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Development of Normal Tissue Complication Probability Model for Trismus in Head and Neck Cancer Patients Treated With Radiotherapy: The Role of Dosimetric and Clinical Factors

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Abstract. *Background/Aim: The aim of this study was to develop a normal tissue complication probability (NTCP) model for trismus in head and neck cancer (HNC) patients treated with radiotherapy (RT). Patients and Methods: Prospective measurements of maximum inter-incisal opening (MIO) were performed at baseline and 6 months after definitive RT in 132 HNC patients. The primary endpoint of this study was defined when a patient fulfilled both of the following criteria: 1) MIO at 6 months after RT ≤35 mm and 2) MIO at 6 months after RT ≤80% of baseline MIO. Eleven clinical factors and a wide range of dosimetric factors (mean dose, maximum dose, V5, V10, V20, and V40) in twelve organs at risk (OARs) were chosen as candidate prognostic variables. Results: Thirty out of 132 patients (23%) developed the primary endpoint. Multivariate logistic regression analysis revealed that the mean dose to the contralateral mandible joint (p=0.001) and baseline MIO (p=0.027) were independent prognostic factors. Conclusion: A multivariable NTCP model for trismus in HNC patients treated with RT was established including the mean dose to contralateral mandible joint and baseline MIO.*

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Trismus after radical radiotherapy has a major impact on quality of life (QoL) of head and neck cancer (HNC) patients (1-4). Previous studies have shown that rehabilitation of radiation-induced trismus is difficult to treat (5-8). Trismus is considered to result from slowly progressive fibrosis of the mandible joints and muscles involved in mandibular movements (9-11). Some data exist on the relationship between dosimetric factors of organs at risk (OARs) and trismus in univariate analysis and multivariate analysis (12-19). However, limited data exist on the relation among dosimetric factors of OARs, clinical factors, and trismus in multivariate analysis (20). Therefore, it remains unclear which risk OARs, dose-volume parameters and patient factors contribute most to the development of trismus. Therefore, identification of the most important prognostic factors and establishment of a multivariable prediction model for trismus is of major importance. Therefore, the aim of this prospective study was to develop a multivariable normal tissue complication probability (NTCP) model for trismus in HNC patients treated with RT using dosimetric and clinical factors by multivariate logistic regression analysis.

Patients and Methods

Patients and eligibility criteria. Between July 2007 and August 2010, 132 HNC patients who received definitive RT with or without systemic treatment at the department of Radiation Oncology of the UMCG were included in this retrospective analysis of prospectively collected data. All patients were subjected to the standardised follow-up program (SFP), as previously described (21), including a prospective evaluation of the maximum inter-incisal opening (MIO) routinely before and 6 months after curative (chemo-) radiotherapy (CH)RT. To be included in the analysis, patients had to fulfill the

following eligibility criteria: 1) HNC originating in the oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx; 2) treated with definitive RT either alone or in combination with chemotherapy or cetuximab; 3) no previous surgery, RT and/or chemotherapy; 4) no previous malignancies; 5) no distant metastases; 6) planning-computed tomography (CT) and three-dimensional dose distributions available prior to and 6 months after completion of (CH)RT; 7) no efforts of reducing dose in potential organs at risks (OARs) for trismus; 8) alive with no recurrences 6 months after RT, and: 9) no rehabilitation or medication for trismus. The study population used for this analysis was composed of 132 patients who fulfilled all these eligibility criteria. The majority of the patients were male (77%) and the mean age of the study population was 62 years, ranging from 33 to 89 years. The number of the patients treated with concurrent systemic therapy was 40 (30%). The demographic and tumor characteristics of this study population are listed in Table I.

Table I. *Patients characteristics and treatment parameters.*

Age	
Median (years)	62
Range	33-89
Gender	
Male	102
Female	30
Site	
Oral cavity	4
Nasopharynx	2
Oropharynx	43
Hypopharynx	15
Larynx	68
Tumor classification	
T1	19
T2	53
T3	27
T4	33
Node classification	
N0	62
N1	15
N2a	3
N2b	11
N2c	39
N3	2
Stage	
I	14
II	45
III	14
IV	59
Histology	
Squamous cell carcinoma	130
Undifferentiated large cell carcinoma	2
Baseline maximum inter-incisal opening	
Median (mm)	42
Range	19-70
Fractionation	
Conventional	37
Accelerated	95
Bilateral neck irradiation	
Yes	99
No	33
Chemotherapy or Cetuximab	
Yes	40
No	92

Endpoints. MIO, was assessed using a commercially available device named Terabyte® (Atos Medical, Hörby, Sweden). In patients with an edentulous maxilla and not wearing dentures, the distance between the incisal edge of the alveolar ridge in the mandibular central incisor of the right (location 41) and that in the maxillary central incisor of the right (location 11) can be measured. In edentulous patients wearing dentures, the distance between the upper and lower dentures (location 41 and 11) can be measured.

To evaluate trismus due to RT, MIO was measured at baseline and at 6 months after RT. The 6 months interval was chosen because radiation-induced trismus usually becomes apparent between 3 and 6 months after completion of RT (22).

Trismus, the primary endpoint of this study, was defined when a patient fulfilled both following criteria:

1) MIO at six months after RT ≤35 mm,
2) MIO at six months after RT ≤80% of baseline MIO.

The first criterion was chosen because it demonstrated the most significant cut-off point of trismus in a previous study and is considered clinically relevant (23). The second criterion was chosen because the mean MIO at 6 months after RT was 80% of that of baseline by the report of Wang *et al*. (24). In the first diagnosis, some patient's MIO was less than or equal to 35 mm. Therefore, the second criterion was needed based on the reference.

Treatment. RT was delivered with linear accelerators (LINIAC) using megavoltage equipment. In all patients, a planning CT scan was made in supine position. All patients were treated with three dimensional conformal RT (3D-CRT) or intensity modulated radiation therapy (IMRT). Patient position was fixed with a five-point individual thermoplastic mask (Posicast® thermoplastics, CIVICO, Orange, IA, USA) in combination with a standard head support (Posifix® supine headrest, CIVICO). Position verification was carried out by using a shrinking action level correction protocol (SAL-protocol), using an electronic portal imaging device (EPID). Patients with early glottic cancer were treated with a fractionation dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were only irradiated at the primary site. The 26 laryngeal cancer patients received local therapy. Their data are an important part of this study as a control, although their OARs for trismus did not receive a significant dose. Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary RT of the more advanced cases, which were considered not eligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were generally treated with 6 fractions per week with a second fraction on Friday afternoon with minimum interval of 6 h, up to a total dose of 70 Gy in 6 weeks. Most of the patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumor and swelling lymph nodes to a total dose of 70 Gy.

Contouring of organs at risk. OARs potentially related to trismus were delineated according to an institutional atlas and according to the report by Teguh *et al*. (12) including the ipsilateral and contralateral medial pterygoid muscles, lateral pterygoid muscles, masseter muscles, mandible joints, mandible joints + 5 mm, and temporal muscles. OARs were delineated by radiation oncologists (M. M and HP. B). The dose-volume parameters (mean dose, maximum dose, V5, V10, V20, and V40) in each OARs were extracted.

Statistics. Pearson correlation matrixes were produced twice (Table II and Figure 1) in order to check for high correlation between potential prognostic determinants. In case of high Pearson correlation coefficients, these variables were reduced to avoid the problem of multicollinearity, which may negatively affect the generalizability of the model. Table II was used to decide the representative dose-volume parameter of each OARs. Figure 1 was used to decide the clinical factors and the dosimetric factors for univariate regression analysis.

Next, the variables after the reference of Pearson correlation matrixes (Table II and Figure 1) initially included in the univariate logistic regression model are shown in Table III. Then, a multivariate logistic regression analysis was carried out including only variables that were significant in the univariate logistic regression model. For each patient, predictive values (*i.e*., NTCP values) were calculated for each set of prognostic variables based on the regression coefficients according to the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{ where}$$

$$S = \beta_0 + \sum_{i=1}^{n} \beta i \cdot Xi$$

Results

Prevalence of trismus. At 6 months after completion of treatment, 30 out of 132 patients (23%) showed trismus six months after RT.

Variable selection procedure and NTCP models for trismus. We produced the first Pearson correlation matrix to identify the dose-volume parameters of all OARs that were strongly (Pearson correlation coefficient ≥0.8) or moderately (Pearson correlation coefficient ≥0.7) correlated (Table II). Strong or moderate correlation was observed among many dose-volume parameters within each OAR. Therefore, we decided to make the mean dose of each OARs represent the dose-volume parameters of each OARs, while the V5, V10, V20, V40 and maximum dose of each OARs were excluded from further analyses. The mean dose, in general, showed good correlations with other dose-volume parameters. We decided to not enter the mean dose to temporal muscles in the second Pearson correlation matrix, because the average of the mean doses to the ipsilateral and contralateral temporal muscles was relatively low, *i.e*., only 4.4 Gy and 3.6 Gy, respectively, and not expected to be important.

Next, the variables (which were reduced by the above procedure) with the second Pearson correlation matrix are shown in Figure 1. We selected the variables that showed less than four very strong correlations (Pearson correlation coefficient ≥0.85) for the univariate regression analysis. Eventually, clinical factors and three dosimetric factors, including the mean doses to contralateral mandible joint, contralateral masseter muscle and the ipsilateral medial pterygoid muscle were selected for entering the univariate regression analysis.

In the univariate logistic regression analysis (Table III), all three dosimetric factors showed a significant association with trismus. In addition, conventional RT [*versus* (*vs*.) accelerated RT], oral cavity, nasopharyngeal, oropharyngeal, or hypopharyngeal cancer (*vs*. laryngeal cancer), N2b-3 (*vs*. N0-2a), female (*vs*. male), Stage III-IV (*vs*. Stage I-II), and systemic therapy + RT (*vs*. RT alone) and baseline MIO were also significant factors associated with trismus in the univariate analysis.

A multivariate logistic regression analysis was carried out including only the significant variables shown above in the univariate logistic regression analysis. The multivariate regression analysis eventually revealed two independent prognostic factors, including the mean dose to the contralateral mandible joint and baseline MIO. The average Dmean to the contralateral mandible joint in patients with trismus was 18 Gy [95% confidence interval (CI)=12.4-23.6 Gy], which was significantly higher than that observed among those without trismus, which was 7.7 Gy (95%CI=5.8-9.7 Gy) (*t*-test: p=0.001). The average baseline MIO among patients with trismus was 38.3 mm (95% CI=35.4-41.3 mm), which was significantly lower compared to that observed among those without trismus, which was 43.2 mm (95%CI=41.4-44.9 mm) (*t*-test: p=0.008). The distribution of all 132 mean doses to the contralateral mandible joint and baseline MIO are shown in Table IV. The NTCP-value for each variable is shown in Table V. The bar graph of the NTCP model based on the two variables and the quick reference are shown in Figure 2 and Figure 3, respectively. The goodness of fit of this model was confirmed in Hosmer and Lemeshow test (p=0.182). The calibration of this model is shown in Figure 4 and confirmed the goodness of fit of this model. The NTCP-value for each individual patient can be calculated by the following regression formula:

$\text{NTCP} = (1+e^{-s})^{-1}$, where
S=0.494+[Mean dose to contralateral mandible joint (Gy) ×0.061]+[Baseline MIO (mm) × (–0.06)]

Discussion

The innovation and intensification of RT techniques and schedules together with the addition of systemic treatment has led to improved prognosis of HNC (25-30). Consequently, the prevalence of patients suffering from late toxicity is rising

Table II. *The first Pearson correlation matrix of the dosimetric factors (mean dose, maximum dose, V5, V10, V20 and V40) of the twelve organs at risk (OARs). Strong (≥0.8) and moderate (≥0.7) correlations are shown in bold and italics, respectively. The mean dose in each OARs was chosen for the representative of each OARs, while the maximum dose, V5, V10, V20 and V40 of each OARs were excluded from further analyses.*

Ipsilateral mandible joint	Ipsilateral mandible joint					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.957**	*0.762*	**0.832**	**0.912**	**0.808**
Maximum dose	**0.957**	1	**0.868**	**0.911**	**0.898**	0.671
V5	*0.762*	**0.868**	1	**0.919**	*0.713*	0.341
V10	**0.832**	**0.911**	**0.919**	1	**0.827**	0.406
V20	**0.912**	**0.898**	*0.713*	**0.827**	1	0.597
V40	**0.808**	0.671	0.341	0.406	0.597	1
Contralateral mandible joint	Contralateral mandible joint					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.968**	*0.755*	**0.851**	**0.906**	*0.757*
Maximum dose	**0.968**	1	*0.761*	**0.848**	**0.859**	0.677
V5	*0.755*	*0.761*	1	**0.843**	0.597	0.295
V10	**0.851**	**0.848**	**0.843**	1	*0.767*	0.380
V20	**0.906**	**0.859**	0.597	*0.767*	1	0.623
V40	*0.757*	0.677	0.295	0.380	0.623	1
Ipsilateral mandible joint + 5 mm	Ipsilateral mandible joint + 5 mm					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.911**	**0.804**	**0.872**	**0.947**	**0.860**
Maximum dose	**0.911**	1	**0.938**	**0.938**	**0.886**	0.635
V5	**0.804**	**0.938**	1	**0.948**	*0.790*	0.439
V10	**0.872**	**0.938**	**0.948**	1	**0.897**	0.524
V20	**0.947**	**0.886**	*0.790*	**0.897**	1	*0.726*
V40	**0.860**	0.635	0.439	0.524	*0.726*	1
Contralateral mandible joint + 5 mm	Contralateral mandible joint + 5 mm					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.932**	**0.806**	**0.903**	**0.939**	*0.788*
Maximum dose	**0.932**	1	**0.867**	**0.919**	**0.859**	0.602
V5	**0.806**	**0.867**	1	**0.885**	0.661	0.374
V10	**0.903**	**0.919**	**0.885**	1	**0.836**	0.495
V20	**0.939**	**0.859**	0.661	**0.836**	1	*0.727*
V40	*0.788*	0.602	0.374	0.495	*0.727*	1
Ipsilateral temporal muscle	Ipsilateral temporal muscle					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	*0.758*	**0.954**	**0.980**	**0.980**	**0.925**
Maximum dose	*0.758*	1	*0.784*	*0.716*	0.668	0.567
V5	**0.954**	*0.784*	1	**0.975**	**0.924**	*0.789*
V10	**0.980**	*0.716*	**0.975**	1	**0.979**	**0.875**
V20	**0.980**	0.668	**0.924**	**0.979**	1	**0.938**
V40	**0.925**	0.567	*0.789*	**0.875**	**0.938**	1

Table II. *Continued*

Table II. *Continued*

Contralateral temporal muscle	Contralateral temporal muscle					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	*0.788*	**0.961**	**0.969**	**0.957**	*0.773*
Maximum dose	*0.788*	1	*0.796*	*0.701*	0.632	0.533
V5	**0.961**	*0.796*	1	**0.954**	**0.887**	0.639
V10	**0.969**	*0.701*	**0.954**	1	**0.967**	0.669
V20	**0.957**	0.632	**0.887**	**0.967**	1	*0.759*
V40	*0.773*	0.533	0.639	0.669	*0.759*	1
Ipsilateral masseter muscle	**Ipsilateral masseter muscle**					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.852**	**0.874**	**0.912**	**0.956**	**0.942**
Maximum dose	**0.852**	1	**0.923**	**0.893**	**0.870**	*0.704*
V5	**0.874**	**0.923**	1	**0.984**	**0.931**	0.688
V10	**0.912**	**0.893**	**0.984**	1	**0.970**	*0.748*
V20	**0.956**	**0.870**	**0.931**	**0.970**	1	**0.837**
V40	**0.942**	*0.704*	0.688	*0.748*	**0.837**	1
Contralateral masseter muscle	**Contralateral masseter muscle**					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.862**	**0.888**	**0.936**	**0.963**	**0.843**
Maximum dose	**0.862**	1	**0.855**	**0.845**	**0.820**	0.649
V5	**0.888**	**0.855**	1	**0.958**	**0.877**	0.555
V10	**0.936**	**0.845**	**0.958**	1	**0.953**	0.621
V20	**0.963**	**0.820**	**0.877**	**0.953**	1	*0.717*
V40	**0.843**	0.649	0.555	0.621	*0.717*	1
Ipsilateral medial pterygoid muscle	**Ipsilateral medial pterygoid muscle**					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.891**	**0.905**	**0.935**	**0.955**	**0.979**
Maximum dose	**0.891**	1	**0.956**	**0.938**	**0.916**	**0.857**
V5	**0.905**	**0.956**	1	**0.993**	**0.975**	**0.889**
V10	**0.935**	**0.938**	**0.993**	1	**0.994**	**0.924**
V20	**0.955**	**0.916**	**0.975**	**0.994**	1	**0.949**
V40	**0.979**	**0.857**	**0.889**	**0.924**	**0.949**	1
Contralateral medial pterygoid muscle	**Contralateral medial pterygoid muscle**					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.887**	**0.849**	**0.917**	**0.962**	**0.969**
Maximum dose	**0.887**	1	**0.896**	**0.906**	**0.894**	**0.821**
V5	**0.849**	**0.896**	1	**0.955**	**0.874**	*0.769*
V10	**0.917**	**0.906**	**0.955**	1	**0.951**	**0.857**
V20	**0.962**	**0.894**	**0.874**	**0.951**	1	**0.941**
V40	**0.969**	**0.821**	*0.769*	**0.857**	**0.941**	1

Table II. *Continued*

Table II. *Continued*

Ipsilateral lateral pterygoid muscle	Ipsilateral lateral pterygoid muscle					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.901**	**0.870**	**0.923**	**0.956**	**0.964**
Maximum dose	**0.901**	1	**0.953**	**0.931**	**0.901**	**0.811**
V5	**0.870**	**0.953**	1	**0.965**	**0.914**	*0.741*
V10	**0.923**	**0.931**	**0.965**	1	**0.978**	**0.820**
V20	**0.956**	**0.901**	**0.914**	**0.978**	1	**0.888**
V40	**0.964**	**0.811**	*0.741*	**0.820**	**0.888**	1
Contralateral lateral pterygoid muscle	Contralateral lateral pterygoid muscle					
	Mean dose	Maximum dose	V5	V10	V20	V40
Mean dose	1	**0.915**	**0.810**	**0.896**	**0.948**	**0.906**
Maximum dose	**0.915**	1	**0.901**	**0.929**	**0.897**	*0.726*
V5	**0.810**	**0.901**	1	**0.925**	**0.819**	0.547
V10	**0.896**	**0.929**	**0.925**	1	**0.945**	0.658
V20	**0.948**	**0.897**	**0.819**	**0.945**	1	*0.789*
V40	**0.906**	*0.726*	0.547	0.658	*0.789*	1

and becomes increasingly relevant. Xerostomia and dysphagia have been considered as the representative toxicities affecting QoL (31-33). However, recently it has been shown that trismus may affect QoL in HNC patients as well (1-4). Morimoto *et al*. recorded that the prevalence of trismus after RT was 13% in Japanese HNC patients. The prevalence ranges from 5% to 50% (34-43). In the current study, the prevalence was within this range.

Fibrosis of the mandible joints and/or muscles involved in mouth opening is considered as the main cause of radiation-induced trismus. The mandible joint is covered with a capsule and divided into the upper and lower joint cavity by the articular disk. The articular disk consists of fibrocartilage. While opening the mouth, depression (hinge motion in lower joint cavity) and protrusion (sliding motion in upper joint cavity) in the mandible joint take place simultaneously (44). Movement of the mandible joint is extremely sensitive to relative minor changes of the anatomy and therefore this complicated movement could be disturbed by fibrosis of the irradiated mandible joint. This hypothesis is further confirmed by the findings of magnetic resonance imaging (MRI) in patients with trismus, which demonstrated muscle fibrosis, mandible joint, mandibular condyle sclerosis, mandibular ramus signal change, and joint capsular thickening (45). Fibroblasts, which may normally serve as the primary collagen-producing cells, are responsible for excess extracellular matrix collagen production, which may eventually lead to loss of smooth movement of the mandible joint. In chronic inflammation by irradiation, tumor necrosis factor alpha (TNFα) expression has been shown to be involved in the activation of macrophages in injured tissue, which leads to the release of downstream fibrogenic cytokines. These cytokines include fibroblast growth factor 2 (FGF2) and transforming growth factor beta 1 (TGFβ1). FGF2 is chemotactic and mitotic for fibroblasts, whereas TGFβ1 stimulates fibroblast proliferation and premature end-differentiation (9).

There are some studies on the relationship between trismus and dosimetric factors of OARs. Teguh *et al*. showed a significant correlation between the mean dose to the masseter muscles and the pterygoid muscles with trismus (12). Goldstein *et al*. found a linear relationship between dose to mandible joint and pterygoid muscle and MIO. In that study, functional impairment of the mandible joint already appeared at a relatively low dose level (from 14.9 Gy) (13). These investigators reported that in the univariate analysis the dose to pterygoid muscle, masseter muscle or mandibular joint was significantly associated with trismus.

The five reports demonstrated a significant dose-effect relationship between ipsilateral masseter or pterygoid muscle and trismus in the multivariate analysis (14-18). The three reports demonstrated that the clinical factors; tumor location, gender, baseline MIO, baseline age, dentition, free soft tissue transfer after surgery, reirradiation, chemotherapy, natural logarithm of time post-RT, and overall treatment time of RT correlated with trismus in multivariate analysis (43, 46, 47).

Using dosimetric and clinical factors, Kraaijenga *et al*. recently reported that the NTCP model was established by the mean dose to ipsilateral masseter muscle, the mean dose

	Age	Sex	Lo	T	N	Stage	His	Base	Accel	Bil	Sys	MDIMJ	MDCMJ	MDIMJ5	MDCMJ5	MDIMM	MDCMM	MDILPM	MDCLPM	MDIMPM	MDCMPM
Age	1	-0.068	0.158	-0.051	-0.319	-0.268	-0.127	0.209	0.217	-0.307	-0.085	-0.29	-0.186	-0.287	-0.25	-0.314	-0.283	-0.268	-0.241	-0.258	-0.286
Sex	-0.068	1	-0.293	0.134	0.23	0.168	0.078	-0.335	-0.012	0.131	0.161	0.2	0.147	0.197	0.182	0.3	0.185	0.313	0.226	0.307	0.194
Lo	0.158	-0.293	1	-0.313	-0.429	-0.403	-0.109	0.102	0.448	-0.339	-0.375	-0.615	-0.497	-0.626	-0.588	-0.769	-0.595	-0.74	-0.649	-0.8	-0.617
T	-0.051	0.134	-0.313	1	0.57	0.774	0.054	-0.153	-0.469	0.55	0.497	0.411	0.331	0.416	0.413	0.564	0.616	0.469	0.475	0.494	0.59
N	-0.319	0.23	-0.429	0.57	1	0.841	0.194	-0.185	-0.534	0.503	0.47	0.568	0.542	0.581	0.633	0.662	0.716	0.637	0.662	0.606	0.701
Stage	-0.268	0.168	-0.403	0.774	0.841	1	0.125	-0.157	-0.522	0.671	0.502	0.532	0.466	0.547	0.584	0.68	0.763	0.61	0.618	0.643	0.756
His	-0.127	0.078	-0.109	0.054	0.194	0.125	1	-0.001	-0.199	0.069	0.128	0.352	0.343	0.354	0.358	0.227	0.247	0.263	0.296	0.158	0.201
Base	0.209	-0.335	0.102	-0.153	-0.185	-0.157	-0.001	1	0.123	-0.09	-0.153	-0.195	-0.132	-0.181	-0.151	-0.225	-0.211	-0.208	-0.173	-0.117	-0.17
Accel	0.217	-0.012	0.448	-0.469	-0.534	-0.522	-0.199	0.123	1	-0.306	-0.59	-0.557	-0.548	-0.574	-0.557	-0.534	-0.555	-0.577	-0.606	-0.489	-0.537
Bil	-0.307	0.131	-0.339	0.55	0.503	0.671	0.069	-0.09	-0.306	1	0.341	0.402	0.291	0.415	0.44	0.633	0.701	0.481	0.472	0.673	0.743
Sys	-0.085	0.161	-0.375	0.497	0.47	0.502	0.128	-0.153	-0.59	0.341	1	0.483	0.393	0.492	0.444	0.503	0.492	0.535	0.509	0.47	0.502
MDIMJ	-0.29	0.2	-0.615	0.411	0.568	0.532	0.352	-0.195	-0.557	0.402	0.483	1	0.777	0.997	0.886	0.83	0.73	0.92	0.868	0.711	0.714
MDCMJ	-0.186	0.147	-0.497	0.331	0.542	0.466	0.343	-0.132	-0.548	0.291	0.393	0.777	1	0.784	0.885	0.626	0.68	0.732	0.836	0.557	0.646
MDIMJ5	-0.287	0.197	-0.626	0.416	0.581	0.547	0.354	-0.181	-0.574	0.415	0.492	0.997	0.784	1	0.895	0.836	0.745	0.927	0.877	0.726	0.73
MDCMJ5	-0.25	0.182	-0.588	0.413	0.633	0.584	0.358	-0.151	-0.557	0.440	0.444	0.886	0.885	0.895	1	0.758	0.806	0.859	0.94	0.7	0.782
MDIMM	-0.314	0.3	-0.769	0.564	0.662	0.68	0.227	-0.225	-0.534	0.633	0.503	0.83	0.626	0.836	0.758	1	0.862	0.902	0.806	0.929	0.859
MDCMM	-0.283	0.185	-0.595	0.616	0.716	0.763	0.247	-0.211	-0.555	0.701	0.492	0.73	0.68	0.745	0.806	0.862	1	0.791	0.857	0.838	0.96
MDILPM	-0.268	0.313	-0.74	0.469	0.637	0.61	0.263	-0.208	-0.577	0.481	0.535	0.92	0.732	0.927	0.859	0.902	0.791	1	0.893	0.843	0.802
MDCLPM	-0.241	0.226	-0.649	0.475	0.662	0.618	0.296	-0.173	-0.606	0.472	0.509	0.868	0.836	0.877	0.94	0.806	0.857	0.893	1	0.758	0.854
MDIMPM	-0.258	0.307	-0.8	0.494	0.606	0.643	0.158	-0.117	-0.489	0.673	0.47	0.711	0.557	0.726	0.7	0.929	0.838	0.843	0.758	1	0.879
MDCMPM	-0.286	0.194	-0.617	0.59	0.701	0.756	0.201	-0.17	-0.537	0.743	0.502	0.714	0.646	0.73	0.782	0.859	0.96	0.802	0.854	0.879	1

Figure 1. *The second Pearson correlation matrix of the clinical and dosimetric variables for trismus. Very strong correlations (≥0.85) are colored in red. In the dosimetric factors, MDCMJ, MDIMPM, and MDCMM showed less than 4 red colors. The three dosimetric factors were chosen for univariate logistic regression analysis. In addition, all clinical factors were chosen for univariate analysis. Lo: Location; T: T classification; N: N classification; His: histology; Base: baseline maximum inter-incisal opening; Accel: accelerated radiotherapy; Bil: bilateral neck radiotherapy; Sys: systemic therapy; MDIMJ: mean dose to ipsilateral mandible joint; MDCMJ: mean dose to contralateral mandible joint; MDIMJ5: mean dose to ipsilateral mandible joint + 5 mm; MDCMJ5: mean dose to ipsilateral mandible joint + 5 mm; MDIMM: mean dose to ipsilateral masseter muscle; MDCMM: mean dose to contralateral masseter muscle; MDILPM: mean dose to ipsilateral lateral pterygoid muscle; MDCLPM: mean dose to contralateral lateral pterygoid muscle; MDIMPM: mean dose to ipsilateral medial pterygoid muscle; MDCMPM: mean dose to contralateral medial pterygoid muscle.*

Table III. *Univariate logistic regression analysis of candidate prognostic variables for trismus after Pearson correlation matrixes (Table II and Figure 1).*

Predictor	β	Odds ratio	95%CI	*p*-Value	AUC
Age	–0.04	0.96	0.93-1.00	0.07	0.61
Female *vs*. male	1.07	2.91	1.20-7.10	0.018	0.61
Oral cavity, nasopharyngeal, oropharyngeal or hypopharyngeal cancer *vs*. laryngeal cancer	1.59	4.89	1.92-12.44	0.001	0.68
T3 or T4 *vs*. T1 or T2	0.59	1.79	0.79-4.08	0.163	0.57
N2b, N2c or N3 *vs*. N0, N1 or N2a	1.28	3.61	1.54-8.46	0.003	0.66
Stage III or Stage IV *vs*. Stage I or Stage II	1.23	3.42	1.35-8.67	0.01	0.64
Undifferentiated large cell carcinoma *vs*. squamous cell carcinoma	1.25	3.50	0.21-57.41	0.383	0.51
Maximum inter-incisal opening	–0.07	0.94	0.89-0.98	0.01	0.67
Conventional radiotherapy *vs*. accelerated radiotherapy	1.68	5.36	2.20-12.80	<0.001	0.69
Bilateral neck radiotherapy *vs*. local or ipsilateral neck radiotherapy	0.95	2.58	0.83-8.05	0.1	0.58
Systemic therapy with radiotherapy *vs*. radiotherapy alone	1.50	4.49	1.90-10.60	0.001	0.67
Mean dose to ipsilateral medial pterygoid muscle	0.03	1.03	1.01-1.06	0.001	0.73
Mean dose to contralateral masseter muscle	0.05	1.05	1.02-1.09	<0.001	0.70
Mean dose to contralateral mandible joint	0.06	1.07	1.03-1.10	<0.001	0.75

CI: Confidence interval; AUC: area under the curve; *vs*.: *versus*.

to ipsilateral medial pterygoid muscle, and the baseline MIO (20). Thus, limited data exist on the relation among dosimetric factors of OARs, clinical factors, and trismus in a multivariate NTCP model.

In the current study, the mean dose to contralateral mandible joint and baseline MIO were independent prognostic factors for trismus in the multivariate analysis. In addition, the NTCP model for trismus after RT was established with these two variables. Baseline MIO should be noted that it may be related to our definition of trismus. It might not be intuitive that mean dose to contralateral mandible joint was more significant than those of the ipsilateral masseter or the pterygoid muscle mentioned above. One possible reason for why the mean dose to the mandible joint was more important than that to other OARs is that the joint tissues are more sensitive to radiation induced-damage and/or that movement of the mandible joint is more complicated than muscle function, and are thus more prone to the effects of a lower dose (13). In addition, it could be hypothesized that the contralateral mandible joint played the most important role as this joint is the main compensator for trismus in the long-term process of fibrosis. We would like to emphasize that, to the best of our knowledge, this study is a unique prospective research that detected the significant clinical and dosimetric factors related to trismus using an actual measurement of MIO with multiple logistic regression analysis.

In order to avoid or improve trismus in HNC survivors, some strategies may be considered. First, based on the results of the current studies, constraint for the contralateral mandible joint could be employed, which may be different among individual patients based on their baseline MIO. For example, in a patient with a baseline MIO of 40 mm, the probability of trismus would be 33% if the dose to the contralateral mandible joint is 20 Gy, but can be decreased to 21% and 17% if the dose is reduced to 10 Gy and 5 Gy, respectively. Although there are a few reports on reducing trismus by IMRT (38, 48, 49), no optimal dose constraints for the mandible joints have been established. Our study adds information to such RT practice.

Second, our prediction model may identify patients at high risk for developing trismus and who may benefit from a preventive exercise program early during or directly after treatment. Such rehabilitation programs are currently available for HNC patients (5, 6, 50-52).

Table IV. *Distributions of the mean dose to the contralateral mandible joint and the baseline maximum inter-incisal opening.*

Variable	n	With trismus (n=30)	Without trismus (n=102)
D_{mean} to the contralateral mandible joint (Gy)			
0 to 10	88	12 (40%)	76 (75%)
10 to 20	20	7 (23%)	13 (13%)
20 to 40	18	7 (23%)	11 (11%)
40 to 60	6	4 (13%)	2 (2%)
Baseline maximum inter-incisal opening (mm)			
0 to 30	11	4 (13%)	7 (7%)
31 to 40	47	15 (50%)	32 (31%)
41 to 50	52	9 (30%)	43 (42%)
51 to 70	22	2 (7%)	20 (20%)

D: Dose; n: number of patients.

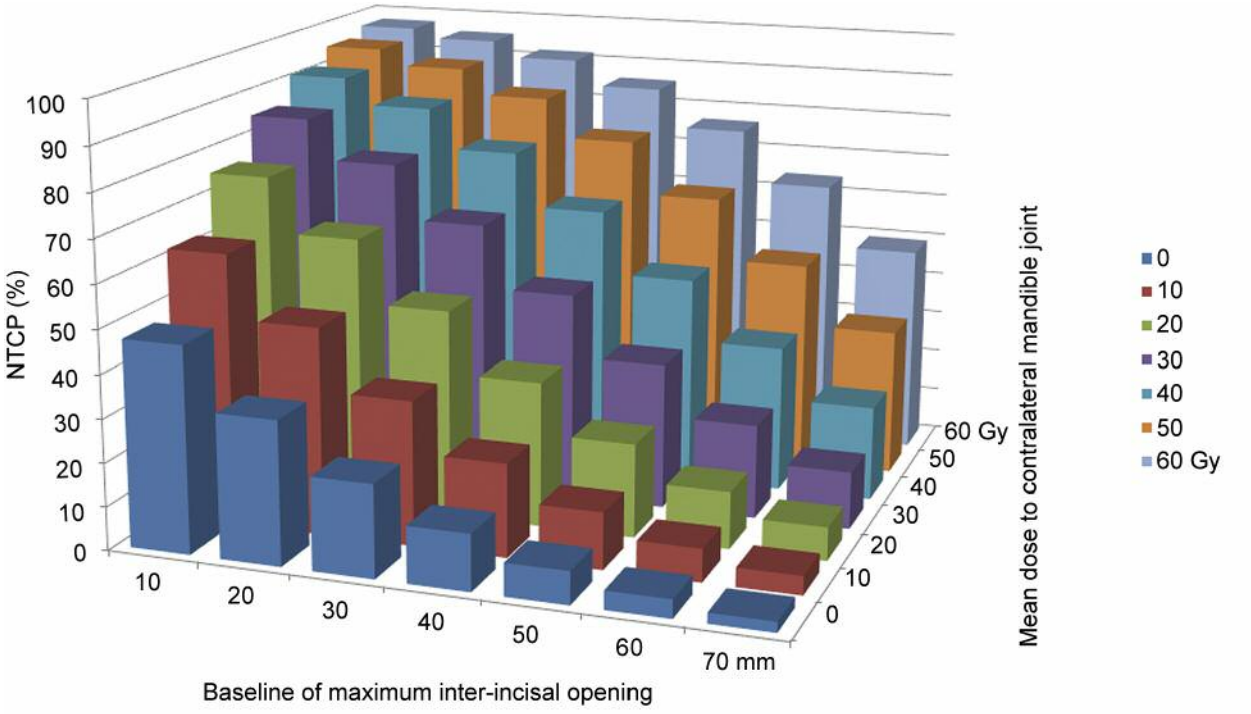

Figure 2. *Normal tissue complication probability (NTCP) model for trismus in head and neck cancer patients treated with radiotherapy.*

Baseline of maximum inter-incisal opening	Mean dose to contralateral mandible joint												
	0 Gy	5 Gy	10 Gy	15 Gy	20 Gy	25 Gy	30 Gy	35 Gy	40 Gy	45 Gy	50 Gy	55 Gy	60 Gy
5 mm	55%	62%	69%	75%	80%	85%	88%	91%	93%	95%	96%	97%	98%
10 mm	47%	55%	62%	69%	75%	81%	85%	88%	91%	93%	95%	96%	97%
15 mm	40%	47%	55%	62%	69%	75%	81%	85%	88%	91%	93%	95%	96%
20 mm	33%	40%	48%	55%	63%	69%	75%	81%	85%	88%	91%	93%	95%
25 mm	27%	33%	40%	48%	55%	63%	70%	76%	81%	85%	89%	91%	93%
30 mm	21%	27%	33%	40%	48%	55%	63%	70%	76%	81%	85%	89%	91%
35 mm	17%	21%	27%	33%	40%	48%	56%	63%	70%	76%	81%	85%	89%
40 mm	13%	17%	21%	27%	33%	41%	48%	56%	63%	70%	76%	81%	85%
45 mm	10%	13%	17%	22%	27%	34%	41%	48%	56%	63%	70%	76%	81%
50 mm	8%	10%	13%	17%	22%	27%	34%	41%	48%	56%	63%	70%	76%
55 mm	6%	8%	10%	13%	17%	22%	27%	34%	41%	48%	56%	63%	70%
60 mm	4%	6%	8%	10%	13%	17%	22%	27%	34%	41%	49%	56%	64%
65 mm	3%	4%	6%	8%	10%	13%	17%	22%	28%	34%	41%	49%	56%
70 mm	2%	3%	4%	6%	8%	10%	13%	17%	22%	28%	34%	41%	49%

Figure 3. *Quick reference matrix of normal tissue complication probability (NTCP) for trismus in head and neck cancer patients treated with radiotherapy.*

Third, pentoxifylline, which is a suppressor of TNFα (9, 10), or microcurrent therapy may be useful to prevent or relieve trismus in the same high-risk group for developing trismus (53). To verify efficacy of the above-mentioned approach, future prospective trials are warranted.

Conclusion

We developed a multivariable prediction model for trismus, after definitive RT with or without systemic treatment for HNC, consisting of the mean dose to contralateral mandible

Table V. *Multivariable logistic regression model for trismus.*

	β	*p*-Value	Odds ratio	95% Confidence interval
Mean dose to contralateral mandible joint (Gy)	0.061	0.001	1.062	1.027-1.1
Baseline maximum inter-incisal opening (mm)	–0.06	0.027	0.942	0.893-0.993
Constant	0.494			

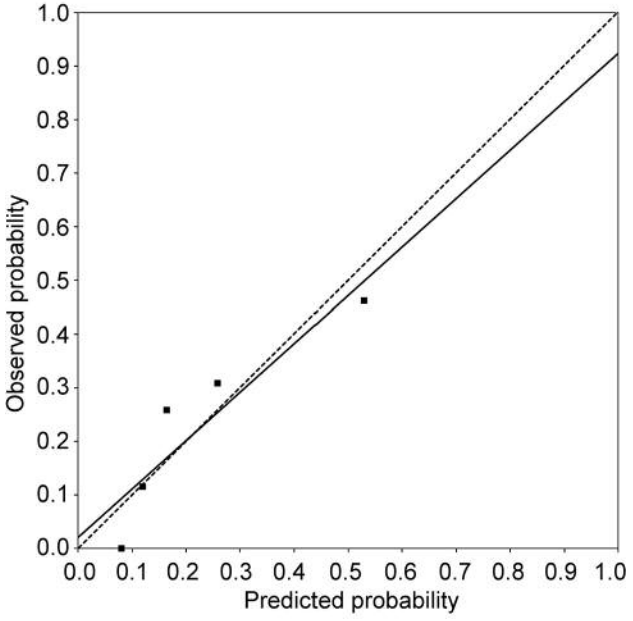

Figure 4. *Calibration of a predictive model for patient-related trismus based on two prognostic factors, which were the baseline of maximum inter-incisal opening and the mean dose to contralateral mandible joint. Dashed line indicates perfect agreement. Solid line represents the fit of the observed versus the expected probability.*

joint and baseline MIO. This NTCP model can be used to define dose constraint in clinical practice.

Conflicts of Interest

The are no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and design: Henk P. Bijl, Arjen van der Schaaf, and Johannes A. Langendijk. Acquisition of data: Masahiro Morimoto, Henk P. Bijl, Roel J.H.M. Steenbakkers, Olga Chouvalova, and Johannes A. Langendijk. Analysis and interpretation of data: Masahiro Morimoto, Henk P. Bijl, Arjen van der Schaaf, Cheng-Jian Xu, Yasuo Yoshioka, Teruki Teshima, and Johannes A. Langendijk. Writing, review, and/or revision of the manuscript: Masahiro Morimoto, Yasuo Yoshioka, and Johannes A. Langendijk.

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