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Original Research Article

Prospective observational evaluation of radiation-induced late taste impairment kinetics in oropharyngeal cancer patients: Potential for improvement over time?

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ABSTRACT

Background and purpose: Taste impairment is a common radiation-induced toxicity in head and neck cancer (HNC) patients acutely. However, data on the potential for recovery and the time dependent course of late taste impairment are limited.

Materials and methods: As part of an IRB-approved observational prospective study, HNC patients underwent serial surveys including the MD Anderson Symptom Inventory - Head and Neck module (MDASI-HN). For our analysis, we extracted MDASI-HN taste item results from oropharyngeal cancer patients treated with intensity-modulated radiotherapy or volumetric modulated arc therapy and at least two taste assessments after ≥1 year from end of radiotherapy (RT).

Results: 1214 MDASI taste items from 326 patients between 1 and 13 years post-RT were included. Median prescribed dose to the high-dose clinical target volume (CTV1) was 66.0 Gy, with 180 patients (55%) receiving chemotherapy. Taste markedly improved in the first years from end of RT, but plateaued after year 5. In patients with taste assessment in subsequent years, a significant reduction in taste impairment was found from the second to the third year ($p = 0.001$) and tended towards significance from the third to the fourth year ($p = 0.058$). Multivariate analysis revealed treatment site as significant factor in the sixth year from RT and CTV1 dose and age in the seventh year.

Conclusion: Radiation-induced taste impairment may improve over an extended time interval, but becomes relatively stable from year 5 post-RT. Direct characterization of RT-induced taste impairment and the calculation of normal tissue complication probability should include consideration of the time-dependent course in taste recovery.

1. Introduction

Taste impairment can affect patients with tumors of various sites, but is most commonly reported in patients with head and neck cancer (HNC) [1]. Although many HNC patients suffer from taste impairment, little notice is given to that symptom, despite the fact that taste impairment can lead to further problems like weight loss [2] and reduced quality of life (QoL) [3].

Taste impairment can occur as hypergeusia (increased taste), hypogeusia (decreased taste), ageusia (loss of taste) or dysgeusia (altered taste) [4]. Various assessment tools have been described, including subjective measures within head and neck specific quality of life questionnaires [5–7], and objective measurements with electrogustrometry or taste solutions (chemogustrometry) [8], covering the five taste sensations sweet, sour, salty, bitter and umami. The most commonly used QoL questionnaire in head and neck cancer patients is the "EORTC QLQ H&N 35" from the European Organization for Research and Treatment of Cancer

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(EORTC) [9]. Other common head and neck QoL assessment tools include the University of Washington QoL questionnaire ("UW-QoL") [10] or the MD Anderson Symptom Inventory Head and Neck module ("MDASI-HN") [11].

In general, taste can be impaired by direct damage to the taste buds, the peripheral nerves, or injury of the central nervous system such as the temporal lobe [12,13]. It may also be a result of the cancer itself [14], or can be therapy-associated in cases of oral surgery [15], radiotherapy (RT) [16] and/or chemotherapy [17]. Loss of sense of smell can also disrupt taste in cases of treatment involving the olfactory bulbs or nasal cavity as well as in laryngectomy patients who no longer breathe through their nose [18,19]. Nearly all HNC patients who undergo RT experience hypogeusia and metallic taste, acutely [20]. Most of these patients will recover from their taste impairment to a certain degree over time [21]; however, data on the time-dependent course of late taste impairment is very limited. Often these data are retrospective, involve a heterogeneous population, e.g. different head and neck primary tumor subsites, and are mainly restricted to only one year from RT. The purpose of this study was to prospectively analyze the temporal change in taste for patients who underwent RT for oropharyngeal cancer (OPC) using serially assessed patient-reported outcomes (PRO), in order to identify the time interval for potential taste recovery.

2. Materials and methods

2.1. Study procedure

Patients selected for this study are part of an ongoing, prospective symptom survey at the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center. Approval for study conduction, data collection and analysis was obtained from the institutional review board. All study procedures have been performed in concordance with the Helsinki Declaration of 1975, as revised in 2000. Study-specific informed consent was obtained from all participating patients.

The eligible population, adult HNC patients who were at least six months out from curative intent radio(chemo)therapy, were asked to complete the MDASI-HN module via telephone interview or at a routine clinic follow-up visit. Among other symptoms, study participants thereby rated the severity of taste ("Your problem with tasting food at its worst?") on an 11-point Likert scale from 0 ("not present") to 10 ("as bad as you can imagine"). For our analysis purposes and based on previously published thresholds [22,23], symptoms were considered as none (if rated as 0), mild (>0 and <5), moderate (≥5 and <7) or severe (≥7) [11].

2.2. Patient characteristics

Patient characteristics were obtained from the Research Electronic Data Capture (RedCap) study database and from medical records in Epic (Epic Systems Corporation, Verona, WI). For this analysis, study participants were included based on the above-mentioned eligibility criteria, treated for OPC with intensity modulated radiotherapy treatment (IMRT) or volumetric modulated arc therapy (VMAT), with at least two MDASI taste assessments after ≥1 year from end of RT. MDASIs obtained at time points <12 months from end of treatment (first year) were excluded to minimize the capture of acute/subacute taste disturbances.

2.3. Treatment

All patients had undergone CT simulation and were immobilized with bite block and/or head, neck and shoulder thermoplastic mask. To allow for better positional reproducibility [24], a customized tongue-depressing oral stent was usually placed in cases of base of tongue (BOT) tumors and a tongue-lateralizing oral stent in case of T1-2 tonsil tumors. RT was delivered with IMRT, commonly using 5 to 7 non-coplanar fields, or VMAT, with the aim to cover at least 95% of the target volume with the prescribed dose. Fig. 1 presents an example of a typical treatment plan for a BOT cancer patient. In case of small tonsil cancer with no or unilateral neck involvement, unilateral RT has been considered.

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 24 (IBM, Armonk, NY) and JMP Pro 14 (SAS Institute, Cary, NC). Descriptive statistics were applied to analyze patient and treatment characteristics and the severity of taste impairment from the second to the tenth year post-RT. For patients with taste assessments at several time points within the same year from RT, the mean MDASI score was calculated and used for further analysis (if not specifically indicated otherwise). Wilcoxon signed-rank test was performed to test for significant differences in taste impairment between different time points. Mann-Whitney *U* test, Kruskal-Wallis test and independent *t*-test (after testing for equality of variances with Levene's test) was used for analysis of factors influencing taste impairment. Multivariate analysis (binary logistic regression) was performed after proof of multicollinearity (cut-off value 0.7). For this hypothesis generating dataset, an a priori non-Bonferroni $\alpha \leq 0.05$ was considered significant.

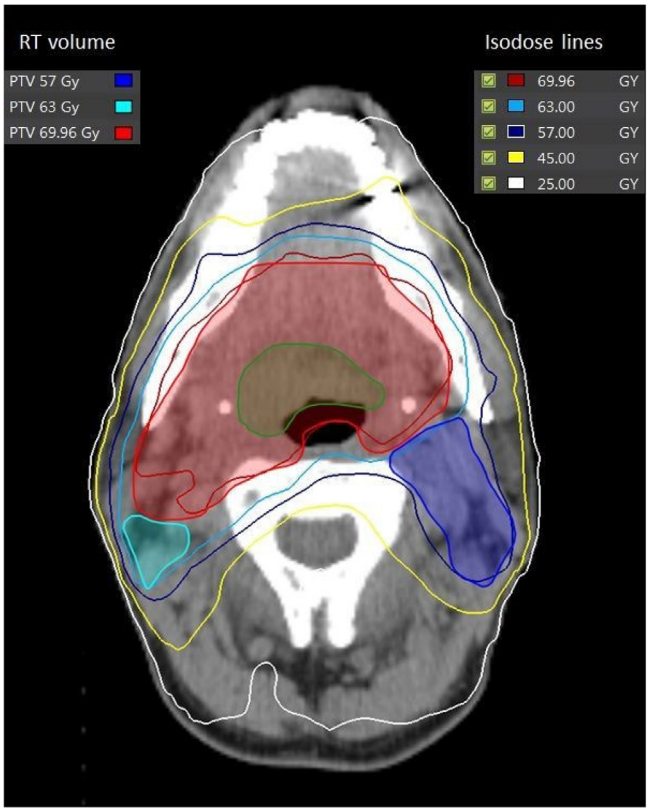

Fig. 1. Example of a typical intensity modulated radiotherapy treatment plan in a patient with T3 N2c base of tongue tumor (highlighted in green) receiving 69.96 Gy in 33 fractions. Especially the posterior 2/3 of the tongue receives high doses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

Three hundred twenty-six patients who completed 1214 MDASI taste questions were available for analysis with 101 patients with at least three assessments in following years. The taste item responses ranged from the second to the thirteenth year post-RT (12 – 158 months). Table 1 and Suppl. Table A show the patient characteristics regarding gender, age, race, tumor site, tumor/nodal stage and treatment-related factors. All patients had squamous cell carcinoma. The most common dose fractionation schemes were 66 Gy in 30 fractions (n = 162, 50%), followed by 69.96 Gy in 33 fractions (n = 116, 36%). Three patients stopped early with RT at 57.64, 58.0 and 59.4 Gy.

A total of 180 patients (55%) received chemotherapy. The most common concurrent chemotherapy regimen was weekly cisplatin followed by high dose cisplatin every third week and weekly carboplatin. Only one patient received a non-platinum-based concurrent chemotherapy with Docetaxel. Concurrent targeted therapy was administered in 14% of the patients (n = 45), usually with Cetuximab and in three cases with Vandetanib.

Mean and median MDASI taste score was 3.0 and 2.0 in the second year after RT, respectively, and markedly improved until year five from end of treatment. At the sixth year post-RT, taste recovery plateaued as shown on Table 2. The proportion of patients with moderate/severe taste impairment decreased from 31% (second year) to about 10% from the seventh year (Table 2). In the same time interval the proportion of patients without any taste changes increased from 26% (second year) to about 40%.

Most of the patients with initial no/mild taste impairment remained in this category (87%) in subsequent surveys (Table 3). Only 13% scored an increase in taste impairment to moderate/severe in further assessments, with the majority (73% of patients with further follow-up) returning to no/mild taste impairment on subsequent questionnaires. About 2/3 of patients with initial moderate/severe taste impairment improved during their follow-up to no/mild taste impairment, and then remained in this category (70% excluding patients with no further follow-up). The patients whose taste impairment worsened again afterwards to moderate/severe less frequently described no/mild taste impairment again (20% of patients with further follow-up).

To better understand the impairment of taste over time, only MDASI items from patients who reported taste in two consecutive years were analyzed in Table 4. A significant improvement in taste was found from the second to the third year ($p = 0.001$) and tended towards significance from the third to the fourth year ($p = 0.058$).

Uni- and multivariate analysis was conducted to determine the contribution of relevant clinicopathologic and treatment factors (sex, age, treatment site, T stage, N stage, high-dose clinical target volume (CTV1) dose, chemotherapy) on taste impairment. The time points were selected where the mean MDASI values for all patients became stable and at which >100 patients had taste assessments, which was in the sixth and the seventh year post-RT. Whereas in the sixth year from RT, the treatment site (BOT vs. tonsil cancer) ($p = 0.009$ in multivariate analysis) influenced the rate of moderate/severe taste impairment, it was the total dose ($p = 0.028$ in multivariate analysis) and age ($p = 0.036$ in multivariate analysis) in the seventh year (Suppl. Table B, C).

Although not a significant factor for taste impairment in the multivariate analysis in the sixth and seventh year from RT, there may be a distinct trend in taste recovery for the chemotherapy- and non-chemotherapy cohort (Suppl. Table D). While the MDASI taste item scores were comparable in the second and third year, as well as from the seventh year on, a significant difference could be found in the fifth ($p = 0.044$) and sixth year ($p = 0.018$) with lower taste alteration in the non-chemotherapy cohort and a trend towards significance in the fourth ($p = 0.058$) year after end of RT. However, this analysis was confounded by a higher CTV1 dose, higher T and N stage and more BOT cancer in the chemotherapy cohort (Suppl. Table E).

Table 1
Patient and treatment characteristics of the whole study cohort (n = 326 patients).

	n (%)‡
Sex	
Male	274 (84.0%)
Female	52 (16.0%)
Age at RT start [years]	
Mean (SD)	56.8 (8.8)
Median	56.0
Range	29–84
Race	
Caucasian	313 (97.9%)
Asian	3 (0.9%)
Black or African American	2 (0.6%)
American Indian or Alaska Native	2 (0.6%)
Primary tumor site	
Tonsil	179 (54.9%)
BOT	147 (45.1%)
Tumor stage	
T1	122 (37.4%)
T2	125 (38.3%)
T3	57 (17.5%)
T4	22 (6.7%)
Nodal stage	
N0	31 (9.5%)
N+	295 (90.5%)
CTV1 dose [Gy]	
Mean (SD)	67.8 (2.4)
Median	66.0
Range	57.64–72.5
Treatment fractions	
Mean (SD)	31.9 (2.6)
Median	30
Range	27–40
Chemotherapy	
Any kind	180 (55.2%)
Induction	114 (35.0%)
Concurrent	107 (32.8%)
Adjuvant	2 (0.6%)
Targeted therapy	
Concurrent	45 (13.8%)

‡ if not indicated otherwise; BOT: base of tongue, CTV1: high dose clinical target volume, n: number of patients, RT: radiotherapy, SD: standard deviation.

4. Discussion

In this study, it was demonstrated that long-term taste impairment after radio(chemo)therapy for OPC is reported by a large proportion of patients and that gradual improvement can continue years after treatment and even into survivorship. This study represents the largest patient cohort with assessments for taste specifically (not "senses" including taste and smell) after more than one year after IMRT/VMAT and additionally it is the only study with measurements at more than two different time points after two years (Table 5). Moreover, this cohort is relatively homogenous in that all patients were treated with uniform radiation techniques (IMRT/VMAT) to a single head and neck subsite.

Several investigators have studied the impact of radiation technique on taste impairment. Rathod et al. found a significant worse taste/smell in patients 6 months from 3D head and neck RT compared to IMRT [25]. Leung et al. also reported a significant worse taste/smell for 2D-RT, followed by 3D-RT and IMRT [26]. Pow et al. found lower taste impairment after 2D-RT compared to IMRT, but this was non-significant [27].

Table 2
Taste impairment measured with the MDASI questionnaire for the whole cohort of oropharyngeal cancer patients (n = 326). Mean and median MDASI taste scores and the number and percentage of patients with no, mild, moderate and severe symptoms are shown.

Year after RT	2nd year	3rd year	4th year	5th year	6th year	7th year	8th year	9th year	10th year
n	88	103	92	102	117	112	69	57	23
MDASI taste score									
Mean (SD)	3.0 (2.9)	2.6 (2.7)	2.5 (2.8)	1.9 (2.3)	1.6 (2.4)	1.5 (2.2)	1.7 (2.0)	1.5 (2.1)	1.8 (1.8)
Median	2.0	2.0	1.5	1.0	0.5	0.83	1.0	2.0	1.0
No symptoms	23 (26.1%)	26 (25.2%)	27 (29.3%)	38 (37.3%)	55 (47.0%)	49 (43.8%)	20 (29.0%)	24 (42.1%)	9 (39.1%)
Mild symptoms	38 (43.2%)	57 (55.3%)	46 (50.0%)	47 (46.1%)	47 (40.2%)	50 (44.6%)	44 (63.8%)	26 (45.6%)	12 (52.2%)
Mod. symptoms	13 (14.8%)	8 (7.8%)	10 (10.9%)	12 (11.8%)	9 (7.7%)	9 (8.0%)	1 (1.4%)	4 (7.0%)	2 (8.7%)
Severe symptoms	14 (15.9%)	12 (11.7%)	9 (9.8%)	5 (4.9%)	6 (5.1%)	4 (3.6%)	4 (5.8%)	3 (5.3%)	0 (0.0%)

Mod: moderate, n: number of patients, RT: radiotherapy, SD: standard deviation.

Table 3
Flowchart showing the change in taste impairment of all 326 patients over the whole study period (12 – 158 months) measured with the MDASI questionnaire. The majority of patients with initial no/mild taste impairment remained in this category, whereas most of the patients with initial moderate/severe taste impairment improved to no/mild symptoms in subsequent assessments. Patients were considered as stable if their taste impairment was graded in the same category (no/mild or moderate/severe) for at least two subsequent taste assessments without any further change.

Taste impairment at first MDASI measurement	**Subsequent dynamic in taste impairment (1-5 MDASI assessments per patient)**				
No/mild TI: n=254 (77.9%)	Increase to moderate/severe TI: n=32 (12.6%)	Decrease to no/mild TI: n=16 (50.0%)	Increase to moderate/severe TI: n=2 (12.5%)	Decrease to no/mild TI: n=1 (50.0%)	NA: n=1 (100%)
				NA: n=1 (50.0%)	
			Stable at no/mild TI: n=6 (37.5%)		
			NA: n=8 (50.0%)		
		Stable at moderate/severe: n=6 (18.7%)			
		NA: n=10 (31.3%)			
	Stable at no/mild: n=222 (87.4%)				
Moderate/severe TI: n=72 (22.1%)	Decrease to no/mild TI: n=49 (68.1%)	Increase to moderate/severe TI: n=11 (22.4%)	Decrease to no/mild TI: n=1 (9.1%)	Stable at no/mild TI: n=1 (100%)	
			Stable at moderate/severe TI: n=4 (36.4%)		
			NA: n=6 (54.5%)		
		Stable at no/mild TI: n=26 (53.1%)			
		NA: n=12 (24.5%)			
	Stable at moderate/severe TI: n=23 (31.9%)				

n: number of patients, NA: not further assessed / no further follow-up available, TI: taste impairment.

Table 4
Temporal change in taste measured with the MDASI questionnaire in oropharyngeal cancer patients post-RT. Only patients with consecutive taste assessments in subsequent years post-RT were included for analysis of taste between the respective years.

2nd year		3rd year		4th year		5th year		6th year		7th year		8th year		9th year		10th year	
n	66		48		46		50		66		40		34		11		
MDASI taste score																	
Mean	3.3	2.4	3.0	2.4	2.5	2.0	1.9	2.1	1.5	1.5	1.5	1.5	2.0	1.8	1.0	2.0	
(SD)	(3.0)	(2.6)	(2.9)	(2.9)	(3.0)	(2.5)	(2.3)	(2.9)	(2.1)	(2.3)	(1.9)	(1.7)	(2.5)	(2.4)	(1.3)	(2.2)	
Median	3.0	2.0	2.0	2.0	1.5	1.0	1.0	1.0	0.5	0.5	1.0	1.0	1.25	1.0	0.0	2.0	
Mean absolute change (SD)	-0.9 (2.2) p=0.001		-0.5 (2.1) p=0.058		-0.5 (2.2) p=0.350		+0.3 (2.5) p=0.750		+/-0.0 (1.5) p=0.978		-0.1 (1.2) p=0.766		-0.1 (1.4) p=0.691		+1.0 (2.2) p=0.233		

n: number of patients, SD: standard deviation.

Comparison of these results to other studies is difficult, as only two other studies detailed in Table 5 included OPC patients only [22,23]. No study has compared radiation-induced taste impairment between patients grouped into different head and neck treatment sites (i.e. oral cavity, nasopharynx, oropharynx, hypopharynx, larynx). For example, one could expect that patients irradiated for an oral cavity tumor will exhibit more severe taste impairment due to the higher dose to the taste buds of the tongue, compared to hypopharynx cancer patients. Furthermore, there might be a different trajectory of recovery among patients receiving systemic therapy as shown in our study.

In addition, comparisons are difficult between studies due to the differing instruments used to assess taste impairment. Only a superficial comparison can be done across these different studies, and our results can be directly compared only within our center, as the MDASI is neary exclusively used at the MD Anderson Cancer Center.

Table 5
Overview of studies with taste assessments in HNC patients ≥ 1 year after external beam RT (no re-irradiation) using advanced techniques like IMRT only, sorted by type of assessment and time of publication.

Author, year of publication	n[‡]	Tumor site and stage	RT technique	Surgery[†]	CT / TT	Time point of taste assessment (range)	QoL questionnaire / subcategory (Scale: best-worst)	Taste results
Chen, 2019 [32]	88	HNC I-IV (OC, NP, OP, HP, L, Others)	IMRT	43%	78%	BL, Median 27 m* (12–114)	EORTC H&N35 Taste (0 – 100)	BL: 10, ≥1y post-RT: 20 (unclear if mean or median) 30.7% with long-term TI; only operation method (partial vs. total glossectomy) sign. on multivariate analysis Primary RT/RCT patients only: mean dose < 50 Gy/≥50 Gy to OC: 14.3%/28.3% with TI Primary RCT only: mean dose < 50 Gy/≥50 Gy to OC: 9.1% / 40.0% with TI
Janssens, 2016 [31]	269	L T2-4 N0-3 (N stage from Janssens 2012 [33])	NA (RT 2001–2008)	NA	0%	BL, EoT, 6 m, 12 m, 24 m post-BL	EORTC H&N35 Senses (0 – 100)	Mean, BL: 8, EoT: 47, 6 m: 22, 12 m: 19, 24 m: 18 (all estimates from Figure). At 2y, 18% reported "quite a bit" or "very much" changes in senses (ARCON trial, accelerated RT with 1:1 carbogen + nicotinamide)
Tribius, 2015 [34]	111	HNC TX-4 N0-3 (OP, OC, HP/L, NP, Nose, CUP)	IMRT	70%	53%	BL, EoT, 6-8 w, 6 m, 12 m post-RT	EORTC H&N35 Senses (0 – 100)	Mean, BL: 21, EoT: 61, 6-8 w: 45, 6 m: 40, 12 m: 35
Metreau, 2014 [35]	47	HNC III-IV (L, HP/L)	NA (RT 2000–2008)	55%	45%	Mean 46.7 m (CRT, 12–106) – 48.5 m* (TL + RT, 12–102), (all at least 1 y after TL or CRT)	EORTC H&N35 Senses (0 – 100)	Mean, TL + RT: 51.9, CRT: 23.0 Median, TL + RT: 58.3, CRT: 16.6
Rathod, 2013 [25] (Gupta, 2012 [36])	32 (60 incl. 3D-RT)	HNC I-IV (OP, HP, L)	IMRT	0%	91%	BL (n = 29), 3 m (n = 26), 6 m (n = 26), 12 m (n = 21), 18 m (n = 17), 24 m (n = 18) post-RT	EORTC H&N35 Senses (0 – 100)	Mean, BL: 9, 3 m: 21, 6 m: 13, 12 m: 12, 18 m: 11, 24 m: 13
Wan Leung, 2011 [26]	142 (640 incl. 2D-/3D-RT)	HNC I-IV (NP, OC, HP, OP, L)	IMRT	48%	65%	Median 3.1 y (2.0–6.5) post-tx	EORTC H&N35 Senses (0 – 100)	Mean: 20.6
Pow, 2006 [27]	24 (45 incl. 2D-RT)	NP II	IMRT	NA	0%	BL, 2 m, 6 m, 12 m post-RT	EORTC H&N35 Senses (0 – 100)	Mean, BL: 6.9, 2 m: 42.4, 6 m: 27.1, 12 m: 20.1
Sakthivel, 2017 [37]	26 (36 incl. non-RT)	OC T1-2 N0-2	NA (RT 2011–2015)	100%	NA	Mean 45 m, median 34 m* (14–65 m for all 36 pts)	UW-QoL Taste (100 – 0)	Percentage, 0: 0%, 30: 8%, 70: 88%, 100: 4% Mean: 68.1
Chen, 2014 [38]	50	HNC T0-4 (OP, OC, NP, L/HP, CUP)	IMRT	34% PORT, 38% ND	CCT: 40%	3y, 5y post-RT	UW-QoL Taste (100 – 0)	Mean, 3y: 84.0, 5y: 87.7 Taste (most) food normally: Percentage at 3y: 88%, 5y: 92%
O'Neill, 2011 [21]	143	HNC I-IV, 5 recurrences (OP, L, OC, SG, HP, Thyroid, Sinus)	IMRT	54%	68%	BL (n = 69), d1-100, 101–200, 201–300, 301–400, 401–500, 501–600, 601–700, 701–800 (n = 13–63 per TP and PG dose ≥ 26 Gy or < 26 Gy; n = 108 with FU ≥ 6 m from tx start)	UW-QoL Taste (100 – 0)	Patients with lowest mean PG dose ≥26 Gy/<26 Gy (all estimates from Figure), mean: d1-100: 80/83, 101–200: 27/38, 201–300: 45/54, 301–400: 50/60, 401–500: 53/73, 501–600: 58/69, 601–700: 68/69, 701–800: 63/70
Williamson, 2011 [39]	41	L T1-4	NA (RT 2003–2010)	27%	NA	Median 18.5 m (2–55) post-tx	UW-QoL Taste (100 – 0)	Mean: 78.9 Median, T ≤ 2/T > 2: 91.7/61.3, N0/N+ 86.0/41.5, RT/combined tx with surgery, CT±RT/ RCT: 90.3/71.1/50.0
Rampling, 2003 [40]	92	HNC NA (53% III-IV) (L,P, Others)	NA	NA	NA	BL (n = 27), 3–12 m (n = 23), >1y post-tx (n = 42)	UW-QoL Taste (100 – 0)	Mean, BL: 88, <1y: 70, >1y: 79 (all estimates from Figure)
Eraj, 2017 [23]	79	OP T1-4 N0-3	96% IMRT, 4% unilateral neck RT	15%	61%	Median 46 m (6–117) post-RT	MDASI-HN Taste (0 – 10)	Mean: 2.81 Moderate/severe TI (score ≥ 5), All: 29%, BOT 33%, Tonsil 22%, T1/2: 21%, T3/4: 41%, CCT: 39%, RT only: 18% Severe TI (score ≥ 7), All: 22%, BOT 22%, Tonsil: 19%, T1/2: 11%, T3/4: 38%, CCT: 34%, RT only: 8%

Table 5 (*continued*)

Author, year of publication	n‡	Tumor site and stage	RT technique	Surgery†	CT / TT	Time point of taste assessment (range)	QoL questionnaire / subcategory (Scale: best-worst)	Taste results
Gunn, 2015 [22]	139	Tonsil T1-2 N0-2b	IMRT	24%	38%	>24 m FU*	MDASI-HN Taste (0 – 10)	Mean, All: 1.58 Bilateral neck RT (n = 30)/RCT (n = 38): mean: 1.90/1.68, mild TI (score < 5): 86%/90%, moderate TI (score 5–6): 7%/5%, severe TI (score 7–10): 7%/5% Unilateral neck RT (n = 56)/RCT(n = 15): mean: 1.55/0.73, mild TI :86%/100%, moderate TI: 5%/0%, severe TI: 5%/0%
Ganzer, 2015 [41]	10	HNC III-IV (OC, OP, L, L/OP)	IMRT	50%	100%	Mean 72.5 m (37–132) post-RCT	Vanderbilt Head and Neck Symptom Survey 2.0 Taste (0 – 10)	Altered taste, mean: 2.60 Less desire to eat, mean: 0.80 Altered foods chosen, mean: 2.70 Decreased food eaten, mean: 0.30
Patterson, 2014 [42]	18	NP I-IV	IMRT	NA	72%	Median 24 m (6–42) post-RT	OHRQoL Dysgeusia (1 – 4)	Percentage: 1: 22%, 2: 17%, 3: 39%, 4: 22%
Van Gestel, 2011 [43]	78	HNC I-IV (OP, OC, NP, L, SG, Sinus, HP, CUP, Nose, EAC)	IMRT	45%	47%	Median 19 m (0–52) from RT start	RTOG Taste loss (yes/no)	Percentage with taste loss: 14%

‡ Whole patient cohort in brackets; †Any tumor-associated head neck surgery, pre- or post-RT; *Not mentioned if from start or end of treatment. BL: baseline, BOT: base of tongue, CCT: concurrent chemotherapy, CRT: concurrent chemoradiotherapy, CUP: cancer of unknown primacy, d: day, EAC: external auditory canal, EoT: end of treatment, FU: follow-up, fx: fraction, HNC: head and neck cancer, HP: hypopharynx, IMRT: intensity modulated radiotherapy, incl.: including, L: larynx, n: number of patients, N: nodal stage, NA: not assessed / not specified, ND: neck dissection, NP: nasopharynx, OC: oral cavity, OP: oropharynx, PORT: postoperative radiotherapy, QoL: quality of life, RCT: radiochemotherapy, RT: radiotherapy, SG: salivary gland, T: tumor stage, TL: total laryngectomy, TT: targeted therapy, TI: taste impairment, TP: time point, tx: treatment, vs: versus, y: year.

Three studies have assessed taste impairment at two or more time points > 1 year after RT. The largest series found a decrease in the so-called "senses" category (taste and smell) of the EORTC H&N35 questionnaire [28]. In parallel, the percentage of patients reporting a "senses" score of >10 points above their baseline value before RT, decreased from 60% 1 year after RT to 48% after 5 years. A second study also using the EORTC H&N35 questionnaire in 32 HNC patients found a relatively stable alteration in "senses" [25]. The reason for these extremely low and stable values compared to other studies remains unclear. The third study employed the UW-QoL questionnaire and grouped HNC patients, dependent on the time point when the taste sensation after RT was reported, into 100 day time interval categories to show a continuous improvement in taste impairment up to 2 years post-treatment [21].

Riva et al. have published the only study (to our knowledge) with objective taste measurements >1 year after RT [29]. Similar to this study it was found that even after a follow-up of 2–10 years (median 4.9), the majority of the 30 nasopharyngeal cancer (NPC) patients still suffered from taste changes (53% vs. 7% in "healthy" control group). Although all four taste sensations were impaired in the taste strips test, it was only significant for bitter and sour compared to the control group. Despite the strength of this study with a healthy control group and objective taste assessment of the different taste sensations, the impact of chemotherapy (i.e. TPF) and varying radiation techniques on taste impairment hampers comparison.

This study has some limitations. The patients had no baseline MDASI taste scores available prior to cancer-related treatment. Nevertheless, from previous studies from this institution using the same questionnaire, and from publications of other centers that used different subjective quality of life (QoL) assessment tools, it is known that taste is only slightly affected before treatment [20,30,31]. Rosenthal et al. analyzed different symptoms with the MDASI questionnaire in 149 HNC patients undergoing RT/RCT, and the mean MDASI taste score was 0.75/0.93 at baseline, respectively [20]. Sio et al. found a baseline taste score of 1.1 for 81 IMRT and IMPT OPC patients before treatment [30]. Assuming that the patients in this study had similar baseline MDASI taste scores, taste still did not return to baseline values even 10 years after completion of therapy, in spite of improvement over time. Although the correlation between acute and late taste changes would have been interesting, this could not be analyzed within this cohort, as no MDASI measurements have been obtained during RT. Another limitation is that no patients reported taste every year in follow-up, which limited longitudinal analysis. Nevertheless, over 100 patients in this study had at least three taste assessments in consecutive years from RT. It is unknown which patients declined study participation or partially participated in the surveys. This may lead to an over-representation of either patients with severe late toxicities, who were glad to be asked for their problems, or an under-representation of those with less severe toxicity who were thankful for their successful treatment and therefore more likely willing to participate. Furthermore, the patients responses collected at a routine follow-up or per telephone interview may be different. Also, the MDASI, like other QoL questionnaires, does not discriminate between the different taste qualities, but as taste is the result of the interplay of all five taste qualities together, the questionnaire represents a good global estimate of the patients burden due to taste changes. Furthermore, patients may acclimate to their taste level over time and thus no longer perceive taste impairment with the same intensity. While we haven't analyzed in detail the dosimetric influence on taste changes for IMRT patients in this manuscript, this is planned as the next step.

5. Conclusions

Radiation-induced taste impairment can significantly vary, and may improve over time, but becomes relatively stable from year 5 post-RT. Direct characterization of the RT-related oral/nutritional sequelae and the calculation of any normal tissue complication probability should account for time-dependent recovery. To our knowledge, this represents the largest series of sequential taste assessments, and thus is a benchmark for future prospective and multi-site efforts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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