Preventive rehabilitation in patients treated with chemoradiation for advanced head and neck cancer
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Dysphagia and trismus after concomitant chemo-IMRT in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures

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(submitted)
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**ABSTRACT**

**Purpose:** Assessment of side effects (dysphagia, trismus and xerostomia) of chemo-IMRT in relation to dose parameters of structures involved in swallowing, mastication, and salivation.

**Methods:** Prospective study in 55 patients with advanced head and neck cancer treated with Cisplatin-based chemo-IMRT. Data were derived—before, at 10-weeks and 1-year posttreatment—objectively by videofluoroscopy (penetration and aspiration score (PAS)), and mouth-opening measurements (trismus), and subjectively from a structured study-specific questionnaire. Mean radiation-doses were calculated for delineated swallowing structures (inferior (IC), middle (MC), and superior pharyngeal constrictors (SC)), mastication structures (masseter, temporalis, and pterygoid muscles, and mandibular condyl), and parotid glands.

**Results:** At 10-weeks, mean doses to the IC were significant predictors for laryngeal penetration and/or aspiration (12 patients (25%); p=0.028 Odds 1.099). One-year posttreatment 18 patients (50%) reported problems with swallowing solids, which was significantly associated with the mean doses to the masseter (p=0.027 Odds 1.070). Trismus occurred in 7 patients (15%) at 10-weeks posttreatment, and in 3 patients (6%) at 1-year. The doses to the masseter and pterygoid muscles were significant predictors of trismus at 10-weeks (p=0.021 Odds 1.086, and p=0.031 Odds 1.050, respectively). At 1-year posttreatment mean doses to the masseter and pterygoid muscles were strong significant predictors for subjective mouth-opening problems (9 patients (25%); p=0.005 Odds 1.114, and p=0.006 Odds 1.068, respectively). For $V_{40}$, comparable significant predictors were found. Doses to parotid glands did not predict any of the toxicity endpoints.

**Conclusions:** Dose-effect relationships exist between objective and subjective dysphagia and trismus parameters, and mean doses/$V_{40}$ to critical swallowing and mastication structures. No thresholds were found, but delineating organs at risk for treatment planning is essential to reduce potentially damaging radiation doses to these structures.
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) [1-3]. Reduction of xerostomia, e.g., can be achieved by keeping the dose to the contra-lateral salivary gland below 26 Gy [4;5]. Moreover, it appears possible to limit the dose to the musculature involved in swallowing and mastication without compromising radiation to the tumor site(s) [1;6]. In many institutes, therefore, IMRT has become the standard of care in head and neck cancer. 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. A systematic review of Roe et al. [1] (papers published between January 1998 and December 2009) found only one prospective longitudinal study (Feng et al. [7]) that consistently evaluated oropharyngeal swallow function, using both objective instrumental measures, as well as patient self-reports alongside established toxicity scores. 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.

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 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 [8;9]. Earlier, we reported that no significant functional differences between these two preventive exercise groups were found at 10-weeks and 1-year posttreatment. As in the previous study, the results of these two groups could be pooled for the dose-effect part of the study [8;9]. This paper aims to answer the following questions: can the previously reported objective and
subjective functional outcomes at 10-weeks and at 1-year posttreatment be related to the mean radiation dose to the muscles/structures involved in swallowing and mastication? Secondly, is there a relationship between the mean dose to the parotid glands and the functional outcomes and xerostomia? Finally, when analyzing the percentages of patients showing functional problems and receiving dose-volumes >40 Gy ($V_{40}$) on the organs at risks (in swallowing and mastication), are the results comparable to those reported in the literature?

PATIENTS AND METHODS

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, which was approved by the local medical ethical committee. Written informed consent was obtained from all patients. 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. 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 fractions administered over 7 weeks with IMRT.

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 [2]. Delineation of the swallowing and mastication structures was done using the methods described by Levendag et al., and Teguh et al. (Fig. 1) [10;11]. Dose volume histograms (DVH’s) were calculated for all delineated structures.

The mean doses and volume receiving more than 40 Gy ($V_{40}$) was recorded for the swallowing muscles (inferior (IC), middle (MC) and superior pharyngeal constrictor (SC) muscles), the mastication structures involving chewing and mouth opening (masseter-, temporalis-, and pterygoid muscles, and mandibular condyl) and the parotid glands.

The objective and subjective toxicity endpoints (e.g. dysphagia, trismus and xerostomia) at 10-weeks and 1-year posttreatment were correlated with the mean doses, and with the dose volumes >40 Gy ($V_{40}$).
To assess organ function before, at approximately 10-weeks, and 1-year after completing chemo-IMRT a multidimensional assessment protocol was used, which has been published previously [12]. In short, the protocol included measuring the maximum interincisor mouth opening (MIO) by the TheraBite Range of Motion Scale. A pathological limited mouth opening (trismus) was defined as an interincisor distance of \( \leq 35 \text{ mm} \) [13]. Standard videofluoroscopy (VFS) was used 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). All swallow studies were scored by two observers: the first author (LvdM), and one other experienced speech language pathologist. Intra- and inter-observer reliability was consistently high (0.88 and 0.98, respectively). Additionally, quality of life was assessed using a structured, study-specific questionnaire, which includes detailed and symptom-specific questions relevant for this specific cancer group [8;9]. Exercise program was not found to be a predictor of any the analyzed toxicity endpoints (Odds
nor did the mean doses received to the delineated structures in the 2 exercise groups differ. This accord with the previous published functional outcomes at 10-weeks and 1-year posttreatment, where no significant differences between the two exercise groups were found either. Hence, as already mentioned above in the introduction, the groups were pooled for this dose-effect study \[8;9\].

**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 and saliva glands contoured: 1. Right and left lateral medial pterygoid muscles, 2. Right and left masseter muscle, 3. Right and left temporal muscle, 4. Right and left mandibular condyl, 5. Right and left parotid gland.

**Statistical analysis**

All statistical analyses were performed in PASW Statistics version 18 (SPSS, Inc, Chicago, Illinois).

Initially the mean dose volume histograms (DVHs) were calculated, and in dual structures, the mean dose of the means was evaluated. Pair-wise relationships of the mean doses of the delineated structures were assessed using Pearson correlation coefficients.

Mean dose and $V_{40}$ distributions were composed using the Wilcoxon rank sum test. If there were significant differences in distribution for patients with and without complaints $p < .05$, odds ratio's were estimated in a logistic regression model. The binary logistic regression analyses were performed to predict the probability of developing dysphagia/trismus or experiencing swallowing or mouth opening problems and the mean dose to the delineated structures.

For all analyses, a $P$-value of $<.05$ (two-tailed) was considered statistically significant.
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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. At approximately 10-weeks posttreatment (range 9-12 weeks; one outlier at 16 weeks) 48 of the 55 patients had completed the chemo-IMRT treatment successfully. 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 posttreatment (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. For example, the mean doses to the IC correlated stronger with the mean doses to the adjacent MC (r=.841; p=.000), than with the SC (r=.429; p=.002). The parotid glands received on average mean doses of 34.41 Gy (range 18.1 – 65.1), of which 76% received a dose <26 Gy on the contra lateral parotid gland.

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Overall mean dose (Gy) ± SD</th>
<th>Overall mean dose range (Gy)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>IC</td>
<td>56.9 ± 14.4</td>
<td>0.0 – 71.0</td>
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<td>MC</td>
<td>63.3 ± 11.4</td>
<td>2.8 – 71.6</td>
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<tr>
<td>SC</td>
<td>63.0 ± 10.0</td>
<td>10.6 – 71.4</td>
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<tr>
<td>Masseter muscle</td>
<td>20.3 ± 13.0</td>
<td>3.4 – 61.1</td>
<td>&lt;.01**</td>
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<tr>
<td>Temporalis muscle</td>
<td>5.2 ± 7.9</td>
<td>0.4 – 36.1</td>
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<tr>
<td>Pterygoid muscle</td>
<td>31.7 ± 20.6</td>
<td>5.3 – 68.5</td>
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<tr>
<td>Mandibular condyl</td>
<td>13.1 ± 13.4</td>
<td>1.7 – 49.1</td>
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<td>Parotid gland</td>
<td>34.4 ± 13.2</td>
<td>18.1 – 65.1</td>
<td>&lt;.05*</td>
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</table>

SD = Standard Deviation; IC = inferior constrictor muscle; MC = middle constrictor muscle; SC = superior constrictor muscle

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Evaluation of swallowing outcomes

Videofluoroscopy

At 10-weeks after chemo-IMRT, videofluoroscopy studies showed overt aspiration (N=3) and/or laryngeal penetration (N=9) in 12 of the 48 evaluable patients (25%). The only significant predictor of the occurrence of aspiration or laryngeal penetration is the mean dose to the inferior constrictors (IC) (p=.028; Table 3). With every 1 Gy mean dose increase, the odds ratio is 1.099.
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The distribution of the mean doses to the IC is visualized in Fig. 2. At 1-year, 7 of the evaluable 36 patients (19%), showed aspiration (N=1) and/or laryngeal penetration (N=6), but no longer was there a significant relationship between the mean doses to the IC or one of the other pharyngeal constrictors.

![Figure 2](image)

**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.

**Questionnaire assessment**

At 10-weeks posttreatment, consumption of solids was the main remaining swallowing problem reported by 27 of the 46 patients (59%), but all were able to return to oral feeding. However, no significant associations between the mean doses received to swallowing or mastication structures and the noted problems with swallowing solids were found.

At 1-year, still half of the patients (18/36; 50%) reported problems with swallowing solids. This endpoint associated significantly with the mean doses to the masseter muscles (p=.027), but not with those to the swallowing structures. With every 1 Gy increase of the mean dose to the masseter, the odds ratio is 1.070 (Table 3 and Fig. 3).
<table>
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<td>Questionnaire</td>
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<td>Parotid gland</td>
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IC = inferior constrictor muscle; MC = middle constrictor muscle; SC = superior constrictor muscle; V 40 = dose volumes >40 Gy
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Figure 3 | Logistic regression of the mean dose to the masseter muscle and the probability experiencing problems swallowing solids at 1-year (1Y) post-treatment (p=.027; Odds ratio 1.070); .00 = no problems, 1.00= problems.

Evaluation of the mastication outcomes

Mouth opening measurement

Ten weeks posttreatment 7 of the 48 patients (15%) had trismus (maximum mouth opening ≤ 35 mm). The primary tumor site of these 7 patients was the nasopharynx (N=1) or the oral cavity/oropharynx (N=6).

The only two significant predictors of the occurrence of trismus were the mean doses to the masseter (p=.021) and pterygoid muscles (p=.031). With every 1 Gy dose increase, the odds ratio is 1.086, and 1.050, respectively (Table 3).

At 1-year there were still 3 patients (3/36; 8%) showing trismus (nasopharynx N=1; oral cavity/oropharynx N=2), but there was no longer any significant relationship with the mean doses to the masseter or one of the other mastication muscles/structures.
Questionnaire assessment
At 10-weeks post chemo-IMRT, the structured study-specific questionnaire revealed that 11 patients (23%) reported a decreased maximum interincisor mouth opening (MIO), ranging from a little bit too severely decreased. However, the mean dose to any of the mastication structures was not a predictor for this patients’ reported MIO issue.

At 1-year, still 9 of 36 patients (25%) experienced problems with opening their mouth and this endpoint correlated significantly with the mean radiation doses to the delineated mastication structures. The mean doses to the masseter and pterygoid muscles are strong significant predictors of the patients’ reported problems with MIO (p=.005 and p=.006, respectively). With every 1 Gy increase of the mean dose, the odds ratios are 1.114 and 1.068, respectively (Table 3).

Evaluation of the saliva outcomes
Questionnaire assessment xerostomia
Ten weeks posttreatment, 35 patients (73%) rated their saliva production as much less (N=26) or less (N=9). Nine patients (19%) experienced no differences in saliva production, and the remaining 4 patients (8%) rated their saliva production as higher (N=2) or much higher (N=2). The mean radiation doses to the parotid glands did not significantly predict the subjective xerostomia outcome or other toxicity endpoints.

At 1-year, 28 patients (78%) still reported saliva production to be much less (N=16) or less (N=12), 17% of the patients (N=6) as equal, and 2 patients (6%) as higher compared to baseline. Again, no significant relationships were found between the mean doses to the parotid glands and patients’ reported decrease in saliva production or one of the other subjective or objective toxicity endpoints.

With respect to the cut-off point of 26 Gy for parotid gland sparing, at 10-weeks 76% of the patients had received <26 Gy to the contra lateral parotid gland, and at 1-year this figure was 73%. All patients in the >26 Gy groups reported xerostomia, whereas in the <26 Gy group 24% at 10-weeks and 27% at 1-year posttreatment reported the absence of xerostomia. These differences were also not statistically significant.

Dose volumes >40 Gy (V_{40})
Overall, the predictors of the V_{40} were the same as those for the mean doses. V_{40} of the masseter and pterygoid muscles were significant predictors for objective mouth opening problems (trismus) at 10-weeks with odds ratios of 1.036, and 1.017, respectively. At 1-year posttreatment, V_{40} of the masseter and pterygoid muscles were again significant
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predictors, now for subjective complaints of restricted mouth opening, with odds ratios of 1.044, and 1.019, respectively (Table 3).

No significant predictors for objective or subjective swallowing problems were found at the $V_{40}$, neither for the delineated structures, nor for xerostomia and dose volumes of more than 40 Gy on the parotid glands.

DISCUSSION

The presented data show that the first aim of this paper can be answered positively. There are dose-effect relationships between objective and subjective dysphagia and trismus endpoints, and the mean doses to the critical swallowing and mastication structures. In summary, objective dysphagia (PAS), correlated significantly with mean doses to the IC at 10-weeks, but this correlation disappeared 1-year posttreatment. At 1-year posttreatment there was only a significant correlation between patient-reported problems with swallowing solids and the doses received to the masseter muscles. With respect to trismus, significant associations were found with the mean doses to the masseter and pterygoid muscles at 10-weeks. Moreover, there was a significant correlation between patient-perceived limited mouth opening and the doses to the masseter- and pterygoid muscles at 1-year, which was not found 10-weeks posttreatment. Based on these results it can be concluded that both objective and subjective measurements are needed to find dose relationships. In accordance with Roe et al. [1], we conclude that measuring at different time points after treatment is important to see how dose relationships vary over time.

As explained in the introduction, comparing these findings with similar literature is not straightforward, since only a few authors investigated data prospectively, both pre- and posttreatment, and included objective and subjective measures [1,6]. Feng et al. included 36 patients with Stage III–IV oropharyngeal or nasopharyngeal cancer, and found significant correlations between aspiration (assessed with videofluoroscopy) and the doses to the pharyngeal constrictors (IC, MC, and SC), with 44% (16/36) of patients aspirating at 3 months [7]. These authors also found a significant association between the swallowing related quality of life scores (HNDQOL and UWQOL) and the mean doses to the pharyngeal constrictors [7]. In their study, the mean SC doses showed the strongest association with worsening scores of HNDQOL-items on swallowing solids. In the present study, a significant relationship was found only between the PAS and the doses to the IC, with 25% (12/48) patients aspirating at that time point. Interestingly, in our study only 3 of these 12 patients showed overt aspiration, so the actual aspiration frequency seems less in our study. We found, no dose relationships for patient-reported swallowing issues. The
small range of mean doses (to especially the SC (mean 63.0, range 10.6 – 71.4 Gy)) in the present study may explain why our dose relationships differed from Feng et al. If there are no patients that received a low dose to the SC, differences will not be seen. Unlike the study of Feng et al. our patients executed preventive rehabilitation programs that ran parallel to the chemo-IMRT and this possibly also explains these differences. The, exercise programs trained the musculature and structures involved in swallowing and mastication, and showed a good overall feasibility and satisfactory compliance [8;9]. Although not the topic of this paper, it is noteworthy to mention once again that these swallowing exercises strengthen the pharyngeal muscles, potentially compensating for the negative effects of the radiation doses, as intimated by the low aspiration incidence. Feng et al. more recently published a prospective IMRT study in 73 oropharyngeal cancer patients, in which significant associations between dysphagia endpoints (i.e. aspiration, PAS, and the Eating Domain and the UW swallowing score) and mean doses to the pharyngeal constrictors, laryngeal and esophageal structures were found [14]. Interestingly, the authors mentioned in the discussion that “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.” The question remains whether swallow therapy should be reactive as suggested, or rather should be proactive. Based on our previous reported findings, we believe it should be proactive [8;9]. Eisbruch et al. [15] recently published the long-term results (up to 2-years posttreatment) of Feng et al.’s study (2007). These authors again concluded that swallowing organs’ mean doses correlated significantly with long-term worsening of swallowing. In that study a ‘complication’ related to the videofluoroscopy-based aspiration score was defined as an increase in aspiration, and a ‘complication’ in the patient-reported score was based on the observation of the longitudinal trend of the posttreatment scores compared to baseline scores. The highest significant correlation was found between all dysphagia measures and the mean doses to pharyngeal constrictors. In the present study no significant correlations between the objective swallowing outcomes and mean doses to any of the three pharyngeal constrictors was found. Again, our small range of mean doses to especially the SC is the most likely explanation, although. The small number of patients still showing objective swallowing problems at 1-year posttreatment, and the wide range of mean doses could also explain this lack of (statistical) significance.

Only a few studies have investigated the relationship between radiation doses and mouth opening/trismus [11;16;17]. In our prospective study a significant correlation was found between the measured and the perceived mouth opening, and the mean doses to most mastication structures. The most important structures related to developing mouth-opening problems are
the masseter- and the 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 [11]. This result is not surprising, because these two structures are most adjacent to the nasopharynx, oral cavity, and oropharynx area (Fig. 1). Two other IMRT studies did not differentiate between “with” or “without chemotherapy” [16,17]. 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. In one of the studies all patients were routinely instructed by physicians or nurses to perform mouth opening exercises following the onset of radiotherapy [17]. Unfortunately, they did not report compliance with, and effect of these exercises. Moreover, it must be noted that both studies only included patients with nasopharyngeal tumors, and that patients were not treated uniformly, either receiving IMRT alone or with concomitant chemo-IMRT.

When the primary tumor site is close to one of the delineated structures and muscles, those will receive higher mean doses, resulting in more functional problems. Although we found no significant correlations between the various tumor sites and functional outcomes, it is therefore not surprising that patients with trismus had a primary tumor close to the masseter. At 1-year, one of the three remaining patients with overt trismus had a tumor in the nasopharynx, one in the tonsil and one in the retromolar trigone. Such patients are at higher risk of developing 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. However, with only 3 patients showing trismus at 1-year, it is not surprising that significant site-specific dose relationships were not found at that time point. For perceived mouth opening problems, the opposite time-relation was found. Perceived problems with mouth opening were less at 10-weeks than 1-year posttreatment. Acute sequels of chemo-IMRT still present at 10-weeks, such as pain, fibrosis, edema, and nausea might have masked other problems. At 1-year posttreatment when the acute toxicities have disappeared, functional outcomes such as limited mouth opening were more salient.

The second aim of this study was to analyze whether there is a relationship between the mean doses to the parotid glands and functional outcomes and xerostomia. No significant correlations were found between patients’ reported saliva production and mean doses to the parotid gland. An explanation might be that parotid glands are routinely outlined for IMRT planning in our Institute. Although no significant overall correlations or differences between patients <26 Gy versus >26 Gy on the contra lateral parotid gland were found, individual patients might experience severe to moderate saliva reduction; this aspect should therefore be taken into account [2].
Finally, finding significant correlations between the V40 of the mastication muscles and trismus only at 10-weeks could again be explained by the fact that too few patients showed trismus at 1-year. Comparison with other studies is hampered, because most studies focus on dose-effect relationships for swallowing musculature and not for mastication structures. Furthermore, other dose volumes were employed, varying from V35 to V70 with 5% increments [7;18]. In the present study, no significant dose-volume associations were found between the V40 of the swallowing muscles and swallowing endpoints. Feng et al. also looked at dose effects, and concluded that patients aspirating after 3 months had received mean pharyngeal constrictor doses >60 Gy or a V65 > 50% [7]. In addition, Schwartz et al. investigated candidate dosimetric predictors of the long-term objective (videofluoroscopy) and subjective swallowing dysfunction in oropharyngeal cancer patients [19]. They found that a V65 > 30% for high superior pharyngeal constrictors was predictive for objective swallowing dysfunction. If we had examined more dose volumes, we might have found similar results. Nevertheless, 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, mastication structures, and parotids 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 [20] and should definitely be considered in future studies of this kind.

CONCLUSIONS
The present study shows that dose relationships between objective as well as subjective dysphagia and trismus measures and the mean doses or V40 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 for treatment planning is essential to reduce potentially damaging radiation doses to these structures.
ACKNOWLEDGEMENT

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Reference List