Prediction models for tube feeding dependence in head and neck radiotherapy

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Chapter 3

Management of prophylactic tube feeding in head and neck cancer patients treated with concurrent chemotherapy

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ABSTRACT

BACKGROUND AND PURPOSE

Head and neck cancer (HNC) patients receiving concurrent chemoradiotherapy (CRT) often use feeding tubes during treatment to avoid malnutrition. A prophylactic percutaneous endoscopic gastrostomy (PEG) is usually considered when patients are expected to be dependent on enteral feedings for over 6 weeks, while patients with expected use below 6 weeks are preferably managed by reactive strategies, e.g., by applying nasogastric feeding tube (NG tube) use in case of severe dysphagia and/or significant weight loss. Prophylactic PEG tube placement during treatment is considered to have a negative impact on long-term swallowing function. Prediction models indicating the risk of long-lasting tube feeding dependence to assist decision making on prophylactic PEG tube placement are currently not available.

Therefore, the main objective of this study was to develop multivariable prediction models for long-lasting tube feeding dependence in the acute phase ($TF_{>6weeks}$), defined as tube feeding use at > 6 weeks, and for the total duration of tube feeding dependence ($TF_{duration}$). These models can support identifying patients who may benefit from prophylactic PEG, rather than a reactive strategy.

MATERIALS AND METHODS

The study population was composed of 197 patients with HNC treated with curatively intended concurrent CRT with bilateral neck irradiation by VMAT or IMRT between 2007 and 2017. All patients were managed with a prophylactic PEG approach and did not use their feeding tube at baseline. Logistic and linear regression analysis was performed on patient-, treatment- and dose variables for both endpoints.

RESULTS

Thirty-five patients (17.8%) required tube feeding for less than 6 weeks of which 15 patients (7.6%) did not use their feeding tube at all.

At multivariable analysis, the $TF_{>6weeks}$ model included only the D_{mean} to the contralateral submandibular gland and the $TF_{duration}$ model included baseline percentage weight loss (defined as percentage of total body weight lost during the 6 months prior to radiation), pain medication use at start and the D_{mean} to the contralateral parotid gland. However, both models showed poor model

performance. All patients with nasopharyngeal carcinoma used their feeding tube more than 6 weeks (average duration of 26.1 weeks).

CONCLUSIONS

It remains difficult to accurately identify HNC patients that might benefit from prophylactic or therapeutic feeding tube strategies. Patients with either nasopharyngeal carcinoma or those with significant weight loss at baseline have the highest risks of becoming tube feeding dependent for a longer period of time and, in these patients, prophylactic PEG tube placement should be seriously considered.

3.1 Introduction

The addition of concurrent chemotherapy to radiotherapy in head and neck cancer (HNC) has led to a significant improvement of overall survival [1,2]. However, this survival benefit has come at the cost of an increase in treatment-related side effects, such as swallowing dysfunction. Severe swallowing dysfunction requires enteral feeding during and immediately after treatment and in some cases may result in persistent tube feeding dependence [3–5]. Enteral feeding can be managed with a reactive or prophylactic strategy. Prophylactic PEG tube placement is usually considered when feeding tube dependence is expected to persist for more than 6 weeks [6]. As tube feeding dependence severely affects quality of life in HNC patients, this side effect is clinically relevant and should be prevented [7–12].

In our centre, all HNC patients planned for concurrent CRT receive prophylactic PEG tube placement regardless of the presence of pre-treatment dysphagia or weight loss. However, this policy has been under debate as an increasing percentage of patients no longer require tube feeding during treatment due to the routine introduction of more advanced radiation techniques [13]. Moreover, some studies have suggested a negative effect of prophylactic PEG tube placement on long-term swallowing function [3–5,14–16].

Ideally, prophylactic PEG tube placement should be restricted to patients with a high risk of long-lasting tube feeding dependence in the acute phase (e.g., > 6 weeks), while a reactive strategy would be preferable for low-risk patients (e.g., use < 6 weeks). However, prediction models for long-lasting tube feeding dependence to support a more individualized decision-making are currently lacking.

Therefore, the aim of this study was to develop multivariable prediction models for: 1) tube feeding dependence for more than 6 weeks in the acute phase of concurrent chemoradiation ($TF_{>6weeks}$) and 2) the total duration of feeding tube dependence ($TF_{duration}$).

3.2 Materials and methods

3.2.1 Patients

The population of this prospective cohort study was composed of 197 patients with HNC treated with curative CRT at the University Medical Center Groningen (UMCG)

between June 2007 and December 2017. Patients were eligible for the study in case they had squamous cell carcinoma originating in the larynx, oropharynx, oral cavity, hypopharynx or nasopharynx. Since 2007, all HNC patients treated at our department have participated in a standard follow-up program (SFP) with prospective data registration (Clinical trials NCT 02435576). The details on this SFP have been reported previously [17].

All patients were planned for definitive concurrent CRT including both sides of the neck using VMAT or IMRT. All patients received a prophylactic PEG tube just prior to or during the first week of treatment. Patients that were treated with post-operative chemoradiotherapy were excluded from this analysis. Where PEG tube placement was not possible, percutaneous radiological gastrostomy (PRG) was performed.

Since we were primarily interested in treatment-related swallowing dysfunction, patients who actively used the PEG tube prior to treatment (n=44) were excluded. Also, patients who did not have a prophylactic PEG tube installed for other reasons were excluded (n=4). Additionally, we excluded patients with a local and/or regional recurrence and/or distant metastases within 6 months after treatment (n = 61) because it would complicate the interpretation of the results due to the diversity in the type of recurrence and subsequent treatments (e.g., surgery, radiotherapy, chemotherapy or a combination of these).

3.2.2 Chemoradiotherapy

Radiotherapy treatment planning and delivery have been described in detail in previous reports [17]. In summary, patients were treated with IMRT or VMAT with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks).

The SWOARs were delineated according to the international consensus guidelines as described by Brouwer et al [18].

Chemotherapy for HNSCC consisted of either concomitant cisplatin 100 mg/m^2 on day 1, 22 and 43, weekly cisplatin for 7 weeks at 40 mg/m^2, or 3 cycles of carboplatin (300-350 mg/m^2) on day 1 and 5-fluorouracil (5-FU) on day 1-4 as a continuous infusion (600 mg/m^2/24 hours) every 3 weeks. Patients with nasopharyngeal carcinoma received concurrent cisplatin (100 mg/m^2) on day 1, 22 and 43, and 3 cycles of adjuvant cisplatin (80 mg/m^2) and 5-FU on day 1-4 as continuous infusion (1000 mg/m^2/24 hours) every 4 weeks.

3.2.3 Follow-up schedule and assessments

The need for enteral feeding was assessed weekly by a dietician. Patients were instructed to only use the PEG tube when oral feeding became insufficient. The decision to remove the PEG tube was made at the discretion of the treating physician or dietician.

The date that patients stopped using enteral nutrition was retrospectively retrieved from the medical record of the dietician. For two patients the exact date could not be identified so the end of the month in which the patient had stopped enteral feeding was therefore used instead. Speech therapy for swallowing rehabilitation was offered in cases of severe and persistent swallowing problems after completion of treatment.

3.2.4 Endpoints

The two primary endpoints of this study were: 1) long-lasting tube feeding dependence in the acute phase during concurrent chemoradiation defined as lasting for > 6 weeks ($TF_{>6weeks}$), and; 2) total duration of tube feeding dependence ($TF_{duration}$) in weeks.

Patients who used their PEG tube were encouraged to oral intake as much as possible and only to use their feeding tube when oral intake was insufficient or impossible. Patients were considered tube feeding dependent if oral intake was insufficient of impossible.

3.2.5 Statistical analysis

Candidate prognostic factors were selected based on a recently published literature review [19]. Of the dosimetric parameters, only the mean dose (D_{mean}) values to the swallowing organs-at-risk and to the salivary glands were included in the analysis. Additionally, we included several patient- and treatment related characteristics as candidate predictors.

The statistical methods used for this analysis have been extensively described in previous reports [20]. All statistical analyses were performed using R version 3.6.3. Multiple imputation was performed with 10 imputation sets using the mice [21] package to compensate for missing values and limit bias introduced by non-randomness of missing data for the variables oral cavity mean dose (missing in 3 patients), pack years (missing in 115 patients), BMI at intake (missing in 2 patients) and mean dose to the ipsilateral submandibular gland (missing in 1 patient).

All analyses were performed on each imputation set and the results were pooled according to Rubin's rules. A univariable regression analysis was performed to investigate the crude association of the candidate predictor variables with both endpoints. For the dichotomous endpoint ($TF_{>6weeks}$) logistic regression analysis was used, while for the continuous endpoint ($TF_{duration}$) linear regression analysis was performed. A log transformation was applied to the continuous endpoint ($TF_{duration}$) to compensate for skewness of its distribution. Categorical variables were regrouped such that their univariable prediction performance was maximised in terms of p-value of the likelihood ratio test. Prior to multivariable analysis, candidate predictor variables were checked for collinearity (Spearman correlation > 0.8) with other candidates. Subsequent multivariable prediction model development was performed using forward variable selection based on the Bayesian Information Criterion (BIC). Model performance was measured by explained variance (R^2, for linear regression only), calibration (measured with intercept and slope), and discrimination (measured with the c-statistic or 'area under the curve', AUC). Model development was internally validated using bootstrapping with 100 repetitions to estimate variable selection frequencies and optimism of the performance measures. The model performance measures were subsequently corrected for optimism. The developed models were used to predict $TF_{duration}$ (in weeks) and the probability of $TF_{>6weeks}$. Various hypothetical strategies for conditional PEG tube placement were considered, each based on comparing a model prediction value to a threshold, with the aim to use PEG tube placement only for patients with $TF_{duration}$ longer than 6 weeks. Accuracies of these strategies were calculated for a range of threshold values by comparing the resulting hypothetical pre-treatment decisions with the actual values of $TF_{>6weeks.}$

3.3 Results

From our prospective follow-up program, 197 patients treated with primary concurrent CRT and bilateral neck irradiation with IMRT or VMAT were identified.

***Table 3.1**. Pre-treatment characteristics.*

Variable		**Total cohort**	
		Number	**%**
Sex	Male	142	72.1%
	Female	55	27.9%
Age	18-65 years	159	80.7%
	> 65 years	38	19.3%
T-classification	Tis-T2	75	38.1%
	T3-T4	122	61.9%
N-classification	N0	18	9.1%
	N1-N3	179	90.9%
WHO performance status	0	171	86.8%
	1	26	13.2%
Primary site	Larynx	29	14.7%
	Oropharynx	127	64.5%
	Oral cavity	4	2.0%
	Hypopharynx	16	8.1%
	Nasopharynx	18	9.1%
	Double tumours*	3	1.5%
HPV status	Negative	21	16.5%
(in oropharyngeal primary)	Positive	45	35.4%
(n = 127)	Unknown	61	48.0%
EBV status	Negative	4	22.2%
(in nasopharyngeal primary)	Positive	11	61.1%
(n = 18)	Unknown	3	16.7%
Chemotherapy type	Concomitant carboplatin/5FU	172	87.3%
	Concomitant cisplatin	12	6.1%
	Concomitant cisplatin + adjuvant cisplatin/5FU	13	6.6%

***Table 3.1**. Pre-treatment characteristics*. (continued)

Variable		Total cohort	
		Number	%
Surgery	No surgery	143	72.6%
	Diagnostic tonsillectomy	12	6.1%
	Tracheostoma	3	1.5%
	Post-chemoradiotherapy neck dissection	39	19.8%
Baseline weight loss	No weight loss	107	54.3%
	Weight loss 1-10%	72	36.6%
	Weight loss > 10%	18	9.1%
Baseline BMI	Normal weight (18.5 - 25.0 kg/m^2)	88	44.7%
	Underweight (<18.5 kg/m^2)	7	3.6%
	Overweight (>25 - 30.0 kg/m^2)	67	34.0%
	Obese (>30 kg/m^2)	35	17.8%
Baseline swallowing	No swallowing problems	149	75.6%
	Mild swallowing problems, soft diet	43	21.8%
	Moderate swallowing problems, liquid diet	5	2.5%
Smoking	Never	28	14.2%
	Quit > 1 year before treatment	44	22.3%
	Quit ≤ 1 year before treatment	46	23.4%
	Smoking at baseline	79	40.1%
Alcohol use	Never	22	11.2%
	Quit > 1 year before treatment	17	8.6%
	Quit ≤ 1 year before treatment	26	13.2%
	Alcohol use at baseline	132	67.0%
Pain medication at start	No	118	59.9%
	Yes	79	40.1%
Pain medication baseline	No pain medication	118	59.9%
	Non-opioids	37	18.8%
	Opioids (+/- other types)	37	18.8%
	Other (e.g. methadone, TCA's)	5	2.5%
Social status baseline	Living with partner	145	73.6%
	Living alone	52	26.4%

Abbreviations: TCA: Tricyclic antidepressants.

* Double tumours of oropharynx/oral cavity (n = 2) and larynx/oral cavity (n = 1)

The baseline characteristics and details on systemic treatment are depicted in Table 3.1 and 3.2, respectively. Overall radiotherapy treatment time varied from 42 to 53 days, with a mean and median overall treatment time of 46 days. The mean difference between the time interval between PEG tube placement and removal (29.3 weeks) and the length of actual tube feeding use (Mean: 36.4 weeks) was 7.1 weeks.

Table 3.2. *Treatment characteristics and treatment toxicity.*

Variable		**Total cohort**	
		Number	**%**
Chemotherapy			
	Concomitant Carbo/5FU total	172	87.3%
	1 cycle	2	1.0%
	2 cycles	58	29.4%
	3 cycles	112	56.9%
	Concomitant Cis total	25	12.7%
	1 cycle	2	1.0%
	2 cycles	9	4.6%
	3 cycles	10	5.1%
	4 cycles	2	1.0%
	5 cycles	2	1.0%
	Adjuvant Cis/5FU total (nasopharynx only)	13	6.6%
	1 cycle	2	1.0%
	2 cycles	1	0.5%
	3 cycles	10	5.1%
Reason less cycles/incomplete systemic treatment (n = 77)			
	Blood count disturbances	42	21.3%
	Electrolyte disturbances	1	0.5%
	Ototoxicity	5	2.5%
	Nefrotoxicity	4	2.0%
	Liver toxicity	4	2.0%
	Allergic reaction	2	1.0%
	Complications during treatment	4	2.0%
	Intercurrent infection	5	2.5%
	General malaise	8	4.0%
	Contraindicated medication use	1	0.5%
	Patient choice	1	0.5%

Table 3.2. *Treatment characteristics and treatment toxicity.* (continued)

Variable	Total cohort	
	Number	**%**
Reason dose reduction chemotherapy (n = 13)		
Blood count abnormalities	7	3.6%
Decreased renal function	2	1.0%
Elevated liver enzymes	1	0.5%
Cardiac history	1	0.5%
Reason not registered	2	1.0%
Candida during/after treatment		
No	106	53.8%
During treatment (week 1-7)	83	42.1%
After treatment (week 8-12)	8	4.1%

In 134 patients (68.0%), tube feeding use started in week 1 to 4 and in 45 (22.8%) in weeks 5 to 7 during treatment. Three patients (1.5%) required tube feeding only after completion of treatment and 15 patients (7.6%) did not use their feeding tube at all (Figure 3.1).

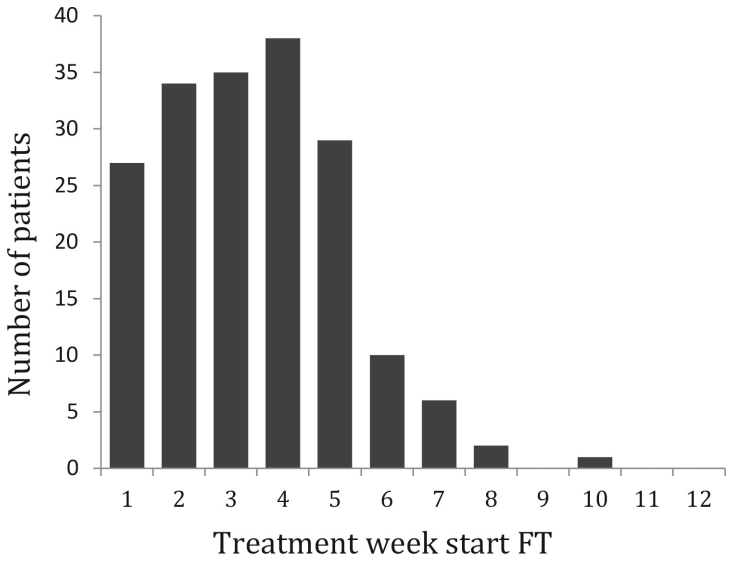

Figure 3.1. *Treatment week with start of feeding tube use.*

Of the 182 patients requiring tube feeding use, thirty-five patients (17.8%) required use for < 6 weeks and 162 patients (82.2%) required use ≥ 6 weeks (Table

3.S1 (Supplemental material) and Figure 3.2). All 18 patients with nasopharyngeal carcinoma used their feeding tubes for longer than six weeks. The mean $TF_{duration}$ for this group was 26.1 weeks (range 14.1 – 67.9 weeks).

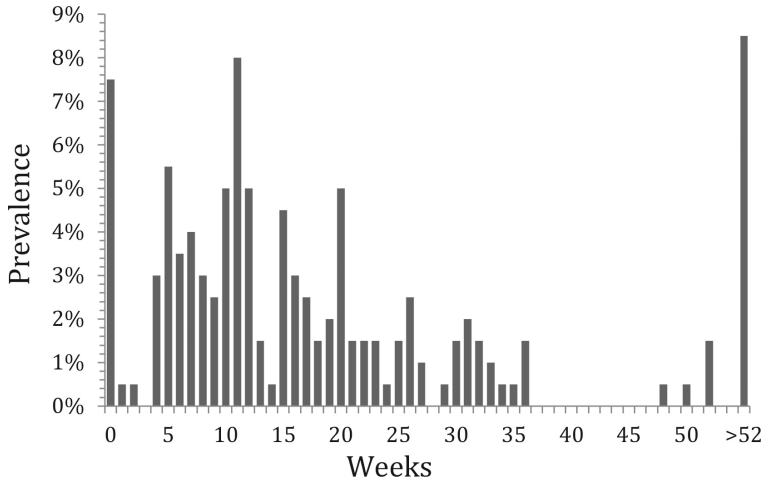

Figure 3.2. *Duration of feeding tube use (in weeks).*

The PCM medius D_{mean} and PCM inferior D_{mean} were collinear with the supraglottic D_{mean}. The same was true for the PCM inferior D_{mean} and the glottic area D_{mean}. As all these candidate explanatory variables may be important to predict both endpoints, we decided to consider these DVH parameters as candidate variables in the initial analysis. However, none of these collinear candidate variables were selected during multivariable analysis, so no further action to deal with collinearity was needed.

The results of univariable analyses are shown in Table 3.S2 (Supplemental material) and the multivariable models and performance parameters are shown in Table 3.3.

D_{mean} to the contralateral parotid gland, percentage baseline weight loss and pain medication use at the start of treatment were significantly associated with $TF_{duration}$. D_{mean} to the contralateral submandibular gland was identified as the only predictor for $TF_{>6weeks}$. Note that model performance was rather poor for both endpoints, particularly model calibration (Table 3.3).

Table 3.3. *Multivariable analyses for tube feeding use and dependence and performance measures.*

Candidate	$TF_{duration}$		$TF_{>6weeks}$	
	Coefficient	**P-value**	**Coefficient**	**P-value**
Intercept	1.142		-2.263	
Pain medication use at start (yes vs. no)	0.365	0.021		
Percentage baseline weight loss	0.050	0.003		
Contralateral parotid D_{mean}	0.042	<0.001		
Contralateral submandibular D_{mean}			0.067	0.007
Performance measures				
Calibration intercept (*)	0.529		0.670	
Calibration intercept (**)	0.529		0.658	
Calibration slope (*)	0.802		0.507	
Calibration slope (**)	0.802		0.507	
R-squared (*)	0.186			
R-squared (**)	0.087			
AUC (*)	0.683		0.663	
AUC (**)	0.630		0.533	

Abbreviations: AUC: area under the curve.

NOTE: Variable selection based on BIC.
* apparent performance of the nominal model.
** performance corrected for optimism using bootstrapping.

Figure 3.S1 (Supplemental material) shows the ROC curves of both models. The decision accuracies of the models to select patients with at most 6 weeks tube feeding dependence for a reactive feeding tube placement strategy are depicted in Table 3.S3 (Supplemental material). Both models' predictions are rather inaccurate, with high numbers of either false positives or false negatives for every value of the decision threshold.

The analysis was repeated in the data with complete cases before imputation and this resulted in identical models, indicating that imputation did not influence the modelling process.

Bootstrap validation resulted in the selection of 28 different variables for each model from at least one of the bootstrap samples. The selection frequencies were moderate or low with a maximum of 70% for the endpoint total duration of tube feeding use in weeks and 47% for the endpoint tube feeding use > 6 weeks.

Short- and long term complications were experienced by several patients.

A total of three patients (1.5%) developed peristomal wound infection and in one patient this was reason to drop the final course of carboplatin/5-FU. Apart from pain complaints from the PEG, there were no other major complications from PEG placement.

Hyperbaric oxygen treatment was given during follow-up to 13 patients (6.6%). Dilatation of the esophagus was performed in 7 patients (3.6%).

Five patients consulted a speech pathologist during the follow-up period due to severe swallowing complaints with aspiration. Four out of these five patients were still tube feeding dependent at 12 months after treatment.

Forty percent of patients used pain medication before treatment. Thirty-seven patients were taking either weak or strong opiates (either with or without other pain medication or neuropathic pain medication) at the start of treatment and another 42 patients used other pain medications (paracetamol, non-selective non-steroidal anti-inflammatory drugs, methadone or neuropathic pain medication) (Table 3.1). A total of 81% of patients used opioids during treatment; most of them started using pain medication between week 3 and 7 (52%).

Compliance to the advice of the dietician during treatment was a reported problem in seven patients. In six of these patients, this resulted in a shorter use of enteral feeding than advised, but in one patient this resulted in longer use of enteral feeding.

3.4 Discussion

The main aim of this study was to develop prediction models for $TF_{>6weeks}$ and $TF_{duration}$ to identify patients in which prophylactic PEG tube placement can be avoided.

Both models had poor performance, especially regarding calibration only moderate discrimination was obtained. Consequently, we were not able to develop a multivariable prediction model to accurately identify patients who are expected to benefit most from either prophylactic or therapeutic tube feeding. The only subset with a high risk of long term tube feeding dependence were those with

nasopharyngeal cancer and/or severe weight loss or dysphagia before commencing treatment.

Of all patients treated with concurrent chemoradiation, 17.8% of the patients used their feeding tube for less than 6 weeks and 7.6% did not use their feeding tube at all. The rate of non-use in our study is comparable to the rates reported in other studies ranging from 9% to 19.8% [22,23]. The low rate of non-use is probably one of the reasons behind the poor performance of the models. If a prophylactic PEG tube is inserted, the threshold for patients for using their feeding tube when it is inserted already will be relatively low, and it is very likely that it is used even when not absolutely necessary. This is different when using a reactive approach, where the threshold to decide on using a nasogastric or PEG tube will be higher and other options might be more readily considered.

The rate of tube feeding dependence at 6 months in this prophylactically managed cohort was 15.2%, which is somewhat lower than reported in other studies [24–29]. It should be noted however, that we excluded patients in which a PEG tube was placed already prior to treatment because of moderate to severe baseline weight loss and/or swallowing problems.

In the univariable analysis, the dose to individual salivary glands was equally relevant compared to the dose to individual swallowing structures. At multivariable analysis, however, the dose to (contralateral) salivary glands proved to be a better predictor for both endpoints than dose to any of the swallowing structures and the oral cavity.

It is not completely clear why the dose to the contralateral parotid gland is more relevant for tube feeding dependence during treatment than the dose to the swallowing structures, while for late tube feeding dependence at 6 months after treatment or beyond, the dose to the oral cavity and the pharyngeal constrictors are the most important predictors [29,30]. A possible explanation is that the tolerance dose of the salivary glands is lower than that of the swallowing structures leading to early salivary dysfunction and subsequent swallowing problems, while late severe swallowing problems are mainly related to late fibrosis of the swallowing muscles itself.

Pre-treatment percentage weight loss was an independent predictor for $TF_{duration}$. This is in line with previous studies [31,32]. Patients with significant baseline weight loss meet the criterion for critical weight loss (usually considered ≥5% in 1

month or ≥10% in 6 months) earlier, which is observed in 30-55% of HNC patients at the time of diagnosis, often resulting in artificial nutrition and ultimately enteral feeding at an earlier stage during treatment [33].

Preventing malnutrition by means of enteral feeding is considered relevant since malnutrition, together with superimposing acute treatment-related toxicities, results in treatment interruptions which in turn results in lower tumour response rates, increased morbidity and higher mortality rates [34–39]. Two randomised controlled trials aimed at determining the optimal enteral feeding strategy in locally advanced HNC patients treated with CRT. In these trials patients were randomly assigned to a prophylactic PEG strategy versus a reactive nasogastric tube strategy [16,40]. These studies were closed early due to poor accrual. Of the 42 patients that were enrolled, only 33 patients received the strategy to which they were randomised. In these studies patients receiving a prophylactic PEG were less likely to have feeding tube dislodgement. At 6 weeks and 6 months after treatment, there was no difference in absolute weight loss and weight between the two treatment groups. The median duration of tube feeding dependence in the prophylactic group was, however, twice as long (139 days) than among those who were assigned to the reactive strategy (66 days). Moreover, the total costs of PEG tube placement were almost ten times higher than those for nasogastric feeding tubes (736 dollars vs. 76 dollar).

In conclusion, we were not able to develop reliable prediction models to identify patients that will benefit most from either a prophylactic or reactive tube feeding strategy. We identified a small subset of patients who required tube feeding for a longer period of time, i.e., patients with nasopharyngeal carcinoma and those with critical weight loss prior to treatment.

3.5 References

[1] J. P. Pignon, A. le Maitre, E. Maillard, J. Bourhis, and M.-N. C. Group, "Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients," *Radiother. Oncol.*, vol. 92, no. 1, pp. 4–14, Jul. 2009.

[2] J. Bourhis *et al.*, "Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial.," *Lancet. Oncol.*, vol. 13, no. 2, pp. 145–153, Feb. 2012.

[3] B. T. McLaughlin *et al.*, "Management of patients treated with chemoradiotherapy for head and neck cancer without prophylactic feeding tubes: The University of Pittsburgh experience," *Laryngoscope*, vol. 120, no. 1, pp. 71–75, 2010.

[4] S. Langmore, G. P. Krisciunas, K. V Miloro, S. R. Evans, and D. M. Cheng, "Does PEG use cause dysphagia in head and neck cancer patients?," *Dysphagia*, vol. 27, no. 2, pp. 251–259, Jun. 2012.

[5] B. Sethugavalar *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.*, vol. 59, pp. 80–85, Aug. 2016.

[6] R. Scott and T. E. Bowling, "Enteral tube feeding in adults.," *J. R. Coll. Physicians Edinb.*, vol. 45, no. 1, pp. 49–54, Mar. 2015.

[7] D. L. Ronis, S. A. Duffy, K. E. Fowler, M. J. Khan, and J. E. Terrell, "Changes in quality of life over 1 year in patients with head and neck cancer," *Arch. Otolaryngol. Head. Neck Surg.*, vol. 134, no. 3, pp. 241–248, 2008.

[8] J. E. Terrell *et al.*, "Clinical predictors of quality of life in patients with head and neck cancer," *Arch. Otolaryngol. Head. Neck Surg.*, vol. 130, no. 4, pp. 401–408, Apr. 2004.

[9] R. P. Morton, V. L. Crowder, R. Mawdsley, E. Ong, and M. Izzard, "Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy," *ANZ J. Surg.*, vol. 79, no. 10, pp. 713–718, 2009.

[10] S. N. Rogers, R. Thomson, P. O'Toole, and D. Lowe, "Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer.," *Oral Oncol.*, vol. 43, no. 5, pp. 499–507, May 2007.

[11] M. Wells *et al.*, "Predictors of quality of life in head and neck cancer survivors up to 5 years after end of treatment: a cross-sectional survey.," *Support. care cancer Off. J. Multinatl. Assoc. Support. Care Cancer*, vol. 24, no. 6, pp. 2463–2472, Jun. 2016.

[12] N. P. Nguyen *et al.*, "Impact of dysphagia on quality of life after treatment of head-and-neck cancer.," *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 61, no. 3, pp. 772–778, Mar. 2005.

[13] M. F. Madhoun, M. M. Blankenship, D. M. Blankenship, G. A. Krempl, and W. M. Tierney, "Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)?," *World J. Gastroenterol.*, vol. 17, no. 8, pp. 1004–1008, Feb. 2011.

[14] M. C. Ward *et al.*, "Impact of feeding tube choice on severe late dysphagia after definitive chemoradiotherapy for human papillomavirus-negative head and neck cancer.," *Head Neck*, vol. 38 Suppl 1, pp. E1054-60, Apr. 2016.

[15] A. M. Chen *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.*, vol. 78, no. 4, pp. 1026–1032, Nov. 2010.

[16] J. Corry *et al.*, "Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing (chemo)radiation," *Head Neck*, vol. 31, no. 7, pp. 867–876, Jul. 2009.

[17] M. E. M. C. Christianen *et al.*, "Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study.," *Radiother. Oncol.*, vol. 105, no. 1, pp. 107–114, Oct. 2012.

[18] C. L. Brouwer *et al.*, "CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines," *Radiother. Oncol.*, Aug. 2015.

[19] K. Wopken, H. P. Bijl, and J. A. Langendijk, "Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer: A systematic review of literature.," *Radiother. Oncol.*, vol. 126, no. 1, pp. 56–67, Jan. 2018.

[20] W. Schaake, A. van der Schaaf, L. V van Dijk, A. C. M. van den Bergh, and J. A. Langendijk, "Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients.," *PLoS One*, vol. 13, no. 7, p. e0197757, 2018.

[21] G.-O. K. Buuren van S, "mice: Multivariate Imputation by Chained Equations in R," *J. Stat. Softw.*, vol. 45, no. 3, pp. 1–67, 2011.

[22] T. E. Brown, M. D. Banks, B. G. M. Hughes, C. Y. Lin, L. M. Kenny, and J. D. Bauer, "Comparison of Nutritional and Clinical Outcomes in Patients with Head and Neck Cancer Undergoing Chemoradiotherapy Utilizing Prophylactic versus Reactive Nutrition Support Approaches.," *J. Acad. Nutr. Diet.*, vol. 118, no. 4, pp. 627–636, Apr. 2018.

[23] W. Yang *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*, vol. 31, no. 2, pp. 206–213, 2016.

[24] B. Li *et al.*, "Clinical-dosimetric analysis of measures of dysphagia including gastrostomy-tube dependence among head and neck cancer patients treated definitively by intensity-modulated radiotherapy with concurrent chemotherapy," *Radiat. Oncol.*, vol. 4, p. 52, Nov. 2009.

[25] S. Murono, A. Tsuji, K. Endo, S. Kondo, N. Wakisaka, and T. Yoshizaki, "Factors associated with gastrostomy tube dependence after concurrent chemoradiotherapy for hypopharyngeal cancer," *Support. Care Cancer*, vol. 23, no. 2, pp. 457–462, Feb. 2015.

[26] J. S. Magnuson *et al.*, "Increased likelihood of long-term gastrostomy tube dependence in head and neck cancer survivors without partners," *Head Neck*, vol. 35, no. 3, pp. 420–425, 2013.

[27] M. K. Bhayani *et al.*, "Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence," *Head Neck*, vol. 35, no. 11, pp. 1634–1640, Nov. 2013.

[28] K. Wopken *et al.*, "Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer," *PLoS One*, vol. 9, no. 4, p. e94879, Apr. 2014.

[29] K. Wopken *et al.*, "Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer," *Radiother. Oncol.*, vol. 113, no. 1, pp. 95–101, 2014.

[30] L. Van den Bosch *et al.*, "Comprehensive toxicity risk profiling in radiation therapy for head and neck cancer: A new concept for individually optimized treatment.," *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 157, pp. 147–154, Apr. 2021.

[31] J. W. Jang, R. J. Parambi, S. M. McBride, T. A. Goldsmith, A. S. Holman, and A. W. Chan, "Clinical factors predicting for prolonged enteral supplementation in patients with oropharyngeal cancer treated with chemoradiation," *Oral Oncol.*, vol. 49, no. 5, pp. 438–442, 2013.

[32] N. Lescut *et al.*, "Evaluation of a predictive score for malnutrition in patients treated by irradiation for head and neck cancer: a retrospective study in 127 patients," *Cancer Radiother.*, vol. 17, no. 7, pp. 649–655, Nov. 2013.

[33] H. Jager-Wittenaar, P. U. Dijkstra, A. Vissink, B. F. A. M. van der Laan, R. P. van Oort, and J. L. N. Roodenburg, "Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: an explorative study.," *Support. care cancer Off. J. Multinatl. Assoc. Support. Care Cancer*, vol. 15, no. 9, pp. 1045–1050, Sep. 2007.

[34] C. G. Gourin, M. E. Couch, and J. T. Johnson, "Effect of weight loss on short-term outcomes and costs of care after head and neck cancer surgery.," *Ann. Otol. Rhinol. Laryngol.*, vol. 123, no. 2, pp. 101–110, Feb. 2014.

[35] A. Paccagnella *et al.*, "Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy," *Support. Care Cancer*, vol. 18, no. 7, pp. 837–845, Jul. 2010.

[36] A. Farhangfar *et al.*, "Nutrition impact symptoms in a population cohort of head and neck cancer patients: multivariate regression analysis of symptoms on oral intake, weight loss and survival.," *Oral Oncol.*, vol. 50, no. 9, pp. 877–883, Sep. 2014.

[37] S. Felder *et al.*, "Association of nutritional risk and adverse medical outcomes across different medical inpatient populations.," *Nutrition*, vol. 31, no. 11–12, pp. 1385–1393, 2015.

[38] A. Lin *et al.*, "Metabolic abnormalities associated with weight loss during chemoirradiation of head-and-neck cancer.," *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 63, no. 5, pp. 1413–1418, Dec. 2005.

[39] S. Bieri *et al.*, "Early morbidity after radiotherapy with or without chemotherapy in advanced head and neck cancer. Experience from four nonrandomized studies.," *Strahlentherapie und Onkol. Organ der Dtsch. Rontgengesellschaft ... [et al]*, vol. 179, no. 6, pp. 390–395, Jun. 2003.

[40] J. Corry *et al.*, "Randomized study of percutaneous endoscopic gastrostomy versus nasogastric tubes for enteral feeding in head and neck cancer patients treated with (chemo)radiation," *J. Med. Imaging Radiat. Oncol.*, vol. 52, no. 5, pp. 503–510, 2008.

3.S Supplemental material

Table 3.S1. *Tube feeding use and dependence.*

Variable	Total cohort	
	Number	%
FT use until death	**5**	**2.5%**
FT use until last FU	**8**	**4.1%**
Tube feeding dependence 6 months	**30**	**15.2%**
No feeding tube use at 6 months follow-up	167	84.4%
Tube feeding dependence 12 months	**15**	**7.6%**
No feeding tube use at 12 months follow-up	165	83.8%
Less than 12 months follow-up	9	4.6%
Locoregional/distant recurrence before 12 months follow-up	6	3.1%
Second primary before 12 months follow-up	1	0.5%
Lost to follow up	1	0.5%
Tube feeding dependence 24 months	**7**	**3.6%**
No feeding tube use at 24 months follow-up	128	65.0%
Less than 24 months follow-up	39	9.8%
TLE for afunctional larynx before 24 months follow-up	1	0.5%
Locoregional/distant recurrence before 24 months follow-up	11	5.6%
Second primary before 24 months follow-up	1	0.5%
Deceased (other primary) before 24 months follow-up	3	1.5%
Deceased (unknown cause) before 24 months follow-up	4	2.0%
Lost to follow-up	3	1.5%

Abbreviations: FT: Feeding tube, TLE: Total laryngeal extirpation.

Table 3.S2. *Univariable analyses for tube feeding use and dependence.*

Variables	$TF_{duration}$		$TF_{>6weeks}$	
	Coefficient	**P-value**	**Coefficient**	**P-value**
Year start radiotherapy	-0.119	<0.001	-0.198	0.010
Living alone (vs. not living alone)	0.082	0.662	0.431	0.346
Age	0.009	0.411	-0.022	0.422
Female sex	-0.024	0.895	0.521	0.253
Current or former smoking (yes vs. no)	-0.031	0.859	0.152	0.691
Current or former alcohol use (yes vs. no)	0.075	0.718	-0.212	0.664
Pack years	0.007	0.066	0.012	0.196

Table 3.S2. *Univariable analyses for tube feeding use and dependence.* (continued)

Variables	$TF_{duration}$		$TF_{>6weeks}$	
	Coefficient	**P-value**	**Coefficient**	**P-value**
Pain medication use at start (yes vs. no)	0.470	0.005	0.788	0.060
Mild swallowing problems baseline (vs. no)	0.083	0.679	-0.032	0.942
Moderate swallowing problems baseline [vs. no]	1.126	0.031	15.06	0.989
Percentage baseline weight loss	0.063	<0.001	0.137	0.022
BMI at intake	-0.036	0.041	-0.031	0.418
Tumour in oral cavity (vs. larynx)	-0.715	0.122	-1.322	0.145
Tumour in pharynx (vs. larynx)	0.000	0.999	-0.282	0.625
Cisplatin mono conc. (vs. Carboplatin/5FU conc.)	0.196	0.570	0.172	0.830
Concomitant chemotherapy complete (vs. not completed)	0.153	0.365	0.306	0.415
Ipsilateral parotid D_{mean}	0.024	<0.001	0.030	0.092
Contralateral parotid D_{mean}	0.042	<0.001	0.050	0.025
Ipsilateral submandibular D_{mean}	0.022	0.201	-0.002	0.970
Contralateral submandibular D_{mean}	0.048	<0.001	0.067	0.007
Oral cavity D_{mean}	0.021	0.016	0.021	0.298
PCM superior D_{mean}	0.026	0.002	0.031	0.086
PCM medius D_{mean}	0.026	0.003	0.031	0.112
PCM inferior D_{mean}	0.013	0.043	0.018	0.218
PCM total D_{mean}	0.054	<0.001	0.071	0.014
Supraglottic D_{mean}	0.017	0.008	0.022	0.123
Glottic area D_{mean}	0.012	0.059	0.011	0.458
Cricopharyngeus D_{mean}	0.012	0.100	0.012	0.476
Cervical esophagus D_{mean}	0.009	0.181	0.008	0.610

Abbreviations: BMI: body mass index, conc: concomitant, PCM: pharyngeal constrictor muscle, Dmean: mean dose.

* Normal weight defined as BMI 18.5 - 25.0 kg/m2

* Mild swallowing problems defined as requiring a soft diet

NOTE: for $TF_{duration}$ and $TF_{>6weeks}$ the PCM medius D_{mean} [C=0.81] and PCM inferior D_{mean} [C=0.85] are collinear with supraglottic Dmean and PCM inferior D_{mean} [C=0.91] is collinear with glottic area D_{mean}. They were included as candidate variables in the initial analysis, since they may be important to predict the endpoints.

NOTE: No important variables are excluded due to collinearity.

NOTE: Cisplatin-based chemotherapy and moderate swallowing problems at baseline were not taken into account due to the small number of patients.

Table 3.S3. *Decision accuracies in selecting total duration of feeding tube use (in weeks) [a], 6 weeks or less of tube feeding use (selecting for a reactive approach) [b].*

a.

Threshold in weeks	Selected	TP	FP	TN	FN	PPV	NPV	Sensitivity	Specificity	Mean FT use
1	0	0	0	162	35	NaN	0.822	0.000	1.000	NaN
2	0	0	0	162	35	NaN	0.822	0.000	1.000	NaN
3	0	0	0	162	35	NaN	0.822	0.000	1.000	NaN
4	1	1	0	162	34	1.000	0.827	0.029	1.000	0.000
5	4	3	1	161	32	0.750	0.834	0.086	0.994	5,893
6	11	5	6	156	30	0.455	0.839	0.143	0.963	9.363
7	21	6	15	147	29	0.286	0.835	0.171	0.907	12.074
8	36	11	25	137	24	0.306	0.851	0.314	0.846	10.325
9	48	15	33	129	20	0.313	0.866	0.429	0.796	10.193
10	67	20	47	115	15	0.299	0.885	0.571	0.710	10.414
11	79	22	57	105	13	0.279	0.890	0.629	0.648	11.387
12	96	24	72	90	11	0.250	0.891	0.686	0.556	12.725

NOTE: model overestimates at lower predicted values

b.

NTCP threshold	Selected	TP	FP	TN	FN	PPV	NPV	Sensitivity	Specificity	Mean FT use
0.10	0	0	0	162	35	NaN	0.822	0.000	1.000	NaN
0.20	1	1	0	162	34	1.000	0.827	0.029	1.000	0.000
0.30	1	1	0	162	34	1.000	0.827	0.029	1.000	0.000
0.40	1	1	0	162	34	1.000	0.827	0.029	1.000	0.000
0.50	1	1	0	162	34	1.000	0.827	0.029	1.000	0.000
0.60	3	2	1	161	33	0.667	0.830	0.057	0.994	9.857
0.70	7	4	3	159	31	0.571	0.837	0.114	0.981	11.163
0.75	32	8	24	138	27	0.250	0.836	0.229	0.852	11.870
0.80	70	20	50	112	15	0.286	0.882	0.571	0.691	16.621
0.90	172	32	140	22	3	0.186	0.880	0.914	0.136	25.498

NOTE: model underestimates at higher predicted values
Abbreviations: TP: true positive, FP: false positive, TN: true negative, FN: false negative, PPV: positive predictive value, NPV: negative predictive value, FT: feeding tube

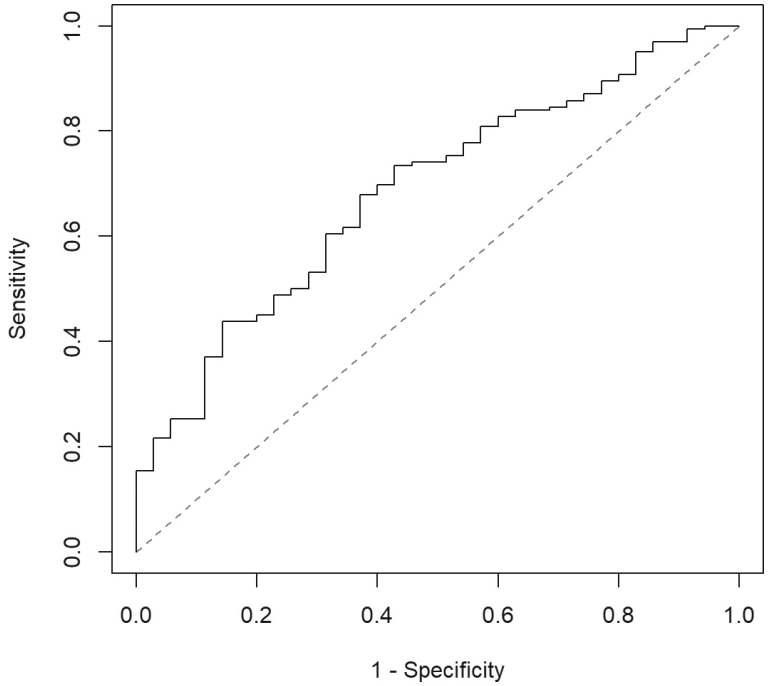

Figure 3.S1a. *ROC curve for the* $TF_{duration}$ *model.*

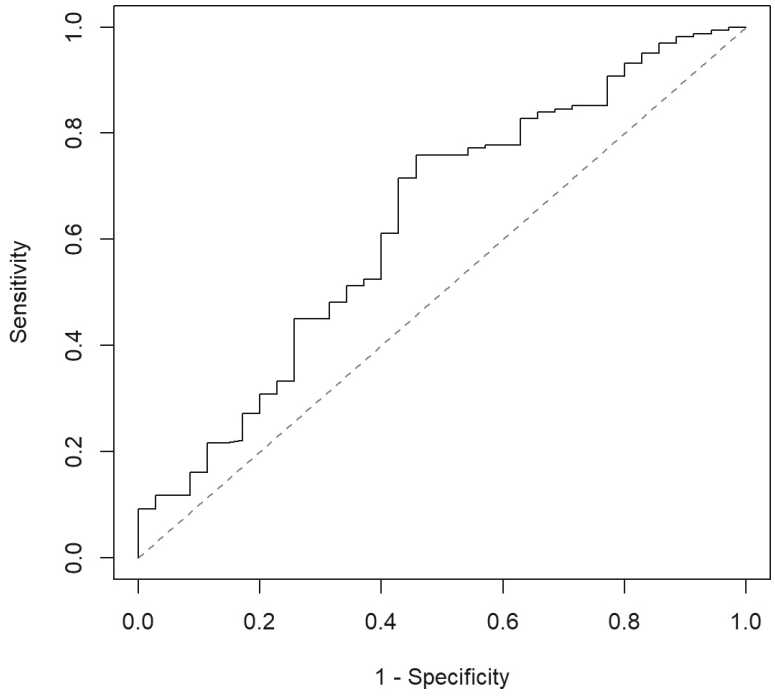

Figure 3.S1b. *ROC curve for the* $TF_{>6\ weeks}$ *model.*