Trismus in head and neck cancer patients

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Predictors for trismus in patients receiving radiotherapy

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ABSTRACT

Purpose: Trismus, a restricted mouth opening, in head and neck cancer patients may be caused by tumour infiltration in the masticatory muscles, radiation induced fibrosis or scarring after surgery. It may impede oral functioning severely. The aims of our study were to determine (1) the incidence of trismus at various time points and (2) the patient, tumour, and treatment characteristics that predict the development of trismus after radiotherapy in head and neck cancer patients using a large database (n=641).

Methods: Maximal mouth opening was measured prior to and 6, 12, 18, 24, 36, and 48 months after radiotherapy. Patient, tumour, and treatment characteristics were analysed as potential predictors for trismus using a multivariable logistic regression analysis.

Results: At six months after radiotherapy, 28.1% of the patients without trismus prior to radiotherapy developed trismus for the first time. At subsequent time points the incidence declined. Over a total period of 48 months after radiotherapy, the incidence of trismus was 3.6 per 10 person years at risk. Patients who had a tumour located in the oral cavity, oropharynx or nasopharynx, and the salivary glands or ear, and who had a longer overall treatment time of radiotherapy, were more likely to develop trismus in the first six months after radiotherapy. Maximal mouth opening was a predictor for developing trismus at all time points.

Conclusions: Incidence of trismus is 3.6 per 10 person years at risk. Tumour localization and overall treatment time of radiotherapy are predictors for developing trismus the first six months after radiotherapy. Maximal mouth opening is a significant predictor for developing trismus at all time points. Regular measurements of maximal mouth opening are needed to predict trismus.

INTRODUCTION

Many patients with head and neck cancer suffer from trismus (a mouth opening of 35 millimetres (mm) or less), especially after radiotherapy.[1,2] Fibrosis is considered one of the biological mechanisms leading to late radiation-induced side effects.[3-5] When the temporomandibular joint and masticatory muscles are irradiated, there is a risk of developing trismus.[6,7] This risk increases in proportion to radiation dose and irradiated volume of relevant anatomical structures.[2,8,9]

The reported prevalence of trismus after radiotherapy for head and neck cancer ranges from 25% to 42%.[2,9] This wide range in percentages can be explained by differences in inclusion criteria, tumour characteristics, interval from treatment and/or treatment modality in studies. A previous study showed that the maximal mouth opening decreases rapidly in the first nine months after radiotherapy (mean decrease 2.4% per month). This restriction in mouth opening may become severe and irreversible over time.[5]

Recently, a multivariate prediction model for the course of mouth opening during and after radiotherapy was published.[10] Although that model can be used to statistically predict the course of mouth opening, the clinical application is limited because of its complexity. Prediction of trismus may enable clinicians to subscribe preventive exercise therapy (for example using the Dynasplint Trismus System® or the TheraBite® Jaw Motion Rehabilitation System™) for the patients at risk.[11,12]

In this prospective longitudinal cohort study, we aimed to determine (1) the incidence of trismus at various time points and (2) the patient, tumour, and treatment characteristics that predict the development of trismus after radiotherapy in head and neck cancer patients using a large database (n=641).

MATERIAL AND METHODS

Participants

Head and neck cancer patients who received definitive or postoperative external beam radiotherapy at the department of Radiation Oncology of the University Medical Center Groningen were entered in a prospective data registration program. Prospective assessment of acute and late toxicity and patient-reported outcome measures were included. Radiotherapy was given alone or in combination with chemotherapy or cetuximab. For our study, we used data of patients entered in the program from March 2007 until June 2011. The Ethics Committee approved our study and the study was carried out according to the regulations of our institute. Patients were invited to participate in this program and asked for permission to use their data for the program and other scientific purposes. Refusal of participation was recorded in their medical record. Patients receiving radiotherapy for a primary tumour located outside the head and neck region, intra cranially, in the nasal vestibule, or on the skin, were excluded from the analyses because treatment of these tumours were not expected to influence mouth opening. Patients without data about maximal mouth opening were excluded, as well as patients who died during radiotherapy or within 6 months thereafter.

Data

Patient characteristics were gender (male, female), age at start of radiotherapy (years), deceased (yes, no), dental status (dentate, partially edentulous, edentulous, unknown), and change in dental status (yes, no). Tumour characteristics were localization of the primary tumour (oral cavity, oropharynx or nasopharynx, salivary glands or ear, hypopharynx or supraglottic larynx, glottic or subglottical larynx, nasal cavity or maxillary sinus, unknown primary tumour), T classification based on the Union for International Cancer Control (UICC) TNM classification 2009 (T0, T1, T2, T3, T4, unknown), and squamous cell carcinoma (yes, no). Treatment characteristics recorded were surgery (yes, no), neck dissection (yes, no), radiotherapy primary tumour (yes, no), total dose of radiation (Gy), fraction dose of radiation (Gy), overall treatment time of radiotherapy (months), chemotherapy (yes, no), and exercise therapy for trismus (yes, no).

Mouth opening

Prior to radiotherapy (T0), maximal mouth opening was measured in mm, using a sliding calliper. Maximal mouth opening measurements were performed by well instructed nurses. All concerned nurses were trained in measuring maximal mouth opening by the

head and neck radiation oncologists prior to the measurements. A limited number of nurses were working at the department of Radiation Oncology during the study period. Patients were asked to open their mouth as far as possible and the distance between the incisal edges of the 11 and 41 (or of the dental prosthesis) was measured. When patients were edentulous and did not wear a dental prosthesis, the alveolar ridge of mandible and/or maxilla was used (region 11 and 41). The maximal mouth opening was measured again during subsequent time points: 6 (T6), 12 (T12), 18 (T18), 24 (T24), 36 (T36), and 48 (T48) months after radiotherapy. Changes in dental status were recorded in the database. Trismus was noted as present if maximal mouth opening was 35 mm or less. This cut-off point correlates best with perceived restrictions of mouth opening.[13,14]

Statistics

Analyses were performed using IBM SPSS Statistics Program version 22.0. Patients with no missing mouth opening measurements before their last recorded measurement were coded as 'without missing data' and patients with missing mouth opening measurements were coded as 'missing data'. Differences between patients with and without missing data were analysed using a Chi-Square test, t-test for independent samples, or Mann-Whitney U test, as appropriate.

To calculate the incidence of trismus, the number of patients who developed trismus for the first time after radiotherapy was calculated and divided by the number of patients who were at risk of developing trismus for the first time. Patients having trismus prior to radiotherapy were excluded from the incidence analyses. Patients who had no trismus at the last assessment, but with missing data at previous time points, were also excluded from the incidence analyses since they might have had trismus at those missing time points. To calculate the incidence based on person years at risk, patients with missing data before the time point when trismus was recorded for the first time and who had no trismus prior to radiotherapy, were included in the calculation; we assumed that trismus developed half way in the period between two recorded time points.

Multivariate logistic regression analyses were performed to predict trismus at the subsequent time points. Patient, tumour, and treatment characteristics were selected as potential predictors. For example, at T0, we used potential predictor variables to predict the risk of developing trismus at T6. Similarly, at T6 we used potential predictor variables to predict the risk of developing trismus at T12.

The potential factors: gender, age, localization of the primary tumour, squamous cell carcinoma, T4 classification, total dose of radiation, fraction dose of radiation, overall treatment time of radiotherapy, surgery, chemotherapy, and maximal mouth opening at previous time point were entered in the model.[9,10,14-16] Thereafter, variables were removed if they did not contribute significantly to the regression equation ($p<0.05$).

As part of validation, the results of the calculations of incidence and of the regression analyses were compared to the results of patients without missing data. From the results of the regression analyses, the risk of developing trismus was calculated for a hypothetical patient who had a nasopharynx carcinoma and was treated with radiotherapy for six weeks.

RESULTS

Patient, tumour, and treatment characteristics

Data from 788 patients who received radiotherapy in the head and neck region were entered in the prospective data registration program; in total, 145 patients were excluded according to the exclusion criteria.[10] Additionally, two patients with a rare type of tumour (myxofibrosarcoma and epitheloid angiosarcoma) were excluded for statistical reasons. Thus, the study population consisted of 641 patients (81.3%), involving 436 patients without missing data regarding maximal mouth opening. Patients with and patients without missing data were compared. Significant differences between these groups were found in the variables deceased, overall treatment time of radiotherapy, and chemotherapy (Table 1).

Of the 641 patients, 42 (6.6%) changed dental status; 20 of these patients (3.1%) changed from dentate to edentulous, 15 patients (1.9%) changed from partially edentulous to edentulous, and 5 patients (0.8%) changed from dentate to partially edentulous. The change in dental status was unknown for 2 patients (0.3%).

Prevalence

Prior to radiotherapy, 34.8% of the patients had trismus (Table 2). Relative to patients who did not have trismus prior to radiotherapy, trismus prior to radiotherapy was significantly associated with female gender ($p<0.001$), a higher age ($p=0.002$), tumours located in the oral cavity and salivary glands or ear ($p<0.001$), T4 tumours ($p=0.002$), and a history of surgery ($p<0.001$) (Supplementary Table 1).

Incidence

The incidence of trismus in the total period of 48 months after radiotherapy was 3.6 per 10 person years at risk. At T6, 28.1% of the patients at risk developed trismus for the first time (Table 2). Patients with a tumour located in the oropharynx or nasopharynx ($p=0.004$), and with a history of chemotherapy ($p=0.024$) were more likely to develop trismus at T6 (Supplementary Table 1). The incidence of trismus declined at subsequent time points. No new cases of trismus developed after T36 (Table 2).

No major differences were seen when the results of the incidence of trismus of the study population were compared to the results of the patients without missing data (Supplementary Table 2).

Table 1. Patient, tumour, and treatment characteristics.

	Study population	Without missing data	With missing data	
	n (%)	n (%)	n (%)	p*
Patient characteristics				
Male gender	451 (70.4)	312 (71.6)	139 (67.8)	0.332
Age (years); Mean (SD)	62.3 (12.5)	62.4 (12.6)	61.9 (12.5)	0.698†
Deceased	199 (31.0)	161 (36.9)	38 (18.5)	<0.001
Dental status				0.510
Dentate	241 (37.6)	156 (35.8)	85 (41.5)	
Partially edentulous	77 (12.0)	53 (12.2)	18 (8.8)	
Edentulous	319 (49.8)	219 (50.2)	100 (48.8)	
Unknown	4 (0.6)	3 (0.7)	1 (0.5)	
Change in dental status	42 (6.6)	30 (6.9)	12 (5.9)	
Tumour characteristics				
Localization of the primary tumour				0.584
Oral cavity	132 (20.6)	93 (21.3)	39 (19.0)	
Oropharynx or nasopharynx	162 (25.3)	109 (25.0)	53 (25.9)	
Salivary glands or ear	66 (10.3)	46 (10.6)	20 (9.8)	
Hypopharynx or supraglottic larynx	115 (17.9)	76 (17.4)	39 (19.0)	
Glottic or subglottic larynx	116 (18.1)	77 (17.7)	39 (19.0)	
Nasal cavity or maxillary sinus	24 (3.7)	20 (4.6)	4 (2.0)	
Unknown primary	26 (4.1)	15 (3.4)	11 (5.4)	
T classification				0.931
T0	6 (0.9)	3 (0.7)	3 (1.5)	
T1	112 (17.5)	77 (17.7)	35 (17.1)	
T2	191 (29.8)	129 (29.6)	62 (30.2)	
T3	99 (15.4)	68 (15.6)	31 (15.1)	
T4	183 (28.5)	128 (29.4)	55 (26.8)	
Unknown	38 (5.9)	25 (5.7)	13 (6.3)	
Squamous cell carcinoma	512 (79.9)	351 (80.5)	161 (78.5)	0.562
Treatment characteristics				
Surgery	248 (38.7)	175 (40.1)	73 (35.6)	0.272
Neck dissection	316 (33.7)	142 (32.6)	74 (36.1)	0.378
Radiotherapy primary tumour	610 (95.2)	418 (95.7)	192 (96.6)	0.410
Total dose of irradiation; Med (IQR)	70 (66;70)	66 (66;70)	70 (66;70)	0.413‡
Fraction dose of irradiation; Med (IQR)	2 (2;2)	2 (2;2)	2 (2;2)	0.709‡
Overall treatment time of radiotherapy (months); Med (IQR)	1.28 (1.3;1.5)	1.4 (1.3;1.5)	1.3 (1.2;1.4)	0.041‡
Chemotherapy	465 (72.5)	137 (31.4)	39 (19.0)	0.001
Exercise therapy for trismus	21 (3.3)	14 (3.2)	7 (3.4)	0.893

Med: Median. IQR: Interquartile range.
*: p of the comparison between patients with and patients without missing data. †: Results of t-test for independent samples. ‡: Results of Mann-Whitney U test. All other p values were the result of Chi-Square test.

Table 2. Trismus at T0, T6, T12, T18, T24, T36, and T48.

Time point	Total*	No trismus	Trismus	No trismus to Trismus	Trismus to no trismus	At risk for trismus for the first time	Incidence
	n	n (%)	n (%)	n (%)	n (%)	n	n (%)
T0 **T6**	414	270 (65.2) 239 (57.7)	144 (34.8) 175 (42.3)	76 (28.1)	45 (31.3)	270	76 (28.1)
T6 **T12**	365	225 (61.6) 229 (62.7)	140 (38.4) 136 (37.3)	35 (15.6)	39 (27.9)	164	19 (11.6)
T12 **T18**	349	225 (64.5) 212 (60.7)	124 (35.5) 137(39.3)	40 (17.8)	27 (21.8)	126	14 (11.1)
T18 **T24**	328	192 (58.5) 202 (61.6)	136 (41.5) 126 (38.4)	19 (9.9)	29 (21.3)	95	7 (7.4)
T24 **T36**	213	133 (62.4) 133 (62.4)	80 (37.6) 80 (37.6)	13 (9.8)	13 (16.3)	51	3 (5.9)
T36 **T48**	114	74 (64.9) 69 (60.5)	40 (35.1) 45 (39.5)	8 (10.8)	3 (7.5)	22	0

*: Number of patients for which observations are available for the time period.
For example: Initially, 270 patients had no trismus, of which 76 changed status, they developed trismus and 194 did not change status, they remained without trismus. In total 144 patients did have trismus of which 45 changed status to 'no trismus' and 99 did not change status, they kept trismus. At T0, 270 patients were at risk to develop trismus for the first time. Of these 270 patients, 76 developed trismus for the first time.

Multivariate logistic regression analyses

In the prediction model, a smaller mouth opening at T0, a longer overall treatment time of radiotherapy, and tumours located in the oral cavity, oropharynx or nasopharynx, and the salivary glands or ear all resulted in significantly higher odds for developing trismus at T6. A smaller mouth opening at T6 and a tumour located in the oral cavity led to significantly higher odds of developing trismus at T12.

However, for the prediction of developing trismus at T18, T24, T36, and T48, only mouth opening at the previous time point contributed significantly to the regression equation (Table 3). No major differences were seen when the results of the regression analyses of the study population were compared to the results of the patients without missing data (Supplementary Table 3).

Risk calculation

As an example of applying the prediction model, arbitrarily chosen characteristics of the hypothetical patient (nasopharynx carcinoma, radiotherapy for six weeks) were entered in the multivariable logistic regression equation (Figure 1).

No major differences were seen when the results of the risk calculation of the study population were compared to the results of the patients without missing data (Supplementary Figure 1).

Table 3. Output multivariate logistic regression analyses at T6, T12, T18, T24, T36, and T48.

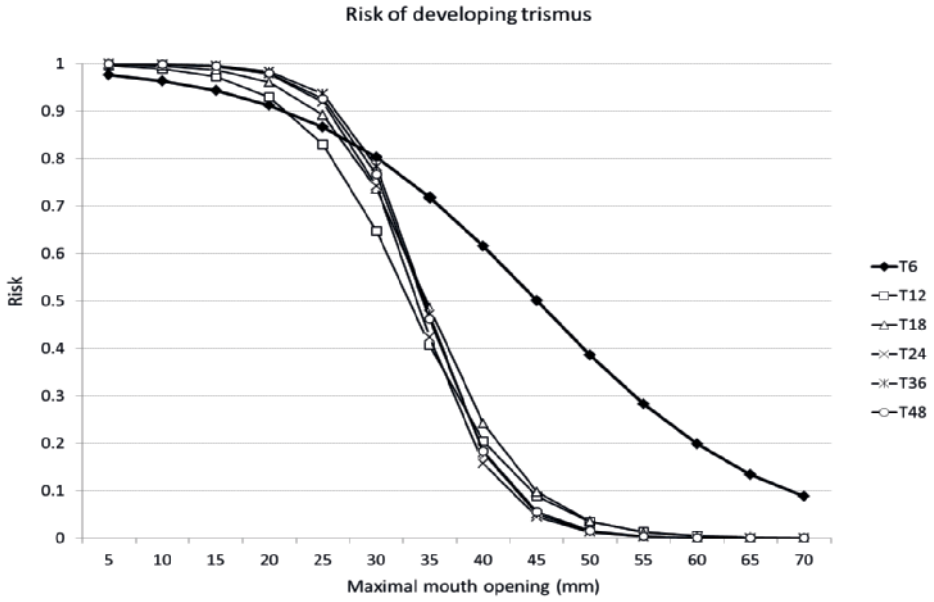
		β	OR	95% Confidence Interval		Sig.
				Lower	Upper	
Prediction mouth opening at T6						
Percentage correctly predicted (Nagelkerke's R^2)	73.9 (0.334)					
Mouth opening at T0		-0.09	0.91	0.89	0.93	<.001
Overall treatment time (in months)		1.72	5.58	1.80	17.32	0.003
Oral cavity		0.82	2.28	1.06	4.91	0.035
Oropharynx or nasopharynx		1.44	4.21	2.04	8.68	<0.001
Salivary glands or ear		1.15	3.15	1.29	7.68	0.012
Hypopharynx or supraglottic larynx		0.31	1.37	0.61	3.06	0.445
Nasal cavity or maxillary sinus		0.69	2.00	0.54	7.41	0.299
Unknown primary tumour		-0.62	0.54	0.13	2.29	0.401
Constant		0.19	1.20			0.840
Prediction mouth opening at T12						
Percentage correctly predicted (Nagelkerke's R^2)	81.4 (0.506)					
Mouth opening at T6		-0.20	0.82	0.79	0.86	<0.001
Oral cavity		1.32	3.74	1.44	9.74	0.007
Oropharynx or nasopharynx		0.61	1.83	0.76	4.42	0.177
Salivary glands or ear		0.74	2.10	0.78	5.65	0.140
Hypopharynx or supraglottic larynx		0.53	1.70	0.61	4.69	0.309
Nasal cavity or maxillary sinus		1.13	3.09	0.72	13.33	0.130
Unknown primary tumour		1.05	2.86	0.73	11.24	0.133
Constant		5.89	361.58			<0.001
Prediction mouth opening at T18						
Percentage correctly predicted (Nagelkerke's R^2)	81.7 (0.533)					
Mouth opening at T12		-0.22	0.81	0.77	0.84	<0.001
Constant		7.53	1858.14			<0.001
Prediction mouth opening at T24						
Percentage correctly predicted (Nagelkerke's R^2)	85.4 (0.657)					
Mouth opening at T18		-0.27	0.76	0.72	0.81	<0.001
Constant		9.26	10535.35			<0.001
Prediction mouth opening at T36						
Percentage correctly predicted (Nagelkerke's R^2)	88.3 (0.655)					
Mouth opening at T24		-0.28	0.76	0.70	0.81	<0.001
Constant		9.70	16309.72			<0.001

Table 3. (Continued)

		β	OR	95% Confidence Interval		Sig.
				Lower	Upper	
Predict mouth opening at T48						
percentage correctly predicted (Nagelkerke's R^2)	85.0 (0.641)					
Mouth opening at T36		-0.27	0.76	0.69	0.84	<0.001
Constant		9.23	10195.45			<0.001

β: Regression coefficient. OR: Odds ratio. Nagelkerke R^2: Nagelkerke's R Square.
*: Percentage correctly predicted. Glottic or subglottic larynx is used as reference category.

Figure 1. Risk of developing trismus at T6, T12, T18, T24, T36, and T48.



Arbitrarily chosen characteristics of a hypothetical patient were entered in the multivariable logistic regression equation as a reference category. This hypothetical patient had a nasopharynx carcinoma and was treated with radiotherapy for 6 weeks.

DISCUSSION

Key results

In our population of head and neck cancer patients, the incidence of trismus is highest six months after radiotherapy and declines thereafter (Table 2). The incidence of trismus was 3.6 per 10 person years at risk, calculated over the total period of 48 months after radiotherapy. The best predictors for developing trismus in the first six months after radiotherapy are tumours located in the oral cavity, oropharynx or nasopharynx and the salivary glands or ear, and a longer overall treatment time of radiotherapy. At all time points, maximal mouth opening measurement at the previous time point was a significant predictor for developing trismus at the subsequent time point (Table 3).

Prevalence

As stated earlier, already 34.8% of the head and neck cancer patients had a trismus prior to radiotherapy. Patients with a tumour located in the oral cavity and salivary glands or ear, were more likely to have trismus prior to radiotherapy, possibly because of tumour infiltration near the masticatory muscles. Additionally, patients with a history of surgery were more likely to have trismus prior to have radiotherapy, probably due to the formation of scarring after surgery.

Incidence

For the calculation of incidence, most patients had measurements at time points T0 and T6. Thereafter, the number of patients who had subsequent measurements declined. This decline was due to patients who deceased after T6 and due to patients for whom measurements were not completed in the inclusion period (right censored data).

The results in Table 2 show that the incidence of trismus was highest from T0 to T6. Thereafter, the incidence for trismus declined. This was also observed in two other studies. [5,17] The first study showed a rapid decrease in mouth opening between the first and ninth month after radiotherapy.[5] The second study showed a rapid decrease in maximal mouth opening of 0.9% per month during the first six months after radiotherapy and this reduction decreased over time to 0.3% per month, and reduced even further between the second and fifth year after radiotherapy.[17] Both studies included only patients suffering from nasopharyngeal carcinomas. In our study, patients with head and neck tumours at different localizations were included, which probably increases the generalizability of our results.

The decline in incidence at subsequent time points can be related to recovery from the short-term effects of radiotherapy. In a small group of patients with nasopharyngeal carcinomas (n=17), recovery occurred between the fifth and twelfth month after radiotherapy. [18] Due to this recovery, patients with trismus at a time point can change to no trismus at a later time point. Remarkably, in our study, recovery from trismus still occurred up to 48 months after radiotherapy (Table 2).

Risk calculation

A longer overall treatment time of radiotherapy leads to a higher risk of developing trismus six months after radiotherapy. A higher risk for a longer overall treatment time may be related to the treatment modality given. In general, in our center, patients who receive chemotherapy are treated for seven weeks, while patients who receive radiotherapy only are treated for six weeks. It could be assumed, that patients with a longer overall treatment time of radiotherapy have received chemoradiotherapy predominantly. A combination of chemotherapy and radiotherapy is a more intensive and extensive approach, which would be expected to lead to more fibrosis and hence more trismus.

In our study, we found no significant association between the prescribed total dose and fraction dose of radiotherapy and trismus. In a retrospective study, an association between difficulties with opening the mouth and the radiation dose to the masseter muscles, pterygoid muscles, coronoid process, and mandibular condyle was found.[19] It is expected that significant dose-effect relationships will be found when using specific three-dimensional distribution parameters to relevant anatomical structures.

Future studies

Analysis of specific dose distribution and anatomical structures such as the masticatory muscles and temporomandibular joint could improve the identification of patients at risk of developing trismus. We did not include the effect of the three-dimensional dose distributions in our analysis as this is part of a future, separate project in which multivariable normal tissue complication probability models will be used.

Study limitations and strengths

A limitation of our study was the measurement procedure of mouth opening that was performed by different assessors of the department of Radiation Oncology, which might have introduced a measurement error. However, it is stated that maximal mouth opening

can be assessed reliably, regardless of the assessor, therefore we expect this error to be small.[20] Another limitation was the change in dental status during the course of the study. A relatively small percentage of the patient changed dental status (6.6%). Most patients changed for dentate to (partially) edentulous or from partially edentulous to edentulous, thereby resulting predominantly in an increase of mouth opening measurement. However, this does not reflect real recovery from trismus itself. The calendar dates regarding dental status changes were not available in the database, thus no direct link between dental status and the variation in number of patients with and without trismus could be made.

No other causes for trismus than secondary to the head and neck cancer were investigated.

Conclusion

The incidence of trismus is 3.6 per 10 person years at risk based on a follow-up of 48 months after radiotherapy. Tumour localization and overall treatment time of radiotherapy are significantly associated with developing trismus at T6. Maximal mouth opening at previous time point is significantly associated with trismus at all subsequent time points. Because maximal mouth opening is an important predictor, regular measurements of maximal mouth opening are needed to predict trismus. High-risk patients identified by the presence of predictors for trismus can be offered preventive measures.

Supplementary Table 1. Comparison between patients with no trismus at T0, with trismus at T0, and trismus at T6.

	No trismus at T0 (*n*=370)		Trismus at T0 (*n*=196)		Trismus at T6 (*n*=76)		Significance of the difference between patients with no trismus and trismus at T0			Significance of the difference between patients with trismus at T0 and T6		
	n	%*	n	%*	n	%*	Value	DF	*p*	Value	DF	*p*
Patient characteristics												
Male gender	285	77	115	58.7	52	68.4	20.82	1	<0.001	2.195	1	0.138
Age	63.7[a]	12.1[b]	60.2[a]	13.2[b]	63.2[a]	12.9[b]	3.5[c]	1.3; 5.7[d]	0.002	-3.04[c]	-6.5; 0.5[d]	0.088
Tumour characteristics												
Tumour localization												
Oral cavity	52	14.1	61	31.1	12	15.8	54.7	6	<0.001	19.053	6	0.004
Oropharynx or nasopharynx	101	27.3	46	23.5	34	44.7						
Salivary glands or ear	27	7.3	30	15.3	8	10.5						
Hypopharynx or supraglottic larynx	81	21.9	21	10.7	11	14.5						
Glottic or subglottic larynx	88	23.8	18	9.2	9	11.8						
Nasal cavity or maxillary sinus	12	3.2	11	5.6	1	1.3						
Unknown primary tumour	9	2.4	9	4.6	1	1.3						
T4 tumour	90	24.3	72	36.7	21	27.6	9.7	1	0.002	2.017	1	0.156
Squamous cell carcinoma	306	82.7	150	76.5	60	78.9	3.12	1	0.077	0.182	1	0.67
Treatment characteristics												
Surgery	99	26.8	115	58.7	21	27.6	55.51	1	<0.001	21.108	1	<0.01
Chemotherapy	107	28.9	57	29.1	33	43.4	0.002	1	0.968	5.086	1	0.024

*: Percentage correctly predicted, DF: Degrees of freedom , a: mean, b: standard deviation, c: difference in means, d: 95% confidence interval.

Supplementary Table 2. Trismus at T0, T6, T12, T18, T24, T36, and T48 for patients without missing data only.

Time point	Total*	No trismus	Trismus	No trismus to Trismus	Trismus to no trismus	At risk for trismus for the first time	Incidence
	n	n (%)	n (%)	n (%)	n (%)	n	n (%)
T0 **T6**	353	230 (65.2) 210 (59.5)	123 (34.8) 143 (40.5)	60 (26.1)	40 (32.5)	230	60 (26.1)
T6 **T12**	297	190 (64.0) 190 (64.0)	107 (36.0) 107 (36.0)	32 (16.8)	32 (29.9)	152	19 (12.5)
T12 **T18**	264	173 (65.5) 160 (60.6)	91 (34.5) 104 (39.4)	31 (17.9)	18 (19.8)	122	14 (11.5)
T18 **T24**	228	139 (61.0) 142 (62.3)	89 (39.0) 86 (37.7)	15 (10.8)	18 (20.2)	95	7 (7.4)
T24 **T36**	125	78 (62.4) 82 (65.6)	47 (37.6) 43 (34.4)	6 (7.7)	10 (21.3)	51	3 (5.9)
T36	59	37 (62.7)	22 (37.3)	5 (1.4)	6 (27.2)	22	0

*: Number of patients for which observations are available for the time period.
For example: Initially, 230 patients had no trismus, they were at risk of developing trismus for the first time, of which 60 changed status, they developed trismus and 170 did not change status, they remained without trismus. In total 123 patients did have trismus of which 40 changed status to 'no trismus' and 83 did not change status, they kept trismus. At T0, 230 patients were at risk to develop trismus for the first time. Of these 230 patients, 60 developed trismus for the first time.

Supplementary Table 3. Output multivariate logistic regression analyses at T6, T12, T18, T24, T36, and T48 for patients without missing data only.

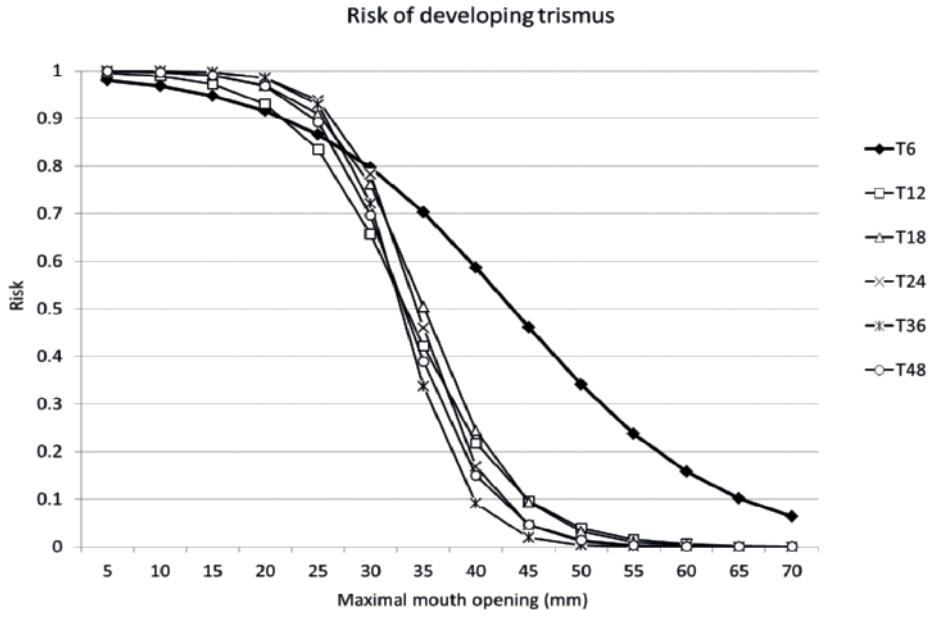
		β	OR	95% Confidence Interval		Sig.
				Lower	Upper	
Prediction mouth opening at T6						
percentage correctly predicted (Nagelkerke's R^2)	73.9(0.338)					
Mouth opening at T0		-0.10	0.90	0.88	0.93	<0.001
Overall treatment time (months)		1.73	5.62	1.68	18.84	0.005
Oral cavity		0.69	1.99	0.87	4.54	0.101
Oropharynx or nasopharynx		1.33	3.80	1.72	8.39	0.001
Salivary glands or ear		1.08	2.93	1.13	7.64	0.028
Hypopharynx or supraglottic larynx		0.46	1.59	0.66	3.80	0.301
Nasal cavity or maxillary sinus		0.45	1.56	0.38	6.42	0.535
Unknown primary tumour		-1.01	0.36	0.07	2.01	0.246
Constant		0.48	1.62			0.632
Prediction mouth opening at T12						
percentage correctly predicted (Nagelkerke's R^2)	81.5 (0.488)					
Mouth opening at T6		-0.19	0.82	0.78	0.87	<0.001
Oral cavity		1.74	5.69	1.98	16.40	0.001
Oropharynx or nasopharynx		0.80	2.23	0.84	5.95	0.109
Salivary glands or ear		0.69	2.00	0.65	6.08	0.224
Hypopharynx or supraglottic larynx		0.60	1.82	0.60	5.56	0.291
Nasal cavity or maxillary sinus		1.13	3.08	0.65	14.68	0.158
Unknown primary tumour		1.49	4.43	0.85	23.21	0.078
Prediction mouth opening at T18						
percentage correctly predicted (Nagelkerke's R^2)	81.4 (0.556)					
Mouth opening at T12		-0.23	0.80	0.75	0.84	<0.001
Constant		8.04	3096.67			<0.001
Prediction mouth opening at T24						
percentage correctly predicted (Nagelkerke's R^2)	86.8 (0.665)					
Mouth opening at T18		-0.29	0.75	0.70	0.81	<0.001
Constant		9.92	20420.54			<0.001
Prediction mouth opening at T24						
percentage correctly predicted (Nagelkerke's R^2)	88.0 (0.726)					
Mouth opening at T18		-0.32	0.72	0.64	0.82	<0.001
Oral cavity		2.20	9.02	0.97	84.19	0.054
Oropharynx or nasopharynx		1.10	3.00	0.38	23.46	0.296
Salivary glands or ear		1.33	3.80	0.33	43.95	0.285
Hypopharynx or supraglottic larynx		3.73	41.60	4.27	405.41	0.001

Supplementary Table 3. (Continued)

		β	OR	95% Confidence Interval		Sig.
				Lower	Upper	
Nasal cavity or maxillary sinus		0.57	1.77	0.13	23.35	0.665
Unknown primary tumour		1.18	3.24	0.14	75.67	0.465
Constant		9.60	14707.06			<0.001
Predict mouth opening at T48						
percentage correctly predicted (Nagelkerke's R^2)	83.1 (0.642)					
Mouth opening at T36		-0.26	0.77	0.68	0.88	<0.001
Constant		8.52	5028.63			<0.001

β: Regression coefficient. OR: Odds ratio. Nagelkerke R2: Nagelkerke's R Square. Glottic or subglottic larynx is used as reference category.

Supplementary Figure 1. Risk of developing trismus at T6, T12, T18, T24, T36, and T48 months for patients without missing data only.



Arbitrarily chosen characteristics of a hypothetical patient were entered in the multivariable logistic regression equation as a reference category. This hypothetical patient had a nasopharynx carcinoma and was treated with radiotherapy for 6 weeks.

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