, Tx (ref)	1	0.262	0.358	0.311
T2, T3, T4	1.430 (0.766–2.670)			
N classification (TNM)				
N0, N1 (ref)	1	**0.008**	0.645	0.561
N2, N3	1.906 (1.186–3.062)			
Radiosensitizing systemic therapy				
Platinum (carbo-/cis-) (ref)	1	**0.004**	0.753	−0.655
Cetuximab	0.471 (0.283–0.783)			
Mean RT dose on contralateral submandibular gland (Gy)	1.017 (1.001–1.034)	**0.037**	0.017	0.015
Mean RT dose on contralateral parotid gland (Gy)	1.050 (1.017–1.084)	**0.003**	0.049	0.042

Abbreviations: ref, reference; OR, Odds ratio; CI, confidence interval; BMI, body mass index; RT, radiotherapy; WHO PS, World Health Organization Performance status; TNM-classification, tumor, node, metastasis classification according to the 7th edition [52]; Gy, Gray. Bold values denote statistical significance at the p<0.050 level.
[a] Texture modified diet includes ground, minced, liquid, or full tube feeding without oral intake.

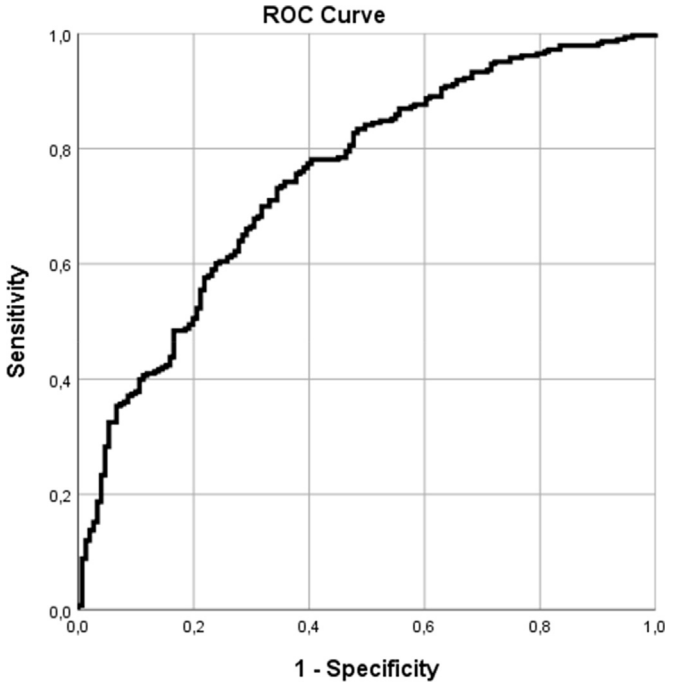

Fig. 2. Receiver operating characteristic curve of the prediction model before internal validation (AUC 74,8%; 95% CI 70.1–79.6%), indicating the good discriminative performance of the model.

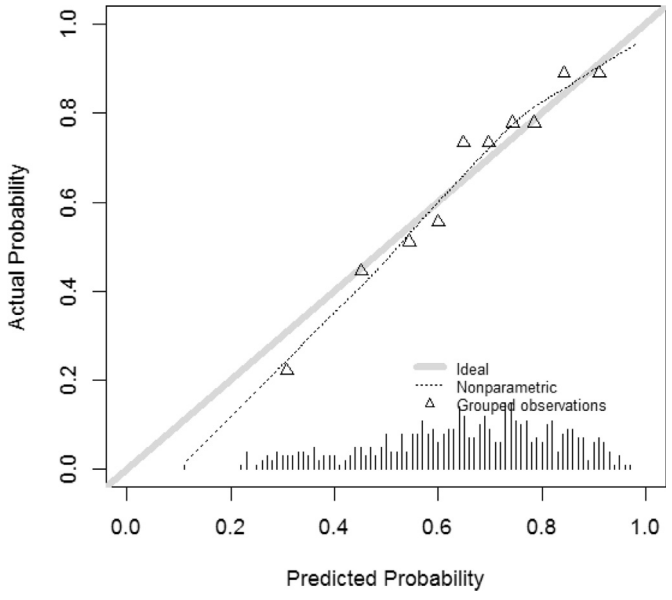

Fig. 3. Calibration plot with the actual probability of the use of tube feeding for at least four weeks by predicted probability. The triangles indicate quantiles of patients with a similar predicted probability of the use of tube feeding for at least four weeks.

cancer centers. External validation is required to develop and widespread implement this model as a generalizable decision aid for prophylactic feeding tube insertion with consistent cut off values. By combining our data we will preferably develop one tool for the identification of LAHNSCC patients treated with CRT/BRT who need prophylactic gastrostomy placement.

5. Conclusion

We developed and internally validated a prediction model that is intended to estimate TF-dependency for at least four weeks in LAHNSCC patients treated with CRT/BRT. This model can be used as

a tool to support personalized decision making on prophylactic gastrostomy insertion.

Statement of authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content.

Funding

This research was supported by the NUTRIM Graduate Programme.

Conflict of Interest

None declared.

Acknowledgments

None.

References

[1] Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.
[2] Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
[3] Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33–40.
[4] Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[5] Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66:253–62.
[6] Beijer YJ, Koopman M, Terhaard CH, Braunius WW, van Es RJ, de Graeff A, et al. Outcome and toxicity of radiotherapy combined with chemotherapy or cetuximab for head and neck cancer: our experience in one hundred and twenty-five patients. Clin Otolaryngol 2013;38:69–74.
[7] Langenberg M, Terhaard CH, Hordijk GJ, Es RJ, Voest EE, de Graeff A, et al. Simultaneous radio- and chemotherapy for squamous cell carcinoma of the head and neck in daily clinical practice: 5 years experience in a University Hospital. Clin Otolaryngol Allied Sci 2004;29:729–34.
[8] Colasanto JM, Prasad P, Nash MA, Decker RH, Wilson LD. Nutritional support of patients undergoing radiation therapy for head and neck cancer. Oncology 2005;19:371–9. discussion 380-2, 387.
[9] Wang C, Vainshtein JM, Veksler M, Rabban PE, Sullivan JA, Wang SC, et al. Investigating the clinical significance of body composition changes in patients undergoing chemoradiation for oropharyngeal cancer using analytic morphomics. SpringerPplus 2016;5:429.
[10] Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. Head Neck 2007;29:893–900.
[11] Capuano G, Grosso A, Gentile PC, Battista M, Bianciardi F, Di Palma A, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. Head Neck 2008;30:503–8.
[12] Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. Br J Cancer 2004;91:447–52.
[13] Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN guidelines on enteral nutrition: Non-surgical oncology. Clin Nutr 2006;25:245–59.
[14] Orell-Kotikangas H, Osterlund P, Makitie O, Saarilahti K, Ravasco P, Schwab U, et al. Cachexia at diagnosis is associated with poor survival in head and neck cancer patients. Acta Otolaryngol 2017;137:778–85.
[15] Bishop S, Reed WM. The provision of enteral nutritional support during definitive chemoradiotherapy in head and neck cancer patients. J Med Imaging Radiat Sci 2015;62:267–76.
[16] Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. Nutrients 2015;7:265–76.
[17] Brown TE, Spurgin AL, Ross L, Tripcony L, Keller J, Hughes BG, et al. Validated swallowing and nutrition guidelines for patients with head and neck cancer: identification of high-risk patients for proactive gastrostomy. Head Neck 2013;35:1385–91.
[18] Garrow JS, James WPT, Ralph A. In: Human nutrition and dietetics. 10th. Edinburgh: Churchill Livingstone; 2000. p. 490.
[19] Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2010;78:1026–32.
[20] Chen AM, Li BQ, Jennelle RL, Lau DH, Yang CC, Courquin J, et al. Late esophageal toxicity after radiation therapy for head and neck cancer. Head Neck 2010;32:178–83.
[21] Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg 2013;139:1127–34.
[22] Strijbos D, Keszthelyi D, Bogie RMM, Gilissen LPL, Lacko M, Hoeijmakers JGJ, et al. A systematic review and meta-analysis on outcomes and complications of percutaneous endoscopic versus radiologic gastrostomy for enteral feeding. J Clin Gastroenterol 2018;52:753–64.
[23] Grant DG, Bradley PT, Pothier DD, Bailey D, Caldera S, Baldwin DL, et al. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. Clin Otolaryngol 2009;34:103–12.
[24] van der Linden NC, Kok A, Leermakers-Vermeer MJ, de Roos NM, de Bree R, van Cruijsen H, et al. Indicators for enteral nutrition use and prophylactic percutaneous endoscopic gastrostomy placement in patients with head and neck cancer undergoing chemoradiotherapy. Nutr Clin Pract 2017;32:225–32.
[25] Madhoun MF, Blankenship MM, Blankenship DM, Krempl GA, Tierney WM. Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)? World J Gastroenterol 2011;17:1004–8.
[26] Leemans LES CR, Langendijk JA, de Boer JP, Terhaard CHJ, Roodenburg JLN, Klomp FWJ, et al. Richtlijn hoofd-halstumoren 2014;18.
[27] Brown TE, Getliffe V, Banks MD, Hughes BG, Lin CY, Kenny LM, et al. Validation of an updated evidence-based protocol for proactive gastrostomy tube insertion in patients with head and neck cancer. Eur J Clin Nutr 2016;70:574–81.
[28] Karsten RT, Stuiver MM, van der Molen L, Navran A, de Boer JP, Hilgers FJM, et al. From reactive to proactive tube feeding during chemoradiotherapy for head and neck cancer: a clinical prediction model-based approach. Oral Oncol 2019;88:172–9.
[29] Sanguineti G, Rao N, Gunn B, Ricchetti F, Fiorino C. Predictors of PEG dependence after IMRT+/-chemotherapy for oropharyngeal cancer. Radiother Oncol 2013;107:300–4.
[30] Blanchard EM, Moon J, Hesketh PJ, Kelly K, Wozniak AJ, Crowley J, et al. Comparison of platinum-based chemotherapy in patients older and younger than 70 years: an analysis of Southwest Oncology Group Trials 9308 and 9509. J Thorac Oncol 2011;6:115–20.
[31] de Boer J, de Bruijn A, Daems MJM, Kuin-Sluijter W, Li YY, Leijtens H, et al. Landelijke multidisciplinaire richtlijn Neusmaagsonde. Verpleegkundigen & Verzorgenden Nederland 2011;(November):112.
[32] Stuurgroep ondervoeding, (2019). Kiezen toedieningsweg. Retrieved from https://www.stuurgroepondervoeding.nl/stappen-sondevoeding
[33] Kruizenga H, Beijer S, Waal GH, Jonkers-Schuitema C, Klos M, Remijnse-Meester BW, et al. Richtlijn ondervoeding. Stuurgroep Ondervoeding 2017;(August):36.
[34] Brown TE, Wittholz K, Way M, Banks MD, Hughes BG, Lin CY, et al. Investigation of p16 status, chemotherapy regimen, and other nutrition markers for predicting gastrostomy in patients with head and neck cancer. Head Neck 2017;39:868–75.
[35] Cheng SS, Terrell JE, Bradford CR, Ronis DL, Fowler KE, Prince ME, et al. Variables associated with feeding tube placement in head and neck cancer. Arch Otolaryngol Head Neck Surg 2006;132:655–61.
[36] Lawson JD, Gaultney J, Saba N, Grist W, Davis L, Johnstone PA. Percutaneous feeding tubes in patients with head and neck cancer: rethinking prophylactic placement for patients undergoing chemoradiation. Am J Otolaryngol 2009;30:244–9.
[37] Mortensen HR, Overgaard J, Jensen K, Specht L, Overgaard M, Johansen J, et al. Factors associated with acute and late dysphagia in the DAHANCA 6 & 7 randomized trial with accelerated radiotherapy for head and neck cancer. Acta Oncol 2013;52:1535–42.
[38] Sachdev S, Refaat T, Bacchus ID, Sathiaseelan V, Mittal BB. Age most significant predictor of requiring enteral feeding in head-and-neck cancer patients. Radiat Oncol 2015;10:93.
[39] Setton J, Lee NY, Riaz N, Huang SH, Waldron J, O'Sullivan B, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. Cancer 2015;121:294–301.
[40] Strom T, Trotti AM, Kish J, Rao NG, McCaffrey J, Padhya TA, et al. Risk factors for percutaneous endoscopic gastrostomy tube placement during chemoradiotherapy for oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 2013;139:1242–6.
[41] Wermker K, Jung S, Huppmeier L, Joos U, Kleinheinz J. Prediction model for early percutaneous endoscopic gastrostomy (PEG) in head and neck cancer treatment. Oral Oncol 2012;48:355–60.

[42] Bhayani MK, Hutcheson KA, Barringer DA, Lisec A, Alvarez CP, Roberts DB, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck 2013;35:1634–40.
[43] Kanayama N, Kierkels RGJ, van der Schaaf A, Steenbakkers R, Yoshioka Y, Nishiyama K, et al. External validation of a multifactorial normal tissue complication probability model for tube feeding dependence at 6months after definitive radiotherapy for head and neck cancer. Radiother Oncol 2018;129:403–8.
[44] Matuschek C, Bolke E, Geigis C, Kammers K, Ganswindt U, Scheckenbach K, et al. Influence of dosimetric and clinical criteria on the requirement of artificial nutrition during radiotherapy of head and neck cancer patients. Radiother Oncol 2016;120:28–35.
[45] Poulsen MG, Riddle B, Keller J, et al. Predictors of acute grade 4 swallowing toxicity in patients with stages III and IV squamous carcinoma of the head and neck treated with radiotherapy alone. Radiother Oncol 2008;87:253–9.
[46] Yang W, McNutt TR, Dudley SA, Kumar R, Starmer HM, Gourin CG, et al. Predictive factors for prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement and use in head and neck patients following intensity-modulated radiation therapy (IMRT) treatment: Concordance, discrepancies, and the role of gabapentin. Dysphagia 2016;31:206–13.
[47] Brown TE, Crombie J, Spurgin AL, Tripcony L, Keller J, Hughes BG, et al. Improving guideline sensitivity and specificity for the identification of proactive gastrostomy placement in patients with head and neck cancer. Head Neck 2016;38(Suppl 1):E1163–71.
[48] Murono S, Tsuji A, Endo K, Kondo S, Wakisaka N, Yoshizaki T. Factors associated with gastrostomy tube dependence after concurrent chemoradiotherapy for hypopharyngeal cancer. Support Care Cancer 2015;23:457–62.
[49] Barnhart MK, Ward EC, Cartmill B, Robinson RA, Simms VA, Chandler SJ, et al. Pretreatment factors associated with functional oral intake and feeding tube use at 1 and 6 months post-radiotherapy (+/- chemotherapy) for head and neck cancer. Eur Arch Oto-Rhino-Laryngol 2017;274:507–16.
[50] Gokhale AS, McLaughlin BT, Flickinger JC, Beriwal S, Heron DE, Ferris RL, et al. Clinical and dosimetric factors associated with a prolonged feeding tube requirement in patients treated with chemoradiotherapy (CRT) for head and neck cancers. Ann Oncol 2010;21:145–51.
[51] Lavo JP, Ludlow D, Morgan M, Caldito G, Nathan CA. Predicting feeding tube and tracheotomy dependence in laryngeal cancer patients. Acta Otolaryngol 2017;137:326–30.
[52] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[53] Vangelov B, Smee RI. Clinical predictors for reactive tube feeding in patients with advanced oropharynx cancer receiving radiotherapy +/- chemotherapy. Eur Arch Oto-Rhino-Laryngol 2017;274:3741–9.
[54] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–9.
[55] Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart 2012;98:683–90.
[56] Harrell FE. Regression modeling Strategies. 2nd 2015.
[57] Hosmer DW, Lemeshow S. Applied logistic regression. 2nd. New York: Wiley; 2000.
[58] R Foundation for Statistical Computing. R: A language and environment for statistical computing. 351. Vienna, Austria: R Core Team; 2018.
[59] Frowen J, Cotton S, Corry J, Perry A. Impact of demographics, tumor characteristics, and treatment factors on swallowing after (chemo)radiotherapy for head and neck cancer. Head Neck 2010;32:513–28.
[60] Mortensen HR, Jensen K, Aksglaede K, Behrens M, Grau C. Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters. Radiother Oncol 2013;107:288–94.
[61] Akst LM, Chan J, Elson P, Saxton J, Strome M, Adelstein D. Functional outcomes following chemoradiotherapy for head and neck cancer. Otolaryngol Head Neck Surg 2004;131:950–7.
[62] Dijkema T, Raaijmakers CP, Braam PM, Roesink JM, Monninkhof EM, Terhaard CH. Xerostomia: a day and night difference. Radiother Oncol 2012;104:219–23.
[63] Houweling AC, Philippens ME, Dijkema T, Roesink JM, Terhaard CH, Schilstra C, et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2010;76:1259–65.
[64] Houweling AC, Dijkema T, Roesink JM, Terhaard CH, Raaijmakers CP. Sparing the contralateral submandibular gland in oropharyngeal cancer patients: a planning study. Radiother Oncol 2008;89:64–70.
[65] Brown T, Banks M, Hughes BGM, Lin C, Kelly L, Bauer J. Tube feeding during treatment for head and neck cancer - adherence and patient reported barriers. Oral Oncol 2017;72:140–9.
[66] Hoek J, Bloemendal KM, van der Velden LA, van Diessen JN, van Werkhoven E, Klop WM, et al. Nephrotoxicity as a dose-limiting factor in a high-dose cisplatin-based chemoradiotherapy regimen for head and neck carcinomas. Cancers 2016;8.
[67] Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head Neck 2012;34:1–9.
[68] Salas S, Baumstarck-Barrau K, Alfonsi M, Digue L, Bagarry D, Feham N, et al. Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: prospective randomized trial. Radiother Oncol 2009;93:503–9.
[69] Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia 2012;27:251–9.
[70] Oozeer NB, Corsar K, Glore RJ, Penney S, Patterson J, Paleri V. The impact of enteral feeding route on patient-reported long term swallowing outcome after chemoradiation for head and neck cancer. Oral Oncol 2011;47:980–3.
[71] Sethugavalar B, Teo MT, Buchan C, Ermis E, Williams GF, Sen M, et al. Impact of prophylactic gastrostomy or reactive NG tube upon patient-reported long term swallow function following chemoradiotherapy for oropharyngeal carcinoma: a matched pair analysis. Oral Oncol 2016;59:80–5.
[72] Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: a randomized controlled study. Head Neck; 2017; 39(5): 908-915.
[73] Goff D, Coward S, Fitzgerald A, Paleri V, Moor JW, Patterson JM. Swallowing outcomes for patients with oropharyngeal squamous cell carcinoma treated with primary (chemo)radiation therapy receiving either prophylactic gastrostomy or reactive nasogastric tube: a prospective cohort study. Clin Otolaryngol 2017;42(6):1135–40.
[74] Prestwich RJ, Teo MT, Gilbert A, Williams G, Dyker KE, Sen M. Long-term swallow function after chemoradiotherapy for oropharyngeal cancer: the influence of a prophylactic gastrostomy or reactive nasogastric tube. Clin Oncol 2014;26:103–9.
[75] Kraaijenga SAC, Molen LV, Stuiver MM, Takes RP, Al-Mamgani A, van den Brekel MWM, et al. Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. Head Neck 2017;39:1943–61.