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From reactive to proactive tube feeding during chemoradiotherapy for head and neck cancer: A clinical prediction model-based approach

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ABSTRACT

Objectives: Feeding tubes are placed unnecessarily in a proportion of head and neck cancer (HNC) patients treated with chemoradiotherapy (CRT) when prophylactic tube placement protocols are used. This may have a negative impact on the risk of long-term dysphagia. Reactive tube placement protocols, on the other hand, might result in weight loss and treatment interruption. The objective of this study is to identify patients at risk for prolonged tube dependency in order to implement a personalized strategy regarding proactive tube placement.
Materials and methods: A retrospective study was performed in a consecutive cohort of HNC patients treated with primary CRT for whom a reactive tube placement protocol was used. A prediction model was developed to predict prolonged (> 90 days) feeding tube dependency. Model performance and clinical net benefit of the model were assessed.
Results: Of the 336 included patients, 229 (68%) needed a feeding tube during CRT and 151 (45%) were prolonged feeding tube dependent. The prediction model includes the predictors pretreatment BMI, weight loss, Functional Oral Intake Scale and T-stage. Discriminatory ability is fair (area under the ROC-curve of 0.69) and calibration is adequate (Hosmer and Lemeshow test $p = .254$). The model shows net benefit over current practice for probability thresholds from 35 to 80%.
Conclusion: The developed model can be used to select patients for proactive feeding tube placement during primary CRT for HNC. The nomogram with easily obtainable parameters is a useful tool for clinicians to support shared decision making regarding proactive tube placement.

Introduction

Chemoradiotherapy (CRT) is widely used in advanced stage head and neck cancer (HNC). Common side effects of radiotherapy are dysphagia and weight loss [1], and concomitant chemotherapy increases the prevalence of these toxicities [2]. Malnourishment and/or dehydration resulting from mucositis, loss of taste, xerostomia, and impaired swallowing function can cause feeding tube dependency in a proportion of patients during treatment [3]. However, numerous studies have shown that still a considerable proportion of patients maintain their oral intake during CRT [4,5].

Reactive feeding tube (RFT) placement, placement of a feeding tube (i.e. nasogastric tube (NGT) or a percutaneous radiological gastrostomy (PRG)) reactive to excessive weight loss (> 5% over three months

or > 10% over six months), dehydration or aspiration, has a role in decreasing the incidence of (long-term) functional problems. Maintaining oral intake, along with targeted preventive exercises, prevents non-use atrophy of the swallowing muscles [6–9]. This is therefore standard of care in HNC patients treated with CRT in the Netherlands Cancer Institute. Frequent monitoring of patients' oral intake is thereby mandatory to timely identify patients requiring a feeding tube to lower the risk of weight loss, dehydration and treatment interruption associated with RFT [10–13]. On the other hand, prophylactic feeding tube placement may prevent this [14–16], but at the same time convicts all patients tube feeding, whereas this would be unnecessary in a substantial proportion.

Both protocols thus have advantages and disadvantages and it would be beneficial if one could predict whether a reactive or

prophylactic approach would be most appropriate for a given patient (i.e. personalized medicine) [17]. Predictive factors for tube placement and (prolonged) dependency have been identified [16,18–27]. These factors include radiotherapy variables, tumor and nodal stage, and weight loss prior treatment. However, a clinically applicable prediction model to select HNC patients treated with CRT for proactive tube feeding in high risk patients is, to our knowledge, still lacking.

Therefore, we hypothesized that clinical decision-making on proactive tube placement could be aided by a prediction model based on the known predictive factors. The model should enable accurate identification of patients at risk of prolonged (> 90 days) tube dependency during primary CRT. This would allow for a personalized strategy regarding proactive/reactive tube placement, feeding and supportive care (e.g. swallowing exercises).

Materials and methods

Ethical considerations

This study does not fall under de scope of the Medical Research Involving Human Subjects Act, which was confirmed by the medical research ethics committee of the Netherlands Cancer Institute (METC18.0589/N18TFC).

Patient selection

All patients treated with primary, cisplatin-based CRT for head and neck squamous cell carcinoma in the Netherlands Cancer Institute between January 2008 and October 2016 were included. Patients with previous treatment in the head and neck area (except neck dissections and skin malignancies), more than one primary tumor, or distant metastases were excluded.

Data collection

We extracted the following variables retrospectively from the medical file: gender, age, comorbidity including the Adult Comorbidity Evaluation-27 (ACE-27) index, tumor site-, T- and N-stage (AJCC 7th edition), general tumor stage, tumor human papilloma virus (HPV) status, tongue base involvement, and radiotherapy and chemotherapy doses. Clinical parameters, assessed prior to CRT at the first appointment, included Body Mass Index (BMI), weight loss (none, < or > 10% over six months), pain in the throat and/or mouth and dysphagia (patient-reported swallowing problems). Additionally, the Functional Oral Intake Scale (FOIS) was obtained, which is a validated tool reflecting functional oral intake, scored by health professionals on a seven-point ordinal scale with lower scores indicating more problems (1 = no oral intake; 7 = total oral intake without restrictions) [28]. When not explicitly mentioned in the medical record, the FOIS was scored in retrospect. The timing of tube placement, tube type (nasogastric tube (NGT) or a percutaneous radiological gastrostomy (PRG)), and length of dependency were assessed, with time between tube placement and removal defined as length of dependency. Finally, neck dissections within the first 90 days after CRT were assessed.

Chemoradiotherapy, feeding tube policy and swallowing exercises

According to protocol, radiotherapy was given with 6 MV photons up to 70 Gray (Gy) in 35 fractions in seven weeks with sequential or simultaneous integrated boost according to the IMRT technique (either step and shoot or VMAT). Patients receiving sequential boost got an elective dosage of 46 Gy (23 fractions of 2 Gy) on the primary tumor and bilateral neck, with a total dosage of 70 Gy (35 fractions of 2 Gy) on the tumor and involved lymph nodes. Patients receiving simultaneous integrated boost were given an elective dosage of 54.25 Gy (35 fractions of 1.55 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy).

Concurrent chemotherapy consisted of cisplatin. This was administered intravenously in low-dose (6 mg/m^2 daily during the first five weeks of radiotherapy), intermediate-dose (40 mg/m^2 weekly), or high-dose (100 mg/m^2 at day 1, 22 and 43 of radiotherapy).

A reactive tube placement protocol was used for all patients, with placement reactive to excessive weight loss (> 5% over three months or > 10% over six months), dehydration or proven aspiration based on videofluoroscopy. Tubes are removed in case oral intake is adequate and/or aspiration is resolved. All patients are seen by the SLP and dietitian for clinical check-up and counseling before CRT and all were enrolled in the preventive swallowing exercise program according to the Institution's protocol [29]. We expect high compliance to the program because of intensive monitoring by an SLP at least until 90 days post CRT.

Endpoint definition

The endpoint of the prediction model was prolonged feeding tube dependency, defined as placement of a tube (NGT or PRG) before the end of CRT, which stayed in situ for more than ninety days, because by that time the acute local treatment-related toxicities have subsided and ongoing functional impairment like xerostomia and dysgeusia have become more stable. Also, in all patients with a feeding tube the need for the tube is reassessed every two weeks by the dietitian.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 23.0 and R 3.3.2 [30,31]. *P* values < .05 were considered statistically significant. Univariable logistic regression analysis was used to assess the association of baseline variables with prolonged feeding tube dependency in this sample. Subsequently, a multivariable logistic regression model was developed, for which we considered known predictors based on theoretical considerations and pre-existing evidence. These candidate predictors were T-stage, BMI, dysphagia, weight loss and FOIS. The FOIS was dichotomized (7 = normal diet and < 7 = abnormal diet) due to the low number of patients with scores < 7. Variables were not subject to selection based on statistical significance [32], but variables with a contradicting sign of the regression coefficient (i.e. contradicting current clinical knowledge and/or biological plausibility) were excluded from the model. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) and *p* values of the final model are presented. Linear predictor scores were calculated for use in calibration and discrimination analysis.

Discrimination and calibration were assessed to evaluate the performance of the model. The area under the receiver-operation characteristic (ROC) curve was estimated to assess discriminative ability (0.5 = no discriminative ability and 1.0 = perfect discrimination). From a value of 0.7, the discriminative ability of the model is fair. For calibration (agreement between predicted and observed probabilities), the goodness-of-fit test (Hosmer-Lemeshow test) was used, with *p* values > .05 indicating good calibration. Bootstrapping analysis with 200 samples was used to internally validate the model and estimate shrinkage factors per predictor for future use. A nomogram (with regression coefficients after shrinkage) is presented to easily estimate the probability of prolonged tube dependency per patient.

Clinical usefulness was examined by means of decision curve analysis [33]. In this analysis, net benefit is calculated as the difference between true positive (i.e. tube placement justified) counts and false positive (i.e. tube placement not-justified) counts, weighted by the relative harm of a false-positive and false-negative result, over a range of threshold probabilities (p_t). In the context of the current study, these threshold probabilities indicate the level of risk for long term feeding-tube dependency at which a patient or surgeon would opt for proactive placement. Net benefit can be interpreted as the increase in the proportion of patients receiving the appropriate treatment through use of

the prediction model, compared to a situation in which all patients would (or would not) receive the treatment [34].

In a post-hoc secondary analysis, associations between prolonged tube dependency and timing of tube placement during CRT, and neck dissection within 90 days after CRT were assessed univariably.

Results

Patient, tumor and treatment characteristics

Between January 2008 and October 2016, 449 patients were treated with cisplatin-based chemoradiotherapy for head and neck cancer in the Netherlands Cancer Institute. Of this consecutive cohort, 113 were excluded (postoperative CRT ($n = 34$), history of head and neck cancer ($n = 30$), more than one primary tumor ($n = 28$), induction chemotherapy ($n = 14$) and distant metastases ($n = 7$)). Of the final cohort ($n = 336$), most had stage IV disease (87%) and a pharyngeal tumor (86%). In 145 patients (43%), weight loss (less or more than 10%) was present before CRT. Problems with swallowing were reported by 150 patients (45%). Baseline FOIS was normal (7) in 231 patients (69%). The remaining 31% had FOIS 6 ($n = 35$), 5 ($n = 39$), 4 ($n = 21$) or 2 ($n = 1$). The FOIS was scored retrospectively in 226 patients (67%) according to structured and complete reporting of the speech language pathologist (SLP) and/or dietitian. Patient, tumor and treatment characteristics are presented in Tables 1a and 1b.

Tube feeding

Of the 336 patients, 229 (68%) received tube feeding during CRT with dependencies ranging from 3 to 2185 days. Of these 229 patients, 161 patients (70%) received an NGT, of which 112 were converted to a PRG, and 68 patients (30%) only received a PRG. Median dependency was 59 days (range 3–216 days) for patients who only received an NGT, 161 days (range 56–2185 days) for who received an NGT with conversion to a PRG, and 171 days (range 6–1142 days) for who directly received a PRG. In 151 patients (45%) prolonged (> 90 days) tube feeding was needed and 81 patients (24%) needed the tube longer than 180 days. At 90 days post CRT 11 patients (7 (64%) with a tube in situ) had died of pneumonia ($n = 2$), oral bleeding ($n = 1$), multi-organ failure ($n = 1$), progressive disease ($n = 2$), diverticulitis/sepsis ($n = 1$), and in four cases cause of death was unknown.

Fig. 1 shows the number of tube placements per week of CRT and the percentage prolonged placements. Of the 41 and 18 patients who started tube feeding before and in the first week of CRT respectively, 55 (93%) became prolonged dependent. Of these 55 patients, 28 (51%) initially received an NGT, which was later converted to a PRG. Most patients received their tube in the fourth week of CRT ($n = 47$) of whom 62% became prolonged dependent.

Univariable analysis

Univariable logistic regression analysis indicated that T4-stage tumor (OR 3.29; 95% CI 1.50–7.18, $p = .003$), initially lower BMI (per 1 unit increase OR 0.89; 95% CI 0.85–0.94, $p < .001$), weight loss over the past six months ($< 10\%$ OR 1.94; 95% CI 1.17–3.22, $p = .010$ and $> 10\%$ OR 5.96; 95% CI 2.98–11.94, $p < .001$), pain (OR 1.74; 95% CI 1.12–2.69, $p = .013$), dysphagia (OR 2.15; 95% CI 1.39–3.33, $p = .001$) and an FOIS below 7 (OR 3.36; 95% CI 2.05–5.51, $p < .001$) were associated with an increased risk of prolonged feeding tube dependency (Tables 1a and 1b).

Risk prediction model

The initial multivariable model included the known predictors T-stage, BMI, dysphagia, weight loss and the FOIS. The regression coefficient of dysphagia was -0.09 (SE 0.32) and was therefore excluded

from the final model. Statistically significant prediction in the final model were BMI (OR 0.93; 95% CI 0.88–0.99, $p = .019$) and $> 10\%$ weight loss over the last six months before treatment (OR 2.66; 95% CI 1.15–6.39, $p = .024$) (see Table 2).

Model performance

The area under the ROC-curve was 0.69 indicating fair discrimination (see Fig. 2). The Hosmer and Lemeshow test showed agreement between predicted and observed probabilities within risk strata, indicating adequate calibration ($p = .254$).

Internal validation

Shrinkage factors per predictor, assessed by means of bootstrapping analysis with 200 repetitions, are listed in Table 2. These factors indicate the difference between the mean regression coefficient of the 200 bootstrap samples and the initial model. For future use of the model, the regression coefficients after shrinkage should be used. In order to easily estimate the probability of prolonged feeding tube dependency per patient, a nomogram after shrinkage is provided in Fig. 3.

Decision curve analysis

Fig. 4 represents the net benefit of applying the model for each risk threshold. The decision curve shows that the prediction model has net benefit over current practice which includes reactive feeding tube placement (treat none), for probability thresholds from 35 to 80%.

Influence of factors after (start of) CRT

Timing of placement is associated with prolonged tube dependency. Patients who received a tube before or in the first week of CRT ($n = 59$) have a higher risk of prolonged tube dependency (OR 25.92; 95% CI 9.12–73.69, $p < .001$). Per day later after start of CRT, patients have a lower risk of prolonged tube dependency (OR 0.95; 95% CI 0.93–0.97, $p < .001$).

Patients who received a neck dissection within the first 90 days after CRT ($n = 8$) did not have a significantly higher risk of prolonged feeding tube dependency (OR 2.08; 95% CI 0.49–8.84, $p = .322$), however, group size was small.

Discussion

The aim was to develop a prediction model to estimate the risk of prolonged (> 90 days) feeding tube dependency, which can be helpful in deciding on proactive tube placement for patients receiving primary CRT for HNC. In univariable analysis, T4-stage tumor, BMI, weight loss, pain, dysphagia and FOIS below 7 were significant risk factors. The multivariable prediction model included T-stage, BMI, weight loss, and FOIS which resulted in a model with fair discriminative ability and adequate agreement between predicted and observed probabilities.

The model and corresponding nomogram include easily obtainable parameters and are therefore a practical tool for clinicians to estimate the risk of prolonged feeding tube dependency. This aids in shared decision making regarding proactive placement in high risk patients, preventing treatment interruption with benefits on tumor control [35]. Identifying low risk patients can prevent unnecessary tube placements, reducing complications of placement (e.g. infection, bleeding, and perforation), reducing costs and preventing non-use atrophy of swallowing muscles [36]. With a shift from authority-based medicine towards shared decision-based practice, the estimated risk can be used to inform patients and make educated decisions [37].

To assess the clinical net benefit of decisions based on the prediction model, decision curve analysis was performed [33]. This analysis showed that a decision regarding proactive placement based on the

Table 1a
Patient and tumor characteristics with univariable analysis presented in odds ratios and *p* values. Boldfaced *p* values are significant.

		Number of patients (%)				Univariable analysis	
		> 90 days feeding tube dependent (*n* = 151)	< 90 days feeding tube dependent (*n* = 185)	Total (*n* = 336)		OR (95% CI)	*p* value
Length of tube feeding (days) Median (range)		196 (91–2185)	0 (0–89)	77 (0–2185)		–	–
Patient characteristics Gender							0.191
	Male	102 (68)	137 (74)	239 (71)	Male	1.00	
	Female	49 (33)	48 (26)	97 (29)	Female	1.37 (0.85–2.20)	
Age (years) Mean (SD)		60 (9)	60 (10)	60 (9)		1.00 (0.97–1.02)	0.695
ACE-27							0.409
	0	51 (34)	78 (42)	129 (38)	0	1.00	
	1	55 (36)	60 (32)	115 (34)	1	1. 40 (0.84–2.33)	0.193
	2	36 (24)	35 (19)	71 (21)	2	1.57 (0.88–2.82)	0.128
	3	9 (6)	12 (7)	21 (6)	3	1.15 (0.45–2.92)	0.773
Tumor characteristics Tumor site							0.432
	Oral cavity	11 (7)	7 (4)	18 (5)	Oral cavity	1.00	
	Oropharynx	79 (52)	107 (58)	186 (55)	Oropharynx	0.47 (0.17–1.27)	0.135
	Nasopharynx	17 (11)	22 (12)	39 (12)	Nasopharynx	0.49 (0.16–1.54)	0.222
	Hypopharynx	34 (23)	31 (17)	65 (19)	Hypopharynx	0.70 (0.24–2.03)	0.508
	Larynx	9 (6)	15 (8)	24 (7)	Larynx	0.38 (0.11–1.34)	0.133
	Nose/paranasal sinus	1 (1)	3 (2)	4 (1)	Nose/paranasal sinus	0.21 (0.02–2.47)	0.215
T-stage							**0.003**
	T1	11 (7)	28 (15)	39 (12)	T1	1.00	
	T2	24 (16)	46 (25)	70 (21)	T2	1.33 (0.57–3.12)	0.515
	T3	45 (30)	56 (30)	101 (30)	T3	2.05 (0.92–4.55)	0.080
	T4	71 (47)	55 (30)	126 (38)	T4	3.29 (1.50–7.18)	**0.003**
N-stage							0.197
	N0	19 (13)	19 (10)	38 (11)	N0	1.00	
	N1	11 (7)	27 (15)	38 (11)	N1	0.41 (0.16–1.05)	0.063
	N2	111 (74)	125 (68)	236 (70)	N2	0.89 (0.45–1.76)	0.734
	N3	10 (7)	14 (8)	24 (7)	N3	0.71 (0.26–2.00)	0.522
Tumor stage							0.096
	Stage II	2 (1)	1 (1)	3 (1)	Stage II/III	1.00	
	Stage III	13 (9)	29 (16)	42 (13)	Stage IV	1.76 (0.91–3.40)	
	Stage IV	136 (90)	155 (84)	291 (87)			
HPV status							0.094
	Negative	66 (44)	78 (42)	144 (43)	Negative	1.00	
	Positive	24 (16)	47 (25)	71 (21)	Positive	0.60 (0.33–1.09)	
	Unknown	61 (40)	60 (32)	121 (36)			
Tongue base involved							0.456
	No	95 (63)	109 (59)	204 (61)	No	1.00	
	Yes	56 (37)	76 (41)	132 (39)	Yes	0.85 (0.54–1.32)	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SD = standard deviation.

model instead of providing all or no patients a prophylactic tube, has net benefit for probability thresholds between 35 and 80%. Since this falls within a plausible range of probability thresholds likely to be considered by clinicians and patients, we assume use of the model has clinical benefit in most cases. For patients or clinicians who would consider proactive placement at probability thresholds below 35% however, a treat all policy would yield the same net benefit [33].

Patients who receive a feeding tube before the start of CRT have an increased risk on prolonged feeding tube dependency. The vast majority (*n* = 55/59; 93%) of patients who received a feeding tube before or in the first week of CRT became prolonged feeding tube dependent. We therefore advise to directly place a PRG instead of an NGT in these patients, avoiding the disadvantages of an NGT including discomfort, prolonged feeding times, shorter tube lifetime and cosmetic grievances.

This study also supports a reactive approach, since the later the placement, the lower the risk of prolonged dependency, thus optimal patient support to maintain oral intake along with preventive swallowing exercises seems to make earlier return to oral intake more likely.

Several studies have investigated predictive factors for prolonged feeding tube dependency in patients treated with CRT for advanced HNC [16,18,20,22,23,25,26]. The predictors found in our study were broadly in accordance with these studies except for the predictors dysphagia, nodal stage and high dose bilateral neck irradiation. Firstly, pre-existing (subjective) dysphagia was a consistent predictive factor in other studies [16,24,25]. In our study, univariable analysis showed a significant association but this association was no longer present in multivariable analysis. An explanation for this might be that in some previous studies dysphagia was assessed by means of validated

Table 1b
Treatment characteristics and clinical parameters with univariable analysis presented in odds ratios and *p* values. Boldfaced *p* values are significant.

		Number of patients (%)				Univariable analysis	
		> 90 days feeding tube dependent (*n* = 151)	< 90 days feeding tube dependent (*n* = 185)	Total (*n* = 336)		OR (95% CI)	*p* value
Treatment characteristics							
High dose irradiation on bilateral neck							0.534
	No	88 (58)	114 (62)	202 (60)	No	1.00	
	Yes	63 (42)	71 (38)	134 (40)	Yes	1.15 (0.74–1.78)	
Planned dose chemotherapy							0.965
	Low	41 (27)	48 (26)	89 (27)	Low	1.00	
	Intermediate	3 (2)	4 (2)	7 (2)	Intermediate	0.88 (0.19–4.15)	0.870
	High	107 (71)	133 (72)	240 (71)	High	0.94 (0. 58–1.54)	0.810
Clinical parameters (obtained prior to CRT)							
BMI		23.3 (4.5)	25.4 (4.4)	24.5 (4.6)		0.89 (0.85–0.94)	**< 0.001**
Mean (SD)							
Pretreatment weight loss							**< 0.001**
	No	65 (43)	126 (68)	191 (57)	No	1.00	
	< 10%	46 (31)	46 (25)	92 (27)	< 10%	1.94 (1.17–3.22)	**0.010**
	> 10%	40 (27)	13 (7)	53 (16)	> 10%	5.96 (2.98–11.94)	**< 0.001**
Pretreatment pain							**0.013**
	No	59 (39)	97 (52)	156 (46)	No	1.00	
	Yes	92 (61)	87 (47)	179 (53)	Yes	1.74 (1.12–2.69)	
	Unknown	0 (0)	1 (1)	1 (0)			
Pretreatment dysphagia							**0.001**
	No	68 (45)	118 (64)	186 (55)	No	1.00	
	Yes	83 (55)	67 (36)	150 (45)	Yes	2.15 (1.39–3.33)	
Pretreatment FOIS							**< 0.001**
	7 (normal diet)	83 (55)	148 (80)	231 (69)	7	1.00	
	6	18 (12)	17 (9)	35 (10)	< 7	3.36 (2.05–5.51)	
	5	27 (18)	12 (7)	39 (12)			
	4	16 (11)	5 (3)	21 (6)			
	2	1 (1)	0 (0)	1 (0)			
	Unknown	6 (4)	3 (2)	9 (3)			

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SD = standard deviation.

questionnaires whereas in our study the variable was less reliably obtained from notes in the medical file.

The second consistent predictive factor for tube dependency in literature is advanced nodal stage [16,22,25,26,38]. The influence of this factor could not be estimated in our cohort due to the lack of variation among nodal stages (70% of the patients had stage N2). This, however, will most likely not influence generalizability because the other variables in the model are independent predictive factors.

Previous studies suggest a predictive value of radiotherapy dose [16,26,39]. We, however, did not use parameters such as bilateral neck
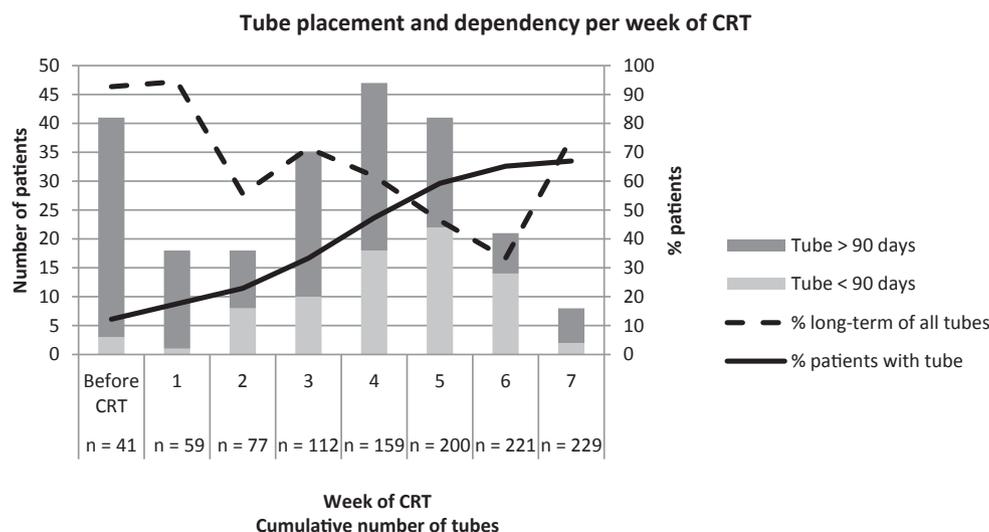

Fig. 1. Left y-axis: Number of tube placements (< and > 90 days in situ) per week of CRT Right y-axis: Percentages of patients with a tube and percentage of prolonged (> 90 days) tube placements of all tube placements. Cumulative numbers of patients with tubes below x-axis.

Table 2
Multivariable logistic regression analysis with prolonged (> 90 days) feeding tube dependency as outcome presented in odds ratios and *p* values. Boldfaced *p* values are significant. The regression coefficients and shrinkage factors assessed by bootstrap analysis with 200 repetitions are also presented.

		Multivariable analysis		Regression coefficient (SE)	Shrinkage factor (SE)
		OR (95% CI)	*p* value		
T-stage	T1	1.00			
	T2	1.16 (0.48–2.90)	0.750	0.15 (0.46)	−0.012 (0.544)
	T3	1.46 (0.64–3.54)	0.381	0.38 (0.44)	−0.025 (0.516)
	T4	2.07 (0.92–4.91)	0.087	0.73 (0.43)	−0.005 (0.488)
BMI (1 unit increase)		0.93 (0.88–0.99)	**0.019**	−0.07 (0.03)	−0.002 (0.034)
Weight loss	No	1.00			
	< 10%	1.43 (0.82–2.48)	0.207	0.36 (0.28)	0.009 (0.296)
	> 10%	2.66 (1.15–6.39)	**0.024**	0.98 (0.43)	0.051 (0.492)
FOIS	7	1.00			
	< 7	1.72 (0.94–3.14)	0.076	0.54 (0.31)	0.018 (0.308)

Abbreviations: BMI = body mass index, CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SE = standard error.
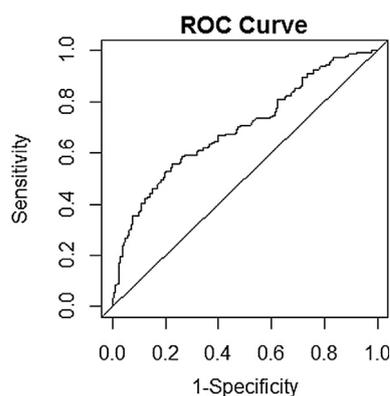

Fig. 2. Discriminative ability of the model displayed in an ROC-curve. Area under the ROC-curve is 0.69.

irradiation or constrictor dose as predictors, because we aimed to develop a prediction model based on readily available clinical parameters, easy to use in daily practice. Despite the advantage of this model concept, the absence of such radiotherapy data has to be considered one of the limitations of this study.

A few studies have made an attempt at predicting the risk on prolonged tube feeding dependency [19,21,27,39]. In contrast to ours, these included heterogeneous populations with regard to tumor stage and treatment modalities with only a proportion of patients being treated with primary CRT (17–60%), which compromises their generalizability to the CRT population. Also, all studies included patients who received a prophylactic feeding tube, which puts them at risk for selection bias.

The strengths of this study include the large dataset with all patients treated with primary CRT for a broad range of tumor localizations compared to previously published work, which enables the construction of an accurate prediction model. Also, a reactive placement protocol was used for all patients. In case a prophylactic placement strategy would have been applied in a proportion of patients, the risk of selection bias would have been high.

Limitations of the study include its retrospective nature. We do not think that the results are affected by this because the number of missing variables was low and most likely random. A prospective study design is preferred in developing a prediction model. However, considerable amount of time is needed to include sufficient patients prospectively. The current data is therefore the best available and the only way to enable risk estimation of prolonged feeding tube dependency. Another limitation of this study is the lack of consistent criteria used in practice
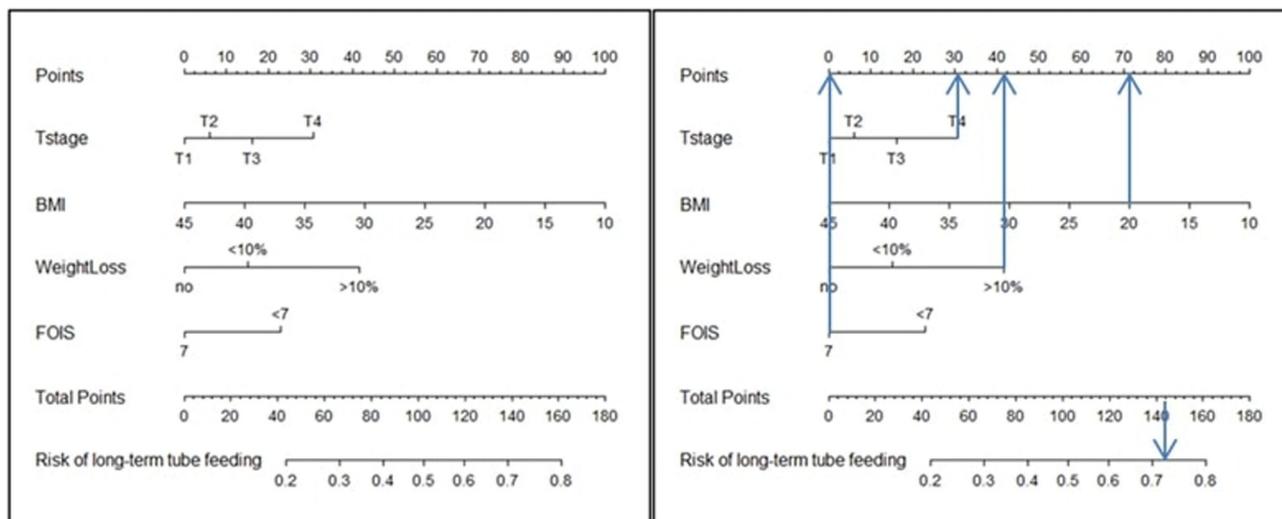

Fig. 3. Left: Nomogram of prediction model. With this nomogram the risk of tube feeding can easily be calculated for each patient by drawing a line from the line of each predictor to the points-scale at the top of the nomogram. If these points are added, a line from the total points scale below to the risk of tube feeding scale can be drawn to obtain the risk of prolonged tube feeding. Right: Patient example with T4 tumor, BMI of 20, > 10% weight loss and an FOIS of 7. Risk of prolonged feeding tube dependency is 73%.
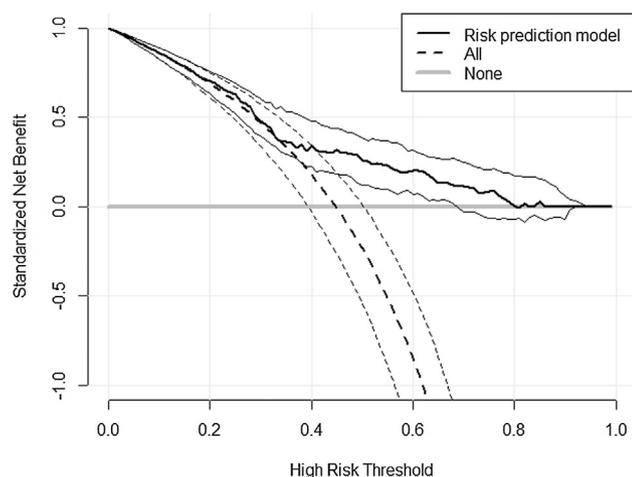
Fig. 4. Decision curve analysis. Solid black line: Net benefit of risk prediction model relative to reactive feeding tube placement protocol in all patients with 95% confidence intervals. Dashed black line: Net benefit of providing all patients a prophylactic feeding tube or treat all with 95% confidence intervals ("All"). Solid grey line: Reference, reactive feeding tube placement protocol in all patients or treat none ("None"). The decision curve shows that the prediction model has net benefit for risks from 35 to 80% over current practice which includes reactive feeding tube placement (treat none).

to decide the timing of tube feeding, which contributed to disagreement of observed and predicted probabilities. Moreover, some misclassification of high and low risk patients can also be explained by patients who refused tube feeding.

The model was developed for use with patients receiving primary CRT and all included patients were offered preventive swallowing exercises. Given the specific population for which the model is intended (advanced head and neck cancer patients with CRT, all enrolled in a preventive exercise program), we would not recommend using it for clinical decision making tool with patients receiving other HNC-treatment, unless with utmost caution.

The same data was used to develop as well as evaluate the model. Ideally, future research includes external validation of the models discrimination, calibration and net benefit, in comparable as well as more heterogeneous populations. However, since the currently presented model is the best available evidence and its application is not associated with serious risks, in our view the model can be used in clinical practice prior to external validation to provide the clinician with an estimation of the risk.

The risk on prolonged feeding tube dependency may also be influenced by timing of tube placement and by other factors that are not known prior CRT, such as weight loss and mucositis evolving during treatment. Future research should look into the value of including such factors as predictors in a time-updated risk prediction model, which allows for recalculation of the risk at each moment in time, by incorporating the change in clinical status.

Conclusion

The developed risk prediction model can be used to select patients for proactive feeding tube placement during primary CRT for HNC. The nomogram with easily obtainable parameters is a useful tool for clinicians to estimate the risk on prolonged feeding tube dependency to support shared decision making regarding tube placement.

Conflict of interest

None declared.

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