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Dysphagia after chemoradiotherapy

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 $\geqslant$60 Gy (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.
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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

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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 et al. [5], Cartmill et al. [16], Nutting et al. [4], Bhide et al. [18], 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 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 logopedic 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.

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

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)

IMRT treatment planning

All patients received 100-mg/m^2 Cisplatin as a 40 min IV infusion on days 1, 22, and 43, and concurrent radiotherapy of 70 Gy in 35 daily fractions of 200 rad (2 Gy) 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.

Regions of interest and study endpoints

Target delineation was done on computed tomography images in treatment position. The clinical target volumes (CTVs) were expanded uniformly by 0.5 cm to yield their respective planning target volumes (PTVs). 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 Fig. 1) [10,20]. Dose–volume histograms (DVHs) 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