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CLINICAL INVESTIGATION

Prediction of Radiation-Induced Parotid Gland-Related Xerostomia in Patients With Head and Neck Cancer: Regeneration-Weighted Dose

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Purpose: Despite improvements to treatment, patients with head and neck cancer (HNC) still experience radiation-induced xerostomia due to salivary gland damage. The stem cells of the parotid gland (PG), concentrated in the gland's main ducts (stem cell rich [SCR] region), play a critical role in the PG's response to radiation. Treatment optimization requires a dose metric that properly accounts for the relative contributions of dose to this SCR region and the PG's remainder (non-SCR region) to the risk of xerostomia in normal tissue complication probability (NTCP) models for xerostomia.

Materials and Methods: Treatment and toxicity data of 1013 prospectively followed patients with HNC treated with definitive radiation therapy (RT) were used. The regeneration-weighted dose, enabling accounting for the hypothesized different effects of dose to the SCR and non-SCR region on the risk of xerostomia, was defined as D_{reg} PG = D_{mean} SCR region + $r \times$ D_{mean} non-SCR region, where D_{reg} is the regeneration-weighted dose, D_{mean} is the mean dose, and r is the weighting factor. Considering the different volumes of these regions, $r > 3.6$ in D_{reg} PG demonstrates an enhanced effect of the SCR region. The most predictive value of r was estimated in 102 patients of a previously published trial testing stem cell sparing RT. For each endpoint, D_{reg} PG, dose to other organs, and clinical factors were used to develop NTCP models using multivariable logistic regression analysis in 663 patients. The models were validated in 350 patients.

Results: Dose to the contralateral PG was associated with daytime, eating-related, and physician-rated grade ≥2 xerostomia. Consequently, r was estimated and found to be smaller than 3.6 for most PG function−related endpoints. Therefore, the contribution of D_{mean} SCR region to the risk of xerostomia was larger than predicted by D_{mean} PG. Other frequently selected predictors were pretreatment xerostomia and D_{mean} oral cavity. The validation showed good discrimination and calibration.

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Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

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Conclusions: Tools for clinical implementation of stem cell sparing RT were developed: regeneration-weighted dose to the parotid gland that accounted for regional differences in radiosensitivity within the gland and NTCP models that included this new dose metric and other prognostic factors.

Introduction

Survival of patients with head and neck cancer (HNC) substantially improved during the past decades.[1] About 70% of these patients receive radiation therapy (RT), often resulting in radiation-induced toxicities considerably affecting patients' quality of life.[2,3] Therefore, insight in treatment-related symptoms in long-term survivors of HNC has gained increasing attention.[4-6]

Xerostomia is one of the most frequently experienced late radiation-induced toxicities.[3,7] For example, the prevalence of moderate-to-severe patient-rated xerostomia at 12 months after treatment in a recent study including 750 patients was 37%.[8] Along with other factors, dose to the parotid glands plays a role in the risk of developing xerostomia.[8-13] Despite the population-based improvements achieved by parotid gland sparing RT,[11,14] sufficient dose reduction to the parotid glands is not always possible during individualized dose optimization, and patients still experience xerostomia.[15] Therefore, investigators have studied ways to spare the regions of the parotid glands containing the salivary stem cells during radiation treatment planning.[16-20]

Preclinical work by Lombaert et al showed the presence of parotid gland stem cells in mice salivary glands.[21] Next, van Luijk et al demonstrated in rats and humans that the regional variation in the radiation response of the parotid gland was explained by the non-uniform distribution of its stem cells, which are primarily located in the gland's main ducts.[17] Subsequently, a prospective study investigated an approach to spare these parotid gland stem cells by reducing dose to the stem cell rich (SCR) regions. These regions were geometrically defined: the center of the SCR regions was determined based on previous research[17] and subsequently enlarged with a margin of uncertainty, as described in more detail in Steenbakkers et al.[18] Steenbakkers et al showed that dose to the SCR region was the strongest dosimetric predictor for the development of patient-rated moderate-to-severe daytime xerostomia and physician-rated grade ≥2 xerostomia.[18] Furthermore, Fried et al showed that mean parotid duct dose improved the models predicting patient-rated general xerostomia.[20] This was in line with a study by Sari et al, who concluded that dose to the parotid gland stem cells is at least as predictive for patient-rated xerostomia as dose to the whole parotid glands.[19] In addition, Huang et al showed that sparing of the superficial parotid lobe, which may have lowered the dose to the parotid gland stem cells because the proposed SCR region is in the cranial-lateral region of the parotid gland, reduced the incidence of xerostomia 12 months after RT.[22]

However, the dose-effect relationship between the remainder of the parotid gland (non-SCR region) and xerostomia is yet unknown. Indeed, other mechanisms, such as fibrosis in the non-SCR region, might also contribute to degeneration of the parotid gland.[17] Furthermore, preclinical studies showed that acinar cell self-duplication may contribute to tissue homeostasis under normal conditions.[23,24] Therefore, a new dose metric, accounting for the relative contribution of dose to the SCR and non-SCR region, might improve the prediction of xerostomia.

Several studies have demonstrated that radiation dose to other organs at risk (OARs), such as the submandibular glands and the oral cavity, can also contribute to xerostomia.[8,10,19,25-27] These additional dosimetric risk factors and other clinical risk factors, such as pretreatment xerostomia, were also found in earlier published and validated normal tissue complication probability (NTCP) models for xerostomia (Table E1 of the supplementary materials). However, because the critical role of the SCR region in parotid gland damage and related xerostomia has been demonstrated,[17,18] it should be considered as an OAR in the development of new NTCP models. In addition, current NTCP models only predict general patient-rated xerostomia[28] and physician-rated xerostomia.[29] However, work by Dijkema et al indicates that more specific xerostomia endpoints, such as daytime and nighttime xerostomia, may be predicted more accurately.[30] Furthermore, these specific endpoints might provide new opportunities during treatment optimization, from which the patient will eventually benefit.

Therefore, the aim of this study was to provide models for clinical implementation of stem cell sparing RT to be able to reduce radiation-induced xerostomia related to parotid gland function. First, a new dose metric, properly accounting for the relative contribution of dose to the SCR and non-SCR region to the risk of xerostomia, was developed. Subsequently, this new parameter was included in newly developed and validated multivariable NTCP models that also properly account for other prognostic factors.

Materials and Methods

Results are reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.[31]

Study design

This is a retrospective analysis of prospectively collected data. All consecutive included patients were treated at the

University Medical Center Groningen (UMCG) in the Netherlands and participated in a prospective data registration program (SFP, ClinicalTrials.gov number NCT02435576), of whom 102 patients also participated in the earlier conducted stem cell sparing study[18] (SCS-RT study, ClinicalTrials.gov number NCT01955239). Since the SFP is part of clinical practice, the Dutch Medical Research Involving Human Subjects Act was not applicable, and the requirement of informed consent was waived by the local ethics committee.

Eligibility criteria

Eligible patients with a minimum age of 18 years were treated with curatively intended definitive RT, with or without concomitant systemic treatment, for pathologically confirmed stage I-IV HNC originating from the larynx, pharynx, or oral cavity. Exclusion criteria were neck dissection before irradiation, previous head and neck irradiation, or less than 2 years follow-up since end of treatment.

Treatment

Radiation techniques according to the standard of care at the time of treatment were used: 3-dimensional conformal RT (3D-CRT), intensity modulated RT (IMRT), volumetric modulated arc therapy, and intensity modulated proton therapy (IMPT). The radiation treatment has been previously described in detail.[32,33] In summary, patients younger than 70 years of age with early disease received accelerated fractionated RT, whereas those deemed fit enough with locally advanced disease received concurrent platinum-based chemoradiation. If chemotherapy was contraindicated, patients received accelerated RT with concurrent cetuximab. Patients ≥70 years of age were treated with conventional RT. In addition, in patients included in the intervention arm of the SCS-RT study, dose to the SCR regions was further reduced while keeping the dose to the whole parotid glands the same.[18] Target volumes and OARs were contoured according to international guidelines.[34,35] The SCR regions were delineated using in-house developed software as described by Steenbakkers et al.[18]

Endpoints

The role of the parotid gland dose was assessed for several types of xerostomia. If a relation with dose to the parotid gland was found, the endpoints were further investigated. In total, 6 prospectively scored xerostomia items were evaluated, all addressing different aspects of radiation-induced xerostomia. Five items were scored by the patient using a 4-point Likert scale (*not at all* vs *a little* vs *quite a bit* vs *very much*), including general xerostomia ("Do you have a dry mouth?"; question 41 of the European Organisation for Research and Treatment for Cancer Quality of Life Questionnaire Head and Neck module[28]), daytime xerostomia ("Have you had a dry mouth during the day?"; question 1 of the Groningen Radiotherapy-Induced Xerostomia (GRIX) questionnaire[36]), eating-related xerostomia ("Have you had difficulties with eating due to dry mouth?"; question 3 of the GRIX questionnaire[36]), activity-related xerostomia ("Have you had a dry mouth during activities?"; question 4 of the GRIX questionnaire[36]), and nighttime xerostomia ("Have you had a dry mouth during the night?"; question 7 of the GRIX questionnaire[36]). Physician-rated xerostomia, scored by the treating physician during the follow-up appointments according to Common Terminology Criteria for Adverse Events, version 4.03,[29] was also analyzed because it included evaluation of alterations in diet. Patient-rated xerostomia was dichotomized as none-to-mild (ie, *not at all* or *a little*) versus moderate-to-severe (ie, *quite a bit* or *very much*) and physician-rated xerostomia as grade 0 to 1 versus grade ≥2. All endpoints were assessed at 6, 12, and 24 months after treatment.

Candidate predictors for development of NTCP models

Candidate predictors were assessed before treatment and were derived from the prospective data registration and the radiation treatment planning system. An overview of all patient- and treatment-related candidate predictors is given in Table E2. For example, various levels of pretreatment complaints and mean dose to the SCR regions, non-SCR regions, parotid glands, submandibular glands, oral cavity, and buccal mucosa were considered as candidate predictors for all endpoints. In addition, for endpoints evaluating oral intake (ie, eating-related xerostomia and physician-rated xerostomia), doses to swallowing OARs were considered as well (ie, superior, middle, and inferior pharyngeal constrictor muscles [PCMs], cricopharyngeal inlet muscle, supraglottic larynx, and cervical esophagus). If applicable, OARs were considered ipsilateral (ie, receiving the highest radiation dose), contralateral (ie, receiving the lowest radiation dose), and combined.

New dose metric

To properly account for the different regions in the parotid gland (ie, the ipsilateral and contralateral SCR and non-SCR region) and the effect of dose to these regions on the risk of xerostomia, the regeneration-weighted dose (D_{reg}) to the parotid glands was introduced. This new dose metric was developed by estimating the weighting factor r in the D_{reg} to the parotid gland as mean dose (D_{mean}) SCR region + $r \times D_{mean}$ non-SCR region, for which the D_{reg} was the best predictor of xerostomia.

However, the high correlation between mean dose to the SCR regions and the whole parotid glands in most available clinical cohorts (example depicted in Fig. E1 of the supplementary materials) complicates elucidating the effect of the SCR region in radiation-induced xerostomia.[18,37] Therefore,

this new dose metric was developed in the 102 patients participating in the SCS-RT study.[18] The randomized controlled trial design reduced collinearity between dose to the SCR regions and the whole parotid glands by actively changing the dose to the SCR region in the intervention arm (Fig. E1).[18] Consequently, this cohort was particularly suitable to estimate the relative contributions of dose to the SCR and non-SCR regions to the risk of xerostomia.

The mean volumes of the combined parotid glands, SCR regions, and non-SCR regions in the SCS-RT study cohort were, respectively, 60.9 cm^3, 13.3 cm^3, and 47.7 cm^3 (Table 1). Therefore, in our population, for $r = 3.6$, the D_{reg} corresponds to the D_{mean}, indicating that both regions contribute according to their volumes. Although the non-SCR region contained most of the interpatient variation in parotid gland anatomy, whereas the volume of the SCR region was relatively reproducible owing to the geometric definition, the value of 3.6 resembled the average of weighting factors per patient (Fig. E2). Alternatively, $r < 3.6$ corresponds to an enhanced effect of dose to the SCR region on the risk of xerostomia.

Statistical analysis

Descriptive statistics were presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous parameters and as frequencies (percentages) for discrete parameters. All reported *P* values were 2-sided and considered statistically significant at the $\leq$.05 level.

Missing data were mainly present in side-effect scores and were handled by using multiple imputation, in which imputation models were built by using all available information, estimating the distribution of the variables that have a missing value.[38,39] All analyses were performed in each of the 10 imputation sets, and the results were pooled.[40]

The models for stem cell sparing RT were developed in several steps using data from different patient cohorts (Fig. 1). A total of 1013 patients were available for this study. The new dose metric was developed in the 102 SCS-RT study patients (Fig. 1, steps 1 and 2). To attain a trustworthy model validation, a minimum of 100 events in the validation cohort (Fig. 1, step 4) was needed.[41] Because the endpoint of daytime xerostomia at 12 months after RT was a priori considered the most relevant endpoint, the validation cohort needed at least 100 patients with this endpoint. The most recently treated patients were considered as most representative of currently treated patients, for whom the model would be used. Therefore, the data split resulted in a validation cohort consisting of 350 most recently treated patients after exclusion of the SCS-RT study patients. Lastly, the development cohort consisted of the remaining 561 patients and the 102 SCS-RT study patients (Fig. 1, step 3). An overview of cohorts and treatment periods can be found in Fig. E3.

First, the role of the parotid gland in the development of xerostomia was analyzed using multivariable logistic regression analysis with stepwise forward selection based on the Bayesian information criterion. Candidate predictors were the parotid gland and the parotid gland substructures (ie, SCR and non-SCR regions) (Fig. 1, step 1). If none of these were selected in the majority of the 10 imputation sets at any time point of a side-effect, model development was terminated. More details about this step can be found in the supplementary materials (Table E3).

Second, the weighting factor r in D_{reg} parotid gland = D_{mean} SCR region + $r \times D_{mean}$ non-SCR region was estimated (Fig. 1, step 2). Per endpoint, a likelihood landscape of models including pretreatment xerostomia and the D_{reg} to the parotid gland was created, with r varying from 0 to 15 by steps of 0.01. The optimal r value was selected based on the model performance, specifically the deviance.

Third, the role of other dosimetric and clinical risk factors was determined in the development cohort (Fig. 1, step 3). An extensive description of the method used for NTCP model development was earlier published by Van den Bosch et al.[8,39] Based on the number of patients available for model development and following Riley et al,[42] using a margin of error of 5%, mean absolute predictor error of 5%, Nagelkerke R^2 statistic of 0.15, and expected shrinkage factor of 0.9, we were able to include a maximum of 7 or 8 predictors in the models, depending on the outcome predicted. Nonlinearity of and collinearity between candidate predictors and overfitting were handled by considering transformations of candidate predictors, developing submodels for highly correlated candidate predictors, and using a bootstrapping procedure to adjust model coefficients and thus the model's performance for optimism, respectively.[39]

All time points were independently assessed, resulting in 3 NTCP models per xerostomia endpoint. Because the SCS-RT study cohort was optimal for assessing the role of the D_{reg} to the parotid gland and for estimating the weighting factor r, the results of the previous 2 steps were integrated in the model development in the larger development cohort. For time points with a role for the parotid glands (Fig. 1, step 1), D_{reg} parotid gland was forced into the model as a predictor (Fig. 1, step 3) because the predictive value of D_{reg} for optimal sparing of the parotid glands could be missed in the development cohort due to the arbitrary selection of predictors in a data set with high collinearity (Fig. E1). For time points without a role for the parotid gland (Fig. 1, step 1), D_{reg} parotid gland was not forced into the model but only considered as candidate predictor during model development (Fig. 1, step 3), because the absence of a role for the parotid gland might have been owed to the limited power of the SCS-RT study cohort.

Fourth, the developed models were externally validated in the validation cohort (Fig. 1, step 4). The model validation consisted of 2 steps. First, we assessed the performance of the model in the validation cohort. Then, we applied a closed-testing procedure to determine the extent of needed updates to the model to account for potential miscalibration of the model in the validation cohort (ie, recalibration-in-the-large, recalibration, or model revision were analyzed).[39]

Results from both steps were interpreted in combination to determine the required model update, if any. Discrimination performance of all developed models was quantified with the area under the receiver operating characteristic curve (AUC). Calibration performance was assessed graphically by a calibration plot and quantified with a calibration intercept and slope.

All analyses were performed in R, version 4.0.5.

Results

This study was composed of 1013 patients treated with definitive RT plus or minus systemic treatment (chemotherapy or cetuximab), of whom 663 patients were used for model development and 350 patients for model validation. At the time of final data retrieval (January 15, 2022), 539 patients had died. The number of missing data is given in Table E4.

Contribution of SCR region and non-SCR region to risk of xerostomia

The first 2 steps of the analyses were performed in the 102 SCS-RT study patients. Patient, tumor, and treatment characteristics are given in Table 1. The prevalence of the xerostomia endpoints is shown in Table 2 and Fig. E4.

Using multivariable logistic regression analysis in this cohort (Fig. 1, step 1), a dose-effect relationship with D_{mean} contralateral parotid gland and/or parotid gland substructures was found for daytime xerostomia, eating-related xerostomia, and physician-rated grade ≥2 xerostomia at various time points (Table E3). No further analyses were performed for general xerostomia, activity-related xerostomia, and nighttime xerostomia, because no dose-effect relationships with the parotid glands were found (Table E3).

Subsequently, the weighting factor r in the D_{reg} to the parotid gland was estimated (Fig. 1, step 2). As shown in Table 3 and Fig. 2, r was always less than 3.6, except for eating-related xerostomia at 24 months after treatment. This means that D_{mean} SCR region contributed more to the risk of developing xerostomia than D_{mean} non-SCR region. Although r did not always significantly differ from 3.6 (confidence intervals are depicted with dotted lines in Fig. 2), use of D_{reg} improved the prediction of xerostomia compared with the currently used D_{mean}. Therefore, D_{reg} parotid gland is a new dose metric to achieve optimal sparing of the parotid glands.

NTCP model development: Identification of additional predictors

Prediction models were developed (Fig. 1, step 3) using the development cohort of 663 patients in the SFP, including the 102 SCS-RT study patients. Because of the inclusion criteria of the SCS-RT study,[18] these patients differed significantly from the additional 561 patients in the SFP with regard to tumor location and staging, treatment characteristics such as treatment modality and neck irradiation, and consequently, dose to OARs (Table 1).

The regression coefficients and performance of the developed NTCP models and the exact number of events per candidate variable are shown in the supplementary materials (Tables E5-E11, Figs. E5-E7). An overview of the selected predictors is given in Table 4. In line with the literature, other OARs were also found to be associated with xerostomia. The most frequently selected additional dosimetric predictors were D_{mean} oral cavity, D_{mean} superior pharyngeal PCM, and D_{mean} submandibular glands (respectively present in 8, 4, and 3 of the 9 models) (Table 4). Furthermore, the clinical predictor pretreatment xerostomia was selected for almost all endpoints (present in 8 of the 9 models) (Table 4). After correction for optimism, the AUC of the NTCP models ranged from 0.66 to 0.77, whereas the calibration intercept and slope ranged from −0.080 to 0.022 and 0.886 to 1.004, respectively (Tables E6, E8, and E10 and Figs. E5-E7).

NTCP model validation performance

The prediction models were validated (Fig. 1, step 4) in a separate cohort of 350 patients in the SFP. Since the validation cohort was selected based on time of treatment after exclusion of SCS-RT study patients, this cohort differed from the previous 2 cohorts. It consisted of significantly more patients with worse performance status, larynx tumors, and fewer nodal metastases, resulting in fewer patients receiving systemic treatment and elective neck irradiation, compared with the development cohort (Table 1). Moreover, because of the improvement of radiation treatment planning over time and the introduction of IMPT, the dose to normal tissues was lower in the validation cohort than in the development cohort (Table 1). This lower OAR dose probably contributed to a lower prevalence of side-effects in the validation cohort (Table 2 and Fig. E4).

The validation of the NTCP models in the independent cohort showed AUCs ranging from 0.65 to 0.79, calibration intercepts from −0.892 to 0.272, and calibration slopes from 0.798 to 1.167 (Tables E6, E8, and E10). This was confirmed by the proposed model adaptations (Table E12). Only the models for physician-rated grade ≥2 xerostomia at 6 and 12 months after treatment required an adaptation (ie, recalibration-in-the-large) (Table E12). Since only an update of the intercept was required, as was expected because of the much lower prevalence of these endpoints in the validation cohort (Table 2), the overall association between the predictors and the outcome (ie, the calibration slope) was similar in the development and validation cohorts. As such, the update of the model can be considered minor. These models were updated to improve performance using the validation cohort because these patients

Table 1 Patient, tumor, and treatment characteristics per patient cohort

Characteristic	Development cohort				Validation cohort	
	SCS-RT study n = 102	SFP patients n = 561	*P* value (SCS-RT study vs. SFP patients)	Total n = 663	SFP patients n = 350	*P* value (validation vs. development)
Sex, No. (%)			.46[§]			.16[§]
Female	30 (29)	142 (25)		172 (26)	76 (22)	
Male	72 (71)	419 (75)		491 (74)	274 (78)	
Age, mean (SD), y	62 (10)	63 (10)	.41[†]	63 (10)	65 (10)	<.001[†,*]
WHO PS, No. (%)			.06[‡]			.001[‡,*]
0	78 (76)	372 (66)		450 (68)	201 (57)	
1-3	24 (24)	189 (34)		213 (32)	149 (43)	
Smoking history, No. (%)			.51[‡]			.88[‡]
Current smoker	47 (46)	282 (50)		329 (50)	171 (49)	
Not smoking	55 (54)	279 (50)		334 (50)	179 (51)	
Alcohol history, No. (%)			.95[‡]			.03[‡,*]
Current drinker	71 (70)	396 (71)		467 (70)	222 (63)	
Not drinking	31 (30)	165 (29)		196 (30)	128 (37)	
Tumor location, No. (%)			<.001[§,*]			.001[§,*]
Larynx	12 (12)	252 (45)		264 (40)	176 (50)	
Hypopharynx	10 (9)	59 (10)		69 (10)	25 (7)	
Oropharynx	70 (69)	194 (35)		264 (40)	112 (32)	
Nasopharynx	5 (5)	24 (4)		29 (4)	7 (2)	
Oral cavity	5 (5)	32 (6)		37 (6)	30 (9)	
Tumor stage, No. (%)[‖]			.57[§]			.22[§]
Tis-2	47 (46)	279 (50)		326 (49)	157 (45)	
T3-4	55 (54)	282 (50)		337 (51)	193 (55)	
Nodal stage, No. (%)[‖]			<.001[§,*]			<.001[§,*]
N0	14 (14)	252 (45)		266 (40)	195 (56)	
N1-3	88 (86)	309 (55)		397 (60)	155 (44)	
Metastatic stage, No. (%)[‖]			.34[§]			1.00[§]
M0	101 (99)	561 (100)		662 (100)	350 (100)	
M1	1 (1)	0 (0)		1 (0)	0 (100)	
Tumor stage, No. (%)[‖]			<.001[§,*]			.10[§]
I-II	8 (8)	177 (32)		185 (28)	116 (33)	
III-IV	94 (92)	384 (68)		478 (72)	234 (67)	
Treatment modality, No. (%)			<.001[§,*]			<.001[§,*]
Conventional RT	20 (19)	96 (17)		117 (18)	126 (36)	
Accelerated RT	15 (15)	231 (41)		246 (37)	121 (35)	
Chemoradiation	61 (60)	178 (32)		238 (36)	84 (24)	
Accelerated RT with cetuximab	6 (6)	56 (10)		62 (9)	19 (5)	
Fractionation schedule, No. (%)			<.001[§,*]			.09[§]
5 times a week	82 (80)	279 (50)		361 (54)	211 (60)	
6 times a week	20 (20)	282 (50)		302 (46)	139 (40)	
RT technique, No. (%)			<.001[§,*]			<.001[§,*]
3D-CRT	0 (0)	83 (15)		83 (12)	0 (0)	
IMRT/VMAT	102 (100)	478 (85)		580 (88)	322 (92)	
IMPT	0 (0)	0 (0)		0 (0)	28 (8)	
Neck irradiation, No. (%)			<.001[§,*]			.09[§]
No	0 (0)	110 (20)		110 (17)	78 (22)	
Unilateral	0 (0)	16 (3)		16 (2)	8 (2)	

(*Continued*)

Table 1 (*Continued*)

Characteristic	Development cohort				Validation cohort	
	SCS-RT study n = 102	SFP patients n = 561	*P* value (SCS-RT study vs. SFP patients)	Total n = 663	SFP patients n = 350	*P* value (validation vs. development)
Bilateral	102 (100)	435 (77)		537 (81)	264 (76)	
Volume of OARs, mean (SD), cm^3						
Parotid glands	60.9 (18.0)	54.9 (17.5)	.001†	55.9 (17.7)	61.8 (17.8)	<.001†,*
SCR regions	13.3 (1.8)	12.5 (2.2)	<.001†	12.6 (2.2)	13.7 (1.8)	<.001†,*
Non-SCR regions	47.7 (17.4)	42.4 (16.6)	.004†	43.2 (16.8)	48.1 (17.0)	<.001†,*
Submandibular glands	18.4 (4.9)	18.4 (4.8)	.96†	18.4 (4.8)	17.9 (4.5)	.16†
Dose to OARs, median (IQR), Gy						
Parotid glands	26.3 (21.3-32.2)	30.0 (18.3-39.1)	.07#	29.4 (19.8-38.1)	20.3 (12.1-27.1)	<.001#,*
Contralateral	21.8 (17.7-28.0)	25.6 (13.3-32.8)	.07#	25.2 (15.9-32.4)	17.1 (5.7-22.5)	<.001#,*
Ipsilateral	29.7 (24.0-37.2)	33.5 (20.6-45.5)	.17#	32.9 (22.0-43.8)	23.0 (13.7-31.8)	<.001#,*
SCR regions	16.9 (12.2-25.4)	25.7 (13.4-36.0)	<.001#,*	24.3 (13.2-34.5)	14.2 (7.0-21.0)	<.001#,*
Contralateral	11.7 (9.0-18.1)	21.1 (9.9-28.1)	<.001#,*	19.3 (9.2-26.9)	10.7 (3.3-16.5)	<.001#,*
Ipsilateral	20.7 (13.8-28.9)	29.0 (16.4-44.6)	.001#,*	27.7 (15.2-42.7)	17.4 (7.7-25.2)	<.001#,*
Non-SCR regions	28.8 (23.1-36.2)	31.1 (18.9-40.5)	.44#	30.7 (20.6-39.8)	22.2 (12.8-29.2)	<.001#,*
Contralateral	23.3 (19.8-30.7)	26.4 (14.3-35.2)	.48#	26.0 (16.8-34.7)	19.0 (6.4-24.6)	<.001#,*
Ipsilateral	33.2 (26.4-39.4)	35.2 (21.8-46.6)	.56#	34.6 (22.8-45.2)	24.7 (15.2-34.1)	<.001#,*
Submandibular glands	60.5 (57.7-64.0)	59.2 (44.6-64.9)	.006#,*	59.5 (49.1-64.7)	51.1 (35.1-59.4)	<.001#,*
Oral cavity	50.4 (44.8-55.9)	44.1 (23.3-55.6)	<.001#,*	45.8 (27.5-55.8)	30.9 (15.4-46.2)	<.001#*
Buccal mucosa	40.6 (35.2-48.5)	35.8 (11.0-48.6)	.001#,*	37.7 (17.1-48.6)	24.8 (7.7-38.5)	<.001#,*
PCM	52.5 (47.7-58.4)	54.4 (40.9-60.3)	.75#	53.9 (43.3-59.9)	44.1 (32.0-53.3)	<.001#,*
Superior	58.2 (51.5-62.4)	52.4 (32.1-62.9)	<.001#,*	53.9 (34.6-62.7)	38.1 (21.5-55.7)	<.001#,*
Middle	55.9 (49.6-62.3)	57.8 (42.9-65.0)	.85#	57.3 (44.5-64.8)	47.2 (32.9-59.5)	<.001#,*
Inferior	40.0 (33.3-56.3)	59.7 (48.8-66.8)	<.001#,*	57.6 (44.8-66.5)	51.2 (38.9-62.8)	<.001#,*
Supraglottic larynx	45.4 (34.7-61.4)	60.1 (48.7-66.9)	<.001#,*	58.5 (46.1-66.6)	52.3 (39.0-64.9)	<.001#,*
Cricopharyngeal inlet muscle	37.0 (30.5-42.2)	50.9 (43.8-58.3)	<.001#,*	49.4 (41.4-57.4)	37.9 (29.4-48.3)	<.001#,*
Cervical esophagus	28.1 (20.3-37.7)	44.3 (26.9-50.1)	<.001#,*	42.4 (22.4-49.4)	26.9 (9.9-37.7)	<.001#,*
Integral dose, median (IQR), Gy•cm^3	1.7•10^5 (1.4•10^5-2.0•10^5)	1.7•10^5 (1.1•10^5-2.0•10^5)	.01#,*	1.7•10^5 (1.2•10^5-2.0•10^5)	1.4•10^5 (8.6•10^4-1.8•10^5)	<.001#,*

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; Gy = gray; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; non-SCR regions = parotid glands minus stem cell rich regions; OARs = organs at risk; PCM = pharyngeal constrictor muscle; RT = radiation therapy; SCR = stem cell rich; SCS-RT study = stem cell sparing radiotherapy study (ClinicalTrials.gov number NCT01955239)[18]; SFP = prospective data registration program (ClinicalTrials.gov number NCT02435576); VMAT = volumetric modulated arc therapy; WHO PS = World Health Organization performance score.

§ χ^2 test.

† One-way analysis of variance test.

‡ Pooled χ^2 test.

Kruskal-Wallis test.

‖ Tumor staging was according to the 7th edition of the *American Joint Committee on Cancer Staging Manual.*

* Statistically significant.

were most comparable with currently treated patients (Tables E13-E14 and Fig. E8).

Discussion

The current study aimed to develop tools for stem cell sparing RT that properly account for regional variations in regenerative capacity of the parotid gland and its effect on the regional impact of dose on response. The first tool was a new dose metric, D_{reg} parotid gland, which showed for most investigated endpoints that D_{mean} SCR region contributed more to the risk of developing xerostomia related to parotid gland function than D_{mean} non-SCR region. Second, NTCP models were developed using prospectively collected data of 1013 patients with HNC, which showed a role for D_{reg}

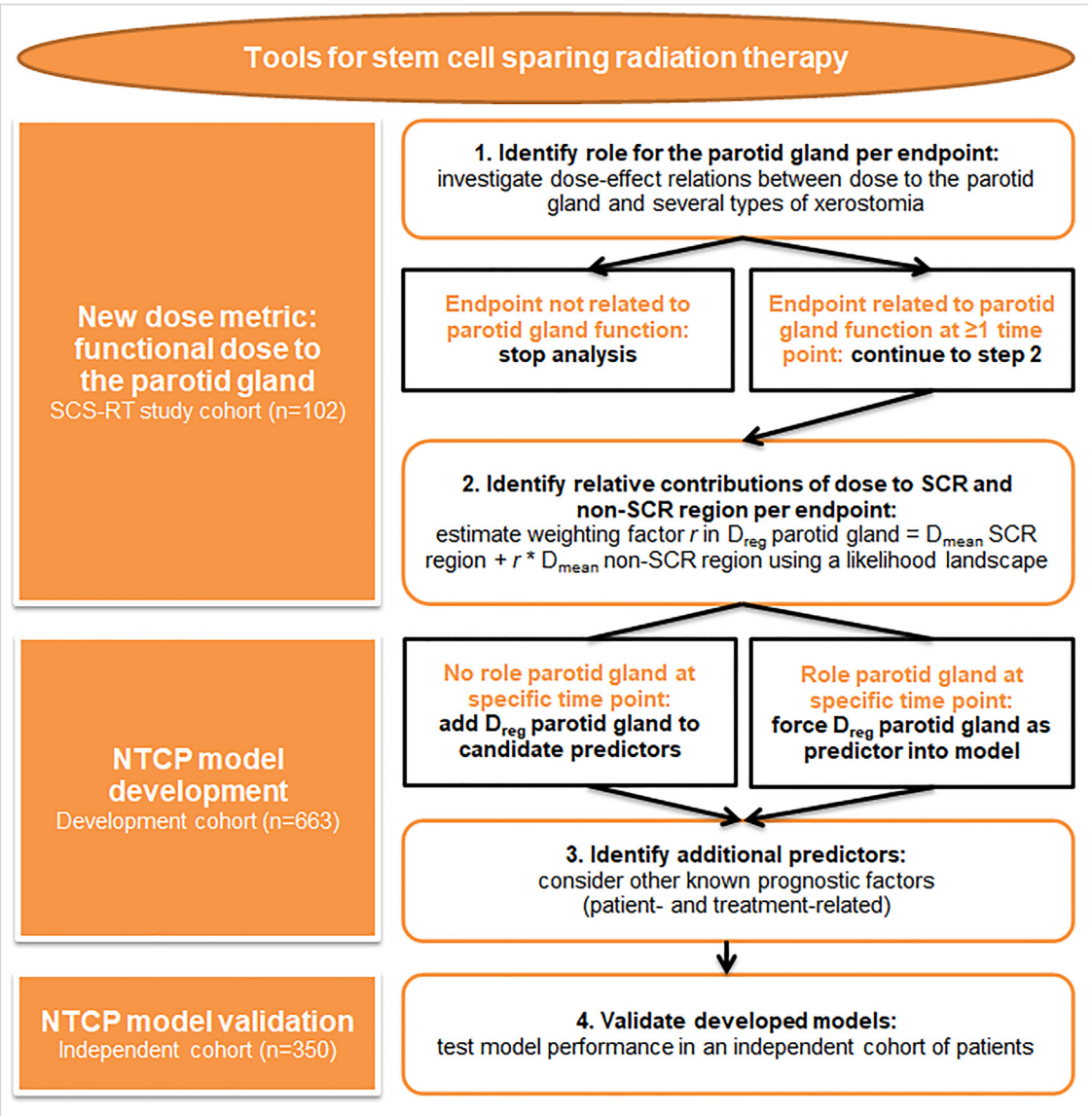

Fig. 1. Flow chart of development of stem cell–sparing radiation therapy tools. *Abbreviations:* D_{mean} = mean dose; D_{reg} = regeneration-weighted dose; non-SCR region = parotid gland minus stem cell–rich region; NTCP = normal tissue complication probability; SCR = stem cell rich; SCS-RT study = stem cell sparing radiotherapy study (ClinicalTrials.gov number NCT01955239)[18].

parotid gland, as well as additional predictors, such as pretreatment xerostomia and the mean dose to the oral cavity, the superior PCM, and the submandibular glands.

Parotid gland function-related xerostomia

The first step in developing tools for stem cell sparing RT was to investigate the association between the dose to the parotid gland and radiation-induced xerostomia. A significant dose-effect relation between D_{mean} contralateral parotid gland and patient-rated moderate-to-severe daytime and eating-related xerostomia and physician-rated grade ≥2 xerostomia was demonstrated. In contrast with other studies,[8,11–13,25,26,43,44] no role for the dose to both parotid glands in the development of patient-rated moderate-to-severe general xerostomia was found. The absence of a significant association between dose to the parotid glands and general xerostomia in the SCS-RT study cohort may be the result of a trend toward fewer patients with severe dry mouth, as observed in our clinic and confirmed in literature.[45,46] This is most likely owed to the constant improvement of radiation treatment techniques such as the introduction of parotid gland sparing RT as standard practice. This finding supports the need for more subtle measurement methods of xerostomia, such as the GRIX developed by Beetz et al,[36] the xerostomia questionnaire by Eisbruch et al,[10] or the xerostomia inventory by Thomson et al.[47] In addition, no significant relationship between dose to the parotid glands and patient-rated moderate-to-severe activity-related and nighttime xerostomia was found. This was expected and in line with

Table 2 Prevalence of adverse effects in different patient cohorts

	SCS-RT study cohort (n = 102)		Development cohort (n = 663)		Validation cohort (n = 350)	
	Prevalence, %	Events, No.	Prevalence, %	Events, No.	Prevalence, %	Events, No.
General xerostomia						
6 mo after RT	58.8	60	46.5	308	42.9	150
12 mo after RT	49.6	51	36.7	243	35.7	125
24 mo after RT	47.9	49	34.8	230	34.2	120
Daytime xerostomia						
6 mo after RT	48.0	49	39.3	260	33.3	116
12 mo after RT	44.1	45	33.4	221	30.7	107
24 mo after RT	38.8	40	31.6	209	31.4	110
Eating-related xerostomia						
6 mo after RT	38.5	39	25.6	170	20.6	72
12 mo after RT	42.7	44	26.9	178	18.7	66
24 mo after RT	30.3	31	24.8	164	19.2	67
Activity-related xerostomia						
6 mo after RT	45.3	46	37.4	248	31.7	111
12 mo after RT	47.8	49	34.8	231	30.5	107
24 mo after RT	39.2	40	32.8	217	29.6	104
Nighttime xerostomia						
6 mo after RT	56.0	57	41.7	277	38.1	133
12 mo after RT	45.3	46	37.9	252	36.0	126
24 mo after RT	44.6	45	35.2	233	32.5	114
Physician-rated grade ≥2 xerostomia						
6 mo after RT	30.6	31	33.5	222	13.2	46
12 mo after RT	24.	25	28.9	192	10.9	38
24 mo after RT	24.5	25	27.4	182	14.0	49

Abbreviation: RT = radiation therapy; SCS-RT study = stem cell sparing radiotherapy study (ClinicalTrials.gov number NCT01955239)[18].

Dijkema et al,[30] because the parotid glands produce saliva mainly during eating and drinking.[48] Therefore, no NTCP models were developed for these endpoints, because the aim of this study was not necessarily to replace existing adequate models but to provide a regeneration-weighted dose metric that would allow the implementation of stem cell sparing RT to reduce xerostomia related to parotid gland function.

Table 3 Weighting factor *r* in regeneration-weighted dose to the parotid glands*

	M06	M12	M24
Daytime xerostomia	0.70	0.04	1.23
Eating-related xerostomia	0.00	0.53	4.49
Physician-rated grade ≥2 xerostomia	1.08	0.33	0.02

Abbreviations: M06 = 6 months after treatment; M12 = 12 months after treatment; M24 = 24 months after treatment.

* Because no role for dose to the parotid glands was found for general, activity-related, and nighttime xerostomia, no new dose metric was estimated for these endpoints.

Regeneration-weighted dose to the parotid gland accounting for larger contribution of dose to the SCR region

Although previous studies have already shown that the parotid gland is not a homogeneous organ,[17,49,50] the majority of radiation treatment plans are still optimized on D_{mean} parotid glands. To try to describe the potential nonhomogeneous response of the gland to radiation, the current study introduced D_{reg} parotid gland, defined as D_{mean} SCR region + $r \times D_{mean}$ non-SCR region, in which the weighting factor r accounts for the relative contribution of the dose to the SCR and the non-SCR region to the risk of a side-effect. This dose metric was developed in a unique cohort of patients participating in a previously published trial testing

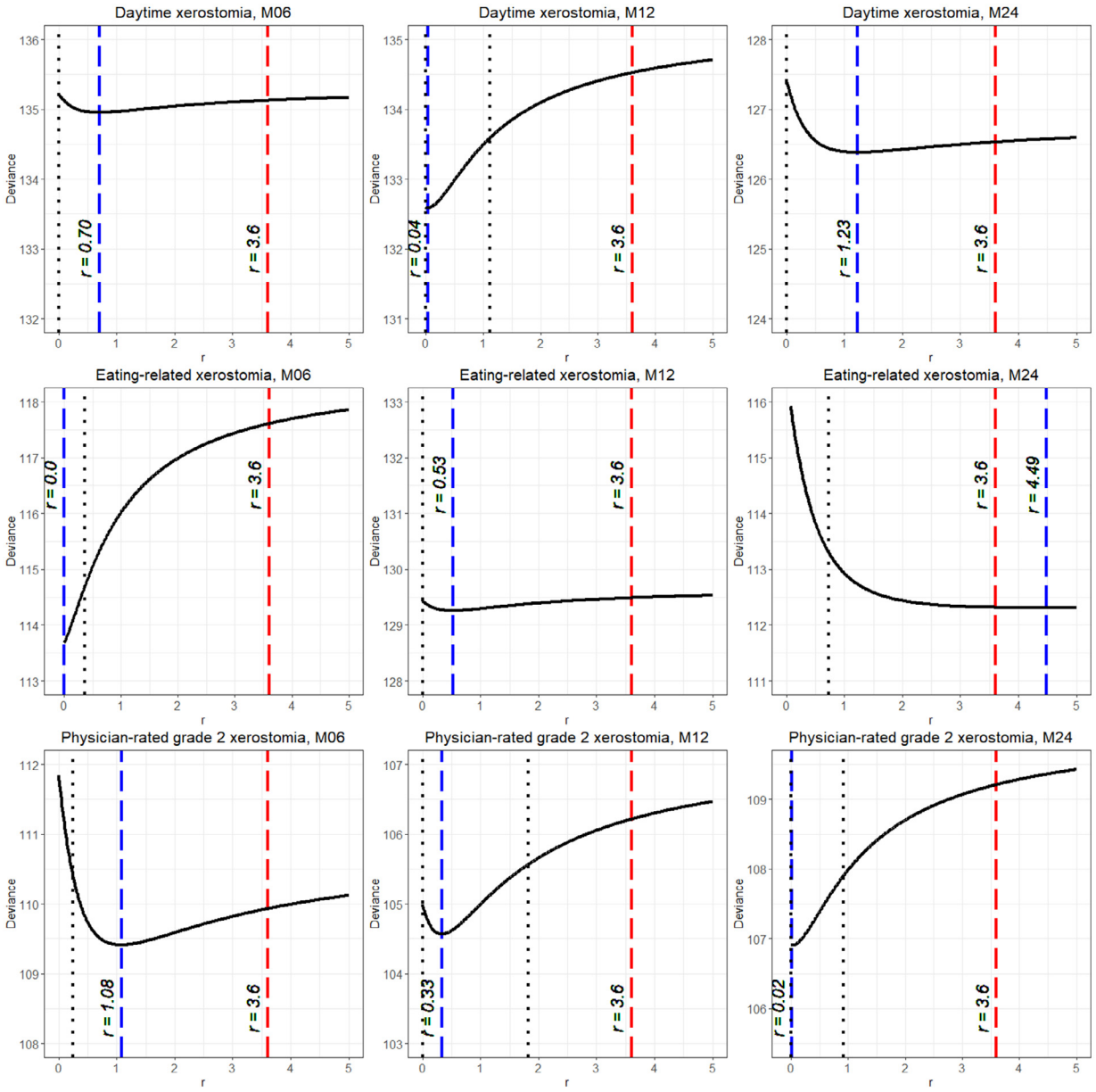

Fig. 2. Development of a new dose metric: regeneration-weighted dose to the parotid gland. The *x*-axis shows values of *r*; the *y*-axis shows deviance (lower values indicate better performance); blue dashed lines indicate the most predictive value for *r*; red dashed lines indicate the value for *r* for which D_{reg} parotid gland corresponds to D_{mean} parotid gland; black dotted lines indicate 95% confidence intervals of *r* (the border of the confidence interval is out of the graph's range if not shown). Because the optimal *r* was always less than 5, the *x*-axis was limited to *r* values between 0 and 5. Because no role for dose to the parotid glands was found for general, activity-related, and nighttime xerostomia, no new dose metric was estimated for these endpoints. *Abbreviations:* D_{mean} = mean dose; D_{reg} = regeneration-weighed dose; M06 = 6 months after treatment; M12 = 12 months after treatment; M24 = 24 months after treatment; *r* = weighting factor *r* in D_{reg}.

stem cell sparing RT.[18] This SCS-RT study cohort was a unique, suitable cohort to determine the relative contributions of the dose to the SCR and non-SCR regions. Its randomized design with specific dose reduction to the SCR region in the intervention arm resulted in the required variation in dose distribution within the parotid glands.[18,37]

Except for the endpoint eating-related xerostomia at 24 months after RT, all other endpoints for the estimations of *r* in D_{reg} parotid gland were smaller than 3.6 (ie, value for the parotid gland volume ratio). This showed that the relative contribution of dose to the SCR region was larger than indicated by D_{mean} parotid gland.

This finding was consistent with a recent publication testing superficial parotid lobe–sparing IMRT,[22] in which Huang et al showed that dose reduction to the superficial parotid lobe, in which the parotid gland's stem cells are

Table 4 Selected dosimetric and clinical predictors in NTCP models for xerostomia*

	Daytime xerostomia			Eating-related xerostomia			Physician-rated grade ≥2 xerostomia		
	M06	M12	M24	M06	M12	M24	M06	M12	M24
Dosimetric predictor									
D_{reg} contralateral parotid gland	-	+	+	+	-	+	+	+	+
D_{mean} ipsilateral parotid gland	-	-	-	-	-	+	-	-	-
D_{mean} submandibular glands	-	+	+	-	+	-	-	-	-
D_{mean} oral cavity	+	+	-	+	+	+	+	+	+
D_{mean} buccal mucosa	-	-	-	+	-	-	-	-	-
D_{mean} superior PCM	-	-	-	+	+	-	-	+	+
Clinical predictor									
Pretreatment xerostomia	+	+	+	+	+	+	+	+	-

Abbreviations: D_{mean} = mean dose; D_{reg} = regeneration-weighted dose; M06 = 6 months after treatment; M12 = 12 months after treatment; M24 = 24 months after treatment; NTCP = normal tissue complication probability; PCM = pharyngeal constrictor muscle.
* Selection of predictors per endpoint is indicated by +.

roughly located, resulted in less radiation-induced xerostomia.[22] In addition, Buettner et al showed that a relatively higher dose to the medial-caudal part of the parotid gland was preferred over a homogeneous low dose in the entire parotid gland.[50] This confirmed the larger relative contribution to radiation-induced xerostomia of the cranial part containing the major ducts[50] in which the parotid gland's stem cells are located.[17]

Additional clinical and dosimetric predictors for radiation-induced xerostomia

The current study identified pretreatment xerostomia and D_{mean} oral cavity, D_{mean} superior PCM, and D_{mean} submandibular glands as other independent predictors during model development. These results were in line with the literature. First, xerostomia experienced before RT is a well-known and recognized predictor for the presence of xerostomia after treatment.[8,10,12,18,27] Second, the dose-effect relationship of D_{mean} submandibular glands and D_{mean} oral cavity with xerostomia was found in many studies.[5,8,10,18,25,27] Third, at first glance, the selection of D_{mean} superior PCM seems to be different from the literature. However, it is a known OAR in studies predicting dysphagia.[8,33,51] This is in agreement with our study, because the superior PCM was only selected as an OAR for endpoints evaluating oral intake. To our knowledge, other studies investigating xerostomia with effects on diet did not consider doses to the swallowing structures as candidate predictors, and therefore, no direct comparisons could be made. Furthermore, in addition to a role in swallowing, it could be that the superior PCM was selected during model development as a surrogate OAR for the newly discovered tubarial salivary glands.[52]

Subsequently, performance of the developed NTCP models during external validation was comparable with the performance of other validated NTCP models using clinical and dosimetric parameters to predict xerostomia (Table E1). However, the performance of the models could not be tested in another study cohort with reduced collinearity between dose to the parotid glands and the SCR regions, because the only appropriate cohort was already used during model development. In addition, a relatively small subset of our patients was treated with 3D-CRT or IMPT. The dose distribution realized using these techniques differs from the dose distribution following the most frequently used techniques (ie, IMRT or volumetric modulated arc therapy). Even though this variability was beneficial during model development, the potentially changed biologic effect of dose during IMPT due to the linear energy transfer effects did add uncertainty. Although this potential effect could not be tested because the subgroup of patients treated with proton therapy was too small, model validation in the mixed validation cohort showed good performance. Moreover, future users are recommended to validate our developed models in their own population to assess potential need for adjustments owed to differences between the populations. However, despite the need for recalibration-in-the-large in our own external validation, the overall association between the predictors and the outcome remained similar. Therefore, treatment optimization based on D_{reg} parotid glands is likely a valid approach for stem cell sparing RT.

Lastly, although the previous SCS-RT study was negative for the primary endpoint (ie, no difference in parotid gland salivary flow between the 2 study arms was observed),[18] the current study showed new evidence for stem cell sparing RT. A possible reason for the absence of a significant difference between the 2 study arms in the SCS-RT study was the intra-arm dose variability.[18] However, the average NTCP calculated with the developed models was always lower in favor of the stem cell sparing RT arm (Table E15). Therefore, stem cell sparing RT was actually beneficial during individualized treatment dose optimization.

Possible limitations

The current study had some limitations. First, because the parotid gland stem cells are not visible on computed tomography scans, the SCR regions were geometrically defined based on previous research.[17,18] Although this method inevitably introduces some uncertainty, all parotid gland subvolumes associated with parotid gland function identified in other studies[50,53-56] contained our SCR region. Second, outcome data were missing in about 22%, 27%, and 37% of the study sample at 6, 12, and 24 months after RT, respectively. The main reason for missing data was loss to follow-up (eg, tumor recurrence or patient's death), and only a small portion of missing data was due to noncompliance.[18] Moreover, our rates of missingness were low compared with other studies.[8,13,43] Third, results of the multiple imputation techniques used to handle missing data may be associated with uncertainties, especially for endpoints at 24 months after treatment with substantial amounts of missing data. However, because complete case analysis reduces precision and can introduce bias,[57-59] we preferred multiple imputation techniques over complete case analysis to account for missing data. Fourth, the number of SCS-RT study patients used for the development of the new dose metric was limited (n = 102), resulting in less power and corresponding to slightly poorer events per candidate variable (Table E11) for some endpoints, such as eating-related xerostomia at 24 months after RT. The likelihood plots and 95% confidence intervals shown in Fig. 2 illustrate the level of uncertainty in determining the value of *r*. Despite this fact, external validation showed that these data were sufficient to result in reliable estimations of the combined contributions of both parotid gland substructures. However, to obtain values of *r* significantly differing from 3.6 while testing the hypothesized different effects of SCR and non-SCR region dose on the risk of xerostomia, re-estimation of the weighting factor *r* should be performed in a larger cohort of patients with HNC treated with stem cell sparing RT. Fifth, only the mean doses to the OARs were explored during the estimations of D_{reg} parotid gland and the NTCP model development. Unfortunately, it was not possible to test more dose-volume histogram parameters due to the available power. Sixth, the current study was a single-center study. Although the data of the validation cohort were not used during model development, it should be noted that the patients were still from the same institute.

Conclusion

The current study showed that the relative contribution of the dose to the SCR region to the risk of radiation-induced, parotid function–specific xerostomia was larger than the relative contribution of the dose to the non-SCR region for most endpoints. To account for these different contributions of substructures within the parotid gland, we introduced a new dose metric, the regeneration-weighted dose to the parotid glands, and used it to develop multivariable NTCP models for endpoints in which the parotid gland was found to play a role. This new dose metric, as well as these NTCP models, can therefore be used during the clinical implementation of stem cell sparing RT strategies.

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