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Original Article

Comprehensive toxicity risk profiling in radiation therapy for head and neck cancer: A new concept for individually optimised treatment

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ABSTRACT

Background and purpose: A comprehensive individual toxicity risk profile is needed to improve radiation treatment optimisation, minimising toxicity burden, in head and neck cancer (HNC) patients. We aimed to develop and externally validate NTCP models for various toxicities at multiple time points.
Materials and methods: Using logistic regression, we determined the relationship between normal tissue irradiation and the risk of 22 toxicities at ten time points during and after treatment in 750 HNC patients. The toxicities involved swallowing, salivary, mucosal, speech, pain and general complaints. Studied predictors included patient, tumour and treatment characteristics and dose parameters of 28 organs. The resulting NTCP models were externally validated in 395 HNC patients.
Results: The NTCP models involved 14 organs that were associated with at least one toxicity. The oral cavity was the predominant organ, associated with 12 toxicities. Other important organs included the parotid and submandibular glands, buccal mucosa and swallowing muscles. In addition, baseline toxicity, treatment modality, and tumour site were common predictors of toxicity. The median discrimination performance (AUC) of the models was 0.71 (interquartile range: 0.68–0.75) at internal validation and 0.67 (interquartile range: 0.62–0.71) at external validation.
Conclusion: We established a comprehensive individual toxicity risk profile that provides essential insight into how radiation exposure of various organs translates into multiple acute and late toxicities. This comprehensive understanding of radiation-induced toxicities enables a new radiation treatment optimisation concept that balances multiple toxicity risks simultaneously and minimises the overall toxicity burden for an individual HNC patient who needs to undergo radiation treatment.

In recent decades, the survival rate of head and neck cancer (HNC) patients has improved significantly due to intensified treatment regimens and an increased incidence of relatively favourable Human Papillomavirus associated oropharyngeal cancer [1–5]. As patients' life expectancy is prolonged, the need to prevent treatment related toxicities that affect the quality of life and daily functioning of HNC patients has become increasingly relevant [6,7].

Radiotherapy plays an important role in the treatment of HNC patients and can induce various, sometimes severe, toxicities [6–11]. As the risk of radiation-induced toxicity mainly depends on the level of radiation exposure to surrounding organs at risk (OAR), minimising radiation dose to these OAR without compromising tumour control, is crucial [12,13]. Recent technological advancements have led to an increased flexibility in the dose deposition, allowing dose reductions in particular OAR [14–16]. However, dose exposure to OAR cannot be completely avoided and in many cases specific OAR are spared at the cost of others [13]. In current clinical practice, this is generally guided by universal dose constraints, often based on QUANTEC recommendations, which are applied to a limited set of OAR in all patients, aiming to prevent only a few toxicities (e.g. mean dose to both parotid glands < 25 Gy to reduce the risk of xerostomia, mean dose to pharyngeal constrictors < 50 Gy to reduce the risk of dysphagia) [17,18]. To account for the complexity of toxicity prevention and fully exploit the potential of recent technological advancements, this current optimisation approach should be redirected towards a more comprehensive and individualised approach that aims to

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simultaneously prevent many toxicities by minimising the radiation dose to all relevant OAR instead of a selected few.

To reach an optimal balance between tumour control and toxicity prevention in individual patients, detailed information on the relationship between normal tissue irradiation and the risk of a wide range of radiation-induced toxicities is required. Normal tissue complication probability (NTCP) models can describe these relationships and can be used in clinical practice to obtain the optimal dose distribution for each individual patient [19–21]. Unfortunately, for many toxicities, suitable NTCP models, that contain the most relevant OAR with reliable dose–response estimates, are lacking. In addition, most models that are available did not use the OAR definitions as defined in the international consensus guidelines [22], nor have they been externally validated [23]. Consequently, their generalisability is limited, impeding their clinical use [24,25].

The aim of this study was to develop and externally validate NTCP models for a comprehensive set of 22 common radiation-induced toxicities at ten time points during and after treatment, based on the latest OAR definitions [22]. These models converge into a comprehensive individual toxicity risk (CITOR) profile that can be used in clinical practice to minimise the overall toxicity burden of a radiation treatment for an individual HNC patient.

Material and methods

An extended description of the methods and results can be found in the supplementary appendix. Results are reported following the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guidance [26,27].

Study design

This is a prospective cohort study. Patients in the development cohort were treated at the University Medical Centre Groningen (UMCG) in The Netherlands, from January 2007 to June 2016. Patients in the validation cohort were treated at three Dutch centres: Maastro Clinic from May 2012 to June 2016, the Radiotherapeutic Institute Friesland from May 2014 to December 2016, and the UMCG from July 2016 to December 2017. All patients were consecutively included in a data registration program as part of routine clinical practice, with prospective assessment of patient, tumour, and treatment characteristics, as well as radiation-induced toxicities (Clinical trials NCT02435576). Since the Dutch Medical Research Involving Human Subjects Act is not applicable to data collection as part of routine clinical practice, the requirement of informed consent was waived by the ethics committee.

Eligibility criteria

Patients were eligible for inclusion if they met the following criteria: (1) squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx or larynx, (2) stage I-IV cancer without distant metastases, (3) treated with primary radiotherapy, with or without concomitant chemotherapy or cetuximab, (4) no neck dissection, (5) no previous HNC treatment (excluding laser resection of small glottic lesions), (6) no history of a malignancy in the previous five years (excluding basal cell carcinoma or cervical carcinoma in situ), (7) no synchronous tumours outside the head and neck region, (8) no induction chemotherapy, and (9) no fraction dose higher than 2.4 Gy.

Treatment

Details on the received radiation treatment of the development cohort have been previously described [28,29]. In summary, patients were treated according to the Dutch guidelines for HNC, meaning patients below 70 years of age with stage I-II disease received accelerated radiotherapy or conventional fractionated radiotherapy, while those with locally advanced disease (stage III-IV) were treated with concurrent platinum based chemoradiation. Elderly patients (>70 years of age) were treated with conventional fractionation alone. Accelerated radiotherapy with weekly cetuximab was reserved for younger patients deemed unfit for chemotherapy or for some elderly patients in good general condition with locally advanced disease. Patients of the validation cohort were treated similarly except for minor variations in fractionation scheduling or administration of chemotherapy. In all patients, 28 OAR were recontoured on planningCT scans to comply with international consensus guidelines (Table S1) [22].

Toxicity outcomes

Toxicity outcomes consisted of 22 dichotomised toxicities (nine physician-rated and 13 patient-reported) that were derived from 18 prospectively scored items. Physician-rated items were dichotomised grade 0–1 vs grade 2–4, and patient-reported items none-mild vs moderate-severe. Additionally, a separate more severe outcome was derived for four items: grade 0–2 vs grade 3–4 physician-rated dysphagia and mucositis, and none-moderate vs severe patient-reported xerostomia and sticky saliva. Table S2 lists all toxicity outcomes and the toxicity items from which they were derived. An overview of the dichotomisation criteria is provided in Table S3. All toxicity outcomes were grouped into six toxicity domains: swallowing, salivary, mucosal, speech, pain and a general domain. Toxicity outcomes were scored at fixed intervals: weekly during treatment from week three to seven, and at 12 weeks after start of treatment for acute toxicities and every six months after the end of treatment up to two years for late toxicities (Table S4). Not all toxicities were scored at all time points, which led to a total of 202 toxicity outcomes.

Candidate predictors

To reduce the number of candidate predictors and the risk of developing overfitted, optimistic and less generalisable NTCP models, we carefully preselected the predictors under study per toxicity domain based on prior knowledge and clinical expertise. In general, candidate predictors consisted of patient, tumour, and treatment characteristics, including dose parameters of OAR. For a complete list of candidate predictors per toxicity domain refer to Table S5.

Statistical analysis

Missing data was only present in baseline toxicity scores and toxicity outcomes. Multiple imputation was used to account for missing data, including missing data due to death [30]. Only variables with less than ten available data values were not imputed because of probable unreliable estimated imputed values. This was only the case for some toxicity outcomes in some validation centres, which were therefore excluded from the validation cohort for the external validation of that specific toxicity outcome. The centres used for the external validation of each toxicity outcome are listed in Table S8. All the presented results are pooled results [31].

Multivariable logistic prediction models were obtained and externally validated for all 22 toxicities, at all time points separately, according to a recently published strategy that addressess key challenges in modeling radiation-induced toxicity [30]. In short, first separate NTCP models were developed for acute (at week six of treatment) and late (six months after treatment) grade 2–4 and moderate-severe toxicity outcomes, so-called ‘primary

models'. This was done using logistic regression with Bayesian information criterion-based stepwise forward selection, modified to allow that highly correlated predictors could retain in the model with aggregated coefficients [30]. Also, non-linear associations of continuous predictors with the outcomes were assessed. Then, all primary models were internally validated using a bootstrapping procedure and adjusted for optimism by uniform shrinkage of the model regression coefficients [32]. Subsequently, the internally validated primary models were tested and, if needed, updated at the remaining acute and late time points, and toxicity severities, using a closed testing procedure, resulting in so-called 'secondary models' (Table S13) [30,33]. By doing so, model predictors remain consistent across time points and toxicity severities. A schematic overview of primary and secondary models is provided in Fig. S1.

All primary and secondary models were then externally validated by assessing their performance on the validation cohort in terms of discrimination, quantified with the area under the receiver operating characteristic curve (AUC), and calibration, quantified with a calibration intercept and slope.

Results

The development cohort included 750 HNC patients. Patient, tumour and treatment characteristics can be found in Table 1. The prevalence of all toxicity outcomes at all time points ranged from 1 to 78% (Table S11). Thirty-six primary and 166 secondary models were developed. Table 2 shows the identified predictors per toxicity outcome. Fifteen dose predictors (dose to 14 OAR and integral dose, i.e., the planned energy deposition within the whole body, defined as the product of the mean radiation dose to the whole body and its volume) were associated with at least one toxicity. Four OAR were identified as predictors for swallowing toxicity: cricopharyngeal inlet muscle, oral cavity, pharyngeal constrictor muscles (PCM), and supraglottic larynx. Salivary toxicity was associated with integral dose and buccal mucosa, oral cavity, parotid and submandibular glands. For mucosal toxicity the oral cavity was identified as relevant OAR. Four OAR were associated with speech problems: arytenoids, glottic area, oral cavity, and supraglottic larynx. For pain related toxicities, buccal mucosa, mandible, oral cavity, and supraglottic larynx were identified as predictors. Lastly, for general complaints, integral dose and brain, brainstem, and PCM were associated. Fig. 1 schematically illustrates how the OAR of each toxicity domain anatomically relate to each other. Besides the dose predictors, baseline toxicity, treatment modality, and tumour site were important predictors for many toxicities (Table 2). The median AUC of the primary models after internal validation was 0.71 (interquartile range (IQR): 0.68–0.75) (Table S87). The median calibration intercept and slope after internal validation were −0.011 (IQR: −0.087–0.004) and 0.954 (IQR: 0.911–0.971), respectively (Tables S89 and S90). The secondary models had a median AUC of 0.72 (IQR: 0.69–0.76) and a median calibration intercept and slope of 0.000 (IQR: −0.031–0.079) and 1.005 (IQR: 0.951–1.096), respectively (Tables S87, S89 and S90). For all model coefficients and performance measures refer to Tables S15–S90.

The validation cohort included 395 HNC patients. This cohort was similar to the development cohort in terms of age, sex, tumour site, T- and N-stage, and neck irradiation, but differed in terms of treatment technique, accelerated schedules, prescribed radiation dose, and radiation dose to OAR (Table 1). Also, the prevalence of missing outcome data was higher in this cohort (Table S9). The prevalance of all toxicity outcomes in the validation cohort ranged from 0 to 70% (Table S12). External validation of all models showed a median AUC of 0.67 (IQR: 0.62–0.71) (Table S88). The median calibration intercept and slope were 0.134 (IQR: −0.144–0.449) and 0.703 (IQR: 0.509–0.939) respectively (Tables S91 and S92).

In the Supplementary Excel file we provide a tool to calculate a comprehensive individual toxicity risk (CITOR) profile for an individual patient. Fig. 2 shows the CITOR profile of an example patient: a 57 year old man with a T4N2cM0 oropharyngeal tumour, treated with accelerated radiotherapy.

Discussion

We present a comprehensive individual toxicity risk (CITOR) profile for HNC patients treated with definitive radiotherapy with or without systemic agents. The CITOR-profile encompasses NTCP models for 22 common toxicities at ten time points during and after treatment. It provides crucial insight into the relationship between irradiation of multiple OAR simultaneously and a wide range of toxicity risks. Consequently, it enables comprehensively optimised treatment through prioritised dose reduction to various OAR.

The CITOR-profile is very valuable for clinical practice. Firstly, patients can be better informed about the clinical impact of their treatment by using the NTCP models to translate the physical dose distribution into a CITOR-profile, showing the predicted toxicity risks. More importantly, the extensive insight into the dose–response relationships provided by the CITOR-profile, can be used to individualise treatment optimisation and obtain an optimal dose distribution, that simultaneously balances multiple toxicity risks and results in the lowest overall toxicity burden for that patient. Ideally, this is done by incorporating all NTCP models in the optimiser of the treatment planning system [19]. Alternatively, institutions can guide their optimisation process by determining the priority of OAR to spare, based on the expected gain in toxicity reduction of the CITOR-profile. Additionally, this approach allows for the comparison of alternative treatment plans in terms of clinical impact by comparing their predicted CITOR-profiles. This enables individualised treatment selection, including patient selection for emerging treatment techniques such as proton therapy [34,35]. Before applying the models in clinical practice, we encourage institutions to critically evaluate them. We transparently reported multiple modeling aspects (following TRIPOD [26]) to facilitate this evaluation and allow the assessment of the risk of bias according to PROBAST guidelines [24,36]. For models that showed poor performance at external validation, an additional validation and update in local institutional data if needed, is advised before clinical application.

We identified 14 OAR to be involved in one or more toxicities. The oral cavity was the predominant OAR associated with 12 toxicities over five toxicity domains. Other important OAR included the parotid glands (eight toxicities), submandibular glands (six toxicities), the buccal mucosa (five toxicities), and pharyngeal constrictor muscles (five toxicities). The extensive involvement of the oral cavity is an interesting finding since, previously, irradiation of the oral cavity has mainly been associated with oral mucositis, xerostomia and dysgeusia [37–42]. Also, the buccal mucosa has not previously been identified as a relevant OAR that should be avoided. Our results suggest that specifically reducing the dose to the oral cavity should be a top priority during treatment planning. In addition to the 14 OAR, the integral dose was found to be predictive for particular toxicities. We hypothesise that a higher integral dose results in more inflammation, causing specific symptoms, such as fatigue, and nausea and vomiting [7,12,43]. Additionally, the integral dose might be a surrogate predictor for other anatomical or functional structures that have not yet been identified as specific OAR.

A major strength of this study is that the models were developed on the largest cohort with prospectively scored toxicity reported to date. Moreover, all OAR were recontoured according to international consensus guidelines [22]. Addition-

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

Characteristics	Development cohort (n = 750)		Validation cohort (n = 395)		p-value
Center (%)					<0.001
UMCG	750	(100)	143	(36)	
Maastro	0	(0)	200	(51)	
RIF	0	(0)	52	(13)	
Mean age (sd)	63	(10.25)	64	(9.35)	0.11
Sex (%)					0.70
Male	560	(74.7)	290	(73.4)	
Female	190	(25.3)	105	(26.6)	
Tumour site (%)					0.59
Oral cavity	44	(5.9)	22	(5.6)	
Oropharynx	271	(36.1)	140	(35.4)	
Nasopharynx	30	(4)	15	(3.8)	
Hypopharynx	71	(9.5)	50	(12.7)	
Larynx	334	(44.5)	168	(42.5)	
T-stage (%)					0.87
Tis-T2	363	(48.4)	194	(49.1)	
T3-4	387	(51.6)	201	(50.9)	
N-stage (%)					0.26
N0	333	(44.4)	190	(48.1)	
N+	417	(55.6)	205	(51.9)	
Neck irradiation (%)					0.08
No	147	(19.6)	66	(16.7)	
Unilateral	18	(2.4)	18	(4.6)	
Bilateral	585	(78)	311	(78.7)	
Treatment technique (%)					<0.001
3D-CRT	86	(11.5)	6	(1.5)	
IMRT	546	(72.8)	7	(1.8)	
VMAT	118	(15.7)	382	(96.7)	
Treatment modality (%)					<0.001
Conventional RT	149	(19.9)	126	(31.9)	
Accelerated RT	294	(39.2)	110	(27.8)	
Chemoradiation	242	(32.3)	134	(33.9)	
Accelerated RT with cetuximab	65	(8.7)	25	(6.3)	
Prescribed dose (%)					<0.001
60 Gy	0	(0.0)	19	(4.8)	
64 Gy	1	(0.1)	0	(0.0)	
66 Gy	71	(9.5)	23	(5.8)	
68 Gy	0	(0.0)	80	(20.3)	
70 Gy	676	(90.1)	268	(67.8)	
72 Gy	2	(0.3)	0	(0.0)	
84 Gy	0	(0.0)	5	(1.3)	
Median mean dose to OAR in Gy (IQR)					
Arytenoids	64.8	(45.4–68.3)	63.2	(43.7–69.0)	0.71
Buccal mucosa	35.5	(10.1–48.4)	21.2	(2.3–35.3)	<0.001
Brain	1.9	(0.8–3.3)	1.0	(0.5–2.0)	<0.001
Brainstem	6.9	(1.9–13.5)	2.7	(1.1–7.8)	<0.001
Cricopharyngeal inlet	48.9	(40.7–56.7)	46.0	(36.9–52.5)	<0.001
Glottic Area	65.6	(46.2–68.7)	60.7	(40.9–68.9)	0.008
Mandible	38.5	(21.2–45.9)	27.2	(7.4–36.7)	<0.001
Oral cavity	43.9	(22.3–55.6)	32.7	(12.4–45.1)	<0.001
Parotid glands	28.0	(15.9–37.0)	21.2	(11.5–27.6)	<0.001
PCM inferior	57.6	(45.8–66.3)	54.9	(43.8–66.4)	0.12
PCM middle	55.7	(41.2–64.3)	54.9	(42.2–64.2)	0.65
PCM superior	52.3	(29.3–62.6)	42.2	(25.0–57.8)	<0.001
Submandibular glands	58.9	(44.6–64.3)	51.9	(37.5–58.9)	<0.001
Supraglottic	57.9	(46.1–66.4)	56.7	(43.0–67.4)	0.79
Median integral dose in Gy·cm^3 (IQR)	$1.6{\cdot}10^5$	($1.1{\cdot}10^5$-$2.0{\cdot}10^5$)	$1.3{\cdot}10^5$	($0.9{\cdot}10^5$-$1.6{\cdot}10^5$)	<0.001

UMCG = University Medical Center Groningen, RIF = Radiotherapeutic Institute Friesland, 3D-CRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy, VMAT = volumetric modulated arc therapy, RT = radiotherapy, OAR = organ at risk, IQR = interquartile range, PCM = pharyngeal constrictor muscle.
P-values were obtained with Chi square test for categorical variables and non-parametric test for continuous variables, except for age for which a t-test was used.

ally, a sophisticated model development and validation strategy was used that includes assessment of non-linear transformations and deals with multicollinearity, enabling the models to better describe response relationships and include multiple highly correlated OAR [30]. Furthermore, the CITOR-profile provides a multidimensional risk prediction, i.e., predicting different toxicities, with different severities and at multiple time points. Such a profile provides valuable extended information to effectively optimise treatment and avoid detrimental shifts of dose to other OAR. This is a major step forward compared to current practice where in most cases rigid dose constraints to a few OAR or single toxicity predictions are considered. Finally, all models were externally validated, thereby evaluating their generalisability. Most models had a good or fair validation performance, although this also depended on data quality and case-mix variations.

Table 2
Model predictors per toxicity outcome.

	Dose predictors													Other predictors					
	Arytenoids	Brain	Brainstem	Buccal mucosa	Crico	Glottic area	Integral [illegible]	Mandible	Oral cavity	Parotid glands	PCM sup, mid, inf	Submand. glands	Supraglottic larynx	Age	Baseline toxicity	Baseline weight	Gender	Treatment modality	Tumour site
Swallowing domain																			
Grade 2-4 dysphagia									•		•				•			•	•
Grade 3-4 dysphagia									•		•				•			•	•
Grade 2-4 aspiration					•						•		•		•				
Moderate-severe aspiration											•				•				
Salivary domain																			
Moderate-severe xerostomia				•					•	•		•			•				
Severe xerostomia				•					•	•		•			•				
Grade 2-4 xerostomia				•					•	•					•				
Moderate-severe sticky saliva										•		•			•				
Severe sticky saliva										•		•			•				
Grade 2-4 sticky saliva				•			•		•	•		•							
Moderate-severe loss of taste									•	•				•					
Grade 2-4 loss of taste									•	•		•							
Mucosal domain																			
Grade 2-4 mucositis									•										
Grade 3-4 mucositis									•									•	
Speech domain																			
Moderate-severe hoarseness	•					•													•
Moderate-severe speech problems									•				•		•				•
Pain domain																			
Moderate-severe oral pain				•					•						•				
Moderate-severe throat pain													•		•			•	•
Moderate-severe jaw pain								•							•				
General domain																			
Grade 2-4 weight loss							•				•					•	•		
Moderate-severe nausea & vomiting		•	•				•								•				
Moderate-severe fatigue		•					•								•				

Crico = cricopharyngeal inlet muscle, PCM = pharyngeal constrictor muscle, sup = superior, mid = middle, inf = inferior.

The following caveats should be considered in interpreting the models of this study. First, all patients were treated with photon-based radiotherapy. It is currently unclear to what extent these prediction models are generalisable to proton-based radiotherapy, although Blanchard et al. have shown that photon-derived prediction models appear to be valid for patients treated with proton therapy [44]. Second, not all relevant toxicities are included in this CITOR-profile. Therefore, critical OAR related to toxicities not included, e.g. hypothyroidism, cerebrovascular events, hearing loss, should not be neglected during treatment planning. Third, in future research the model development strategy can be further improved to refine the models. Possible improvements include ordinal modeling, dealing with competing risks due to death, and time-to-event analysis for late (≥two years after treatment) toxicities without recovery. In addition, considering the multicentre character of the data, a combined analysis of development and validation cohorts in an internal-external cross-validation may have been preferred [45]. However, the data from centres of the validation cohort were not of sufficient size, which is why the models were developed in one centre and validated in a pooled validation cohort instead. Finally, we mainly used the mean dose to represent the dose delivered to OAR. This reduces a three-dimensional dose distribution on a CT scan to a single parameter. The use of voxel-wise analysis or generalised uniform equivalent dose might better preserve essential characteristics of the three-dimensional dose distribution [46,47]. However, by using (transformed) mean doses, the models are easier to interpret and implement in clinical practice.

With the aim of further improving radiation treatment in clinical practice, we are currently investigating the impact of the various toxicities on quality of life. This could lead to individual quality of life optimised radiation treatment. Additionally, we will clinically validate the models by comparing the predicted and observed CITOR-profiles, while optimising our clinical treatment plans using the CITOR-profile. On the basis of the current and future research, models can be tested and adjusted continuously on newly treated patients, with the aim of improving their accuracy and performance and evolving into a rapidly learning health care system [48].

In conclusion, this is the first study providing a comprehensive individual toxicity risk profile for HNC patients treated with definitive radiotherapy. It follows the latest international guidelines for OAR definition and has improved on common problems in prediction model development and validation. Due to its novel insight into response relationships and its consequences for treatment in clinical practice, the presented CITOR-profile is the next essential step in moving towards individualised radiation treatment pursuing toxicity-free survival.

Disclaimers

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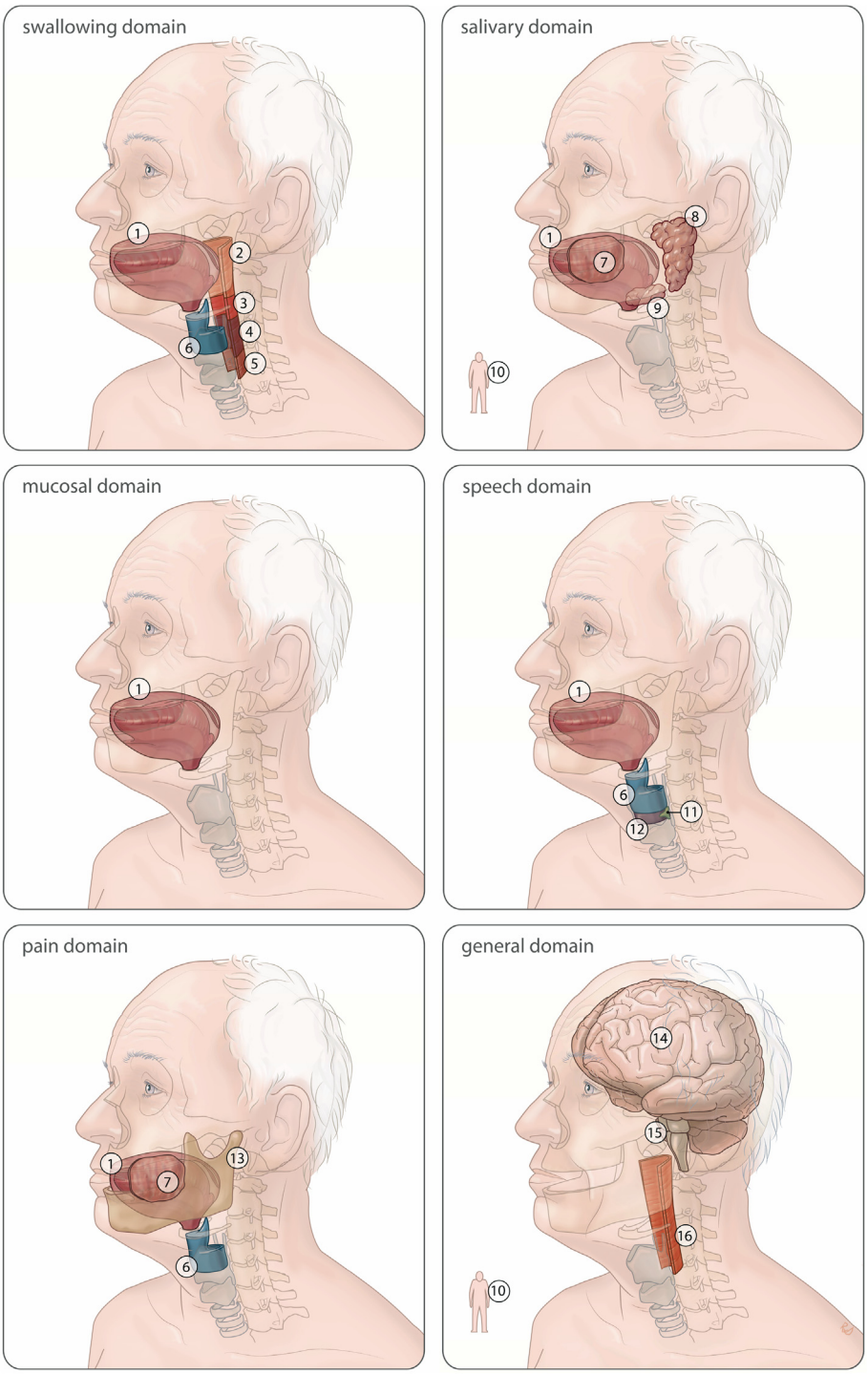

Fig. 1. Schematic overview of organs at risk identified as predictors per toxicity domain. 1: oral cavity, 2: superior pharyngeal constrictor muscle (PCM), 3: middle PCM, 4: inferior PCM, 5: cricopharyngeal inlet muscle, 6: supraglottic larynx, 7: buccal mucosa*, 8: parotid gland*, 9: submandibular gland*, 10: integral dose, 11: arytenoid*, 12: glottic area, 13: mandible, 14: brain, 15: brainstem, 16: combined superior, middle and inferior PCM. * For paired structures only one side is depicted.

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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.2021.01.024.

	Week since start of treatment						Months after end of treatment			
	3	4	5	6	7	12	6	12	18	24
Swallowing domain										
Grade 2-4 dysphagia	67%	84%	87%	91%	91%	56%	42%	37%	31%	35%
Grade 3-4 dysphagia	24%	43%	45%	56%	56%	27%	5%	7%	9%	9%
Grade 2-4 aspiration	11%	11%	17%	28%	18%	9%	10%	12%	14%	19%
Moderate-severe aspiration	23%	24%	35%	45%	45%	28%	13%	13%	16%	16%
Salivary domain										
Moderate-severe xerostomia	64%	69%	76%	76%	76%	69%	68%	59%	59%	59%
Severe xerostomia	34%	29%	40%	40%	40%	26%	25%	25%	25%	18%
Grade 2-4 xerostomia	18%	37%	52%	61%	66%	38%	15%	12%	10%	12%
Moderate-severe sticky saliva	58%	61%	66%	73%	73%	58%	48%	37%	51%	51%
Severe sticky saliva	14%	22%	27%	36%	38%	20%	18%	13%	13%	19%
Grade 2-4 sticky saliva	28%	51%	66%	75%	75%	40%	12%	12%	9%	12%
Moderate-severe loss of taste	39%	60%	70%	70%	70%	59%	28%	19%	19%	19%
Grade 2-4 loss of taste	44%	53%	82%	64%	75%	48%	23%	9%	12%	8%
Mucosal domain										
Grade 2-4 mucositis	36%	63%	80%	86%	86%	21%				
Grade 3-4 mucositis	5%	15%	33%	47%	39%	3%				
Speech domain										
Moderate-severe hoarseness	3%	8%	13%	20%	20%	9%	5%	8%	8%	15%
Moderate-severe speech problems	16%	20%	22%	29%	29%	16%	15%	20%	24%	24%
Pain domain										
Moderate-severe oral pain	67%	67%	71%	71%	69%	48%	39%	31%	31%	25%
Moderate-severe throat pain	66%	70%	70%	75%	75%	52%	22%	18%	18%	18%
Moderate-severe jaw pain	28%	28%	35%	35%	35%	26%	26%	26%	20%	20%
General domain										
Grade 2-4 weight loss	1%	3%	3%	6%	15%	25%	39%	35%	35%	20%
Moderate-severe nausea & vomiting						24%	18%	18%	40%	38%
Moderate-severe fatigue						67%	64%	64%	70%	70%

Fig. 2. Comprehensive individual toxicity risk (CITOR) profile of a 57 year old man with a T4N2cM0 oropharyngeal tumour treated with accelerated radiotherapy. For each toxicity outcome, the risk of developing the toxicity at different time points during and after treatment is predicted using the NTCP models. The color shading represents the degree of the predicted risks, with a more intens red color indicating higher predicted risks.

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