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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

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ABSTRACT

Background and Purpose:

Prospective assessment of dysphagia and trismus in chemo-IMRT head and neck cancer patients in relation to dose-parameters of structures involved in swallowing and mastication.

Material and Methods:

Assessment of 55 patients before, 10-weeks (N=49) and 1-year post-treatment (N=37). Calculation of dose-volume parameters for swallowing (inferior (IC), middle (MC), and superior constrictors (SC)), and mastication structures (e.g. masseter). Investigation of relationships between dose-parameters and endpoints for swallowing problems (videofluoroscopy-based laryngeal Penetration-Aspiration Scale (PAS), and study-specific structured questionnaire) and limited mouth-opening (measurements and questionnaire), taking into account baseline scores.

Results:

At 10-weeks, volume of IC receiving ≥60Gy (V60) and mean dose IC were significant predictors for PAS. One-year post-treatment, reported problems with swallowing solids were significantly related to masseter dose-parameters (mean, V20, V40 and V60) and an inverse relationship (lower dose related to a higher probability) was observed for V60 of the IC. Dose-parameters of masseter and pterygoid muscles were significant predictors of trismus at 10-weeks (mean, V20, and V40). At 1-year, dose-parameters of all mastication structures were strong predictors for subjective mouth-opening problems (mean, max, V20, V40, and V60).

Conclusions:

Dose-effect relationships exist for dysphagia and trismus. Therefore treatment plans should be optimized to avoid these side effects.

KEYWORDS: head and neck cancer, chemo-IMRT, radiation doses and dose-volumes, dysphagia, trismus, swallowing and mastication structures.

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INTRODUCTION

This last decade awareness of the functional sequels of radiotherapy (RT) has grown. Intensity-Modulated Radiation Therapy (IMRT) is one of the approaches reducing side effects by limiting the RT doses to structures vital for function. Several studies have shown that IMRT in head and neck cancer treatment reduces overall adverse effects such as xerostomia and dysphagia, and thus improves quality of life, even when chemotherapy is added to IMRT (chemo-IMRT) [1-5]. It appears possible to limit the dose to the musculature involved in swallowing and mastication without compromising radiation to the tumor site(s) [2,3,5,6]. In many institutes, therefore, IMRT has become the standard of care in head and neck cancer.

Swallowing and mastication are highly complex mechanisms, which involve several nerves, muscles, and connective tissue structures. Three important swallowing muscles are the inferior, middle, and superior constrictors, innervated by the vagal nerve [7,8]. Disruption of normal swallowing function (dysphagia), may lead to (silent) aspiration, laryngeal penetration, more than normal residue after the swallow and/or reflux [1,7-12]. The structures involved in mastication are the pterygoid, masseter, and temporalis muscles, and the mandibular condyle [13]. Restricted and/or painful mouth opening affect normal chewing and eating, and impair speech and oral hygiene [14,15]

Studies that focused on radiation dose reduction and or structure avoidance, unfortunately, cannot easily be compared, because of their heterogeneity in tumor sites and treatment protocols, their overall retrospective nature, and their lack of objective assessments [1,16]. A systematic review of Roe et al. [1] (papers published between January 1998 and December 2009) found only one prospective longitudinal study that consistently evaluated oropharyngeal swallow function, using both objective instrumental measures, as well as patient self-reports alongside established toxicity scores [17]. Three months after treatment with chemo-IMRT, the oropharyngeal cancer patients showed significant correlations between videofluoroscopy and patient-reported swallowing deterioration, and the dose to the pharyngeal constrictors. Roe et al. concluded that more prospective, longitudinal studies including baseline assessments with pre-determined follow-up evaluation at multiple time points are vital in developing an understanding of the impact of IMRT on swallowing outcomes [1]. Also, other recently published reviews e.g. Wang (2011), Cartmill (2012), Nutting (2012), Bhide (2012) and colleagues, concluded that although the evidence is small, a number of dosimetric constraints might be influential in minimizing the negative impact on swallowing, and potentially on nutritional outcomes [4,5,16,18] . However, the number of significant methodological weaknesses in the current available literature must be acknowledged when interpreting the data, and Cartmill et al., therefore, suggested that future studies examining the predictive power of dosimetric factors need to include pretreatment data, and a more standardized, validated measurement protocol [16].

To minimize the side effects of chemo-IMRT, the Netherlands Cancer Institute recently conducted a prospective Randomized Controlled Trial (RCT) "*Prevention of trismus, swallowing and speech problems in patients treated with chemoradiation for advanced head and neck cancer*". All

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patients in this study received chemo-IMRT, concurrently performing preventive swallowing and mouth opening exercises. The randomization in this study concerned the comparison of two preventive swallowing exercise programs intended to strengthen and stretch swallowing and mastication musculature and structures. One program concerned standard logopaedic exercises and the other a novel exercise program using a jaw mobilization device (TheraBite, Atos Medical AB, Sweden) that strengthened and stretched the same muscles/structures [11]. Earlier, we reported that no significant functional differences between these two preventive exercise groups were found at 10-weeks post-treatment. As in the previous study, the results of these two groups could be pooled for the dose-effect part of the study [11].

This paper aims to answer the following questions: can these previously reported objective and subjective functional outcomes at 10-weeks, but also at 1-year post-treatment be related to the mean radiation dose to the muscles/structures involved in swallowing and mastication? Secondly, can the percentages of patients showing functional problems be related to different dose-volumes (low dose V20, intermediate dose V40, and high dose V60) on the organs at risks in swallowing and mastication?

MATERIALS AND METHODS

Patient characteristics

Patients with advanced stage squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx treated at our Institute with chemo-IMRT were enrolled in this study. Informed written consent was obtained from all patients prior to participation in the study. Patients were included when they had advanced stage (III and IV), functional or anatomical inoperable disease, and when able to comprehend and conduct the exercises in the swallowing programs mentioned in the introduction. Of the 72 consecutive patients screened during the accrual period of 20 months (2006-2008), 55 met the inclusion criteria. There were 44 males and 11 females with a median age of 58 years (range 32-79 years). Table 1 shows the patient characteristics.

IMRT treatment planning

All patients received 100-mg/m2 Cisplatin as a 40 minutes IV infusion on days 1, 22, and 43, and concurrent radiotherapy of 70 Gy in 35 daily fractions of 200 rad (2Gy) to a total dose of 7000 rad administered over 7 weeks with sequential boost IMRT. IMRT was calculated using the Pinnacle treatment planning system (Philips, Netherlands), 95% of the Planning Target Volume (PTV) had to receive 95% of the prescribed dose. The maximum dose allowed to the spinal cord was 50 Gy. Typically, the treatment setup consisted of a five angle coplanar setup and an optional caudal oblique irradiation field with a total number of segments between 40 and 80.

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Table 1. Patient characteristics at 10-weeks and 1-year after chemo-IMRT (N=48 en N=36)

Characteristics	Pre-treatment N (%)	Post-treatment (10-weeks) N (%)	Post-treatment (1-year) N (%)
N	55	48	36
Age in years			
Median	57	57	58
Range	32-79	32-78	39-77
Sex			
Male	44 (80)	38 (79)	27 (75)
Female	11 (20	10 (21)	9 (25)
T Classification			
T1	8 (15)	8 (17)	7 (19)
T2	15 (27)	15 (31)	12 (33)
T3	21 (38)	8 (38)	13 (36)
T4	11 (20)	7 (15)	4 (11)
N Classification			
N0	6 (11)	4 (8)	3 (8)
N1	15 (27)	14 (29)	13 (36)
N2	28 (51)	25 (53)	15 (42)
N3	6 (11)	5 (10)	5 (14)
Stage			
III	17 (31)	16 (33)	14 (39)
IV	38 (69)	32 (67)	22 (61)
Tumor site			
Oral cavity/oropharynx	29 (53)	23 (48)	15 (42)
Laryngo/hypopharynx	19 (35)	18 (38)	15 (42)
Nasopharynx	7 (13)	7 (15)	6 (17)
Rehabilitation program			
Standard exercises	28 (51)	24 (50)	17 (47)
Experimental exercises	27 (49)	24 (50)	19 (53)

Regions of interest and study endpoints

Target delineation was done on computed tomography images in treatment position. The clinical target volumes (CTV's) were expanded uniformly by 0.5 cm to yield their respective planning target volumes (PTV's). Organs at risk such as parotid glands were delineated in every patient as a routine in the Netherlands Cancer Institute, and for the 'spared' parotid gland the target was to keep the mean dose below 26 Gy [19]. Delineation of the swallowing and mastication structures was done using the methods described by Levendag et al., and Teguh et al. (see Figure 1) [10,20]. Dose-volume histograms (DVH's) were calculated for all delineated structures. Analyzed were the maximum dose, the mean dose (mean of mean when it concerns dual structures) and the low (V20), intermediate (V40) and high (V60) dose-volumes (normalized volumes, percentages, and when it concerned dual structures mean of V20, V40, and V60, respectively) for the swallowing muscles (inferior (IC), middle (MC) and superior pharyngeal constrictor (SC) muscles), and the mastication structures involving chewing and mouth opening (masseter -, temporalis-, and pterygoid muscles, and mandibular condyle).

The objective and subjective toxicity endpoints (e.g. dysphagia, trismus and xerostomia) at 10-weeks and 1-year post-treatment compared to baseline results were correlated with the mean, and maximum doses (dual structures: mean of mean), and with the dose-volumes V20, V40, and V60 (normalized volumes, %, dual structures mean of V20, V40, and V60, respectively).

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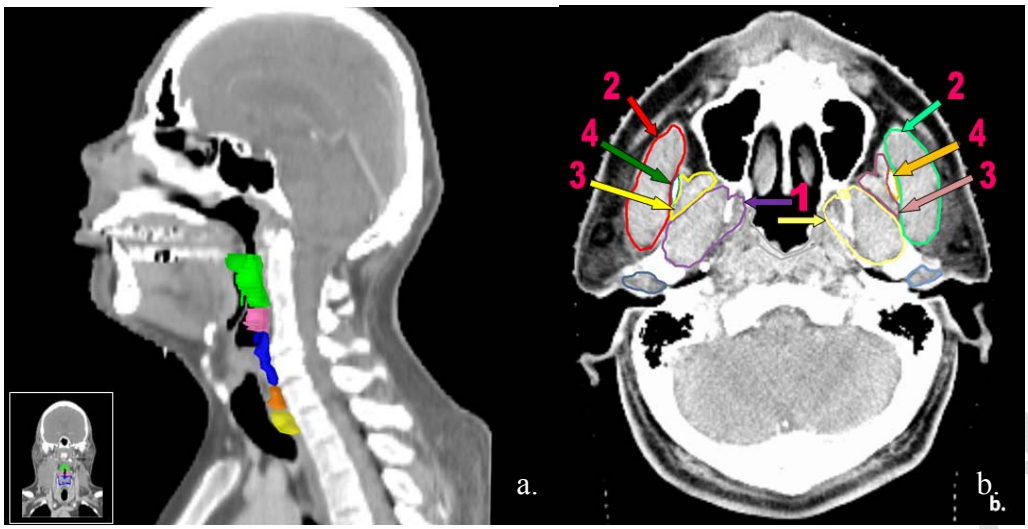

Figure 1. Delineated structures

a. Three-dimensional example of swallowing structures contoured: Green; superior constrictor muscle, Pink; middle constrictor muscle, Blue; inferior constrictor muscle, (Orange; cricopharyngeal muscle, Yellow; proximal esophagus).

b. Two-dimensional example of mastication structures contoured: 1. Right and left lateral medial pterygoid muscles, 2. Right and left masseter muscle, 3. Right and left temporalis muscle, 4. Right and left mandibular condyle.

For each endpoint of the study we excluded patients for whom the endpoint of interest was already present at baseline. Since the presence of the tumor in a certain anatomical region is in these cases probably related with both a high local dose and the functional problem of interest, these patients have to be excluded in order to estimate true dose-effect relationships.

Multidimensional assessment protocol

To assess organ function before (baseline), at approximately 10-weeks, and 1-year after completing chemo-IMRT a multidimensional assessment protocol was used, which has been published previously [17]. In short, the protocol included standard videofluoroscopy (VFS) to evaluate swallowing function by using the Penetration and Aspiration Scale (PAS; score 1: material does not enter the airway, to score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject) of Rosenbek et al. [21]. All swallow studies were scored by two experienced observers, and intra- and inter-observer reliability was consistently high (0.88 and 0.98, respectively). The maximum interincisor mouth opening (MIO) was measured by the TheraBite Range of Motion Scale. A pathological limited mouth opening (trismus) was defined as an interincisor distance of ≤ 35 mm [22]. Additionally, a structured, study-specific questionnaire was used, which was based on the EORTC C30 and HN35 but includes more detailed and symptom-specific questions relevant for this specific cancer group [17].

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Statistical analysis

The predictive value of dose parameters for the measured endpoints was evaluated in a binary logistic regression model (trismus, penetration/aspiration, and selected items on questionnaire). Statistical analyses were performed in IBM© SPSS© for Windows (release 20.0, IBM Corp.). For all analyses, a p-value of ≤05 (two-tailed) was considered statistically significant.

Table 2. Mean doses, and ranges to the organ at risk (N=48) involved in swallowing, and mouth opening

Organ at risk#	Overall mean dose (Gy) ± SD	Overall mean dose range (Gy)
Inferior Constrictor	56.9 ± 14.4	0.0 – 71.0
Middle Constrictor	63.3 ± 11.4	2.8 – 71.6
Superior Constrictor	63.0 ± 10.0	10.6 – 71.4
Masseter muscle	20.3 ± 13.0	3.4– 61.1
Temporalis muscle	5.2 ± 7.9	0.4– 36.1
Pterygoid muscles	31.7 ± 20.6	5.3 – 68.5
Mandibular condyle	13.1 ± 13.4	1.7 – 49.1

SD = Standard Deviation

RESULTS

Of the 55 patients included, 29 patients (53%) had a primary cancer in the oral cavity/oropharynx, 19 patients (35%) in the laryngo/hypopharynx, and 7 patients (13%) in the nasopharynx (table 1). A total of 48 patients had completed the chemo-IMRT treatment successfully and could be evaluated at 10 weeks after the end of treatment (range 9-12 weeks; one outlier at 16 weeks). Six patients discontinued the treatment because of death (N=2), progressive disease (N=2), patient refusal (N=1), and change of treatment plan (N=1). Further, dosimetric data of 1 patient was missing. At 1-year post-treatment (median 52 weeks, range 48-59 weeks), all 36 disease free patients were evaluable for functional outcomes and IMRT dose.

The mean doses of the delineated structures are given in Table 2. There were high correlations between the mean doses for all structures, in particular in case of adjacent structures. For example, the mean doses to the IC correlated stronger with the mean doses to the adjacent MC (r=.841; p<.001), than with the SC (r=.429; p=.002).

With respect to tumor location, for nasopharynx patients (N=7), zero cases of abnormal PAS scores were observed at baseline, 10 weeks and 1 year, whereas for patients with a tumor in the oral cavity area, 4/23 case at baseline, 6/23 cases at 10 weeks and 3/14 cases at 1 year had abnormal PAS scores. For laryngo/hypopharynx patients, these numbers were 5/18, 6/18 and 2/14, respectively. For trismus, most cases were observed for oral cavity tumors (baseline: 2/23, 10 weeks: 6/23, 1 year: 2/14). Thus with respect to tumor location it can be concluded that none of the nasopharynx patients

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showed PAS abnormalities, whereas significantly more cases of trismus at 10-weeks were observed in oral cavity patients (p=0.04).

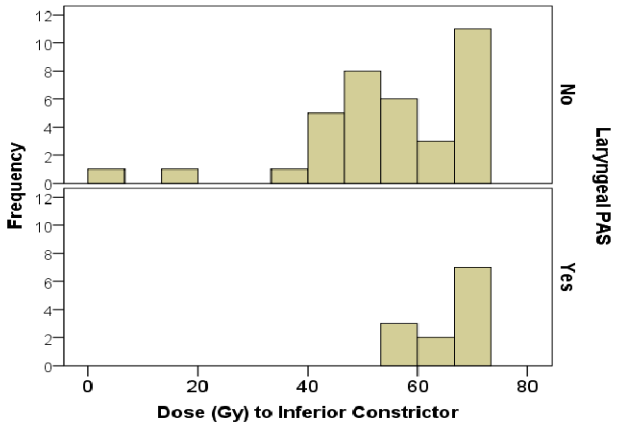

Figure 2. The distribution of the mean doses to the inferior constrictors in patients that showed no laryngeal penetration or aspiration (score 0) and patients that showed laryngeal penetration or aspiration (score 1) on the videofluoroscopy assessment (PAS) 10-weeks post-treatment.

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Evaluation of swallowing outcomes

Videofluoroscopy

Prior to treatment 9 of the 55 included patients (16%) showed already overt aspiration and/or laryngeal penetration on the videofluoroscopy studies and were therefore excluded from further dose-effect relationship analyses. At 10-weeks after chemo-IMRT, 8 of the 39 evaluable patients (21%) showed overt aspiration (N=1) and/or laryngeal penetration (N=5). The significant predictor of the occurrence of aspiration or laryngeal penetration is the mean dose to the inferior constrictors (IC) (p=.05; see supplementary material file Table A). With every 1 Gy mean dose increase, the odds ratio is 1.11. Also dose-volume V60 to the IC is a significant predictor.

At 1-year, 5 of the evaluable 36 patients (14 %), showed aspiration (N=1) and/or laryngeal penetration (N=4) of whom 3 (8%) also showed swallowing problems at 10 weeks post-treatment. No longer was there a significant relationship between the radiation doses to the IC or one of the other pharyngeal constrictors.

Questionnaire assessment

Prior to treatment, 8 of the 55 patients (15%) already experienced severe swallowing difficulties and were therefore excluded from dose-effect relationship analyses. At 10-weeks post-treatment, consumption of solids was the main remaining swallowing problem reported by 14 of the remaining 40 patients (35%), but all were able to return to oral feeding. The significant predictor of the reported

swallowing problems is the dose-volume V60 to the IC and the mean dose to the masseter muscle (supplementary material file Table B).

At 1-year, 9 of the remaining 32 patients (28%) reported problems with swallowing solids of whom 13 (36%) already experienced problems at 10 weeks post-treatment. This endpoint did not significantly associate with radiation doses to the swallowing structures, but only with the mean dose, and dose-volumes V20, V40 and V60 to the masseter muscle.

Evaluation of the mastication outcomes

Mouth opening measurement

Prior to treatment 5 of the 55 randomized patients (9%) showed a mean maximum interincisor mouth opening (MIO) of ≤35mm (=trismus) and as already explained in the method section were excluded from the dose-effect relationship analyses. Ten weeks post-treatment 6 of the remaining 44 patients (14%) had trismus and the primary tumor site of these 6 patients was the nasopharynx (N=1) or the oral cavity/oropharynx (N=5), but this difference in tumor location was not significant.

The only two significant predictors of the occurrence of trismus 10 weeks post-treatment were the radiation doses to the masseter and pterygoid muscles. For both muscles the dose-volumes V20 and V40, and the mean doses are significantly associated with trismus (see supplementary material file Table C). Thus, the higher the mean doses to the masseter and pterygoid muscles the higher the probability that patients will develop trismus 10-weeks post-treatment.

At 1-year post-treatment only 2 patients (2/35; 6%) still showed trismus (nasopharynx N=1; oral cavity/oropharynx N=1, NS). This number was too small for statistical analyses.

Questionnaire assessment

Prior to treatment the structured study-specific questionnaire revealed that 10 of the 55 included patients (18%) reported a little decreased maximum interincisor mouth opening (MIO). One patient already experienced a severely decreased MIO, and this patient was excluded from further dose-effect relationship analyses. At 10-weeks post chemo-IMRT, 9 of the 47 evaluable patients (19%) reported a decreased MIO compared to baseline. The only predictor for this reported decrease in MIO was dose-volume V40 to the masseter muscle (p=.035), with every 1 Gy mean dose increase, the odds ratio is 1.041 (see supplementary material file Table D).

At 1-year, 7 of 35 patients (20%) experienced a decrease in problems with opening their mouth of which all 7 patients also reported problems at 10 weeks. This endpoint correlated significantly with the radiation doses to all delineated mastication structures. To the masseter and pterygoid muscles the dose-volumes V20, V40, and V60, the maximum dose, and the mean doses are all significant predictors of the patients' reported problems with MIO at 1-year post-treatment (see supplementary material file Table D). The distribution of the dose-volumes V20, V40 and V60 at the

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pterygoid muscles and the probability of developing mouth-opening problems at 1 year post-treatment are visualized in Figure 3.

Related to the mandibular condyle the dose-volumes V20 and the maximum doses are significant predictors and related to the temporalis muscle only the maximum doses are.

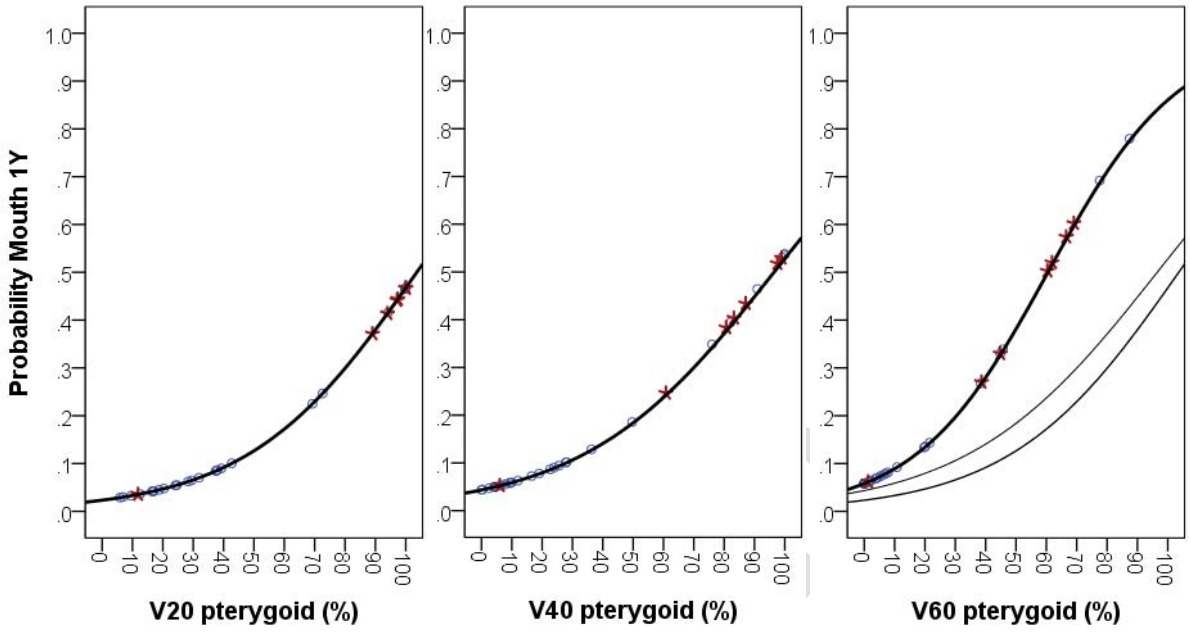

Figure 3. Results of Logistic regression for the dose-volume parameters V20, V40 and V60 of the pterygoid muscle. The graph shows the predicted probability of subjective mouth opening problems 1-year post-treatment as a function of the irradiated relative volume (%).
The dose volume points of patients with and without the complaint are indicated on the estimated curve (∗= problems, ○ = no problems).

DISCUSSION

The presented data show that the first question of this paper can be answered positively. There are dose-effect relationships between the radiation doses to the critical swallowing and mastication structures and dysphagia and trismus endpoints. In summary, objective dysphagia (PAS), correlated significantly to the inferior constrictor (IC). Subjective patient-reported problems with swallowing solids at 10 weeks post-treatment correlated with the radiation dose to the IC and masseter muscle, and at 1-year post-treatment to the masseter muscle. With respect to trismus, significant associations were found with the radiation doses to the masseter and pterygoid muscles at 10-weeks. Finally, there was a significant correlation between patient-perceived limited mouth opening and the radiation doses to the masseter-, pterygoid-, temporalis muscles, and the mandibular condyle at 1-year, which was only found to the masseter muscle at 10-weeks post-treatment.

Based on these results it can be concluded that both objective and subjective measurements are valuable for finding dose-relationships. Besides, objective and subjective problems do not have to

occur simultaneous. In accordance with Roe et al., and Cartmill et al. [1,16], we conclude that measuring at different time points with inclusion of baseline measurements is important to see how dose relationships vary over time and which severe functional problems already exist before treatment, likely caused by the tumor.

As already mentioned in the introduction, comparing these findings with similar literature is not straight forward, since only a few authors investigated data prospectively, both pre- and post-treatment, and included objective and subjective measures [6,24]. Feng et al. published 2 prospective studies that included patients with oropharyngeal and/or nasopharyngeal cancer, and found significant correlations between dysphagia endpoints (i.e. assessed with videofluoroscopy and questionnaires) and the doses to the pharyngeal constrictors (IC, MC, and SC) [9,25]. These authors also found a significant association between the swallowing related quality of life scores (HNQOL and UWQOL) and the mean doses to the pharyngeal constrictors. In their study, the mean SC doses showed the strongest association with worsening scores of HNQOL-items on swallowing solids. Eisbruch et al. [26] recently published the long-term results (up to 2-years post-treatment) of Feng et al.'s study (2007) [9]. These authors again concluded that swallowing organs' mean doses correlated significantly with long term worsening of swallowing. In that study the highest significant correlation was found between all dysphagia measures and the mean doses to pharyngeal constrictors. In the present study significant correlations between the objective and subjective swallowing outcomes and radiation doses to the IC was found. Our small ranges of mean doses to especially the SC (mean 63.0, range 10.6 – 71.4 Gy) is the most likely explanation for the lack of (statistical) significance in this respect. If there are no patients that received a low dose to the SC, differences will not be seen.

Only a few studies have investigated the relationship between radiation doses and mouth opening/trismus [20,27,28]. In our prospective study a significant correlation was found between the measured and the perceived mouth opening, and the radiation doses to most mastication structures. The most important structures related to developing mouth-opening problems are the masseter and pterygoid muscles. Teguh et al., who retrospectively analyzed 56 patients with oropharyngeal cancer by means of quality of life questionnaires, concluded that there was a steep dose relationship between the mean doses to the masseter and pterygoid muscles [20]. This result is not surprising, because these two structures are most adjacent to the nasopharynx, oral cavity, and oropharynx area (Figure 1). Two other IMRT studies did not differentiate between "with" or "without chemotherapy" [27,28]. Both studies concluded that IMRT was able to reduce the radiation doses to the temporal-mandibular joints and likely reduced the incidence and severity of radiation-induced trismus.

When the primary tumor site is close to one of the delineated structures and muscles, it is possible that functional problems exist at baseline, related to the local damage or obstruction caused by tumor tissue, making it difficult to judge further effects of radiation treatment. To estimate true dose-effect relationships functional problems that were already present at baseline should be excluded from the analyses. Since most studies did not include baseline measurement, it is unclear if some

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functional problems that were reported after treatment were already present at baseline. However, patients that already show functional problems at baseline are at higher risk of developing dysphagia/trismus, because even with IMRT it is impossible to avoid the relevant structures and at the same time deliver the required doses to the primary tumor. In this respect, it is important to provide these patient information and start with preventive therapy as Feng et al. [25] also stated: "it is unlikely that technology alone will completely eliminate dysphagia and that additional strategies like customization of treatment intensity to predictors of tumor control, improved cytoprotection, better targeted radio sensitization, and prompt swallow therapy when indicated are required for additional progress."

Finally, analyzing the different dose-volumes to the different structures (second research question) no thresholds were found. Nevertheless, it can be concluded that the mean doses to the masseter muscle is the strongest/most important predictor and the higher the dose volumes, the higher the probability a functional problem will occur. In the literature, no clear thresholds were reported either [9,29]. Feng et al. also looked at dose-volume effects, and concluded that patients aspirating after 3 months had received mean pharyngeal constrictor doses >60 Gy or a V65> 50% [9,25]. In addition, Schwartz et al. investigated candidate dosimetric predictors of the long-term objective (videofluoroscopy) and subjective swallowing dysfunction in oropharyngeal cancer patients [30]. They found that a dose-volumes V65 > 30% for high superior pharyngeal constrictors was predictive for objective swallowing dysfunction. All authors rightfully noted that their findings motivated further efforts to reduce the doses to the swallowing structures, especially to the pharyngeal constrictor muscles.

Limitations of the present study

In the present study, the effects on the pharyngeal constrictor muscles, and mastication structures were analyzed. It is clearly of interest to also evaluate the influence of the mean radiation doses on other key structures involved in swallowing (e.g. the base of tongue, supraglottic larynx, glottis, upper esophageal sphincter, and the esophagus). This was indeed recommended recently by a panel of experts [24] and should definitely be considered in future studies of this kind.

CONCLUSIONS

The present study shows that dose relationships between dysphagia and trismus measures and the radiation doses to the critical swallowing-, and mastication structures exist. However, since dose relationships seem to vary at different measurement points, a strict multidimensional assessment protocol, including objective and subjective assessment, is mandatory. No thresholds were found, but delineation of organs at risk, especially the masseter muscle, for treatment planning is essential to reduce potentially damaging radiation doses to these structures.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Table A. Significances (binary logistic regression) for the delineated structures and the toxicity endpoint: **PAS yes/no** (10 weeks: n=39, 8 events, 1Y too less events for analyses)

PAS	Time	V20		V40		V60		Max		Mean	
		OR	P	OR	P	OR	P	OR	P	OR	P
IC	10 wks	X		X		1.023	***0.05***	1.94	0.12	1.11	***0.05***
MC	10 wks	X		X		1.024	0.19	1.30	0.41	1.13	0.21
SC	10 wks	X		X		1.00	0.80	1.50	0.25	1.00	0.99
Masseter	10 wks	0.99	0.48	0.98	0.49	0.99	0.76	1.01	0.81	0.98	0.47

Dose-volumes V20, V40, and V60, Maximum radiation dose, and Mean radiation dose
OR = Odds Ratio's
P = p-value; significant correlations ≤.05
PAS = penetration and aspiration score, problem yes/no
IC = inferior constrictor muscle; MC = middle constrictor muscle; SC = superior constrictor muscle
X: too little variation in dose parameter: more than 35 patients have 100% volumes.

Table B. Significances (binary logistic regression) for the delineated structures and the toxicity endpoint: **Questionnaire: Swallowing solid food, problem yes/no** (10 weeks: n=40, 14 events, 1Y: n=32, 9 events).

QUEST SWALLOWING	Time	V20		V40		V60		Max		Mean	
		OR	P	OR	P	OR	P	OR	P	OR	P
IC	10 wks	X		X		0.98	***0.05***	0.99	0.66	0.97	0.22
	1Y					0.98	0.08	1.01	0.76	0.97	0.21
MC	10 wks	X		X		0.99	0.35	1.013	0.74	0.99	0.79
	1Y					1.00	0.99	1.028	0.62	1.011	0.75
SC	10 wks	X		X		1.015	0.22	1.036	0.57	1.080	0.19
	1Y					1.027	0.11	1.030	0.64	1.15	0.11
Masseter	10 wks	1.020	0.06	1.030	0.15	1.24	0.07	1.031	0.27	1.061	***0.05***
	1Y	1.035	***0.009***	1.078	***0.006***	1.48	***0.015***	1.079	0.06	1.13	***0.005***

Dose-volumes V20, V40, and V60, Maximum radiation dose, and Mean radiation dose
OR = Odds Ratio's
P = p-value; significant correlations ≤.05
IC = inferior constrictor muscle; MC = middle constrictor muscle; SC = superior constrictor muscle
X: too little variation in dose parameter: more than 35 patients have 100% volumes.

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Table C. Significances (binary logistic regression) for the delineated mastication structures and the toxicity endpoint: **trismus yes/no (≤35 mm max mouth opening)** (10 weeks: n=44, 6 events, 1Y too less events for analyses).

TRISMUS	Time	V20		V40		V60		Max		Mean	
		OR	P	OR	P	OR	P	OR	P	OR	P
Masseter	10 wks	1.038	***0.019***	1.042	***0.040***	1.13	0.32	1.11	0.053	1.099	***0.017***
Pterygoids	10 wks	1.041	***0.023***	1.034	***0.019***	1.028	0.059	1.32	0.077	1.058	***0.024***
Mandibula	10 wks	1.016	0.14	1.007	0.78	X	X	1.035	0.090	1.042	0.16
Temporalis*	10 wks	1.011	0.65	1.019	0.69	X	X	1.041	***0.046***	1.034	0.49

Dose-volumes V20, V40, and V60, Maximum radiation dose, and Mean radiation dose
OR = Odds Ratio's
P = p-value; significant correlations ≤.05
X = outside dose range: less than 10 patients have volumes >0.5%.
*Temporalis muscle received relatively low dose, and relatively small dose range between patients.

Table D. Significances (binary logistic regression) for the delineated structures and the toxicity endpoint: **Questionnaire: (Max) Interincisor mouth Opening (MIO) problem yes/no** (10 weeks: n=47, 9 events, 1Y: n=35, 7 events).

QUEST MIO	Time	V20		V40		V60		Max		Mean	
		OR	P	OR	P	OR	P	OR	P	OR	P
Masseter	10 wks	1.015	0.16	1.041	***0.035***	1.24	0.053	1.063	0.11	1.058	0.053
	1Y	1.040	***0.010***	1.065	***0.011***	1.42	***0.015***	1.18	***0.013***	1.12	***0.009***
Pterygoids	10 wks	1.016	0.14	1.013	0.20	1.015	0.23	1.044	0.34	1.024	0.19
	1Y	1.037	***0.020***	1.033	***0.016***	1.047	***0.009***	1.20	***0.037***	1.062	***0.016***
Mandibula	10 wks	1.01	0.28	1.00	0.89	X	X	1.018	0.29	1.025	0.35
	1Y	1.023	***0.045***	1.020	0.39			1.054	***0.025***	1.059	0.064
Temporalis*	10 wks	0.99	0.79	0.99	0.72	X	X	1.019	0.20	0.99	0.85
	1Y	1.009	0.67	1.014	0.75			1.042	***0.024***	1.03	0.49

Dose-volumes V20, V40, and V60, Maximum radiation dose, and Mean radiation dose
OR = Odds Ratio's
P = p-value; significant correlations ≤.05
X = outside dose range: less than 10 patients have volumes >0.5%.
*Temporalis muscle received relatively low dose, and relatively small dose range between patients.

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