

LETTER TO THE EDITOR

Risk structures for radiation-induced trismus in head and neck cancer

To the Editor,

Treating head and neck cancer (HNC) is challenging as the tumors are located in a critical area where many essential functions originate. Amongst the late appearing side effects after radiotherapy (RT) for HNC, restricted mouth opening (trismus) occurs in more than one third of patients and have been described as persisting or even worsening five years after completed RT [1–3]. Trismus can lead to difficulties in eating, chewing, maintaining oral hygiene, and potentially to malnutrition and weight loss [2–6].

Irradiation of the temporomandibular joint (TM joint) and muscles of mastication, especially doses to the masseter and the pterygoid muscles, have been reported to be associated with radiation-induced trismus [7–11]. However, available data diverge as to which anatomical structure is more critical for trismus after RT in HNC. The aim of this prospective study was, therefore, to investigate if the use of both objectively and subjectively determined trismus can shed further light on this issue.

Material and methods

Additional information on the study population (inclusion/exclusion criteria), treatment, and statistics can be found in the appendix (available online at <http://www.informahealthcare.com>).

Study population

This study includes patients treated for HNC with external beam RT (EBRT) only or EBRT in combination with brachytherapy, with or without chemotherapy, but not with surgery. They were treated during 2007–2012 and were prospectively followed with respect to mouth opening measured in millimeters, maximal interincisal opening (MIO), and with two validated patient-reported outcome (PRO) instruments, the Gothenburg Trismus Questionnaire (GTQ) [12] and the European Organization for Research and Treatment of Cancer Head and Neck Questionnaire (EORTC QLQ-HN35) [13]. Patients were assessed before RT and at three, six and 12 months after RT.

Treatment and structure doses

EBRT was planned based on computed tomography (CT) imaging and was given as three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). The EclipseTM treatment planning system was used for treatment planning (version 10.0.39, Varian Medical Systems, Palo

Alto, CA, USA); no dose constraints for the mastication structures were applied. Prescribed doses were typically 1.7/2.0 Gy per fraction two/one time(s) per day, five days per week to a total dose of 64.6/68.0 Gy.

For each patient, the masseter muscles, the temporal muscles, the pterygoid muscles (medial pterygoid and lateral pterygoid), the TM joint, the ganglion pterygopalatine (ganglion PPT), and the soft palate were consistently contoured on the CT images used for treatment planning (Supplementary Figure 1, available online at <http://www.informahealthcare.com>) Absorbed doses for all risk structures were re-calculated according to the planned EBRT dose distribution of the original treatment plan and structure-specific dose-volume histograms (DVH) were exported. Unfortunately, reliable 3D brachytherapy dose contributions to tissues outside the tumor volume could not be estimated for most patients due to lack of image information. Instead of excluding all patients who had received brachytherapy, for each patient in question, we retained those structures where the brachytherapy absorbed dose contribution could be ignored (based on available information, Supplementary Table 1, available online at <http://www.informahealthcare.com>).

Evaluation of trismus and endpoints

The three investigated endpoints reflected any occurrence of trismus during the first year of follow-up. Endpoint 1 = trismus defined as MIO ≤ 35 mm according to Dijkstra et al. [14], endpoint 2 = trismus defined as “Moderate” – “Very much” according to the five-category answering scale of the single item “Limitation in opening mouth” by GTQ [12], and endpoint 3 = trismus defined as “Quite a lot” – “Much” according to the four-category answering scale of the single item “Restricted mouth opening” by EORTC QLQ-HN35 [13].

Statistics

All bilateral structures were analyzed as ipsi-, contra- and bilateral structures with corresponding mean absorbed RT doses. Correlations between doses of different structures were calculated using Pearson’s correlation coefficients; comparisons between structure doses in trismus and non-trismus patients were made using Student’s t- and Wilcoxon rank-sum tests. Potential dose predictors for trismus were tested in univariable logistic regression (UVA) and in multivariable logistic regression (MVA) together with ACE-27, age, chemotherapy, height, and smoking. $p < 0.05$ was considered statistically significant; inclusion criterion for variables in MVA was $p < 0.10$. A model’s discriminative ability was assessed by the area under the receiver operating characteristic (ROC) curve (AUC). The analyses were performed using the statistical software SAS[®] version 9.2 (Cary, NC, USA).

Results

Patient characteristics, treatment information, and baseline outcome information for the 216 patients analyzed in this work are given in Supplementary Table 2 (available online at <http://www.informahealthcare.com>); detailed structure dose information in Table 1. Tumor of the oropharynx was most common (70% of patients) followed by tumors of the oral cavity (13% of patients). A majority had stage IV disease at time of diagnosis (57%); 85% of the patients had mild or no comorbidity according to ACE-27. According to the MIO criteria, 14 patients (6%) had trismus at baseline and were excluded from analyses involving the MIO endpoint. For GTQ and EORTC QLQ-HN35, the corresponding figures were 24 (11%) and 18 (8%). During the first year of follow-up, 122 patients (56%) developed trismus according to MIO, 111 (51%) according to GTQ and 66 (31%) according to EORTC QLQ-HN 35.

Regardless of trismus assessment approach, doses to the masseter muscle and the TM joint were significantly higher in trismus patients than in non-trismus patients (Supplementary Table 3a–c, available online at <http://www.informahealthcare.com>). Rates of trismus according to MIO, GTQ, and EORTC QLQ-HN35 by different dose intervals are presented for selected structures in Figure 1; increasing dose typically resulted in higher frequency of trismus. Doses of the lateral pterygoid, the temporal muscle, the TM joint, and the ganglion PPT were strongly correlated (Pearson's correlation coefficients ≥ 0.80 ; Supplementary Table 4, available online at <http://www.informahealthcare.com>).

Results from logistic regression for doses to bilateral and ipsilateral risk structures were comparable with models of similar discriminative ability (Table 2 and Supplementary Table 5a, available online at <http://www.informahealthcare.com>); doses to contralateral risk structures generally resulted in models with weaker discriminative ability (Supplementary Table 5b). Results for the bilateral structures are, therefore, presented in the following unless otherwise stated (cf. number of structures/patients analyzed in Table 1; a detailed version of Table 2 is also presented as Supplementary Table 6a–c, available online at <http://www.informahealthcare.com>).

For all three endpoints, we found that dose to the masseter and the TM joint were statistically significant predictors of trismus in UVA. In MVA, smoking and height were additional factors of importance for trismus according to MIO; ACE-27 was of importance for trismus according to GTQ, and height was of importance for trismus according to EORTC QLQ-HN35. Dose to the ipsilateral masseter as predictor for trismus according to GTQ, adjusted for ACE-27, provided the model with the overall best discriminative ability for available data ($N = 181$; $AUC = 0.78$).

To investigate the relationship between the different risk structures doses as predictors for trismus, MVA with forward selection was performed (Supplementary Table 7, available online at <http://www.informahealthcare.com>). For MIO, the dose to the masseter muscle together with smoking was suggested as a final model. For GTQ, the dose to the masseter and ACE-27 was suggested, and for EORTC QLQ-HN35, the dose to the masseter muscle only. The ROC curves for the final models are presented in Supplementary Figure 2 (available online at <http://www.informahealthcare.com>); model performance is assessed in Supplementary Table 8 (available online at <http://www.informahealthcare.com>).

Discussion

We found that the masseter muscle mean absorbed dose was a robust predictor for both objectively determined trismus according to MIO and patient-reported trismus according to GTQ and EORTC QLQ-HN35. Clinical factors of importance were ACE-27, height, and smoking. Amongst the three investigated endpoints, trismus according to MIO provided similar results to GTQ and resulted in models with better discriminative ability than models predicting the EORTC QLQ-HN35 endpoint.

When analyzing trismus using either of the investigated methods of assessment, dose to the ipsilateral masseter muscle dose provided the model with the best discriminative ability. Other studies have also suggested that dose to the masseter is associated with a higher risk of trismus [8,9,11]. In particular, both Lindblom et al. [8] and, and more recently, Rao et al. [9] found dose to the ipsilateral masseter muscle to provide superior statistics in predicting trismus (defined by

Table 1. Mean absorbed doses, volumes, and standard deviations for potential trismus risk structures.

Risk structures	n = patients analyzed	Ipsilateral	Contralateral	Bilateral
		Mean dose $\pm$ SD (Gy) Volume $\pm$ SD (cm ³)	Mean dose $\pm$ SD (Gy) Volume $\pm$ SD (cm ³)	Mean dose $\pm$ SD (Gy) Volume $\pm$ SD (cm ³)
Masseter	181	41.5 $\pm$ 11.0 17.9 $\pm$ 5.8	29.8 $\pm$ 9.9 15.9 $\pm$ 5.1	35.7 $\pm$ 9.1 33.9 $\pm$ 10.9
Lateral pterygoid	210	32.2 $\pm$ 21.0 5.7 $\pm$ 1.5	20.9 $\pm$ 16.8 4.8 $\pm$ 1.4	26.5 $\pm$ 18.1 10.6 $\pm$ 2.8
Medial pterygoid	123	59.9 $\pm$ 10.4 8.6 $\pm$ 2.1	46.5 $\pm$ 13.7 7.5 $\pm$ 2.1	53.2 $\pm$ 10.8 16.1 $\pm$ 4.1
Temporalis	210	7.2 $\pm$ 7.3 19.7 $\pm$ 5.8	4.9 $\pm$ 5.3 17.3 $\pm$ 5.2	6.1 $\pm$ 6.2 37.1 $\pm$ 10.9
TM joint	216	21.6 $\pm$ 19.0 2.1 $\pm$ 0.7	12.5 $\pm$ 12.6 1.6 $\pm$ 0.8	17.1 $\pm$ 15.0 3.7 $\pm$ 1.4
Ganglion PPT	216	13.2 $\pm$ 18.8 0.4 $\pm$ 0.2	10.3 $\pm$ 16.0 0.3 $\pm$ 0.2	11.8 $\pm$ 17.2 0.6 $\pm$ 0.3
Soft palate	123			58.9 $\pm$ 14.2 1.9 $\pm$ 1.0

Risk structures receiving substantial dose from brachytherapy (more than a maximum absorbed doses of 3.0 Gy or more than mean absorbed doses of 2.0 Gy) were excluded from analysis of that specific structure.

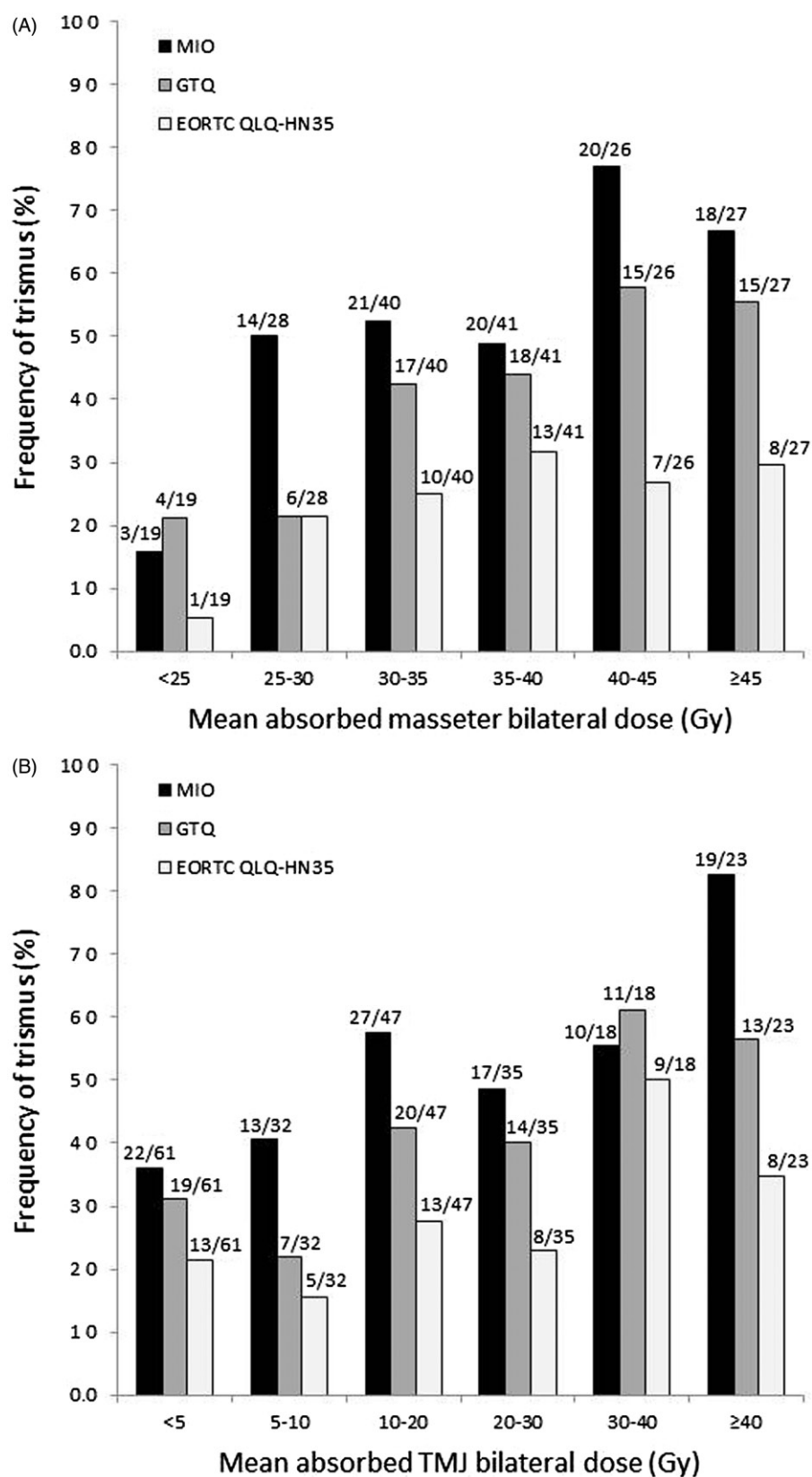


Figure 1. The relationships between dose to the masseter muscle and trismus (A) and the temporo-mandibular joint and trismus (B). Trismus according to MIO (maximal interincisal opening) ≤ 35 mm, GTQ (Gothenburg Trismus Questionnaire) answering categories 3–5, and EORTC QLQ-HN35 (European Organization for Research and Treatment of Cancer Head and Neck Questionnaire) answering categories 3–4.

Table 2. Logistic regression and ROC analysis of risk structure doses as predictors for trismus in head and neck cancer patients treated with radiotherapy (bilateral mean dose).

Risk structure	Logistic regression analysis	MIO		GTQ		EORTC QLQ-HN35	
		p-Value	AUC	p-Value	AUC	p-Value	AUC
Masseter	Univariable	<0.01	0.69	<0.01	0.71	<0.01	0.63
	Multivariable	<0.01	0.76	<0.01	0.78	<0.01	0.72
Lateral pterygoid	Univariable	<0.01	0.69	<0.01	0.64	0.09	0.59
	Multivariable	<0.01	0.74	<0.01	0.73	0.11	0.61
Medial pterygoid	Univariable	<0.01	0.67	0.15	0.58	0.16	0.56
	Multivariable	0.04	0.75	0.06	0.73	0.07	0.69
Temporal	Univariable	<0.01	0.68	0.02	0.64	0.36	0.57
	Multivariable	0.07	0.69	0.02	0.70	0.68	0.60
TM joint	Univariable	<0.01	0.66	<0.01	0.65	0.02	0.61
	Multivariable	<0.01	0.72	<0.01	0.74	0.03	0.62
Ganglion PPT	Univariable	0.02	0.67	0.18	0.62	0.49	0.55
	Multivariable	0.10	0.69	0.09	0.67	0.91	0.59
Soft palate	Univariable	0.20	0.56	0.69	0.57	0.75	0.50
	Multivariable	0.30	0.72	0.75	0.69	0.70	0.65

ACE-27, Adult Comorbidity Evaluation 27; AUC, area under the ROC-curve; EORTC QLQ HN35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck 35; GTQ, Gothenburg Trismus Questionnaire; MIO, maximal interincisal opening; ROC, receiver operating characteristics. For MIO, results from multivariable analysis are adjusted for smoking and height; for GTQ, adjusted for ACE-27, and for EORTC QLQ-HN 35.

MIO ≤ 35 mm and CTCAE grade ≥ 1 , respectively) than dose to other investigated structures (pterygoids (both), TMJ (13), and temporalis (9)). Lindblom et al. assessed a similarly treated HNC cohort (N=124) as investigated in this study, but with somewhat lower trismus rates (25%). Rao et al. assessed patients treated with IMRT only (N=421) and, as can be expected, with even lower trismus rates (11%). Although there are differences in design between these studies and the present study, together these results suggest that the masseter muscle dose is a robust predictor for trismus with respect to both trismus assessment method and RT treatment approach. It is particularly interesting to note that MIO and GTQ provided very similar results for our data. Although at a GTQ-comparable trismus cutoff, results by the more commonly used EORTC QLQ-HN35 diverged substantially from both MIO and GTQ and resulted in models with weaker discriminative ability.

Strengths of this study include the large study population with prospectively collected clinical data including several different methods of assessing trismus. Numbers of missing data was low. Selection-induced problems were avoided by consecutive inclusion of patients. The 12-month follow-up inclusion criterion was established as it is unusual that patients develop trismus later than 12 months after RT completion [15]. Possible confounding factors, such as dose from brachytherapy, were accounted for in our analyses and predicted trismus rates by our models were in corresponded well with the observed rates. In line with others, we based our analyses on mean absorbed structure doses as this dose metric have been reported suitable to describe relationships between various mastication structures and trismus [7–11]. Acknowledging that DVH points typically are strongly correlated, it is not likely that investigating other dose or volume metrics for our purpose of identifying critical structures for radiation-induced trismus would have altered the presented results substantially. For the same reason, it is unlikely that a fractionation corrected representation of dose would have changed the presented inter-relationships between the investigated structures. As an example, $R^2=0.99$ for masseter muscle mean

absorbed and fractionation corrected dose in our data. When generalizing the results from this study, it needs to be kept in mind that our study population originates from one center, and depend on the existing treatment techniques and prescribed doses during the studied period of time. Our trismus rates were also in the high-end range compared with other studies. This is a consequence of the selected endpoint in this study (defined as the accumulation of any event during the first year after RT), which was selected to account for that some of the patients had undergone a trismus-exercise program to improve mouth opening ability [16].

In conclusion, we found that predictive models based on dose to the masseter muscle were robust with respect to trismus assessment method and had the ability to well separate patients with trismus from non-trismus patients within the first year after RT. Patients receiving high radiation dose to the other investigated structures, in particular the lateral pterygoid muscle or the TM joint, can be expected to be at risk for radiation-induced trismus. Being a smoker or having other comorbidity may increase this risk, but more advanced multi-organ dose-response modeling than presented here is needed to describe these relationships in detail. Accumulated evidence, however, still suggest that the masseter muscle is a suitable candidate for trismus sparing techniques in cases where mastication structure doses can be lowered without jeopardizing tumor control.

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Disclosure statement

No conflicts of interest exist for any of the authors involved.

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Nina Pauli and Caterina Finizia

Department of Otorhinolaryngology, Head and Neck Surgery,
Institute of Clinical Sciences, Sahlgrenska Academy at the University
of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

Caroline E. Olsson

Department of Radiation Physics, Institute of Clinical Sciences,
Sahlgrenska Academy at University of Gothenburg, Gothenburg,
Sweden

 caroline.olsson@rccvast.se

Niclas Pettersson

Department of Medical Physics and Biomedical Engineering,
Sahlgrenska University Hospital, Gothenburg, Sweden

Mia Johansson and Hedda Haugen

Department of Oncology, Institute of Clinical Sciences, Sahlgrenska
Academy at the University of Gothenburg, Sahlgrenska University
Hospital, Gothenburg, Sweden

Ulrica Wilderö and Gunnar Steineck

Division of Clinical Cancer Epidemiology, Department of Oncology,
Institute of Clinical Sciences, Sahlgrenska Academy at University of
Gothenburg, Gothenburg, Sweden

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LETTER TO THE EDITOR

Bilateral avascular necrosis of the femoral head following treatment of Ewing's sarcoma

To the Editor,

Avascular necrosis (AVN) of the femoral head is a rare skeletal disease usually presenting with vague symptoms from the hip or lower pelvis. Risk factors include alcoholism, use of corticosteroids, prior pelvic irradiation and various medical

disorders, e.g. sickle cell disease, systemic lupus erythematosus and Gaucher's disease. The pathophysiology remains unclear, but is believed to include an altered microcirculation and disruption of the blood supply to the femoral head [1,2].

Ewing's sarcoma (ES) accounts for about 3% of all pediatric and adolescent malignancies and remains the second most common primary bone tumor [3]. Following the introduction of combined modality treatment, the prognosis has dramatically improved with an expected survival of 70–80% for patients presenting with localized disease [4]. Treatment consists of multi-agent chemotherapy, including anthracyclines and alkylating agents with risk of acute and late toxicities, the latter including potential cardiac, gonadal and renal damage [5].