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Journal

Acta Oncologica, 55(1)

ISSN

0284-186X

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Publication Date

2016-01-02

DOI

10.3109/0284186x.2015.1037864

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Acta Oncologica, 2015; Early Online: 1–6

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ORIGINAL ARTICLE

Dose-volume factors correlating with trismus following chemoradiation for head and neck cancer

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ABSTRACT

Background. To investigate the dose-volume factors in mastication muscles that are implicated as possible causes of trismus in patients following treatment with intensity-modulated radiotherapy (IMRT) and concurrent chemotherapy for head and neck cancers.

Material and methods. All evaluable patients treated at our institution between January 2004 and April 2009 with chemotherapy and IMRT for squamous cell cancers of the oropharynx, nasopharynx, hypopharynx or larynx were included in this analysis (N = 421). Trismus was assessed using CTCAE 4.0. Bi-lateral masseter, temporalis, lateral pterygoid and medial pterygoid muscles were delineated on axial computed tomography (CT) treatment planning images, and dose-volume parameters were extracted to investigate univariate and multimetric correlations.

Results. Forty-six patients (10.9%) were observed to have chronic trismus of grade 1 or greater. From analysis of baseline patient characteristics, toxicity correlated with primary site and patient age. From dose-volume analysis, the steepest dose thresholds and highest correlations were seen for mean dose to ipsilateral masseter (Spearman's rank correlation coefficient Rs = 0.25) and medial pterygoid (Rs = 0.23) muscles. Lyman-Kutcher-Burman modeling showed highest correlations for the same muscles. The best correlation for multimetric logistic regression modeling was with V_{68Gy} to the ipsilateral medial pterygoid (Rs = 0.29).

Conclusion. Chemoradiation-induced trismus remains a problem particularly for patients with oropharyngeal carcinoma. Strong dose-volume correlations support the hypothesis that limiting dose to the ipsilateral masseter muscle and, in particular, the medial pterygoid muscle may reduce the likelihood of trismus.

Trismus, which refers to an inability to fully open the mouth, has several causes, including tumor infiltration into the muscles of mastication, or as a side effect of surgery or radiation therapy [1]. The consequent impact on oral nutrition, impairment of speech, oral hygiene, and general discomfort, can result in significant morbidity [1,2]. While radiation therapy has been reported to induce chronic trismus with a late onset, an understanding of the dose-volume parameters causing radiation-induced trismus is limited. Previous studies report incidence rates between 5% and 50% in patients treated with head and neck radiotherapy [2,3]. Muscle damage and fibrosis have been proposed as causes for this late toxicity of radiation [4–6]. Movement of the jaw is predominantly controlled by the paired muscles of mastication consisting of the masseter (M), temporalis (T), medial pterygoid (MP) and lateral pterygoid (LP) muscles [7]. In this study we examine correlations between dose-volume parameters for the muscles of mastication and the resulting development of trismus in patients following treatment with intensity-modulated radiotherapy (IMRT) and chemotherapy for head and neck cancers.

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(Received 21 January 2015; accepted 30 March 2015)

ISSN 0284-186X print/ISSN 1651-226X online © 2015 Informa Healthcare
DOI: 10.3109/0284186X.2015.1037864

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Materials and methods

Patient population

This was an institutional review board approved retrospective cohort study. Between January 2004 and April 2009, 798 patients were treated at our institution with head and neck IMRT for squamous cell carcinomas of the nasopharynx (NPC), oropharynx (OPC), hypopharynx (HPC) and larynx. Patients were treated to a prescribed dose of 70 Gy (median dose) and received concurrent systematic therapy (predominantly cisplatin). Patients with, local failure, less than six months follow-up, postoperative cases, those treated with RT alone, unrestorable treatment plans were excluded. In order to eliminate cases where trismus was not clearly treatment related, five patients with OPC and one NPC patient who had trismus both before and after treatment were excluded. Eleven patients experienced trismus prior to treatment but not afterward and were included in the analysis. Of the remaining 421 patients who were eligible for analysis, 46 had NPC, 290 OPC, 18 HPC and 67 laryngeal cancers (Table I).

Table I. Demographic characteristics of patients.

Characteristic	n	%
Gender		
Male	345	82
Female	76	18
Race		
White	342	81
Other	79	19
Primary site		
Oropharynx	290	69
Larynx	67	16
Nasopharynx	46	11
Hypopharynx	18	4
T stage (AJCC 7th ed)		
1	89	21
2	168	40
3	108	26
4	56	13
N stage		
0	47	11
1	92	22
2	269	64
3	13	3
Overall stage		
II	19	4
III	108	26
IV	294	70
Age		
≤55 years	191	45
>55 years	230	55
KPS*		
≤80	80	20
>80	327	80

Toxicity assessment

The evaluation for trismus is routinely evaluated and documented at each visit for all patients at our institution. Patients were typically assessed for trismus every four months for the first two years after treatment, every six months for years 3–5 and then annually. Chronic trismus was assessed using the CTCAE version 4.0 in which Grade 1 toxicity is defined as decreased range of motion without impaired eating, Grade 2 toxicity by decreased range of motion requiring small bites, soft foods or purees, and Grade 3 toxicity with decreased range of motion with inability to adequately aliment or hydrate. The maximum CTCAE grade during the follow-up period was used for scoring. The analyzed endpoint included Grade 1 and greater.

Anatomic structures analyzed

Using our institutional radiation treatment planning system, the paired M, T, LP and MP muscles caudal to the inferior orbital fissure were delineated on axial computed tomography (CT) treatment planning images for each patient. Muscles were further characterized into ipsilateral (I) or contralateral (C) depending on the site of the primary tumor (Supplementary Figure 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864). These muscles had not been initially delineated or used as avoidance structures factored in the original treatment planning. Dose-volume histograms (DVHs) for the eight muscles (MI, MC, TI, TC, LPI, LPC, MPI, and MPC) were extracted and combined with relevant clinical parameters (Table I) for further analysis.

Statistical analysis of clinical and dose-volume factors

DVH parameters based on the physical dose were extracted using the Computational Environment for Radiotherapy Research (CERR) [8]. DVH parameters included the mean dose, the fractional volume receiving greater than x Gy dose (Vx) and the minimum dose to the 'hottest' x fraction of the structure (Dx). Univariate and multivariate logistic analyses were performed using the open-source dose response explorer system (DREES) [9] and Stata/MP (Ver. 12.1, StataCorp, TX, USA). Model selection using bootstrap technique to avoid overfitting was completed with Stata and DREES. Further modeling using the Lyman-Kutcher-Burman (LKB) model and the generalized equivalent uniform dose (gEUD) was performed in Matlab [10,11] to investigate the impact of the different DVH regions on the correlation. LKB model parameters (a, m, D50) and confidence intervals were determined using maximum

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likelihood fitting and by employing the bootstrap technique (2000 samples and refits). Confidence intervals for the binary outcome were determined using the exact binomial distribution [12]. Spearman's rank correlation coefficient (Rs) was used to summarize correlations due to its robustness for non-linear relationships.

Results

With a median follow-up time of 33 months (range 6–68), 46 patients (10.9%) were found to have chronic trismus. The majority had grade 1 trismus (38 patients), though both grade 2 (5 patients) and grade 3 toxicity (3 patients) were identified. Trismus was seen in 14.1% of patients with OPC, 6.5% of patients with NPC, 3.0% of patients with laryngeal tumors and no patients with HPC.

Univariate and multivariate analysis of clinical parameters correlating with the development of chronic trismus was performed (Table II). Tumor primary site, but not T-stage, showed a strong correlation with the development of trismus ($p < 0.001$). Age demonstrated a significant negative correlation with trismus ($p = 0.01$).

The mean doses delivered to each muscle are shown in Figure 1. Logistic regression fitting was performed using the mean dose for each muscle, as shown in Figure 2. Fitting coefficients, 95% CIs, and the area under operating receiver curve (AUC) for the mean dose parameters of the eight muscle structures are provided in Supplementary Table I (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864). The mean dose corresponding to a 10% risk of trismus was 40 Gy for MI and 64 Gy for MPI.

Both the absolute (cm^3) and relative (%) V_{1Gy} to V_{100Gy} were included for the eight muscles, as well as $D_{1\%}$ to $D_{100\%}$. Supplementary Figure 2A and B (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864) shows the resulting correlations and corresponding p-values between trismus and (Vx) to each muscle using the logistic model for different dose levels. The optimal cut-off using receiver operating curve (ROC) in DREES were absolute V68Gy and V47Gy for MPI and MI muscles, respectively. Dose-volume correlations for the absolute V_{68Gy} for the MPI ($Rs = 0.29$) and absolute V_{47Gy} for the MI ($Rs = 0.26$) are shown in Supplementary Figure 2C and D to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864, respectively. Dose correlations for Dx values, which were less significant, are shown in Supplementary Figure 3 (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864).

Table II. Correlation of clinical parameters with trismus (Grade ≥ 1).

Characteristic	Univariate analysis (p-value)	Multivariate analysis (p-value)
Gender	0.09	0.27
Race	0.14	0.21
Primary site	<0.001	0.002
T stage	0.59	0.44
N stage	0.53	0.63
Overall stage	1.0	0.23
Age	0.01	0.01
KPS	0.21	0.56

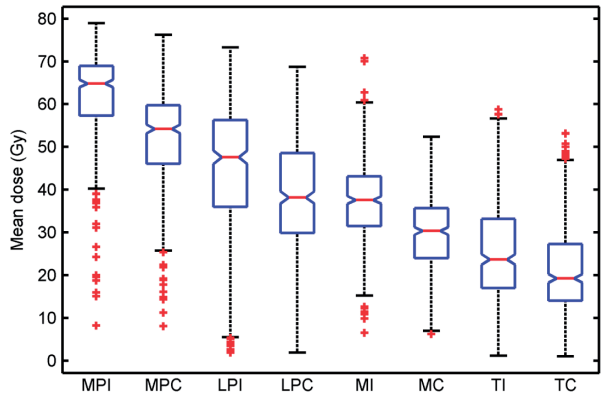

Figure 1. The distribution of the mean dose for each muscle structure. The box plot shows the median, 25th and 75th percentiles. The whiskers indicate the 95% level and values outside that range are shown as red points.

LKB modeling incorporating the gEUD was performed for MI and MPI muscles as shown in Figures 3 and 4. The best LKB fit parameters were ($a = 6.8$, $m = 0.19$, $D50 = 86$Gy) for the MPI and ($a = 8.7$, $m = 0.25$, $D50 = 71$Gy) for the MI muscle. The best fit parameters and 95% confidence intervals are shown in Supplementary Table II (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864).

Stepwise model selection in DREES using multimetric logistic regression with 250 bootstrap samples was performed (Supplementary Table III, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864). A logistic model using a single parameter (absolute volume V_{68Gy}) for the MPI ($AUC = 0.76$, $p < 0.001$) provided the best correlation. Incorporating the clinical parameter age into the model selection slightly improved the model ($Y = -0.03$*Age + 0.09*Vx(MPI,x = 68 Gy); $AUC = 0.78$, $p < 0.001$). A three-parameter model incorporating age and gEUD for MPI and MI yielded slightly lower AUC ($Y = -0.03$ *Age + 0.07*gEUD(MI, a = 8.7) + 0.07*gEUD(MPI, a = 6.8); $AUC = 0.75$, $p < 0.001$).

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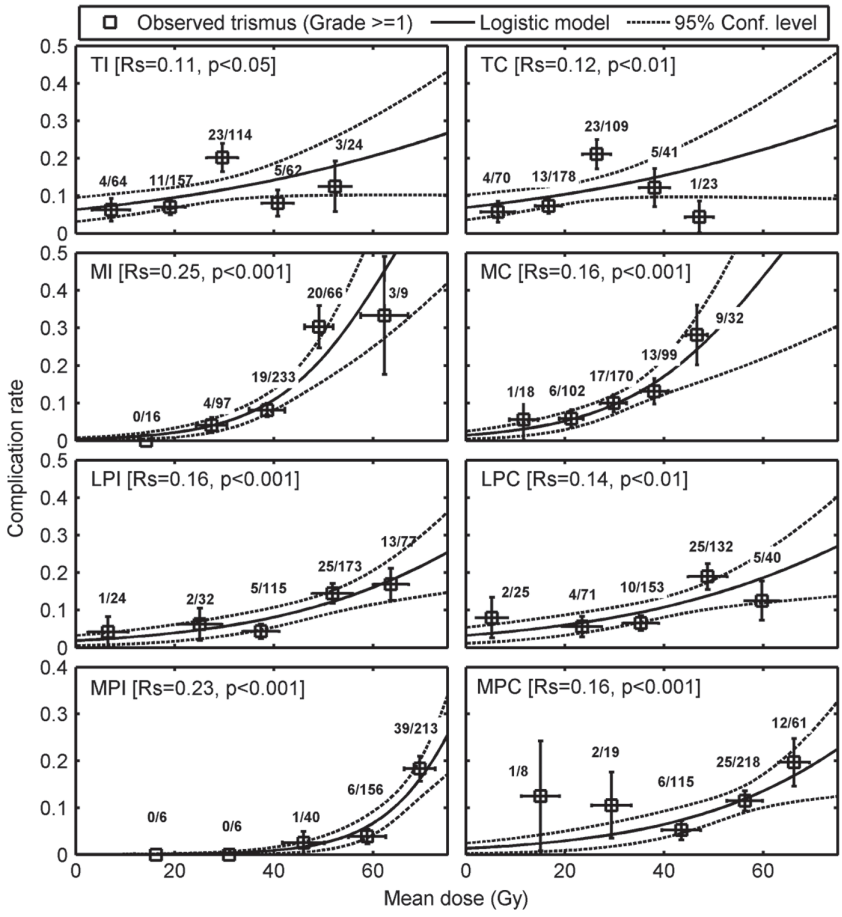

Figure 2. Logistic fit based on mean dose for each muscle structure. There is significant correlation between trismus and mean dose to all muscles. Solid line indicates the best fit of the logistic model while the dashed lines indicate the 95% confidence level. Error bars on the x-axis corresponds to one standard deviation while the error bars on the y-axis represent the 95% confidence level using the exact binomial distribution.

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Discussion

This analysis is based on one of the largest cohorts reported for chemoradiation-related trismus. The overall rate of trismus in our series (11%) was low compared to other published series [2]. Severe trismus (Grade 2 or 3) occurred in only eight of the 46 patients with trismus. The use of IMRT [13] and an institutional program instructing patients to perform daily range of motion exercises [14] may have contributed to these low rates.

Despite low overall rates, chemoradiation-induced trismus remains a problem, particularly for patients with OPC. While patients with laryngeal cancer, HPC or NPC had minimal trismus rates (0%, 3% and 6%, respectively), 14% of patients with OPC experienced chronic trismus. Both univariate and multivariate analysis confirmed tumor primary site as the most predictive clinical parameter. This is readily explained by the immediate proximity of the muscles of mastication to the oropharynx. Contrary to the usual impact of age on toxicity, in this study, age inversely correlated with trismus. Of note, there was not a significant difference in follow-up between younger and older patients that might explain this difference. Neither T-stage nor N-stage correlated with trismus.

Due to their proximities to the mucosa where primary squamous cell tumors arise, the more medially positioned muscles (MP & LP) received higher mean doses than the lateral muscles (T & M) as was shown in Figure 1. While mean doses to all eight muscles correlated with trismus, mean doses to MI ($Rs = 0.23$) and MPI ($Rs = 0.25$) were the most statistically significant (Figure 2). The LKB model using gEUD demonstrated similar correlations with trismus to MI ($Rs = 0.25$) and MPI ($Rs = 0.24$) compared to logistic regression based on mean dose (Figures 3 and 4). The large value for the parameter ($a > 1$) emphasizes that the higher dose part of the DVH is driving the correlations; which would be consistent with an etiology of local damage, followed over time by the development of fibrosis, leading to

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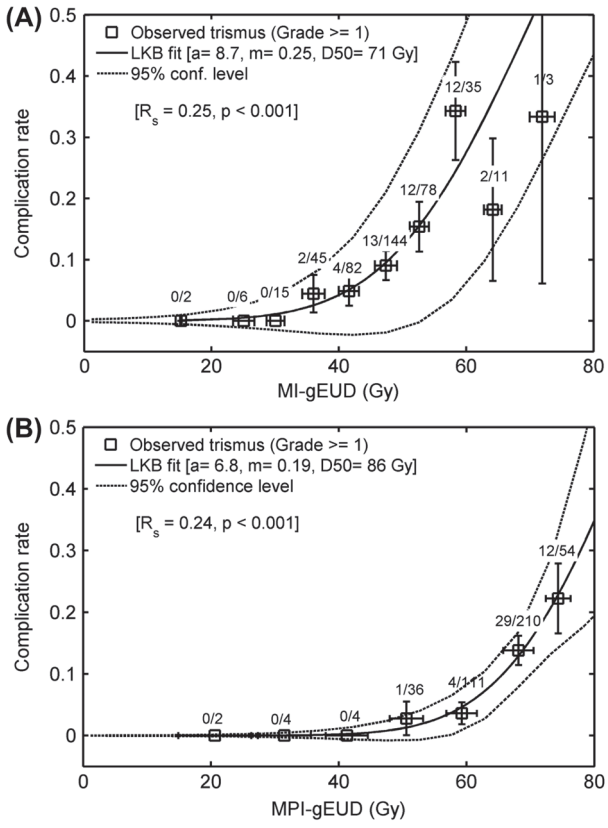

Figure 3. Lyman-Kutcher-Burman model for trismus. The incidence of trismus as a function of the gEUD for the MI (A) and MPI (B). Solid line indicates the maximum-likelihood fit of the Lyman-Kutcher-Burman (LKB) to the original data. Dashed lines indicate the 95% significance level of the fit using a boot-strapped pseudo dataset derived from the original data. Both models clearly indicate that the correlation is driven by the higher doses, with *a* values much greater than 1, which, in contrast, would indicate a preference for the mean dose.

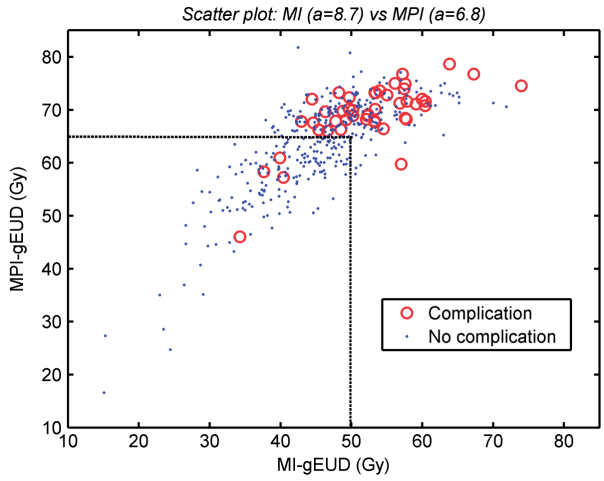

Figure 4. Combined gEUD scatter plot with MI versus MPI. A higher incidence of trismus is clearly observed for gEUD value of 50 Gy for MI (a = 6.8) and 65 Gy for MPI (a = 8.7) as indicated by the dashed lines. Red circles indicate patients who developed trismus (G ≥ 1) while blue dots represent patients without complications.

trismus. Both the ipsilateral masseter (MI) and the ipsilateral medial pterygoid (MPI) muscles show superior correlations to trismus on univariate and multivariate modeling. Although V_{68Gy} of the MPI muscle was chosen on multimetric analysis, a role for the M muscle cannot be dismissed based on the current dataset. Despite this, the higher dose threshold of the MPI muscle dose-response curves, the slightly better dose-volume correlations, and the lack of significance of M dose-volume parameters in a multimetric model, would support a clinical focus on MPI as the likely key source of trismus.

Dose to all structures correlated at some level with trismus, which is not unexpected given the proximity of the muscles of mastication to each other. As the muscles of mastication had not originally been used as avoidance structures during treatment planning for these patients, broad dose gradients extending across these muscles exist in most of the plans. As correlations for a given structure may indirectly represent correlations for an adjacent muscle due to this dose "spill-over", multimetric modeling was utilized. Indeed higher dose correlations were found for the MI and MPI on univariate analysis consistent with prior studies identifying the M and P muscles [2,4,6].

Intriguingly, the highest univariate dose correlations are seen with the most centrally positioned muscle, the MP, and the most lateral muscle, the M. Both muscles share a common role in functioning as elevators of the mandible which close the mouth when contracted [15]. Similarly, both the MP and M muscles are heavily multipennate, unlike the LP and T muscles [7,15]. Multipennate muscles utilize diagonally oriented muscle fibers of short length arranged in a fan or feather-like pattern [7]. Interestingly, though the LP is in close physical proximity to the MP, it does not demonstrate the same dose sensitivity despite exposure to comparable dose ranges in our series. While some prior studies refer to the LP and MP muscles as a single functional unit [4,5], we recommend delineation of these muscles into distinct structures due to their differences in function, muscle fiber structure and apparent dose responses.

There are several potential limitations of the current study. We chose to evaluate these muscle groups based on their prominent roles in jaw movement. However, it is possible a structure not evaluated in this analysis contributes to toxicity. We are evaluating the potential for other critical structures using alternative dosimetric analysis strategies. Also, our study used CTCAE criteria for grading of trismus, in contrast to other studies that have employed measurements of incisor-to-incisor distance upon maximal mouth opening as an arguably more objective metric.

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These measures were not available for this cohort. However, there is a strong correlation between the measured maximal interincisal distance and patient-reported trismus [6]. As for all such dose-volume toxicity studies, the results only apply for the range of treatment and clinical parameters in the dataset studied. These results need to be tested in other relevant patient cohorts.

Conclusion

The development of trismus following chemoradiation is well correlated with high doses to the MI and MPI on univariate analysis and the high dose volume to the MPI upon multivariate analysis. The mean dose corresponding to a 10% risk of trismus was 40 Gy for MI and 64 Gy for MPI. The current analysis suggests limiting the high dose volume of the MPI to V_{68Gy} of less than 10 cm^3, or more generally, limiting the corresponding gEUD (with best fit parameters $a = 6.8$, $m = 0.19$, and $D50 = 86$Gy) to less than approximately 50 Gy, could reduce the chance of developing toxicity. The high value for the gEUD parameter ($a = 8.7$ for MI; $a = 6.8$ for MPI) suggests that the high dose region of the DVH is driving the correlation with trismus. We hasten to add, however, that any potential impact on tumor control should be carefully evaluated. Given the potential proximity of pharyngeal tumor to the immediately located MPI, this could pose a competing treatment planning limitation for tumor coverage. We caution that tumor control should routinely take priority in the treatment planning process.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Satheeshkumar PS, Mohan MP, Jacob J. Restricted mouth opening and trismus in oral oncology. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:709–15.

[2] Louise Kent M, Brennan MT, Noll JL, Fox PC, Burri SH, Hunter JC, et al. Radiation-induced trismus in head and neck cancer patients. Support Care Cancer 2008; 16:305–9.

[3] Dijkstra PU, Kalk WW, Roodenburg JL. Trismus in head and neck oncology: A systematic review. Oral Oncol 2004; 40:879–89.

[4] Teguh DN, Levendag PC, Voet P, van der Est H, Noever I, de Kruijf W, et al. Trismus in patients with oropharyngeal cancer: Relationship with dose in structures of mastication apparatus. Head Neck 2008;30:622–30.

[5] van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol 2013;106:364–9.

[6] Lindblom U, Gärskog O, Kjellén E, Laurell G, Levring Jäghagen E, Wahlberg P, et al. Radiation-induced trismus in the ARTSCAN head and neck trial. Acta Oncol 2014;53:620–7.

[7] Hannam AG, McMillan AS. Internal organization in the human jaw muscles. Crit Rev Oral Biol Med 1994;5: 55–89.

[8] Deasy JO, Blanco AI, Clark VH. CERR: A computational environment for radiotherapy research. Med Phys 2003; 30:979–85.

[9] El Naqa I, Suneja G, Lindsay PE, Hope AJ, Alaly JR, Vicic M, et al. Dose response explorer: An integrated open-source tool for exploring and modelling radiotherapy dose-volume outcome relationships. Phys Med Biol 2006; 5:5719–35.

[10] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123–35.

[11] Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. Med Phys 1997; 24:103–10.

[12] Morisette JT, Khorram S. Exact binomial confidence interval for proportions. Photogramm Eng Remote Sens 1998: 281–3.

[13] Chen YY, Zhao C, Wang J, Ma HL, Lai SZ, Liu Y, et al. Intensity-modulated radiation therapy reduces radiation-induced trismus in patients with nasopharyngeal carcinoma: A prospective study with > 5 years of follow-up. Cancer 2011;117:2910–6.

[14] Tang Y, Shen Q, Wang Y, Lu K, Peng Y. A randomized prospective study of rehabilitation therapy in the treatment of radiation-induced dysphagia and trismus. Strahlenther Onkol 2011;187:39–44.

[15] Koolstra JH. Dynamics of the human masticatory system. Crit Rev Oral Biol Med 2002;13:366–76.

Supplementary material available online

Supplementary Table 1–III and Figures 1–3 to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1037864

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