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Trismus in head and neck cancer patients

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Criterion for trismus in head and neck cancer patients: a verification study

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van der Geer SJ, van Rijn PV, Kamstra JI, Roodenburg JLN, Dijkstra PU.
Criterion for trismus in head and neck cancer patients: A verification study.
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ABSTRACT

Purpose: Several cut-off points for trismus in head and neck cancer patients have been used. A mouth opening of 35 mm or less is most frequently used as a cut-off point. Due to the variation in cut-off points, the prevalence, prognostic factors and treatment outcomes of trismus cannot be studied uniformly. To provide uniformity, we aimed to verify the cut-off point of 35 mm or less. Additionally, we aimed to determine associated covariates with patients' perception of difficulties opening the mouth.

Methods: In a cross-sectional design, we measured the mouth opening in 671 head and neck cancer patients at the department of Oral and Maxillofacial Surgery, at the University Medical Center Groningen. The cut-off point was determined using the Receiver Operating Characteristic curve and Youden index, with perceived difficulties opening the mouth as criterion for trismus. Cut-off points for significant covariates were also determined.

Results: The Youden index was highest at 35 mm, with a sensitivity of 0.71 and a specificity of 0.86. Of the covariates analysed, the covariate 'treatment modality' was significantly associated with perceived difficulties opening the mouth. The highest Youden index for patients treated with surgery alone was 37 mm and for patients treated with radiotherapy alone 33 mm.

Conclusions: The cut-off point of 35 mm or less for trismus was confirmed in this large head and neck cancer population. It is recommended to use this cut-off point for future research. Patients receiving different treatment modalities may perceive difficulties opening the mouth differently.

INTRODUCTION

Trismus, a restricted mouth opening, in head and neck cancer patients may be caused by ingrowth of the tumour in the masticatory muscles or by fibrosis after surgery or radiotherapy. Trismus can hamper normal oral intake, dental hygiene, social activities, oncological follow-up, and dental treatment.¹⁻⁵

Cut-off points for trismus have been determined based on the dental status of patients: 35 mm for dentate patients and 40 mm for edentulous patients.² Other cut-off points for trismus are based on the severity of the restriction, such as 35 mm for moderate trismus and 20 or 25 mm for severe trismus.^{6,7} Based upon the severity of the restriction, grades have also been used: grade 2 for a mouth opening of 10 to 20 mm, grade 3 for a mouth opening of 5 to 10 mm, and grade 4 for a mouth opening less than 5 mm.⁸ Sometimes cut-off points seem to be chosen arbitrarily.⁹ Due to the various cut-off points used, prognostic factors for trismus or the effectiveness of therapy for trismus cannot be analysed in a uniform manner and cannot be interpreted for the head and neck cancer population in general easily.

The most commonly used cut-off point is 35 mm or less.^{1,10-12} A study determined this cut-off point on the basis of perceived restrictions reported by head and neck cancer patients.¹³ The percentage correctly predicted trismus was 81%, with a sensitivity of 0.71, and a specificity of 0.98. Another study had a similar cut-off point of less than 35 mm based upon reported problems with chewing and diet.¹⁴ The sample sizes were 89 and 100 patients, resulting in little or no statistical power to perform covariate analyses.

The aim of the present study was to verify the cut-off point of 35 mm or less for trismus in a large head and neck cancer population. Firstly, we determined the cut-off point for trismus based upon perceived difficulties opening the mouth. Secondly, we determined cut-off points for significant covariates.

MATERIALS AND METHODS

Patient selection

This cross-sectional study included patients who visited the Department of Oral and Maxillofacial Surgery at the University Medical Center Groningen (UMCG) (the Netherlands) for head and neck cancer between November 2012 and January 2015. Patients were included if they had a malignant tumour located in the upper aerodigestive tract, unknown primaries with metastases in the head and neck region, or a major salivary gland tumour. Patients were excluded if they were younger than 18 years, were not diagnosed with head and neck cancer, had rare types of tumours, had missing data regarding maximal mouth opening (MMO), or had missing data regarding their perception of difficulties opening the mouth. Our study was carried out according to the regulations of our institute. The Medical Ethical Committee of the UMCG concluded that our research was not subject to the Medical Research (Human Subject) Act (METc number 2016.692).

MMO measurements and difficulties opening the mouth

MMO measurements were performed by surgeons, nurse practitioners or residents, using the OraStretch® Range-of-Motion Scale, as part of routine patient care. MMO was measured during every follow-up visit. As patients had several follow-up visits during the study period, multiple MMO measurements were recorded. In our analysis, we used only the first recorded MMO measurement of each included patient. MMO and dental status were recorded on a separate registration form. If the mouth opening was measured at the right upper central incisor and the right lower central incisor (of own dentition or prosthesis), the dental status was recorded as "dentate". If the alveolar ridges at the former location of the right upper and lower central incisor were used as measurements points, the dental status was recorded as "edentulous". If the alveolar ridge was used as the measurement point for one jaw, and the right upper or lower central incisor for the other jaw, the dental status was recorded as "partially edentulous". Because the scale of the OraStretch® Range of Motion Scale has a maximum of 52 mm, patients who had a MMO of 52 mm or more were measured using a sliding calliper (in mm). After recording the MMO, the patients were asked if they perceived difficulties opening the mouth (yes, no).

Additional data

Besides the data on the registration form, additional data was retrieved from the patient information system used in the UMCG, including:

Tumour localization (tongue, floor of mouth, maxilla (including the maxilla, hard palate, and maxillary sinus), mandible, cheek, major salivary glands (including the parotid gland, submandibular gland, and sublingual gland), oropharynx (including the oropharynx, base of tongue, retromolar space, tonsils and soft palate), hypopharynx and larynx, lip, unknown primary), cT classification based on the Union for International Cancer Control (UICC) TNM classification 2009 (TX, T1-2, T3-4, unknown), and treatment modalities (no treatment, surgery alone, radiotherapy alone, combination of surgery and radiotherapy). Patients were recorded as having received radiotherapy if they received primary radiotherapy or a combination of radiotherapy and chemotherapy.

Primary analysis

Data was analysed using a receiver operating characteristic (ROC) curve, in which MMO was compared to patients' perception of difficulties opening the mouth. Based on the ROC curve, we calculated the Area Under the Curve (AUC), sensitivity, specificity, and Youden Index. We determined the discriminant validity of patients perceiving difficulties opening the mouth to be perfect if the area under the curve (AUC) was 1, highly accurate if ≥ 0.9 , moderately accurate if $0.7 \geq \text{AUC} < 0.9$, less accurate if $0.5 \geq \text{AUC} < 0.7$, and non-informative if the AUC was 0.5.¹⁵ The Youden Index was calculated as follows: $(\text{sensitivity} + \text{specificity}) - 1$.¹⁶ We determined a cut-off point for trismus on the basis of the highest Youden Index score.

Covariate analysis

We used a t-test for independent samples to analyse an association between patients' perception of difficulties opening the mouth and age. We used a Chi-Square test to analyse associations between patient's perception of difficulties opening the mouth and gender, dental status, and different treatment modalities. When a significant association between perceived difficulties opening the mouth and a covariate was found ($p < 0.05$), separate ROC curves were plotted for that covariate. Cut-off points for the subgroups of that covariate were determined in the same way as for the total group.

Post-hoc analysis

In case the results of the performed analyses need more clarification or insight in the data, additional analyses were performed.

RESULTS

Patient characteristics

MMO measurements of 839 patients were recorded. In total, 168 patients were excluded, because they were not diagnosed with head and neck cancer (n=77), had rare types of tumours concerning localizations (for example pyriform sinus, ethmoid sinus, sphenoid sinus), metastases of primary tumours that were not part of head and neck oncology (for example mamma or kidney), or histology (neuroblastoma, lymphoma, Merkel-cell carcinoma) or a combination (n=29), or had missing data regarding MMO measurement or their perception of difficulties opening their mouth (n=62). In total, 134 patients had a MMO larger than 52 mm, of whom 109 were measured using a sliding calliper. Of 25 patients, the MMO was set on 52 mm because a sliding calliper was unavailable during the visit. The final study population consisted of 671 patients (80.0%) (Table 1). In our final study population, 278 patients (41.4%) were treated with surgery alone, 130 patients (19.4%) were treated with radiotherapy alone, and 215 patients (32.1%) were treated with a combination of surgery and radiotherapy.

MMO measurements versus difficulties opening the mouth

In total, 109 (16.2%) patients perceived difficulties with opening the mouth. These patients had a mean MMO of 30.1 mm (95% Confidence Interval (CI): 28.0; 32.1 mm) (Figure 1A). Patients who did not perceive difficulties with opening their mouth had a mean MMO of 44.5 mm (95% CI: 43.8; 45.2 mm).

Primary analysis

The AUC of the ROC curve of the total study population was 0.846 (95% CI: 0.803; 0.889) (Figure 2A). The Youden index was highest at 35 mm (0.569) with a sensitivity of 0.706 and a specificity of 0.863 (Table 2).

Covariate analysis

No significant difference in age was found between patients who perceived difficulties opening the mouth and those who did not ($p=0.804$). No significant difference was found in gender ($p=0.756$) and in dental status ($p=0.439$) between patients who perceived difficulties opening the mouth and those who did not. Patients who were treated with radiotherapy alone perceived difficulties opening the mouth more often than patients who were treated with surgery alone ($p<0.001$) (Table 3).

We plotted a ROC curve for patients who were treated with surgery alone and patients who were treated with radiotherapy alone (Figure 2B,2C). The AUC of the ROC curve for surgery alone was 0.784 (95% CI: 0.667 to 0.901). The Youden Index was highest at a MMO of 37 mm (0.496), with a sensitivity of 0.636 and a specificity of 0.859 (Table 2).

The AUC of the ROC curve for radiotherapy alone was 0.811 (95% CI: 0.705; 0.917). The Youden Index was highest at a MMO of 33 mm (0.560), with a sensitivity of 0.667 and a specificity of 0.893.

Table 1. Patient, tumour and treatment characteristics.

	Total (n=671)	Surgery only (n=278)	Radiotherapy only (n=130)
	n(%)	n(%)	n(%)
Patient characteristics			
Male	360 (53.7)	143 (51.4)	82 (63.1)
Age (years), range 11-96; mean (SD)	63.4 (13.5)	62.6 (13.7)	63.9 (11.3)
Maximal mouth opening , range 7-73; mean (SD)	42.2 (10.6)	45.0 (8.8)	41.3 (11.1)
Dental status			
Dentate	526 (78.4)	234 (84.2)	95 (73.1)
Edentulous	99 (14.8)	33 (11.9)	25 (19.2)
Partially edentulous	42 (6.3)	9 (3.2)	10 (7.7)
Missing	4 (0.6)	2 (0.7)	0 (0.0)
Tumour characteristics			
Localization of primary tumour			
Tongue	148 (22.1)	89 (32.0)	7 (5.4)
Floor of mouth	82 (12.2)	39 (14.0)	13 (10.0)
Maxilla	34 (5.1)	17 (6.1)	7 (5.4)
Mandible	49 (7.3)	23 (8.3)	1 (0.8)
Cheek	19 (2.8)	8 (2.9)	1 (0.8)
Major salivary glands	70 (10.4)	30 (10.8)	5 (3.8)
Oropharynx	94 (14.0)	24 (8.6)	45 (34.6)
Hypopharynx and larynx	32 (4.8)	0 (0.0)	24 (18.5)
Lip	52 (7.7)	27 (9.7)	14 (10.8)
Unknown primary	12 (1.8)	2 (0.7)	8 (6.2)
Missing	79 (11.8)	19 (6.8)	5 (3.8)
T classification			
TX	9 (1.3)	1 (0.4)	2 (1.5)
T1, T2	410 (61.1)	230 (82.7)	60 (46.2)
T3, T4	143 (21.3)	18 (6.5)	56 (43.1)
Missing	109 (16.2)	29 (10.4)	12 (9.2)
Treatment characteristics			
No treatment	48 (7.2)	0 (0.0)	0 (0.0)
Surgery	278 (41.4)	278 (100.0)	0 (0.0)
Radiotherapy	130 (19.4)	0 (0.0)	130 (100.0)
Combination of surgery and radiotherapy	215 (32.1)	0 (0.0)	0 (0.0)

Figure 1. Box and whisker plots concerning maximal mouth opening in relation to patients' perception of difficulties opening the mouth of the total study population (A), of the population who were treated with surgery only (B), and patients who were treated with radiotherapy only (C).

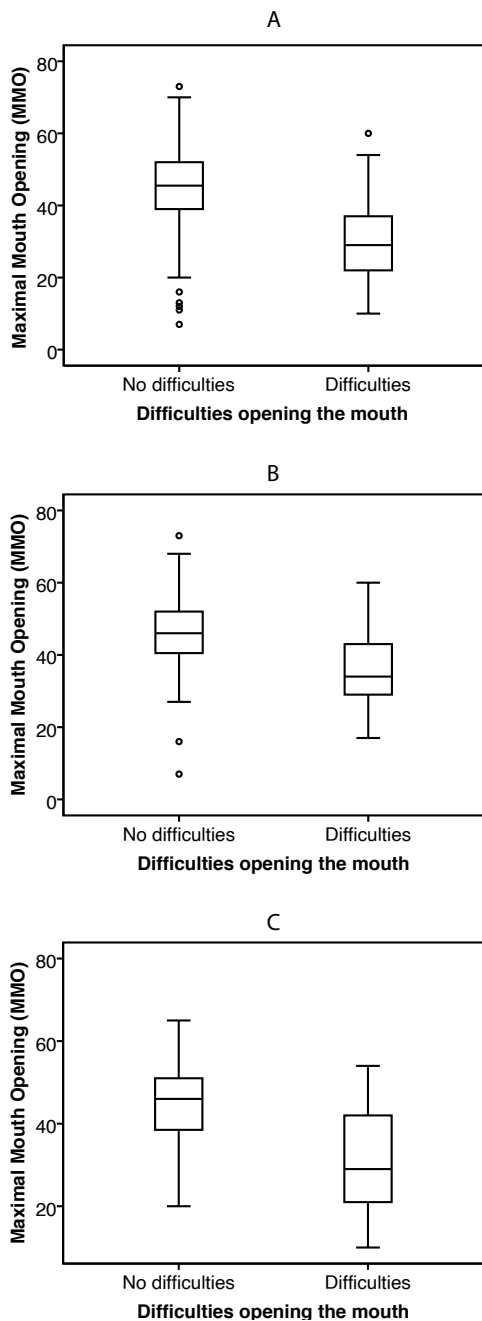


Figure 2. Receiver Operating Characteristic curve comparing maximal mouth opening (mm) with patients' perception of difficulties opening the mouth for the total study population (A), the population who were treated with surgery only (B), and patients who were treated with radiotherapy only (C).

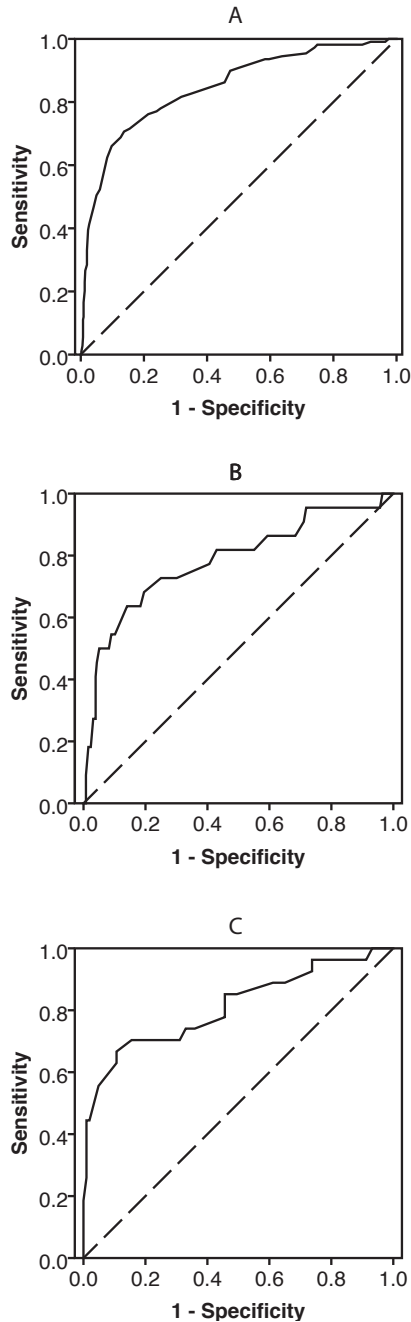


Table 2. Sensitivity, Specificity and Youden Index for maximal mouth opening measurements.

Cut-off point (mm)	Total study population (n=671)			Surgery only (n=278)			Radiotherapy only (n=130)		
	Sensitivity	Specificity	J	Sensitivity	Specificity	J	Sensitivity	Specificity	J
20	0.202	0.988	0.189	0.091	0.992	0.083	0.259	0.990	0.250
21	0.229	0.988	0.217	0.091	0.992	0.083	0.259	0.990	0.250
22	0.266	0.986	0.252	0.091	0.992	0.083	0.370	0.990	0.361
23	0.284	0.980	0.265	0.091	0.992	0.083	0.370	0.990	0.361
24	0.312	0.980	0.292	0.091	0.992	0.083	0.407	0.990	0.398
25	0.330	0.980	0.311	0.091	0.992	0.083	0.444	0.990	0.435
26	0.394	0.977	0.371	0.091	0.992	0.083	0.444	0.981	0.425
27	0.413	0.973	0.386	0.182	0.984	0.166	0.444	0.981	0.425
28	0.468	0.959	0.427	0.182	0.977	0.158	0.481	0.971	0.452
29	0.505	0.950	0.455	0.273	0.969	0.241	0.519	0.961	0.480
30	0.523	0.940	0.462	0.273	0.961	0.234	0.556	0.951	0.507
31	0.624	0.916	0.540	0.409	0.961	0.370	0.630	0.893	0.523
32	0.642	0.909	0.551	0.455	0.957	0.412	0.630	0.893	0.523
33	0.661	0.902	0.563	0.500	0.949	0.449	0.667	0.893	0.560 ^a
34	0.688	0.874	0.562	0.500	0.918	0.418	0.704	0.845	0.548
35	0.706	0.863	0.569 ^a	0.545	0.910	0.456	0.704	0.835	0.539
36	0.716	0.845	0.561	0.545	0.898	0.444	0.704	0.816	0.519
37	0.761	0.786	0.548	0.636	0.859	0.496 ^a	0.704	0.767	0.471
38	0.771	0.760	0.530	0.636	0.816	0.453	0.704	0.748	0.451
39	0.780	0.747	0.527	0.682	0.805	0.487	0.704	0.718	0.422
40	0.807	0.698	0.505	0.727	0.750	0.477	0.704	0.689	0.393
41	0.817	0.681	0.498	0.727	0.730	0.458	0.741	0.670	0.411
42	0.826	0.653	0.479	0.727	0.699	0.426	0.741	0.641	0.382
43	0.862	0.544	0.407	0.773	0.594	0.366	0.778	0.544	0.321
44	0.899	0.527	0.426	0.818	0.570	0.388	0.852	0.544	0.396
45	0.908	0.500	0.408	0.818	0.547	0.365	0.852	0.505	0.357

J= Youden Index, ^a=Highest Youden Index score.

Table 3. Comparison between patients with and without difficulties opening the mouth.

	No difficulties opening the mouth (n=562)		Difficulties opening the mouth (n=109)		χ^2	DF	p
	n	%	n	%			
Patient characteristics							
Male gender	303	53.9	57	52.3	0.096	1	0.756
Age	63.4 ^a	13.7 ^b	63.7 ^a	12.4 ^b	-0.35 ^c	-3.1;-2.4 ^d	0.804*
Dental status					1.646	2	0.439
Dentate	445	79.7	81	74.3			
Partially edentulous	34	6.1	8	7.3			
Edentulous	79	14.2	20	18.3			
Treatment characteristics							
Treatment modality					33.528	3	<0.001
No treatment	44	7.8	4	3.7			
Surgery only	256	45.6	22	20.2			
Radiotherapy only	103	18.3	27	24.8			
Surgery and radiotherapy	159	28.3	56	51.4			

%: column percentage, χ^2 : Results of Chi-Square test, DF: Degrees of freedom, a: mean, b: standard deviation, c: difference in means, d: 95% confidence interval, *: t- test for independent samples.

Post-hoc analysis

To provide insight into the possible association between the time from treatment (surgery or radiotherapy) to measurement and patients' perception of difficulties opening the mouth (yes, no), we performed additional analysis. The Mann-Whitney U test showed that the period from treatment to measurement differs significantly in relation to the perceived difficulties with opening the mouth ($p=0.010$) and in relation to the treatment modality (surgery or radiotherapy) ($p<0.001$) (Table 4). In the multivariate logistic regression analysis, treatment modality was significantly associated with perceived difficulties opening the mouth ($p=0.005$), but the period from treatment to measurement does not ($p=0.569$).

As we found a 4 mm difference between the cut-off points for different treatment modalities, we performed a Mann-Whitney U test in order to give insight into a possible association between treatment modalities and the influence on MMO. The test showed that the MMO was not significantly different after surgery alone or radiotherapy alone for the patients who perceived difficulties when opening the mouth ($p=0.078$) (Table 4).

Table 4. Analysis of time from treatment to measurement (months) in patients with and without difficulties opening the mouth and in patients who were treated with surgery only or radiotherapy only and analysis of maximal mouth opening measurement, only of patients who perceived difficulties when opening the mouth, who were treated with surgery only or radiotherapy only, using the Mann-Whitney U-test.

	No difficulties opening the mouth (n=399)		Difficulties opening the mouth (n=92)			
	Median	IQR	Median	IQR	MWU	<i>p</i>
Time from treatment to measurement^a	28.2	8.9;58.3	16.1	2.1;48.0	15,174.0	0.010
	Surgery only (n=220)		Radiotherapy only (n=80)			
	Median	IQR	Median	IQR	MWU	<i>p</i>
Time from treatment to measurement^a	33.9	12.6;67.4	9.6	1.5;31.7	4856.5	<0.001
	Surgery only (n=22)		Radiotherapy only (n=27)			
	Median	IQR	Median	IQR	MWU	<i>p</i>
Maximal mouth opening measurement^b	34.0	29.0;43.3	29.0	20.0;43.0	209.5	0.078

^a: 48 patients received no treatment, 132 received treatment after the measurement moment. ^b: Only the patients are included who perceived difficulties when opening the mouth, IQR: Interquartile range, MWU: Mann-Whitney U test.

DISCUSSION

Key results

For the total study population, the cut-off point for trismus was 35 mm or less. For patients who were treated with surgery alone, the cut-off point was 37 mm or less and for patients who received radiotherapy alone 33 mm or less.

Interpretation

We found that patients who were treated with radiotherapy alone perceived difficulties opening the mouth at a smaller mouth opening (33 mm) compared to patients who were treated with surgery alone (37 mm). Postoperative symptoms, such as pain, scarring and trismus, are immediately noticeable for the patient. After radiotherapy, MMO decreases more gradually.¹⁷ On average, during radiotherapy (first 9 weeks), the MMO decreased with 1.3% per month. In the first 9 months after radiotherapy, the MMO decreased 2.4% per month.¹⁷ Between 12 and 24 months after radiotherapy, the MMO decreased 0.2% per month. This gradual decrease in MMO was also confirmed in another study.¹⁸ The prevalence of trismus in head and neck cancer patients after radiotherapy treatment was: 32% after 3 months, 34% after 6 months, and 38% after 12 months.¹⁸ As the MMO decreases gradually, patients may have the ability to adapt in the meantime and therefore may experience mouth opening restrictions at a smaller mouth opening.

Our assumption that patients adapt to the mouth opening restriction in time, is confirmed in our data. The period from treatment to measurement is significantly associated with perceived difficulties opening the mouth. Taking the treatment modality into account, in a multivariate logistic regression analysis, the period from treatment to measurement was not significantly associated with perceived difficulties opening the mouth. Therefore, for clinical use, only the treatment modality should be taken into account.

We observed a 4 mm difference between the cut-off points of different treatment modalities, but we also found that MMO was not significantly different after surgery alone or radiotherapy alone for the patients who perceived difficulties when opening the mouth. Therefore, we prefer to speak of a trend for an earlier perception of difficulties when opening the mouth in patients treated with surgery alone compared to patients receiving radiotherapy alone.

Other studies

One study also determined the cut-off of 35 mm or less. That study performed one additional covariate analyses, for dental status, but did not find a significant difference.¹³ We were able to analyse other covariates: we found a significant difference regarding treatment modalities as covariates, but not for dental status. A second study, determined the cut-off point for trismus on the basis of reported problems with chewing and diet. This study determined the cut-off point of less than 34 mm. They determined the cut-off point in groups of 5 mm instead of 1 mm, which could therefore have resulted into a different cut-off point compared to our study. They did not perform additional covariate analyses.¹⁴

Study limitations and strengths

A limitation of our study is that the time intervals between cancer treatment and MMO measurements differed, as the MMO was measured during regular check-up visits. For example, one patient had a measurement 3 months post-treatment, while another patient had a measurement 24 months post- treatment. This difference could have led to an underestimation of patients who perceived difficulties opening the mouth, as some patients could already have adapted to their new MMO and would not perceive difficulties opening the mouth.

Another possible limitation is that several professionals measured maximal mouth opening, which could have introduced an inter-observer measurement error. Nonetheless, a previous study shows that inter- observer variability is minimal.¹⁹

As the sliding calliper was not always available during the MMO measurements, 25 patients could not be measured. Their MMO was set on 52 mm. We expect that the patients with a MMO larger than 52 mm do not perceive difficulties when opening the mouth. Therefore, the results of the mean MMO of patients who do not perceive difficulties when opening the mouth might be slightly lower than the actual mean MMO.

The strength of our study is the large study population and many MMO measurements. Due to our large database, we were able to perform covariate analyses with enough statistical power. Due to our covariate analyses, we were able to make a distinction between the patients' perception of difficulties when opening the mouth after receiving radiotherapy or surgery. Now clinicians can take into account that patients' perception of a restricted mouth opening differ after surgery or radiotherapy. As the cut-off point of 35 mm or less is now confirmed in a large head and neck cancer population, clinicians

could use this cut-off point as an indicator to start preventive measures. We recommend to use this cut-off point for future research as well; to explore prognostic factors for trismus, to report prevalences of trismus and for evaluating the effectiveness of therapy for trismus.

Conclusion

We have verified the cut-off point of 35 mm or less for trismus in the total head and neck cancer population. Patients receiving different treatment modalities could differ in their perception of difficulties opening their mouth. To improve comparison of future studies concerning trismus in head and neck cancer patients, we recommend using the cut-off point of 35 mm or less.

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