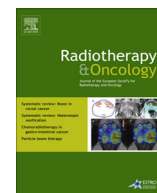


Contents lists available at [ScienceDirect](http://ScienceDirect.com)

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Late effects in head and neck radiotherapy

Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer



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ARTICLE INFO

Article history:

Received 3 April 2014

Received in revised form 16 July 2014

Accepted 22 September 2014

Available online 16 October 2014

Keywords:

Head and neck cancer
IMRT
(chemo-)radiotherapy

ABSTRACT

Background and purpose: Curative radiotherapy/chemo-radiotherapy 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 multivariable normal tissue complication probability (NTCP) model for tube feeding dependence 6 months (TUBE_{M6}) after definitive radiotherapy, radiotherapy plus cetuximab or concurrent chemoradiation based on pre-treatment and treatment characteristics.

Materials and methods: The study included 355 patients with HNC. TUBE_{M6} was scored prospectively in a standard follow-up program. To design the prediction model, the penalized learning method LASSO was used, with TUBE_{M6} as the endpoint.

Results: The prevalence of TUBE_{M6} was 10.7%. The multivariable model with the best performance consisted of the variables: advanced T-stage, moderate to severe weight loss at baseline, accelerated radiotherapy, chemoradiation, radiotherapy plus cetuximab, the mean dose to the superior and inferior pharyngeal constrictor muscle, to the contralateral parotid gland and to the cricopharyngeal muscle.

Conclusions: We developed a multivariable NTCP model for TUBE_{M6} to identify patients at risk for tube feeding dependence. The dosimetric variables can be used to optimize radiotherapy treatment planning aiming at prevention of tube feeding dependence and to estimate the benefit of new radiation technologies.

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Head and neck cancer (HNC) can have a profound impact on swallowing function [1–5]. The treatment of these patients with radiotherapy (RT), chemoradiation (CRT) or radiotherapy plus cetuximab (CetRT) may further affect swallowing function, eventually leading to tube feeding dependence. Incidences of tube feeding dependence at 2 years after treatment of up to 51% have been reported [6–10]. Ronis et al. showed that at 1 year after treatment, the presence of a feeding tube was the most powerful predictor of

quality of life in HNC patients [11], thus indicating the clinical importance of preventing tube feeding dependence.

One strategy for preventing swallowing dysfunction is to reduce the dose to anatomical structures that are important for swallowing by using advanced radiation delivery techniques such as intensity modulated radiotherapy (IMRT) [12–18]. However, radiotherapy treatment optimization requires information on the most important dose–volume parameters. A multivariable model is used for this purpose. However, no multivariable normal tissue complication probability (NTCP) models have yet been published on tube feeding dependence after curative RT or CRT for HNC. Therefore, the main objective of this study was to develop a multivariable NTCP model for tube feeding dependence.

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Materials and methods

Patients

The population of this multicenter prospective cohort study was composed of 355 consecutive patients treated at two different institutions. These patients with cancer of the mucosal surfaces of the larynx, oropharynx, oral cavity, hypopharynx, nasopharynx, paranasal sinuses, with tumors of the salivary glands and patients with lymph node metastases from an unknown primary tumor, received curative primary RT, CRT or CetRT.

Baseline weight loss was defined as the percentage of total body weight lost during the 6 months prior to radiation, with 1–10% weight loss defined as moderate weight loss, and more than 10% defined as severe weight loss (assessed by either the dietician or radiation oncologist).

Treatment

Treatment details have been previously described [19,20]. In summary, all patients were treated with either conventional 3D conformal radiotherapy (3D-CRT) or IMRT to a total dose ranging between 50 and 70 Gy. Patients treated with concomitant CRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). Chemotherapy consisted of cisplatin 100 mg/m² on day 1, 22 and 43, or 3 cycles of carboplatin (300–350 mg/m²) on day 1 and 5-fluorouracil (5-FU) on day 1–4 as a continuous infusion (600 mg/m²/24 h) every 3 weeks. All patients treated with CRT received a prophylactic percutaneous endoscopic gastrostomy (PEG) feeding tube prior to commencing treatment. Patients with stage I–II and those with stage III–IV who were considered not eligible for CRT were treated with accelerated RT with (2.0 Gy per fraction, 6 times per week up to 66–70 Gy in 6 weeks). Since 2008, patients with locally advanced (stage III–IV) tumors, in whom chemotherapy was considered not feasible, have been treated with cetuximab using a loading dose of 400 mg/m² 1 week prior to RT and a weekly dose of 250 mg/m² during accelerated RT.

At both institutions, prophylactic PEG tube placement was the standard of care in all patients treated with curative concomitant chemoradiation. Furthermore, patients were instructed not to use the PEG tube unless oral feeding became insufficient due to side effects of the treatment. 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.

As we were primarily interested in radiation-induced swallowing dysfunction, patients that used a feeding tube at baseline were excluded from this analysis. Moreover, patients had to be free of local recurrence or distant metastases at the time of assessment of swallowing dysfunction (i.e. 6 months after treatment).

Therapeutic 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 to be temporary. In case of severe swallowing problems during early treatment and/or if the problems were expected to continue for a longer period of time, there was a preference for PEG tube placement. Referral to a speech therapist for swallowing rehabilitation was only used in case of persisting severe swallowing problems after completion of radiotherapy/chemoradiotherapy.

Follow-up schedule and assessments

The primary endpoint was tube feeding dependence either by PEG or nasogastric tube at 6 months after completion of treatment (TUBE_{M6}). Patients were considered tube feeding dependent if oral intake was limited or not possible at all and the feeding tube was actually used. All patients participated in a standard follow-up program (SFP) with prospective data registration. Acute and late radiation-induced side effects, as well as tube feeding dependence, were assessed by the treating physicians.

Contouring of organs at risk

The swallowing organs at risk (SWOARs) were delineated by two radiation oncologists, according to the guidelines for SWOAR contouring as described by Christianen et al. [21]. These organs include the superior, middle and inferior PCM, the cricopharyngeal muscle, the esophagus inlet muscle (EIM), the cervical esophagus, the base of tongue and the supraglottic and glottic larynx. The parotid and submandibular salivary glands and spinal cord were delineated according to the guidelines described by van de Water et al. [22].

IMRT treatment planning

The definition of the clinical target volumes was used as previously described [23,24]. At one institution the pencil beam algorithm was used for dose calculation and at the other institution the collapsed cone algorithm.

For each patient, two Planning Target Volumes (PTVs) were defined: a prophylactic PTV to which a total dose of either 46 or 54.25 Gy was prescribed (PTV₄₆ or PTV₅₄) for elective node levels, and a therapeutic PTV for which the prescribed total dose was either 60 or 70 Gy (PTV₆₀ or PTV₇₀) for the primary tumor and pathological lymph nodes. Each patient received between 30 and 35 fractions. The dose values were not corrected for fraction size effects. The different dose levels were treated with either a simultaneous integrated boost (SIB) or a consecutive boost technique.

For each patient, an IMRT treatment plan was created. At least 98% of each PTV had to be covered by 95% of the prescribed dose, and the maximum doses delivered to the spinal cord, brainstem, optic nerves and optic chiasm were not allowed to exceed 54, 60, 54 and 54 Gy, respectively. The maximum planned dose was not allowed to exceed 77 Gy, and the volume receiving 75 Gy was not allowed to be larger than 2 cm³. The dose to the parotid and submandibular glands and other unspecified tissues outside of the prophylactic PTV was reduced as much as possible [16].

Statistical analysis

The variance inflation factor (VIF) was calculated to check for high collinearity between variables. For each SWOAR multiple dosimetric variables were available in the dataset. However, because these were generally highly collinear among each other we selected only the mean dose as candidate variables for each SWOAR.

To develop the prediction model, firstly a univariable analysis was performed for the set of candidate predictor variables to show the raw uncorrected effects of each variable for TUBE_{M6}. Secondly, the least absolute shrinkage and selection operator (LASSO) method was used, which is a multivariable logistic regression analysis with a constraint on the absolute magnitude of the regression coefficients [25,26]. This method included all candidate predictor variables in the modeling process, but only a subset of variables are eventually included in the model; the coefficients of variables

that have negligible effects are set to zero. The LASSO method has been successfully applied to build a normal tissue complication probability (NTCP) model for HNC patients [27]. Given the inclusion of categorical variables in the current data, the group LASSO (a variant of LASSO) was used for building the prediction models.

For this analysis, 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. The package 'grpreg' was used to build the group LASSO model. The amount of shrinkage was selected by optimizing the Bayesian information criterion (BIC) over the regularization path. To validate the prediction power of the model, a 10-fold cross-validation scheme with random resampling was applied and repeated 100 times. The same scheme was used to calculate the confidence intervals of the model coefficient estimates. In the cross-validation scheme the amount of model shrinkage was allowed to vary.

Model performance was described using various validation measures [28,29]. 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.

To evaluate whether the actual model performance was within the expected range as predicted by the model, we performed Monte-Carlo simulation to generate the expected distributions of the performance measures based on the model predictions. Then we calculated the *p*-value of the actual model performance measures based on the observed outcomes with respect to the expected distribution.

Finally, a Hosmer–Lemeshow test with 10 groups was performed to evaluate the calibration of the model. The statistical significance level for all tests was set to *p* < 0.05.

Results

Univariable analysis

The patient population consisted of 355 patients: 76% male and 24% female with a mean age of 62 years. The patients and treatment characteristics are listed in Table 1. Out of 355 patients, 38 (10.7%) 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 of oropharynx, nasopharynx and hypopharynx, CRT, bilateral neck irradiation, weight loss at baseline and swallowing dysfunction at baseline were all significantly associated with TUBE_{M6}. In addition, significant associations with TUBE_{M6} were found for the mean doses to most SWOARS, except for the PCM inferior, the cricopharyngeal muscle and the glottis (Table 2).

LASSO analysis

Following the LASSO model learning procedure, the multivariable model with the best performance consisted of the following variables: moderate and severe weight loss prior to treatment, advanced T-stage, bilateral irradiation of the neck, accelerated radiotherapy, combined treatment with radiotherapy and chemotherapy, combined treatment with radiotherapy and cetuximab and accelerated radiotherapy. In addition, the mean dose to the PCM superior, to the PCM inferior, to the contralateral parotid gland and to the cricopharyngeal muscle, respectively, were included in the model (Table 3).

In individual cases, the risk of tube feeding dependence at 6 months after treatment can be estimated using the following equation:

Table 1
Pre-treatment characteristics.

Variable	Total cohort		
	Number	%	
Sex	Male	270	76
	Female	85	24
Age	18–65 years	227	64
	>65 years	128	36
T-classification	Tis-T1	57	16
	T2	158	45
	T3	78	22
	T4	62	18
N-classification	N0	202	57
	N1	33	9
	N2	3	1
	N2a	12	3
	N2b	31	9
	N2c	67	19
Primary site	N3	7	1
	Larynx	189	53
	Oropharynx	100	28
	Oral cavity	18	5
	Hypopharynx	27	8
	Nasopharynx	17	5
Treatment modality	Other	4	1
	Conventional radiotherapy	56	16
Radiation technique	Accelerated radiotherapy	197	56
	Chemoradiation	88	25
	Radiotherapy + cetuximab	14	4
	3D-conformal radiotherapy	181	51
Neck irradiation	Intensity modulated radiation therapy	174	49
	Primary alone	62	18
	Primary + ipsilateral neck	22	6
	Primary + ipsilateral and contralateral neck	271	76
Baseline weight loss	No weight loss	238	67
	Weight loss 1–10%	95	27
	Weight loss >10%	22	6
Baseline swallowing	No swallowing problems	302	85
	Mild swallowing problems, soft diet	49	14
	Moderate swallowing problems, liquid diet	4	1

$$\text{NTCP} = (1 + e^{-S})^{-1}$$

where, $S = -11.70 + (\text{advanced T-stage} * 0.43) + (\text{moderate weight loss} * 0.95) + (\text{severe weight loss} * 1.63) + (\text{accelerated radiotherapy} * 1.20) + (\text{chemoradiation} * 1.91) + (\text{radiotherapy plus cetuximab} * 0.56) + (\text{mean dose PCM superior} * 0.071) + (\text{mean dose PCM inferior} * 0.034) + (\text{mean dose contralateral parotid} * 0.006) + (\text{mean dose cricopharyngeal muscle} * 0.023)$

The regression coefficients of the variables included in the model are listed in Table 4. For the dosimetric variables in the equation the dose in Gy can be filled in, while for all the other variables 0 (=no) or 1 (=yes) can be filled in.

The variance inflation factor (VIF) showed collinearity (VIF > 5) for the dosimetric variables but not for the non-dosimetric variables. The VIF was ≤5 for all the variables that were included in the eventual model, indicating only minor collinearity for these variables.

Model performance at internal validation was excellent, with an actual AUC of 0.88 (not statistically different from the AUC expected from Monte Carlo simulations, *p* = 0.66; Appendix 1). The discrimination slope had a value of 0.27 (*p* = 0.78). The Hosmer–Lemeshow chi square had a value of 5.53 (*p*-value 0.70) indicating good agreement between expected and observed rates (Appendix 2). The calibration plot (Fig. 1) illustrates that the

Table 2
Results of the univariable logistic regression analysis with tube feeding dependence at 6 months (TUBE_{M6}) as primary endpoint.

Variable	Univariable analysis		
	Odds ratio	(95% CI)	p-Value
Sex	Female	1.00	
	Male	0.75	(0.35–1.58)
Age	18–65 years	1.00	
	>65 years	0.30	(0.12–0.74)
T-classification	Tis-T2	1.00	
	T3–T4	5.98	(2.73–13.08)
N-classification	N0	1.00	
	N+	7.08	(3.02–16.58)
Primary Site	Larynx	1.00	
	Oral cavity	5.78	(0.98–34.03)
	Nasopharynx	6.17	(1.04–36.46)
	Oropharynx	13.82	(4.62–41.28)
	Hypopharynx	16.19	(4.36–60.13)
Treatment modality	Conventional radiotherapy	1.00	
	Accelerated radiotherapy	1.29	(0.27–6.16)
	Radiotherapy + cetuximab	4.50	(0.58–35.21)
	Chemoradiation	10.71	(2.43–47.32)
Radiation technique	3D-conformal radiotherapy	1.00	
	Intensity modulated radiation therapy	1.69	(0.85–3.35)
Neck irradiation	Local/unilateral	1.00	
	Bilateral	6.39	(1.50–27.10)
Baseline swallowing (grading according to RTOG)	No swallowing problems	1.00	
	Mild swallowing problems, soft diet	3.21	(1.46–7.04)
	Moderate swallowing problems, liquid diet	11.08	(1.50–82.06)
Baseline weight loss	No weight loss	1.00	
	1–10% weight loss	4.11	(1.88–8.98)
	>10% weight loss	13.04	(4.66–36.50)
PCM superior mean dose (Gy)	1.09	(1.05–1.13)	<0.001
PCM middle mean dose (Gy)	1.14	(1.07–1.21)	<0.001
PCM inferior mean dose (Gy)	1.02	(0.99–1.05)	0.255
Cricopharyngeus muscle mean dose (Gy)	1.01	(0.99–1.03)	0.486
EIM mean dose (Gy)	1.03	(1.01–1.05)	0.004
Supraglottis mean dose (Gy)	1.07	(1.02–1.12)	0.003
Glottis mean dose (Gy)	1.00	(0.98–1.02)	0.983
Ipsilateral parotid gland mean dose (Gy)	1.06	(1.03–1.08)	<0.001
Contralateral parotid gland mean dose (Gy)	1.06	(1.04–1.08)	<0.001
Ipsilateral submandibular gland mean dose (Gy)	1.13	(1.06–1.19)	<0.001
Contralateral submandibular gland mean dose (Gy)	1.10	(1.05–1.14)	<0.001
Cervical esophagus mean dose (Gy)	1.04	(1.02–1.06)	0.001
Base of tongue mean dose (Gy)	1.07	(1.04–1.11)	<0.001

Abbreviations: RTOG, Radiation Therapy Oncology Group; PCM, pharyngeal constrictor muscle; EIM, esophageal inlet muscle. For dose variables OR: increase per 1 Gy increase in dose.

* n = 4, no OR calculated.

Table 3
Results of the LASSO analysis with tube feeding dependence at 6 months (TUBE_{M6}) as primary endpoint.

Variable	OR	OR 95% CI	p-Value
T-classification			
Tis-T2	1.00		
T3–T4	1.53	(1.17–2.06)	<0.001
Baseline weight loss			
No weight loss	1.00		
Moderate weight loss (1–10%)	2.58	(2.01–3.19)	<0.001
Severe weight loss (>10%)	5.08	(3.32–7.30)	<0.001
Treatment modality			
Conventional fractionation	1.00		
Radiotherapy + cetuximab	1.74	(1.50–2.01)	<0.001
Accelerated fractionation	3.33	(2.40–4.53)	<0.001
Chemoradiation	6.73	(4.00–10.98)	<0.001
Dosimetric variables			
PCM superior mean dose (Gy)	1.07	(1.04–1.09)	<0.001
PCM inferior mean dose (Gy)	1.03	(1.01–1.05)	0.006
Contralateral parotid mean dose (Gy)	1.01	(1.00–1.02)	0.14
Cricopharyngeal muscle mean dose (Gy)	1.02	(1.01–1.03)	0.004

Abbreviations: OR, odds ratio; CI, confidence interval; PCM, pharyngeal constrictor muscle.

For dose variables OR: increase per 1 Gy increase in dose.

observed NTCP-values of TUBE_{M6} in this cohort are in close proximity of the predicted NTCP-values. At double cross validation (10-fold × 100 cycles) the AUC was good with a value of 0.85 (SD 0.007).

Discussion

In the current study, we developed a multivariable NTCP model for tube feeding dependence after curative RT, CRT or CetRT in HNC patients based on pretreatment and treatment variables, including dosimetric parameters. The final multivariable model consisted of several prognostic variables that can be used to identify patients at high risk for persistent tube feeding dependence and to optimize radiotherapy treatment planning based on the mean doses to 4 critical structures, including the superior PCM, the inferior PCM, the cricopharyngeal muscle and the contralateral parotid gland. Model performance was excellent.

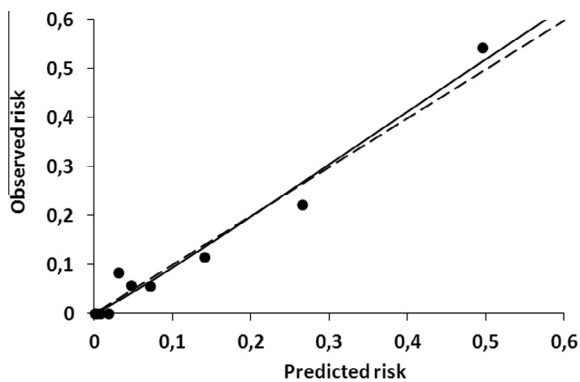
These results are in line with previous studies [12,13,30–32], and also with a recent study specifically looking at tube feeding requirement [33], since we found that the dose to the inferior and superior pharyngeal constrictor muscle, and the cricopharyngeal

Table 4

The regression coefficients and multiplication values for the variables included in the model for tube feeding dependence.

Variable	Regression coefficient	95% CI	Multiplication value
Constant	−11.7	(−13.47 to −8.47)	–
T-classification			
T3–T4	0.43	(0.16–0.73)	0 = no, 1 = yes
Baseline weight loss			
Moderate weight loss (1–10%)	0.95	(0.70–1.16)	0 = no, 1 = yes
Severe weight loss (>10%)	1.63	(1.20–1.99)	0 = no, 1 = yes
Treatment Modality			
Radiotherapy + cetuximab	0.56	(0.40–0.70)	0 = no, 1 = yes
Accelerated radiotherapy	1.20	(0.87–1.51)	0 = no, 1 = yes
Chemoradiation	1.91	(1.39–2.40)	0 = no, 1 = yes
Dosimetric variables			
PCM superior mean dose (Gy)	0.071	(0.044–0.082)	Dose in Gy
PCM inferior mean dose (Gy)	0.034	(0.006–0.053)	Dose in Gy
Contralateral parotid mean dose (Gy)	0.006	(0–0.019)	Dose in Gy
Cricopharyngeal muscle mean dose (Gy)	0.023	(0.006–0.034)	Dose in Gy

Abbreviations: PCM, pharyngeal constrictor muscle; Gy, gray.

**Fig. 1.** Calibration plot for the predictive model for tube feeding dependence at 6 months (TUBE_{M6}) at internal validation. The solid line represents the calibration graph of the model and the black points represent the Hosmer–Lemeshow groups. The dashed line represents the identity line.

muscle are predictors for tube feeding dependence. We also found that the dose to the contralateral parotid gland was identified as a significant prognostic factor for TUBE_{M6}. To our knowledge, ours is the first study to find such a relationship. This is in line with normal physiology, given that the parotid glands are largely responsible for salivary output during meals [34] and with previous research on reducing the dose to the parotid glands using IMRT in patients with HNC [35,36]. Our results are also supported by a study on xerostomia after CRT [37]. Another prospective study found that both xerostomia ($p = 0.038$) and dysphagia ($p = 0.0032$) were reduced if both salivary glands were spared [38]. Swallowing difficulties are, therefore, probably caused by a combination of damage to pharyngeal constrictors and xerostomia.

The results of the current study confirm that next to reducing the dose to the pharyngeal musculature, further reduction of the contralateral parotid gland dose may contribute to prevention of severe swallowing dysfunction in terms of tube feeding dependence.

We did not find an association between the mean dose to the ipsilateral parotid gland and TUBE_{M6}. Usually, the mean dose to the ipsilateral parotid gland is higher than the mean dose to the contralateral gland, and in many cases beyond the tolerance dose despite the use of IMRT. Recent studies have shown that only the mean dose to the contralateral parotid gland was associated with xerostomia [39], which supports our findings.

A number of authors reported on radiation delivery technologies aiming at optimizing the dose to swallowing organs at risk

[12–17]. Amin et al. showed that by using IMRT planning to reduce the dose to the pharyngeal constrictor muscles and the larynx and esophageal inlet muscle, the duration of PEG-tube dependence could be reduced by 4.9 months [18]. Currently, a prospective study on swallowing-sparing IMRT is ongoing at our own department, and the results will be available soon.

The present study also showed that the risk of TUBE_{M6} doubled in patients treated with accelerated RT compared to conventional fractionation. This confirms the importance of treatment modalities on TUBE_{M6}. In other studies, patients treated with CRT and CetRT also had markedly increased risks of TUBE_{M6} [6,10].

In contrast to our results, the DAHANCA study on locoregional tumor control in squamous-cell carcinoma [40] showed no increase in late toxicity, including dysphagia, in patients treated with accelerated radiotherapy. This is probably due to a number of differences in the study designs: (1) 69% of the patients in our study population treated with accelerated radiotherapy received bilateral neck irradiation, while in the DAHANCA study only 28% of patients treated with accelerated radiotherapy had a node positive neck; (2) after a maximum of 50 Gy in 5 weeks, they reduced the fields to include only the initially macroscopically known gross tumor volume with a margin of 1 cm. (3) the neck could be treated with electrons to reduce the dose to the spinal cord, while in our current study, 54 Gy was given to the neck with photons. However, it should be noted that the primary endpoint in the current analysis was set to 6 months after completion of treatment, and that tube feeding dependence may reflect consequential acute effects that may further decrease over time.

In the study by Bonner et al. [41], patients treated with CetRT were compared with patients treated with radiotherapy only. In that study, no increase in acute and late toxicity was seen in patients treated with CetRT compared to the group treated with only radiotherapy, whereas in our study patients treated with CetRT had an increased risk of TUBE_{M6}. The policy at both institutions is to reserve CetRT for patients with stage III–IV HNC who are not eligible for CRT, and thus represent a population with lower performance and more co-morbidity. Therefore, the higher incidence in this subgroup may reflect a higher vulnerability for side effects rather than the additional effect of cetuximab to radiotherapy.

A possible limitation of our study is that all patients treated with CRT received prophylactic PEG placement. Consequently, no conclusions can be made about the effect of prophylactic PEG tube placement on late tube feeding dependence. The usefulness of prophylactic PEG tube placement is currently under debate. Some studies have suggested that prophylactic PEG tube placement may not always be necessary, which is supported by the results of Madhoun et al., indicating that about half of patients used their

PEG-tube for 2 weeks or less [42]. Other studies have suggested that prophylactic PEG tube placement resulted in worse diet outcome [43]. One study reported more persistent dysphagia and a greater need for pharyngoesophageal dilatation after PEG tube placement [44]. Williams et al. [45] found that enteral feeding was markedly prolonged with prophylactic gastrostomy as compared to nasogastric feeding tubes that were placed when medically required. However, in our study patients were encouraged to continue supplementary oral feeding for as long as possible and were also encouraged to commence oral feeding as soon as possible after completion of treatment.

In a future study, we are going to look into automated model-based optimized planning of IMRT plans for head and neck cancer patients. This is aimed at sparing the structures that are included in this model, without compromising tumor coverage.

Conclusion

The present study is the first to provide a multivariable NTCP model for tube feeding dependence after curative RT, CRT or CetRT in a population-based cohort of patients with HNC. Future studies could use this model to identify patients at risk for tube feeding dependence after treatment who may benefit from prophylactic measures.

Funding source

This work was funded by the Dutch Cancer Society (Grant No. RUG 2008-3983). The funding source played no role in the design or conduct of the study, the analyses, the interpretations of the data, or in the preparation of this manuscript.

Conflicts of interest

B. Slotman has received travel support and honorarium from Varian medical systems and BrainLAB AG. All remaining authors have declared no conflicts of interest.

The Department of Radiation Oncology of the University of Groningen, University Medical Center Groningen has research agreements with Philips, Elekta, RaySearch and Mirada.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2014.09.013>.

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