Trismus in head and neck cancer patients

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Prognostic factors for a restricted mouth opening (trismus) in head and neck cancer patients: a systematic review

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ABSTRACT

Purpose: To prescribe early trismus therapy, prognostic factors influencing the restricted mouth opening should be identified first. Our aim is to present an overview of these factors in head and neck cancer patients.

Methods: Pubmed, Cochrane, EMBASE and CINAHL were searched using terms related to head and neck cancer and mouth opening. Risk of bias was assessed using the 'Quality in Prognosis Studies' tool. A best evidence synthesis was performed.

Results: Of the identified 1418 studies, 53 were included. Three studies had built a prognostic multivariate model for a restricted mouth opening.

Conclusions: Head and neck cancer patients will most likely develop a restricted mouth opening when they have a large tumour near the masticatory muscles that requires extensive cancer treatment. A restricted mouth opening most likely occurs within six months after cancer treatment. Further research is necessary on factors related to healing tendency or pain intensity.

Registration: Prospero CRD42017071400.

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INTRODUCTION

Trismus, a restricted mouth opening, is considered to be one of the three most burdensome side effects after head and neck cancer treatment.[1-3] Daily activities, such as speaking, eating, and swallowing, become more difficult.[4-6] As a consequence, trismus impacts the quality of life.[7,8]

In order to prevent or to treat trismus, stretching regimens are often prescribed to increase mouth opening.[9] In 2016, a systematic review analysed the effects of various stretching regimens, but none of them was found to be superior.[10] It has been suggested that early initiation of a therapy for trismus results in a greater improvement in mouth opening.[11] However, when the effectiveness of an early, preventive stretching regimen was analysed, no significant difference between the exercise group and control group was found.[12] Not all the patients may have been at risk for trismus, which would have hindered the detection of the effectiveness of the therapy. Moreover, the group of patients not at risk of developing trismus was unnecessarily burdened with an intensive stretching regimen.

Thus, factors influencing trismus should be identified so that only the patients at risk for trismus are subjected to therapy. Previous studies examined the factors associated with trismus but the criteria they applied varied (e.g., a maximal mouth opening (MMO) of less than 20 mm[13] or less than 35 mm[14]). They used different assessment methods (e.g., objective measurement using a millimetre scale[15,16] or perceived difficulties opening the mouth using questionnaires[17,18]), or different study populations (e.g., patients receiving radiotherapy[15,19] or chemoradiotherapy[19,20]). There is no recent systematic review available on prognostic factors for trismus in head and neck cancer patients in general.

The aim of this systematic review is to identify the prognostic factors for trismus (measured objectively and subjectively) in patients treated for head and neck cancer.

MATERIALS AND METHODS

The protocol for this systematic review is registered in Prospero (Register code: CRD42017071400). The study will be reported according to the PRISMA statement.

Literature Search

Four databases were searched for eligible studies: PubMed, Cochrane, EMBASE and CINAHL. The search strategy was developed in cooperation with an information specialist and included MesH terms and free text regarding head and neck cancer and mouth opening (Supplementary text 1). All the databases were searched in November 2017. An update was performed in July 2019.

Eligibility criteria

Prospective longitudinal studies were included if at least two measurement moments, regarding objective measurements of trismus (trismus and MMO) or subjective assessments of trismus (perceived difficulties with opening the mouth), were reported. No distinction was made between active or passive mouth opening measurements. Studies of trismus therapies were excluded, unless they reported data on a restricted mouth opening of a control group that did not receive a form of trismus therapy. (Systematic) reviews, in vitro studies, comments, letters to the editor and case reports of less than 10 patients were excluded. There were no language or time restrictions. Studies written in languages that could not be understood by the authors were translated. Additionally, a full-text version had to be available in order to be included for further assessment and data extraction.

Study selection

After removing any duplicates, the titles and abstracts were assessed for inclusion independently by JG, PR and PD. JG and PD independently assessed the full text versions for inclusion. Any disagreements between them were resolved by discussion. In case no consensus could be reached, a third observer (KD) was consulted. Inter-observer reliability was measured through Cohen's Kappa and percentage of agreement.

Google Scholar, the references of the relevant systematic reviews and the references of the eligible studies were checked by JG for studies missed in the database search. When a study was considered eligible, the full text paper was screened and assessed by JG and PD independently, according to the original protocol.

The studies that only reported descriptive data and did not perform any statistical tests to analyse the influence of factors on trismus, MMO, or perceived difficulties opening the mouth, were excluded.

Data extraction

One reviewer (JG) extracted all required information from the studies, which included sample size, patient characteristics (age, gender), tumour characteristics (tumour localization, T classification, N classification, tumour stage, histology), treatment characteristics (treatment modality), and method of outcome measurements (number of measurement points reported, follow-up time). Percentage of patients with trismus (based on a cut-off point), difference in means or medians of MMO between two measurements (one measurement after treatment minus measurement before treatment) were recorded. In case of multivariate prognostic models, the estimated effects and 95% confidence intervals were extracted.

A second reviewer (PD) extracted data from a random sample of eight studies containing only univariate analyses and the three studies containing multivariate analyses. In case any data was missing or needed clarifying, the corresponding authors were contacted by e-mail.

Risk of bias assessment

Included studies were assessed by JG and PD on risk of bias using the 'Quality In Prognosis Studies' tool (QUIPS).[21] This tool is designed to assess the risk of bias in prognostic studies. The tool assesses the following items: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The risk of bias can be scored low, moderate or high. We added the option "not applicable" which could be chosen in case the studies did not provide adequate information to be able to assess that specific domain. As attrition is commonly high in studies including head and neck cancer patients due to early decease, we predefined the following criteria: when the study attrition is more than 20%, but no specifications are given, we assessed the study as high risk of bias on the study attrition domain. When the study attrition is more than 20%, but specifications are given, we assessed the study as moderate risk of bias on the study attrition domain. For the statistical analysis and reporting domain, we scored a high risk of bias if the effect of only one factor on restricted mouth opening was analysed.

JG and PD were authors of two studies. These studies were assessed by two independent assessors, KD and BG, to reduce the risk of assessor bias.

To assess the overall risk of bias of a study, it was recommended to score the overall risk of bias as "low" if at least all, or the most important domains (determined a priori), were rated as having a low risk of bias.[21] On that basis, we determined the overall risk of bias to be low, if at least 5 out of 6 domains were scored with a low risk of bias and the domains "study confounding" and "statistical analysis and reporting" were scored with a low risk of bias. These two domains are of major importance for analysing the influence of factors on trismus, MMO or perceived difficulties opening the mouth.

In case of disagreement between the reviewers, a consensus meeting was held. If no consensus could be reached, a third reviewer (KD) gave a binding verdict.

Best evidence synthesis

Due to clinical and methodological heterogeneity between the included studies, we did not perform a meta-analysis. Instead, we performed a best evidence synthesis. Three main domains were taken into account in order to rate the level of evidence: quality, quantity and consistency.[22,23] We determined the evidence to be strong if two or more studies (quantity) with an overall low risk of bias (quality) and relatively consistent findings (consistency) of the analysed factors across the studies was found. Evidence was determined to be moderate when evidence was provided including one study with an overall low risk of bias and relatively consistent findings of the analysed factors across the studies. Evidence was determined to be limited when evidence was provided by studies with an overall high risk of bias and relatively consistent findings of the analysed factors across the studies. Evidence was determined to be limited/moderate when evidence was provided by a study with an overall high risk of bias, but in which a multivariate prognostic model was presented. The evidence was determined to be conflicting in case there were inconsistencies between the findings of the analysed factors found across the studies.

RESULTS

Study selection

The first search resulted in 1703 hits. After duplicate removal, 1199 papers were included for title and abstract assessment (Cohen's Kappa: 0.533, agreement 90%). Although 141 were deemed suitable for full text assessment after a consensus meeting (Cohen's Kappa: 0.577, agreement 81%), 40 papers were excluded: 37 were abstracts only (e.g., conference abstract or poster abstract), one was a review, one was a comment in a forum, and one full- text could not be retrieved. The corresponding author was requested to provide the full text article, but no response was received. A further 59 of the available full text papers were excluded because they did not fulfil the inclusion criteria.

The additional check in Google Scholar and the references of the relevant studies and (systematic) reviews, resulted in 16 other papers.[5,17,24-37] After reading the full text, two did not meet the inclusion criteria.[20,24] A total of 56 studies were included for risk of bias assessment and data extraction. During the data extraction process, an additional 7 studies were excluded, because no statistical analysis was performed to identify any factors influencing trismus (n=4)[27,38-40] or because exercises to increase mouth opening had been undertaken (n=2)[26,41], or because only one measurement moment was reported (n=1)[42] (Figure 1).

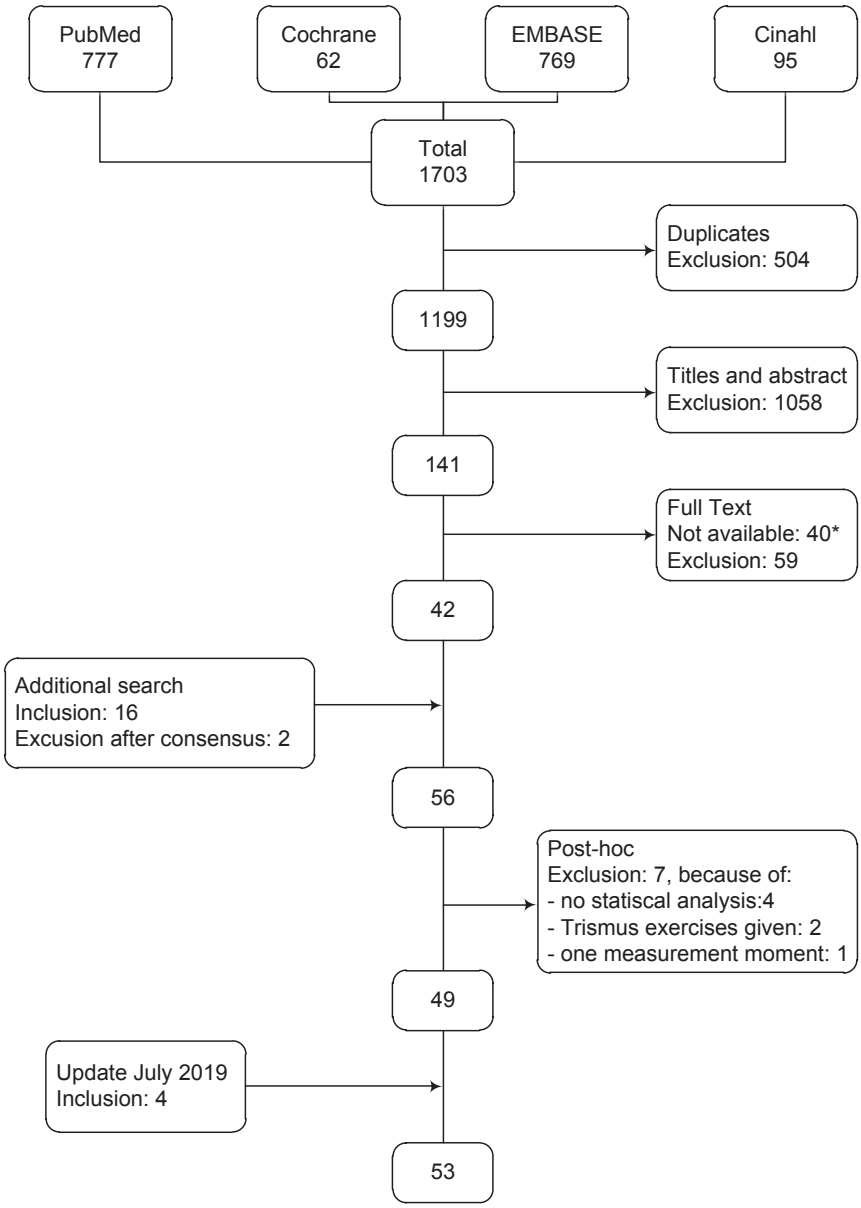
After an update of the search and the removal of duplicates, 203 additional papers were identified. After assessing the titles and abstracts (Cohen's Kappa: 0.378, agreement 80%), were included for assessment of the full text (Cohen's Kappa: 0.493, agreement 76%). Eventually, four of those studies were included. [43-46]

The above procedures resulted in a final selection of 53 studies.[5,13-20,28-37,43,45-77]

Study characteristics

Sample sizes ranged from 14 to 641 patients (Table 1). The number of measurement moments ranged from 2 to 20. The longest follow-up period was 5 years.

Figure 1. Flow chart.



*: studies were not available, because: 37 were abstracts only (e.g. conference abstract or poster abstract), one was a review, one was a comment in a forum, and one full- text could not be retrieved.

Table 1. Data extraction objective and subjective measurements.

Author (year)	Sample size (n)	Age Mean (SD) OR *Median* [range]	Ratio Male: Female	Histology	Tumour localization	Stage	Treatment modality*	#measures †	FU ‡	Remarks
Objective measurements - cut-off point for trismus										
Yan et al (2003)[13]	112	44.6 [14-71]	83:29	-	Nasopharynx	I-IV	**RT**	7	60	
Scott et al (2011) [14]	64	59 (10)	40:24	SCC	Oral cavity, Oropharynx	T:1-4 N:0,+	**S,**(C)RT	3	6	
Lee et al (2012)[47]	152	-	-	-	HNC	Disease:1-4	**S**,(C)RT	3	>6	
Pauli et al (2013)[48]	75	62 [35-86]	45:30	-	HNC	T: 0-4 UICC:I-IV	S,(C)RT	4	12	P: Pauli et al (2016)[49]
Pauli et al (2016)[49]	216	60 [29-87]	155:62	-	HNC	T:x-4	(C)**RT**	4	12	
van der Geer et al (2016)[50]	641	62.3 (12.5)	451:190	-	HNC	T:x-4	S,(C)**RT**	7	48	T: Kamstra et al (2015)[15]
Objective measurements - maximal mouth opening measurements										
Goldstein et al (1999)[51]	58	-	-	-	HNC	-	**RT**	2	6-12	
Wang et al (2005)[52]	17	<50y (n=8), >50y (n=9)	13:4	-	Nasopharynx	T:1-4 N:0-3 Disease:I-III	**RT**	20	48	
Bragante et al (2012)[54]	26	59.0 (8.8) [45-74]	26:0	-	HNC	INCA:I-IVB	(C)**RT**	3	0	
Mucke et al (2012)[55]	96	62.8 (8.9) [41-82]	58:38	SCC	anterior floor of the mouth	T:1-4 N:0-3	**S,**(C)RT	2	2-24	
Lyons et al (2013)[56]	62	<50y (n=26), ≥50y (n=36)[b]	33:29	-	HNC	T:1-4 N:0-3	S,(C)**RT**	2	12-36	
Lazarus et al (2014)[57]	29	58.5 (9.2) [41-78]	23:6	-	HNC	AJCC:I-IVA	**(C)RT**	3	6	
Safdar et al (2014)[58]	65	Group1: 59.7(11.5) Group2: 60.6(13.4)	45:20	-	HNC	T:1-4	**S**	2	6	Group1: platysma reconstruction Group2: submental reconstruction

Table 1. (Continued)

Author (year)	Sample size (n)	Age Mean (SD) OR *Median* [range]	Ratio Male: Female	Histology	Tumour localization	Stage	Treatment modality*	#measures †	FU ‡	Remarks
Wetzels et al (2014)[16]	143	Group1: 68.4(12.2) Group2: 66.9(12.6) Group3: 62.3 (12.9)	Group1: 17:17 Group2: 28:26 Group3: 33:22	-	Oral cavity	T:1-4	S,RT	4	12	Group1: maxilla Group2: mandible Group3: tongue/ floor of mouth
Bragante et al (2015)[53]	56	58.7 (10.8)	52:4	-	UADT	Disease: I –IV	S,(C)**RT**	2	0	
Fong et al (2015)[59]	27	58.7 (9.5)	16:11	-	Nasopharynx	AJCC:I-IV	S,(C)**RT**	4	12 AI	Control Group only
Kamstra et al (2015)[15]	641	62.3 (12.5)	451:190	-	HNC	T:0-4, N:0-3	S,(C)**RT**	7	48	
Manaktala et al (2015)[60]	24	-	-	-	HNC	-	**RT**	5	18 Gy	
Nayar et al (2016)[61]	55	-	-	-	HNC	-	S,**RT**	2	1-2	
Al-Saleh et al (2017)[43]	16	Group1: 54.2(12.5) Group2: 50.6(11.9)	Group1: 6:3 Group2:5:2	-	Oral cavity, Oropharynx	T:1-4 N:0-3	**S**	2	1.5-2	Group1 mandibulotomy surgery Group 2 transoral surgery
Lalla et al (2017)[62]	372	59.8 (10.9)	284:88	SCC	HNC	-	S,(C)**RT**	2	6	
Thor et al (2017)[63]	196	60 (11)	141:55	-	HNC	T:0-4 N:0-4	(C)**RT**	4	12	P: Pauli et al (2016)[57]
Subjective measurements										
De Graeff et al (1999)[17]	75	*60* [29-75]	54:21	SCC	Oral cavity, Oropharynx	AJCC:I-IV	**S,**RT	3	12	P: De Graeff et al (2000)[29]
De Graeff et al (2000)[29]	107	*60* [31-73]	86:21	SCC	HNC	AJCC:0-IV	S,RT	5	36	
Epstein et al (2000)[5]	357	63 [18-88]	256:101	-	HNC	Disease:I-IV	S,(C)RT	6	12	
Bjordal et al (2001)[28]	20	53.4 [38-78]	12:8	-	HNC	AJCC:I-IV	**RT**	3	6	

Table 1. (Continued)

Author (year)	Sample size (n)	Age Mean (SD) OR *Median* [range]	Ratio Male: Female	Histology	Tumour localization	Stage	Treatment modality*	#measures †	FU ‡	Remarks
Hammerlid et al (2001)[18]	232	61 [18-85]	162:70	-	HNC	Disease:I-IV	S,(C)RT	5	36	
Ohrn et al (2001)[33]	18	55.4(9.0) [38-73]	10:8	SCC ACA	HNC	-	(C)**RT**	4	1	
Wiltfang et al (2003) [34]	53	54.2 [34-78]	48:5	SCC	Oral cavity	UICC:0-IV	**S**,(C)**RT**	4	24	
Fang et al (2004)[30]	77	*50* [22-78]	77:0	SCC	HNC	AJCC: III,IV	**S, RT**	2	24	P: Fang et al (2005)[31]
Abendstein et al (2005)[64]	167	61 [18-86]	116:51	-	HNC	Disease:I-IV	S,(C)RT	3	60	P: Bjordal et al (2001)[28]
Fang et al (2005)[31]	149	*53* [25-81]	138:11	SCC	HNC	AJCC: III,IV	(C)**RT**	2	12	
Nordgren et al(2005)[32]	60	Group1: 56 Group2: 57	-	-	HNC	T:2-4 N: 0,+ AJCC:III,IV	**(C)RT**	3	1	Group1:72 Gy, 6wk Group2:80.4 Gy,7wk
Urdaniz et al (2005)[37]	89	60	68:21	-	Pharynx	Disease:I-IV	S,(C)**RT**	4	60	P: Bjordal et al (2001)[28]
Borggreven et al (2007)[65]	80	58 [23-74]	47:33	SCC	Oral cavity, Oropharynx	T:2-4, N:0-3	**S,**RT	3	12	
Oates et al (2007)[20]	14	-	-	-	Nasopharynx	T:1-4 N: 0-3	**(C)RT**	5	24	
Bozec et al (2008)[66]	65	61.2 (9.3) [40-85]	49:16	-	HNC	T: 2-4 N:0-3	**S,**RT	3	12	
Bozec et al (2009)[67]	41	62.3 (9.6) [43-85]	33:8	SCC	Oral cavity, Oropharynx	T:2-4 N:0-3 AJCC:II-IV	**S**,(C)RT	3	12	P: Bozec et al (2009)[67]
Rizvi et al (2009)[68]	37	51.8 (9.6)	18:19	-	HNC	T:3,4 N:1,2	**S,**RT	4	6	
Vergeer et al (2009)[35]	241	Group1:≤65y(n=95),>65y (n=55) Group2:≤65y(n=68),>65y(n=23)	Group1: 104:46 Group2: 51:40	SCC	HNC	T:0-4 N:0-3, UICC:I-IV	S,(C) **RT**	5	12	Group1: 3D-RT Group2 : IMRT

Table 1. (Continued)

Author (year)	Sample size (n)	Age Mean (SD) OR *Median* [range]	Ratio Male: Female	Histology	Tumour localization	Stage	Treatment modality*	#measures †	FU ‡	Remarks
Yoshimura et al (2009)[69]	56	*63* [25-88]	46:10	SCC	Oral cavity	T:1-3	**LDR-BT**	4	12	
Chan et al (2012)[36]	185	50.2 (11.4) [24-81]	151:34		Recurrent Nasopharynx	-	**S,(C)RT**	2	6	
Al-Mamgani et al (2013)[70]	207	<65y (n=142), ≥65y (n=65)	143:64	-	Oropharynx	T:1-4 N:0-3 AJCC:I-IV	(C)**RT**	5	18	
Kumar et al (2013)[74]	60	Group1: *55* [33-65] Group2: *51* [31-65]	Group1: 25:3 Group2: 29:3	SCC	HNC	T:1-3 N:0-2b AJCC: I-IV	**RT**	6	24	Group1: 3D-RT Group2: IMRT
Rathod et al (2013)[71]	83	Group1: 52.0 [22-81] Group2: 53.4 [28-76]	Group1: 28:15 Group2: 27:13	-	Nasopharynx	T:4 N:3 UICC:2-4	**(C)RT**	5	24	Group1: CRT + ERF Group2: CRT
Zhao et al (2014)[72]	40	*56* [20-65]	33:7	-	HNC	Stage: I-IVA	S,(C)**RT**	3	3	
Arslan et al (2015)[73]	111	Group1: 55.3 (12.4) Group2: 53.4 (11.2)	Group1: 47:8 Group2: 49:7	SCC	HNC	Stage:3-4b	(C)**RT**	3	6	
Landstrom et al (2015)[75]	19	56.6	12:7	SCC ACA	HNC	T:1,2	**(C)**RT	2	12	
Rao et al (2016)[19]	421	≤55y (n=191), >55y (n=230)	345:76	SCC	Pharynx, Larynx	T:1-4 N:0-3 AJCC: II-IV	**(C)RT**	12	*Med* 33	
Dzioba et al (2017)[76]	117	58.2 (13.3)	71:46	SCC	Tongue (oral cavity)	T:1-4 AJCC: I-IVA	**S,**(C)RT	4	12	
Gao et al (2018)[77]	77	<60y (n=48), ≥60y (n=29)	41:36	SCC ACC	Tongue	-	**S**	3	12	
Tribius et al (2018)[46]	161	60.4 (10.4)	110:51		HNC	UICC T:1-4 N:0-3	**RT**	3	24	BL=AT

Table 1. (Continued)

Author (year)	Sample size (n)	Age Mean (SD) OR *Median* [range]	Ratio Male: Female	Histology	Tumour localization	Stage	Treatment modality*	#measures †	FU ‡	Remarks
Veluthattil et al (2019)[45]	25	≤60y (n=21), >60y (n=4)	11:14	SCC	Oral cavity	Stage: 4A-4C	**RT**	2	2	

*: the text in bold indicates that all the patients in this study received that particular treatment modality.
†: number of measurement points reported
‡: follow-up period (in months after treatment)
§: calculated from data reported.

Abbreviations:
Histology; SCC: squamous cell carcinoma, ACA: adenocarcinoma, ACC: adenoid cystic carcinoma.
Tumour localization; HNC: head and neck cancer, UADT: upper aero-digestive tract.
Stage: T: Tumour classification, N: nodes classification, UICC: stage according to Union for International Cancer Control, INCA: stage according to Instituto Nacional de Câncer (National Institute of Cancer Brazil), AJCC: stage according to American Joint Committee on Cancer.
Treatment modality; S: surgery, RT: radiotherapy, C: chemotherapy, (C)RT: chemoradiotherapy, LDR-BT: low-dose-rate interstitial brachytherapy.
Remarks; P: partial overlap of study population, T: Total overlap of study population, AI: after intervention, Gy: Gray of radiation, wk: week, 3D-RT: three-dimensional radiotherapy, IMRT: intensity modulated radiotherapy, ERF: extracorporeal radiofrequency.

Risk of bias assessment

The overall Cohen's Kappa bias assessment score was 0.310 (52% agreement). The source or study population was not described (adequately) in the majority of the studies. These studies were scored with "N/A" on the study participation domain (n=32; 60%) (Table 2).[5,13,16,18,20,28,30,32,36,37,43,45-47,51-58,60,61,64,65,68,69,72,73,75,77] Eleven studies (21%) did not report attrition rate.[13,19,33,35,51,55,61,70,72,73,77] Some did not report the attrition rate because only the patients with complete data were included. Four studies (8%) were scored with "N/A" on the outcome measurement domain[14,16,55,60]: two studies did not describe the measurement method [55,60] and two studies used a non-validated measurement method (extra-oral measurements) [14,16]. The majority of the studies were scored with a high risk of bias concerning the statistical analysis and reporting domain (n=42; 79%) because they lacked a multivariate analysis.[5,13,14,17,18,20,28-37,43,45-47,51,52,54-58,60-68,70,72-75,77]

Distinguishing the outcome measurements

A distinction was made between objective (e.g., using a ruler or calliper) or subjective (e.g., using a patient' questionnaire) assessments of restricted mouth opening. An additional distinction was made between the objective studies, namely using a restricted mouth opening as a cut-off point (n=6)[13,14,47-50] or a decrease in MMO measured in millimetres (n=16).[15,16,43,51-63]

The subjective analyses assessed the perception of a restricted mouth opening either using the EORTC QLQ H&N35 (n=29)[17,18,20,28-37,45,46,64-77] or an addendum similar to the EORTC QLQ H&N35 (n=1)[5] or Common Terminology Criteria for Adverse Events (CTCAE) (n=1).[19] The Gothenburg Trismus Questionnaire (GTQ) (n=3) was used as a secondary endpoint to assess trismus.[48,49,63]

Univariate analyses

In 16 studies, a single prognostic factor for a decrease in MMO and the patients' perception of difficulties with opening the mouth was analysed over time (Table 3).[14,16,35,43,46,53-58,62,65,71,72,74] Regarding patient related factors, a significant effect was found in relation to gender (in one study in the period between before and after treatment)[14] and the -509 genotype.[56] Patients with a homozygous T allele (TT) in the -509 genotype had a greater reduction in MMO than those with a homozygous C allele (CC) or heterozygous C allele (CT). Tumour related factors included large reductions in MMO when the tumour was located near the oral cavity or oropharynx.[53,54] Less reduction was found in other areas, such as the nasopharynx, hypopharynx, larynx, or lymph drainage areas.[53,54] No significant effects were found in relation to T classification or N classification.[14,16,65] Cancer treatment

also resulted in a reduction in MMO, with the most occurring after chemoradiotherapy and the least after surgery.[14] The MMO decreased directly after surgery but increased in the six months thereafter. When patients received (chemo) radiotherapy, the MMO decreased directly after the treatment, but did not increase in the six months thereafter. The MMO decreased even more with an increase in radiation dose.[54]

Patients who were given conventional three-dimensional radiotherapy, instead of intensity modulated radiotherapy, perceived more difficulties opening the mouth.[35,71] Also, patients who underwent chemotherapy without the addition of extracorporeal radiofrequency perceived more difficulties with opening the mouth compared with those who received additional extracorporeal radiofrequency.[72] Regarding the remaining factors, a greater reduction in MMO was found when mucositis was present compared to when mucositis was not present.[53] MMO was not significantly reduced in relation to alcohol consumption and smoking factors.[16] Patients with a lower social economic status perceived more difficulties with opening the mouth than patients with a middle or high social economic status.[46]

Table 2. Quality assessment using the QUIPS tool.

Author (year)	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome measurement	Study Confouding	Statistical Analysis and Reporting	Overall risk of bias
Objective measurements – cut- off point for trismus							
Yan et al (2003) [13]	N/A	N/A	L	L	H	H	H
Scott et al (2011) [14]	H	H	L	N/A*	L	H	H
Lee et al (2012)[47]	N/A	H	L	L	M	H	H
Pauli et al (2013)[48]	M	L	L	L	L	M	H
Pauli et al (2016)[49]	L	M	M	L	M	M	H
van der Geer et al (2016)[50]	M	H	L	L	M	L	H
Objective measurements - maximal mouth opening measurements							
Goldstein et al (1999) [51]	N/A	N/A	L	L	M	H	H
Wang et al (2005) [52]	N/A	M	L	L	H	H	H
Bragante et al (2012) [54]	N/A	M	L	L	M	H	H
Mucke et al (2012)[55]	N/A	N/A	L	N/A	H	H	H
Lyons et al (2013)[56]	N/A	M	L	M	L	H	H
Lazarus et al (2014) [57]	N/A	M	L	L	H	H	H
Safdar et al (2014) [58]	N/A	L	L	L	H	H	H
Wetzels et al (2014) [16]	N/A	M	L	N/A*	L	L	H
Bragante et al (2015) [53]	N/A	L	L	L	L	L	L
Fong et al (2015) [59]	H	M	L	L	H	M	H
Kamstra et al (2015)[15]	L	H	L	M	M	L	H
Manaktala et al(2015) [60]	N/A	L	L	N/A	H	H	H
Nayar et al (2016)[61]	N/A	N/A	L	L	H	H	H
Al-Saleh et al (2017) [43]	N/A	H	L	M	H	H	H
Lalla et al (2017) [62]	H	H	L	M	H	H	H
Thor et al (2017) [63]	M	H	L	L	H	H	H

Table 2. (Continued)

Author (year)	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome measurement	Study Confouding	Statistical Analysis and Reporting	Overall risk of bias
Subjective measurements							
De Graeff et al (1999)[17]	L	M	L	L	H	H	H
De Graeff et al (2000) [29]	L	M	L	L	M	H	H
Epstein et al (2000) [5]	N/A	H	L	L	M	H	H
Bjordal et al (2001)[28]	N/A	L	L	L	H	H	H
Hammerlid et al 2001) [18]	N/A	L	L	M	L	H	H
Ohrn et al (2001) [33]	M	N/A	L	L	H	H	H
Wiltfang et al (2003) [34]	L	M	L	L	H	H	H
Fang et al (2004) [30]	N/A	M	L	L	H	H	H
Abendstein et al (2005)[64]	N/A	L	L	L	M	H	H
Fang et al (2005) [31]	L	L	L	L	H	H	H
Nordgren et al(2005) [32]	N/A	M	L	L	M	H	H
Urdaniz et al (2005)[37]	N/A	L	L	L	M	H	H
Borggreven et al (2007) [65]	N/A	L	L	L	M	H	H
Oates et al (2007)[20]	N/A	L	L	L	H	H	H
Bozec et al (2008) [66]	L	H	L	L	L	H	H
Bozec et al (2009) [67]	L	M	L	L	L	H	H
Rizvi et al (2009) [68]	N/A	L	L	M	H	H	H
Vergeer et al (2009) [35]	M	N/A	L	L	H	H	H
Yoshimura et al (2009)[69]	N/A	M	M	L	L	M	H
Chan et al (2012) [36]	N/A	L	L	L	H	H	H
Al-Mamgani et al (2013) [70]	L	N/A	L	L	M	H	H
Rathod et al (2013) [71]	L	H	L	L	L	L	L
Zhao et al (2014)[72]	N/A	N/A	L	L	H	H	H
Arslan et al (2015) [73]	N/A	N/A	L	L	H	H	H
Kumar et al (2013) [74]	L	L	L	L	H	H	H
Landstrom et al (2015)[75]	N/A	L	L	L	H	H	H
Rao et al (2016) [19]	H	N/A	L	M	L	L	H
Dzioba et al (2017)[76]	L	H	L	L	M	M	H
Gao et al (2018) [77]	N/A	N/A	L	L	H	H	H
Tribius et al (2018) [46]	N/A	L	N/A	L	H	H	H
Veluthattil et al (2019) [45]	N/A	M	L	L	H	H	H

*:extra-oral measurement
N/A: not applicable
L: low risk of bias
M: moderate risk of bias
H: high risk of bias

Table 3. Overview of patient, tumour, treatment, and other characteristics as prognostic factors for decrease in maximal mouth opening (objective) and patients' perception of difficulties opening the mouth (subjective).

Patient characteristics	Time points of analysis	Age			Gender		Dental status		-509 Genotype		
Objective measures											
		<55	55-64	65+	Male	Female	Dentate	Edentulous			
Scott et al (2011)[14]	AT-BT	-11[-21;-2]	-4[-13;-1]	-3[-12;1]	-8[-16;-2][a]	-2[-11;1][a]	-6[-14;-2]	-9[-22;0]			
	6M-BT	-6[-11;1]	-4[-10;3]	-5 [-]	-5[-11;2]	-1[-10;3]	-4[-10;3]	-10[-23;0]			
									CC -509 genotype	CT -509 genotype	TT -509 genotype
Lyons et al (2013)[56]	AT-BT								-8.5 [-4.5;-13.0][b]	-17.0 [-8.0;-26.0][b]	-26.5 [-33.0;-15.0][b]
					Male	Female	Dentate	Edentulous			
Wetzels et al (2014)[16]	AT-BT				-14.3 (-)[A]	-14.9 (-)[A]	-13.8 (-)[A]	-14.5(-)[A]			
	6M-BT				-9.0 (-)[A]	-9.2(-)[A]	-8.1(-)[A]	-9.3(-)[A]			
	12M-BT				-8.7(-)[A]	-8.5(-)[A]	-8.1(-)[A]	-8.5(-)[A]			
					Male	Female					
Lalla et al (2017)[62]	6M-BT				-3.3(-)[A]	-3.0(-)[A]					

Table 3. (Continued)

Tumour characteristics	Time points of analysis	Localization					Stage				
Objective measures											
		Oral	Oropharynx				T-stage 1,2	T-stage 3,4	N-stage 0	N-stage +	
Scott et al (2011)[14]	AT-BT	-7[-14;-2]	-5[-16;-1]				-5[-14;-1]	-9[-18;-1]	-5[-14;-1]	-8[-16;-1]	
	6M-BT	-4[-10;2]	-9[-]				-3[-10;3]	-9[-16;1]	-3[-10;3]	-8[-13;1]	
		Mouth	Oropharynx	Hypo-pharynx	Larynx	Drainage area	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
Bragante et al (2012)[54]	AT-BT	-11.0(1.7)[b]	-11.5(7.8)[b]	-2.0(0.0)[b]	-5.3(6.3)[b]	-2.8(4.5)[b]	-8.0 (-)	-0.8 (1.5)	-7.8 (5.9)	-4.5 (5.9)	-6.3 (6.9)
			Oropharynx	Others			AJCC 1-3	AJCC 4			
Lazarus et al (2014)[57]	3M-BT		-4.1(-)[A]	-5.0(-)[A]			-3.5(-)[A]	-4.8(-)[A]			
	6M-BT		-3.8(-)[A]	-6.2 (-)[A]			-4.1 (-)[A]	-5.0(-)[A]			
		Maxilla	Mandible	Tongue and floor of mouth			T1	T2	T3	T4	
Wetzels et al (2014)[16]	AT-BT	-19.1(-)[a,A]	-15.5(-)[a,A]	-10.7(-)[a,A]			-12.0(-)[A]	-16.7(-)[A]	-17.3(-)[A]	-15.0(-)[A]	
	6M-BT	-15.1(-)[a,A]	-9.6(-)[a,A]	-5.0(-)[a,A]			-5.7(-)[A]	-10.4(-)[A]	-14.5(-)[A]	-13.8(-)[A]	
	12M-BT	-11.8(-)[a,A]	-8.1(-)[a,A]	-7.5(-)[a,A]			-7.1(-)[A]	-9.4(-)[A]	-10.8(-)[A]	-12.0(-)[A]	
		Oral Cavity and Oropharynx[r]		Naso-pharynx Hypo-pharynx and Larynx[r]							
Bragante et al (2015)[53]	AT-BT	-5.64(6.42)[a]		-1.68 (6.27)[a]							

Table 3. (Continued)

Subjective measures									
		Oral cavity	Oropharynx				T2	T3,4	
Borggreven et al (2007)[65]	6M-BT	10.6(-)	24.2(-)				23.5(-)	14.3(-)	
	12M-6M	5.6(-)	-11.5(-)				-11.1(-)	3.3(-)	
Treatment characteristics		**Treatment modality**			**Reconstruction**				**Radiation dose**
Objective measures									
		No RT	RT	CRT	No free-flap	Soft-free flap	Composite free flap		
Scott et al (2011)[14]	AT-BT	-8[-14;-2]	-5[-13;1]	-9[-]	-2[-9;-1]	-6[-16;-2]	-11[-12;0]		
	6M-BT	-1[-9;4][a]	-7[-15;0][a]	-7[-][a]	-1[-10;4]	-5[-11;1]	-4[-]		
			RT	CRT					Total dose
Bragante et al (2012)[54]	AT-BT		-5.5 (6.0)	-4.4 (5.5)					R=-0.164 [a]
		S only	S+RT	S+RT+ ORN					
Mucke et al (2012)[55]	AT-BT	-22.5%[b]	-49.2% [b]	-49.0% [b]					
					Platysma flap	Submental flap			
Safdar et al (2014)[58]	6M-BT				-3.7 (-1.8)[a,B]	-4.7 (-1.6)[a,B]			
		S only	S+RT	RT	No surgery	Local flap	Myocutaneous or free flap	Bone graft/ flap	
Wetzels et al (2014)[16]	AT-BT	-13.4(-)[a,A]	-18.2(-)[a,A]	-7.1(-)[a,A]	-11.1(-)[A]	-22.9(-)[A]	-17.9(-)[A]	-17.4(-)[A]	
	6M-BT	-4.5(-)[a,A]	-15.0(-)[a,A]	-8.2(-)[a,A]	-5.5(-)[A]	-20.9(-)[A]	-12.9(-)[A]	-12.7(-)[A]	
	12M-BT	-4.6(-)[a,A]	-13.9(-)[a,A]	-8.0(-)[a,A]	-5.9(-)[A]	-14.6(-)[A]	-11.9(-)[A]	-9.8(-)[A]	
		Mandibu-lotomy surgery	Transoral surgery						
Al-Saleh et al (2017)[43]	1.5-2AT-BT	11.7 (-)[a,A]	5.4 (-)[a,A]						

Table 3. (Continued)

Subjective measures			
		3D-RT	IMRT
Vergeer et al (2009)[35]	6W-BT	8.8(-)[b,A]	-7.4(-)[b,A]
	6M-BT	11.9(-)[b,A]	1.3(-)[b,A]
		RT	CRT
Kumar et al (2013)[74]	1M-BT	-3.7(-)[a,A]	-12.3(-)[a,A]
	6M-BT	0.0(-)[a,A]	-17.06(-)[a,A]
		3D-RT	IMRT
Rathod et al (2013)[71]	3M-BT	6(-)[b,A]	-4(-)[b,A]
	6M-BT	16(-)[b,A]	-3(-)[b,A]
	12M-BT	-2(-)[b,A]	-2(-)[b,A]
	18M-BT	2(-)[b,A]	-4(-)[b,A]
	24M-BT	8(-)[b,A]	-9(-)[b,A]
		CRT+ ERF	CRT
Zhao et al (2014)[72]	6M-AT	-3.5 (-)[a,A]	17.1 (-)[a,A]
	12M-AT	-2.6 (-)[a,A]	18.2 (-)[a,A]
	18M-AT	-6.6 (-)[a,A]	20.4 (-)[a,A]
	24M-AT	-6.4 (-)[a,A]	19.0 (-)[a,A]

Table 3. (Continued)

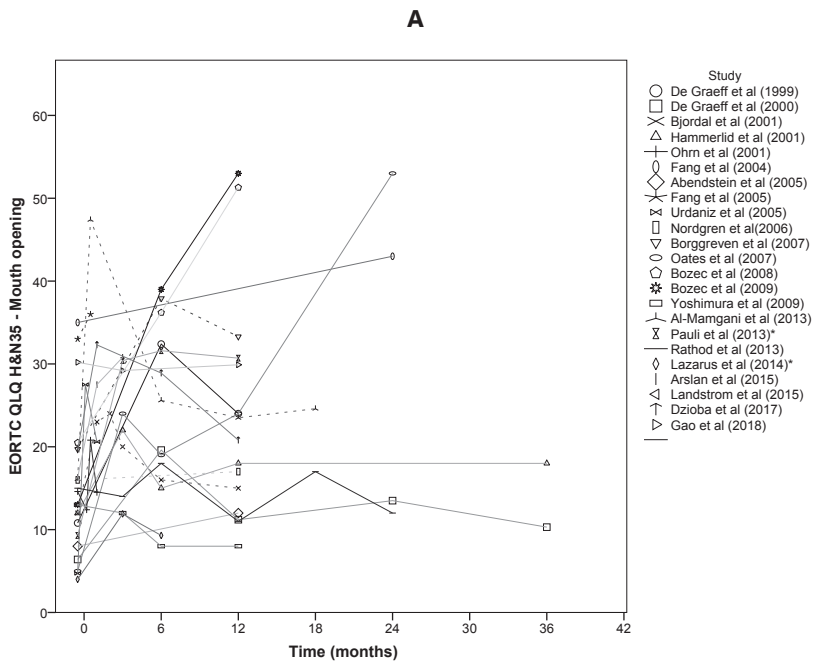
Other characteristics		Smoking		Alcohol (>1 daily)		Mucositis		SES		
Objective measures										
		Yes	No	Yes	No					
Wetzels et al (2014)[16]	AT-BT	-12.9 (-)[A]	-15.4(-)[A]	-14.8(-)[A]	-14.3(-)[A]					
	6M-BT	-8.9(-)[A]	-9.1(-)[A]	-9.1(-)[A]	-9.0(-)[A]					
	12M-BT	-8.9(-)[A]	-8.2(-)[A]	-10.5(-)[A]	-7.6(-)[A]					
						Yes	No			
Bragante et al (2015)[53]	AT-BT					-5.9(6.6)[a]	-0.6 (5.3)[a]			
Objective measures										
								Low	Middle	High
Tribius et al (2018)[46]	24M-AT							-12.3(-)[a,A]	-30.5(-)[a,A]	-30.6(-)[a,A]

Number of decimals are reported as the authors have reported it. In case two or more decimals are given, 1 decimal is reported.
For the objective measures, a decrease (a negative value), means a worse restricted mouth opening. For the subjective measures, an increase (a positive value), means a worse restricted mouth opening.
a: significant
b: significant in some analyses
A: difference between mean scores calculated
B: Conversion centimeters to millimeters
**[**]: median[interquartile range]
**(**): mean score(standard deviation)
Abbreviations:
AT: after oncological treatment
BT: before oncological treatment
(n)W: number of weeks after oncological treatment
(n)M: number of months after oncological treatment
(-): not reported
AJCC: stage according to American Joint Committee on Cancer
RT: radiotherapy
ORN: osteoradionecrosis
CRT: chemoradiotherapy
3D-RT: three-dimensional radiotherapy
IMRT: intensity modulated radiotherapy
ERF: extracorporeal radiofrequency
SES: socioeconomic status

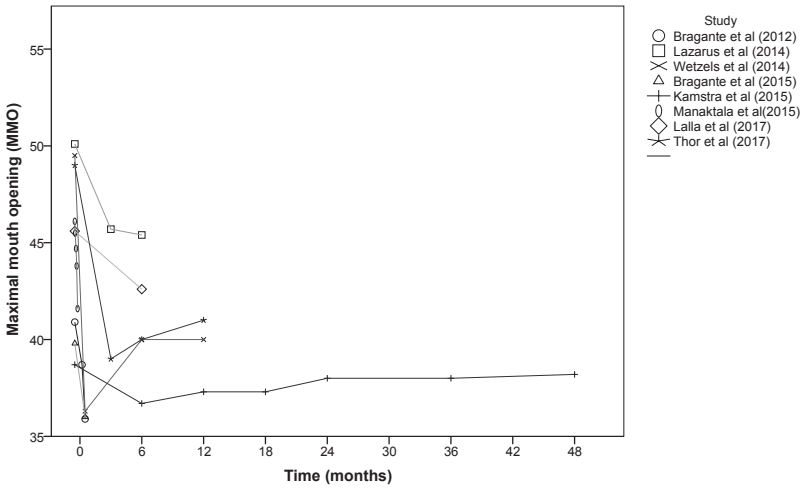
Timing

The highest percentage of patients developed trismus directly after treatment and it continued to increase in the six months thereafter (Figure 2A). The percentage of patients with trismus seemed to stabilize 12 months after treatment. MMO decreased directly after treatment and in the six months thereafter (Figure 2B) and appeared to stabilize 12 months after treatment. Patients' perception of difficulties with opening the mouth was highly diverse (Figure 2C). The majority of the patients perceived difficulties with opening the mouth directly after treatment, but thereafter the perception varied considerably.

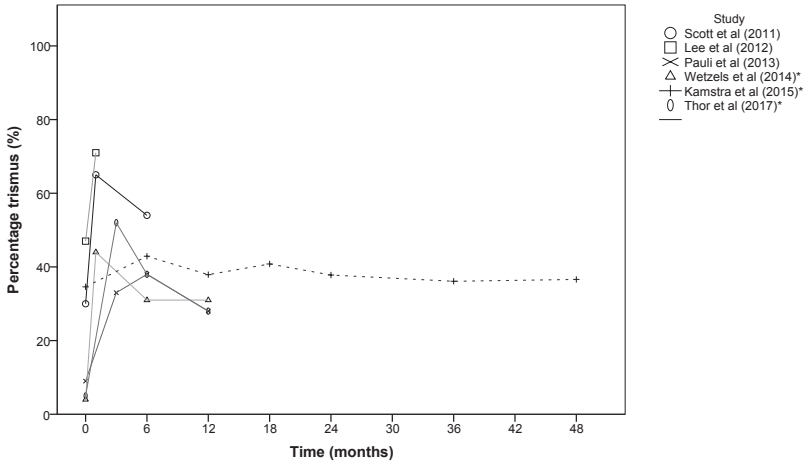
Figure 2. Longitudinal evaluation of percentage of patients with trismus (A), maximal mouth opening (B), and patient's quality of life score- domain: difficulties opening the mouth (C).



B



C



*after study name: secondary outcome
Broken lines displays studies that had overlapping data with other studies. The studies that contained the largest sample size are displayed as straight lines.

The figures were based on 29 studies. Other studies were not included because: they did not report data on restricted mouth opening at time points before and after oncological treatment (n=14)[19,34-36,43,46,49,51,55,56,59,61,72,74]; the trismus scores were reported as a cumulative incidence[13]; MMO was reported as a normalized value[52]; a mean reduction[58]; or as a median score[14]; or the scores of the questionnaires were not transformed into symptom scores(n=3)[5,44,68] or were reported as a median score[45,75]. The data from studies that included the same study population as another study were not displayed either.[50]

Multivariate analyses

Three studies built multivariate prognostic models (Table 4).[15,53,76] Two studies analysed factors affecting MMO[15,53], and one study analysed the factors affecting perceived difficulties with opening the mouth[76]. Presence of mucositis, deterioration of overall functioning (according to the Karnofsky Performance Status Scale), tumours located near the oral cavity, oro- and nasopharynx, nasal cavity and maxillary sinus, shorter time after radiotherapy, female gender, a small baseline mouth opening, large tumour (T stage 4), higher age, and a great target volume (radiotherapy) were significantly associated with a decrease in MMO. A combination of oncological treatment modalities (surgery and (chemo) radiotherapy) and shorter time after oncological treatment) were associated with perceived difficulties with opening the mouth.

Best evidence synthesis

There is moderate evidence that the presence of mucositis and a deterioration of overall functioning (according to the Karnofsky Performance Status Scale) results in a reduction of MMO. There is limited to moderate evidence that target volume, time after treatment, and baseline mouth opening results in a reduction of MMO, and that time after treatment results in higher scores of perceived difficulties opening the mouth. There is conflicting evidence that the factors age localization, age, T classification, reconstruction after surgery, different types of treatment modalities, and gender affect MMO, and that the different types of treatment modalities affect perceived difficulties opening the mouth as well.

Conflicting evidence was mainly the result of a different categorization of a particular factor across the studies. For instance, a significant association between factor tumour localisation and MMO was found, if tumour localisation was categorized in the two categories: “oral cavity and oropharynx” versus “nasopharynx, hypopharynx and larynx”.[53]

However, no significant association was found between factor tumour localisation and MMO, if tumour localisation was categorized in the two categories “oral cavity” versus “oropharynx”.[14]

Significant associations were found between a reduction in MMO and the factors: T classification: if stage 4 was compared to other stages; treatment modalities, if multiple treatment modalities were compared to a single treatment modality or (chemo)radiotherapy was compared to surgery more than six months after treatment; reconstruction, if platysma flap was compared with a submental flap. A significant association between higher scores on perceived difficulties opening the mouth and the factor treatment modality was found, if multiple treatment modalities were compared to one single treatment modality or chemoradiotherapy was compared to radiotherapy alone. The largest reductions on MMO were found for a greater target volume (limited to moderate evidence) and the presence of mucositis after radiotherapy (moderate evidence) (Table 4, estimated effects). The greatest increases for perceived difficulties opening the mouth were found for a combination of treatment modalities given (conflicting evidence) and time after treatment (limited to moderate evidence) (Table 4, estimated effects).

Table 4. Prognostic factor models for restricted mouth opening.

Study	Outcome measure	Method for including factor in model	Performed analysis		Factors in the final model	Estimated effect	
Objective measurement – maximal mouth opening							
Bragante et al (2015) [53]	Reduction in maximal mouth opening	Bivariate analysis (p<0.20)	Linear regression analysis	Enter (p<0.05)		B	95% Confidence Interval
					Change in diet consistency after radiotherapy	-0.29	-4.27;3.69
					Radiation field – oral cavity and oropharynx	-2.83	-6.61;0.96
					Mucositis after radiotherapy*	-4.19	-7.62;-0.80
					Difference in Karnofsky Performance Scale*,†	0.12	0.02;0.24
					Disease stage: III/IV	-0.90	-4.26;6.07
Kamstra et al (2015)[15]	Change in maximal mouth opening	Theoretical plausability	Linear mixed model analysis	Backward stepwise selection (p<0.05) (-log likelihood criterion)		B	95% Confidence Interval
					Intercept	12.88	10.00;15.77
					Location		
					Oral cavity	1.57	-3.50;6.63
					Oro- and nasopharynx	1.04	-4.09;6.18
					Salivary glands and ear	2.56	-2.57;7.68
					Hypo- and supraglottic larynx	3.56	-1.61;8.73
					Glottic- and subglottic larynx	4.40	-0.76;9.57

Table 4. (Continued)

Study	Outcome measure	Method for including factor in model	Performed analysis	Factors in the final model	Estimated effect	
				Nasal cavity and maxillary sinus	1.26	-4.00;6.53
				Unknown primary	-	N/A
				Time after radiotherapy	4.00	3.38;4.63
				Male gender	1.10	0.11;2.08
				Mouth opening before treatment	0.69	0.65;0.73
				Tumour stage: T4	-1.14	-2.16;-0.11
				Age	-0.05	-0.08;-0.01
				Target volume on primary tumour	-4.76	-9.36;-0.17
				Oral cavity*time	0.69	-0.47;1.85
				Oropharynx or nasopharynx*time	0.47	-0.70;1.64
				Salivary glands or ear*Time	0.91	-0.26;2.08
				Hypopharynx or supraglottic larynx*Time	1.27	0.09;2.45
				Glottic or subglottic larynx*Time	1.48	0.30;2.66
				Nasal cavity or maxillary sinus*Time	0.62	-0.57;1.82
				Unknown primary*Time	-	N/A
				Mouth opening before treatment*Time	-0.10	-0.11;-0.09
				Male gender*Time	0.32	0.11;0.54
				Baseline age centered at 60 years*Time	-0.01	-0.02;0.00
				Tumour stage T4*Time	-0.27	-0.50;-0.05
				Target volume on primary tumour*Time	-1.69	-2.75;-0.64

Table 4. (Continued)

Study	Outcome measure	Method for including factor in model	Performed analysis		Factors in the final model	Estimated effect	
Subjective measurements							
Dzioba et al (2017)[76]	EORTC QLQ HN35[c]		Mixed effect regression analysis	p>0.05 exclusion interaction terms p>0.05 exclusion for treatment		B	95% Confidence Interval
					Baseline	14.65	7.4;21.9
					Surgery and radiotherapy	2.24	-7.6;12.0
					Surgery and chemoradiotherapy	14.59	5.5;23.7
					1 month after treatment	12.42	5.2;19.6
					6months after treatment	11.30	3.7;18.9
					1 year after treatment	2.86	-5.3;11.0

a: significantly contributing to the model
b: Karnofsky Performance Scale: an index used to classify functional impairment, using a scale of 0-100.
c: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Head and Neck cancer Module 35: a validated quality of life questionnaire, specifically for head and neck cancer related symptoms.

Table 5. Best evidence synthesis of prognostic factors on MMO and on scores for perceived difficulties opening the mouth.

Prognostic factor	Studies	Number of patients per study	Total number of patients	Associations (+,-,+/-)	Level of evidence
Maximal mouth opening reduction					
Disease stage	[54;57;**53**]	26;29;56	111	-	Moderate
Presence of mucositis	[53;**53**]	56	56	+	Moderate
Deterioration of overall functioning (Karnofsky Performance Status Scale*)	[**53**]	56	56	+	Moderate
Diet consistency	[**53**]	56	56	-	Moderate
Larger target volume	[**15**]	641	641	+	Limited/ Moderate
Shorter time after treatment	[**15**]	641	641	+	Limited/ Moderate
Smaller baseline mouth opening	[**15**]	641	641	+	Limited/ Moderate
Localization	[16;53;**15**]	143;56;641	840	+	Conflicting†
† *Oral cavity (predominantly maxilla) and oropharynx vs. other localizations*	54	26	26	+/-	
	[14;57;**53‡**]	64;29;56	149	-	
Age	[**15**]	641	641	+	Conflicting†
	[14]	64	64	-	
T classification	[**15**]	641	641	+	Conflicting†
† *T classification stage 4 versus other stages.*	[14;16]	64;143	207	-	
Reconstruction	[58]	65	65	+	Conflicting†
† *Platysma flap versus submental flap*	[14;16]	64;143	207	-	
Treatment modalities	[16;43]	143;16	159	+	Conflicting†
† *multiple treatment modalities vs. single treatment modality;*	[14 ;55]	64;96	160	+/-	
† *(Chemo) radiotherapy vs. surgery >6months*	[54]	26	26	-	
Gender	[**15**]	641	641	+	Conflicting
	[14]	64	64	+/-	
	[16;62]	143;372	515	-	
Dental status	[14;16]	64;143	207	-	Limited
Alcohol	[16]	143	143	-	Limited
Smoking	[16]	143	143	-	Limited
N classification	[14]	64	64	-	Limited
-509 genotype	[56]	62	62	+/-	Limited
Higher radiation dose	[54]	26	26	+	Limited

Table 5. (Continued)

Prognostic factor	Studies	Number of patients per study	Total number of patients	Associations (+,-,+/-)	Level of evidence
Increased score on perceived difficulties opening the mouth					
Shorter time after treatment	[**76**]	117	117	+	Limited/ Moderate
Treatment modalities	[74;**76**]	111;117	228	-	Conflicting†
	[35;71]	241;60	301	+/-	
† multiple treatment modalities vs. single treatment modality; †chemo radiotherapy vs. radiotherapy † three dimensional radiotherapy versus intensity modulated radiotherapy >6 months					
Higher Social Economic Status	[46]	161	161	+	Limited
No addition of electrofrequency	[72]	83	83	+	Limited
Localization	[65]	80	80	-	Limited
T stage	[65]	80	80	-	Limited

[number]: reference of study, univariate analysis
[**number**]: reference of study, multivariate analysis
+: significant association found between factor and outcome measure
-: no significant association found between factor and outcome measure
+/-: partial association found between elements within a factor and outcome measure
*:Karnofsky Performance Scale: an index used to classify functional impairment, using a scale of 0-100.
†: significant associations found between factor and outcome measure on the basis of a particular categorization.
‡: This study analysed the effects of "radiation field in the area of the oral cavity and oropharynx' on maximal mouth opening, and is therefore included as part of the potential prognostic factor: "localization".

DISCUSSION

Key results

A restricted mouth opening is most likely in head and neck cancer patients who have a large tumour near the masticatory muscles that requires extensive cancer treatment. A restricted mouth opening is most likely to occur in the first six months after cancer treatment.

Quality of studies

Overall, the quality of the studies was poor. Most studies had a high risk of bias. Two studies had a low risk of bias, but these studies did not built a multivariate prognostic model. Factors that were most likely to affect trismus, MMO, or perceiving difficulties opening the mouth, were identified and described. These studies had moderate, limited or conflicting levels of evidence. Levels of strong evidence were not reached. Nonetheless, this systematic review gives insight into the factors that should be taken into account in future research on a restricted mouth opening in head and neck cancer patients.

Prognostic factors

Moderate evidence was found for the influence of mucositis after radiotherapy on a reduction in MMO.[53] The effect of mucositis on mouth opening is probably related to the associated healing tendency and the associated pain, since it was noted that MMO decreased in the presence of mucositis and increased when the mucositis resolved.[78] The effects of pain on MMO, analysed in the form of pain medication or alcohol (which may act as a pain killer as well) have also been reported.[16,47,48] The effects of factors related to the healing tendency or pain intensity on a restricted mouth opening should be explored further in future studies.

The healing process might also influence the impact of other factors (such as time after treatment and different types of treatment modalities) on a restricted mouth opening. If time passes, it is likely that the affected tissues will heal. The MMO might become less restricted or even increase over time.[15] The healing process might also differ per treatment modality. For instance, in one study, the differences in MMO reduction between surgery and (chemo) radiotherapy over time were displayed: patients who had surgery had a decrease in MMO directly after treatment, but the MMO increased in the six months thereafter, whereas the patients who received (chemo) radiotherapy had a decrease in MMO directly after treatment, but the MMO did not increase in the six months thereafter. The healing process after (chemo) radiotherapy takes more time than after surgery.[14]

Besides the healing process, tumour localization might influence MMO as well, although the evidence is conflicting. The greatest reduction in MMO is most likely when the tumour is located near risk structures. Risk structures involve the temporomandibular joint and the masticatory muscles. A decrease in MMO and an increase in perceived difficulties with opening the mouth were found when the tumour was located in proximity of these risk structures, such as the oral cavity, oro- and nasopharynx, nasal cavity and maxillary sinus.

A former systematic review on risk factors for trismus included only one study (the Goldstein et al.[51]) that found that the MMO was reduced by 18%, SD 17% when the temporomandibular joint and/or the pterygoid muscles were affected.[9] A later review concluded that the masticatory related structures generally affect MMO, but the masseter muscle had the strongest influence.[79] More recently, the ipsilateral medial pterygoid muscle[19,80] and the masseter muscle[49,80] were identified as the structures most likely to result in a decrease in MMO.

A larger target volume, and also a stage 4 tumour, resulted in a large reduction of MMO.[15] Both findings are in contrast with other studies.[14,16,54,57,65] Presumably, a significant effect was found for such a large tumour, because more risk structures were involved and more extensive cancer treatment was necessary.

There is limited to moderate evidence that baseline mouth opening affect MMO.[15] A smaller baseline mouth opening results in a larger decrease in MMO. This large decrease in MMO means that the risk of trismus will be greater. As an elaboration of this found effect, a baseline mouth opening of 46 mm or less was determined, as a cut-off point for developing trismus.[80]

The described effects of gender and age on MMO are conflicting. One study found that males tend to have a larger decrease over time than females.[14]Another study found that the decrease was the same in males and females over time.[16] Yet another study found that females had a higher risk of a decrease in mouth opening than males.[15] Regarding age, one study found that the mouth opening of younger patients decreased more over time than of older patients. [14]However, another study found that older patients had a higher risk of a decrease in mouth opening than younger patients. [15]The effects of gender and age may have been confounded by other factors not reported or analysed in those studies. For instance, the genotype of the patients might have influenced the effect.[56] Patients with the homozygous TT -509 genotype experienced a greater reduction in MMO than patients

with the homozygous CC or heterozygous CT -509 genotype. However, the evidence for the influence of the -509 genotype is limited.

Objective and subjective measures over time

Diverse patterns were seen over time regarding perceived difficulties with opening the mouth. Patients' perceptions of difficulties with opening the mouth might be influenced by different factors over time, such as pain, dry mouth, overall emotional functioning, or treatment modalities.[81,82]

Strength and limitations

The strength of this study is that we had no restriction concerning publication year or publication language. Four databases were searched in order to include as many studies as possible. Due to the different aims of the studies and subsequently the different designs of the studies, it was challenging to structure and interpret the data. Due to clinical and methodological heterogeneity no meta-analysis was conducted. Instead, we performed a best evidence synthesis. Due to this synthesis we were still able to gain insight into which prognostic factors should be taken into account from the 53 included studies. The results of this systematic review should be viewed cautiously because of high risk of bias in the source studies.

We used the QUIPS tool to assess bias but it was not really suitable for those studies whose primary aim was not to analyse trismus prognostic factors, making it difficult to assess the studies. Hence, the overall kappa score was low.

Future research

Large sample size studies are recommended with multiple structured measurement moments to analyse prognostic factors. The effects of factors related to healing tendency and pain intensity on trismus, decrease in MMO, and perceived difficulties with opening the mouth should be studied further.

Conclusion

A restricted mouth opening is most likely when the head and neck cancer patient has a large tumour located in close proximity to the mastication muscles or temporomandibular joint that requires extensive cancer treatment. A restricted mouth opening will most likely occur in the first six months after cancer treatment. More research is needed on the effect of factors related to healing tendency and pain intensity on a restricted mouth opening.

Supplementary text 1. Search Strategy

PubMed

(((“Head and Neck Neoplasms”[Mesh] OR head and neck cancer*[tiab] OR head and neck neoplasm*[tiab] OR head and neck carcinom*[tiab] OR head and neck tumo*[tiab] OR cancer of the mouth[tiab] OR cancer of the oral cavity[tiab] OR cancer of the neck[tiab] OR cancer of the head[tiab] OR cancer of the pharynx[tiab] OR carcinoma of the oral cavity[tiab] OR mouth cancer*[tiab] OR oral cancer*[tiab] OR mouth neoplasm*[tiab] OR oral neoplasm*[tiab] OR oral carcinoma*[tiab] OR mouth carcinoma*[tiab] OR oral tumo*[tiab] OR mouth tumo*[tiab] OR squamous cell carcinoma*[tiab]) AND (“Trismus”[Mesh] OR trismus[tiab] OR mouth open*[tiab] OR limited mouth[tiab] OR (mouth[tiab] AND opening[tiab]) OR interincisal distance[tiab] OR interincisor distance[tiab] OR interincisal opening[tiab] OR lockjaw[tiab] OR lock jaw[tiab] OR jaw closure[tiab] OR jaw opening[tiab] OR range of motion[tiab])))

Cochrane

(MESH descriptor:[Head and Neck Neoplasms] or head and neck cancer*; ti,ab,kw or head and neck neoplasm*; ti,ab,kw or head and neck carcinoma*;ti,ab,kw or head and neck tumor*;ti,ab,kw or cancer of the mouth;ti,ab,kw or cancer of the oral cavity;ti,ab,kw or cancer of the neck;ti,ab,kw or cancer of the head;ti,ab,kw or cancer of the pharynx;ti,ab,kw or carcinoma of the oral cavity;ti,ab,kw or mouth cancer*;ti,ab,kw or oral cancer*;ti,ab,kw or mouth neoplasm*;ti,ab,kw or oral neoplasm*;ti,ab,kw or oral carcinoma*;ti,ab,kw or mouth carcinoma*;ti,ab,kw or oral tumo*;ti,ab,kw or mouth tumo*;ti,ab,kw or squamous cell carcinoma*;ti,ab,kw) AND (MESH descriptor [Trismus] or trismus;ti,ab,kw or mouth open*;ti,ab,kw or limited mouth;ti,ab,kw or (mouth;ti,ab,kw and opening;ti,ab,kw) OR interincisal distance;ti,ab,kw or interincisor distanc;ti,ab,kw or interincisal opening;ti,ab,kw OR lockjaw;ti,ab,kw or lock jaw;ti,ab,kw or jaw closure;ti,ab,kw or jaw opening;ti,ab,kw or range of motion;ti,ab,kw)))

EMBASE

('head and neck neoplasm' OR 'head and neck cancer*':ti,ab OR 'head and neck neoplasm*':ti,ab OR 'head and neck carcinom*':ti,ab OR 'head and neck tumo*':ti,ab OR 'cancer of the mouth':ti,ab OR 'cancer of the oral cavity':ti,ab OR 'cancer of the neck':ti,ab OR 'cancer of the head':ti,ab OR 'cancer of the pharynx':ti,ab OR 'carcinoma of the oral cavity':ti,ab OR 'mouth cancer*':ti,ab OR 'oral cancer*':ti,ab OR 'mouth neoplasm*':ti,ab OR 'oral neoplasm*':ti,ab OR 'oral carcinoma':ti,ab OR 'mouth carcinom*':ti,ab OR 'oral tumo*':ti,ab OR 'mouth tumo*':ti,ab OR 'squamous cell carcinoma*':ti,ab) AND ('trismus'/exp OR trismus:ti,ab OR 'mouth open*':ti,ab OR 'limited mouth':ti,ab OR (mouth:ti,ab AND opening:ti,ab) OR 'interincisal distance':ti,ab OR 'interincisor distance':ti,ab OR 'interincisal opening':ti,ab OR lockjaw:ti,ab OR 'lock jaw':ti,ab OR 'jaw closure':ti,ab OR 'jaw opening':ti,ab OR 'range of motion':ti,ab)

Cinahl

(AB (head and neck cancer* OR head and neck neoplasm* OR head and neck carcinoma* OR head and neck tumor* OR cancer of the mouth OR cancer of the oral cavity OR cancer of the neck OR cancer of the head OR cancer of the pharynx OR carcinom of the oral cavity OR mouth cancer* OR oral cancer* OR mouth neoplasm* OR oral neoplasm* OR oral carcinoma* OR mouth carcinoma* OR oral tumo* OR mouth tumo* OR squamous cell carcinoma*) OR TI (head and neck cancer* OR head and neck neoplasm* OR head and neck carcinoma* OR head and neck tumor* OR cancer of the mouth OR cancer of the oral cavity OR cancer of the neck OR cancer of the head OR cancer of the pharynx OR carcinom of the oral cavity OR mouth cancer* OR oral cancer* OR mouth neoplasm* OR oral neoplasm* OR oral carcinoma* OR mouth carcinoma* OR oral tumo* OR mouth tumo* OR squamous cell carcinoma*)) AND (AB (trismus OR mouth open* OR limited mouth OR interincisal distance OR interincisor distance OR interincisal opening OR lockjaw OR lock jaw OR jaw closure OR jaw opening OR range of motion) OR TI (trismus OR mouth open* OR limited mouth OR interincisal distance OR interincisor distance OR interincisal opening OR lockjaw OR lock jaw OR jaw closure OR jaw opening OR range of motion))

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