Development and Validation of a Prediction Model for Tube Feeding Dependence after Curative (Chemo-) Radiation in Head and Neck Cancer

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Abstract

Background: Curative radiotherapy or chemoradiation for head and neck cancer (HNC) may result in severe acute and late side effects, including tube feeding dependence. The purpose of this prospective cohort study was to develop a prediction model for tube feeding dependence 6 months (TUBEM⁶) after curative (chemo-) radiotherapy in HNC patients.

Patients and Methods: Tube feeding dependence was scored prospectively. To develop the multivariable model, a group LASSO analysis was carried out, with TUBEM⁶ as the primary endpoint (n = 427). The model was then validated in a test cohort (n = 183). The training cohort was divided into three groups based on the risk of TUBEM⁶ to test whether the model could be extrapolated to later time points (12, 18 and 24 months).

Results: Most important predictors for TUBEM⁶ were weight loss prior to treatment, advanced T-stage, positive N-stage, bilateral neck irradiation, accelerated radiotherapy and chemoradiation. Model performance was good, with an Area under the Curve of 0.86 in the training cohort and 0.82 in the test cohort. The TUBEM⁶-based risk groups were significantly associated with tube feeding dependence at later time points (p < 0.001).

Conclusion: We established an externally validated predictive model for tube feeding dependence after curative radiotherapy or chemoradiation, which can be used to predict TUBEM⁶.

Introduction

Patients with head and neck cancer (HNC) often receive intensive anticancer treatment such as radiotherapy as single modality or in combination with chemotherapy and/or targeted agents such as cetuximab. Many patients may have severe difficulties maintaining adequate nutritional intake prior to treatment. This is caused by local tumor growth, which leads to swallowing dysfunction, trismus, odynophagia, dysgeusia and aspiration. In addition, anticancer therapy causes severe side effects such as acute mucositis and xerostomia inducing swallowing dysfunction. After completing such therapy, a substantial proportion of patients without baseline swallowing dysfunction ultimately develop persistent or even progressive swallowing dysfunction. In some cases they require tube feeding for a long period of time [1].

Recently it was shown that swallowing dysfunction has a major impact on health-related quality of life [2]. With grade III–IV swallowing dysfunction according to the RTOG Late Radiation Morbidity Scoring System, the most important general dimensions of health-related quality of life were moderately to severely affected. Moreover, swallowing dysfunction has been associated with psychological distress not only in patients themselves, but also in their spouses [3]. These results demonstrate that swallowing dysfunction in general, and tube feeding dependence in particular, are clinically relevant long-term side effects after curative (chemo-) radiotherapy.

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Moreover, high-intensity treatment regimens have resulted in improved survival, but with higher rates of tube feeding dependence in these survivors [4,5]. The prevalence of patients with long-term tube feeding dependence is therefore expected to increase.

Previous studies have shown that the dose to the larynx and pharyngeal musculature in radiotherapy treatment of HNC is associated with the risk of long-term swallowing dysfunction [6–8] and are considered swallowing organs at risk. Advanced radiation delivery techniques such as intensity modulated radiotherapy (IMRT) have been used to reduce the radiation dose to the swallowing organs at risk [9]. Promising results have been reported on the use of swallowing exercises before and during treatment to reduce the risk of persisting swallowing dysfunction after curative (chemo-) radiotherapy [10,11]. Thus, predictive models that can identify patients at increased risk of tube feeding dependence after curative (chemo-) radiotherapy before starting treatment would allow selection of suitable candidates for preventive strategies, such as swallowing sparing IMRT and/or preventive swallowing exercises.

Therefore, the main purpose of this study was to develop a prediction model for tube feeding dependence after curative (chemo-) radiotherapy in HNC based on pretreatment characteristics that can be used to improve selection of patients, prior to treatment, for these preventive measures and/or support decision making with regard to the treatment strategy in an early stage (e.g. definitive radiotherapy versus primary surgery). This prediction model was validated in an external and independent prospective cohort to further support its general applicability.

**Material and Methods**

**Ethics statement**

All patients were subjected to a prospective data registration program in which complications and treatment results in terms of local control and survival are prospectively assessed. This is done within the framework of routine clinical practice in which outcome and complications are systematically scored as part of a quality assurance program. All data obtained and used for this study has been anonymized.

The (Dutch) Medical Research Involving Human Subjects Act is not applicable to data collection as part of routine clinical practice and use of these data for scientific papers regarding the quality assurance program. Only research that is within the scope of the Medical Research Involving Human Subjects Act needs approval from an (accredited) ethics committee. Therefore, the hospital ethics committee (the Medisch Ethische Toetsingscommissie; METc) concluded that data collection by this program is regarded as part of routine patient care and granted us a waiver from needing ethical approval for the conduct of this study.

In the Netherlands a patient of course has to give his/her consent for the collection of the extra data on behalf of the quality assurance program and the use of these data for scientific papers regarding the quality assurance program. However, according to Dutch legislation, consent is free of form, and verbal consent is sufficient. Therefore, patients were asked to participate in this quality assurance program and asked for permission to use their data for the program and scientific papers regarding the program. Refusal of participation was recorded in their medical record.

**Patients**

The population of this prospective cohort study was composed of 610 consecutive patients with carcinoma of the mucosal surfaces of the larynx, oropharynx, oral cavity, hypopharynx and nasopharynx, who received curative radiotherapy with or without chemotherapy or cetuximab. Data from patients treated at our hospital were used to develop the prediction model (training cohort: 427 patients), while data from patients treated at another hospital were used to externally validate the model (test cohort: 183 patients).

Baseline weight loss was defined as the percentage of total body weight lost during the 6 months prior to radiation, with 1 to 10% weight loss defined as moderate and more than 10% defined as severe weight loss.

As we were primarily interested in radiation-induced swallowing dysfunction, patients that used a feeding tube at baseline were excluded from this analysis (RTOG grade 3–4). Moreover, patients had to be free of local recurrence or distant metastases at the time of assessment of swallowing dysfunction.

**Treatment**

All patients were treated either with conventional 3D conformal radiotherapy (3D-CRT) or IMRT. The dose to the parotid glands was reduced as much as possible. In the cohorts included in this analysis, no dose constraints for the swallowing organs at risk were used.

Patients undergoing concomitant chemoradiotherapy were treated with conventional fractionation (2.0 Gray (Gy) per fraction, 5 times per week up to 70 Gy in 7 weeks). Patients with stage I–II and stage III–IV tumors who were considered ineligible for (chemo-) radiotherapy were treated with accelerated radiotherapy with a concomitant boost technique (2.0 Gy per fraction, 6 times per week up to 70 Gy in 6 weeks). Since 2008, patients with locally advanced (stage III–IV) tumors, for whom chemotherapy was considered infeasible, have been treated with cetuximab using a loading dose of 400 mg/m² one week prior to radiotherapy and a weekly dose of 250 mg/m² during accelerated radiotherapy (2.0 Gy per fraction, 6 times per week up to 70 Gy in 6 weeks).

In the training cohort, concomitant chemotherapy consisted of cisplatin 100 mg/m² on days 1, 22 and 43. In the test cohort, concomitant chemotherapy consisted of 3 cycles of carboplatin (300–350 mg/m²) on day 1 and 5-fluorouracil (5-FU) on days 1 to 4 as a continuous infusion (600 mg/m²/24 hours) every 3 weeks.

At both institutions, prophylactic PEG tube placement was standard of care in all patients treated with curative concomitant chemoradiation and patients were instructed to refrain from using the PEG-tube. In patients with significant weight loss (>5% weight loss in 1 month or >10% in 6 months or BMI <18.5 kg/m²) and/or severe nutritional intake (less than half of daily requirements for energy, proteins or fluids) and/or severe swallowing dysfunction prior to treatment, PEG tubes were placed prior to treatment. However, these patients were excluded from the analysis.

Reactive placement of feeding tubes was used for patients with significant weight loss or swallowing dysfunction during treatment; in this situation a nasogastric feeding tube was placed during treatment if swallowing problems were considered temporarily and expected to recover soon. In case of severe swallowing problems early during treatment and/or expected to sustain for a longer period of time, there was a preference for PEG-tube placement.

**Follow up schedule and assessments**

In both hospitals, acute and late radiation-induced side effects were prospectively assessed according to the RTOG/EORTC Acute and Late Radiation Morbidity Scoring System. Tube feeding dependence was scored separately. For the present analysis, the primary endpoint was tube feeding, either with PEG (percutaneous endoscopic gastrostomy) or nasogastric tube at 6 months after completion of treatment (TUBE6M). Patients were...
considered tube feeding dependent if a feeding tube was present and used because oral intake was limited or impossible.

**Definition of risk groups**

The total population of the training cohort was divided into three risk groups based on the risk on TUBEM6. The division into low, intermediate and high risk groups was arbitrary: patients were considered low risk when the probability for TUBEM6 was ≤5%, intermediate risk when this value was >5–15% and high risk for values >15%. To determine whether the model could be extrapolated for the same patients at later time points, the positive and negative predictive values for TUBEM6 were calculated at 12, 18 and 24 months.

**Statistics**

After the regression analysis, the variance inflation factor was calculated to check for high correlations between candidate prognostic variables. There were no high correlations and, therefore, no changes were made to the variables.

For the development of the prediction model the least absolute shrinkage and selection operator (LASSO) method was used, which is a logistic regression analysis with a bound on the absolute magnitude of the regression coefficients [12]. This method includes all variables in the modeling process but only a subset of predictor variables are eventually included in the model, setting the coefficients of variables that have negligible effects to zero. The LASSO method has been successfully applied to build Normal Tissue Complication (NTCP) models for HNC patients [13]. Given the inclusion of categorical variables in the current data, the group-LASSO (variant of LASSO) was used for building the prediction models. The amount of shrinkage was selected by optimizing the Bayesian information criterion (BIC) over the regularization path.

The environment for statistical computing R (R Development Core Team, R: A language and Environment for statistical Computing, Version 2.15, Vienna, 2012) was used to do the calculation. The package ‘gpreg’ was used to build the group-LASSO model.

For the selected variables \( x_i \) and their fitted coefficients \( \beta_i \), the Normal Tissue Complication Probability (NTCP) is given by:

\[
NTCP = (1 + e^{-S})^{-1}, \text{ in which } \\
S = \beta_0 + \sum_{i=1}^{n} \beta_i x_i
\]

Model performance was described using different validation measures [14,15]. The discriminating ability of the model was described by the area under the curve (AUC) value based on the Receiver Operating Characteristics curve. The discrimination slope was calculated as the absolute difference between the mean predicted NTCP value for patients with and without the outcome. The calibration of the model reflects the agreement between observed outcomes and predictions. The calibration slope and intercept were calculated as described by Miller et al. [16]. To evaluate whether the model performance measures based on the observed outcomes differed from their expected values, we used Monte-Carlo to generate the expected distributions and calculated p-values. Finally, a Hosmer-Lemeshow test with 10 groups was performed to evaluate the calibration of the model.

**Results**

**Univariate analysis of the training cohort**

The training cohort consisted of 427 patients, 77% male and 23% female with a mean age of 62 years. The pretreatment characteristics of the patients are listed in Table 1. Out of 427 patients, 55 (12.9%) were tube feeding dependent at 6 months after completion of treatment. In the univariate analysis, younger age, higher T-classification, higher N-classification, primary tumor site other than the larynx, concomitant chemoradiation, bilateral irradiation, weight loss at baseline and swallowing dysfunction at baseline were significantly associated with TUBEM6 (Table 2).

**Group-LASSO analysis in training cohort**

The LASSO analysis arrived at a multivariable model containing 5 variables with non-zero coefficients: weight loss prior to treatment, T-classification and N-classification, bilateral irradiation of the neck, and treatment modality, including accelerated radiotherapy and chemoradiotherapy (Table 3).

In individual cases, the risk of TUBEM6 can be estimated using the following equation:

\[
NTCP = (1 + e^{-S})^{-1},
\]

where \( S = -3.69 + (T\text{-stage} \times 1.01) + (N\text{-stage} \times 0.87) + (\text{severe weight loss} \times 0.82) + (\text{moderate weight loss} \times 1.51) + (\text{bilateral neck irradiation} \times 0.35) + (\text{accelerated radiotherapy} \times 0.25) + (\text{chemoradiotherapy} \times 0.41)
\]

The risk of TUBEM6 can also be estimated by using the nomogram (Figure 1). In the training cohort, model performance was excellent, with an AUC of 0.86. The discrimination slope had a value of 0.21. The Hosmer-Lemeshow chi square had a value of 9.35 (p-value 0.3) indicating good agreement between expected and observed rates.

**External validation**

The test cohort consisted of 183 patients, 73% male and 27% female, with a mean age of 62 years. The training and test cohort differed significantly with regard to T-classification, N-classification, the applied treatment modalities and radiation techniques, and weight loss at baseline (Table 1). Out of 183 patients, 27 (14.8%) were tube feeding dependent at 6 months after completion of treatment. Model performance in the external test cohort was good, with an AUC of 0.82 (Expected: 0.80, 95% CI: 0.72–0.86, p-value: 0.8) and a discrimination slope of 0.20 (Expected: 0.19, 95% CI: 0.13–0.25, p-value 0.6). The calibration graph (Figure S1) illustrates that the observed NTCP-values of TUBEM6 in the test cohort are in close proximity of the predicted NTCP-values. The Hosmer-Lemeshow test showed no statistically significant difference between predicted and measured outcomes in the test cohort (Table S1).

**Relationship with tube feeding dependence at subsequent time points**

The prevalence of tube feeding dependence was 6.9% (23 of 335 patients at risk) at 12 months (TUBEM12); 3.6% (9 of 251 patients at risk) at 18 months (TUBEM18) and 4.0% (8 of 200 patients at risk) at 24 months (TUBEM24). TUBEM6 was very predictive for tube feeding dependence at later time points. The negative predictive values of TUBEM6 for TUBEM12, TUBEM18, TUBEM24 were 97.1%, 99.1% and 98.9%, respectively, indicating that almost all patients who were not tube feeding dependent at 6 months remained independent at subsequent time points. The positive predictive values of TUBEM6 for TUBEM12, TUBEM18, TUBEM24 were...
TUBEM24 were 50.0%, 36.8% and 40.0%, respectively, indicating recovery from tube feeding dependence in more than half of the patients.

Discussion

The purpose of the current study was to develop and validate a prediction model for tube feeding dependence 6 months after curative (chemo-) radiotherapy in HNC patients. Such a model could be used in clinical practice to predict which patients are at risk for long-term tube feeding dependence, prior to treatment, and would thus be suitable candidates for preventive measures such as swallowing exercises and/or swallowing sparing IMRT.

In the LASSO analysis, five independent prognostic factors for TUBEM6 were identified: advanced T-stage (T3–T4), positive N-stage, weight loss at baseline, bilateral irradiation of the neck, and treatment modality. Model performance in both the training cohort and the test cohort from another hospital was good to excellent, which confirms the generalization ability of the model.

A prediction model as presented in this study is increasingly desirable due to the more aggressive treatment regimens that are being used in HNC, including altered fractionation schedules for radiotherapy, concomitant (chemo-) radiotherapy or both. These intensive cancer treatments have improved loco-regional control and overall survival [17–19] but at the expense of an increase in radiation-induced side effects [20] in particular long-term swallowing dysfunction [21].

Prophylactic feeding tube placement is standard practice in many institutions to avoid treatment interruptions and unplanned

Table 1. Pre-treatment characteristics in the training cohort and test cohort.

| Variable                        | Training cohort (n = 427) | Test cohort (n = 183) | P-value |
|---------------------------------|--------------------------|----------------------|---------|
| Sex                             |                          |                      |         |
| Male                            | 329 77%                  | 134 73%              | p = 0.311 |
| Female                          | 98 23%                   | 49 27%               |         |
| Age 18–65 years                 |                          |                      |         |
| 18–65 years                     | 269 63%                  | 117 64%              | p = 0.826 |
| >65 years                       | 158 37%                  | 66 36%               |         |
| T-classification                 |                          |                      |         |
| Tis-T1                          | 129 30%                  | 33 18%               | p = 0.002 |
| T2                              | 157 37%                  | 74 40%               |         |
| T3                              | 88 21%                   | 36 20%               |         |
| T4                              | 53 12%                   | 40 22%               |         |
| N-classification                 |                          |                      |         |
| N0                              | 291 68%                  | 88 48%               | p < 0.001 |
| N1                              | 36 8%                    | 19 10%               |         |
| N2a                             | 9 2%                     | 6 3%                 |         |
| N2b                             | 40 9%                    | 16 9%                |         |
| N2c                             | 42 10%                   | 48 26%               |         |
| N3                              | 9 2%                     | 6 3%                 |         |
| Primary site                     |                          |                      |         |
| Larynx                          | 242 57%                  | 91 50%               | p = 0.282 |
| Oropharynx                      | 103 24%                  | 59 32%               |         |
| Oral cavity                     | 28 7%                    | 10 6%                |         |
| Hypopharynx                     | 33 8%                    | 16 9%                |         |
| Nasopharynx                     | 21 5%                    | 7 4%                 |         |
| Treatment modality              |                          |                      |         |
| Conventional radiotherapy       | 148 35%                  | 12 6%                | p < 0.001 |
| Accelerated radiotherapy        | 204 48%                  | 131 72%              |         |
| Chemoradiation                  | 75 17%                   | 40 22%               |         |
| Radiation technique             |                          |                      |         |
| 3D-CRT                          | 379 89%                  | 77 42%               | p < 0.001 |
| IMRT                            | 48 11%                   | 106 58%              |         |
| Neck irradiation                |                          |                      |         |
| Primary alone                   | 106 25%                  | 40 22%               | p = 0.496 |
| Primary + ipsilateral neck      | 33 8%                    | 11 6%                |         |
| Primary + bilateral neck        | 288 67%                  | 132 72%              |         |
| Weigh loss at baseline          |                          |                      |         |
| No weight loss                  | 320 75%                  | 113 62%              | p = 0.002 |
| Weight loss 1–10%               | 84 20%                   | 50 27%               |         |
| Weight loss >10%                | 23 5%                    | 20 11%               |         |
| Baseline swallowing             |                          |                      |         |
| No swallowing problems          | 338 79%                  | 148 81%              | p = 0.601 |
| (grading according to RTOG)      |                          |                      |         |
| Mild swallowing problems, soft diet | 76 18%     | 32 18%               |         |
| Moderate swallowing problems, liquid diet | 13 3%      | 3 2%                 |         |

Abbreviations: 3D-CRT, Three Dimensional Conformal Radiotherapy; IMRT, Intensity-Modulated Radiation Therapy; RTOG, Radiation Therapy Oncology Group.

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hospitalizations because of compromised nutritional intake and/or dehydration [22]; adequate nutrition has been shown to improve tolerance and response rates to (chemo-) radiotherapy [23]. However, others have shown that pretreatment feeding tube placement may lead to increased long-term swallowing dysfunction, longer feeding tube duration and the need for pharyngo-esophageal dilatation [24]. In addition, long-term feeding tube dependence may significantly reduce quality of life after treatment for HNC [22,25]. Terrell et al. [26] showed that feeding tube dependence was the strongest clinical predictor of negative effects on health-related quality of life relative to other medical co-morbidities. It was associated with significantly lower scores on 10 out of 12 collective domains in the Medical Outcomes Study Short Form 36-item Health Survey and HNC quality-of-life instruments.

As already mentioned, at both institutions, prophylactic PEG tube placement was standard of care in all patients treated with curative concomitant chemoradiation and patients were instructed to refrain from using the PEG-tube. In patients with significant weight loss (>5% weight loss in 1 month or >10% in 6 months or BMI <18.5 kg/m²) and/or low nutritional intake (less than half of daily requirements for energy, proteins or fluids) and/or severe swallowing dysfunction prior to treatment, PEG tubes were placed prior to treatment. However, these patients were excluded from the analysis.

Chemoradiotherapy was a prognostic factor in the LASSO analysis. It should be stressed that given the fact that all patients receiving concomitant chemoradiation received prophylactic PEG tube placement, the Odds ratio of 1.51 should be considered the results of this preset combination and that no conclusions can be drawn with regard to these two factors separately. However, given this Odds ratio of 1.51 and the Odds ratio of 1.28 found for accelerated radiotherapy (without prophylactic PEG-tube placement), we believe that the contribution of prophylactic PEG tube feeding is probably limited or absent.

The training cohort and test cohort were from two different hospitals with different chemotherapy regimens in each hospital. In the training cohort, cisplatinum was used while in the test cohort 5-FU in combination with carboplatin was used. The model performance in both cohorts was comparable, which indirectly confirms that there will probably be no major difference between the two chemotherapy regimens.

Given that both advanced T-stage (larger tumors) and N-stage and bilateral irradiation of the neck were prognostic factors for feeding tube dependence at 6 months after (chemo-) radiotherapy, it can be hypothesized that the risk of tube feeding dependence is

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**Table 2. Results of the univariate logistic regression analysis with tube feeding dependence at 6 months (TUBEM6) as primary endpoint in patients included in the training cohort.**

| Variable                      | Univariate analysis | Odds ratio (95% CI) | P-value |
|-------------------------------|---------------------|---------------------|---------|
| Sex                           | Male                | 1.00                |         |
|                               | Female              | 1.61 (0.86–3.00)    | p = 0.135 |
| Age                           | >65 years           | 1.00                |         |
|                               | 18–65 years         | 2.32 (1.18–4.54)    | p = 0.014 |
| T-classification              | Tis-T2              | 1.00                |         |
|                               | T3–T4               | 10.02 (5.08–19.78)  | p<0.001 |
| N-classification              | N0                  | 1.00                |         |
|                               | N+                  | 7.67 (4.05–14.50)   | p<0.001 |
| Primary site                  | Larynx              | 1.00                |         |
|                               | Oral cavity         | 8.63 (2.92–25.51)   | p<0.001 |
|                               | Oropharynx          | 8.74 (3.93–19.47)   | p<0.001 |
|                               | Nasopharynx         | 6.09 (1.70–21.83)   | p = 0.006 |
|                               | Hypopharynx         | 9.71 (3.52–26.79)   | p<0.001 |
| Treatment modality            | Conventional radiotherapy | 1.00    |         |
|                               | Accelerated radiotherapy | 1.77 (0.79–3.99)   | p = 0.167 |
|                               | Chemoradiation      | 7.72 (3.38–17.67)   | p<0.001 |
| Radiation technique           | 3D-CRT              | 1.00                |         |
|                               | IMRT                | 1.67 (0.76–3.67)    | p = 0.202 |
| Neck irradiation              | Local or unilateral irradiation | 1.00 |         |
|                               | Bilateral irradiation | 15.45 (3.71–64.39) | p<0.001 |
| Baseline swallowing           | Grade 0             | 1.00                |         |
| (grading according to RTOG)   | Grade 1–2           | 3.20 (1.62–6.32)    | p = 0.001 |
| Weight loss                   | No weight loss      | 1.00                |         |
| (baseline)                    | 1–10%               | 5.66 (2.93–10.94)   | p<0.001 |
|                               | >10%                | 16.36 (6.42–41.68)  | p<0.001 |

Abbreviations: 3D-CRT, Three Dimensional Conformal Radiotherapy; IMRT, Intensity-Modulated Radiation Therapy; RTOG, Radiation Therapy Oncology Group; CI, Confidence Interval.

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related to the radiation dose distribution in the anatomical structures involved in swallowing, such as the pharyngeal constrictor muscles. A number of authors indeed showed a dose-volume-effect relationships of anatomical structures involved in swallowing and swallowing dysfunction after (chemo-) radiotherapy, such as the pharyngeal constrictor muscles [8,27–29].

Accelerated radiotherapy was also an independent prognostic factor for tube feeding dependence. These results are in line with those presented by Overgaard et al. who showed that accelerated radiotherapy lead to more frequent and longer persisting confluent mucositis than the conventionally treated group and consequently long-term dysphagia [30]. Another more recent updated study, however, showed that accelerated RT does increase acute but not late morbidity, including dysphagia [31].

In the current study, baseline weight loss was also an independent prognostic factor for tube feeding dependence. This

### Table 3. Results of the LASSO analysis with tube feeding dependence at 6 months (TUBEm6) as primary endpoint.

| Variable                              | B     | 95% CI of B | OR     | P-value |
|---------------------------------------|-------|-------------|--------|---------|
| T-classification                      |       |             |        |         |
| T3–T4 vs. Tis-T2                      | 1.01  | (0.79–1.32) | 2.75   | p<0.001 |
| N-classification                      |       |             |        |         |
| N+ vs. N0                             | 0.87  | (0.65–1.10) | 2.39   | p<0.001 |
| Weight loss (baseline)                |       |             |        |         |
| 1–10% weight loss vs. no weight loss  | 0.82  | (0.65–0.99) | 2.27   | p<0.001 |
| >10% weight loss vs. no weight loss   | 1.51  | (1.19–1.83) | 4.53   | p<0.001 |
| Neck irradiation                      |       |             |        |         |
| Bilateral vs. local/unilateral        | 0.35  | (0.06–0.66) | 1.42   | p = 0.011 |
| Treatment modality                    |       |             |        |         |
| Chemoradiation vs. conventional fractionation | 0.41  | (0.16–0.68) | 1.51   | p = 0.001 |
| Accelerated fractionation vs. conventional fractionation | 0.25  | (0.10–0.41) | 1.28   | p = 0.001 |
| Constant                              | –3.69 | (–4.19–3.21) |        |         |

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; B, model coefficient beta.

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Figure 1. Nomogram for tube feeding dependence to determine normal tissue complication probability (NTCP) values for each individual patient. Abbreviations: SF, conventional radiotherapy; ART, accelerated radiotherapy; CRT, chemoradiation.

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Conclusion

The present study is the first to provide an externally validated prediction model for tube feeding dependence after (chemo-) radiation in a population-based cohort of patients with HNC. This model enables clinicians to select patients that have not yet started treatment, based on pretreatment characteristics, who are at greatest risk for tube feeding dependence after treatment, and to implement preventive strategies for them.

Supporting Information

Figure S1 Calibration plots for the predictive model for tube feeding dependence at 6 months (TUBE6M) at internal validation (A) and external validation (B).

(TIF)

Table S1 Performance of the prediction model for TUBE6M.
Abbreviations: AUC, Area Under Curve; H-L, Hosmer-Lemeshow.

(DOC)

Author Contributions

Conceived and designed the experiments: HPB BJS IMVDL JAL. Analyzed the data: KW AVDS SFO JLNR CRL BJS PD RJHMS. Wrote the paper: KW HPB BJS IMVDL JAL. Conceived and designed the experiments: HPB BJS IMVDL JAL. Performed the experiments: KW AVDS SFO JLNR CRL BJS. Analyzed the data: KW AVDS SFO JLNR CRL BJS PD RJHMS IMVDL JAL. Contributed reagents/materials/analysis tools: BJS JAL. Performed the experiments: KW AVDS SFO JLNR CRL BJS. Analyzed the data: KW AVDS SFO JLNR CRL BJS PD RJHMS IMVDL JAL. Performed the experiments: KW AVDS SFO JLNR CRL BJS. Contributed reagents/materials/analysis tools: BJS JAL. Contributed reagents/materials/analysis tools: BJS JAL. Wrote the paper: KW AVDS SFO JLNR CRL BJS PD RJHMS IMVDL JAL. Final approval of manuscript: KW HPB AVDS MEC OC SFO BFAMVDL JAL. RS PD RJHMS IMVDL JAL. Collection and assembly of data: KW MEC OC BFAMVDL PD RJHMS IMVDL JAL. Provision of study material or patients: BJS JAL.

References

1. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, et al (2009) A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol 90: 189-195.
2. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, et al (2008) Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 26: 3770-3776.
3. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, et al (2007) Diet changes in spouses and patients after treatment for head and neck cancer. Laryngoscope 117: 238-241.
4. Ang KK, Harris J, Garden AS, Trotti A, Jones CU, et al (2005) Concomitant boost radiation with concurrent cisplatin for advanced head and neck carcinomas: Radiation therapy oncology group phase II trial 99-14. J Clin Oncol 23: 3008-3015.
5. Staar S, Rudat V, Stuerze B, Dietz A, Volling P, et al (2001) Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multi-center randomized german trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 50: 1161-1171.
6. Caglar HB, Tisher RB, Othuus M, Burke E, Li Y, et al (2008) Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 72: 1110-1118.
7. Eiblach A, Schwarz M, Rasch C, Vanelberg K, Dassen E, et al (2004) Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: Which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 60: 1423-1430.
8. Levenslag PC, Trigu DB, Voet P, van der Est H, Noever I, et al (2007) Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: A dose-effect relationship. Radiother Oncol 85: 64–73.
9. Fung FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, et al (2010) Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: Clinical and functional results. J Clin Oncol 28: 2732–2738.
10. Kron F, Federman AD, Kao J, Milham L, Parker S, et al (2012) Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradation: A randomized trial. Arch Otolaryngol Head Neck Surg 138: 376–382.
11. Carroll WR, Loehr JL, Canon CJL, Bohannon IA, McColloch NL, et al (2008) Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 118: 39-45.
12. Tibshirani R (1996) Regression shrinkage and selection via the lasso. J R Statist Soc B 50: 267-288.
13. Xu CJ, van der Schaar A, Schiöta C, Langendijk JA, Van’t Veld AA (2012) Impact of statistical learning methods on the predictive power of multivariate normal tissue complication probability models. Int J Radiat Oncol Biol Phys 82: 657-664.
14. Vergouwe Y, Moons KG, Steyerberg EW (2010) External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am J Epidemiol 172: 971–980.
15. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, et al (2010) Assessing the performance of prediction models: A framework for traditional and novel measures. Epidemiology 21: 128–138.
16. Miller ME, Langefeld CD, Tierney WM, Hui SL, McDonald CJ (1993) Validation of probabilistic predictions. Med Decis Making 13: 49–58.
17. Pignoni JP, le Maire A, Mailard E, Bourlie J, MACH-NC Collaborative Group (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92: 4–14.
18. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, et al (2006) Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 368: 843–854.
19. Langendijk JA, Leemans CR, Buer J, Berkhof J, Slotman BJ (2004) The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature. J Clin Oncol 22: 4604–4612.
20. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, et al (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: A systematic literature review. Radiat Oncol 66: 253–262.
21. Eiblach A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, et al (2002) Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 53: 23–28.
22. Morton RP, Cenker VL, Mawdesly R, Ong E, Izad M (2009) Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiation. ANZ J Surg 79: 713–718.
23. Salas S, Deville JL, Goeij R, Pignon T, Bagarry D, et al (2008) Nutritional factors as predictors of response to radio-chemotherapy and survival in unresectable squamous head and neck carcinoma. Radiother Oncol 87: 195–200.

24. Mikhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, et al (2001) Enteral nutrition during the treatment of head and neck carcinoma: Is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? Cancer 91: 1785–1790.

25. Nguyen NP, Frank C, Holz CC, Vos P, Smith HJ, et al (2005) Impact of dysphagia on quality of life after treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys 61: 772–778.

26. Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, et al (2004) Clinical predictors of quality of life in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 130: 401–408.

27. Bhide SA, Gulliford S, Kazi R, El-Hariry I, Newbold K, et al (2009) Correlation between dose to the pharyngeal constrictors and patient quality of life and late dysphagia following chemo-IMRT for head and neck cancer. Radiother Oncol 93: 539–544.

28. Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, et al (2011) Predictive modelling for swallowing dysfunction after primary chemoradiation: Results of a prospective observational study. Radiother Oncol.

29. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S (2009) Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: Dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 75: 385–392.

30. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, et al (2005) Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 362: 933–940.

31. Mortensen HR, Overgaard J, Specht L, Overgaard M, Johansen J, et al (2012) Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 randomised trial with accelerated radiotherapy for head and neck cancer. Radiother Oncol 103: 69–75.