ACTA ONCOLOGICA
2022, VOL. 61, NO. 2, 146–152
https://doi.org/10.1080/0284186X.2021.2022204

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE



# The influence of radiation dose on taste impairment in a prospective observational study cohort of oropharyngeal cancer patients

Sonja Stieb[a,b], Grete M. Engeseth[c,d], Abdallah S. R. Mohamed[a], Renjie He[a], Ismael Perez-Martinez[a], Stockton Rock[a], Tanaya S. Deshpande[a], Adam S. Garden[a], David I. Rosenthal[a], Steven J. Frank[a], G. Brandon Gunn[a] and C. David Fuller[a]

[a]Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [b]Center for Radiation Oncology KSA-KSB, Cantonal Hospital Aarau, Aarau, Switzerland; [c]Haukeland University Hospital, Bergen, Norway; [d]Department of Clinical Science, University of Bergen, Bergen, Norway

**ABSTRACT**

**Background:** To analyze the influence of radiation dose on late radiation-associated taste impairment in oropharyngeal cancer (OPC) patients treated with intensity-modulated radiotherapy (IMRT) using the taste bud bearing tongue mucosa as organ at risk.

**Material and methods:** This study is part of an ongoing, prospective observational study. Cancer-free OPC survivors with at least 24 months from IMRT were included in this analysis. Scores for taste impairment and dry mouth were extracted from the MD Anderson Symptom Inventory Head and Neck module (MDASI-HN) with scores of $\geq$5 considered as moderate-to-severe symptoms. The mean dose, minimum and maximum dose to the taste bud bearing tongue mucosa, the ipsi- and contralateral parotid and submandibular glands were extracted and analyzed for correlation with moderate-to-severe taste impairment.

**Results:** One hundred sixteen T1–4 OPC patients were included (81% males, median age: 55). The primary tumor was in the tonsil in 92 cases (79%) and in the base of tongue in 21 cases (18%). Patients were treated with 64.2–72.0 Gy; 37 patients (32%) received concurrent chemotherapy and 22 (19%) concurrent targeted therapy. After a median of 58 months from RT (IQR: 43–68) 38 patients (33%) suffered from moderate-to-severe long-term radiation-associated taste impairment. No dose volume parameter of the taste bud bearing tongue mucosa and the salivary glands was significantly associated with moderate-to-severe taste impairment for the whole patient cohort. For patients without concurrent chemotherapy, the minimum and mean dose to the ipsilateral parotid gland, and the maximum dose to the submandibular gland was significantly associated with late taste impairment (all $p < 0.05$). A significant correlation was found between taste impairment and dry mouth ($p < 0.001$).

**Conclusion:** The dose to the ipsilateral parotid gland seems to play an important role in the development of late taste impairment. The influence of dose to the taste bud bearing tongue mucosa remains unclear and needs further investigation.

**ARTICLE HISTORY**
Received 29 June 2021
Accepted 21 October 2021

**KEYWORDS**
Head and neck neoplasms; oropharyngeal cancer; taste; radiotherapy

## Introduction

Human papillomavirus (HPV) associated oropharyngeal cancer (OPC) patients are an increasing subgroup of younger head and neck cancer (HNC) patients with favorable outcome, even after treatment for advanced stages [1]. After definitive radiochemotherapy, the estimated 5-year overall survival for patients with HPV positive OPC was recently reported as 85%, with locoregional failure in only 10% despite predominantly stage IV disease in that cohort [2]. This favorable outcome leads the attention toward the importance of reducing late treatment-related side effects, which includes xerostomia, dysphagia, mouth/throat sores, or difficulties with teeth and gums [3]. Overall, 20% of patients with OPC suffer from some type of long-term G3–4 toxicity after radiotherapy (RT) [2].

Another common, but highly under-investigated long-term side effect from radiation to the head and neck region, is taste impairment [4]. Although recovery continues over years, taste will not return to pre-therapy levels in the majority of those patients; even five years after end of radiotherapy around 60% of the patients still report taste impairment [5].

In preclinical studies, radiotherapy has been shown to affect the taste progenitor cells within the taste buds [6]. However, previous clinical studies investigating the association between dose and taste impairment, correlated taste with the prescribed dose to the tumor [7], the dose to the whole tongue [8] or to the entire oral cavity [9–11], instead of using a taste specific organ at risk (OAR) structure. Recently, our group presented a contouring guideline for delineation of the taste bud bearing tongue mucosa [12] as

CONTACT Sonja Stieb sonja.stieb@ksa.ch Center for Radiation Oncology KSA-KSB, Cantonal Hospital Aarau, Tellstrasse 25, Aarau, 5001, Switzerland
Supplemental data for this article can be accessed here.

basis for a more advanced dosimetric analysis of taste. The aim of this study was to investigate the impact of radiation dose to this taste specific OAR structure on taste impairment 5 years post-RT in a prospective observational study cohort of exclusively OPC patients treated with intensity-modulated radiotherapy (IMRT).

## Material and methods

### Patients and treatment

The current study is part of an ongoing, Institutional Review Board (IRB)-approved, observational study protocol at The University of Texas MD Anderson Cancer Center to prospectively assess the longitudinal patient-reported symptoms with different Quality of Life (QoL) questionnaires in HNC patients after RT. To fulfill the inclusion criteria in the IRB-approved protocol, patients had to be treated with curative intended photon RT at least six months before study accrual and without evidence of active tumor at time of study inclusion. Questionnaires were self-completed by the patients at regular follow-up visits or *via* telephone interview by study personnel using a study-specific IRB-approved script.

For the purpose of this analysis, we only included patients treated with IMRT for OPC and with taste assessments more than 24 months from end of RT. Patients with locoregional recurrence, chemotherapy for distant metastasis or another primary were excluded; also, patients without retrievable planning CT or RT plan, with major oral surgery, or with an oral stent for immobilization of the tongue during RT (no contouring guideline for the taste bud bearing tongue mucosa available for patients with oral stent).

All patients were immobilized in a 5-point thermoplastic mask during planning CT and treatment. Patients received IMRT with 6 MV photons. Common radiation treatment schedules were 66.0 Gy in 30 fractions, 70.0 Gy in 33 fractions, and 70.0 Gy in 35 fractions, with dose prescribed to the median dose. Unilateral RT was considered for patients with well-lateralized tonsil cancer and bilateral RT applied in all other cases. Concurrent chemotherapy was platinum-based (weekly 35 mg/m$^2$ or 100 mg/m$^2$ three-weekly), and targeted therapy mainly with Cetuximab.

### Toxicity evaluation

Patient-reported taste impairment and dry mouth was extracted from the MD Anderson Symptom Inventory Head and Neck module (MDASI-HN) [13], on which patients had to rate their symptoms on an 11-point Likert scale from 0 (not present) to 10 (as bad as you can imagine). Scores from 1 to 4 were considered as mild symptoms, from 5–6 as moderate, and from 7 to 10 as severe symptoms. Due to the longitudinal nature of the study with several MDASI-HN assessments over time, we selected the MDASI-HN scores nearest to five years post-RT for our analysis, where, according to our previous work, late taste impairment is considered relatively stable [5].

### Organ at risk segmentation and data extraction

The taste bud bearing tongue mucosa structure (Figure 1) was retrospectively delineated on the planning CT by a board-certified radiation oncologist (SS) according to a recently published guideline [12]. Of the two methods described in that paper we used method B, where the taste bud bearing tongue mucosa results from an axial adaptation of a midsagittal contour. The ipsi- and contralateral parotid and submandibular gland, was contoured according to the guideline from Brouwer et al. [14] by the same radiation oncologist. The volume, mean dose ($D_{mean}$), and the minimum ($D_{min}$) and maximum dose ($D_{max}$) of those structures was extracted.

Treatment and patient characteristics were collected from the RedCap study database and the clinical information system EPIC (Epic Systems Corporation, Verona, WI, USA), including age, sex, tumor subsite, stage, HPV/p16 status, prescribed dose, chemotherapy, smoking and alcohol. Heavy smoking was defined as $\geq$30 pack years at start of treatment [15], and heavy alcohol consumption as two or more alcoholic drinks per day during or before start of radiotherapy.

### Statistics

Primary endpoint of this study was moderate-to-severe taste impairment assessed by the MDASI-HN nearest to 5 years post-RT.

Statistical analysis was performed with SPSS Statistics version 24 (IBM statistics, Armonk, NY, USA). Descriptive statistics including mean and median values, range (min–max) and interquartile range (IQR) were used to describe the patient cohort, the occurrence of taste impairment and dry mouth, and the dose received by the taste bud bearing tongue mucosa, and the parotid and submandibular glands. Binary, univariable logistic regression analysis was performed to test for correlations of different variables with moderate-to-severe taste impairment, and ordinal logistic regression analysis to test for correlations with all four symptom categories (no/mild/moderate/severe), and the 11 MDASI-HN scores, respectively. Spearman correlation was used to investigate the correlation of taste impairment and dry mouth. *T*-test (after testing for equal variances with Levene's test), Kruskal–Wallis test, and Fishers exact test was applied to analyze for differences between the groups with no and mild versus moderate-to-severe symptoms, and between the groups with and without concurrent chemotherapy. For this hypothesis-generating study, an *a-priori* non-Bonferroni corrected *p*-value of $\leq$0.05 was considered significant.

## Results

### Study cohort

One hundred and sixteen patients were included in this analysis with a median age of 55 years at start of RT (range: 29−84; IQR: 50−61). The majority of patients was treated for primary tumors in the tonsil ($n = 92$, 79%) and base of tongue (BOT) ($n = 21$, 18%, Table 1). Three patients (3%) had

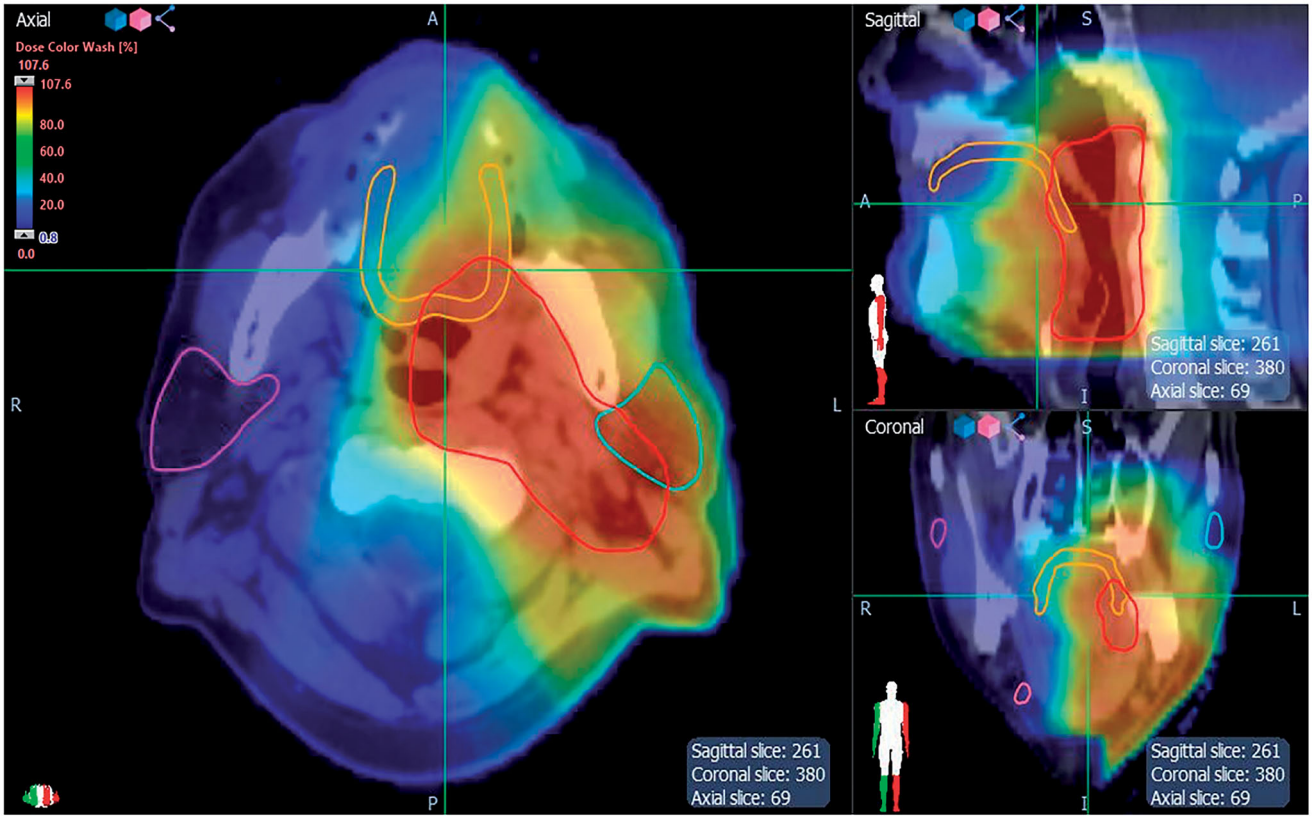


**Figure 1.** Example of the dose distribution (PTV 66 Gy in red) of the taste bud bearing tongue mucosa (orange contour) of a 55-year old patient with T1 and N1 tonsil cancer. Left and right parotid gland contoured in magenta and cyan, respectively.

primary tumors in the glossopharyngeal fold or in the pharyngeal wall. Tumor category was T1 in 37 cases (32%), T2 in 50 (43%), T3 in 19 (16%), and T4 in 8 (7%). The tumor category of two patients (2%) with tonsillar primary could not be classified after tonsillectomy at an outside institution and therefore staged as TX; 99 patients (85%) had pathologic neck nodes (Table 1).

### *Treatment*

Median prescribed dose to the high dose planning target volume (PTV) was 66.0 Gy (range: 64.2−72.0; IQR 66.0−69.96 Gy). Sixty-one patients (53%) received 66.0 Gy in 30 fractions, 42 (36%) 70.0 Gy in 33 fractions, and 6 patients (5%) 70.0 Gy in 35 fractions. 84 patients (72%) received bilateral RT, 32 patients (28%) unilateral. 37 patients (32%) received concurrent platinum-based chemotherapy ($n = 26$ (24%) low dose weekly, $n = 9$ (6%) high dose three-weekly), 22 (19%) concurrent targeted therapy.

### *Taste impairment and dry mouth assessment*

After a median of 58 months from RT (range: 25−109, IQR 43−68) 56 patients (48%) suffered from taste impairment. Moderate-to-severe taste impairment was reported by 38 patients (33%). The median (IQR) MDASI-HN taste score was 0 (0−2), respectively (Table 2).

MDASI-HN scores for taste impairment were significantly correlated with scores for dry mouth ($p < 0.001$, correlation coefficient: 0.361). 22 patients (19%) reported no problems with dry mouth, whereas 56 (48%), 18 (16%), and 20 (17%) reported mild, moderate and severe xerostomia, respectively. The median (IQR) MDASI-HN score for dry mouth was 3 (1−5), respectively (Table 2).

Three patients (8%) with and 15 (19%) without concurrent chemotherapy reported moderate-to-severe taste impairment ($p = 0.133$, Table 2). The MDASI-HN scores for both subcohorts are depicted in Table 2.

### *Correlation of taste impairment with clinical parameters and dose*

Patients with moderate-to-severe taste impairment had significantly more often pathological lymph nodes than patients with no or mild taste impairment ($p = 0.025$). No significant difference could be found for sex, age, tumor subsite, T category, HPV/p16 status, prescribed dose, treatment laterality, chemotherapy, smoking and heavy alcohol consumption (Table 1).

The mean (SD; range) and median (IQR) $D_{mean}$ to the taste bud bearing tongue mucosa of the whole cohort was 47.4 Gy (7.8; 22.6−66.3) and 46.8 Gy (41.6−53.3), respectively. The mean (SD; range) and median (IQR) $D_{mean}$ to the ipsi- and contralateral parotid gland was 37.9 Gy (9.4; 21.5−61.7) and 36.1 Gy (31.0−44.7), respectively, and 18.4 Gy (9.7; 1.2−47.2) and 19.5 Gy (7.8−24.1), respectively. Overall, no statistically significant correlation could be found for $D_{mean}$, $D_{min}$, and $D_{max}$ to the taste bud bearing tongue mucosa, ipsi- and contralateral parotid and submandibular

**Table 1.** Clinical parameters of the whole patient cohort, and for patients with no/mild and moderate/severe taste impairment separately.

| | All patients ($n = 116$) | No/mild taste impairment ($n = 98$) | Moderate/severe taste impairment ($n = 18$) | $p$-value no/mild vs. moderate/severe taste impairment |
|---|---|---|---|---|
| MDASI-HN assessment (months from RT) | | | | $p = 0.29$ |
| Median | 58 | 58 | 62 | |
| Range | 25 −109 | 25–109 | 26–102 | |
| IQR | 43−68 | 43–67 | 45–79 | |
| Sex | | | | $p = 0.33$ |
| Male | 94 (81.0%) | 81 (82.7%) | 13 (72.2%) | |
| Female | 22 (19.0%) | 17 (17.3%) | 5 (27.8%) | |
| Age at RT start (years) | | | | $p = 0.63$ |
| Median | 55 | 55 | 56 | |
| Range | 29–84 | 29–77 | 30–84 | |
| IQR | 50–61 | 50–60 | 51–64 | |
| Tumor subsite | | | | $p = 0.70$ |
| Tonsil | 92 (79.3%) | 77 (78.6%) | 15 (83.3%) | |
| BOT | 21 (18.1%) | 19 (19.4%) | 2 (11.1%) | |
| Others | 3 (2.6%) | 2 (2.0%) | 1 (5.6%) | |
| T category | | | | $p = 0.41$ |
| T1 | 37 (31.9%) | 28 (28.6%) | 9 (50.0%) | |
| T2 | 50 (43.1%) | 46 (46.9%) | 4 (22.2%) | |
| T3 | 19 (16.4%) | 17 (17.3%) | 2 (11.1%) | |
| T4 | 8 (6.9%) | 6 (6.1%) | 2 (11.1%) | |
| TX | 2 (1.7%) | 1 (1.0%) | 1 (5.6%) | |
| *N* category | | | | $p = 0.02$ |
| Node negative | 17 (14.7%) | 11 (11.2%) | 6 (33.3%) | |
| Node positive | 99 (85.3%) | 87 (88.8%) | 12 (66.7%) | |
| HPV/p16 status | | | | $p = 0.58$ |
| Positive | 60 (51.7%) | 51 (52.0%) | 9 (50.0%) | |
| Negative | 6 (5.2%) | 6 (6.1%) | 0 (0%) | |
| Unknown | 50 (43.1%) | 41 (41.8%) | 9 (50.0%) | |
| Smoking status | | | | $p = 0.46$ |
| Heavy smoker | 18 (15.5%) | 17 (17.3%) | 1 (5.6%) | |
| No heavy smoker | 85 (73.3%) | 71 (72.4%) | 14 (77.8%) | |
| Unknown | 13 (11.2%) | 19 (10.2%) | 3 (16.7%) | |
| Alcohol status | | | | $p = 0.43$ |
| Heavy drinker | 15 (12.9%) | 12 (12.2%) | 3 (16.7%) | |
| No heavy drinker | 93 (80.2%) | 81 (82.7%) | 12 (66.7%) | |
| Unknown | 8 (6.9%) | 5 (5.1%) | 3 (16.7%) | |
| Treatment laterality | | | | $p = 1.00$ |
| Unilateral radiotherapy | 32 (27.6%) | 27 (27.6%) | 5 (27.8%) | |
| Bilateral radiotherapy | 84 (72.4%) | 71 (72.4%) | 13 (72.2%) | |
| Prescribed dose to high dose PTV | | | | $p = 0.73$ |
| Median | 66.0 Gy | 66.0 Gy | 66.0 Gy | |
| Range | 64. 2–72.0 Gy | 64.2–72.0 Gy | 66.0–72.0 Gy | |
| Chemotherapy | | | | |
| Concurrent chemotherapy | 37 (31.9%) | 34 (34.7%) | 3 (16.7%) | $p = 0.17$ |
| Concurrent targeted therapy | 22 (19.0%) | 21 (21.4%) | 1 (5.6%) | $p = 0.18$ |
| No concurrent chemo- or targeted therapy | 57 (49.1%) | 43 (43.9%) | 14 (77.8%) | |

BOT: base of tongue; IQR: interquartile range; MDASI-HN: MD Anderson symptom inventory head and neck module; *n*: number of patients if not indicated otherwise; PTV: planning target volume; SD: standard deviation.

gland with moderate-to-severe taste impairment (Table 3). Ordinary logistic regression analysis including all four symptom categories and all 11 MDASI-HN scores, respectively, did not reveal a significant correlation, too.

In the subgroup analysis of patients without concurrent chemotherapy we found that a higher $D_{mean}$ and $D_{min}$ to the ipsilateral parotid gland ($D_{mean}$: 41.3 vs. 35.9 Gy, $p = 0.036$; $D_{min}$: 10.4 vs. 6.6 Gy, $p = 0.024$), and a higher $D_{max}$ to the ipsilateral submandibular gland (72.1 vs. 70.6 Gy, $p = 0.036$) was significantly associated with moderate-to-severe taste impairment (Table 3, Supplementary Table 1, Figure 2). $D_{min}$ of the parotid gland was also significantly associated with taste impairment in both ordinal logistic regression analyses (including the four symptom categories and all 11 MDASI-HN scores, respectively). $D_{max}$ of the ipsilateral parotid gland showed a significant correlation with taste impairment only in the ordinal regression analysis including the four symptom categories (Table 3).

$D_{mean}$ to the taste bud bearing tongue mucosa was higher in patients with moderate-to-severe taste impairment (47.3 Gy vs. 44.6 Gy), but was not significantly correlated with taste impairment in the binary logistic regression analysis ($p = 0.210$) or the ordinal logistic regression analysis (Supplementary Table 1, Table 3).

## Discussion

This is the first study to evaluate the dose toxicity relationship for taste impairment using a taste specific OAR structure. Previously, we could show that the dose to the taste

**Table 2.** MDASI-HN scores for taste impairment and dry mouth of the whole patient cohort, and for patients with and without concurrent chemotherapy seperately.

| | All patients ($n = 116$) | Patients with concurrent chemotherapy ($n = 37$) | Patients without concurrent chemotherapy ($n = 79$) | $p$-value with vs. without concurrent chemotherapy |
|---|---|---|---|---|
| MDASI-HN assessment (months) | | | | |
| Median | 58 | 55 | 59 | |
| Range | 25–109 | 25–91 | 26–109 | |
| IQR | 43–68 | 43–62 | 41–68 | |
| MDASI-HN taste impairment | | | | $p = 0.25$ |
| Mean (SD) | 1.6 (2.4) | 1.2 (2.1) | 1.7 (2.5) | |
| Median | 0 | 0 | 1 | |
| Range | 0–10 | 0–10 | 0–9 | |
| IQR | 0–2 | 0–1 | 0–2 | |
| MDASI-HN taste impairment category | | | | $p = 0.27$ (all categories) |
| No | 60 (51.7%) | 21 (56.8%) | 39 (49.4%) | $p = 0.13$ (no/mild vs. mod./sev.) |
| Mild | 38 (32.8%) | 13 (35.1%) | 25 (31.6%) | |
| Moderate | 12 (10.3%) | 2 (5.4%) | 10 (12.7%) | |
| Severe | 6 (5.2%) | 1 (2.7%) | 5 (6.3%) | |
| MDASI-HN dry mouth | | | | $p = 1.00$ |
| Mean (SD) | 3.6 (3.0) | 3.5 (2.8) | 3.6 (3.0) | |
| Median | 3 | 3 | 3 | |
| Range | 0–10 | 0–10 | 0–10 | |
| IQR | 1–5 | 1–5 | 1–6 | |
| MDASI-HN dry mouth category | | | | $p = 0.58$ |
| No | 22 (19.0%) | 8 (21.6%) | 14 (17.7%) | |
| Mild | 56 (48.3%) | 17 (45.9%) | 39 (49.4%) | |
| Moderate | 18 (15.5%) | 8 (21.6%) | 10 (12.7%) | |
| Severe | 20 (17.2%) | 4 (10.8%) | 16 (20.3%) | |
| Correlation MDASI-HN taste and dry mouth score | | | | |
| $p$-Value | $<0.001$ | 0.04 | 0.001 | |
| Correlation coefficient | 0.36 | 0.34 | 0.37 | |

IQR: interquartile range; MDAS-HNI: MD Anderson symptom inventory head and neck module; mod.: moderate; n: number of patients; SD: standard deviation; sev.: severe.

**Table 3.** Results from the univariate logistic regression analysis; associations between moderate-to-severe taste impairment and dose volume variables for all patients, patients with concurrent chemotherapy and patients without concurrent chemotherapy, respectively.

| | All patients ($n = 116$) | | Patients with concurrent chemotherapy ($n = 37$) | | Patients without concurrent chemotherapy ($n = 79$) | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | $p$-value | OR (95% CI) | $p$-value | OR (95% CI) | $p$-value |
| Tongue mucosa dose (Gy) | | | | | | |
| $D_{mean}$ | 1.003 (0.956–1.052) | $p = 0.90$ | 1.035 (0.852–1.258) | $p = 0.73$ | 1.051 (0.973–1.135) | $p = 0.21$ |
| $D_{min}$ | 0.982 (0.918–1.051) | $p = 0.60$ | 1.031 (0.893–1.190) | $p = 0.68$ | 1.004 (0.925–1.004) | $p = 0.93$ |
| $D_{max}$ | 0.927 (0.791–1.087) | $p = 0.35$ | 0.912 (0.672–1.238) | $p = 0.81$ | 1.027 (0.833–1.265) | $p = 0.81$ |
| Parotid gland dose ipsi (Gy) | | | | | | |
| $D_{mean}$ | 1.043 (0.990–1.099) | $p = 0.11$ | 0.999 (0.888–1.124) | $p = 0.99$ | 1.071 (1.005–1.141) | $p = 0.04^{(2/2)}$ |
| $D_{min}$ | 1.037 (0.978–1.099) | $p = 0.22$ | 0.919 (0.595–1.418) | $p = 0.70$ | 1.140 (1.018–1.276) | $p = 0.02^{(1/1)}$ |
| $D_{max}$ | 0.996 (0.871–1.139) | $p = 0.95$ | 0.969 (0.736–1.277) | $p = 0.55$ | 1.056 (0.884–1.261) | $p = 0.55^{(1/2)}$ |
| Parotid gland dose contra (Gy) | | | | | | |
| $D_{mean}$ | 1.009 (0.959–1.062) | $p = 0.73$ | 1.016 (0.888–1.162) | $p = 0.82$ | 1.022 (0.965–1.082) | $p = 0.46$ |
| $D_{min}$ | 0.970 (0.736–1.274) | $p = 0.83$ | 1.256 (0.548–2.880) | $p = 0.59$ | 0.988 (0.738–1.322) | $p = 0.93$ |
| $D_{max}$ | 0.998 (0.976–1.020) | $p = 0.85$ | 0.994 (0.916–1.078) | $p = 0.89$ | 1.005 (0.981–1.029) | $p = 0.70$ |
| SMG dose ipsi (Gy) | | | | | | |
| $D_{mean}$ | 0.981 (0.845–1.141) | $p = 0.81$ | 0.856 (0.645–1.138) | $p = 0.29$ | 1.097 (0.894–1.345) | $p = 0.38$ |
| $D_{min}$ | 0.960 (0.878–1.049) | $p = 0.37$ | 0.736 (0.533–1.017) | $p = 0.06$ | 1.012 (0.909–1.127) | $p = 0.83$ |
| $D_{max}$ | 1.084 (0.891–1.319) | $p = 0.42$ | 0.919 (0.683–1.236) | $p = 0.58$ | 1.307 (1.015–1.683) | $p = 0.04^{(1/1)}$ |
| SMG dose contra (Gy) | | | | | | |
| $D_{mean}$ | 0.995 (0.973–1.018) | $p = 0.66$ | 0.977 (0.913–1.045) | $p = 0.50$ | 1.004 (0.979–1.030) | $p = 0.74$ |
| $D_{min}$ | 0.994 (0.969–1.021) | $p = 0.67$ | 0.968 (0.902–1.039) | $p = 0.37$ | 1.008 (0.978–1.040) | $p = 0.59$ |
| $D_{max}$ | 0.994 (0.973–1.016) | $p = 0.58$ | 0.986 (0.917–1.059) | $p = 0.70$ | 1.002 (0.978–1.026) | $p = 0.90^{(-/2)}$ |

Values in brackets indicate the $p$-values of the ordinal logistic regression analysis (using the four symptom categories/using all 11 MDASI-HN scores); $^1p < 0.05$; $^2p < 0.1$ in ordinal logistic regression analysis; CI: confidence interval; contra: contralateral; $D^{mean}$: mean dose; $D_{min}$: minimum dose; $D_{max}$: maximum dose; ipsi: ipsilateral; $n$: number of patients; OR: odds ratio; SD: standard deviation; SMG: submandibular gland.

bud bearing tongue mucosa differs significantly from the dose to the whole tongue [12]. It is therefore important to use a taste specific structure for dosimetric analysis of radiation-associated taste impairment instead of the whole tongue or the entire oral cavity.

In our cohort using the taste bud bearing tongue mucosa as OAR, we could not find a correlation of dose to this structure with taste impairment. However, we could find a significant correlation between the mean dose and the minimum dose to the ipsilateral parotid gland, and the maximum dose

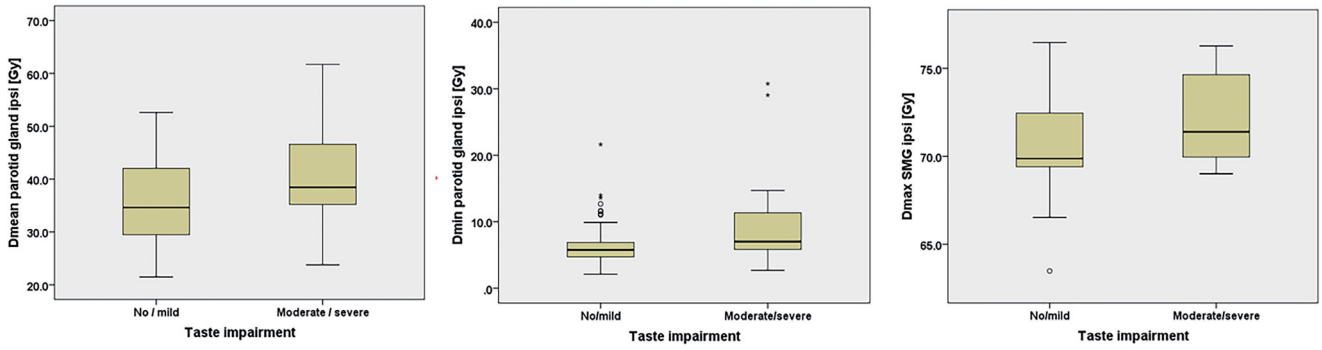


**Figure 2.** Boxplot showing the summary statistics of $D_{mean}$ and $D_{min}$ to the ipsilateral parotid gland and $D_{max}$ to the ipsilateral submandibular gland (SMG) for the non-concurrent chemotherapy patients with no/mild versus moderate/severe taste impairment ($n = 79$).

to the ipsilateral submandibular gland with moderate-to-severe taste impairment in the non-concurrent chemotherapy cohort. This indicates that the dose to the salivary glands might be more relevant for radiation-associated late taste impairment than the dose to the taste bud bearing tongue mucosa. Similar to our findings, Asif et al., using the oral cavity as OAR, did not find a correlation of mean and maximum dose with taste impairment, but could show a significant association between taste impairment and xerostomia [11]. Chen et al. reported a significant dose toxicity relationship between taste and the mean dose to the oral cavity in non-surgical patients, but the correlation with mean dose to the parotid glands was even more significant [10]. No correlation with moderate-to-severe taste impairment however could be found for the contralateral salivary glands in our study. This is reasonable, especially for the contralateral parotid gland, as this OAR was spared in most of the cases in this study. However, other institutions might have different preferences for OAR sparing. An external validation of our findings would be desirable, also as this is the first time that the taste bud bearing tongue mucosa was used for dosimetric analysis.

Of the clinical variables, only the presence of pathologic lymph nodes was significantly different between the group of patients with no or mild versus moderate-to-severe taste impairment. However, we were not able to further differentiate the nodal stage to N0–3 and compare the groups individually. The reason for that was the fact that the patients were accrued over a long time period with change of the American Joined Committee of Cancer (AJCC) TNM staging system for the nodal status in 2017, and HPV status, necessary for re-classification of the patients treated before that time, not available for all patients.

In our cohort, patients with moderate-to-severe taste impairment received concurrent chemotherapy less often than patients with no or mild taste impairment, although the difference was not significant. On the contrary, we showed in our previous publication on 326 OPC patients that the addition of chemotherapy prolonged taste impairment [5]. Since the patients of the current study are a subgroup of the aforementioned study, we assume a bias by excluding the patients with oral stents for whom no contouring guideline for the taste bud bearing tongue mucosa exists, in order to form this cohort. We might by chance have predominantly excluded patients with concurrent chemotherapy having moderate-to-severe taste impairment with this selection procedure. We found it therefore essential to perform a subgroup analysis of the dosimetric impact on taste for the 79 non-concurrent chemotherapy patients, which was not part of the statistical analysis plan initially.

Some limitations of this study need to be emphasized. First, our study cohort does not have baseline MDASI-HN values before cancer-directed therapy. Thus, taste impairment could have been related to other non-therapy-related factors in the past. We correlated taste impairment with heavy alcohol consumption and heavy smoking during or before RT start, but other factors might have played a role. However, according to literature the occurrence of moderate-to-severe taste impairment before radiotherapy can assumed to be low (around 9% in the publication of Sio et al., but with a MDASI-HN cutoff of $\geq$4 for moderate-to-severe taste impairment instead of 5 [16]). Second, patients were not followed-up at regular time intervals with the MDASI-HN questionnaire, e.g., after 1 year, 2 years, etc. post-RT. This is the reason why we couldn't investigate taste impairment at a specific time point. However, according to our previous work, MDASI-HN taste scores of patients queried in consecutive years, significantly improved within the first years post-RT only, and became relatively stable afterwards [5]. Therefore, we restricted patient inclusion to those with taste assessment available at least 24 months from RT. Third, our study cohort with high prevalence of HPV related cancers does not reflect the usual OPC patients elsewhere. Continued tobacco and alcohol consumption may play a more important role in HPV negative patients. Last, other dosimetric parameters might be more important for taste impairment than minimum dose, maximum and mean dose. Besides, dosimetric parameters like D95 and D5 would be more robust than minimum and maximum point dose; it might therefore be better to extract the whole dose volume histogram of the structures for analysis.

## Conclusion

Of the variables studied, only the dose to the ipsilateral parotid and submandibular gland was significantly correlated with late taste impairment in patients who previously received RT for head and neck cancer without concurrent chemotherapy. The dose to the ipsilateral salivary glands

seems therefore to be more important in the development of late taste impairment that the dose to the taste bud bearing tongue mucosa.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

S. Stieb received funding from the Swiss Cancer League [BIL KLS-4300-08-2017]. G.M. Engeseth is funded by the Trond Mohn foundation. S.J. Frank has received grants from C4 Imaging, Eli Lilly, Elekta, and Hitachi. G.B. Gunn is supported by a philanthropic donation made by the Family of Paul W. Beach. C.D. Fuller received funding from the National Institute for Dental and Craniofacial Research Award [1R01DE025248-01/R56DE025248] and Academic-Industrial Partnership Award [R01 DE028290], the National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant [NSF 1557679], the NIH Big Data to Knowledge (BD2K) Program of the National Cancer Institute (NCI) Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Award [1R01CA214825], the NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program [1R01CA218148], the NIH/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the UT MD Anderson CCSG Radiation Oncology and Cancer Imaging Program [P30CA016672], the NIH/NCI Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Award [P50 CA097007] and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) Research Education Program [R25EB025787]. He has received direct industry grant support from Elekta.

## References

[1] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010; 363(1):24–35.

[2] Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019;393(10166):40–50.

[3] Eraj SA, Jomaa MK, Rock CD, Head MDA, Neck Cancer Symptom Working G, et al. Long-term patient reported outcomes following radiation therapy for oropharyngeal cancer: cross-sectional assessment of a prospective symptom survey in patients >/=65 years old. Radiat Oncol. 2017; Sep 912(1):150.

[4] Deshpande TS, Blanchard P, Wang L, et al. Radiation-related alterations of taste function in patients with head and neck cancer: a systematic review. Curr Treat Options Oncol. 2018;19(12):72.

[5] Stieb S, Mohamed ASR, Deshpande TS, MD Anderson Head and Neck Cancer Symptom Working Group, et al. Prospective observational evaluation of radiation-induced late taste impairment kinetics in oropharyngeal cancer patients: potential for improvement over time? Clin Transl Radiat Oncol. 2020;22:98–105.

[6] Nguyen HM, Reyland ME, Barlow LA. Mechanisms of taste bud cell loss after head and neck irradiation. J Neurosci. 2012;732(10): 3474–3484.

[7] Mossman KL. Gustatory tissue injury in man: radiation dose response relationships and mechanisms of taste loss. Br J Cancer Suppl. 1986;7:9–11.

[8] Yamashita H, Nakagawa K, Tago M, et al. Taste dysfunction in patients receiving radiotherapy. Head Neck. 2006;28(6):508–516.

[9] Sapir E, Tao Y, Feng F, et al. Predictors of dysgeusia in patients with oropharyngeal cancer treated with chemotherapy and intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2016;96(2):354–361.

[10] Chen WC, Tsai MS, Tsai YT, et al. Long-Term taste impairment after Intensity-Modulated radiotherapy to treat head-and-Neck cancer: correlations with glossectomy and the mean radiation dose to the oral cavity. Chem Senses. 2019;44(5):319–326.

[11] Asif M, Moore A, Yarom N, et al. The effect of radiotherapy on taste sensation in head and neck cancer patients – a prospective study. Radiat Oncol. 2020;15(1):144.

[12] Stieb S, Mohamed ASR, He R, et al. Development and validation of a contouring guideline for the taste bud bearing tongue mucosa. Radiother Oncol. 2021;157:63–69.

[13] Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck. 2007;29(10):923–931.

[14] Brouwer CL, Steenbakkers RJ, Bourhis J, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG oncology and TROG consensus guidelines. Radiother Oncol. 2015;117(1):83–90.

[15] Elhalawani H, Mohamed ASR, Elgohari B, et al. Tobacco exposure as a major modifier of oncologic outcomes in human papillomavirus (HPV) associated oropharyngeal squamous cell carcinoma. BMC Cancer. 2020;20(1):912.

[16] Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of Patient-Reported outcomes. Int J Radiat Oncol Biol Phys. 2016;95(4):1107–1114.