Prediction of dysphagia

Acute symptoms during the course of head and neck radiotherapy or chemoradiation are strong predictors of late dysphagia ☆

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A B S T R A C T

Purpose: To determine if acute symptoms during definitive radiotherapy (RT) or chemoradiation (CHRT) are prognostic factors for late dysphagia in head and neck cancer (HNC).
Material and methods: This prospective cohort study consisted of 260 HNC patients who received definitive RT or CHRT. The primary endpoint was grade 2–4 swallowing dysfunction at 6 months after completing RT (SWALM6). During treatment, acute symptoms, including oral mucositis, xerostomia and dysphagia, were scored, and the scores were accumulated weekly and entered into an existing reference model for SWALM6 that consisted of dose–volume variables only.
Results: Both acute xerostomia and dysphagia were strong prognostic factors for SWALM6. When acute scores were added as variables to the reference model, model performance increased as the course of treatment progressed: the AUC rose from 0.78 at the baseline to 0.85 in week 6. New models built for weeks 3–6 were significantly better able to identify patients with and without late dysphagia.
Conclusion: Acute xerostomia and dysphagia during the course of RT are strong prognostic factors for late dysphagia. Including accumulated acute symptom scores on a weekly basis in prediction models for late dysphagia significantly improves the identification of high-risk and low-risk patients at an early stage during treatment and might facilitate individualized treatment adaptation.
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Dysphagia is one of the most important side effects after definitive radiotherapy (RT) for head and neck cancer (HNC), also if RT is combined with chemotherapy (CHRT) [1–3]. Approximately one-third of the HNC patients treated with RT or CHRT sustain moderate to severe symptoms that may persist months to years after treatment. These symptoms impair normal swallowing, leading to weight loss and requiring dietary changes. The severity ranges from minor swallowing problems with a normal diet to complete dependence on tube feeding. Previous studies showed that dysphagia has a detrimental impact on quality of life after treatment of HNC [1,4].

Recently, Christianen et al. developed a multivariable Normal Tissue Complication Probability (NTCP) model for grade 2–4 swallowing dysfunction 6 months after completion of treatment (SWALM6), showing that the development of late dysphagia mainly depended on the radiation dose to the swallowing organs at risk (SWOARs), including the superior pharyngeal constrictor muscle (superior PCM) and the supraglottic larynx [5,6]. This multivariable NTCP model enables identification of patients at risk for late dysphagia and the development of new radiation delivery techniques, such as swallowing sparing intensity modulated RT (SW-IMRT) [7,8].

Although this multivariable NTCP model for late dysphagia performed well in terms of discrimination (AUC = 0.80) [6], the explained variance, indicating the relevance of the variables in the model in relation to the endpoint, remained relatively low. The variable toxicity profiles of patients may be explained by individual differences in sensitivity to develop radiation induced side-effects. Furthermore, late toxicity may develop partially as a consequence of early symptoms. Therefore, we hypothesized that patients with early-onset, more severe or longer lasting acute symptoms are at a higher risk of developing late dysphagia.

The first objective of our study was to test the hypothesis that acute symptoms during the course of treatment are significantly

associated to the development of late dysphagia. The second objective was to determine if and to what extent model performance would improve as a result of including acute symptoms as prognostic factors in the reference multivariable NTCP model for SWALM6.

Materials and methods

Patients

We acquired the patient data for our study from the HNC database at our department. All patients with HNC referred for RT or CHRT are subjected to a prospective data collection program in which baseline, acute (weekly during RT) and late (six months after RT) radiation-induced side effects are assessed on a routine basis. For the current study, we included patients who received definitive RT, CHRT or RT with cetuximab for Stage I–IV (M0) squamous cell HNC. We excluded patients who had previously undergone surgery and/or RT in the head and neck region, who had prior malignancies and those with distant metastases or locoregional recurrences at 6 months after treatment. Patients with grade 1–4 dysphagia at the baseline and patients with missing data on acute symptoms in two or more subsequent weeks were also excluded. In 413 cases treated with definitive radiotherapy, chemoradiation or radiotherapy plus cetuximab, the dosimetric data and the SWALM6 scores were both available. Patients were excluded as a consequence of: (1) the exclusion criteria ($n = 82$); (2) missing baseline toxicity data ($n = 1$); or (3) missing acute symptom data ($n = 3$), respectively. Eventually, of the remaining 327 patients, 67 were excluded because of a baseline dysphagia grading of more than zero. The final study population consisted of 260 patients in whom all pretreatment, treatment and toxicity data were prospectively assessed. Table 1 shows the demographic, tumor and treatment characteristics of the study population.

All patient data was obtained as part of a prospective data registration program within the framework of routine clinical practice. The Dutch Medical Research Involving Human Subjects Act is not applicable to data collection as part of routine clinical practice. Therefore the hospital ethics committee exempted this study from the ethical approval requirement.

Endpoint and acute symptoms

The primary endpoint was physician-rated dysphagia grade 2–4 at 6 months after the completion of RT (SWALM6) according to the Late European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) Radiation Morbidity Scoring Criteria [9]. Patients with this endpoint were unable to eat solid food and could only eat semisolid (pureed) food (grade 2) or worse. Acute and late radiation-induced side effects were assessed at the baseline and weekly during the course of treatment. The acute symptom scores for oral mucositis, xerostomia and dysphagia are listed in Table 2. If acute symptom scores were missing for only one week for a particular patient, the scores from the previous week were used.

Treatment

Patients were treated with three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT), with or without concomitant chemotherapy or cetuximab. These treatment regimes have been described previously in more detail [6]. The various organs at risk were delineated on the planning CT according to previously published delineation guidelines [10,11]. All original 3D-CRT and IMRT treatment plans, with the corresponding dose–volume parameters of the organs at risk, were

Table 1
Patient and treatment characteristics and frequencies.

	Number of patients	%
Gender		
Male	197	76
Female	63	24
Age (years)		
Mean age (years)	62.4	
18–65	159	61
>65	101	39
Tumor classification		
Tx	1	0
T1	52	20
T2	115	44
T3	54	21
T4	38	15
Node classification		
N0	140	54
N1	27	10
N2	3	1
N2a	6	2
N2b	38	15
N2c	39	15
N3	7	3
Neck irradiation		
Local or unilateral	86	33
Bilateral	174	67
Primary site		
Larynx	138	53
Hypopharynx	24	9
Oral cavity	6	2
Oropharynx	68	26
Nasopharynx	18	7
Other	6	2
Treatment modality		
5 fractions per week	48	18
6 fractions per week	137	53
Concomitant chemotherapy	65	25
Radiotherapy + cetuximab	10	4
Radiation technique		
3D-CRT	62	24
Parotid sparing IMRT	108	42
Swallowing sparing IMRT	90	35
Patients		
Overlapping with previous study [6]	110	42
Total number of patients	260	100

evaluated in a research version of the Pinnacle[3] treatment-planning system (version 9.1, Philips Radiation Oncology Systems, Fitchburg, WI, USA).

Reference model

First, we evaluated the reference multivariable NTCP model in our cohort (Table 1) by calculating the model value (linear predictor) for each patient with the model intercept and regression coefficients as published by Christianen et al. These values were $-6.09 + (0.057 \times$ mean dose (Gy) in the superior PCM) + $(0.037 \times$ mean dose (Gy) in the supraglottic larynx), and the subsequent NTCP value for each individual patient. In addition, we evaluated the performance of this model in the current study population relative to that in Christianen et al. [6] in terms of explained variance, calibration and discrimination. The linear predictor of the reference model was entered as the reference (baseline) model variable in all subsequent models.

Standardized acute symptoms z-scores

The acute symptom scores were assessed weekly (Table 2). Each acute symptom score was subsequently transformed into a weekly standardized accumulated z-score for two reasons: (1) an accumulated score, calculated by adding the scores of previous weeks, combined the severity and duration of the acute symptom in one value;

Table 2
Physician rated toxicity, frequencies.

Late EORTC/RTOG dysphagia (6 months after RT)	n	%						
EORTC/RTOG grade 0–1	197	76						
EORTC/RTOG grade 2–4	63	24						
Crude acute toxicity scores	Week 3		Week 4		Week 5		Week 6	
	n	%	n	%	n	%	n	%
Oral mucositis								
0 None	99	38	63	25	45	18	41	16
1 Erythema of mucosal membrane	94	36	81	31	71	27	49	19
2 Patchy reaction <1.5 cm	53	21	89	34	86	33	89	34
3 Confluent reaction >1.5 cm	14	5	27	10	58	22	81	31
4 Necrosis or deep ulceration	0	0	0	0	0	0	0	0
Mean accumulated group score (SD)	1.14 (1.16)		2.45 (1.89)		4.05 (2.70)		5.86 (3.57)	
Xerostomia								
0 None	83	32	55	21	47	18	41	16
1 Symptoms without dietary changes	137	53	113	44	91	35	81	31
2 Symptoms with significant dietary changes	38	14	89	34	113	43	132	51
3 Tube feeding, otherwise no adequate intake	2	1	3	1	9	4	6	2
Mean accumulated group score (SD)	1.45 (1.33)		2.60 (1.89)		3.92 (2.48)		5.32 (3.10)	
Swallowing dysfunction								
0 Normal diet	155	60	90	35	71	27	57	22
1 Soft / Pureed food	73	28	88	34	80	31	78	30
2 Liquid diet	16	6	40	15	42	16	45	17
3 Tube feeding with oral intake possible	15	6	37	14	57	22	67	26
4 Tube feeding without oral intake possible	1	0	5	2	10	4	13	5
Mean accumulated group score (SD)	0.82 (1.31)		1.97 (2.16)		3.42 (3.10)		5.03 (4.10)	

Abbreviations: EORTC/RTOG = European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group criteria for adverse effects [9].

(2) standardizing the accumulated scores (i.e., expressing each accumulated score as a number of standard deviations from the average population score) improved the interpretation of a score.

Formulas

For each of the acute symptoms and individual patient (k), an accumulated symptom score ($C_{k,w}$) in a particular week of radiotherapy (w) was calculated by adding up the scores ($S_{k,j}$) of all subsequent weeks (j) from week 1 to week w.

$$C_{k,w} = \sum_{j=1}^{w} S_{k,j}$$

For each week of radiotherapy (w), the mean accumulated acute symptom score (μ_w) and standard deviation (σ_w) were calculated for the whole population of n patients.

$$\mu_w = \frac{1}{n} \sum_{k=1}^{n} C_{k,w}$$

$$\sigma_w = \sqrt{\frac{\sum_{k=1}^{n}(C_{k,w} - \mu_w)^2}{n-1}}$$

Finally, a standardized z-score ($Z_{k,w}$) for the accumulated symptom scores of patient k in week w was defined as

$$Z_{k,w} = (C_{k,w} - \mu_w)/\sigma_w$$

Weekly dynamic models

The acute symptom profile of individual patients became clearer as RT progressed. Because new acute symptom information was added each week, these weekly models were referred to as dynamic models.

The z-scores were available for each patient, each week of RT and each acute symptom type (oral mucositis, xerostomia and dysphagia). The next step was to build subsequent dynamic models for each week (weeks 1, 2, 3, 4, 5, and 6). The variables in a dynamic model consisted of the aforementioned linear predictor of the reference model and the z-scores for the acute symptoms. Then, a stepwise backward (Wald) logistic regression procedure was used to exclude acute symptom variables from the model with p-removal >0.157.

Internal validation and model performance

All dynamic models were subjected to internal validation with a bootstrapping procedure (2000 bootstraps for each analysis) in order to correct (shrink) the models (slope and intercept) for optimism [12]. This was done to obtain realistic regression coefficients for the model variables that are representative for populations similar to the development sample. For each dynamic model, the area under the receiver operating characteristic curve (ROC-curve AUC), the explained variance and calibration were determined. In addition, model improvement measures were determined, i.e., the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI) relative to the reference model were determined for each dynamic model. The NRI quantified the difference in the sum of the sensitivity and specificity between two models (using a >50% NTCP criterion to classify patients as high-risk patients). The IDI quantified the difference in the discrimination slopes of two models. Dynamic models were only accepted for a particular week when these yielded a significantly better ($p < 0.05$) classification and discrimination (NRI and IDI) of patients with and without late dysphagia on the basis of the model predictions compared with the existing reference model.

NTCP calculation

The probability that a patient developed the complication (NTCP), i.e., late dysphagia, was calculated with a logistic regression model

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

with the linear predictor (S) defined as

$$S = \beta_0 + \sum_i \beta_i \cdot x_i$$

where β_0 and β_i were the model parameters and x_i the predictor variables.

Results

Reference model

Of the 260 patients included in the final analyses (Table 1), 63 (24.2%) developed SWALM6 (Table 2). The linear predictor variable obtained from the reference model of Christianen et al. (comprising the intercept, the mean dose in the superior PCM and the mean dose in the supraglottic larynx with corresponding regression coefficients) was a significant factor in all subsequent models in the current study (Table 3). The reference model yielded an AUC value of 0.78 in our cohort (Table 4). This value was comparable (0.80) to the AUC obtained by Christianen et al. [6].

Discarded models and predictors

In univariable analysis, all acute symptom z-scores in weeks 2 through 6 (and acute xerostomia in weeks 1 through 6) were significantly associated with SWALM6 ($p < 0.001$). In the multivariable models, however, oral mucositis was not selected as an independent prognostic factor at any time point ($p > 0.157$). In the multivariable models, acute xerostomia in weeks 1 and 2 was a significant factor for SWALM6. Although the performance of the week 1 and 2 models improved compared to the reference model in our cohort (ROC-curve AUC: 0.792 and 0.804, R^2: 0.276 and 0.300, respectively), these models did not result in a significant NRI, nor a significant IDI compared to the reference model.

Dynamic models

Acute xerostomia and acute dysphagia in weeks 3, 4, 5 and 6 were significant prognostic factors for SWALM6 (Table 3). The dynamic NTCP models in these weeks all performed better than the reference NTCP model in our cohort. Classification of high-risk patients was significantly better with the dynamic models (Table 4). For example, the NRI ranged from 0.212 in week 3 to 0.303 in week 6 ($p < 0.001$). The discrimination slope of the reference model was 0.165, while in the dynamic models it ranged from 0.247 in week 3, to 0.301 in week 6. This corresponds with a statistically significant IDI ($p < 0.001$).

The duration and severity of acute xerostomia and acute dysphagia strongly affected the NTCP values of SWALM6 (Fig. 1). For example, in the quartile of patients who had the worst acute symptoms in week 4, SWALM6 was observed in 54% of the cases. The week 4 model predicted an average NTCP of 54% in this group, compared to 34% on average with the reference model. In the quartile of patients who had the mildest acute symptoms in week 4, SWALM6 was observed in 3% of the cases. The week 4 model predicted an average NTCP of 5% in this group, and the reference model 13% on average.

We verified if other variables, listed in Table 1, improved the final dynamic models as presented in this paper, which however was not the case. This finding corresponds with the previous findings during the development of the reference model.

Table 3
Final models.

Variables	β		OR		
	Uncorrected	Corrected[*]	OR	95% CI	*p*-value
Reference model in current cohort					
Linear predictor reference model [6]	0.881	0.891	2.412	1.734–3.355	<0.001
Intercept	−0.113	−0.105			
Model week 3					
Linear predictor reference model	0.739	0.692	2.094	1.483–2.955	<0.001
Xerostomia z-value	0.427	0.400	1.533	1.047–2.243	0.028
Dysphagia z-value	0.483	0.452	1.620	1.148–2.288	0.006
Intercept	−0.419	−0.444			
Model week 4					
Linear predictor reference model	0.655	0.626	1.926	1.354–2.739	<0.001
Xerostomia z-value	0.368	0.351	1.445	0.945–2.209	0.089
Dysphagia z-value	0.741	0.708	2.099	1.426–3.089	<0.001
Intercept	−0.614	−0.622	0.541		
Model week 5					
Linear predictor reference model	0.612	0.587	1.844	1.293–2.629	<0.001
Xerostomia z-value	0.458	0.439	1.581	1.004–2.491	0.048
Dysphagia z-value	0.725	0.696	2.066	1.383–3.086	<0.001
Intercept	−0.736	−0.737			
Model week 6					
Linear predictor reference model	0.556	0.531	1.743	1.213–2.505	0.003
Xerostomia z-value	0.559	0.534	1.749	1.077–2.840	0.024
Dysphagia z-value	0.768	0.734	2.155	1.410–3.295	<0.001
Intercept	−0.885	−0.878			

Binary endpoint: physician-rated dysphagia grade 2–4 at 6 months after the completion of radiotherapy according to the Late EORTC/RTOG Radiation Morbidity Scoring Criteria [9].
Abbreviations: β = Logistic regression coefficient; EORTC/RTOG = European Organisation for Research and Treatment of Cancer / Radiation Therapy Oncology Group. OR = Odds Ratio; z-value = Standardized mean difference of the accumulated toxicity score ((accumulated patient score − group mean accumulated score)/group standard deviation accumulated score).
  [*] In addition to the uncorrected model parameters the corrected β values after internal validation and model shrinkage are shown.

Table 4
Model performance measures.

Performance measure		Reference model	Week 3 model	Week 4 model	Week 5 model	Week 6 model
Overall	−2 log likelihood	239.1	219.6	209.6	209.4	206.3
	Nagelkerke adjusted R^2	0.256	0.345	0.388	0.389	0.402
Discrimination	ROC-curve AUC (95% CI)	0.781 (0.721–0.840)	0.823 (0.768–0.878)	0.847 (0.796–0.898)	0.846 (0.794–0.897)	0.849 (0.797–0.901)
	Discrimination slope	0.165	0.247	0.288	0.289	0.301
Calibration	Hosmer–Lemeshow test	$X^2 = 10.225$ ($p = 0.250$)	$X^2 = 4.839$ ($p = 0.775$)	$X^2 = 7.316$ ($p = 0.503$)	$X^2 = 2.820$ ($p = 0.945$)	$X^2 = 5.2771$ ($p = 0.728$)
Model improvement	IDI	–	0.082 ($p < 0.001$)	0.122 ($p < 0.001$)	0.124 ($p < 0.001$)	0.135 ($p < 0.001$)
	NRI index	–	0.212 ($p = 0.006$)	0.250 ($p = 0.002$)	0.281 ($p < 0.001$)	0.303 ($p < 0.001$)

Abbreviations: IDI = Integrated Discrimination Improvement (discrimination slope dynamic model − discrimination slope baseline model); NRI = Net Reclassification Improvement (compared to the baseline model and classifying patients with a predicted risk >50% as high risk patients); ROC-curve AUC = area under the receiver operating characteristics curve.
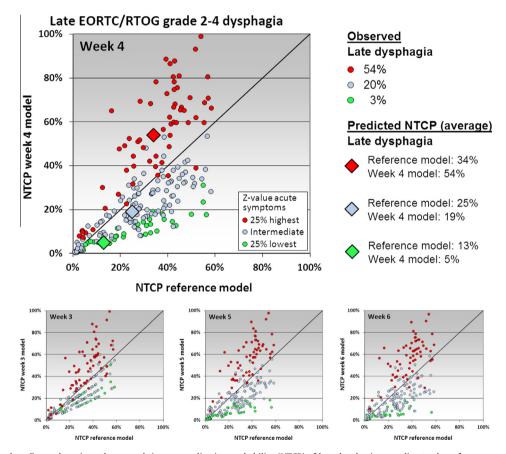

Fig. 1. Reclassification plots. For each patient, the normal tissue complication probability (NTCP) of late dysphagia according to the reference model is plotted against the NTCP according to the dynamic models of weeks 3, 4, 5 and 6. Patients are grouped (and colored) on the basis of the acute symptom scores in the corresponding weeks: the quartile of patients (25%) with the lowest acute symptom scores (green) and the quartile with the highest acute symptom scores (red). The remaining patients (50%) had intermediate acute symptom scores (blue). The diamonds represent the average NTCP values of the patient subgroups.

Discussion

The main objective of the current study was to test the hypothesis that acute symptoms during the course of treatment are significantly associated to the development of late dysphagia. This hypothesis was supported by our data. Acute dysphagia and acute xerostomia in weeks 3–6 of radiotherapy were independent prognostic factors for late RTOG grade 2–4 dysphagia. The second objective concerned the performance of the reference multivariable NTCP model for SWALM6. This performance improved significantly when the weekly accumulated scores for acute dysphagia and acute xerostomia were added as variables: the dynamic models were significantly better at distinguishing patients who developed late dysphagia from those who did not.

These dynamic models could be invaluable in the context of a more personalized treatment approach. Current dose schedules are often based on the average toxicity observed in the total patient population, while our data indicate that, even with the same dose in the SWOARs, some patients sustain more acute dysphagia than average. We demonstrated that these patients also have a higher risk of late dysphagia, and might therefore be considered as candidates for a mid-course re-evaluation of their treatment regimes (dose prescriptions and/or radiotherapy techniques). Several potential means are available to do so. For example, in week 4, when patients develop more than average acute symptoms, the dose in the swallowing structures could be lowered for the remaining fractions, e.g., by decreasing the total dose in the elective target volumes [13], by using adaptive

replanning or by changing to other treatment modalities such as proton therapy (where available) [14]. Conversely, patients who remain free from acute symptoms during the entire course of treatment might be candidates for dose escalation strategies. As the safety and efficacy of such treatment adjustments are not yet clear, these kind of tailored treatment adjustments based on acute symptom profiles may be worthwhile to investigate in future clinical studies.

The rationale behind the main hypothesis of this study was that patients differ in their sensitivity to radiation treatment [15,16], and that patients who are more susceptible to radiation-induced effects are more prone to develop both acute symptoms and late toxicity. Acute symptoms can therefore be regarded as biomarkers for late toxicities and can be used to select patients for adjustment of their treatment parameters, as described above.

Another possible explanation for the findings in our study is consequential late toxicity [17–20]. This is based on the assumption that the radiation dose causes both acute and late toxicity, while the acute toxicity by itself sets in motion a series of effects that ultimately lead to late toxicity. This implies that acute toxicities are at least partly in the causal pathway from radiation dose to late toxicity. Such causality cannot be proven from observational data, and should therefore be studied and established in a biological experimental setting. However, the regression coefficient of the reference model variable became considerably smaller when the acute symptom variables were added to the model. This reduction ranged from 16% in week 3–37% in week 6. This agrees with the possibility that the observed late dysphagia is partially a consequential effect, i.e., caused by acute dysphagia [21,22]. Moreover, it is not entirely clear that the same genetic alterations responsible for radiation sensitivity result in increased acute and late toxicity. It may very well be that some alterations result in sensitivity to acute effects and some to late effects. Our data seem to support that these may be linked. The subset of patients with severe acute toxicity could be the subject of future research with the aim to find out what the biologic cause of their inherit sensitivity is. Another explanation for the variation in observed acute symptoms and late dysphagia might be that the actual delivered dose distribution was not always similar to the planned dose distribution, e.g., changes in patient anatomy may occur during the course of treatment. We are currently investigating such issues as part of an ongoing effort to improve our models.

The linear predictor of the reference model [6], including baseline dose–volume parameters, was used as a variable in all our models. We decided to take this approach instead of fitting a new baseline model to our data to ensure that the outcomes of this study added to the reference model for SWALM6. We verified that this choice did not have an important effect on the results and conclusions of the current study. All models would have fitted slightly better and would have yielded slightly better performance measures, while the differences between the models would remain similar.

Other authors have shown that baseline dysphagia is also a strong prognostic factor for late dysphagia [5,23]. In most cases, dysphagia before the start of RT is caused by other factors, such as local tumor extension or surgery. As we intended to focus on radiation-induced dysphagia, patients with grade 1–4 dysphagia at the baseline were excluded from the analysis. This also accounts for the relatively low incidence (24.2%) of late dysphagia in the current study. Therefore, it should be noted that the models presented in the current study only apply to patients who receive definitive RT for squamous cell head and neck cancer and did not have grade 1–4 dysphagia at the baseline.

In the current study, we used cumulative z-scores as candidate variables for the dynamic prediction models. In patients with other anatomical tumor sites it has been shown that accumulated acute symptom scores are more predictive of late symptoms than peak acute score changes [24]. A cumulative score also offers the ability to express the onset, severity and persistency of the acute symptoms in a single value. The disadvantage of such a value is that it may be hard to interpret and may be different for different toxicities and different scoring systems. To account for that, the acute symptoms scores were accumulated each week and then transformed into standardized z-scores [25], and subsequently entered as variables in the weekly models.

Conclusion

Accumulated acute symptoms during the course of RT appear to be strong predictors of late dysphagia. With the proposed dynamic models, the NTCP of late dysphagia can be estimated and adjusted on a weekly basis during the course of treatment. For individual patients, this may reveal that they are more prone to late dysphagia than expected on the basis of a reference (baseline factors) model. Or conversely, when they develop no acute symptoms at all, they may be less prone to late dysphagia. The dynamic models provide valuable insight into individual therapeutic windows. This new information may potentially be used to adjust the treatment strategy mid-course on the basis of the expected risk of late dysphagia, enabling a more personalized treatment approach.

Conflict of interest statement

The authors state that the research presented in this manuscript is free of conflicts of interest.

References

[1] Langendijk JA, Doornaert P, Verdonck-de Leeuw, et al. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26:3770–6.
[2] Vergeer MR, Doornaert PA, Rietveld DH, et al. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.
[3] Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol 2010;28:2732–8.
[4] Ramaekers BL, Joore MA, Grutters JP, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. Oral Oncol 2011;47:768–74.
[5] Dirix P, Abbeel S, Vanstraelen B, et al. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose–effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2009;75:385–92.
[6] Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol 2012;105:107–14.
[7] van der Laan HP, Christianen MEMC, Bijl HP, et al. The potential benefit of swallowing sparing intensity-modulated radiotherapy to reduce swallowing dysfunction: an in silico planning comparative study. Radiother Oncol 2012;103:76–81.
[8] van der Laan HP, Gawryszuk A, Christianen ME, et al. Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: treatment planning optimization and clinical introduction. Radiother Oncol 2013;107:282–7.
[9] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[10] Christianen ME, Langendijk JA, Westerlaan HE, et al. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. Radiother Oncol 2011;101:394–402.
[11] van de Water TA, Bijl HP, Westerlaan HE. Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia. Radiother Oncol 2009;93:545–52.
[12] Steyerberg EW, Harrell Jr FE, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–81.
[13] Nuyts S, Lambrecht M, Duprez F, et al. Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity. Radiother Oncol 2013;109:323–9.

[14] van der Laan HP, van de Water TA, van Herpt HE. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: a planning comparative study. Acta Oncol 2013;52:561–9.

[15] Ghazali N, Shaw RJ, Rogers SN, et al. Genomic determinants of normal tissue toxicity after radiotherapy for head and neck malignancy: a systematic review. Oral Oncol 2012;48:1090–100.

[16] Barnett GC, West CM, Dunning AM, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009;9:134–42.

[17] Heemsbergen WD, Peeters ST, Koper PC, et al. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys 2006;66:3–10.

[18] Pinkawa M, Holy R, Piroth MD, et al. Consequential late effects after radiotherapy for prostate cancer – a prospective longitudinal quality of life study. Radiat Oncol 2010;5:27.

[19] Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 2006;6:702–13.

[20] Dorr W, Hendry JH. Consequential late effects in normal tissues. Radiother Oncol 2001;61:223–31.

[21] Krull JL, MacKinnon DP. Multilevel mediation modeling in group-based intervention studies. Eval Rev 1999;23:418–44.

[22] MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci 2000;1:173–81.

[23] Mortensen HR, Overgaard J, Jensen K, et al. Factors associated with acute and late dysphagia in the DAHANCA 6 & 7 randomized trial with accelerated radiotherapy for head and neck cancer. Acta Oncol 2013;52:1535–42.

[24] Wedlake LJ, Thomas K, Lalji A, et al. Predicting late effects of pelvic radiotherapy: is there a better approach? Int J Radiat Oncol Biol Phys 2010;78:1163–70.

[25] Barnett GC, West CM, Coles CE, et al. Standardized total average toxicity score: a scale- and grade-independent measure of late radiotherapy toxicity to facilitate pooling of data from different studies. Int J Radiat Oncol Biol Phys 2012;82:1065–74.