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Original Article

Impact of radiation-induced toxicities on quality of life of patients treated for head and neck cancer

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ABSTRACT

Purpose: The aim of this study is to establish the relative impact of physician-rated toxicities and patient-rated symptoms in head and neck cancer (HNC) on quality of life (QOL) and to weigh the various toxicities and symptoms during treatment plan optimization and selection.
Materials and methods: This prospective cohort study comprised 1083 HNC patients (development: 750, validation: 333) treated with definitive radiotherapy with or without chemotherapy. Clinical factors were scored at baseline. Physician-rated and patient-rated outcome measures and QOL (EORTC QLQ-HN35 and QLQ-C30) were prospectively scored at baseline and 6, 12, 18 and 24 months after radiotherapy. The impact of 20 common toxicities and symptoms (related to swallowing, salivary function, speech, pain and general complaints) on QOL (0–100 scale) was established for each time point by combining principal component analysis and multivariable linear regression.
Results: Radiation-induced toxicities and symptoms resulted in a significant decline in QOL of patients with 12.4 ± 12.8 points at 6 months to 16.6 ± 17.1 points at 24 months. The multivariable linear models described the QOL points subtracted for each toxicity and symptom after radiotherapy. For example, xerostomia and weight loss had a significant but minor effect (on average –0.5 and –0.6 points) while speech problems and fatigue had a much greater impact (on average –11.9 and –17.4 points) on QOL. R^2 goodness-of-fit values for the QOL models ranged from 0.64 (6 months) to 0.72 (24 months).
Conclusion: The relative impact of physician-rated toxicities and patient-rated symptoms on QOL was quantified and can be used to optimize, compare and select HNC radiotherapy treatment plans, to balance the relevance of toxicities and to achieve the best QOL for individual patients.

In recent years, considerable progress has been made in the development of prediction models for radiation-induced toxicities for head and neck cancer (HNC) [1]. Multivariable prediction models can be used to predict a wide range of normal tissue complication probabilities (NTCP) [2]. These models can provide guidance in treatment plan optimization [3,4], treatment plan comparison and in the selection of patients for new radiation technologies, such as for proton therapy [5,6]. Knowledge on the optimal dose distribution, i.e., the order in which organs at risk (OAR) should be spared to avoid toxicities, is crucial [7]. Although insight into the relationships between the dose to OARs and the most common toxicities after HNC radiotherapy has been improved, the way that OAR-sparing and avoidance of corresponding toxicities should be prioritized to achieve the optimal treatment plan in terms of QOL still remains to be determined. There is a need to rank toxicities in relation to the general well-being of the patient, in the context of a comprehensive weighted toxicity profile [8,9]. Recent publications have focused on the concept of total toxicity burden (TTB) to assess the impact of various toxicities on QOL in different study arms of clinical trials in a more objective manner [10,11]. The TTB is a weighted sum of occurring toxicities, in which the relative weights of the toxicities are based on the toxicity grades or elicited by a multidisciplinary group of experts based on their impression of the relative impact of the toxicity [11]. There is, however, no expert consensus as to how toxicities after radiotherapy for HNC should be weighted. Moreover, poor correlations have been reported between physician and patient assessments of a patients' quality of life (QOL) [12]. As a result, it is not yet possible to prioritize the various toxicities from being prevented during treatment plan optimization and treatment plan comparison, based on their relative impact on QOL as reported by HNC patients.

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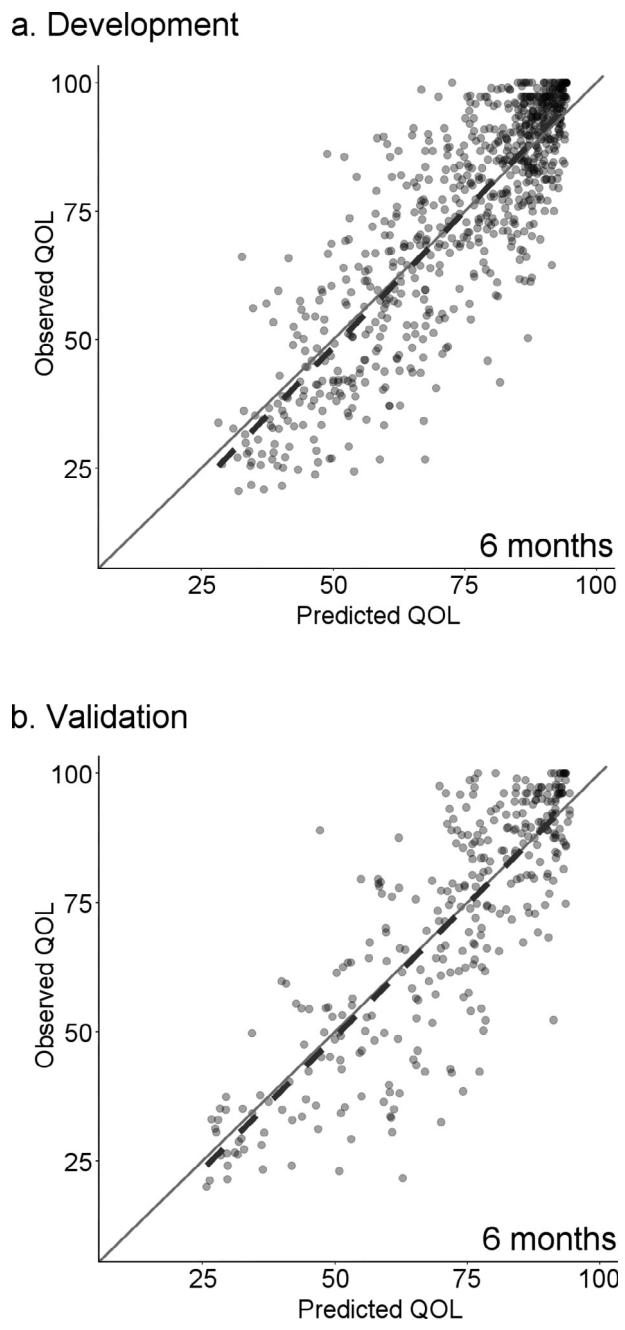

Fig. 1. Observed versus predicted Quality of Life scores with the final model in the (a) development and (b) validation cohorts at 6 months after radiotherapy. Scatter plots are shown with reference and regression lines (dashed).

The aim of this prospective cohort study is to assess the relative impact of a range of common late toxicities and symptoms on the general dimensions of QOL in HNC patients treated with definitive radiotherapy and to develop multivariable models describing the impact of toxicities and symptoms on QOL.

Materials and methods

Patients and radiotherapy

This cohort study examined high quality prospective data of 1083 HNC patients treated with definitive radiotherapy with or without chemotherapy for squamous cell carcinoma located in the oral cavity, pharynx or larynx (Table 1). The development cohort comprised 750 patients treated between January 2007 and June 2016 and the validation cohort comprised 333 patients who had at least 6 months of follow-up and were treated between July 2016 and July 2019. Patient and treatment characteristics and eligibility criteria for the development cohort have been described previously in detail [1]. For the validation cohort, the same eligibility criteria were used, and patients were treated according to the same radiotherapy protocols. The validation cohort is a representative sample of our current patient population. Compared to the development cohort, patients were treated with more advanced radiotherapy techniques: 261 patients (78%) were treated with volumetric-modulated arc therapy (VMAT) and 72 (22%) were treated with intensity modulated proton therapy (IMPT) (Table 1). In patients treated after January 2018, treatment planning was performed with more emphasis on sparing the oral cavity. All patient data was obtained as part of a prospective data registration program within the framework of routine clinical practice (clinicaltrial.gov NCT02435576). 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.

Quality of life

QOL was based on the 6 multi-item scales for the more general dimensions of QOL as assessed by the EORTC QLQ-C30 questionnaire: global QOL, physical functioning, role functioning, emotional functioning, social functioning and cognitive functioning (Table S1). They were scored at baseline and at 6, 12, 18 and 24 months after completion of radiotherapy [13]. Each dimension was converted to 0–100 scale, according to EORTC guidelines [14], in which higher scores represent better QOL or a higher level of functioning. QOL was then defined as the average score of the six multi-item scales.

Toxicities

Twenty physician-rated toxicities and patient-rated symptoms related to swallowing, salivary function, speech, pain, and general complaints were considered (Table S1). Thirteen patient-rated symptoms were scored using the EORTC QLQ-HN35 and EORTC QLQ-C30 questionnaires [13,15]. Seven physician-rated toxicities were scored according to CTCAEv4 [16]. All toxicities and symptoms were scored at baseline and at 6, 12, 18 and 24 months after completion of radiotherapy. To enable future use of the QOL model in combination with NTCP models, toxicities and symptoms were converted into binary variables. Patients with physician-rated $\geq$ grade 2 toxicities or with moderate-to-severe symptoms were regarded positive for the corresponding toxicities or symptoms. Variables were added for severe xerostomia and severe sticky saliva, $\geq$ grade 3 dysphagia and weight loss $\geq$ 10% relative to baseline.

Multiple imputation and time points

Multiple imputation was used to account for missing data [17,18] (Table S2). Ten imputation sets were created. The methods described below were performed in each imputation set and all results were pooled across imputation sets [19]. QOL models were developed independently for baseline and the time points 6, 12, 18 and 24 months after radiotherapy.

Dimensionality reduction

As regular linear regression analysis including 20 toxicities would suffer from multidimensionality and multicollinearity, we combined principal component analysis (PCA) and linear regres-

Table 1
Patient, tumour and treatment characteristics and dose parameters.

	Development cohort (n = 750)		Validation cohort (n = 333)		p-Value
Age					
mean (sd)	63	(10.3)	65	(10.9)	0.018
Sex (%)					0.101
Male	560	(74.7)	264	(79.3)	
Female	190	(25.3)	69	(20.7)	
Tumour site (%)					0.074
Oral cavity	44	(5.9)	32	(9.6)	
Oropharynx	271	(36.1)	134	(40.2)	
Nasopharynx	30	(4.0)	12	(3.6)	
Hypopharynx	71	(9.5)	24	(7.2)	
Larynx	334	(44.5)	131	(39.3)	
Neck irradiation (%)					0.317
No	147	(19.6)	53	(15.9)	
Unilateral	18	(2.4)	10	(3.0)	
Bilateral	585	(78)	270	(81.1)	
T-stage (UICCv7) (%)					0.053
Tis-T2	363	(48.4)	140	(42.0)	
T3-4	387	(51.6)	193	(58.0)	
N-stage (UICCv7) (%)					0.916
N0	333	(44.4)	149	(44.7)	
N+	417	(55.6)	184	(55.3)	
Treatment technique (%)					<0.001
3D-CRT	86	(11.5)	0	(0.0)	
IMRT	546	(72.8)	3	(0.9)	
VMAT	118	(15.7)	150	(45.0)	
VMAT with Oral cavity sparing	0	(0.0)	122	(36.6)	
IMPT with Oral cavity sparing	0	(0.0)	58	(17.4)	
Treatment modality (%)					<0.001
Conventional RT	149	(19.9)	136	(40.8)	
Accelerated RT	294	(39.2)	76	(22.8)	
Chemoradiation	242	(32.3)	108	(32.4)	
Accelerated RT with cetuximab	65	(8.7)	13	(3.9)	
Prescribed dose (%)					0.889
55–64 Gy	1	(0.1)	1	(0.3)	
66 Gy	71	(9.5)	35	(10.5)	
70 Gy	676	(90.1)	297	(89.2)	
72 Gy	2	(0.3)	0	(0.0)	

RT = radiotherapy; 3D-CRT = 3D conformal radiotherapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric modulated arc therapy; IMPT = intensity modulated proton therapy.

sion. In the first step, un-supervised PCA was performed on all 20 toxicities to obtain 20 uncorrelated principal components (PC). The PCA yielded the loading of each toxicity on each principal component, which was used later in the analysis. For each patient, the principal component values were calculated, and the 20 components were added as variables in the dataset. A calculation example is provided in (Table S3).

Linear regression

In the second step, a linear regression analysis was performed per time point. The endpoint was the QOL score. The candidate predictors included the 20 principal components, baseline QOL, baseline WHO performance score > 0, gender, and age (Table S4). Backward variable selection, based on the Akaike information criterion (AIC), was performed among the candidate predictors. The regression coefficients (β) of the toxicities and symptoms in the final linear regression models were calculated by summing the PC loadings multiplied by the PC β per toxicity and symptom. A detailed example of this calculation can be found in the Supplementary Tables S3. If the QOL model resulted in toxicities or symptoms having positive regression coefficients (suggesting toxicity to have a positive impact on QOL) these regression coefficients were forced to be zero and the model intercept was corrected to account for this adjustment (Table S5). Internal validation by means of a bootstrap procedure was performed to correct model performance (R^2), model slope (regression coefficients) and model intercept for optimism. In order to estimate the impact, of the current statistical methods on the outcomes, an additional sensitivity analysis was performed including alternative statistical methods, e.g., a multivariate analysis of covariance (MANCOVA) (Table S6 and Table S7).

External validation

The final models obtained in the development cohort were tested on the validation cohort using a closed testing procedure [20], modified for use with linear models. This procedure tests whether a revision of the model in the validation cohort would result in a significant model improvement according to a likelihood ratio test. If negative, the original model was accepted. If positive, the model was updated by 1) an update of the model intercept; or 2) a model recalibration; or 3) a model revision. In the case a model revision was advised, all regression coefficients were recalculated using exactly the same variables as in the original model.

Results

Already at baseline (i.e., pre-treatment), toxicities and symptoms affected QOL. At baseline, the average QOL score of patients was reduced by 11 ± 15 points, compared to assuming zero toxicities for all patients. At 6 months, this reduction was 12.4 ± 12.8 points and at 24 months it was 16.6 ± 17.1 points due to toxicities and symptoms (Table 2). On average, the relative impact on QOL ranged from 4% for toxicities or symptoms related to salivary function (e.g., dry mouth and sticky saliva) to 41% for more general symptoms, such as nausea and vomiting and fatigue (Table 3;

Table 2
Observed and predicted Quality of Life scores.

	Observed			Predicted										
				QOL with all toxicities			QOL without any toxicity			QOL with actual toxicities			Toxicity attributed QOL reduction		
Baseline	76.8	±	20.4	14.3	±	2.3	87.9	±	2.3	76.8	±	16.3	−11.1	±	15.3
6 months	74.4	±	21.4	32.9	±	6.4	86.8	±	6.4	74.4	±	17.1	−12.4	±	12.8
12 months	73.3	±	24.0	21.2	±	5.4	87.9	±	5.4	72.9	±	20.7	−15.0	±	17.0
18 months	71.9	±	24.3	28.2	±	4.5	88.4	±	4.5	71.9	±	20.5	−16.5	±	17.8
24 months	71.1	±	24.5	23.8	±	5.4	87.6	±	5.4	71.0	±	20.7	−16.6	±	17.1

Observed Quality of Life (QOL) population average scores (±standard deviations) and population average scores based on model predictions simulating: 1) all patients simulated to be positive for all toxicities and symptoms; 2) all patients simulated to be negative for all toxicities and symptoms; 3) each patient taking into account their actual toxicites. Population average toxicity attributed QOL reductions are obtained by comparing 2) and 3) per patient. Values are based on development cohort data and internally validated prediction models.

Table S5). The impact of the different individual toxicities and symptoms on QOL averaged over the late time points and was lowest for moderate-to-severe xerostomia and weight loss (reductions of 0.5 and 0.6 points) and highest for moderate-to-severe speech problems and fatigue (reductions of 11.8 and 17.4 points; Table 3). Baseline QOL and baseline WHO performance score > 0 were, in addition to the 20 toxicities and symptoms, found to be predictors of QOL. On the different time points, a limited number of toxicities or symptoms had a regression coefficient that was slightly positive and was forced to zero (Table S5). In the external validation cohort, no model updates were needed for the model at 6 months (Fig. 1), whereas a model recalibration was performed for the model at 18 months (Table S5), and model revisions were performed for the models at 12 and 24 months.

The additional MANCOVA analysis showed that the impact of some symptoms on QOL was different for the global QOL and functioning scales. E.g., moderate-to-severe xerostomia seemed to have more impact on global QOL while fatigue seemed to have more impact on function (Table S6).

Discussion

To our knowledge, this is the first study to report on a comprehensive multivariable model to predict QOL that identifies the relative impact on QOL of a wide range of common toxicities and symptoms observed after radiotherapy for HNC. It was demonstrated that the impact of some toxicities and symptoms on QOL (e.g., xerostomia and weight loss) was much less than others (e.g., speech problems and fatigue). This is an important finding as it suggests different priorities for OARs to be spared during radiotherapy, e.g., a higher priority for reducing the integral dose (to prevent fatigue) and a higher priority for reducing the dose to the oral cavity (to prevent dysphagia and speech problems). This may ultimately lead to treatment plans that reduce the impact on QOL of patients.

The findings of this study may contribute significantly to treatment plan selection and treatment plan optimization. With regard to the first clinical application (treatment plan selection): dose distributions can be converted into a QOL prediction for a treatment plan by combining NTCP predictions with the QOL model, i.e., by multiplying the model regression coefficients with the NTCP predictions for the corresponding toxicities and symptoms. When applying the QOL model for treatment plan evaluation, it should be noted that many factors outside this study contribute to the QOL of individual patients. Therefore, the QOL predictions should not be regarded as absolute independent QOL predictions for individual patients. Instead, the QOL predictions are an effective means to compare different treatment plans, as all other patient specific circumstances are constant when alternative treatment plans are considered. Alternative dose distributions can be evaluated in terms of intrinsic impact on QOL, and from a set of alternative treatment plans, the plan with the highest expected QOL can be selected as the final clinical treatment plan.

With regard to the second application (treatment plan optimization), the objective weights for the various OAR can also be based on the intrinsic impact on QOL. For example: objective weights for the dose to an OAR related to a toxicity or symptom that has a minor impact on QOL can be set to a lower value, whereas the objective weights for the dose to an OAR related to a high-impact toxicity or symptom can be set to a higher value. In future implementations of treatment planning systems, dosimetrist-operated iterative manual adjustments of the OAR objective weights, can be replaced by NTCP-based treatment plan optimization. With this method, each OAR has a certain weight in a range of respective NTCP models that are all used as optimization functions by the treatment planning system. This method has been proposed previously with a limited set of equally weighted NTCP models [4], but could be used in conjunction with the QOL model. It allows for the use of more extensive toxicity profiles and prioritizing the higher impact toxicities and symptoms and corresponding OARs to arrive at the optimal treatment plan in terms of predicted QOL.

Although the relative impact of toxicity packages and individual toxicities and symptoms on QOL was generally comparable between different statistical methods, e.g., the current analysis or a univariable MANCOVA, there was some variation in the exact values. The values of individual toxicities and symptoms varied to some degree in bootstrap samples or when the analysis was repeated with different subsets of toxicities or symptoms or at different time points. However, sensitivity analyses, some of which were presented in this paper (Table S7), did not change the general impression of the relative impact of the various toxicities and symptoms nor the conclusions of this paper.

The MANOVA approach was not a successful alternative analysis for the final QOL models. Although it was used to study the impact of the toxicities and symptoms on the different dimensions of QOL (Table S6), it does not allow for multiple binary predictors to be part of the model. Regular and mixed model linear regression methods were also considered, but these methods suffered from multicollinearity between the explanatory variables. This is avoided in the current approach (including PCA) as there is negligible correlation between principal components.

Global QOL and the 5 functioning scales were combined as a composite endpoint. This assumes functioning also constitutes QOL. This may have increased the impact of certain toxicities or symptoms, e.g., according to the MANCOVA speech problems, pain and fatigue have a relatively high impact on function. There is no consensus on this choice of composite QOL endpoint and we admit this remains arbitrary. Sensitivity analysis showed that excluding the function scales or increasing the weight of the global QOL score did not significantly impact the final conclusions of this study.

Table 3
Final Quality of Life models, model performance, coefficients and relative weights.

		Baseline	6 months	12 months	18 months	24 months	6–24 months		
							Average coefficients	Relative weights	Package weights
Model performance									
	R^2	0.63	0.64	0.72	0.71	0.72			
Model regression coefficients and relative weights toxicities and symptoms									
	Intercept	89.45	66.62	74.42	74.89	72.15			
	Baseline QOL		0.28	0.20	0.19	0.22			
	Baseline WHO performance score > 0	−4.89	−3.39	−5.25	−2.98	−3.90			
Swallowing									11%
	Dysphagia, grade 2–4	0.00	−2.06	−3.02	−2.37	−3.09	−2.634	4%	
	Dysphagia, grade 3–4	−0.80	−1.69	−2.33	−0.69	−2.21	−1.729	3%	
	Aspiration, grade 2–4	−0.50	−1.99	−2.16	−2.14	−1.27	−1.892	3%	
	Aspiration, moderate-severe	−4.78	−2.88	−1.74	−2.34	−3.24	−2.550	4%	
Salivary									4%
	Dry mouth, moderate-severe	−2.76	−0.86	−0.20	−0.44	−0.44	−0.487	1%	
	Dry mouth, severe	−3.10	−1.29	0.00	0.00	0.00	−0.324	1%	
	Sticky saliva, moderate-severe	0.00	−0.42	−0.35	−0.91	−0.53	−0.552	1%	
	Sticky saliva, severe	−0.76	−0.47	−2.09	−0.22	−1.23	−1.001	2%	
	Dry mouth, grade 2–4		−0.97	−1.53	−0.17	0.00	−0.668	1%	
	Sticky saliva, grade 2–4		−1.06	−1.24	−1.20	−2.13	−1.405	2%	
	Loss of taste, moderate-severe	−6.67	−0.87	0.00	−1.34	−1.39	−0.898	1%	
	Loss of taste, grade 2–4	−0.40	−0.73	0.00	−0.83	−1.35	−0.726	1%	
Speech									32%
	Hoarseness, moderate-severe	0.00	−1.18	−0.90	−0.60	−3.39	−1.518	2%	
	Speech problems, moderate-severe	−7.29	−9.83	−12.45	−13.71	−11.42	−11.852	19%	
Pain									12%
	Oral pain, moderate-severe	−3.42	−1.95	−1.39	−0.57	−0.73	−1.158	2%	
	Throat pain, moderate-severe	−1.62	−4.44	−6.59	−4.14	−3.38	−4.638	8%	
	Jaw pain, moderate-severe	−2.75	−2.46	−2.46	−1.08	−0.28	−1.571	3%	
General									41%
	Weightloss > 10% over baseline		0.00	−0.08	−0.14	−2.02	−0.560	1%	
	Nausea and vomiting, moderate-severe	−16.61	−3.56	−8.72	−9.15	−8.75	−7.543	12%	
	Fatigue, moderate-severe	−22.12	−15.21	−19.42	−18.10	−16.95	−17.419	28%	

Model performance measures (R^2) and Quality of Life (QOL) models regression coefficients. Models are shown for baseline and subsquent time points after radiotherapy. Average model coefficients are shown for the models at 6 to 24 months. For each toxicity, the model coefficients are converted to a relative weighting on QOL. Corrected weightings are also shown for each of the 5 toxicity domains.
Abbreviations: R^2 = goodness-of-fit measure for linear regression models; QOL = Quality of Life; WHO = World Health Organisation.

Although the current report contains the relative impact of 20 common toxicities, a number of toxicities, such as hearing problems, osteoradionecrosis, tube-feeding dependence, cerebrovascular accidents and others, but also objective measures such as salivary flow measurements or assessments of swallowing function or aspiration by means of video-fluoroscopy, have not yet been included. Furthermore, the current analysis is limited to toxicities and symptoms common in patients receiving definitive radiotherapy for HNC. Patients receiving postoperative radiotherapy sustain specific toxicities and symptoms that have not been taken into account. These will be added in future projects and are expected to slightly alter the relative impact of the toxicities and symptoms in the current model as many toxicities and symptoms are interconnected. The current validation cohort did not include patients from other institutions. It is expected that regional and cultural differences may also have an impact on the results. In the external validation cohort, model updates were needed for the model at 18,12 and 24 months (Table S5). These updates were not due to poor calibration (Figure S1), but rather due to shifts in the relative impact of some of the toxicities (Table S5). These shifts might be

explained by evolving technology (patients treated with protons) or changes in treatment (improved sparing of the oral cavity). It should also be noted that few patients had sufficient follow-up at later time points which may explain the model updates needed for later time points.

Clinical variables such as T-stage, N-stage and systemic treatment were not included as candidate predictors as these were assumed to indirectly impact QOL and rather impact the risk of specific toxicities or symptoms, which are the predictors in this study. Clinical variables and principal components were selected for the final model using Akaike information criterion (AIC)-based backwards selection because a stricter method, such as the Bayesian information criterion or a variable p-value of < 0.05, would limit the number of principal components to on average 4 per analysis (with AIC it was 6–9 over the imputation sets) and some variance explaining the impact of toxicity on QOL would be left out of the model. Conversely, using all principal components would increase the noise of variance not describing the impact of toxicities and symptoms on QOL and the results were observed to be less stable over time points, imputation sets and bootstrap samples. The use of AIC was considered to be the 'sweet spot' in this analysis. Multiple imputation was used to enable the inclusion of more patients and also to avoid bias, e.g., it appeared that patients with a lower QOL score at baseline were less likely to complete late QOL questionnaires. Multiple imputation accounts for such effects.

A number of studies reported previously on the impact of late toxicities or symptoms on QOL in HNC. In most cases, the impact of toxicities or symptoms on QOL was examined in univariable analysis and most studies focused on the impact on QOL of specific individual toxicities or symptoms. Still, the outcomes generally confirm the findings of the current study. Langendijk et al. reported on xerostomia and the higher impact of dysphagia on QOL, highlighting the importance of not only focusing on reduction of the dose to the salivary glands, but also on anatomic structures that are involved in swallowing [9]. Daugaard et al., found that physician-assessed moderate to severe hoarseness and mild, moderate, or severe dysphagia are associated with clinically relevant decreases in patient-reported QOL and functioning, while xerostomia of any severity was not associated with changes in any scale of functioning [8]. The relatively low impact of xerostomia on QOL is also conformed in a study by Jellema et al., who found this impact to be statistically significant but decreasing with time and limited in terms of its effect size (0.05) [21]. Similarly, Dahele et al. did not find a benefit in terms of QOL after significant dose reductions to the parotid glands [22]. The findings in our study are also consistent with the relatively higher impact of dysphagia and hoarseness in reports from Jensen et al. [23]. Other reports from this group confirmed the discrepancies between physician rated and patient rated xerostomia in our study [24].

Although it is important to evaluate individual toxicities or symptoms (Table S8), it is more important to evaluate the impact of various toxicities and symptoms on QOL altogether as part of a comprehensive toxicity profile. It has been demonstrated that patients with multiple conditions showed greater decrements in functioning and well-being than those with only one condition [25]. This is demonstrated by our models and depicted in Table 2: already at baseline, and at various time points after radiotherapy there is a combined impact of the various toxicities and symptoms on QOL. In order to improve QOL after radiotherapy, these should all be addressed simultaneously during treatment plan optimization and evaluation. The knowledge provided in this paper enables weighting various toxicities and symptoms for individual patients prioritizing the prevention of the toxicities and symptoms that have the highest impact on QOL and ultimately enable QOL optimized radiotherapy.

In conclusion, the relative impact of physician-rated and patient-rated toxicities on QOL was quantified and can be used to optimize, compare and select HNC radiotherapy plans to provide the optimal spectrum of toxicities resulting in the best QOL for individual patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.04.011.

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