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Dose-volume correlates of the prevalence of patient-reported trismus in long-term survivorship after oropharyngeal IMRT: a cross-sectional dosimetric analysis.

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2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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MK, CR, SG -Drafted manuscript, undertook supervised analysis and interpretation of data.

KH, CDF - Corresponding authors; primary investigators; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, data collection infrastructure, programmatic oversight, direct oversight of classified personnel, manuscript content and editorial oversight and correspondence.

RC, SL, ASRM – Co-investigators; direct patient care provision, direct toxicity assessment and clinical data collection; interpretation and analytic support

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Conflict of interest:

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Abstract

Purpose—To ascertain the dose-toxicity relationship for the prevalence of self-reported trismus in long-term survivors after intensity-modulated radiotherapy (IMRT) for oropharyngeal carcinoma (OPC).

Materials and Methods—Self-reported mouth opening was ascertained prospectively via a cross-sectional survey of OPC survivors using the intraoral finger-test. RT dose-volume histograms (DVHs) were generated for the following masticatory regions of interest: medial pterygoid, lateral pterygoid, and masseter muscles which were designated as ipsilateral or contralateral to the primary tumor. Trismus was defined as self-reported mouth opening of <3 finger-widths. Recursive partitioning analysis (RPA) was performed to identify the dose-volume thresholds associated with late trismus.

Results—At a median follow-up time of 72 months (95% CI 68–74), 168 of the 587 (29%) survey respondents reported late trismus. Multivariate analysis demonstrated a significant association between late trismus and the following clinical variables: tonsillar primary site, advanced T stage, or higher total RT dose. RPA showed DVH-derived ipsilateral lateral pterygoid (ILP) mean dose of 61 Gy and volume receiving 27 Gy of at least 98.6% were independently associated with late trismus. The association between the ILP dosimetric parameters and the prevalence of late trismus was maintained after adjustment for clinical variables.

Conclusion—The integral dose of IMRT results in unavoidable low/intermediate dose to non-target masticatory muscles that is associated with increased prevalence of late trismus in OPC survivors. Whenever clinically and technically applicable, applying the proposed dosimetric constraints to the ILP ($V_{27} < 98.6$ and $D_{mean} < 61$ Gy) may reduce the prevalence of late trismus after IMRT for OPC patients.

Keywords

Oropharyngeal; patient-reported; trismus; survivorship; IMRT; dosimetric; dose-volume

Introduction

Survivors of oropharyngeal carcinoma (OPC) treated with radiotherapy (RT) risk a host of substantial, lifelong functional impairments. Functional toxicity is of particular interest in OPC survivorship as the rise in biologically favorable HPV-associated disease in younger patients has led to unprecedented numbers of long-term survivors facing late effects of RT at relatively young ages (commonly in their 60s). Thus, it is more imperative than ever to develop and implement proactive risk reduction strategies in these patients to minimize or prevent loss of function and improve quality of life (QOL) after RT [1].

The potentially harmful effects of the RT beam path on surrounding non-target normal structures are well established [2, 3]. Bystander effects vary by treatment modality, tumor burden, and disease site. Although with the high conformity index of intensity modulated radiotherapy (IMRT), the characteristic beam feature (i.e., integral dose) delivers low/intermediate doses to uninvolved normal tissues; this low-dose bath is associated with early and late functional morbidities [4].

Trismus is a potentially devastating late oral morbidity after RT with an incidence rate of 5% to 50% in patients with mixed sites of head and neck cancer (HNC) [5, 6]. Patients with trismus experience restricted or painful mouth opening that may limit oral intake, impair speech, and worsen oral hygiene [7]. The mouth opening is driven by the paired muscles of mastication including the medial and lateral pterygoids and masseters [8]. Therefore, institutional programs that instruct patients for a daily range of motion exercises may contribute to lower rates of trismus [9]. Although the adverse impact of trismus is well known, the exact mechanism and best prevention plans are not well defined [10]. Studies have demonstrated that both the site of disease and the volume of irradiated tissue contribute to the development of trismus. For example, patients receiving RT for laryngeal, hypopharyngeal or nasopharyngeal cancer experience minimal trismus rates at 0%, 3%, and 6%, respectively. In comparison, about 14% of patients receiving RT for OPC had chronic trismus at 33 months (range, 6–68) as defined by Common Toxicity Criteria- Adverse Events, Version 4.0 [10]. Therefore, a better understanding of structure-specific radiation doses across different subsites of HNC that predispose patients to long-term trismus is crucial to improve the QOL of those who undergo organ-preserving RT [7, 10, 11], especially young survivors.

To maximize the benefit of IMRT, structures at risk should be segmented, and dose constraints need be identified. During the plan optimization for patients with OPC, muscles of mastication are usually located in high/intermediate dose regions due to the obligate need to irradiate the high/intermediate risk nodal chain. Even in patients at low risk (i.e., with a negative nodal status), the spatial locations of masticatory structures put these structures within the unavoidable low-dose beam path dose. Consequently, identification of patients at risk for RT-induced chronic or late trismus and characterization of optimal dose constraints for the masticatory structures may reduce the risk of trismus in OPC survivors, who can live decades with RT sequelae.

We hypothesize that radiation dose thresholds to uninvolved masticatory muscles predict the risk of trismus in long-term OPC survivors. Although researchers have investigated trismus as an RT-induced toxicity in HNC patients [10–12], to date, investigation of a dose-toxicity relationship and establishment of radiation dose thresholds for masticatory muscles in a sample consisting exclusively of OPC survivors treated with IMRT is lacking. Therefore, in the present study, we aimed to address this gap. Herein, we correlate the patient-reported trismus scores with the radiation doses delivered to masticatory muscle in long-term OPC survivors who underwent IMRT. Specifically, we sought to determine:

- The relationship between subjective trismus scores and the RT dose delivered to the masticatory muscles;
- The dose-volume thresholds associated with late trismus in OPC survivors after IMRT; and
- Clinical and treatment predictors of late trismus that may identify high-risk patients who could benefit most from proactive trismus rehabilitation programs.

Materials and Methods

Participants

This is a secondary dose-toxicity analysis of a cross-sectional survivorship survey study. Patients given IMRT for OPC at The University of Texas MD Anderson Cancer Center between from January 2000 to April 2014 were sampled from 989 survey respondents (58% response rate). Eligible patients for the survey administration had no evidence of distant metastasis, recurrence or second primary at the time of survey. The survey also asked respondents to verify their cancer free status. Inclusion in this analysis mandated completion of the intraoral 3-finger survey for detection of trismus, pathologically confirmed OPC, and receipt of IMRT as a component of definitive treatment of OPC with restorable treatment plans comprising of non-contrast enhanced simulation CTs and corresponding dosimetric data. To focus on late effects of RT, surveys were acquired at least 12-months following completing of the RT. This survey-based study was approved by the MD Anderson Institutional Review Board, and informed consent was obtained from the participants via survey responses. Our clinics follow NCCN guidelines in terms of indications of single versus combined treatment modalities, and institutional consensus for treating patients with HNC. The techniques and indications of RT for HNC are detailed in our team publications [13, 14].

Survey administration

Participants were asked to complete the survey once. The survey was administered using an adapted version of Dillman's Tailored Design method [15], included 1) a letter of invitation mailed via the US postal service to eligible patients 2–3 weeks prior to the initial contact, 2) delivery of the survey questionnaire to all eligible patients via an online server (Qualtrics, Provo, UT or US postal service); and 3) two reminders mailed to non-responders via US postal service at 2–3 weeks and 4–5 weeks after the initial contact. Participants were contacted using multiple modes of communication, including e-mail (for those with e-mail

addresses on file), via Qualtrics online server or myMDAnderson (a secure, personalized patient website), and US postal service via first-class mail with a return envelope.

Patient-reported trismus

The survey constrained of a single item inquiring about the presence and severity of trismus, which was self-reported by participants based on the number of vertically stacked fingers they could fit between the central incisors or gums. The assessment was carried out by asking two questions: “How wide can you open your mouth?” and “How many fingers can you place between your upper and lower teeth or gums like the picture shown?”

1. Three or more fingers
2. At least two fingers
3. At least one finger
4. Less than one finger (I cannot fit one finger between my teeth or gums)

For analysis, trismus groups were coded as follows: three or more fingers was considered “no trismus,” at least two fingers was considered “mild” trismus, only one finger was considered “moderate” trismus, and inability to fit any fingers was considered “severe” trismus.

Data Collection

Patient, tumor, and treatment characteristics were gathered from electronic medical records. Treatment plans with corresponding dosimetric data for each patient were restored from MDACC archives. The treatment plans were initially created using Pinnacle software (Phillips Medical Systems, Andover, MA). The planning non-contrast computed tomography (CT) scans were then exported to a commercially available deformable image registration and segmentation software program (ADMIRE; Siemens Healthineers, Erlangen, Germany) where regions of interest (ROI) were auto-contoured using an existing atlas dataset [16] and subsequently reviewed by two radiation oncologists (ASRM and MK). Tumor laterality principally was determined according to the tumor epicenter location on treatment plans. The laterality of tumors with significant bulk spanning the midline was assigned based on the side containing the majority of the tumor volume as determined via volumetric analysis. In comparison, the laterality of small or apparently midline tumors was assigned based on the mean dose (D_{mean}) delivered to the parotid glands with the assumption that a higher parotid dose indicates closer proximity to the tumor and therefore small-scale lateralization. Using this information, the medial and lateral pterygoid and masseter muscles were defined as either ipsilateral or contralateral to the primary tumor. The resultant six ROIs (ipsilateral medial pterygoid [IMP], ipsilateral lateral pterygoid [ILP], ipsilateral masseter [IM], contralateral medial pterygoid [CMP], contralateral lateral pterygoid [CLP], and contralateral masseter [CM] muscles) were investigated. ROI specific dose-volume histograms (DVHs) were then generated using CT DICOM files and corresponding dosimetric data (Velocity AI 3.0.1 software, Velocity Medical Solutions, Atlanta, GA), and used in the final analysis, Figure 1.

Statistical Analysis

Descriptive statistics were used. Furthermore, patient and treatment characteristics were characterized via trismus severity stratification using the Kruskal-Wallis test and Pearson chi-square test for group means and categorical variables, respectively. Univariate Cox proportional hazard analysis was performed to identify the impact of clinical characteristics on the prevalence of trismus. Regression analysis was used to assess the association between the clinical variables and prevalence and severity of trismus. The Dmean delivered to each ROIs and its standard deviation (SD) were calculated and compared collectively across trismus severities using the Kruskal-Wallis test. The Dmean was further analyzed for each ROI by comparing possible combinations of trismus severity (none vs. any, none/mild vs. moderate/severe, and none vs. mild vs. moderate/severe) using a Pairwise Wilcoxon rank-sum test.

The patient cohort was then dichotomized according to the presence or absence of trismus, and cumulative group dose DVHs were produced and analyzed using the Wilcoxon rank sum test. Decision tree partitioning analysis or recursive partitioning analysis (RPA) was used to define dosimetric thresholds for the prevalence of trismus as a function of doses delivered to the ROIs. RPA gives the ability to assess the relative contribution of multiple ROIs and to drive exploratory non-model-dependent dose-volume constraints. RPA allows identifying dose-threshold from continuous dose distributions, and omits the effect of multi-collinearity and/or potential hyper-dimensional interactions within/between clinical candidates and dosimetric covariates. With trismus as the discriminant variable, the ROI specific Dmean and volume receiving 1–75 Gy (V1-V75) were used as candidate dosimetric parameters. Receiver operating curve analysis and K-fold cross-validation, with ROC/ AUCs optimization, were used to define dose-volume thresholds associated with late trismus. All statistical analyses were performed using the JMP Pro software program (version 12.1; SAS Institute Inc, Cary, NC).

Results

A total of 587 patients were included (Supplementary Figure 1). Their median age was 58 years. A total of 84% were male and 58% had HPV-associated OPC. The most common primary tumor site was the base of the tongue (49 %) and the great majority (92%) of the patients had a nodal disease at the time of diagnosis. Seventeen percent, 38%, 22% and 24 % of the patients underwent induction chemotherapy (IC) alone, concurrent chemotherapy (CCT), IC+CCRT and IMRT alone, respectively. The mean (\pm SD) radiation dose was 68 ± 2.7 Gy. At a median follow-up time of 72 months (range, 12–192), a total of 168 patients (29%) reported late trismus (mouth opening smaller than 3 fingers). The patients' trismus profile according to their clinicopathological and treatment characteristics is detailed in Table 1. Higher T-category ($p < 0.001$), receipt of chemotherapy ($p < 0.001$), and higher total radiation dose ($p < 0.0001$) were significantly associated with higher trismus severity in univariate analysis, Table 1. Table 2 shows the associations between the clinical variables and the prevalence of late trismus. In multivariate analysis, higher radiation dose, advanced T stage and presentation with tonsillar carcinoma showed a statistically significant association with the presence of late trismus.

The Dmean delivered to all masticatory ROI was statistically associated with the presence and severity of trismus ($p < 0.05$) in univariate analysis, Table 3. Multivariate analysis demonstrated an association between the severity of trismus (none/mild vs. moderate/severe) and Dmean delivered to the ILP and CMP ($p < 0.01$ and 0.02 , respectively).

Figure 2 shows that the Dmean delivered to each ROI was higher in patients who had moderate/severe trismus compared to those with none/mild trismus. Specifically, the Dmeans delivered to IM (45 vs. 36 Gy), IMP (69 vs. 62 Gy), ILP (58 vs. 43 Gy), CM (29 vs. 23 Gy), CMP (56 vs. 44 Gy), and CLP (37 vs. 27 Gy).

Composite DVHs shown in Figure 3 illustrate that patients with late trismus had higher radiation dose delivered to all ROIs compared to those with no self-reported late trismus, with the greatest separation seen in the ILP (Figure 3). We identified ROI-specific dose-volume thresholds associated with the persistent trismus using RPA and decision tree analysis. RPA demonstrated that DVH-derived ILP V27 and Dmean were associated with persistent RT-attributable trismus, specifically a V27 of at least 98.6% and Dmean of 61 Gy (LogWorth 10 and 3.6 respectively). A significant association between the dosimetric parameters of the ILP and the presence of late trismus was maintained after adjustment for clinical variables.

Discussion

In this study, we utilized a prospectively administered patient-reported survey and we found that the 1) prevalence of trismus in long-term OPC survivors treated with IMRT is associated with delivery of higher Dmean to all of the evaluated masticatory muscles, including the ipsilateral and contralateral masseters, medial pterygoids, and lateral pterygoids; 2) Marked separation in cumulative DVHs between patients with and without late trismus was observed in the ILP, even in the low-dose range; and 3) the dose-volume thresholds most associated with persistent trismus include ILP V27 of at least of 98.6 % and Dmean of 61 Gy to ILP.

In the clinical setting, we could only apply the proposed constraints without compromising the tumor control and whenever it is technically feasible. Out of this research effort, it would be of great value if we could bring the clinicians' attention to segment ILP and apply the proposed Dmen constraint. Yet, we cannot ignore the impact of the low integral dose of IMRT beams on the normal tissues.

Multiple factors likely contributed to the development of trismus in patients undergoing RT for HNC. First, malignant tumors can directly invade or cause inflammation of the muscles of mastication or the temporomandibular joint (TMJ) [17]. Second, tumors can impinge upon nerve tracts in the pharynx and oral cavity and induce trismus of the muscles of mastication [8]. Finally, trismus can be a direct sequela of RT which when delivered to the TMJ or muscles of mastication causing fibrosis leading to restricted mobility and decreased mouth opening [18–21], even with treatment advances.

IMRT is an irradiation technique that uses dynamic beam arrangements to create a highly conformal three-dimensional dose field. In the field of HNC, IMRT has most notably been used for parotid sparing treatment and associated with decreased rates of RT-induced

xerostomia [22]. Beyond the parotid glands, IMRT may deliver lower radiation doses to other surrounding normal structures, including the TMJ and muscles of mastication, as evidenced by a 2010 systematic review in which the weighted prevalence trismus rates of in HNC patients were 25.4% for conventional RT but just 5% for IMRT [18]. In our study, we limited study inclusion to OPC patients given IMRT as a component of definitive treatment. While 29% of patients reported any degree of late trismus, only 2.4% of them had late trismus categorized as moderate or severe, which compares favorably with previous reports. Conversely, other studies have demonstrated the trismus incidence rates to be as high as 45% [5]. Such higher reported rate could be explained by differences in the RT modalities used; we included a homogenous group of patients who underwent IMRT rather than a mixed group of patients receiving conformal RT/IMRT, the study outcome (incidence vs. prevalence) and the study design; our study is cross sectional study to determine the prevalence of patient-reported late trismus in OPC survivors.

Currently, standard or universally accepted treatment of trismus is lacking. Proposed interventions (e.g., use of jaw-mobilizing devices, stretching techniques, electrotherapy, hyperbaric oxygen therapy, manual therapies, and pentoxifylline) have had variable success rates [23] [24] [25].

Undoubtedly, the most effective strategy to improve the QOL in HNC survivors, as it relates to jaw and mouth opening, would be to prevent the development of trismus. Thus, implementation of the dose constraints to the non-target normal structures whose irradiation contributes to trismus may help guide decision making during RT planning. Some studies have explored the dose-effect relationship for trismus in HNC patients [7, 10, 26]. Van der Molen et al. showed that the Dmean, Dmax, V20, V40, and V60 for each masticatory structure (masseter, temporalis, and pterygoid muscles and mandibular condyle) were significant predictors of the presence of trismus at 10 weeks after RT in patients with advanced HNC. However, to date, no investigations have established a radiation dose threshold for the muscles of mastication in a cohort limited to patients with OPC receiving IMRT or in long-term OPC survivors. By limiting our analysis to patients with OPC receiving IMRT, we focused on a relatively homogenous group of patients at increased risk for trismus (as compared with patients with laryngeal, HPC, or NPC cancers) who underwent modern RT techniques (IMRT as compared with 3D conformal RT). We also sought to include statistical analyses with a large range of dose-volume parameters to retain some spatial information rather than focusing on the Dmean or pre-determined volumetric parameters. With this focused methodology, we successfully established dose-volume thresholds for the IM, IMP, ILP, CM, CMP, CLP, and C-PGs, above which the prevalence of long-term trismus increased substantially. Moreover, we found trismus to be significantly associated with higher Dmean delivered to the ILP and CMP in the multivariate analysis. In OPC patients with and without trismus, due to the spatial location of the medial masticator muscles (MPs), the IMP muscles are usually within the high/ intermediate dose region. Thus, there was substantially an observed significant differential radiation doses delivered to the ILP and CMP muscles (between patients with and without late trismus), which are relatively far away from the high-dose beam path but still within the low/intermediate dose region.

This analysis has some limitations, including those inherent to a single-center observational study at a tertiary cancer care center. Another potential limitation was the risk of misclassification of trismus as the prevalence and severity of trismus in our study were solely subjective, reported by the patients, as required in this large survivorship survey. More accurate stratification of trismus would require objective measurement of the maximum inter-incisal opening as well as physician and/or dental assessment. However, mandating in-person assessment would likely limit the sample size considerably. Such measurements would ensure capture of even very mild cases of trismus and allow for analyses of continuous rather than binary variables. Also, given the cross-sectional study design, we did not have baseline trismus status uniformly collected but have controlled on regression analysis for T-stage and tumor site, which are the most likely surrogates for baseline trismus. Nonetheless, another analysis of these survey data found this trismus measure to be highly related to quality of life, health utility, symptom interference, and functional status, lending support to the validity of the measure. These data provide insight into the psychosocial and clinical relevance of the presence and severity of trismus.

In conclusion, to the best of our knowledge, this study is the first to identify masticatory muscles dose-volume thresholds associated with persistent trismus in patients with OPC treated with IMRT. The most striking dosimetric differences among patients with and without late trismus were observed to be related to the ILP muscles (specifically, V27 of at least of 98.6 % and Dmean of 61 Gy), both the low dose bath to this muscle and mean dose. These findings may help guide future IMRT treatment planning and decrease the risk of late trismus in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Trismus remains a highly prevalent survivorship concern in the IMRT era.
- Incorporation of patient-reported outcomes into the predictive toxicity models is a must.
- Utilization of the proposed dosimetric constraints may reduce the risk of late trismus after IMRT in oropharyngeal cancer patients.

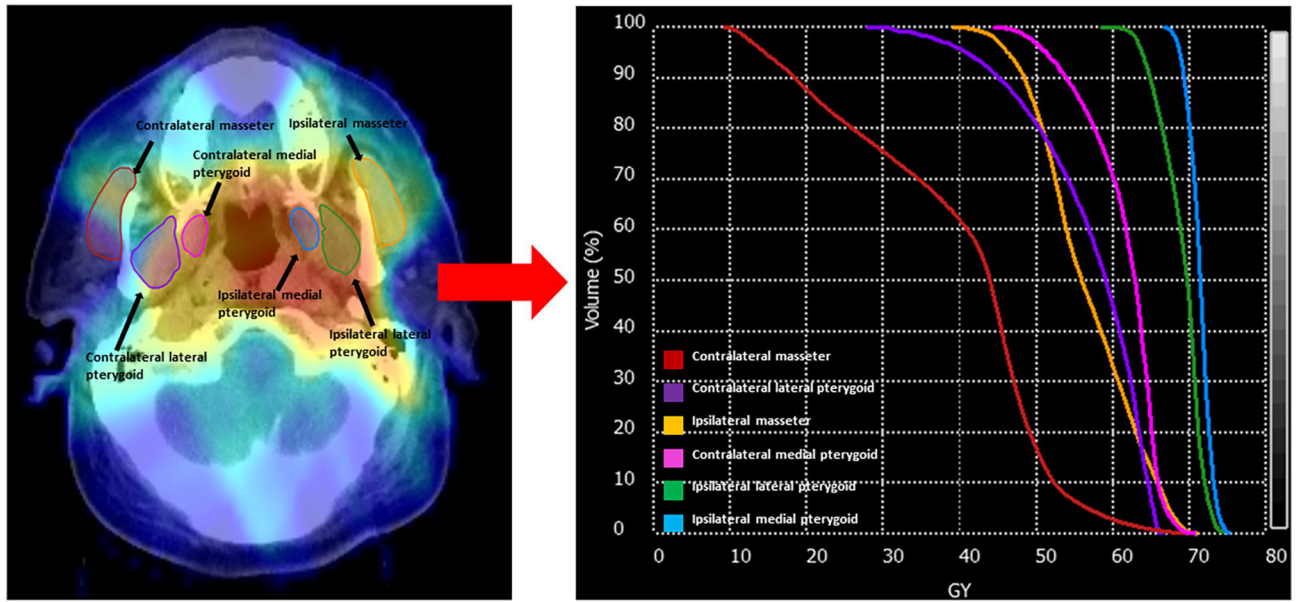


Fig. 1. Patient CT with superimposed treatment plan dose intensity map and segmented structures of interest (left) from which dose volume histograms (DVH) can be produced for analysis (right).

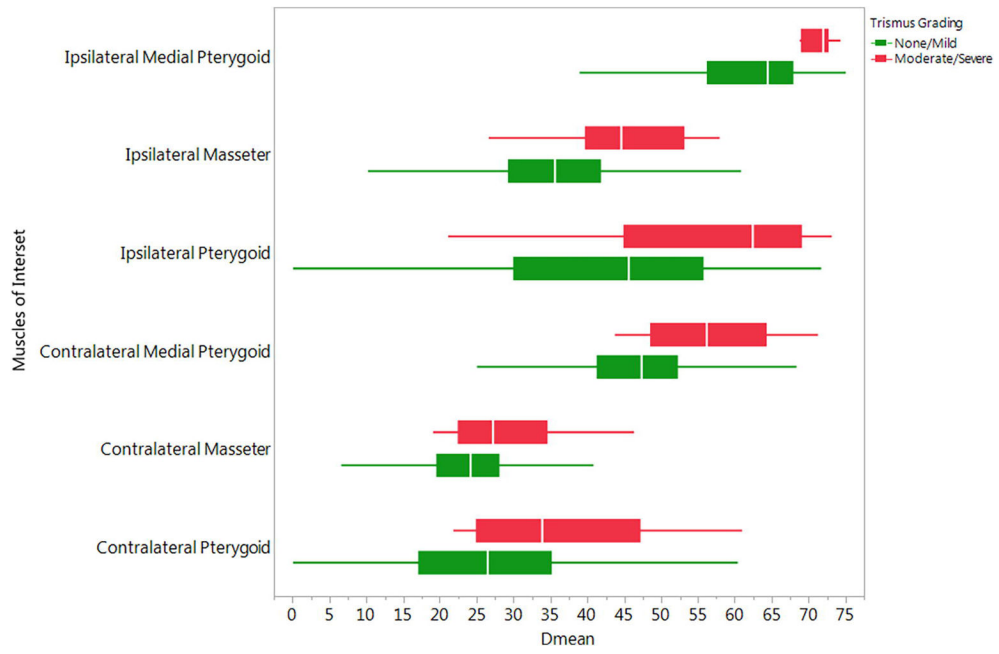


Fig. 2. Whole ROI Dmean dose differentials by Trismus Severity Grouping.

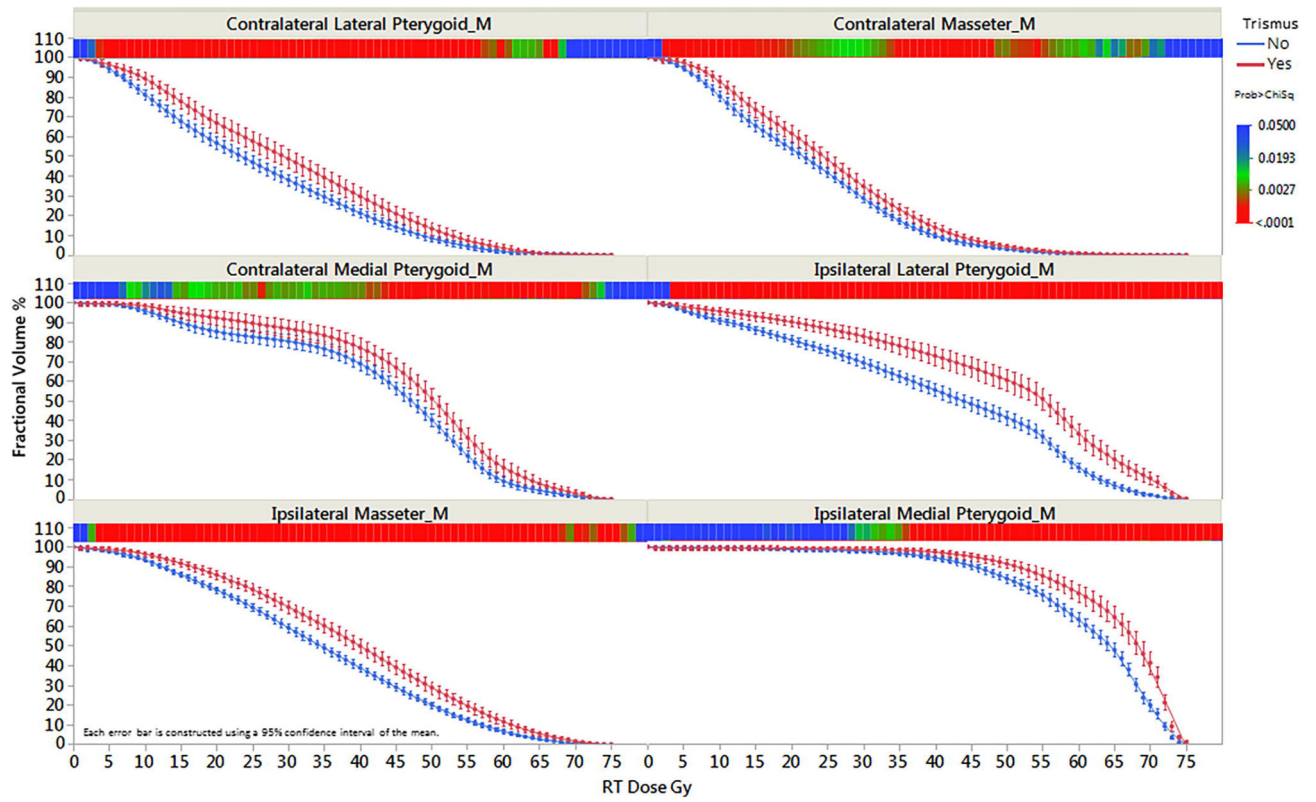


Fig. 3.
Trismus-related structures DVH stratified by presence of trismus.

Table 1.

Patient, tumor, and treatment characteristics

	All patients		No trismus (3 fingers)		Mild trismus (2 fingers)		Moderate/Severe trismus (<2 fingers)		p-value
	n=587		n=419 (71%)		n=154 (26%)		n=14 (3%)		
Covariate	n	%	n	%	n	%	n	%	
Sex									
Male	492	83.8	348	71	132	27	12	2	0.73
Female	95	16.2	71	75	22	23	2	2	
Mean age (years) ± SD	57.69	8.59	57.52	8.62	58.07	8.53	58.57	8.58	0.67
Initial disease site									
Base of tongue	288	49.1	220	76	64	22	4	2	0.59
Tonsil	267	45.5	178	67	81	30	8	3	
NOS	17	2.9	10	60	6	35	1	5	
Soft palate	7	1.2	7	100	-		-	-	
GPS	6	1.0	3	50	2	33	1	17	
Pharyngeal wall	2	0.3	1	50	1	50	-	-	
HPV/p16 status									
Positive	338	57.6	248	73	84	25	6	2	0.33
Negative	42	7.1	29	69	13	31	-	-	
Unknown	207	35.3	142	68	57	28	8	4	
T status									
T1	203	34.6	166	82	34	17	3	1	<0.0001*
T2	229	39.0	161	70	66	29	2	1	
T3	91	15.5	61	67	27	30	3	3	
T4	61	10.4	29	47	26	42	6	1	
Tx	3	0.5	2	67	1	33			
N status									
N0	46	7.8	31	67	14	30	1	2	0.35
N1	81	13.8	61	75	17	2	3	3	
N2a	62	10.6	47	76	14	22	1	2	
N2b	283	48.2	204	72	76	27	3	1	
N2c	103	17.5	67	65	30	29	6	6	
N3	12	2.0	9	75	3	25	-	-	
Mean radiation dose ± SD, Gy	68.12	2.67	67.85	2.46	68.69	3.15	69.84	1.23	<0.0001*
Mean no. fractions ± SD	32.17	2.59	31.9	2.34	32.77	3.10	33.43	2.13	<0.0001*
Chemotherapy									
Induction	98	16.7	76	78	22	22	-	-	0.0001*
Concurrent	220	37.5	155	71	63	29	2	<1	
Induction + Concurrent	129	21.8	75	58	45	36	8	6	

	All patients		No trismus (3 fingers)		Mild trismus (2 fingers)		Moderate/Severe trismus (<2 fingers)		p-value
	n=587		n=419 (71%)		n=154 (26%)		n=14 (3%)		
None	141	24.0	113	80	24	17	4	3	
Surgery									
Yes	12	2.0	11	92	1	8	-	-	0.29
No	575	98.0	408	71	153	27	14	2	
Mean survival time at survey (years) ± SD	5.94	2.86	5.75	2.87	6.41	2.79	6.14	2.71	0.0321*

Abbreviations: SD, Standard deviation; NOS, Not otherwise specified; GPS, Glossopharyngeal sulcus; Gy, Gray Group mean and categorical variables were compared with Kruskal-Wallis test and Pearson's chi-square test, respectively.

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Table 2.

Association between the clinical variables and the presence of trismus

Covariate		OR, 95% CI	Univariate analysis <i>p</i> -value	Multivariate analysis FDR- <i>p</i> -value
Sex			0.42	
	Male	1.12(0.74–2)		
	Female	1		
Mean age (years) ± SD			0.11	
Initial disease site *			0.01	0.04
	Base of tongue	1		
	Tonsil	1.6(1.1–2.3)		
Smoking status			0.12	
	Never	1		
	Current/Former Smoker	1.3(0.9–1.9)		
HPV/p16 status *			0.56	
	Positive	1		
	Negative	1.2(0.1–2.5)		
T status *				
	T1–2	1	<0.0001 *	0.01
	T3–4	2.14(1.45–3.7)		
N status				
	N0–1	1	0.76	
	N2–3	1.1(0.6–1.6)		
Mean radiation dose ± SD, Gy			<0.0001 *	0.01
Chemotherapy				
	None	1	0.0001 *	0.06
	Concurrent	1.69(1.0–2.8)		
	Induction + Concurrent	2.85(1.6–4.9)		
	Induction	1.68(0.6–2.2)		

* patients with unknown/NOS status were excluded.

Table 3:

Dmean of ROIs according to presence and severity of trismus.

Trismus										
ROI	Mean ± SD		P Value *	Mean ± SD			P Value *	Mean ± SD		P Value *
	Yes	Any		None	Mild	Moderate/ Severe		None/ Mild	Moderate/ Severe	
IM	39.29 ± 9.41	34.62 ± 8.89	<0.0001	34.61 ± 8.89	38.76 ± 9.30	45.15 ± 8.94	<.0001	45.15 ± 8.94	35.73 ± 9.18	0.0005
IMP	64.72 ± 8.65	60.71 ± 9.48	<0.0001	60.71 ± 9.48	64.32 ± 8.68	69.08 ± 7.25	<.0001	69.08 ± 7.25	61.68 ± 9.40	<.0001
ILP	49.50 ± 14.87	40.72 ± 14.95	<0.0001	40.72 ± 14.95	48.75 ± 14.72	57.69 ± 14.51	<.0001	57.69 ± 14.51	42.87 ± 15.29	0.0003
CM	25.29 ± 8.10	22.61 ± 8.59	0.0008	22.61 ± 8.59	24.91 ± 7.99	29.44 ± 8.47	0.0014	29.44 ± 8.47	23.23 ± 8.47	0.0317
CMP	47.36 ± 13.10	43.11 ± 14.64	0.0002	43.11 ± 14.64	46.54 ± 13.15	56.30 ± 8.70	<.0001	56.30 ± 8.70	44.03 ± 14.32	0.0006
CLP	29.93 ± 12.78	25.72 ± 12.29	<0.0001	25.79 ± 12.31	29.50 ± 12.17	36.61 ± 13.84	<0.0001	36.61 ± 13.84	26.79 ± 12.37	0.0157

Abbreviations: ROI, Region of n=interest; IM, Ipsilateral masseter; IMP, Ipsilateral medial pterygoid; ILP, Ipsilateral lateral pterygoid; CM, Contralateral masseter; CMP, Contralateral medial pterygoid; CLP, Contralateral lateral pterygoid; SD, Standard deviation.

* Mean values of trismus compared with Wilcoxon rank sum test.