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Xerostomia

Xerostomia: A day and night difference

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ABSTRACT

Purpose: To compare patient-reported xerostomia during daytime and during nighttime with objectively measured parotid and submandibular gland function in a cohort of head-and-neck cancer (HNC) patients treated with RT.

Materials and methods: A cohort of 138 HNC patients underwent objective measurements of parotid (PF) and submandibular (SMF) gland function and completed a xerostomia questionnaire (XQ) before RT, at 6 weeks, 6 months and 1 year after RT. No attempt was made to spare the submandibular gland(s). The XQ contained specific questions concerning the sensation of dry mouth during day- (XD) and nighttime (XN), scored on a 5-point Likert scale. Patients with no or mild (grade 1–3) xerostomia and patients with more severe (grade 4–5) complaints were grouped together.

Results: Before RT, no association existed between dry mouth complaints and PF or SMF. At 6 weeks, 6 months and 1 year after RT; 37%, 51% and 36% had grade 4–5 XD and 65%, 64% and 56% had grade 4–5 XN, respectively. Patients with grade 4–5 XD and XN had significantly worse SMF at all time points after RT compared to patients with grade 1–3 XD and XN, while PF was significantly worse only at 6 weeks after RT. In multivariate analyses, SMF was consistently the most important factor related to XN after treatment. PF significantly influenced XD at 6 weeks and 1 year after RT.

Conclusions: Differentiating between complaints during day- and nighttime in xerostomia research is necessary. Dry mouth at night is a frequent problem after (parotid-sparing) RT for HNC and is explained by submandibular gland dysfunction. Sparing of the contralateral submandibular gland, in addition to parotid gland sparing, may result in improved patient-reported xerostomia.

Radiotherapy (RT) for head and neck cancer (HNC) generally results in high radiation doses to the major salivary glands. The resulting decrease in salivary flow leads to xerostomia and this has a major impact on quality of life in HNC survivors [1,2]. Sparing of the parotid glands using intensity-modulated radiotherapy (IMRT) is feasible and significantly improves parotid gland flow over time in patients treated for HNC [3]. The impact on patient-reported xerostomia remains unclear however. The recent PARSPORT trial showed a significant decrease in patient-reported xerostomia following parotid gland sparing [4]. However, Kam et al. did not show a synchronous improvement in patient-reported xerostomia in a cohort of patients with nasopharyngeal carcinoma randomized to IMRT or conventional RT [5].

The submandibular glands are responsible for most saliva production (60–65%) in the non-stimulated state [6]. During sleep, salivary flow rate is low and originates mainly from the submandibular glands [7,8]. Although HNC patients with xerostomia frequently complain of dry mouth at night, there have been no reports in the literature showing a correlation with submandibular gland function. In contrast to the serous secretion from the parotid glands, the submandibular glands produce a mixed serous and mucous saliva. The mucins herein function as mucosal lubricants that bind water and help to keep the mucosal surfaces in the oral cavity in a hydrated state [9]. Through this mechanism, salivary mucins could have a significant impact on the patient's subjective sensation of moisture. It might also explain the discrepancy between preserved parotid flow and the relative lack of improvement in patient-reported xerostomia.

The aim of this study was to compare patient-reported xerostomia throughout day and night with objective, selectively measured parotid and submandibular gland function in a cohort of HNC patients treated with RT. Because of the mentioned physiologic and diurnal variations in quantity and quality of parotid and

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submandibular saliva, the function of these major salivary glands could have a different impact on xerostomia.

Patients and methods

Patients and radiotherapy

All data were gathered prospectively. In total, 138 patients with HNC were consecutively included in salivary function studies at our department. Conventional RT (CRT) was applied in 46 patients with mainly laryngeal and oropharyngeal cancer that participated in a double-blind, placebo-controlled, randomized clinical trial investigating the effect of pilocarpine on radiation-induced xerostomia [10]. Only the patients that received placebo were included in this analysis. Details on RT treatment planning have been reported previously [3,11]. The prescribed dose to the gross tumor volume (GTV) or postoperative tumor bed was 50–70 Gy in 2 Gy fractions, using mainly opposing lateral photon beams.

After the introduction of IMRT at our department, another 92 patients were included in prospective studies on parotid gland-sparing RT. Details on treatment planning and delineation have been published elsewhere [11,12]. Depending on the concomitant use of chemotherapy, 69 Gy in 30 fractions (simultaneous boost) or 70 Gy in 35 fractions (sequential boost; with chemotherapy) was prescribed to the GTV. Along with the target volumes, the organs at risk (OAR) including the parotid glands were delineated on the planning CT scan. Inverse planned, step-and-shoot IMRT was applied with the intention to spare *both* parotid glands. No attempt was made to spare the (contralateral) submandibular gland(s). All studies described were approved by the Medical Ethics Committee of the University Medical Center Utrecht. Informed consent was obtained from each patient.

Parotid and submandibular flow measurements

Techniques that were used for parotid saliva measurements have been described previously [3,11]. Stimulated salivary flow rates were measured before treatment, 6 weeks, 6 months and at 1 year after RT. Patients were instructed not to eat or drink 60 min before saliva collection. The stimulated parotid saliva was collected for 10 min using Lashley cups after applying citric acid solution (5%) on the mobile part of the tongue every 60 s. For the purpose of this study, saliva from the left and right parotid gland was added together at each time point (parotid gland flow; PF).

At the same time, saliva near Wharton's duct orifices was collected by gentle suction with a micropipette. It represents predominantly salivary flow from the submandibular glands (SMF) but also varying amounts from the sublingual glands. The collected samples were weighted and converted to ml/min assuming the specific gravity of saliva to be 1.0 g/ml. To avoid the influence of diurnal variation in salivary flow, consecutive measurements were scheduled as much as possible at the same daytime for each patient.

Assessment of patient-reported xerostomia

At the same time points at which saliva was collected, all patients were asked to complete a xerostomia questionnaire (XQ). The XQ contains 12 questions and was developed at the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen to evaluate the use of saliva substitutes in patients with xerostomia [13,14]. It was also used in a double-blind, randomized clinical trial investigating the effect of pilocarpine on radiation-induced xerostomia [10]. The XQ contains questions related to xerostomia (dry mouth during day- and nighttime, eating, speaking, swallowing, and sleeping) and is scored on a 5-point Likert scale. A score of '1' means no complaints, while a score of '5' implies complaints are always present.

For the purpose of this study, we were interested only in the two questions addressing the sensation of dry mouth during day- ('Do you have a dry mouth during the day?') and nighttime ('Do you have a dry mouth at night?'). In the current analysis, we dichotomized xerostomia into 'severe' (grade 4–5) or 'none-to-mild' (grade 1–3). This was done for the symptom score during daytime (XD) and at the night (XN). To explore the data, patients were grouped together according to the pattern of complaints at day- and nighttime. Group A consisted of patients with no or mild complaints (grade 1–3) during day- and nighttime. Patients in group B had no or mild complaints during the day (grade 1–3) but had more severe complaints at night (grade 4–5). Group C-patients had severe complaints (grade 4–5) during daytime and at night. The combination of severe complaints during daytime (grade 4–5 XD) and no or mild complaints at night (grade 1–3 XN) occurred very rarely ($n = 3$).

Statistical analysis

Baseline patient characteristics were reported using descriptive statistics (mean, median, ranges or proportions; where appropriate). Differences in PG and SMG flow rate according to the pattern of complaints were analyzed using the Mann–Whitney *U* test. Pre-RT PG and SMG flow rates were compared using the Wilcoxon signed-ranks test. Correlations were calculated using Pearson's correlation coefficient (r).

Table 1
Patient and tumor characteristics, *n* (%).

Gender	
Male	89 (65)
Female	49 (35)
Age (median; range)	59 (35–88)
Tumor site	
Larynx	25 (18)
Hypopharynx	6 (4)
Oropharynx	83 (60)
Nasopharynx	17 (13)
Oral cavity	6 (4)
Unknown primary	1 (1)
T stage	
T1	28 (21)
T2	61 (44)
T3	25 (18)
T4	21 (15)
Tx	3 (2)
N stage	
N0	60 (44)
N1	24 (17)
N2a-b	38 (28)
N2c	13 (9)
N2 nasopharynx	3 (2)
RT modality	
IMRT	92 (67)
CRT	46 (33)
Mean dose (Gy; range)	
PG	36.5 (3.1–68.7)
SMG	59.8 (17.5–72.5)
Surgery	
Tumor ± ND	17 (12)
ND only	12 (9)
None	109 (79)
Chemotherapy	19 (14)

Abbreviations: IMRT, intensity modulated radiotherapy; CRT, conventional radiotherapy; Gy, dose in Gray; PG, parotid gland; SMG, submandibular gland; ND, (ipsilateral) neck dissection.