Trismus in head and neck cancer patients

van der Geer, Joyce

DOI:
10.33612/diss.112040321

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Mouth opening in patients treated for head and neck cancer: a linear mixed model analysis

This chapter is an edited version of:
van der Geer SJ*, van Rijn PV*, Kamstra JI, Roodenburg JLN, Dijkstra PU.
Mouth opening in patients treated for head and neck cancer: a linear mixed model analysis.
[Currently submitted to International Journal of Oral & Maxillofacial Surgery]
**shared first author*

ABSTRACT

Purpose: A severely restricted mouth opening is a common problem in head and neck cancer patients and affects oral functions and quality of life. Aim of this study was to analyse factors associated with a change in mouth opening.

Methods: Maximal mouth opening was measured in head and neck cancer patients (n=730). A linear mixed model was applied to analyse factors associated with mouth opening.

Results: Factors associated with a change in mouth opening were gender (female), age, dental status (dentate, partially edentulous), tumour localization (cheek, unknown primary, maxilla, oropharynx, mandible, major salivary glands, tongue, lip, floor of mouth), cT classification (cT3,4), chemotherapy, radiotherapy, surgery, and reconstruction after surgery (soft tissue flap, soft tissue flap and reconstruction plate, skin graft, and bony tissue flap).

Conclusions: The found factors enable early identification of patients possibly at risk for a reduction in maximal mouth opening.

INTRODUCTION

Trismus, a severe restriction of the mouth opening, is a common problem in head and neck cancer patients[1-3]. Trismus impedes oral functions such as speaking, eating and swallowing[4-6], which may have a negative impact on the quality of life.[7,8] When a mouth opening is severely restricted, oral hygiene may be impaired as well. Additionally, dental examinations and oncological follow-up might be difficult. Hence, prevention of trismus is important. Identifying factors that influence mouth opening may contribute to the prevention of trismus.

Studies which have analysed factors that influence mouth opening either had small sample sizes (n=58[9] or n=17[10]), or focused on one specific tumour localization (such as nasopharyngeal tumours[10]) or on one treatment modality (such as radiotherapy[9-11]).

In this study, we aim to describe and analyse factors which influence mouth opening, using a large sample of head and neck cancer patients with various tumour and treatment characteristics, recruited at a department of Oral and Maxillofacial Surgery.

MATERIALS & METHODS

This prospective cohort study was conducted between November 2012 and February 2015 at the University Medical Center Groningen (UMCG). The Medical Ethics Review Committee of Groningen judged that this study was not subject to the Medical Research (Human Subject) Act (METc number 2016.692). Maximal mouth opening (MMO) was measured in patients who were having a first consultation, a regular or follow-up appointment at the Oncology Division of the Department of Oral and Maxillofacial Surgery. The frequency and timing of the MMO measurements were determined from the patients' appointment dates.

Patients, who had a tumour in the upper aero- digestive tract, or an unknown primary with a metastasis in the head and neck region, or a major salivary gland tumour, were included. Excluded were patients who did not have head and neck cancer, a premalignant lesion, a rare type of tumour, were younger than 18 years of age, or had no data regarding MMO measurements.

The head and neck oncology professionals, oral and maxillofacial surgeons, oral and maxillofacial surgery residents and nurse practitioners measured the patients' mouth openings using an Orastretch Range of Motion Scale (Craniomandibular Rehab Inc., Denver, USA) and recorded the dental status of the patients. This measurement tool is disposable, and has a measuring range from 3 to 52 mm. The patients were instructed to open their mouths as maximally as possible and then the distance was measured. The distance between the edges of the 11 and 41 incisors were measured in patients who were dentate or wore prosthesis. In case patients were not wearing a prosthesis, the distance between the tops of the alveolar ridges (virtual reference point 41/11) were measured. Patients with a mouth opening larger than 52 mm were measured using a sliding calliper (generic model).

Patient-, tumour-, and treatment characteristics were retrieved from the medical records: gender, age (years), tumour localization (tongue, floor of mouth, maxilla [including maxilla, palate, maxillary sinus and nasopharynx], mandible, cheek, major salivary glands [including parotid gland, sublingual gland and submandibular gland], oropharynx [including base of tongue, retromolar space and tonsils], lip, unknown primary, hypopharynx and larynx), clinical and pathological Tumour classification (c/pT classification) based on the Union for International Cancer Control (T1-T2, T3-T4)[12],

histology (squamous cell carcinoma, no squamous cell carcinoma), chemotherapy (yes, no), chemotherapy date, radiotherapy (number of treatments), radiotherapy date, surgery (number of primary tumour operations), surgery date, reconstruction after surgery (skin graft, soft tissue flap, soft tissue flap and reconstruction plate, bony tissue flap), neck dissection (number of treatments), neck dissection date, carbon dioxide laser evaporation (yes, no), photodynamic therapy (yes, no), and exercise therapy (yes, no). As for the reconstruction after surgery: no reconstruction was recorded when primary closure was applied to the wound or no surgery was performed.

A soft tissue flap was recorded in case of a pectoralis major flap, nasolabial flap, anterolateral thigh flap or radial forearm flap. A bony flap was recorded in case of a fibular osteocutaneous flap. If a patient had multiple tumours in the head and neck region, the same characteristics as described above were collected for each tumour separately.

The interval between the last cancer treatment and the MMO measurement was calculated in months (date of MMO measurement minus date of last cancer treatment (surgery, radiotherapy or chemotherapy)). The interval between MMO measurements was calculated in months (date of a particular MMO measurement minus the date of the first MMO measurement).

Statistical analysis

A linear mixed model analysis (first order autoregressive covariance structure) was used to analyse factors influencing mouth opening. This type of analysis means that repeated measurements (at various moments) can be taken into account. Potential factors associated with a change in mouth opening were entered in the statistical model, one by one, namely: gender, (standardised) age, dental status, tumour localization, cT classification, pT classification, histology, chemotherapy, radiotherapy, surgery, reconstruction after surgery, neck dissection, carbon dioxide laser evaporation, photodynamic therapy, and exercise therapy. A factor was removed if the model fit (-2log likelihood criterion) did not increase significantly or when the regression coefficient was not significant. Interaction terms between two factors, or between one factor and the interval of last cancer treatment and MMO measurement, or between one factor and the interval between MMO measurements, were explored. Age was standardised as follows: the mean age of the total group (63.6 years) was subtracted from the age of the patient.

SPSS 22.0 (IBM, Armonk, USA) was used for the data-analysis. A p-value ≤ 0.05 was regarded as significant.

RESULTS

Study population

Initially, 836 patients were measured. Of these patients, 106 were excluded because 77 were not diagnosed with head and neck cancer and 29 had rare types of tumours regarding localization, histology and/or metastases of primary tumours. In total, 138 patients had a mouth opening ≥ 52 mm and 112 of these patients were measured using a sliding calliper. A MMO of 52 mm was recorded for 26 patients in the database because no sliding calliper was available or the patient did not visit the department of Oral and Maxillofacial Surgery any more during the study period. The final total study population consisted of 730 patients.

Patient, tumour, and treatment characteristics are shown in table 1. The mean age (SD) was 63.6 (13.5) years. Most tumours were located in the tongue (25.4%) and the oropharynx (17.2%). The majority of the tumours were squamous cell carcinomas (79.8%). A small group (n=74, 10.1%) had more than one tumour.

Maximal mouth opening measurements

The mean mouth opening at the first measurement was 42.0 mm, SD 10.5. Of the total study population, 300 patients (41.1%) were measured twice or more. Mouth opening measurements at subsequent intervals are shown in Supplementary Table 1.

Factors influencing maximal mouth opening

The factors of the total study population associated with a decrease in mouth opening were: female gender (B -1.64), older age (B -0.08), dental status (dentate(B -6.56), partially edentulous (B -3.57)), tumour localization (highest to lowest decrease in mouth opening: cheek (B -12.11), cT3,4 (B -4.46), unknown primary, maxilla, oropharynx, mandible, major salivary glands, tongue, lip, floor of mouth (B -1.92)), chemotherapy (B -6.57), radiotherapy (B -4.08), surgery (B -2.40), and reconstruction after surgery (highest to lowest decrease in mouth opening: soft tissue flap (B -4.36), soft tissue flap and reconstruction plate, skin graft, and bony tissue flap (B -0.49)) (Table 2).

Table 1. Patient, tumour and treatment characteristics of the total study population (n=730).

Characteristics	Number of patients
	n (%)
Patient characteristics	
Male	388(53.2)
Age (years), Mean (SD)	63.6(13.5)
Dental status	
Dentate	575(78.8)
Partially edentulous	45(6.2)
Edentulous	104(14.2)
Tumour characteristics	
Tumour localization	
Tongue	164(25.4)
Floor of mouth	92(14.2)
Maxilla	36(5.6)
Mandible	51(7.9)
Cheek	21(3.3)
Major salivary glands	73(11.3)
Oropharynx	111(17.2)
Lip	54(8.4)
Unknown primary	12(1.9)
Hypopharynx and larynx	32(5.0)
cT classification	
T1,T2	450(77.4)
T3,T4	155(25.6)
Squamous cell carcinoma	510(78.9)
Treatment characteristics	
Chemotherapy	95(13.0)
Radiotherapy	
No radiotherapy	472(64.7)
#1	236 (32.3)
#2	21(2.9)
#3	1(0.1)
Surgery	
No surgery	224(30.7)
#1	444(60.8)
#2	48(6.6)
#3	13(1.8)
#4	4(0.1)
Reconstruction after surgery	
Skin graft	118(19.2)
Soft tissue flap	38(6.2)
Soft tissue flap and reconstruction plate	14(2.3)
Bony tissue flap	37(6.0)

Table 1. (Continued)

Characteristics	Number of patients
	n (%)
Neck dissection	
No neck dissection	453 (62.1)
#1	251 (34.4)
#2	22 (3.0)
#3	2 (0.3)
#4	1 (0.1)
Carbon dioxide laser evaporation	82(11.3)
Photodynamic therapy	10(1.4)
Other characteristics	
Exercise therapy	47(6.5)

#: number of primary tumour operations or radiotherapy treatment course.

Interaction terms did not contribute significantly to the regression equation. The interval between the last cancer treatment and MMO measurement or the intervals between the different MMO measurements did not have an effect on MMO. When exploring an interaction effect of the interval between the different MMO measurements and radiotherapy, a near significant value was found (p=0.069).

Based on the results of the mixed model analysis, a mean mouth opening can be predicted statistically for a variety of head and neck cancer patients. For example: The maximal mouth opening of a 65-year-old, edentulous female, with a cT3 tumour of the tongue, who received surgery once, can be estimated with the following equation:

Predicted maximal mouth opening = 54.56 (intercept) -1.64 (female) + [(65-63.6) *-0.08] (age) + 0 (edentulous) -4.46 (cT3) -4.26 (Tongue) -2.40 (Surgery) = 41.69 mm.

Table 2. Results of the linear mixed model analysis to predict mouth opening (n=730).

	B	SE	95% Confidence Interval		Sig.
			Lower	Upper	
Patient characteristics					
Gender					
Female	-1.64	0.73	-3.07	-0.21	0.03
Male [RC†]					
Age (per year)	-0.08	0.03	-0.14	-0.02	0.01
Dental status					
Dentate	-6.56	1.04	-8.59	-4.51	<0.01
Partially Edentulous	-3.57	1.69	-6.88	-0.26	0.03
Edentulous [RC†]					
Tumour characteristics					
Tumour localization					
Cheek	-12.11	2.62	-17.26	-6.96	<0.01
Unknown primary	-7.51	4.43	-16.20	1.17	0.09
Maxilla	-7.28	2.26	-11.72	-2.85	<0.01
Oropharynx	-6.93	1.85	-10.56	-3.30	<0.01
Mandible	-6.83	2.20	-11.15	-2.50	<0.01
Major salivary glands	-5.08	2.10	-9.21	-0.95	0.02
Tongue	-4.26	1.87	-7.92	-0.59	0.02
Lip	-4.16	2.11	-8.30	-.015	0.05
Floor of mouth	-1.92	1.98	-5.81	1.96	0.33
Hypopharynx and Larynx [RC†]					
cT classification (reference cT1,2)					
T1,2 [RC†]					
T3,4	-4.46	1.08	-6.58	-2.34	<0.01
Treatment characteristics					
Surgery (number of operations)	-2.40	0.66	-3.70	-1.11	<0.01
Reconstruction after surgery					
Soft tissue flap	-4.36	1.49	-7.30	-1.41	<0.01
Soft tissue flap and reconstruction plate	-1.24	2.79	-6.73	4.24	0.66
Skin graft	-1.12	1.03	-3.15	0.91	0.28
Bony tissue flap	-0.49	1.79	-4.00	3.03	0.78
No reconstruction [RC†]					
Radiotherapy (number of treatment courses)	-4.08	0.68	-5.42	-2.73	<0.01
Chemotherapy	-6.57	1.13	-8.78	-4.36	<0.01
Intercept					
Intercept	54.56	2.04	50.56	58.58	<0.01

[RC†]: Reference category (variable): male (gender); edentulous (dental status); hypopharynx and larynx (tumour localization); no reconstruction (reconstruction).

DISCUSSION

Key results

Factors associated with a restricted MMO are gender, age, dental status, cT classification, tumour localization, chemotherapy, radiotherapy, surgery, and reconstruction after surgery.

Other studies

In our study, gender and age had a subtle, but significant effect on mouth opening. In studies with smaller sample sizes (n=143 and n=64), gender and age were not significantly associated with mouth opening.[13,14] Due to the small sample sizes, there might have been a lack of statistical power to detect these subtle effects.

Studies which took extra-oral measurements did not find a significant effect of dental status on mouth opening.[13,14] The reference points for extra-oral measurements were identical for all the patients (from nose to chin), independent of the dental status. The difference between the resting vertical dimension and maximal mouth opening was calculated. In our study, we took intra-oral measurements and found a significant effect of dental status on mouth opening. The reference points for intra-oral measurements were dependent on the dental status (namely the incisal edge of the incisor or top of alveolar ridge), resulting in different MMO reference points for dentate and (partially) edentulous patients. Therefore, the effects of dental status on mouth opening are more likely to be found when measurements are taken intra-orally.

Previous studies confirmed that tumour localization[11,13,14], tumour stage[11,14], and treatment modality[14,15] have a significant effect on mouth opening. A reduction in mouth opening is more likely to occur when the tumour is located near the masticatory muscles or the temporomandibular joint and when the tumour is larger (T4). A larger tumour affects more surrounding structures. Additionally, larger tumours need more extensive tumour treatment, leading to larger surgical defects and larger radiation fields.

For treatment modalities chemotherapy, radiotherapy, and surgery, a significant effect on mouth opening was found. When exploring the interaction effects of a treatment modality and the time interval between MMO measurements, the effect of “time interval between MMO measurements and radiotherapy” was nearly significant in terms of a reduction in mouth opening. The intervals between the MMO measurements varied in our database.

Hence, a clear pattern could not be detected. Studies which applied a fixed time interval after cancer treatment found an effect of time, especially after radiotherapy.[10,11]

Conflicting results have been found regarding the association between reconstruction after surgery and mouth opening. One cross-sectional and one longitudinal study did not find a significant association between reconstruction after surgery and mouth opening.[14,16] Another study found an association between reconstruction after surgery and trismus.[13] Patients who received a free flap reconstruction often suffered from trismus prior to surgery compared to patients who had not received a free flap. A similar pattern was seen at discharge. As the difference between the reconstruction groups was present before surgery, the association might be based on other factors rather than the reconstruction itself (for instance tumour localization and/or tumour stage). Further research on the effect of reconstruction after surgery on mouth opening is needed.

Clinical relevance

The identified factors affecting mouth opening will enable oncological professionals to predict when to take precautionary measures. Early stretching exercises might be considered to prevent or treat trismus. It seems that the decrease in mouth opening is less in patients who exercise during radiotherapy than those who do not exercise.[17,18] It is important that patients start early and comply in doing mouth opening exercises to improve their mouth opening or to prevent deterioration.[19]

Study strengths and limitations

Our large database increased the statistical power to detect significant effects of various patient, tumour and treatment characteristics on mouth opening. The broad variety of patient, tumour and treatment characteristics in our study population makes the results more generalizable for a large group of head and neck cancer patients.

We were able to identify the factors that influence mouth opening. However, no clear time frame can be given as to when these factors will influence mouth opening, due to the various intervals between the MMO measurements in our study.

The linear mixed model only contains the tumour characteristics of the first primary tumour. The number of patients with more than one tumour was limited thus the tumour characteristics of a second tumour could not be analysed adequately in the model.

On comparing first and second tumour characteristics, we found that they were similar in most of the cases. For example, the second tumour was either in the same location as the first tumour (56.8%) or was located in the immediate vicinity of the first tumour (20.3%). Since the tumour characteristics of the first and subsequent tumour are largely similar, we expect that the effects of second tumour characteristics on mouth opening are similar.

Conclusion

Factors associated with a decrease in mouth opening are gender (female), age, dental status (dentate, partially edentulous), tumour localization (cheek, unknown primary, maxilla, oropharynx, mandible, major salivary glands, tongue, lip, floor of mouth), cT classification (cT3,4), chemotherapy, radiotherapy, surgery, and reconstruction after surgery (soft tissue flap, soft tissue flap and reconstruction plate, skin graft, and bony tissue flap). Patients possibly at risk for a decrease in mouth opening can be identified through these factors and can be encouraged to start exercising early.

Supplementary Table 1. Time intervals between maximal mouth opening measurements and the corresponding maximal mouth opening scores.

Measurement moment	Number of patients included	Months between MMO measurement and MMO measurement 1	MMO
	n	Med (IQR)	Med (IQR)
1	730	0.0(0.0;0.0)	43.0(36.0;49.0)
2	300	5.1(3.0;7.5)	41.0(33.5;46.5)
3	150	8.8(6.0;12.2)	40.0(31.0;46.0)
4	78	12.5(8.7;17.0)	42.5(28.0;48.0)
5	33	13.1(10.0;17.9)	42.0(28.0;46.0)
6	14	14.9(12.6;17.5)	40.0(28.0;43.0)
7	7	15.3(14.0;18.4)	43.0(27.0;46.0)
8	3	18.2(10.8;18.3)	46.0(40.0;52.0)
9	2	16.8(12.2;21.4)	45.0(38.0;52.0)

Median and Interquartile Ranges are reported because of the decreasing number of observations.
MMO: maximal mouth opening (in millimetres).

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