Gustatory Function Following Radiotherapy to the Head and Neck

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Author's Declaration

I declare as the sole author of this thesis that the work presented is my own personal research conducted whilst a research fellow at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research between December 2017 and September 2020. Tables, figures and images are my own work unless acknowledged otherwise.

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Abstract

An intact sense of taste provides pleasure, supports sustenance and alerts the body to potential toxins. Patients with head and neck cancer (HNC) who undergo radiotherapy (RT) are at high risk of developing acute and late taste dysfunction leading to poor oral intake, reduced nutritional status and reduced quality of life (QoL). Technical advances in the delivery of RT and the introduction of intensity-modulated proton therapy (IMPT) offer the opportunity to develop taste preserving strategies by reducing the dose delivered to the gustatory organs-at-risk (OAR). The aim of this thesis is to study the temporal loss and recovery of taste dysfunction following RT to the head and neck.

Chapter 2 is a systematic review and prevalence meta-analysis of 31 studies reporting gustatory outcomes following RT to the head and neck. This chapter confirmed that acute taste dysfunction is common (seen in as many as 96% of patients) and important post RT but also highlights the paucity of high-quality research in this area. Chapter 3 compared patient reported outcomes (PROs) in bilateral versus unilateral RT to the head and neck and explored the relationship between patient reported and clinician reported measures of taste dysfunction, with the latter showing only a 37% sensitivity for the former. Chapter 4 analysed data from a large multi-centre longitudinal study with patient reported gustatory outcomes from over 5000 patients at baseline, 4 months (m) and 12m following diagnosis and treatment for HNC. In those treated with RT or chemo-RT, tumour site was strongly associated with 4m taste dysfunction (oropharynx vs others OR 3.15, 95% CI from 2.53 to 3.91).

These chapters on retrospectively analysed cohorts providing PROs were then supplemented with data collected in two novel studies at the Royal Marsden Hospital (RMH). Chapter 5 was a cross-sectional study of patients 12m following completion of radiation. Chapter 6 was a prospective study with outcomes collected at baseline, end of treatment, 2m, 6m and 12m. Both of these chapters showed that dose to the anterior two-thirds of the tongue was higher in those with taste dysfunction (mean 43.1 Gy vs 32.0 Gy, p=0.013) and that those receiving lower doses were much less likely to experience dysfunction (0-20 Gy 42.9% PRTD vs 20-30 Gy 77.8%).

Publications from this thesis

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List of Abbreviations

2D-RT	2-dimensional radiotherapy
3D-RT	3-dimenstional radiotherapy
ATP	Adenosine triphosphate
BMI	Body mass index
CCK	Cholecystokinin
CCR	Committee for Clinical Research
CRT	Chemo-radiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CBCT	Cone-beam CT
CiTAS	Chemotherapy-induced Taste Alteration Survey
CRO	Clinician reported outcome
CtE	Commissioning through evaluation
CVP	Circumvallate papillae
CTSU	Clinical Trial and Statistical Unit
DSC	Dice similarity coefficient
DVH	Dose volume histogram
EGM	Electrogustometry
EORTC-HNQ	European Organisation for Research and Treatment of Cancer Head and Neck Questionnaire
EORTC-QLQC30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQD2	Equivalent dose in 2 Gy fraction
FilP	Filiform papillae
FolP	Foliate papillae
FFP	Fungiform papillae
FN	False negative
FP	False positive
FPD	Fungiform papillae density
G3+PRTD	Grade 3 or worse patient reported taste dysfunction
G3+PRSD	Grade 3 or worse patient reported smell dysfunction
G3+PRX	Grade 3 or worse patient reported xerostomia
GHS	Global health status
GPCRs	G protein-coupled receptors
Gy	Gray

HEI	Higher Educational Institute
HN5000	Head and Neck 5000
HNC	Head and Neck Cancer
HPC	Hypopharyngeal carcinoma
HPV	Human papillomavirus
ICR	Institute of Cancer Research
IMRT	Intensity-modulated radiotherapy
IMPT	Intensity-modulated proton therapy
LC	Laryngeal carcinoma
LENT/SOMA	Late Effects of Normal Tissue – Subjective, Objective, Management and Analytic
LCFA	Long chain fatty acid
m	Months
NC	Nasal cavity
NHANES	National Health and Nutrition Examination Survey
NTCP	Normal tissue complication probability
NPC	Nasopharyngeal carcinoma
NPY	Neuropeptide Y
OAR	Organs at risk
OC	Oral Cavity
OP	Oropharynx
OPC	Oropharyngeal carcinoma
PBT	Proton beam therapy
PORT	Post-operative radiotherapy
PROs	Patient reported outcomes
PROM	Patient reported outcome measure
PROP	6-n-propylthiouracil
PRTD	Patient-reported taste dysfunction
PTV	Planning target volume
QoL	Quality of life
RCT	Randomised controlled trials
ROI	Region of interest
RT	Radiotherapy
RMH	Royal Marsden Hospital
SCC	Squamous cell carcinoma

SCT	Sinus cavity tumours
SGT	Salivary gland tumours
Shh	Sonic hedgehog
STTA	Subjective Total Taste Acuity
TAS1R1	Taste receptor type 1 member 1
TAS1R2	Taste receptor type 1 member 2
TAS1R3	Taste receptor type 1 member 3
TBCs	Taste bud cells
TC	Thyroid cancer
TN	True negative
TP	True positive
TPD	Taste pore density
UK	United Kingdom
UP	Unknown primary
UWQOL	University of Washington Quality of Life
VAS	Visual analogue scale
VMAT	Volumetric arc therapy

Glossary of Terms

Gustatory – field	encompasses anatomical radiation field that includes any portion of the oral cavity and/or the whole tongue
Gustatory – ROI	encompasses any region of the gustatory field that was defined for research purposes
Gustatory – OAR	defines a specific anatomical target that a dose constraint could be applied to

Chapter 1 – Background

1.1 Introduction

Within the United States and across Europe, head and neck cancer (HNC) comprises 3-4% of all cancer incidence (1,2). More than 550,000 cases are diagnosed globally each year and there are approximately 380,000 deaths annually (3). Despite public health efforts to reduce smoking and alcohol consumption, amongst the United Kingdom (UK) population, the incidence of HNC continues to rise. Projected incidence between 2014 and 2035, is set to rise by 33% (2), in part reflecting a significant increase in the proportion of Human Papilloma Virus (HPV) positive squamous cell carcinoma (SCC) of the oropharynx (OP).

Radical treatment for HNC includes surgery, radiotherapy (RT), chemotherapy or often a multi-modality approach. Technical advances in surgical technique, the use of intensity-modulated radiotherapy (IMRT) and the addition of concomitant chemotherapy have all improved survival outcomes for HNC (4). However, radical treatment continues to carry the burden of late toxicity and morbidity.

Treatment-related taste dysfunction is almost universally reported during and after completion of RT for HNC (5) and, in a proportion of patients, is enduring (6,7).

Recent advances in the delivery of RT using IMRT and proton beam therapy (PBT), for the first time offers an exciting opportunity to study in more detail, the relationship between dose to the gustatory organs-at-risk (OAR) and taste dysfunction. With this, development and implementation of a dose constraint for the preservation of taste may for the first time be feasible.

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1.2 Gustatory Function

1.2.1 Anatomy

The human tongue is a large muscular organ that sits within the oral cavity (OC) and upper portion of the pharynx. It is a highly mobile structure essential for mastication, articulation of speech and serves as the primary organ for gustatory function and taste sensation. The left and right side of the tongue is divided by the median sulcus, apparent as vertical septum of fibrous tissue. A v-shaped groove termed the sulcus terminalis defines the border between the posterior third within the pharynx and anterior two thirds of the tongue within the OC (see figure 1-1).

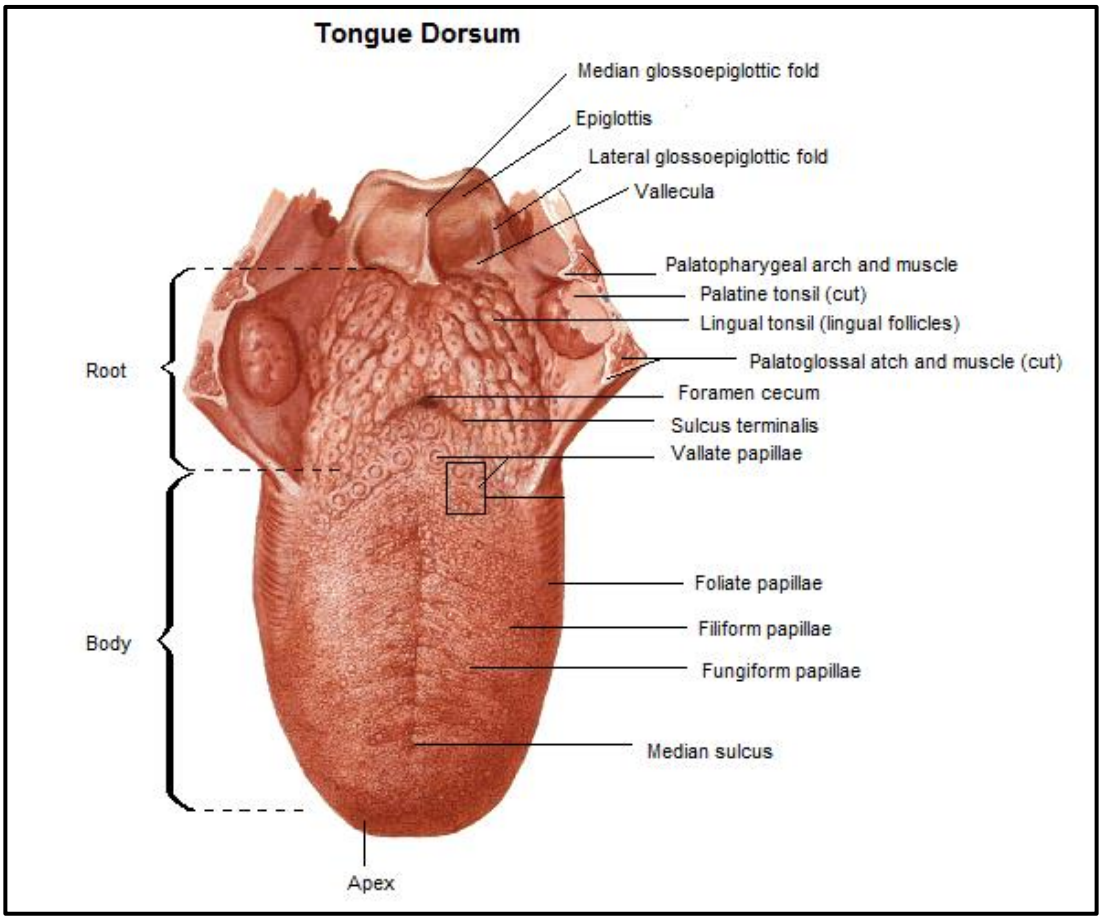


Figure 1-1: Anatomy of the dorsum of the tongue (8)

The motor innervation of the tongue is supplied by the Hypoglossal nerve (cranial nerve XII), except for the palatoglossus muscle which is innervated by the pharyngeal branch of the Vagus nerve (cranial nerve X).

Both sensory and taste innervation of the posterior third of the tongue are supplied by the Glossopharyngeal nerve (cranial nerve IX). Even more posteriorly the mucosa adjacent to the epiglottis is supplied by the superior laryngeal branch of the Vagus nerve (cranial nerve X). Sensory innervation of the anterior two thirds of the tongue is via lingual branch of the mandibular branch (V3) of the Trigeminal nerve (cranial nerve V). Taste sensation from the anterior two thirds of the tongue is innervated by the chorda tympani branch of the Facial nerve (cranial nerve VII) (9).

The dorsum of the tongue is lined with stratified squamous epithelial mucosa. Chemosensory perception of taste is mediated by taste buds which are predominantly found on the mucosal surface of tongue but are also present throughout the OC, pharynx and laryngeal surfaces (10). On the tongue itself, taste buds are contained within the lingual papillae (see figure 1-2). The anterior two thirds of the tongue supports numerous fungiform papillae (FFP) each containing one or more taste buds within the papillae apex. The foliate papillae (FolP) are located on the lateral aspect of the tongue between the junction of the OC and pharynx. Circumvallate papillae (CVP) are seen as large cylindrical projections that form a V-shaped line just adjacent to the sulcus terminalis. The lingual papillae are embedded amongst numerous filiform papillae (FilP) which do not detect taste but serve to create a rough, high friction surface that provides mechanosensory information for tactile motion of food within the OC (9,11).

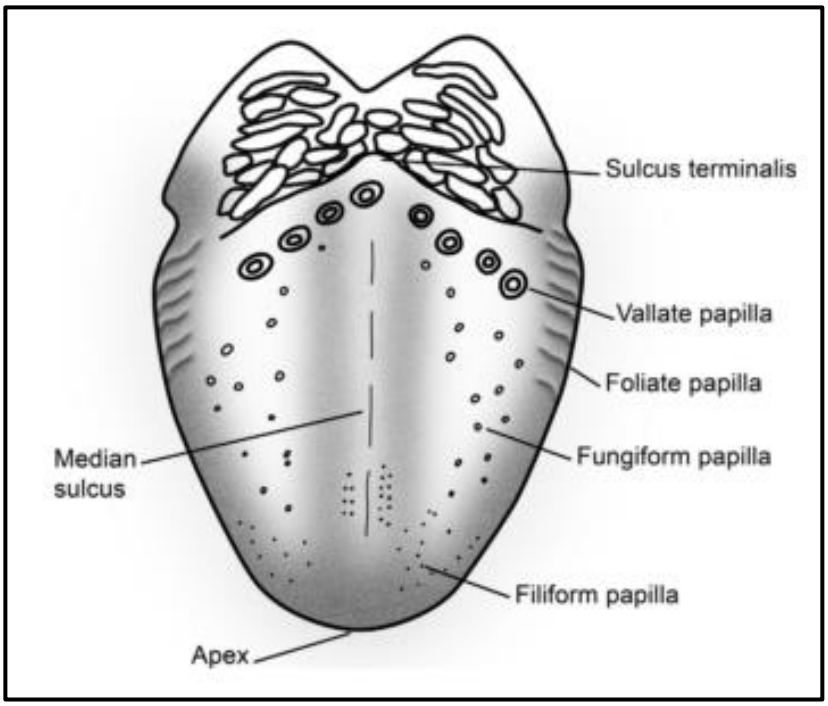


Figure 1-2: Diagram showing location and distribution of the lingual papillae (12)

1.2.2 Gustatory Physiology

1.2.2.1 Taste

From an evolutionary perspective, an intact sense of taste has been paramount for survival. The ability to distinguish sweetness from bitterness, is what allows humans to distinguish a source of calorific sustenance from a potential toxin or poison. This remains an important function of the gustatory system but as society has evolved the human desire for high fat and high sugar foods has prevailed and led to a global obesity epidemic with widespread secondary health implications. The hormonal and neural mechanisms that reinforce excessive overconsumption of food are complex but it is well established that the taste cells at the periphery of the gustatory system play a significant role (13,14).

Traditionally, the four qualities of basic taste are sweet, salty, sour and bitter. In recent decades a fifth modality called umami has been formally recognised. The term describes the savoury taste sensation stimulated by amino acids such as glutamate and aspartate which can be found in a variety of foods including meat, fish and

vegetables (15). There is also growing interest in a sixth modality specific to the detection of fats which may help begin to address the human predilection for fatty foods (16). Lipid content is known to be detected by tactile and olfactory cues however rodent model studies suggest there could be specific long chain fatty acid (LCFA) receptors within the circumvallate papillae that contribute to the oro-sensory perception of dietary fats (17).

Each taste bud contains approximately 50-100 taste bud cells (TBCs) arranged in a structure likened to a bulb of garlic with a taste pore at the apex allowing contact with chemical stimuli (see figure 1-3). Unlike olfactory cells which have a neurogenic lineage, TBCs are epithelial in origin. Morphologically there are three distinct types of taste cell; type I, type II, type III however, functionally there are at least five, which detect sweet, sour, salty, bitter and umami (18).

For decades there was a popular misconception that TBCs were distributed in a way that meant certain areas of the tongue were responsible for detecting certain qualities of taste. This taste map theory has been widely disproven, and it is known that regardless of anatomical location, all taste buds contain all types of TBC, with the ability to detect all basic tastes.

Type I cells represent 50% of all taste cells and are thought to provide structural and functional support. Type II cells represent a further 30% of taste cells and are often referred to as receptor cells. They express G protein-coupled receptors (GPCRs) which identify chemosensory stimuli for sweet, umami and bitter taste. More specifically sweet and umami, are detected by 3 receptors collectively named type 1 taste receptors. Taste receptor type 1 member 1 (TAS1R1) and taste receptor type 1 member 3 (TAS1R3) respond to umami stimuli. Taste receptor type 1 member 2 (TAS1R2) and TAS1R3 respond to sweet stimuli. Bitter taste is detected by a larger family of receptors known collectively as type 2 taste receptors. Type II taste cells either express taste receptor type 1 or taste receptor type 2 GPCRs although each taste bud will contain multiple type II cells allowing response to a spectrum of taste stimuli. Type III cells represent up to 20% of taste cells and detect sour taste through ion gated channels. The cells that detect salt are yet to be defined and is an area of ongoing research (13,19) (see figure 1-3).

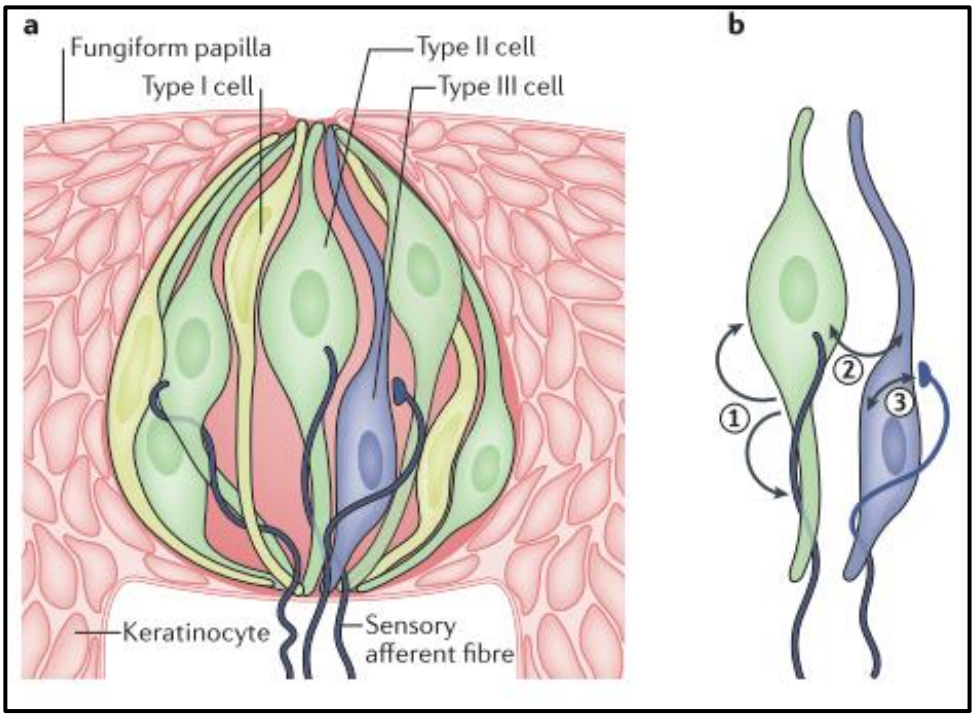


Figure 1-3: Taste cells within taste bud (19)

Taste receptors form synapses with afferent fibres which relay sensory information to the primary gustatory cortex within the insula, via the nucleus tractus solitarius in the brainstem. Communication between taste cells and their afferent fibres is through release of adenosine triphosphate (ATP) and a number of other identified neurotransmitters (13,19). Communication between neighbouring taste cells is also made possible through the release of locally produced hormones and neuropeptides such as cholecystokinin (CKK) and neuropeptide Y (NPY) which through autocrine and paracrine pathways modulate the intensity of taste perception (20).

Mammalian taste bud cells have a limited life span and throughout human life undergo continuous renewal. The majority of taste cell pre-cursors are found in the epithelial basal layer surrounding the taste bud and during differentiation, migrate in to replenish the taste bud. Differentiation of basal progenitors into mature TBCs is regulated by and reliant upon Sonic hedgehog (Shh) signalling centres (21). In the 1960's, the average taste cell life span was shown to be 250 $\pm$ 50 hours (8-12.5 days) (22). More recently, using EdU-labeling to track taste cell turnover in mice, it has since been shown that Type I, II and III cells have varied life spans. The average half-life of a type

II taste cell was shown to be 8 days, versus a much longer half-life of 22 days for type III cells (23).

1.2.2.2 Smell

Olfactory function in humans is incredibly sophisticated. A recent paper attempting to validate the olfactory range, concluded that conservatively, humans have the capacity to discriminate over a trillion olfactory stimuli.

The olfactory mucosa is a small region of neuroepithelial cells found in the middle and superior turbinates and upper nasal septum (24). Each nasal cavity (NC) contains between 6-10 million chemoreceptor cells which at the mucosal periphery have numerous cilia that bind to odorant particles. Neuronal axons pass through the cribriform plate and collectively form the Olfactory nerve (cranial nerve I), terminating in the olfactory bulb. Central processing is within the olfactory cortex.

Neurogenesis is rare in the adult brain. However, one of the few locations where this has been demonstrated to occur is within the olfactory system. A novel study in 2012 used a carbon dating technique to estimate the age of olfactory neurons in cadavers. The research was able to show evidence of post-natal neurogenesis in the dentate gyrus that maintains olfactory neuronal cell population throughout adult life (25).

1.2.3 Gustatory Dysfunction

Gustatory dysfunction is not uncommon. Patients tend to report reduced sense of taste but often the underlying aetiology is related to impaired olfactory function. Results from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES), which surveyed over 3600 people, published the prevalence of self-reported smell alteration and taste alteration as 23% and 19% respectively. Prevalence increased with age and was highest in those >80 years. After controlling for confounding factors the strongest independent risk factor was self-reported xerostomia (26). An earlier retrospective study by the Monell-Jefferson Taste and Smell Clinic specifically looked at the prevalence of complete ageusia (complete loss of taste) or severe generalised hypogeusia (diminished taste across all gustatory qualities) in their chemosensory

clinic population. Only 10 patients, representing 0.85% of their study population were found to have either complete ageusia or severe generalised hypogeusia compared with 32% of patients in this same population demonstrating severe olfactory loss (27).

Gustatory function can be measured using both objective and subjective methods. Objective methods often use chemosensory testing that determine the concentration that a taste stimulus can be detected (detection threshold) or the lowest concentration at which a particular taste quality can be correctly identified (recognition threshold). Electrogustometry (EGM) involves delivering electrical stimuli with ascending amplitude and documenting the threshold at which participants can detect any sensation of taste (28). Subjective methods usually involve patient reported outcomes (PROs) using survey methods though there are currently no validated surveys that are specifically designed to assess dysgeusia in cancer patients.

As described previously, FFP are small mushroom-like lingual papillae that cover the surface epithelium of the anterior two thirds of the tongue. Each papilla contains one or more taste buds which in turn contain numerous taste receptor cells (see figure 1-4). Due to ease of accessibility, they have often been the focus of taste research. The number and distribution of FFP varies widely across the population. This was first demonstrated in 1988 in a small study where 18 cadaveric tongues were analysed using video-microscopy to assess FFP and taste pore density (TPD) (29). A subsequent study was able to show that people who have high fungiform papillae density (FPD) also have higher numbers of taste pores. Furthermore those with higher FPD reported higher taste intensity ratings for sucrose, salt (NaCl) and 6-n-propylthiouracil (PROP) (30).

Following these early studies, the intuitive hypothesis was that people who have a high FPD have superior taste function and that FPD is a reasonable marker for TPD. In the decades that followed a number of studies reported a positive relationship between FPD and taste sensitivity to PROP (31,32) however a larger study with more than 2000 participants was unable to demonstrate this, nor any association between FPD and taste sensitivity to basic taste qualities of sweet, sour salty and bitter (33). A recent publication extensively reviewed the literature in this field and concluded that no linear relationship between FPD and taste sensitivity across any modality could be

found (34). This is likely due to the complexity of chemosensory physiology; considerable variability in FPD across the population; doubts regarding the suitability of FPD as a surrogate for TPD and FFP functionality and the varied methodology and equipment used both for FPD quantification and for objective gustatory testing.

The quantification of FPD usually involves staining the tongue, or region of interest with a blue colourant, most often household blue food colouring. FilP adsorb the blue colourant in contrast to the FFP thereby revealing the FFP as pink spots on a blue background (see figure 1-4). The distribution of FFP varies considerably across the tongue. Currently the most reliable method to estimate the total number of FFP is to analyse a small region 1cm anterior to the tongue tip in the midline. This is on the basis that studies have shown this to be the highest correlate of total FFP count (35).

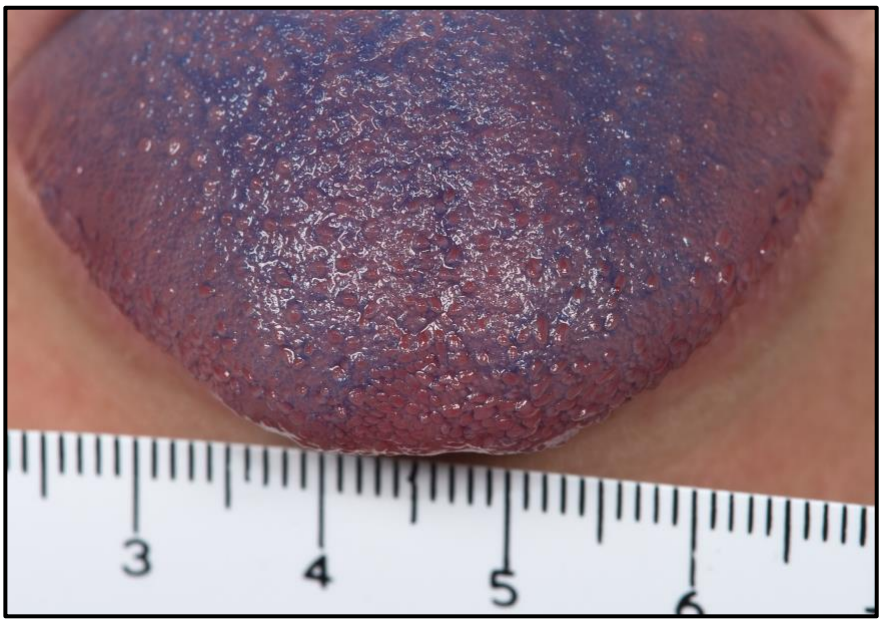


Figure 1-4: High resolution digital photograph of the anterior portion of the tongue. The tongue has been stained blue using household food colouring which highlights the large pink FFP in contrast to the small blue FilP

Traditionally the FPD was counted manually using either filming techniques (video-microscopy, contact endoscopy, confocal laser scanning microscopy), or magnified images (digital photography, digital microscope) or something with direct visualisation methods. The advantages and limitations of each technique have been well documented elsewhere (34) and in the last couple of years there has been interest in developing automated methods to reduce the analysis time and improve the reliability

and consistency across studies by reducing intra-observer discrepancies. The automated algorithms have been validated against manual counting and there it has also been suggested that staining of the tongue with blue dye may be unnecessary (36–38).

Selecting the correct test or scale is very much dependent on time and resources available, data required, the clinical setting and the patient demographic. Measures used and the potential discordance between subjective and objective assessments will be discussed in subsequent chapters.

1.3 Thesis Road Map

Chapter 1: Introduction

Introduction to gustatory anatomy, physiology and dysfunction.

Chapter 2: A systematic review

This chapter provides a systematic and comprehensive review of the literature describing the relationship between RT dose to the gustatory OAR and the pattern of loss and recovery of taste function following RT for HNC.

Chapter 3: Outcomes following unilateral versus bilateral irradiation

This retrospective analysis of prospectively collected data, will compare patient-reported gustatory outcomes following unilateral versus bilateral irradiation to explore the relationship between the volume of OC irradiated and gustatory toxicity. Data for this research has been made available by the Clinical Trials and Statistical Unit (CTSU) at the Institute of Cancer Research (ICR) from the phase III PARSPORT and COSTAR studies.

Chapter 4: A large prospective analysis

This chapter will analyse patient-reported gustatory outcomes in prospectively collected data from over 5000 patients with HNC. This large dataset explores patient and treatment related predictors of taste dysfunction on a scale yet to be seen in the

published literature. Data for this research has been made available by the Head and Neck 5000 (HN5000) Study at the University of Bristol.

Chapter 5: A cross-sectional study 12 months following RT for HNC

This observational study will present both patient reported outcomes (PROs) and objective gustatory outcomes using chemosensory testing, 12m following RT to the head and neck. In addition, it will look more closely at the association between RT dose to the gustatory field and late gustatory dysfunction.

Chapter 6: A prospective study

This observational prospective study will present PRO and objective gustatory outcomes at baseline, immediately following completion of RT, at 2m, 6m and 12m follow up in cohort of patients undergoing RT to the head and neck.

Chapter 7: Thesis discussion

This discussion will summarise and navigate the results from the previous chapters with a focus on how going forward a constraint to prevent taste dysfunction may be developed and implemented for patients with HNC.

1.4 Thesis Aims and Objectives

The primary hypothesis for this thesis, is that there is a dose dependent relationship for taste dysfunction following RT to the head and neck.

The primary aim is to identify a potential organ at risk and dose constraint that could be applied to reduce toxicity for patients going forward.

Secondary aims include

- describing the prevalence of taste dysfunction both at baseline and in the acute and late phases following RT to the head and neck
- explore the relationship between dose and both subjective and objective taste dysfunction

- identify other associated patient and treatment related factors that influence taste dysfunction in those with HNC
- explore the downstream effects of taste dysfunction including the impact on nutritional status and overall QoL
- consider how a dose constraint might be achieved using modern RT techniques and incorporated into standard radiotherapy protocols.

Chapter 2 – Radiation and Dysgeusia: A Systematic Review

2.1 Abstract

BACKGROUND: An intact sense of taste provides pleasure, supports sustenance and alerts the body to potential toxins. HNC patients who receive RT are high-risk for developing radiation-induced taste dysfunction. Advances in delivery of RT offer the opportunity to develop taste-preserving strategies by reducing dose to the gustatory OAR.

METHODS: PubMed, Medline and EMBASE were searched for publications reporting on taste, RT and HNC. Randomised trials, cohort studies and cross-sectional studies were eligible for inclusion.

RESULTS: 31 studies were included in this review. Meta-analysed prevalence of acute taste dysfunction following RT was approximately 96% (95% CI 64 to 100%) by objective measures and 79% (95% CI 65 to 88%) by subjective measures, with the majority of patients showing at least partial recovery. Long-term dysfunction was common, seen in around 25% of patients. Taste dysfunction was associated with important clinical sequalae including weight loss and reduced quality of life (QoL). Taste dysfunction was more common when the OC, and specifically the anterior two-thirds of the tongue, was included in the RT field, suggesting a dose constraint for preservation of taste might be feasible. Proton beat therapy (PBT) and customised bite blocks reduced dose to the gustatory field and subsequent loss of taste, although these findings were not from randomised studies.

CONCLUSIONS: Taste dysfunction following RT is common and negatively affects patients' nutritional status and QoL. Decisions about treatment strategies, including choice of RT modality, dose distribution across the gustatory field and the use of adjuncts like bite blocks may be beneficial. However, evidence of efficacy is, at best, circumstantial. There is a pressing need for randomised studies or large prospective cohort studies with sufficient adjustment for confounders.

KEYWORDS: Gustation; Taste; Dysgeusia; Head and Neck Cancer; Radiation dose; Radiotherapy

2.2 Aims

To provide a systematic and comprehensive review of the relationship between RT dose to the gustatory OAR and the pattern of loss and recovery of taste function following RT for HNC.

2.3 Methods

A search of Medline, EMBASE and Pubmed was conducted for articles reporting on head and neck cancer; radiotherapy; and taste. Searches were conducted on 10th February 2020. Relevant systematic reviews identified by the search were checked for primary studies meeting inclusion criteria. For full search strategy see appendix A.

The inclusion criteria were:

Study population: HNC patients, received RT with or without chemotherapy or surgery.

Study outcomes: detailed assessment of taste either subjectively or objectively.

Study design: randomised controlled trials (RCTs), cohort (retrospective or prospective), cross-sectional.

The exclusion criteria for studies were:

Publications not in English, with only conference abstracts available, where the primary aim was not to investigate taste (except where regardless of intention taste outcomes were reported in sufficient detail to allow for critical appraisal).

Meta-analysis of the proportion of participants with acute dysfunction was performed using the random effects metaprop package in R (39). In this meta-analysis the proportion selected from each individual study was that closest to the conclusion of

RT. Subjective and objective dysfunction were analysed separately. For the latter if results were reported by taste quality, the quality with the highest proportion of dysfunction was used (on the basis that dysfunction in any one quality would represent clinically important dysfunction).

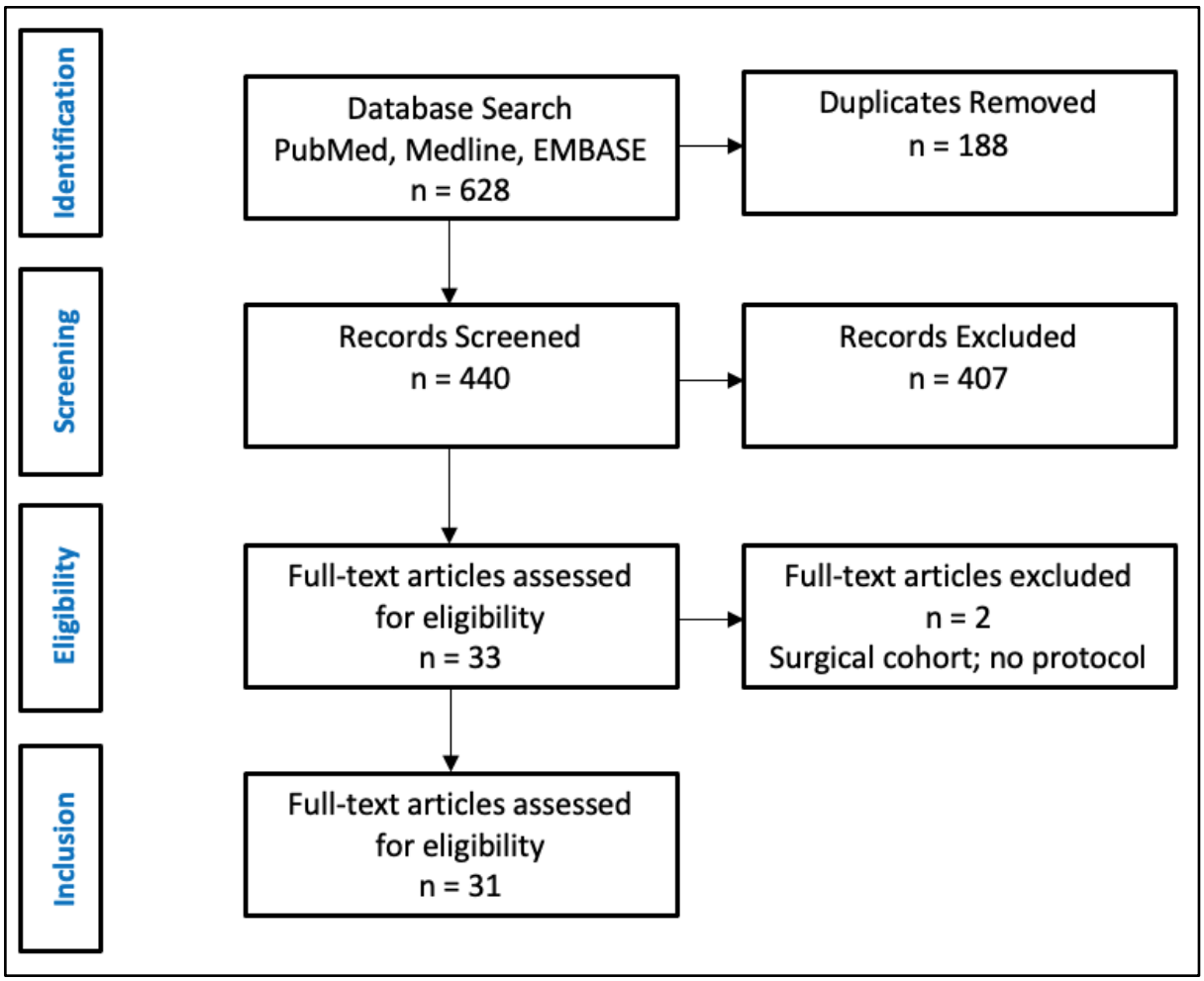


Figure 2-1. PRISMA Flow Diagram: Search outcomes for 'Taste Function Following Radiotherapy to the Head and Neck: A Systematic Review'

2.4 Results

The initial database produced 628 articles with 188 duplicates. 440 titles and abstracts were screened with 33 papers reviewed at the full text stage. Two full-text studies were excluded; the first paper mixed patients from both a surgical and RT cohort (40) and the second had no structured protocol (41).

2.4.1 Methodological limitations

Due to the varied nature of study design type, it was not deemed appropriate to use a methodological checklist approach to critical appraisal and instead methodological limitations across the evidence-base are described narratively.

It is first worth pointing out there were no RCTs looking at interventions or treatment strategies to reduce dose to the gustatory OAR and their specific effects on taste. It is, therefore, difficult definitively to make any statements about causality in terms of approaches to reduce the risk of taste dysfunction including a dose constraint for taste function. The available studies were generally a mix of cross-sectional analyses and longitudinal cohort designs (prospective or retrospective).

Studies were typically small with a mean sample size of 54 (range 13-118). While some studies attempted to compare groups within the total population and look at differential rates of taste dysfunction, the small sample sizes mean that it is difficult to determine if, when no association is apparent, this is truly evidence of no association or merely reflects an underpowered analysis. Only some studies included attempts to adjust for confounders, for example, multivariable regression analysis and, even then, these rarely included all possible confounders and were typically significantly underpowered in terms of the number of variables included. Studies were conducted as early as the 1970s, although there has been a recent increase in publications since 2015.

Finally, it should be noted that studies used a wide variety of measures to assess taste function, including objective tests, PROs (either via a structured validated questionnaire or, frequently with older studies, with little information about reporting) and clinician-reported outcomes. This heterogeneity inevitably leads to some inconsistencies. Studies rarely used more than one measure but, where they did, there was variable evidence of inconsistency between different outcome types.

2.4.2 Evidence Summary

Outcome measures

Gustatory function was measured using both objective and subjective methods.

Objective Measures Used

Objective methods in this review often used chemosensory testing that determined the lowest concentration at which a taste stimulus can be detected (detection threshold) or at which a particular taste quality could be correctly identified (recognition threshold).

Solution-based testing was the first and most frequently adopted method across the studies reviewed (see table 1). Normative values for detection and recognition of sweet, sour, salty and bitter taste have been established and new methods are often validated against these early results (42). The frequently referenced 'three-drop method' involves using a pipette to apply solution to the anterior midline of the tongue; 1 drop contains the taste solution; the other 2 drops are distilled water. The test begins with a low concentration of taste solution and proceeds using a method of ascending limits to establish the threshold at which the taste solution is correctly identified in 3 consecutive attempts (42,43).

Four studies used filter paper strips (44,45) or filter paper discs (46,47) which, similar to solution-based testing, present ascending concentrations of the basic taste qualities to assess both detection and recognition thresholds.

Two studies used EGM which involves delivering electrical stimuli with ascending amplitude and documenting the threshold at which participants can detect any sensation of taste (28,44).

Objective Measure	Study
Solution based	Mossman 1978, 1979, 1982a, 1982b, 1986 Schwartz 1993 Fernando 1995 Maes 2002 Zheng 2002 Shi 2004 Sandow 2006 Kamprad 2008 Mirza 2008 Yamashita 2009 Baharvand 2013 McLaughlin 2013 Negi 2017 Ihara 2018 Barbosa 2019
Filter paper strips	Just 2005 Riva 2015
Electrogustometry (EGM)	Just 2005 Pavlidis 2015
Filter paper discs	Yamashita 2006a, 2006b
Contact endoscopy	Pavlidis 2015

Table 1: Objective measures of taste function used across included studies

Subjective Measures

Early studies from the 1980s used a standard form for subjective outcomes but no further details regarding the questionnaires were available (48–50).

In 2004, Shi et al used a 4-point visual analogue scale for taste loss (VAS) which required patients to place their symptom of taste loss on a scale of 1 to 4 (1 for no symptoms; 2 for mild; 3 for moderate; 4 for severe) (51).

In later decades, studies started using the European Organisation for Research and Treatment of Cancer Head and Neck Questionnaire (EORTC-HNQ) questionnaire (52–54) which assesses a range of toxicities following treatment for HNC, including sense of smell and taste (55). The University of Washington Quality of Life (UWQOL) questionnaire is a similar tool and was used by Sapir et al for their study in 2016 (56).

Two recent studies (57,58) chose to use the Chemotherapy-induced Taste Alteration Survey (CiTAS), an 18-item scale assessing four dimensions of taste including decline in basic taste; discomfort, phantoguesia / parageusia and generalised alterations of taste (59).

The common terminology criteria for adverse events (CTCAE) was used as a clinician-reported objective assessment for dysgeusia in 3 recent studies (57,60,61). This tool is simplistic and categorises patients into groups based on whether dysgeusia has led to dietary changes or not.

Prevalence of taste dysfunction prior to radiotherapy

In order to understand the impact of RT on taste function, a number of studies tested baseline gustatory function or included healthy controls.

All studies that undertook objective chemosensory testing agreed there was a measurable deficit in taste acuity in HNC patients prior to radiation. Rates varied depending on the taste quality assessed with 33-35% reporting partial taste loss in at least one quality (62,63). One very early paper reported baseline dysgeusia rates as high as 96-100% (48). What remains unclear is whether the prevalence of dysfunction in HNC patients is higher than in the wider population even before treatment. Only 2 small prospective studies included a healthy control group and they came to conflicting conclusions. Mirza et al found that HNC patients had worse function than their healthy controls, whereas Sandow et al found no appreciable difference between groups (64,65).

Although prevalence of objective taste dysfunction was 33-35%, studies collecting subjective outcomes (using a variety of different measures) reported baseline taste alteration in 0-36% (51,56–58,62). Those studies that used validated patient-reported questionnaires reported consistent prevalence of around 13-19% (56,58).

While studies went on to assess the impact of possible risk factors (for example smoking, tumour site) on taste dysfunction after RT (see below), no studies reported the effect of risk factors on baseline taste dysfunction

Onset and prevalence of acute taste dysfunction in patients undergoing radiotherapy

Acute dysfunction typically presented 2-4 weeks after treatment initiation (46–48,51,63,65–67). However, not all studies reported at a level of granularity (i.e. weekly during treatment) to determine this precisely. Two studies reported the highest prevalence of dysfunction immediately after completion of RT (57,58). The timing of the onset and peak of dysfunction was consistent whether measured subjectively or objectively.

Subjective acute dysfunction prevalence ranged from 51-100% of patients (48,52,54,57,58,61,62,68,69), while that of objective acute dysfunction ranged from 52-100% (52,56,62,63,67,70,71). The only two studies that showed substantially lower rates of acute dysfunction either used a customised bite block (0% acute taste loss) (60) or used PBT (5.6% acute taste loss) (61). The most commonly reported peak prevalence was around 70-90% (48,51,52,58,62,68). The results of the meta-analysis (figure 2-2) suggest that objective dysfunction (96%, 95% CI 64 to 100%) may be more common than subjective dysfunction (79%, 95% CI 65 to 88%). However these results should be interpreted with caution due to the high degree of heterogeneity in both analysis (I^2 93% and 88% respectively).

Some studies only compared mean scores on continuous outcomes between timepoints and not the percentages of patients at those timepoints breaching clinically important thresholds. This approach only allowed the authors to claim statistically significant differences between timepoints (i.e. that on average the entire cohorts taste function worsened) rather than informing on prevalence of dysfunction (i.e. that x% experienced worsening function to the extent it could be considered important dysfunction).

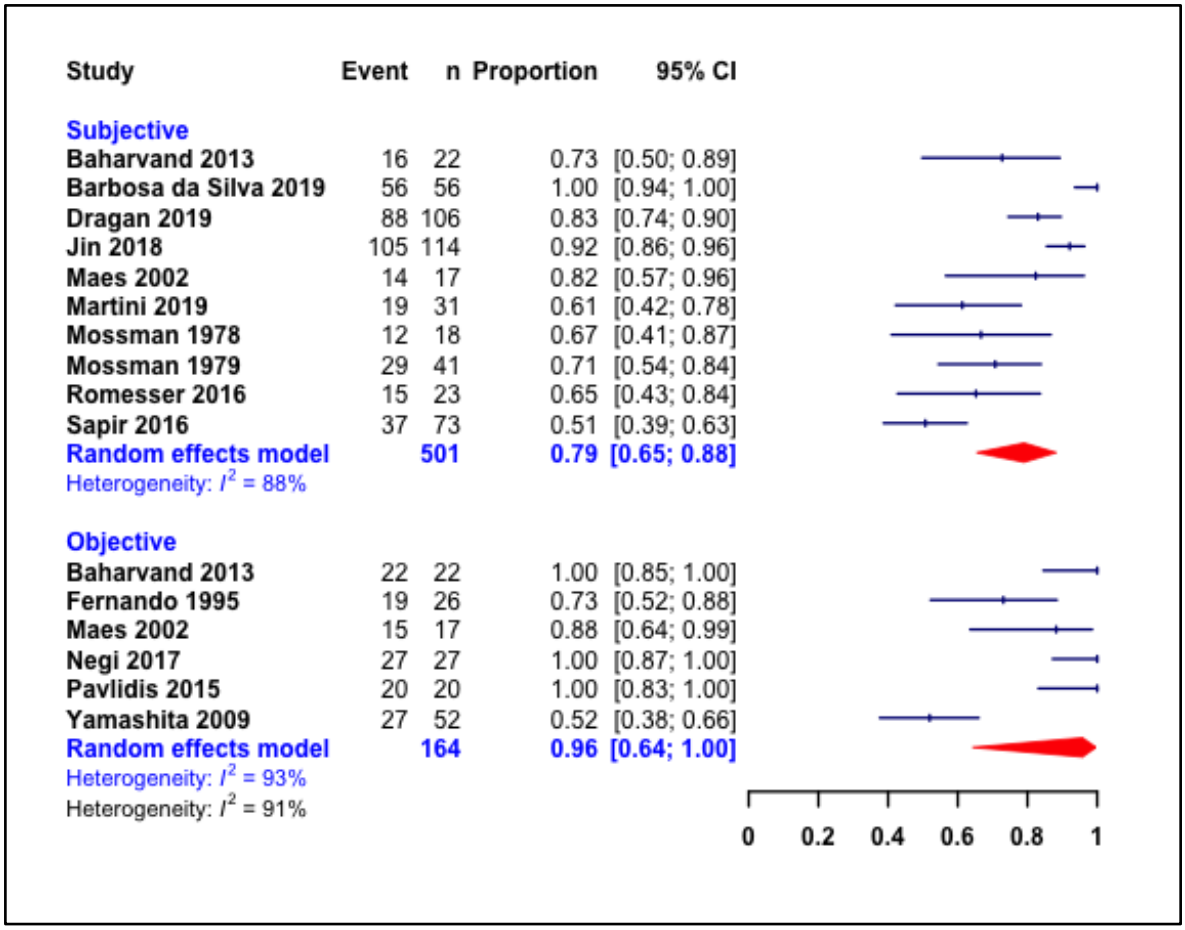


Figure 2-2: Prevalence meta-analysis of objective and subjective acute taste dysfunction

Recovery and prevalence of late effects

In every study, there was evidence of recovery. Subjective taste dysfunction showed signs of recovery 1 month post-completion of RT (57,58). Studies which assessed objective taste dysfunction either during or shortly after radiation found signs of recovery at 2-4 weeks post-treatment (63,70,72). Two studies suggested that recovery is seen in latter weeks of radiation (47,66), however one of those studies adopted an unusual RT schedule with a treatment break after 30 Gy, explaining why recovery was seen at 50 Gy (66).

In terms of the extent of recovery, in some studies all participants had recovered taste function within 3-6 months post-completion of RT (57,65,66,69). However, in other studies, there was evidence of persistent taste dysfunction ranging from 23-50%, 1-2 years post-completion of treatment (46,56,62,64). In those studies reporting only the

mean continuous objective measures (for example Ihara et al 2018), the only possible inference is that by later timepoints (in Ihara et al's study at 3 months post-RT) mean taste function in the entire cohort had returned to being non-significantly different from baseline (73).

The evidence of persistent dysfunction in the longitudinal cohort studies referenced above is consistent with the findings of cross-sectional studies in patients assessed many years after RT. In these studies, while prevalence of dysfunction again ranged considerably, there was clearly some evidence of late toxicity (7,45,53,54,74,75). At 2-3 years, the prevalence of subjective taste dysfunction was 23-53% (45,53,54). Other studies included patients with such a wide range of time since RT (e.g., 3 months to 28 years) that it is difficult to draw wider conclusions about the precise prevalence of taste dysfunction long-term. Due to the wide range in study type and outcome reporting for late effects, these results were not appropriate for meta-analysis.

Differential impacts on taste qualities (sweet, sour, salty, bitter, umami)

Studies using objective testing often attempted to quantify the differential effects on function between the taste qualities. Typically bitter and salt qualities were affected the most and sweet the least, both in terms of peak dysfunction and time to recovery (7,48,52,62,63,68,72), although these findings were not universal (64,69). Two studies looked specifically at umami and found that it was typically affected at lower radiation doses (51) and took longer to recover than other qualities (47).

Relationship between site irradiated, dose, taste dysfunction and the gustatory field

Studies frequently commented on reducing dose to the gustatory field however this region and the gustatory OAR have not been formally defined. This next section discusses the gustatory OAR evidence base in detail but it is worth highlighting that no studies reported on effects in other structures involved in taste mechanisms (for example the brainstem).

Irradiation of the anterior portion of the tongue, where FPD is highest, was associated with objective acute (66) and late (46,72) taste impairment. Zheng et al (66) found that in their cohort the group of patients who had received radiation to this area had worse sweet taste recognition (p=0.02) than those who did not. Yamashita et al came to similar conclusions but for all 4 taste qualities. Yamashita et al also looked at whether the dose to the anterior two-thirds was important and found that there was no difference between groups receiving above or below 20 Gy (46). Kamprad et al found that in their cohort the group receiving whole tongue (as opposed to posterior two thirds only) had a slower recovery of objective function.

Other studies looked at irradiated sites within the OC more broadly. Negi et al found worse (p=0.05) objective acute and late taste dysfunction in those treated for oral cavity / oropharyngeal tumours compared with tumours outside the gustatory field (63). Fernando et al found a statistically significant association between the volume of the tongue in the RT field and acute objective (r=0.59, p=0.0016) and subjective (r=0.78, p=0.0001) taste loss while no such relationship was found for volume of the parotid gland (70). Lastly, Sapir et al found an association between dose to the OC or anterior tongue ($p<0.05$) and late subjective taste dysfunction (56). This effect persisted following multivariate analysis with adjustment for time after treatment, age, sex and within-subject correlation for both OC (p=0.005) and the tongue (p=0.02).

While these studies suggest that reducing dose to the gustatory field may reduce acute and late taste dysfunction, it is worth noting one recent paper from 2019 which found comparable rates of subjective and objective taste dysfunction in those undergoing RT either directed or not directed to the OC (69). There were some suggestions the group with direct OC irradiation had worse taste function, for example a greater proportion reporting ‘qualitative taste distortions’ however the result was not significant (p=0.4).

Few studies analysed the effect of dose in more detail. Mossman 1986 studied a cohort of patients with a treatment volume that included at least 50% of the gustatory field (this region was not described in any further detail). Dose response curves showed that a total dose of 27 Gy equated to a 50% reduction in acute objective taste function compared to normative values (76). In terms of late dysfunction, Mossman et

al 1982, found that the maximum tolerance dose to the gustatory field (defined as the tongue) resulting in a 50% complication rate 5 years after treatment (TD 50/5) was a total dose of 50-65 Gy (7). Sapir et al in 2016 reported a TD50 (dose causing 50% toxicity) of 53-57 Gy mean dose to oral cavity for patient-reported severe dysgeusia 3 months after -completion of RT (56). In 2019, Chen et al reported a mean dose of >50 Gy to the OC was found to be significantly associated with late subjective taste impairment (median follow-up 27 months) (53).

Technical modifications of radiotherapy and impact on taste dysfunction

Early prospective cohort studies by Mossman et al suggested no improvement in taste scores when using neutrons over photons (48,50).

One study compared IMRT with conventional RT and found no benefit in terms of patient-reported taste dysfunction (PRTD). In fact, IMRT was associated with worse ($p<0.05$) objective taste dysfunction for sweet, bitter and salty taste qualities (45).

The only study that looked at the effects of PBT was a small non-randomised cohort comparison in patients with salivary gland (SG) tumours (61), which showed that the PBT group received a statistically significantly lower mean dose to the OC compared with IMRT (0.94 vs 20.6 Gy, $p<0.001$) and, unsurprisingly, had lower rates of acute dysgeusia (5.2% vs 65.2%, $p<0.001$).

In one study, delivering RT to patients using a customised bite block led to a significantly reduced maximum and mean dose to the tongue (~83-90% reduction at CT planning) and no taste dysfunction as assessed with CTCAE v4.0 (60). Customised blocks were suitable for any patient undergoing radiation involving the nasal cavity (NC), paranasal sinuses or oromaxillofacial area. Mean dose of the Dmean (Gy) delivered to the tongue in those without bite blocks was 18.5 Gy $\pm$ 6.2 Gy compared to 1.79 Gy $\pm$ 1.9 Gy. Mean dose of the Dmax (Gy) to the tongue was reduced from 62.92 Gy $\pm$ 6.5Gy to 10.6 Gy $\pm$ 5.3 Gy.

Other risk/modifying factors

In one study, there was a trend towards chemotherapy leading to worse taste outcomes (54). However, on the whole, chemotherapy was mostly found to have no statistically significant impact on taste dysfunction (46,47,52,67,69,75). In one very small study, chemotherapy actually appeared to have a protective effect (77), although this seems biologically questionable.

In terms of association with other treatment modalities, one study reported a fairly intuitive association between glossectomy and taste impairment (53).

Treatment aside, many studies investigated whether other risk factors were associated with taste dysfunction. One study reported a significant association between taste dysfunction and oral hygiene, i.e. worse oral hygiene associated with worse taste function (52). The following factors, when assessed, were typically found to have no association with taste dysfunction – age, gender, education, smoking, alcohol or prior surgery (52,53,69,70,72,74). However as stated in the methodological limitations section, this lack of association may be due to underpowered studies.

Association between taste dysfunction and other outcomes

To understand the importance of taste dysfunction, some studies looked for associations with other adverse clinical outcomes. A significant association was seen between dysfunction and weight loss (58,75), diminished appetite (62), xerostomia (56) and QoL (52).

Jin et al found that in their univariate analysis total subjective taste score, decline in basic taste, general taste alterations, phantogeusia/parageusia and discomfort were all statistically significantly associated with weight loss. However on multivariate analysis, including each of the factors, only discomfort ($p=0.005$) and general taste alterations ($p=0.05$) remained significant (58). McLaughlin et al reported that patients with dysgeusia lost weight from pre-treatment to the date of testing whereas those without dysgeusia actually gained weight ($p=0.037$) (75). Maes et al stated that there

was a positive correlation between prevalence of taste loss and diminished appetite, which was ‘statistically significant but weak’ with no further detail (62).

Although the association with QoL is particularly noteworthy, unfortunately it was from a small study of 22 participants with no attempt to address confounders. This study showed that a variety of QoL domains were statistically significantly worse following RT induced dysgeusia but did not report a comparison group who received RT but did not develop dysgeusia. As such it is difficult to determine the specific contribution of the single toxicity (52).

Some studies investigated further associations between specific taste quality dysfunction and adverse clinical outcomes. There was an association between sweet taste loss and the use of sweeteners and salt taste loss and use of spices (62). Satisfaction with care was negatively associated with umami dysfunction in one Japanese study (51). Interestingly, despite the intrinsic close relationship, no studies investigated the association between taste and smell dysfunction.

Microscopy findings

Finally, a handful of studies have focused on investigating the biological mechanisms underlying the interplay between RT and taste dysfunction using microscopy. Characteristic cell changes were observed following RT (44). Typically, these included cells with a longer shape, without nuclei or with multiple nuclei. Video-microscopy at tissue level also showed a decrease in pore count from pre-treatment to post-treatment (64) and greater alterations in morphology and vascularisation of FFP (77).

Table 2: Summary of clinical studies reporting taste dysfunction following RT to the head and neck						
Author Year	**Country**	**Study Design**	**n =**	**Type of RT**	**Tumour sites**	**Outcome Measure**
Mossman (68) **1978**	USA	CS / PC	27	2D-RT	OC, OP, NP, HP, L, HL, SG	PROM OM
Mossman (48) **1979**	USA	PC	51	2D-RT (photons vs neutrons)	LP, OC, ON, OP, SG, other	PROM OM
Mossman (7) **1982a**	USA	CS	13	2D-RT	OP, OC, HP, L, SG, NP	PROM OM
Mossman (50) **1982b**	USA	PC	84	2D-RT (photons vs neutrons)	LP, OC, OP, ON, SG, other	PROM OM
Mossman (76) **1986**	USA	PC / CS	75	2D-RT	A variety of head and neck sites	OM
Schwartz (74) **1993**	USA	CS	38	2D-RT	OC, OP, NP, SG, CN, neck, healthy controls	PROM OM
Fernando (70) **1995**	UK	PC	26	Conventional	L, OC, OP, HP, SC, E	CRO PROM OM
Maes (62) **2002**	Belgium	CS	73	Conventional	OP, OC, HP, SG, NP, other	PROM OM
Zheng (66) **2002**	Japan	PC	40	Conventional (atypical treatment schedule)	HP, L, NP, OP	OM
Shi (51) **2004**	Japan	PC	30	Conventional (atypical treatment schedule)	L, HP, OP, NP, OC, NV	PROM OM
Just (44) **2005**	Germany	PC	24	Not specified	HP, OP, L, SG	OM
Sandow (65) **2006**	USA	PC	13	Conventional	Unclear (OP and SG)	OM
Yamashita (46) **2006a**	Japan	PC	118	Conventional	L, HP, OP, OC, NP, SC, NC, N, lymphoma, other	OM
Yamashita (47) **2006b**	Japan	PC	51	Conventional	NP, OP, HP, other	OM
Kamprad (72) **2008**	Germany	PC	104	3D conformal	Cancer of the head and neck	OM
Mirza (64) **2008**	USA	PC	25	2D-RT	OP, NP, L, SG and other cancer site controls	OM Microscopy
Yamashita (67) **2009**	Japan	PC	52	Conventional	NP, OP, HP, other	OM
Baharvand (52) **2013**	Iran	PC	22	2D-RT	OC, OP, NP, HP, SG, SC	PROM OM

McLaughlin (75) **2013**	USA	CS	92	Not specified	OC, P, L, SC, other	PROM OM
Pavlidis (77) **2015**	Germany	PC	20	2D-RT	HP, L, OP, SG	OM Microscopy
Riva (45) **2015**	Italy	RC	60	2D-RT, IMRT	NPC and healthy controls	PROM OM
Romesser (61) **2016**	USA	PC	41	IMRT, PBT	SG	CRO
Sapir (56) **2016**	USA	PC	73	IMRT	OP	PROM
Negi (63) **2017**	India	PC	30	3D-Conformal RT	OC, OP, NP, HP, L	OM
Ihara (73) **2018**	USA	PC	30	Not specified	NP, OP, OC, L, SG, HP, UP	OM
Jin (58) **2018**	China	PC	114	IMRT	OC, NP, SG, L, O, T, NS, Ly, HP, other	PROM
Barbosa (69) **2019**	Brazil	PC	56	Conventional	OP, OC, HP, NP, SG	PROM OM
Chen (53) **2019**	Taiwan	PC	88	IMRT	OC, NP, OP, HP, L, other	PROM
Dragan (54) **2019**	Belgium	RC	106	IMRT	OC, OP, L, HP	CRO
Feng (60) **2019**	China	PC	60	IMRT	MS, OC, ON, Ly	CRO
Martini (57) **2019**	Italy	PC	31	IMRT	Oral cavity at least partially included	CRO PROM

2D-RT, 2-dimensional radiotherapy; 3D-RT, 3-dimensional radiotherapy; CN, cervical nodes; CRO, clinician reported outcome measure; CS, Cross-sectional; E, ethmoid; HL, hodgkins lymphoma; HP, hypopharyngeal; IMRT, intensity-modulated radiotherapy; L, larynx; Ly, lymphoma; MS, maxillary sinus; n, number; NP, nasopharyngeal; NS, nasal sinus; NV, nasal vestibule; O, oesophageal; OC, oral cavity; OM, objective measure; ON, olfactory neuroblastoma; OP, oropharyngeal; PBT, proton beam therapy; PC, Prospective cohort; PROM, patient-reported outcome measure; RC, retrospective cohort; RT, radiotherapy; SC, sinus cavity; SG, salivary gland; T, thyroid

Table 2: Summary of clinical studies reporting taste dysfunction following RT to the head and neck

Table 3: Summary of key outcomes from studies included				
Author Year	**Outcomes Measured**	**Time Points**	**Duration of FU post-RT**	**Key Findings**
Mossman (68) **1978**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing Standard form used	PC: pre-RT, during RT, 1 month post-RT	12 months (CS), 1 month (PC)	Impaired 3 weeks after initiation of RT. Scaling impairment occurred before recognition or detection impairment. Bitter and salt detection showed earliest and greatest severity of impairment. Sweet detection was least affected. At 12 months 9/9 patients had subjective taste loss with elevated median detection and recognition thresholds for each quality.
Mossman (48) **1979**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing Standard form used	Pre-RT, during RT, 2 months post-RT	2 months	Impaired 2 weeks after initiation of RT. Gustatory tissue response are equivalent in patients treated with either photons or neutrons Bitter and salt worst affected, with sweet and sour the least.
Mossman (7) **1982a**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing Standard form used	1-7 years post-RT	CS	69% of patients had objective taste loss with bitter and salt detection affected most and sour and sweet the least. TD50/5 = 50-65 Gy (to at least 75% of gustatory field)
Mossman (50) **1982b**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing Standard form used	Pre-RT, during RT	None	Measurable taste loss at baseline in both groups Weeks 2-5 mean taste loss increased by factor of 4 and then decreased after week 5 (photon group) By week 4, there was an 8-fold increase in mean taste loss followed by a decrease (neutron group) No advantage to using neutrons for this normal tissue.
Mossman (76) **1986**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing	During RT, immediately after	Immediately after	Taste loss observed at doses above 20 Gy, increasing rapidly between 40-60 Gy. Doses above 60 Gy show 90% relative taste loss.

Schwartz (74) **1993**	Whole mouth technique with scaled intensity testing Subjective taste assessment	1-19 years post-RT	CS	Evidence for near normal suprathreshold taste intensity performance in irradiated patients Subtle age-related taste impairments identified.
Fernando (70) **1995**	Objective taste testing with a series of solute solutions Subjective questionnaire	Pre-RT, at end of RT, 1 month post-RT	1 month	No relationships between smoking, alcohol, prior surgery or prior treatment and severity of taste loss. Both subjective and objective taste dysfunction was associated with the volume of tongue irradiated, but not with the parotid.
Maes (62) **2002**	Forced choice detection/recognition threshold testing; 3-drop technique with scaled intensity testing Taste questionnaires	Pre-RT, 2, 6, 12-24 months post-RT	Up to 2 yrs post-RT	Taste loss most prominent at 2 months post-RT. 50% had subjective taste loss at 1-2 years post-treatment, objective taste loss in 27-41% depending on taste quality. Bitter and salt worst affected, sweet and sour the least. Association between taste loss and diminished appetite, sweet taste loss and use of sweeteners, salt taste loss and use of spices.
Zheng (66) **2002**	Recognition threshold and supra-threshold taste intensity performance using the whole-mouth taste method for 4 basic tastes	Pre-RT, at 10 Gy intervals and at 6 months or Pre-RT, at 30 Gy and 6 months	6 months post-RT	Taste loss worst at 30 Gy, beginning to recover by 50 Gy, fully recovered by 6 months. Bitter most affected.
Shi (51) **2004**	Whole mouth technique Visual analogue scale	Pre-RT, 15/30/45/60 Gy dose points	No post-RT	No statistically significant difference in sweet, sour, salty and bitter taste thresholds were seen between pre-RT and during RT. At 30 Gy and above, significantly impaired umami taste function was seen ($p = <0.05$).
Just (44) **2005**	Confocal laser scanning microscope Filter paper strips EGM	Between 4th/5th week of RT	No post-RT	Patients complaining of taste disorders during chemoradiotherapy had reduced taste function with both natural and electric stimuli. In these patients LSM indicated epithelial changes of the fungiform papillae with no change of taste bud structure.
Sandow (65) **2006**	Whole mouth technique, Methods of Limits	Pre-RT, 4 weeks in RT, 6 m after RT, 1 yr after RT	1 year	Objective taste thresholds for all qualities elevated at 1 month. All objective taste thresholds back to baseline by 6 months and retained by 12 months.
Yamashita (46) **2006a**	Filter paper disc taste recognition threshold measurements	Pre-RT, weekly until 10-16 weeks, monthly until 14-24 months	24 months after start	Taste loss was not observed with sparing of the anterior portion of tongue. When anterior tongue irradiated, significant impairment in all taste qualities seen from week 3 of RT with some recovery at 4 months. With or without chemotherapy had no effect
Yamashita (47) **2006b**	Filter paper disc taste recognition threshold measurements	Pre-RT, weekly until 10-12 weeks after start	10-12 weeks after start of RT	All 5 taste quality function declined by week 5 and improved from week 1 post RT. With or without chemotherapy had no effect.

Kamprad (72) **2008**	Solution based testing	Pre-RT, 20 Gy, 40 Gy, 60 Gy, 1m, 2m, 3m, 6m	6 months post-RT	All qualities affected roughly equally, most noticeable for bitter/sour/salty. Improved considerably by 1 month post-completion of RT Smokers and alcohol some mild effects at baseline but little effects post-RT. Irradiation of the anterior portion of the tongue was associated with more severe loss of taste and longer recovery for taste function.
Mirza (64) **2008**	Pipette solution based regional taste testing	Pre-RT, 2 weeks, 2 months, 6 months post-RT	6 months post-RT	HNC patients had worse taste scores for bitter/salty/sour than controls. Sour the only quality statistically significantly affected by radiation. Some recovery by 2 months and more so by 6 months for both taste scores and video-microscopy.
Yamashita (67) **2009**	Whole mouth solution based taste recognition threshold measurements	Pre-RT, weekly until 10-12 weeks after start	10-12 weeks after start of RT	Deterioration in taste function between 2nd and 5th weeks after commencing RT. Recovery around 8th week (improved significantly). With or without chemotherapy had no effect.
Baharvand (52) **2013**	Whole mouth solution based technique EORTC QLQ-H&N35	Pre-RT, 3 weeks after RT	3 weeks after RT	All 22 developed taste loss after RT, 6 with total taste loss. Subjective dysgeusia reported by 72.7%. Salty/bitter most affected. No association with age, sex, education, location of malignancy, radiation dose, source, number of sesions, chemo, xerostomia and dysgeusia. Oral hygiene was associated (worse hygiene = lower taste sensitivity. Quality of life was significantly worsened in those with both partial and total taste loss.
McLaughlin (75) **2013**	Whole mouth solution based technique Taste questionnaires	CS	3 months to 28 years post RT	23/92 reporting dysgeusia (huge range of time post-RT). 85/92 had some form of taste dysfunction objectively. Dysgeusia significantly associated with weight loss.
Pavlidis (77) **2015**	EGM, contact endoscopy	Pre-RT, during, end of RT	No post-RT	During RT all patients showed elevated EGM thresholds. RT worse for taste than CT or CRT RT showed greater alterations in morphology and vascularisation of fungiform papillae.
Riva (45) **2015**	Taste strips test Sniffin' sticks test Unclear subjective assessment	Post-RT	At least 2 years	Chemoradiotherapy is associated with late smell and taste disturbance compared to controls. Gustatory function was significantly lower in those treated with IMRT versus conformal techniques.

Romesser (61) **2016**	CTCAE v.40	Weekly during RT, 4/8/12 weeks after, 3 monthly to 2 years, every 6 months afterwards	Median follow up 8.7 months	Mean oral cavity doses in IMRT were 20.6 Gy vs 0.94 Gy in PBRT group. Significantly lower rates of grade 2 acute dysgeusia (65.2% with IMRT vs 5.6% in PBRT).
Sapir (56) **2016**	HNQOL, UWQOL	1/3/6/12m after RT	12 months	13/19% reporting mild dysgeusia at baseline c.f. HNQOL/UWQOL, respectively. Significant association between patient-reported dysgeusia and radiation dose to the oral cavity and anterior portion of the tongue.
Negi (63) **2017**	Forced three-choice, stimulus drop technique	Weekly during RT, monthly until 6 months	6 months	Prior to RT 23-33% of patients had partial taste loss in various qualities. Worst at 4-6 weeks of RT Worst for bitter, sweet least affected. All but bitter beginning recovery from first month onwards.
Ihara (73) **2018**	Solution-based testing, self-perceived intensity	Baseline, 6 weeks, 3 months	3 months	All 4 taste qualities declined in intensity from baseline to 6 weeks By 3 months all 4 qualities were not statistically significantly different from baseline.
Jin (58) **2018**	Self-reported single-item taste assessment and CiTAS	Pre-RT, mid-RT, post-RT, 1-2 months post-RT	1-2 months	13% subjective taste alteration at baseline. Peak of 92.1% STA immediately post-RT. 77.9% 1-2 months post-RT. Among the four subscales of STA only the discomfort score had a significant effect on weight loss.
Barbosa (69) **2019**	Solution-based testing SSSB and PROM	0m, 3m, 6m post-RT	6 months	Both groups showed decrease in mean gustatory scores; recovery in direct group at 3 months versus 6 months in the indirect group (NS); loss was not influenced by sex, age, field of RT, chemo, xerostomia, stage or smoking
Chen (53) **2019**	EORTC QLQ-H&N35	Pre-RT and post treatment at regular intervals not specified.	Median 27 months	At ~27 months, 30.7% (27/88) reporting long-term taste impairment. Glossectomy (OR ~5), stage III/IV associated with taste impairment. Not associated = sex, age, smoking, chemo. Mean dose to OC >/=50 Gy was borderline significantly associated with taste impairment.
Dragan (54) **2019**	RTOG/EORTC scores	Weekly during RT, then monthly, 2-3 monthly for 2 years, 3-6 monthly to 5 years, yearly	Median 31 months	At 12 months, rate of patient-reported dysgeusia was 23% overall (33% in group A post-operative RT; 18% in group B primary RT).
Feng (60) **2019**	CTCAE v4.0	Baseline, weekly during RT, 3 monthly thereafter	Median follow up 25 months	Mean dose to tongue can be reduced by 90% with use of customised bite block Mean doses to tongue reported were 1.79 Gy No dysgeusia reported during follow-up period.

Martini (57) **2019**	CiTAS CTCAE v4.0	Baseline, weekly OT, 1 week, 1m, 6m post RT; patients with oral cavity involvement	6 months	Increase in all elements of dysgeusia reporting were observed, peaking at the 6th week post-radiotherapy. Essentially back to baseline CiTAS by 6 months, recovery seen as early as 1 month.
Gy, gray; CTCAE, common terminology criteria for adverse events; CiTAS, chemotherapy-induced taste alteration scale; CS, cross-sectional; EGM, electrogustometry; OT, on-treat; PC, prospective cohort; RT, radiotherapy;				

Table 3: Summary of key outcomes from studies included

2.4.3 Discussion and Conclusions

The key findings of this systematic review of the literature on taste dysfunction are summarised in box 1 (figure 2-2).

Box 1. Key findings from this systematic review
Taste dysfunction is common, affecting 70-90% of people during RT with bitter and salt taste qualities affected most severely
Taste dysfunction typically recovers partially post-RT but usually there is lingering dysfunction months to years after RT
Minimising RT dose to the OC and specifically the anterior two-thirds of the tongue is likely to reduce the risk of taste dysfunction
PBT and bite blocks may help to achieve this risk reduction
Taste dysfunction is associated with a number of clinically important sequalae, including weight loss, xerostomia and reduce QoL

Figure 2-3: Key findings from this systematic review

Prevalence of taste dysfunction at baseline varied considerably across studies. Dysfunction was more common in those with HNC prior to treatment than in healthy controls. It is plausible that baseline dysfunction may relate to underlying disease, either because of disease within the OC or in those with nasopharyngeal carcinoma (NPC) for example, whereby sense of smell can be altered. Patients with HNC are more likely to be heavy smokers which is known to increase the risk of both olfactory and taste impairment relative to the general population (78).

Peak prevalence of taste dysfunction also varied between 50-100% with the most commonly reported peak prevalence of 70-90%. Meta-analysed summary estimates of 96% for objective dysfunction (95% CI 64 to 100%) and subjective dysfunction of 79% (95% CI 65 to 88%) both contained a high degree of heterogeneity. The heterogeneity in these estimates is likely due to the variability between studies in terms of the patient population, RT technique used, tumour

sites irradiated and methods of recording dysfunction (see table 2). Even with efforts to subdivide outcomes by their objective or subjective nature the heterogeneity persisted, underlining the inconsistent methods of research in this area.

Most studies agreed that following initiation of RT, acute taste dysfunction becomes clinically apparent from 2-4 weeks onwards. Reassuringly, all studies reported evidence of recovery following completion of treatment, although some degree of late toxicity was reported in 23-53% of patients at 2-3 years follow-up.

Objective testing gave insight into the differential impacts of RT on the 5 basic tastes. Often bitter and salt qualities were the worst affected. Interestingly, a recent study suggested that umami might be affected at lower doses than the other 4 taste qualities and this was negatively associated with overall satisfaction of care. This association has not been assessed in any study outside of Japan and it would be interesting to see if the strength of the association between certain taste qualities and satisfaction could be affected by cultural and dietary preferences.

The precise relationship between dose to the gustatory field and toxicity was poorly reported, in part because the gustatory OAR are yet to be formally defined. There was a general consensus that reducing dose to the oral cavity or in particular anterior two-thirds of the tongue is associated with improved taste outcomes. Other research has also shown that reducing dose to the oral cavity outside the planning target volume (PTV) is safe and oncological outcomes are not compromised (79). The constraint for taste however is yet to be determined and research, so far, suggests it may be considerably less than what might be achievable with IMRT using photons. It is biologically plausible that taste dysfunction may be associated with dose to certain other structures involved in taste (for example the brainstem), however no studies included in this review reported on this potential association.

In terms of technical solutions, one study found worse gustatory outcomes in those treated with IMRT. This highlights the importance of being mindful not to

introduce inadvertent dose to the gustatory field when switching from conventional to more conformal techniques, such as IMRT and volumetric-modulated arc therapies (VMAT). This is particularly important in the treatment of a unilateral target volumes although with careful application of dose constraints to the contralateral OC OAR, risk of inadvertent toxicity could be mitigated (80).

Although solution-based tests were the most common objective method of assessing taste, they are inherently time consuming and require meticulous preparation and storage. A number of alternative methods have been developed including edible taste wafers (81), taste testing tablets (82) and non-edible taste strips (43), which were extended to include umami strips (83), and more recently taste strips to detect those patients with low gustatory thresholds and high gustatory sensitivity (84).

With innovative objective taste and smell assessment tools, a combination of both objective chemosensory testing and subjective patient-reported outcome measures should be achievable by most studies. Combining these assessments also provides insight into the relationship or apparent discordance between objective and subjective outcomes. Selecting the correct test or scale is dependent on time and resources available, data required, the clinical setting and the patient demographic.

PROMs in modern research are paramount in assessing toxicity. In many studies subjective PROMs were collected though used a variety of surveys. In order to compare results across studies, it is important for future researchers to be consistent in their survey of choice. Unfortunately, there are currently no validated surveys specifically designed to assess taste dysfunction in cancer patients undergoing RT.

Few studies were able to explore the effect of taste dysfunction on overall QoL. One study did report a significant association which was noteworthy. If this finding was tested in a larger study with adjustment for confounders and taste dysfunction was still found to be a statistically significant predictor of worsened

QoL, it would make a clear case for further research and efforts to minimise toxicity for patients.

The only PBT study included showed remarkably low doses to the gustatory field and, with this, comparably low rates of taste dysfunction. Unfortunately, the study only looked at acute (within 90 days of start of RT) and clinician-reported outcomes (CROs) (by CTCAE, Grade 2+) which may have poorer sensitivity compared with PROMs or objective measures of taste dysfunction. However, assuming CROs had equally low sensitivity in both groups, it is still likely that PBT will have a significant differential benefit over IMRT.

Another way to minimise dose to the tongue was through use of a customised bite block. The study that researched this reported no taste dysfunction at all. This remarkable finding (given the general prevalence of taste dysfunction) suggests that this intervention may be beneficial however the study was highly selective and only included patients with maxillary sinus cancer, upper gingival cancer, nasal lymphoma and olfactory neuroblastoma, all without elective nodal irradiation. In addition, as noted above, the clinician-reported CTCAE v4.0 used to define taste dysfunction may not be sensitive or accurate enough, making the lack of a control group in this study particularly critical.

Strengths of this systematic review include the comprehensive and systematic approach to literature searching and the stratification of findings by outcome (subjective versus objective). While the lack of checklist-based critical appraisal on a study level could be considered a limitation – the variety of methodologies employed in the primary studies made in depth narrative appraisal pragmatically more appropriate.

As always, further research would be informative. The majority of studies in the review were small, non-randomised, often retrospective and did not address confounding. Well conducted studies, either RCTs or large non-randomised cohort studies with adequate consideration of confounding factors are required. This will allow clinical oncologists to confirm or refute the potential benefits of

solutions such as IMRT or PBT that could reduce dose to the gustatory-OAR (e.g. OC; whole tongue; anterior two-thirds of the tongue).

Chapter 3 - Gustatory Function Following Bilateral vs. Unilateral Radiation to The Head and Neck: A retrospective study of prospective data comparing outcomes from the PARSPORT and COSTAR studies

3.1 Background

PARSPORT was a phase 3 multi-centre RCT comparing parotid-sparing IMRT with conventional RT in patients with pharyngeal carcinoma treated with radical intent (85). The study showed that at both 12m and 24m post treatment, patients who had undergone IMRT had significantly better recovery of salivary function (85).

COSTAR, also a phase 3 multi-centre RCT, compared auditory outcomes following cochlear-sparing IRMT versus conventional RT in patients with parotid cancer treated with postoperative radiotherapy (PORT) following parotidectomy (86). Despite using IMRT to meet the required dose constraint for the cochlea, the COSTAR study was unable to correlate this with a reduction in the proportion of patients with clinically relevant hearing loss (86).

Participants in PARSPORT received bilateral RT to the head and neck, whereas participants in COSTAR received unilateral PORT. Both studies collected prospective late radiation toxicity data and QoL data relevant to taste and smell function enabling a comparative analysis of how the volume of OC irradiated may relate to the gustatory toxicity encountered.

3.2 Hypothesis

The development of clinically significant PRTD relates to the volume of OC irradiated and dose (Gy) delivered.

Clinically significant PRTD is associated with reduced overall QoL.

3.3 Aims and objectives

3.3.1 Primary Objectives

To describe the prevalence of grade 3 or worse PRTD (G3+PRTD) and grade 3 or worse patient reported smell dysfunction (G3+PRSD) over time in those treated with bilateral (PARSPORT) or unilateral (COSTAR) irradiation.

To compare the proportion of patients with G3+PRTD and G3+PRSD 6m following completion of RT, in those treated with bilateral (PARSPORT) or unilateral (COSTAR) irradiation.

3.3.2 Secondary Objectives

To compare the proportion of patients with G3+PRTD or G3+PRSD at 0m, 12m and 24m after completion of RT, in those treated with bilateral (PARSPORT) or unilateral (COSTAR) irradiation.

To explore the association between patient and treatment related factors and G3+PRTD following RT to the head and neck in both studies.

To compare the consistency of reporting between PRTD and clinician-reported taste alteration at all-time points in both studies.

To measure the association between G3+PRTD and overall QoL.

To compare typical dosimetry to the gustatory field in bilateral (PARSPORT) and unilateral (COSTAR) irradiation treated with either IMRT or conventional RT.

3.4 Endpoints

Clinically significant PRTD was defined by a score of 3+ on Q44 of the EORTC-HNQ35 (see figure 3-3) (55).

Patient and treatment related factors included:

- Age – measured in years at point of study entry - >60 versus 60 and under
- Sex - male or female
- Stage of disease – stage I/II versus stage III/IV (TNM 7th edition)
- Surgical status - primary RT versus PORT
- Chemo status - use of induction chemotherapy versus no chemotherapy
- Radiotherapy technique - conventional RT versus IMRT
- Patient reported xerostomia (PRX) – defined by a score of 3+ on Q41 of the -HNQ35
- PRSD – defined by a score of 3+ on Q43 of the EORTC-HNQ35

Clinician-reported taste alteration (grade 2 or more) as assessed by the Late Effects of Normal Tissue – Subjective, Objective, Management and Analytic (LENT/SOMA scale) (see figure 3-4) (87,88).

QoL – measured using the global health status (GHS) score from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30) v3.0 (89).

RT dose to gustatory field included mean dose in Gy to:

- Whole OC
- Whole tongue
- Anterior two-thirds of the tongue
- Posterior one-third of the tongue

3.5 Methods

3.5.1 Study Population

This post hoc analysis of two prospective studies included all patients treated within the PARSPORT and COSTAR studies with all available data included for analysis. The inclusion and exclusion criteria for PARSPORT and COSTAR are presented below (see figures 3-1 and 3-2).

Collection of toxicity data was obtained under the ethics approval for each respective study. The comparison of outcomes between studies was awarded higher educational institutional (HEI) approval through The Royal Marsden Committee for Clinical Research (CCR) in collaboration with the ICR.

To be eligible patients must meet the following inclusion criteria:

1. Histologically confirmed squamous cell or undifferentiated carcinoma of the head and neck
2. Tumour arising from the oropharynx or hypopharynx requiring radical radiation of the primary tumour by parallel opposed lateral fields, and bilateral cervical lymph node irradiation
3. High risk of radiation induced xerostomia with conventional radiotherapy due to the irradiation of the majority of both parotid glands (defined as estimated mean dose to both parotid glands greater than 24 Gy using conventional radiotherapy technique)
4. Radiotherapy either as primary therapy or post-operative (adjuvant irradiation). Techniques to be detailed by each centre. Neo-adjuvant chemotherapy is permitted.
5. Stage T1-4, N0-3, M0 disease
6. WHO Performance Status 0-1
7. All patients must be suitable to attend regular follow-up and undergo QL and salivary flow measurements i.e. dependant on cognitive aptitude and long term availability for follow up.
8. All patients must be able to complete self-assessed quality of life questionnaire

A patient is ineligible for this study if any one of the following exclusion criteria are met:

1. Previous radiotherapy to the head and neck region
2. Previous malignancy except non-melanoma skin cancer
3. Pre-existing salivary gland pathology interfering with saliva production
4. Previous or concurrent illness which in the investigators opinion would interfere with either completion of therapy or follow-up
5. Patients with bilateral N3 nodal disease or huge primary tumour (exceeding 10cm in diameter)
6. Prophylactic use of amifostine or pilocarpine is not allowed
7. Concomitant chemotherapy is not permitted
8. Brachytherapy is not allowed as part of the treatment
9. Presence of contralateral lymphadenopathy adjacent to or involving contralateral parotid gland making parotid sparing impossible
10. Tumour of base of tongue where sparing of contralateral parapharingeal space is contraindicated

Figure 3-1: Inclusion / exclusion criteria from PARSPORT study (85)

5.3 Inclusion criteria

Patients must satisfy all of the following to be eligible for the trial:

1. Histologically confirmed malignant tumours of the parotid glands;
2. High risk of radiation induced sensori-neural hearing loss with conventional radiotherapy due to the irradiation of the parotid bed to a dose equivalent of 60 Gy in 2 Gy fractions with photon beams, using the wedge pair technique;
3. Radiotherapy as post-operative therapy (adjuvant irradiation);
4. WHO Performance Status 0-1 (Appendix ~~3~~2); and
5. All patients must be suitable to attend regular follow-up and undergo audiograms and toxicity monitoring and be available for long term follow-up.

5.4 Exclusion criteria

Patients with any of the following are not eligible for the trial:

1. Previous radiotherapy to the head and neck region;
2. Parotid tumours requiring primary radiation
3. Metastases from squamous cell carcinoma of the head and neck to the parotid gland;
4. Benign tumours requiring post operative radiotherapy;
5. Hearing level >60dB in bone conduction at 4000Hz on ipsilateral side at time of study entry (the test is unreliable below this threshold);
6. Previous or concurrent illness, which in the investigators opinion would interfere with either completion of therapy or follow-up;
7. Patients requiring concomitant chemotherapy.

Figure 3-2: Inclusion / exclusion criteria for COSTAR study (86)

3.5.2 Procedures

Both study protocols were reviewed to select study time points where late toxicity data relevant to taste function, smell function and overall QoL was collected and could be compared.

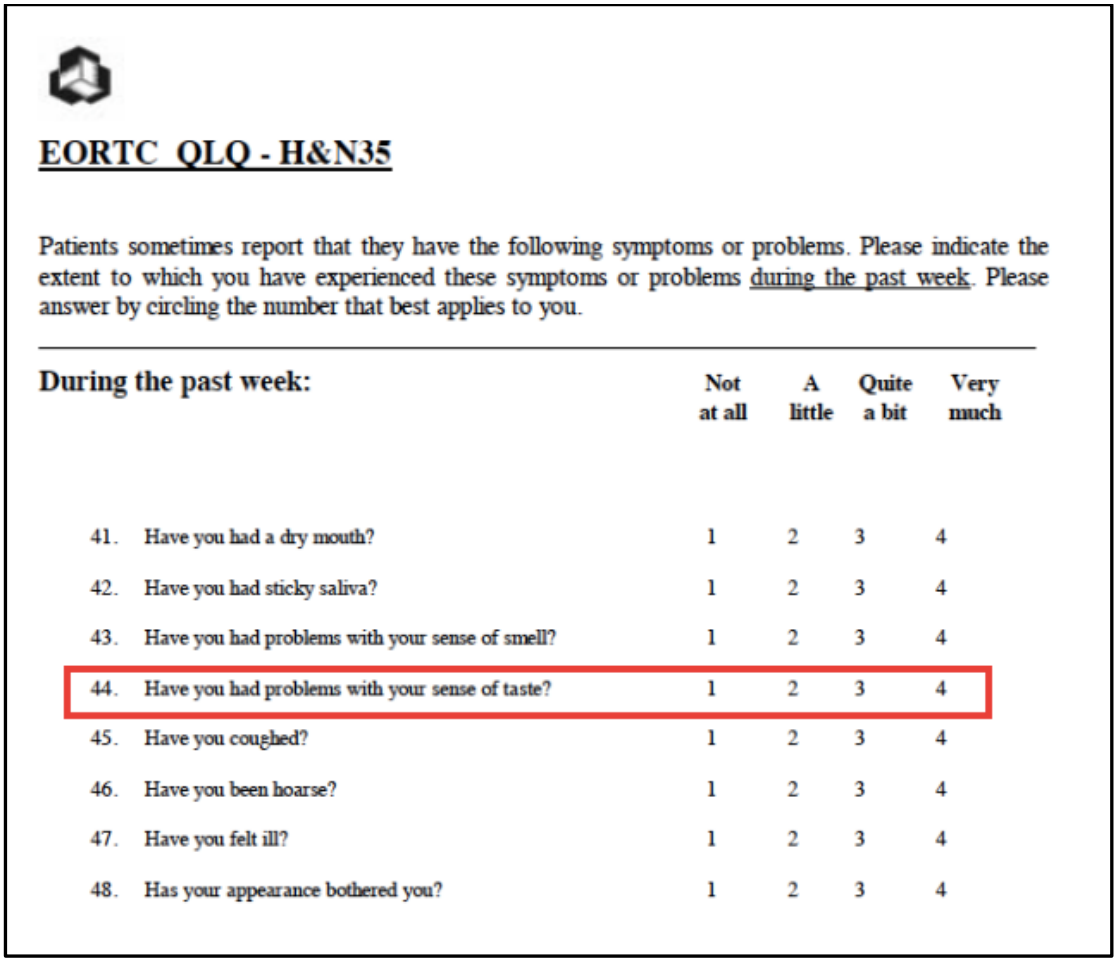
EORTC-QLQC30 and EORTC-HNQ35 were completed in both studies at baseline, 6m, 12m and 24m after completion of treatment.

LENT/SOMA data was collected in both studies at 3m, 6m, 12m, 18m and 24m.

In PARSPORT, for both treatment groups, the primary tumour and involved lymph nodes were treated with 65 Gy in 30 fractions delivered Monday to Friday

over 6 weeks. Post-operative patients received 60 Gy in 30 fractions except in circumstances where there was macroscopic residual disease, whereby 65 Gy in 30 fractions was given. The prophylactic nodal groups at risk of metastatic involvement, received a biologically equivalent dose of 50 Gy in 25 fractions (conventional arm) or 54 Gy in 30 fractions (IMRT arm).

In COSTAR patients were treated post-operatively with 60 Gy or 65 Gy in 30 fractions delivered Monday to Friday over 6 weeks (86).

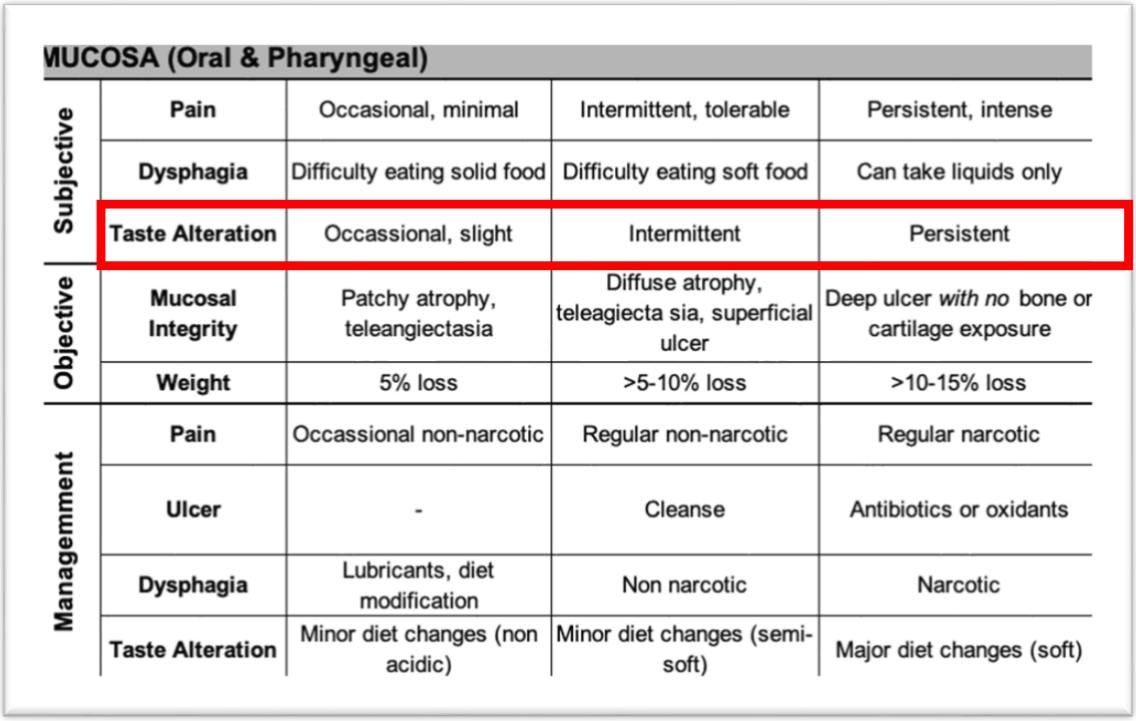


EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Figure 3-3: Extract from EORTC-HNQ35 Questionnaire



MUCOSA (Oral & Pharyngeal)				
Subjective	**Pain**	Occasional, minimal	Intermittent, tolerable	Persistent, intense
	Dysphagia	Difficulty eating solid food	Difficulty eating soft food	Can take liquids only
	Taste Alteration	Occassional, slight	Intermittent	Persistent
Objective	**Mucosal Integrity**	Patchy atrophy, teleangiectasia	Diffuse atrophy, teleagiecta sia, superficial ulcer	Deep ulcer *with no* bone or cartilage exposure
	Weight	5% loss	>5-10% loss	>10-15% loss
Managemment	**Pain**	Occassional non-narcotic	Regular non-narcotic	Regular narcotic
	Ulcer	-	Cleanse	Antibiotics or oxidants
	Dysphagia	Lubricants, diet modification	Non narcotic	Narcotic
	Taste Alteration	Minor diet changes (non acidic)	Minor diet changes (semi-soft)	Major diet changes (soft)

Figure 3-4: Extract from LENT/SOMA scoring manual

3.5.3 Statistical Analysis Plan

The study sample size was determined by the available data from the PARSPORT and COSTAR studies. Combining data from both studies, approximately 130 patients completed a questionnaire at 6m (time point of primary interest). With 130 patients, it was calculated that there would be 80% power to detect a 25% increase in clinically significant taste dysfunction with bilateral irradiation, assuming 25% of patients with unilateral irradiation had clinically significant problems.

Descriptive statistics were used to capture the key characteristics of the cohort. Fisher's exact test was used to compare proportions for dichotomous outcomes. The unpaired t-test was used to compare mean values between groups. Univariate logistic regression was used to investigate the association between potential predictors and PRTD. Diagnostic test accuracy outcomes (sensitivity, specificity) were calculated to compare the performance of objective and subjective measures for defining taste dysfunction.

3.6 Results

Data for 198 patients (106 from COSTAR and 92 from PARSPORT) were made available by the ICR CTSU for inclusion in this analysis. Table 4 summarises patient, tumour and treatment characteristics included in this analysis. Aside from whether patients received unilateral or bilateral RT, there were a number of notable differences in the patient groups at baseline. The unilateral group had more women and only included patients with parotid tumours alone as opposed to oropharyngeal / hypopharyngeal tumours. As such, the unilateral group did not receive any neo-adjuvant chemotherapy and only received RT in the post-operative setting. The proportion of patients with stage III or IV disease was higher in the bilateral group (75.0%) versus the unilateral group (50.5%). Both studies randomised patients to receive either IMRT or conventional RT and therefore the proportions receiving either modality were balanced.

	Unilateral RT (n = 106) **	Bilateral RT (n = 92)	P value
Age (years)			
Mean	58.6 years	58.4 years	0.70
Range	19 – 88 years	37.5 – 82.8 years	
Standard deviation	15.99	9.7	
Sex			
Male	55 (51.9%)	67 (72.8%)	0.003
Female	51 (48.1%)	25 (27.1%)	
WHO performance status			
0 – 1 2 +	106 (100%) 0 (0%)	92 (100%) 0 (0%)	>0.99
Tumour site			
Parotid	106 (100%)	0 (0%)	N/A
Oropharynx	0 (0%)	79 (85.9%)	
Hypopharynx	0 (0%)	13 (14.1%)	
AJCC* stage (TNM 7th edition)			
I and II	51 (49.5%)	23 (25.0%)	0.0006
III and IV	52 (50.5%)	69 (75.0%)	
Neoadjuvant chemotherapy			
Yes	0 (0%)	39 (42.4%)	<0.0001
No	106 (100%)	53 (57.6%)	
Treatment received			
Primary RT	0 (0%)	92 (100.0%)	N/A
Post-operative RT	106 (100%)	0 (0%)	
Radiotherapy technique			
IMRT	55 (51.9%)	48 (52.2%)	>0.99
Conventional	51 (48.1%)	44 (47.8%)	

RT = radiotherapy. IMRT = intensity modulated radiotherapy. N/A = Not Applicable. *American Joint Committee on Cancer-groupings based on TNM staging data collected. **staging for 3 patients included was not available

Table 4: Baseline patient characteristics and treatment details

3.6.1 PARSPORT

Within PARSPORT 92 patients were treated with radical bilateral RT. Neo-adjuvant chemotherapy was used in 39 patients (42.4%) and RT was delivered in the post-operative setting in 23 patients (25%). Patients were randomised to

either parotid sparing IMRT or standard care with 48 (52.2%) receiving IMRT versus 44 (47.8%) receiving conventional RT. Two patients did not complete RT.

3.6.1.1 Prevalence of PRTD and PRSD over time

At baseline the rate of G3+PRTD was 17%. Rates of G3+PRTD peaked at 52%, 3m after completion of RT. Toxicity was persistent at 6m (51%) but by 24m had reduced to 30%. While the focus was the pattern of grade 3+ toxicity, at 3m only 16% described 'no problems at all' with their taste, compared with 60% at baseline. By 24m follow up this had only recovered to 20% (table 5 and figure 3-5).

At baseline the rate of G3+PRSD was 6%. Rates of grade 3+PRSD remained relatively low throughout the study period, peaking at 23%, 12m after RT with signs of resolution over the following 6-12m (table 6 and figure 3-6).

HN35 Q44 (taste)	**0m n = 65**	**3m n = 73**	**6m n = 65**	**12m n = 63**	**18m n = 60**	**24m n = 50**
Grade 1 (not at all)	39 (60%)	12 (16%)	10 (15%)	15 (24%)	13 (22%)	10 (20%)
Grade 2 (a little)	15 (23%)	23 (32%)	22 (34%)	23 (37%)	23 (38%)	25 (50%)
Grade 3 (quite a bit)	5 (8%)	21 (29%)	17 (26%)	15 (24%)	14 (23%)	9 (18%)
Grade 4 (very much)	6 (9%)	17 (23%)	16 (25%)	10 (16%)	10 (17%)	6 (12%)
Grade 3+	11 (17%)	38 (52%)	33 (51%)	25 (40%)	24 (40%)	15 (30%)
Grade 2+	26 (40%)	61 (84%)	55 (85%)	48 (77%)	47 (78%)	40 (80%)

Table 5: PRTD over time for patients treated within the PARSPORT study

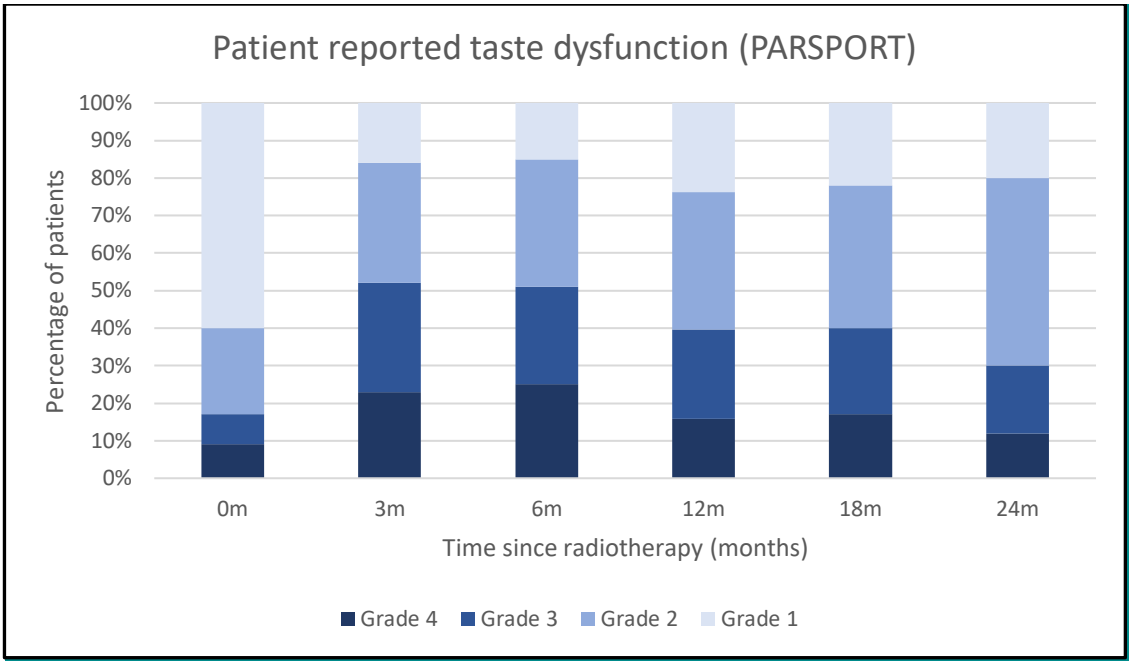


Figure 3-5: PRTD over time for patients treated within the PARSPORT study

HN35 Q43 (smell)	0m n = 68	3m n = 73	6m n = 65	12m n = 62	18m n = 60	24m n = 50
Grade 1 (not at all)	56 (82%)	50 (68%)	42 (65%)	39 (63%)	40 (67%)	33 (66%)
Grade 2 (a little)	8 (12%)	10 (14%)	11 (17%)	9 (15%)	10 (17%)	10 (20%)
Grade 3 (quite a bit)	4 (6%)	9 (12%)	6 (9%)	6 (10%)	7 (12%)	4 (8%)
Grade 4 (very much)	0 (0%)	4 (5%)	6 (9%)	8 (13%)	3 (5%)	3 (6%)
Grade 3+	4 (6%)	13 (18%)	12 (18%)	14 (23%)	10 (17%)	7 (14%)
Grade 2+	12 (18%)	23 (31%)	23 (35%)	23 (38%)	20 (34%)	17 (34%)

Table 6: PRSD over time for patients treated within the PARSPORT study

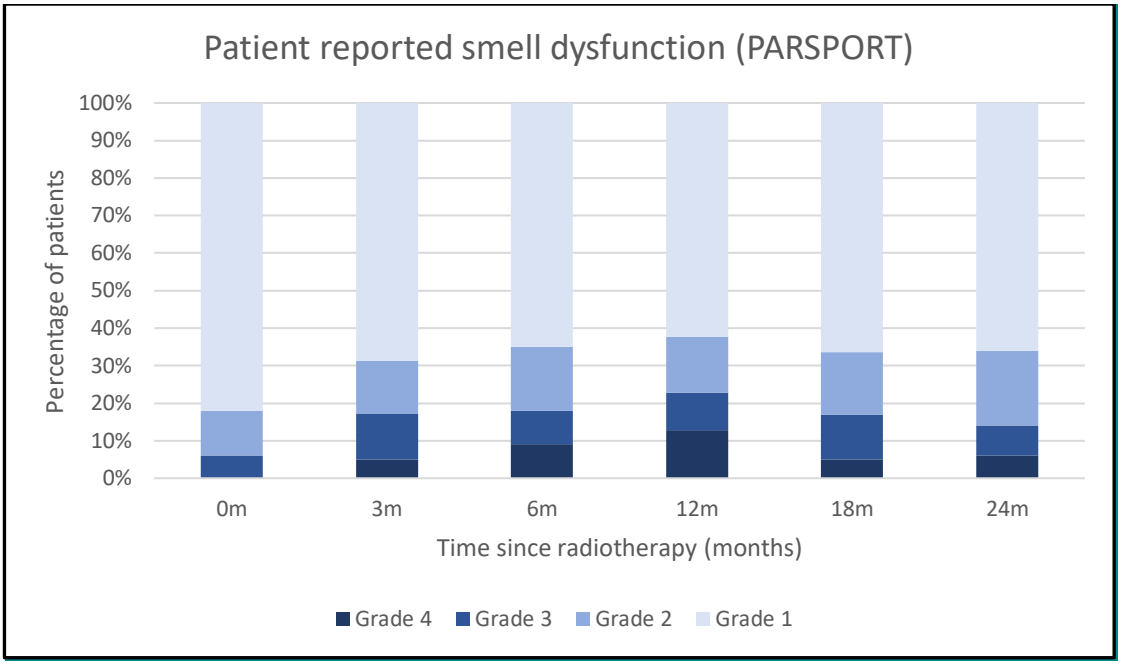


Figure 3-6: Patient reported smell dysfunction over time for patients treated within the PARSPORT study

3.6.1.2 Patient and treatment related factors associated with PRTD

The prevalence of G3+PRTD by age, sex, stage, post-operative status, chemotherapy status, presence of grade 3 or worse patient-reported xerostomia (G3+PRX) and G3+PRSD at each study time point are tabulated below (tables 7-12). Statistically significant associations are highlighted. In general there was a consistent association between G3+PRSD, G3+PRX and G3+PRTD.

	G1/2 PRTD n (%)	G3/4 PRTD n (%)	p value (Fishers exact)
Age >60	24 (82.8%)	5 (17.2%)	>0.999
Age <60	30 (83.3%)	6 (16.7%)	
Male	42 (87.5%)	6 (12.5%)	0.14
Female	12 (70.6%)	5 (29.4%)	
Stage I/II	41 (82.0%)	9 (18.0%)	>0.999
Stage III/IV	13 (86.7%)	2 (13.3%)	
PORT	14 (93.3%)	1 (6.7%)	0.43
Primary RT	40 (80.0%)	10 (20.0%)	
Chemotherapy	21 (77.8%)	6 (22.2%)	0.50
No Chemotherapy	33 (86.8%)	5 (13.2%)	
G1/2 PRX	47 (88.7%)	6 (11.3%)	0.02
G3/4 PRX	7 (58.3%)	5 (41.7%)	
G1/2 PRSD	53 (85.5%)	9 (14.5%)	0.07
G3/4 PRSD	1 (33.3%)	2 (66.7%)	

Table 7: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at baseline

	G1/2 PRTD n (%)	G3/4 PRTD n (%)	p value
Age >60	13 (43.3%)	17 (56.7%)	0.63
Age <60	22 (51.2%)	21 (48.8%)	
Male	27 (46.6%)	31 (53.4%)	0.77
Female	8 (53.3%)	7 (46.7%)	
Stage I/II	11 (61.1%)	7 (38.9%)	0.28
Stage III/IV	24 (43.6%)	31 (56.4%)	
PORT	10 (52.6%)	9 (47.4%)	0.79
Primary RT	25 (46.3%)	29 (53.7%)	
Chemotherapy	16 (47.1%)	18 (52.9%)	>0.999
No Chemotherapy	19 (48.7%)	20 (51.3%)	
G1/2 PRX	8 (61.5%)	5 (38.5%)	0.36
G3/4 PRX	27 (45.0%)	33 (55.0%)	
G1/2 PRSD	34 (56.7%)	26 (43.3%)	0.0015
G3/4 PRSD	1 (7.7%)	12 (92.3%)	

Table 8: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at 3 months

	G1/2 PRTD (n)	G3/4 PRTD (n)	p value
Age >60	14 (58.3%)	10 (41.7%)	0.61
Age <60	19 (50.0%)	19 (50.0%)	
Male	27 (64.3%)	15 (35.7%)	0.02
Female	6 (30.0%)	14 (70.0%)	
Stage I/II	23 (46.9%)	26 (53.1%)	0.57
Stage III/IV	9 (56.3%)	7 (43.8%)	
PORT	8 (47.1%)	9 (52.9%)	>0.999
Primary RT	24 (50.0%)	24 (50.0%)	
Chemotherapy	15 (51.7%)	14 (48.3%)	0.81
No Chemotherapy	17 (47.2%)	19 (52.8%)	
G1/2 PRX	11 (73.3%)	4 (26.7%)	0.04
G3/4 PRX	21 (42.0%)	29 (58.0%)	
G1/2 PRSD	32 (60.4%)	21 (39.6%)	0.0001
G3/4 PRSD	0 (0.0%)	12 (100.0%)	

Table 9: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at 6 months

	G1/2 PRTD (n)	G3/4 PRTD (n)	p value
Age >60	13 (54.2%)	11 (45.8%)	0.60
Age <60	25 (64.1%)	14 (35.9%)	
Male	31 (62.0%)	19 (38.0%)	0.75
Female	7 (53.8%)	6 (46.2%)	
Stage I/II	9 (60.0%)	6 (40.0%)	<0.999
Stage III/IV	29 (60.4%)	19 (39.6%)	
PORT	13 (68.4%)	6 (31.6%)	0.42
Primary RT	25 (56.8%)	19 (43.2%)	
Chemotherapy	15 (57.7%)	11 (42.3%)	0.80
No Chemotherapy	23 (62.2%)	14 (37.8%)	
G1/2 PRX	17 (89.5%)	2 (10.5%)	0.002
G3/4 PRX	21 (47.7%)	23 (52.3%)	
G1/2 PRSD	37 (77.1%)	11 (22.9%)	<0.0001
G3/4 PRSD	1 (7.1%)	13 (92.9%)	

Table 10: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at 12 months

	G1/2 PRTD (n)	G3/4 PRTD (n)	p value
Age >60	8 (34.8%)	15 (65.2%)	0.003
Age <60	28 (75.7%)	9 (24.3%)	
Male	28 (62.2%)	17 (37.8%)	0.56
Female	8 (53.3%)	7 (46.7%)	
Stage I/II	11 (68.8%)	5 (31.3%)	0.55
Stage III/IV	25 (56.8%)	19 (43.2%)	
PORT	25 (56.u8%)	19 (43.2%)	0.55
Primary RT	11 (68.8%)	5 (31.3%)	
Chemotherapy	17 (68.0%)	8 (32.0%)	0.42
No Chemotherapy	19 (54.3%)	16 (45.7%)	
G1/2 PRX	14 (77.8%)	4 (22.2%)	0.09
G3/4 PRX	22 (52.4%)	20 (47.6%)	
G1/2 PRSD	34 (68.0%)	16 (32.0%)	0.01
G3/4 PRSD	2 (20.0%)	8 (80.0%)	

Table 11: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at 18 months

	G1/2 PRTD (n)	G3/4 PRTD (n)	p value
Age >60	9 (52.9%)	8 (47.1%)	0.10
Age <60	26 (78.8%)	7 (21.2%)	
Male	30 (75.0%)	10 (25.0%)	0.14
Female	5 (50.0%)	5 (50.0%)	
Stage I/II	10 (90.09%)	1 (9.1%)	0.14
Stage III/IV	25 (64.1%)	14 (35.9%)	
PORT	23 (65.7%)	12 (34.3%)	0.50
Primary RT	12 (80.0%)	3 (20.0%)	
Chemotherapy	13 (68.4%)	6 (31.6%)	0.40
No Chemotherapy	22 (53.7%)	19 (46.3%)	
G1/2 PRX	16 (84.2%)	3 (15.8%)	0.12
G3/4 PRX	19 (61.3%)	12 (38.7%)	
G1/2 PRSD	32 (74.4%)	11 (25.6%)	0.06
G3/4 PRSD	2 (33.3%)	4 (66.7%)	

Table 12: Prevalence of PRTD by age, sex, stage, post-operative status, chemotherapy, PRX and PRSD at 24 months

Univariate analysis using logistic regression showed no statistically significant association between G3+PRTD and sex, post-operative status, use of neo-adjuvant chemotherapy, more advanced stage III/IV disease or the use of IMRT at any time point during the study (table 13). On the whole, age above or below 60 years, was not associated with a higher prevalence of G3+PRTD except at 18m there was a statistically significant association (p=0.002) though this is likely an anomaly. There was a statistically significant association between G3+PRTD and G3+PRX at baseline (odds ratio 5.60, 95%CI 1.32 to 24.11), 6m (odds ratio 3.80, 95%CI 1.13 to 15.24) and 12m (odds ratio 9.31, 95%CI 2.3 to 63.26). There was also a statistically significant association between G3+PRSD at baseline (odds ratio 11.78, 95%CI 1.03 to 269.5), 3m (odds ratio 15.69, 95%CI 2.82 to 295), 6m (linear dependence where every patient with G3+PRSD also had G3+PRTD), 12m (odds ratio 43.73, 95%CI 7.48 to 840.1), 18m (odds ratio 8.5, 95%CI 1.88 to 60.76) and a trend towards significance at 24m (odds ratio 5.82, 95%CI 1.00 to 46.4). For the purposes of this exploratory analysis, correction for multiple testing was not undertaken.

		0m	3m	6m	12m	18m	24m
Age >60 vs <60	**OR**	1.04	1.37	0.95	1.51	5.83	3.30
	95% CI	0.27 to 3.87	0.54 to 3.54	0.35 to 2.54	0.54 to 4.30	1.93 to 19.20	0.94 to 12.16
Sex F vs M	**OR**	2.92	0.76	0.96	1.40	1.44	3.0
	95% CI	0.73 to 11.43	0.24 to 2.39	0.27 to 3.45	0.40 to 4.84	0.43 to 4.74	0.70 to 13.04
IMRT vs Conventional RT	**OR**	0.59	0.75	0.83	0.54	2.08	0.58
	95% CI	0.15 to 2.20	0.30 to 1.89	0.31 to 2.20	0.19 to 1.49	0.73 to 6.16	0.17 to 1.98
PORT vs primary RT	**OR**	0.29	0.78	1.13	0.61	0.61	0.48
	95% CI	0.01 to 1.71	0.27 to 2.22	0.37 to 3.47	0.18 to 1.84	0.17 to 1.95	0.10 to 1.87
Stage III/IV vs Stage I/II	**OR**	1.43	2.03	1.45	0.98	1.67	5.60
	95% CI	0.32 to 10.14	0.69 to 6.27	0.47 to 4.67	0.30 to 3.35	0.51 to 6.06	0.92 to 108.2
Chemo vs No Chemo	**OR**	1.89	1.07	0.84	1.21	0.56	1.13
	95% CI	0.51 to 7.31	0.42 to 2.70	0.31 to 2.23	0.43 to 3.37	0.19 to 1.61	0.32 to 3.88
G3/4 PRX vs G1/2 PRX	**OR**	5.60	1.96	3.80	9.31	3.18	3.37
	95% CI	1.32 to 24.11	0.58 to 7.13	1.13 to 15.24	2.30 to 63.26	0.96 to 12.69	0.88 to 16.71
G3/4 PRSD vs G1/2 PRSD	**OR**	11.78	15.69	LD	43.73	8.5	5.82
	95% CI	1.03 to 269.5	2.82 to 295.0	LD	7.48 to 840.1	1.88 to 60.76	1.00 to 46.40

Table 13: Univariate analysis to look for predictors of PRTD within the PARSPORT study (Odds Ratio, OR; Confidence Interval, CI; Female, F; Male, M; Chemotherapy, Chemo; LD, linear dependence)

3.6.1.3 Gustatory Function and Overall Quality of Life

Mean changes in overall QoL from baseline in those with and without G3+PRTD were compared at all time points using an unpaired two-tailed t-test. At 3m, 6m, 12m, 18m and 24m after RT, GHS scores were consistently higher (better) in those without G3+PRTD. According to the EORTC guidelines this would be deemed clinically relevant at 18m and 24m (a difference in GHS of 10 is clinically significant) (90) though at no time-point was this statistically significant (table 14).

	3m	6m	12m	18m	24m
G3/4 PRTD	-8.97	-2.67	0.93	-7.89	-6.94
G1/2 PRTD	-4.17	0.69	2.38	6.00	5.95
Difference	4.8	-3.36	1.45	13.89	12.9
95% CI	-21.3 to 11.7	-20.4 to 13.7	-17.9 to 15.1	-31.1 to 3.3	-31.3 to 5.5
p-value	0.56	0.69	0.86	0.11	0.17

Table 14: Mean changes in overall GHS scores in those with or without G3+PRTD in PARSPORT

Mean GHS scores were consistently lower in those with G3+PRTD versus those without and this was statistically significant at all time points following completion of RT (table 15).

	0m	3m	6m	12m	18m	24m
G3/4 PRTD	65.15	54.05	59.38	60.42	54.17	56.67
G1/2 PRTD	70.15	65.24	70.83	75.44	75.93	79.52
Difference	4.91	11.18	11.46	15.02	21.76	22.86
p-value	0.54	0.04	0.04	0.01	0.0003	0.0019

Table 15: GHS scores in those with or without G3+PRTD in PARSPORT

3.6.1.4 PRTD versus Clinician Reported Taste Dysfunction

CROs for taste function are tabulated below (table 16). The agreement between PROs and CROs for taste dysfunction was assessed. It is important to highlight that the grades of dysfunction using the LENT/SOMA or the EORTC HNQOL questionnaire are not directly comparable. However, PRTD was considered clinically relevant if the response was ‘quite a bit” (grade 3) or “very much’ (grade 4) (see figure 3-3). The equivalent description chosen from the LENT/SOMA scale was ‘intermittent’ (grade 2) or ‘persistent’ (grade 3) (see figure 3-4). Similarly, PRTD scored as ‘not at all’ (grade 1) or ‘a little’ (grade 2) was considered equivalent to a LENT/SOMA score of ‘occasional, slight’ (grade 1). The prevalence of clinically relevant taste dysfunction using the LENT/SOMA (clinician reported measure) followed the same pattern as the prevalence of G3+PRTD but was remarkably and consistently lower (table 17 and figure 3-7).

More comparable prevalence was seen when comparing G3+PRTD and any degree of taste dysfunction detected by clinicians using the LENT/SOMA.

LENT/SOMA (Taste)	**3m n = 83**	**6m n = 80**	**12m n = 74**	**18m n = 59**	**24m n = 55**
Grade 0	30 (36%)	30 (38%)	42 (57%)	33 (56%)	33 (60%)
Grade 1	28 (34%)	35 (44%)	23 (31%)	19 (32%)	17 (31%)
Grade 2	16 (19%)	10 (13%)	7 (9%)	5 (8%)	4 (7%)
Grade 3	9 (11%)	5 (6%)	2 (3%)	2 (3%)	1 (2%)
Grade 2+	25 (30%)	15 (19%)	9 (12%)	7 (11%)	5 (9%)
Grade 1+	53 (64%)	50 (63%)	32 (43%)	26 (44%)	22 (40%)

Table 16: Clinician reported taste dysfunction over time for patients treated within the PARSPORT study

	0m	**3m**	**6m**	**12m**	18m	24m
Grade 3+ (quite a bit/very much) HNQ35 Q44	11 (17%)	38 (52%)	33 (51%)	25 (40%)	24 (40%)	15 (30%)
Grade 2+ (intermittent/persistent) LENT/SOMA		25 (30%)	15 (19%)	9 (12%)	8 (13%)	5 (9%)
Grade 1+ (slight/intermittent/persistent) LENT/SOMA		53 (64%)	50 (63%)	32 (43%)	27 (45%)	22 (40%)

Table 17: Comparison of PRTD using HNQ35 Q44 and clinician reported taste dysfunction using LENT/SOMA scale in the PARSPORT study

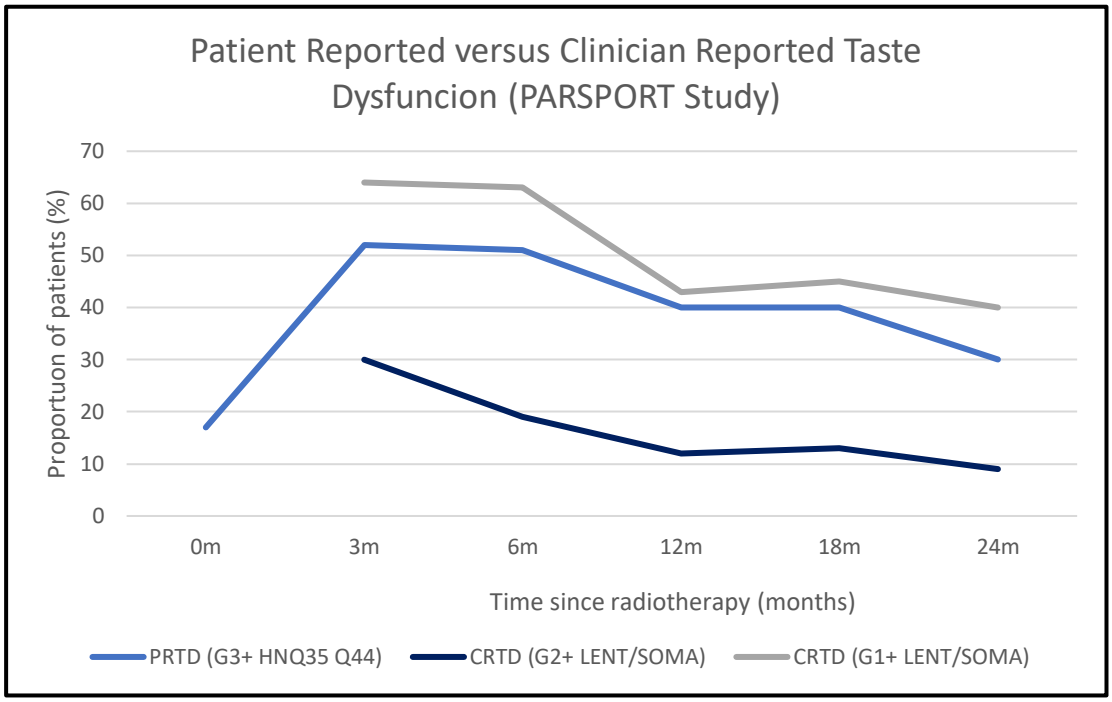


Figure 3-7: Graph showing patient reported (HNQ35 Q44) versus clinician reported taste dysfunction (LENT/SOMA)

There is no validated tool for assessing patient reported outcomes for taste dysfunction. However the sensitivity and specificity for clinicians using the LENT/SOMA at a G2+ threshold to detect patient reported taste dysfunction using the EORTC HNQOL questionnaire was calculated (table 18). Although the LENT/SOMA appears to have reasonable specificity, in this dataset it was arguably not a sensitive tool for detecting PRTD and over time the sensitivity consistently declined (0.37 at 3m, down to 0.09 at 24m).

	TP	TN	FP	FN	Total	Sensitivity	Specificity
3m	13	27	8	22	70	0.37	0.77
6m	10	28	2	19	59	0.34	0.93
12m	3	33	4	19	59	0.14	0.89
18m	3	27	1	17	48	0.15	0.96
24m	1	29	2	10	42	0.09	0.94

Table 18: Sensitivity and Specificity of clinician reported taste dysfunction using LENT/SOMA within the PARSPORT study (TP=true positive; TN=true negative; FP=false positive; FN=false negative)

3.6.2 COSTAR

Of 110 recruited, 106 patients were treated with unilateral RT within the COSTAR study. Patients were randomised to either cochlear sparing IMRT or standard care with 55 receiving IMRT versus 51 receiving conventional radiotherapy. Four patients did not complete RT.

3.6.2.1 Prevalence of PRTD and PRSD over time

Rates of G3+PRTD and G3+PRSD at baseline and during the study follow up period are tabulated below (table 19 and 20). Questionnaire data in particular is lacking at 24m and 60m post completion of treatment. Therefore, results from 24m were interpreted with caution and data from 60m was not analysed (87% missing data).

G3+PRTD was seen in 4% at baseline, peaking at 30% at 6m and falling back to 8% at 24m (table 19 and figure 3-8). G3+PRSD was seen in only 1% at baseline, peaking at 12% at 6 months and then returning to 4% by 24 months (table 20 and figure 3-9).

HN35 Q44 (taste)	**0m n = 95**	**6m n = 70**	**12m n = 70**	**24m n = 56**
Grade 1 (not at all)	80 (84%)	26 (37%)	32 (46%)	29 (52%)
Grade 2 (a little)	11 (12%)	23 (33%)	25 (36%)	23 (41%)
Grade 3 (quite a bit)	3 (3%)	16 (23%)	10 (14%)	2 (4%)
Grade 4 (very much)	1 (1%)	5 (7%)	3 (4%)	2 (4%)
Grade 3+	4 (4%)	21 (30%)	13 (18%)	4 (8%)
Grade 2+	15 (16%)	44 (63%)	38 (54%)	27 (49%)

Table 19: PRTD over time for patients treated within the COSTAR study

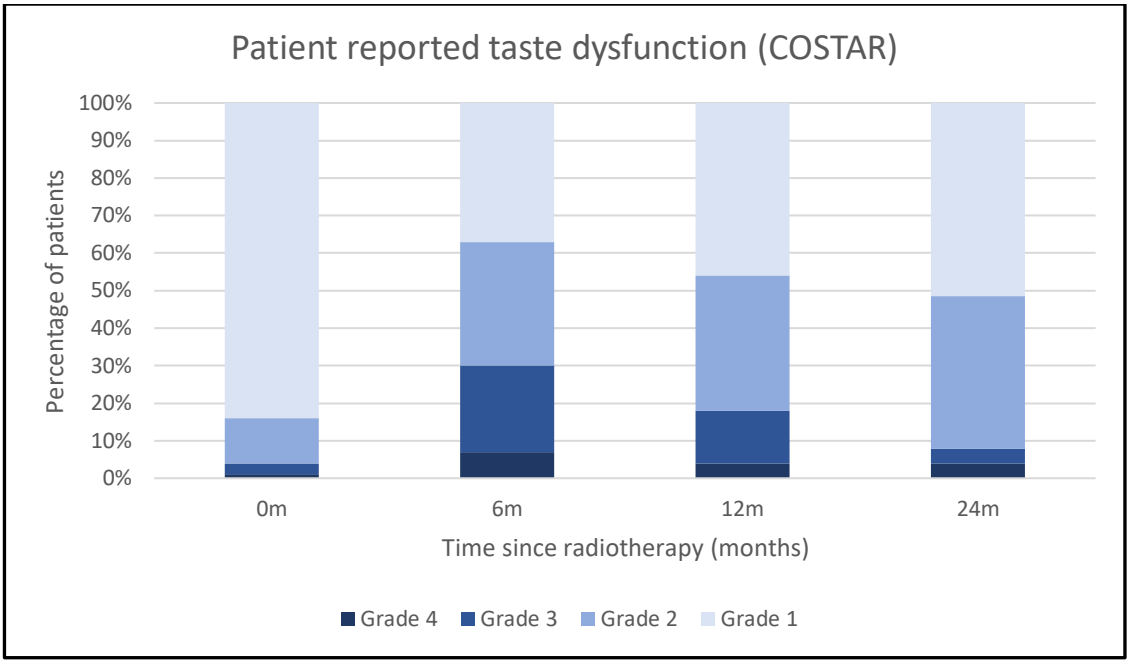


Figure 3-8: PRTD over time for patients treated within the COSTAR study

HN35 Q43 (smell)	**0m N = 95**	**6m N = 71**	**12m N = 70**	**24m N = 57**
Grade 1 (not at all)	88 (93%)	53 (75%)	49 (70%)	43 (75%)
Grade 2 (a little)	6 (6%)	9 (13%)	16 (23%)	12 (21%)
Grade 3 (quite a bit)	1 (1%)	8 (11%)	3 (4%)	1 (2%)
Grade 4 (very much)	0 (0%)	1 (1%)	2 (3%)	1 (2%)
Grade 3+	1 (1%)	9 (12%)	5 (7%)	2 (4%)
Grade 2+	7 (7%)	18 (25%)	21 (30%)	14 (25%)

Table 20. PRSD over time for patients treated within the COSTAR study

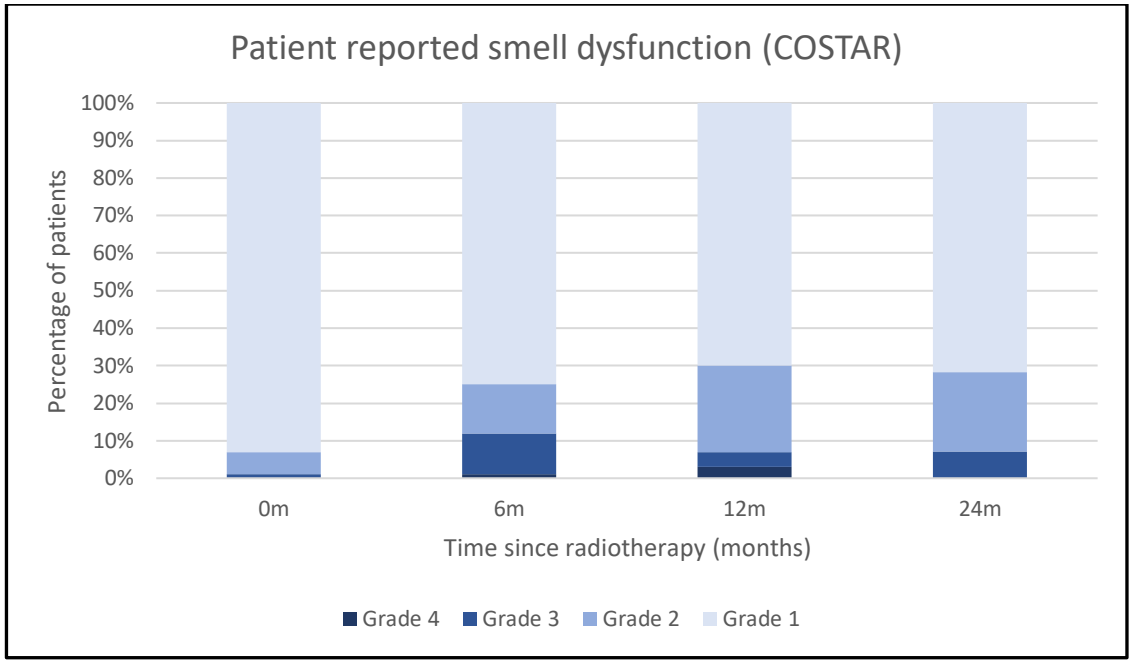


Figure 3-9: PRSD over time for patients treated within the COSTAR study

3.6.2.2 Patient and treatment related factors associated with PRTD

Fisher's exact and univariate logistic regression was used to look for associations between age, sex, stage, G3+PRX, G3+PRSD and G3+PRTD. Results are tabulated below (see table 21-25). On univariate analysis there was a strong association between stage III/IV disease and baseline dysfunction (p=0.04). At baseline, 6m and 12m, G3+PRSD was also strongly associated with G3+PRTD.

	G1/2 PRTD	G3/4 PRTD	p value (Fisher's exact)
Age >60	52 (96.3%)	2 (3.7%)	>0.999
Age <60	39 (95.1%)	2 (4.9%)	
Male	48 (94.1%)	3 (5.9%)	0.62
Female	43 (97.8%)	1 (2.3%)	
Stage I/II	43 (100.0%)	0 (0.0%)	0.04
Stage III/IV	44 (91.7%)	4 (8.3%)	
G1/2 PRX	81 (97.6%)	2 (2.4%)	0.08
G3/4 PRX	10 (83.3%)	2 (16.7%)	
G1/2 PRSD	90 (95.7%)	4 (4.3%)	>0.999
G3/4 PRSD	1 (100.0%)	0 (0.0%)	

Table 21: Prevalence of PRTD by age, sex, stage, PRX and PRSD at baseline

	G1/2 PRTD	G3/4 PRTD	p value (Fisher's exact)
Age >60	28 (68.3%)	13 (31.7%)	0.79
Age <60	21 (72.4%)	8 (27.6%)	
Male	25 (69.4%)	11 (30.6%)	>0.999
Female	24 (70.6%)	10 (29.4%)	
Stage I/II	23 (74.2%)	8 (25.8%)	0.44
Stage III/IV	24 (64.9%)	13 (35.1%)	
IMRT	26 (70.3%)	11 (29.7%)	>0.999
Conventional RT	23 (69.7%)	10 (30.3%)	
G1/2 PRX	26 (76.5%)	8 (23.5%)	0.30
G3/4 PRX	23 (63.9%)	13 (36.1%)	
G1/2 PRSD	49 (79.0%)	13 (21.0%)	<0.0001
G3/4 PRSD	0 (0.0%)	8 (100.0%)	

Table 22: Prevalence of PRTD by age, sex, stage, PRX and PRSD at 6 months

	G1/2 PRTD	G3/4 PRTD	p value (Fisher's exact)
Age >60	34 (82.9%)	7 (17.1%)	0.76
Age <60	23 (79.3%)	6 (20.7%)	
Male	28 (80.0%)	7 (20.0%)	>0.999
Female	29 (82.9%)	6 (17.1%)	
Stage I/II	27 (81.8%)	6 (18.2%)	>0.999
Stage III/IV	29 (82.9%)	6 (17.1%)	
IMRT	32 (84.2%)	6 (15.8%)	0.55
Conventional RT	25 (78.1%)	7 (21.9%)	
G1/2 PRX	37 (92.5%)	3 (7.5%)	0.01
G3/4 PRX	20 (66.7%)	10 (33.3%)	
G1/2 PRSD	57 (87.7%)	8 (12.3%)	0.0001
G3/4 PRSD	0 (0.0%)	5 (100.0%)	

Table 23: Prevalence of PRTD by age, sex, stage, PRX and PRSD at 12 months

	G1/2 PRTD	G3/4 PRTD	p value (Fisher's exact)
Age >60	31 (96.9%)	1 (3.1%)	0.30
Age <60	21 (87.5%)	3 (12.5%)	
Male	26 (96.3%)	1 (3.7%)	0.61
Female	26 (89.7%)	3 (10.3%)	
Stage I/II	25 (96.2%)	1 (3.8%)	0.61
Stage III/IV	24 (88.9%)	3 (11.1%)	
IMRT	29 (93.5%)	2 (6.5%)	>0.99
Conventional RT	23 (92.0%)	2 (8.0%)	
G1/2 PRX	32 (97.0%)	1 (3.0%)	0.29
G3/4 PRX	20 (87.0%)	3 (13.0%)	
G1/2 PRSD	51 (94.4%)	3 (5.6%)	0.14
G3/4 PRSD	1 (50.0%)	1 (50.0%)	

Table 24: Prevalence of PRTD by age, sex, stage, PRX and PRSD at 24 months

		0m	6m	12m	24m
Age >60 vs <60	**OR**	0.75	1.22	0.79	0.23
	95% CI	0.09-6.47	0.43-3.58	0.23-2.74	0.01-1.90
Sex F vs M	**OR**	0.37	0.95	0.83	3.0
	95% CI	0.02-3.03	0.32-2.65	0.24-2.79	0.36-62.84
IMRT vs Conventional	**OR**		0.97	0.67	0.79
	95% CI		0.35-2.74	0.19-2.26	0.09-7.02
Stage III/IV vs Stage I/II	**OR**	LD	1.56	0.93	3.13
	95% CI	LD	0.55-4.60	0.26-3.32	0.37-65.60
G3/4 PRX vs G1/2 PRX	**OR**	8.1	1.84	6.17	4.80
	95% CI	0.89-73.94	0.66-5.40	1.67-29.92	0.57-100.8
G3/4 PRSD vs G1/2 PRSD	**OR**	LD	LD	LD	17.00
	95% CI	LD	LD	LD	0.58-514.2

Table 25. Univariate analysis using logistic regression to look for predictors of G3+PRTD dysfunction within the COSTAR study (LD, linear dependence)

3.6.2.3 PRTD versus Clinician Reported Taste Dysfunction

Table 26 shows the rates of clinician reported taste dysfunction using the LENT/SOMA tool. Table 27 shows the rates of PRTD and the comparative rates identified by clinicians either using a grade 2+ or grade 3+ cut off. Using the

same approach applied to the PARSPORT data, the sensitivity and specificity of using clinician reported LENT/SOMA to detect PRTD was calculated (table 28). As seen within the PARSPORT analysis the sensitivity of the LENT/SOMA to detect clinically significant PRTD was low at 0.24 at 6m, falling to 0.00 at 24m. The prevalence of G3+PRTD was particularly low in the COSTAR cohort which may partially explain the apparent low sensitivity. Specificity was high at all time points.

LENT/SOMA (Taste)	**3m n = 92**	**6m n = 98**	**12m n = 91**	**18m n = 77**	**24m n = 74**	**36m n = 63**	**48m n = 41**
Grade 0	33 (36%)	44 (45%)	60 (66%)	53 (69%)	56 (76%)	53 (84)	35 (85%)
Grade 1	46 (50%)	43 (44%)	27 (30%)	22 (29%)	15 (20%)	9 (14%)	6 (15%)
Grade 2	7 (8%)	7 (7%)	0 (0%)	1 (1%)	1 (1%)	1 (2%)	0 (0%)
Grade 3	6 (7%)	4 (4%)	4 (4%)	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Grade 2+	13 (15%)	11 (11%)	4 (4%)	1 (2%)	3 (4%)	1 (2%)	0 (0%)
Grade 1+	59 (64%)	54 (55%)	31 (34%)	24 (31%)	18 (24%)	10 (16%)	6 (15%)

Table 26: Clinician reported taste dysfunction over time for patients treated within the COSTAR study

	0m	**6m**	**12m**	**24m**
Grade 3+ (quite a bit/very much) HNQ35 Q44	4 (4%)	21 (30%)	13 (18%)	4 (8%)
Grade 2+ (intermittent/persistent) LENT/SOMA		11 (11%)	4 (4%)	3 (4%)
Grade 1+ (slight/intermittent/persistent) LENT/SOMA		54 (55%)	31 (34%)	18 (24%)

Table 27: Comparison of patient reported taste dysfunction using HNQ35 Q44 and clinician reported taste dysfunction using LENT/SOMA scale in the COSTAR study

	TP	TN	FP	FN	Total	Sensitivity	Specificity	Prevalence G3+PRTD
6m	5	45	3	16	69	0.24	0.94	30%
12m	2	56	1	11	70	0.15	0.98	19%
24m	0	48	3	3	54	0.00	0.94	6%

Table 28: Sensitivity and Specificity of clinician reported taste dysfunction using LENT/SOMA within the COSTAR study (TP=true positive; TN=true negative; FP=false positive; FN=false negative). Nb. Prevalence of G3 PRTD is reported for those with both a LENT/SOMA and questionnaire assessment

3.6.2.4 PRTD and Overall QoL

Mean changes in GHS scores in those with or without G3+PRTD were compared using the unpaired two tailed t-test. Although scores were higher (better) at 12m and 24m in those without G3+PRTD, the difference was neither clinically, nor statistically significant (table 29).

	6m	12m	24m
PRTD	0.00	0.00	4.17
No PRTD	0.83	4.25	8.33
Diff	0.83	4.25	4.17
95% CI	-13.55 to 15.22	-16.27 to 7.78	28.37 to 20.03
p-value	0.91	0.48	0.73

Table 29: Mean changes in GHS scores in those with or without patient-reported taste dysfunction in COSTAR

Mean GHS scores in those without G3+PRTD were higher in particular at 6m and 12m though by 24m GHS scores were comparable and there was no statistically significant difference between the group (table 30.)

	0m	6m	12m	24m
PRTD	62.50	62.50	65.38	79.17
No PRTD	73.97	76.87	78.36	80.72
Diff	11.47	14.37	12.98	1.55
p-value	0.28	0.02	0.02	0.87

Table 30: Mean GHS scores in those with or without G3+PRTD in COSTAR (note. low numbers of PRTD at baseline and 24m)

3.6.3 PARSPORT versus COSTAR

3.6.3.1 Comparison of patient reported taste and smell dysfunction over time (PARSPORT versus COSTAR)

Rates of G3+PRTD were consistently higher in those who received bilateral RT for pharyngeal cancers within the PARSPORT study compared with those who received unilateral post-operative RT for salivary gland tumours within COSTAR, and this was statistically significant at all comparable time points including pre-treatment (tables 31-32, figure 3-10). Odds ratios for developing G3+PRTD with bilateral RT (in PARSPORT) versus unilateral RT (in COSTAR) are presented (table 33). Odds ratios were borderline statistically significant at baseline and 6m but clearly significant at 12m and 24m.

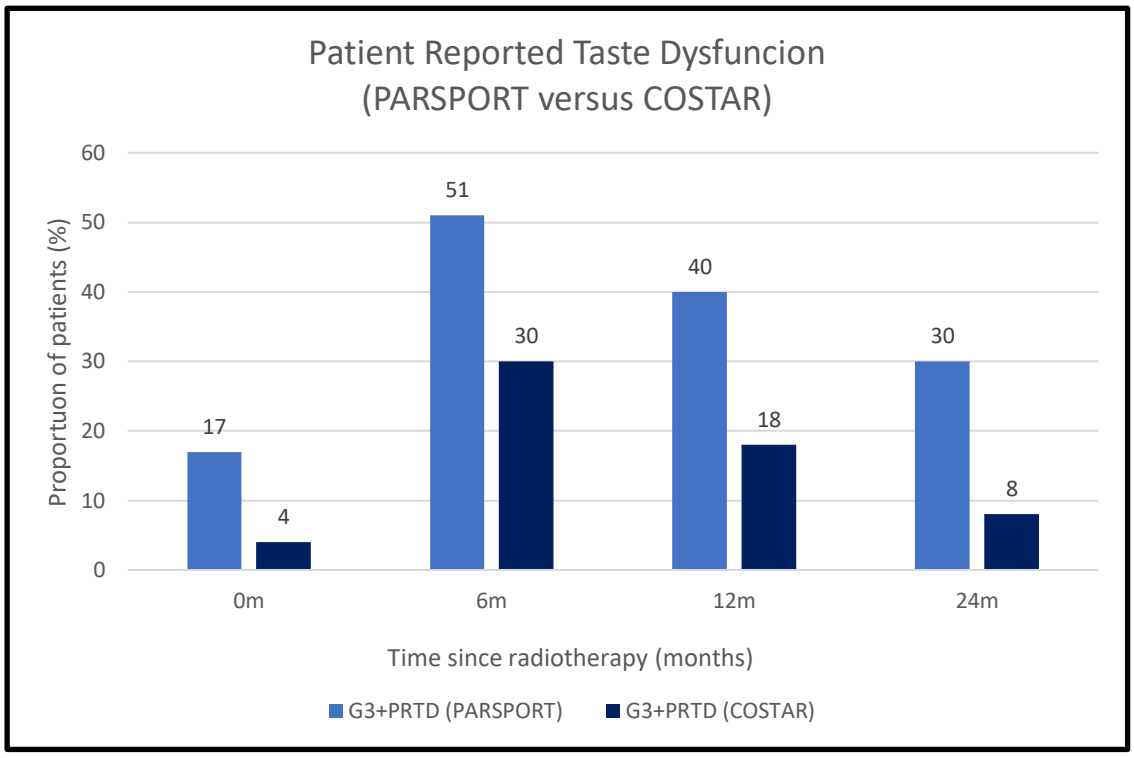


Figure 3-10: Patient reported taste dysfunction over time in those treated with bilateral (PARSPORT) versus unilateral (COSTAR) radiotherapy

	COSTAR		PARSPORT		p value
G3+PRTD	**Yes - n (%)**	**No - n (%)**	**Yes - n (%)**	**No - n (%)**	
0m	4 (4.2%)	91 (95.8%)	11 (16.9%)	54 (83.1%)	0.01
6m	21 (30.0%)	49 (70.0%)	33 (50.8%)	32 (49.2%)	0.02
12m	13 (18.6%)	57 (81.4%)	25 (39.7%)	38 (60.3%)	0.01
24m	4 (7.1%)	52 (92.9%)	15 (30.0%)	35 (70.0%)	0.004

Table 31: Rates of G3+PRTD in unilateral (COSTAR) versus bilateral (PARSPORT) radiotherapy

	COSTAR		PARSPORT		Odds ratio	p value
G3+PRTD	**Yes**	**No**	**Yes**	**No**		
0-24m	42	249	84	159	1.83	<0.0001

Table 32: Rates of G3+PRTD in unilateral (COSTAR) versus bilateral (PARSPORT) as any time point during the study

Time Point	Odds Ratio Estimate	95% CI	p value
0m	3.11	1.01 to 11.65	0.06
6m	1.89	0.94 to 3.88	0.08
12m	3.29	1.45 to 8.06	0.006
24m	5.71	1.75 to 25.83	0.009

Table 33: Odds ratio for G3+PRTD in PARSPORT vs COSTAR at 0m, 6m, 12m and 24m post completion of RT

Figure 3-11 shows the rates of G3+PRSD in each study. Using Fishers exact there was no statistically significant difference in the rates of G3+PRSD at each comparable timepoint (table 34, figure 3-11). When data from all time points was pooled (table 35) the odds ratio for developing G3+PRSD following bilateral RT within the PARSPORT study was 2.53 (p=0.0023).

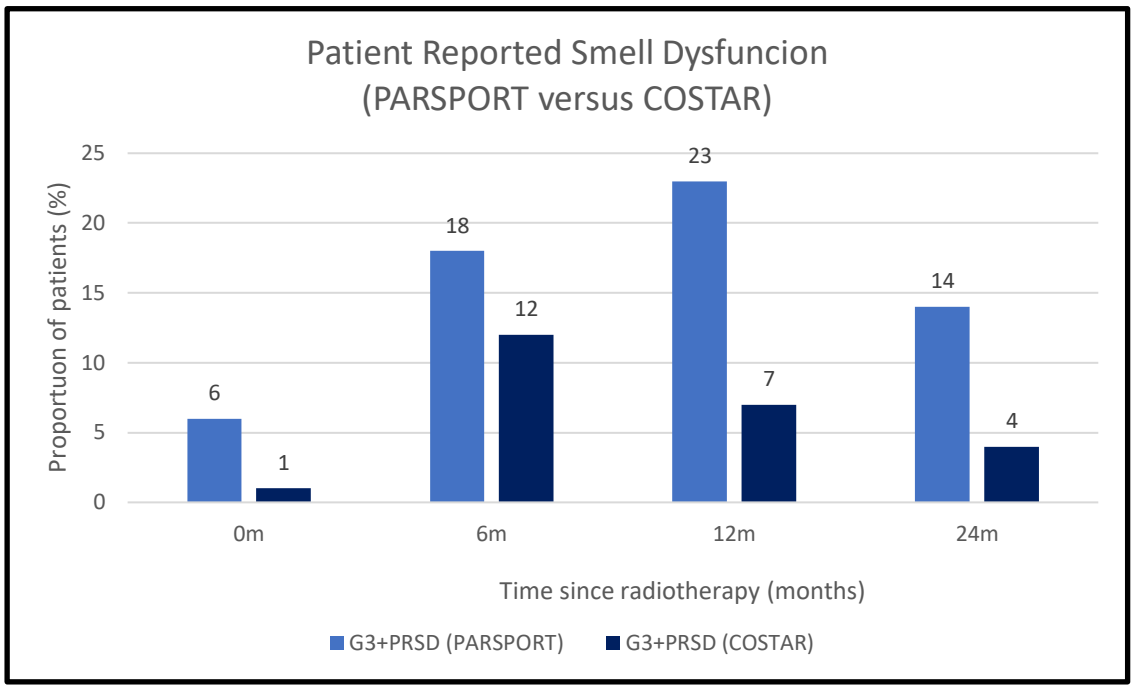


Figure 3-11: G3+PRSD over time in those treated with bilateral (PARSPORT) versus unilateral (COSTAR) radiotherapy

	COSTAR		PARSPORT		p value
PRSD	**Yes**	**No**	**Yes**	**No**	
0m	1	94	4	64	0.16
6m	9	62	12	53	0.48
12m	5	31	14	48	0.43
24m	2	55	7	43	0.08

Table 34: Rates of G3+PRSD in unilateral (COSTAR) versus bilateral (PARSPORT) radiotherapy

	COSTAR		PARSPORT		Odds ratio	p value
PRSD	**Yes**	**No**	**Yes**	**No**		
0-24m	17	242	37	208	2.53	0.002

Table 35: Rates of G3+PRSD in unilateral (COSTAR) versus bilateral (PARSPORT) as any time point during the study

3.6.3.2 Patient and treatment related factors associated with PRTD

Data from both studies were pooled to look for predictor variables associated with G3+PRTD at 6m. Those undergoing bilateral RT were twice as likely to

develop G3+PRTD (p=0.01) though baseline dysfunction was the strongest predictor (odds ratio 8.0, p=0.01).

Variable	Odds Ratio	95% CI	p value
G3 PRTD 0m	8.000	1.93 to 54.38	0.01
Age >60	0.93	0.47 to 1.85	0.83
Female	0.72	0.34 to 1.49	0.37
Stage 3/4	1.83	0.88 to 3.91	0.11
PORT	0.53	0.25 to 1.08	0.08
Chemotherapy	1.54	0.67 to 3.54	0.31
Bilateral RT	2.41	1.20 to 4.93	0.01

Table 36: Univariate logistic regression on pooled results from COSTAR and PARSPORT showing significant predictors of taste dysfunction at 6m

3.6.3.3 PRTD versus clinician reported taste dysfunction

Data from both studies was combined and once again the sensitivity of the LENT/SOMA to detect G3+PRTD was analysed. The same pattern of poor sensitivity which declines over the follow up period was seen (table 37).

	TP	TN	FP	FN	Total	Sensitivity	Specificity
6m	15	73	24	27	139	0.36	0.75
12m	5	89	5	30	129	0.14	0.94
24m	1	77	3	21	102	0.05	0.96

Table 37: Sensitivity and Specificity of clinician reported taste dysfunction using LENT/SOMA from PARSPORT and COSTAR combined (TP=true positive; TN=true negative; FP=false positive; FN=false negative)

3.6.3.4 Example dosimetry for typical PARSPORT and COSTAR participants

Mean RT dose (Gy) to the gustatory OAR were not available for analysis. Archival plans from four patients treated within each study at The Royal Marsden Hospital (RMH) (2 IMRT plans and 2 conventional RT plans) were randomly selected and retrospectively contoured to estimate dosimetry to the gustatory

ROI. Please see Chapter 5 section 5.3.6 for details on how gustatory ROI were contoured. Doses are presented in equivalent dose in 2 Gy per fraction (EQD2).

Within PARSPORT, a 5-field IMRT plan produced mean doses to the OC of 64.3 Gy and 65.1 Gy with even higher doses to the tongue ranging from 63.4 Gy to 67.0 Gy. Conventional planning offered lower doses to the OC of 54.1 Gy and 59.8 Gy with even lower doses to the tongue ranging from 45.8 Gy to 68.9 Gy (table 39). Within COSTAR, mean doses to the OC and tongue were lower than in PARSPORT. It is possible that the COSTAR cohort treated with IMRT received the lowest doses to the gustatory field though more plans would need to be reviewed in order to confirm this (table 38-39).

Patient	Planning Technique	Oral Cavity	Whole Tongue	Anterior 2/3 tongue	Posterior 1/3 tongue
A	5 field IMRT	65.13	66.66	66.43	66.92
B	5 field IMRT	64.27	65.36	63.5	67.0
C	Conventional	54.10	54.01	45.8	68.85
D	Conventional	59.78	61.66	61.64	61.69

Table 38: Mean doses (Gy) in EQD2 (alpha:beta 3) to gustatory organs-at-risk for IMRT versus conventional RT from 4 randomly selected PARSPORT patients

Patient	Planning Technique	Oral Cavity	Whole Tongue	Anterior 2/3 tongue	Posterior 1/3 tongue
A	7 field IMRT	33.04	30.96	23.93	37.54
B	7 field IMRT	38.25	36.55	30.83	42.53
C	Conventional	37.56	35.56	27.01	43.64
D	Conventional	39.45	37.73	33.02	46.45

Table 39: Mean doses (Gy) in EQD2 (alpha/beta 3) for gustatory organs-at-risk for IMRT versus conventional RT from 4 randomly selected COSTAR participants

The rates of G3+PRTD reported at any time point in those receiving IMRT or conventional RT within each study is presented below (figure 3-12). There was no statistically significant difference in the prevalence of any grade of PRTD between IMRT and conventional techniques within COSTAR (p=0.48) or PARSPORT (p=0.49).

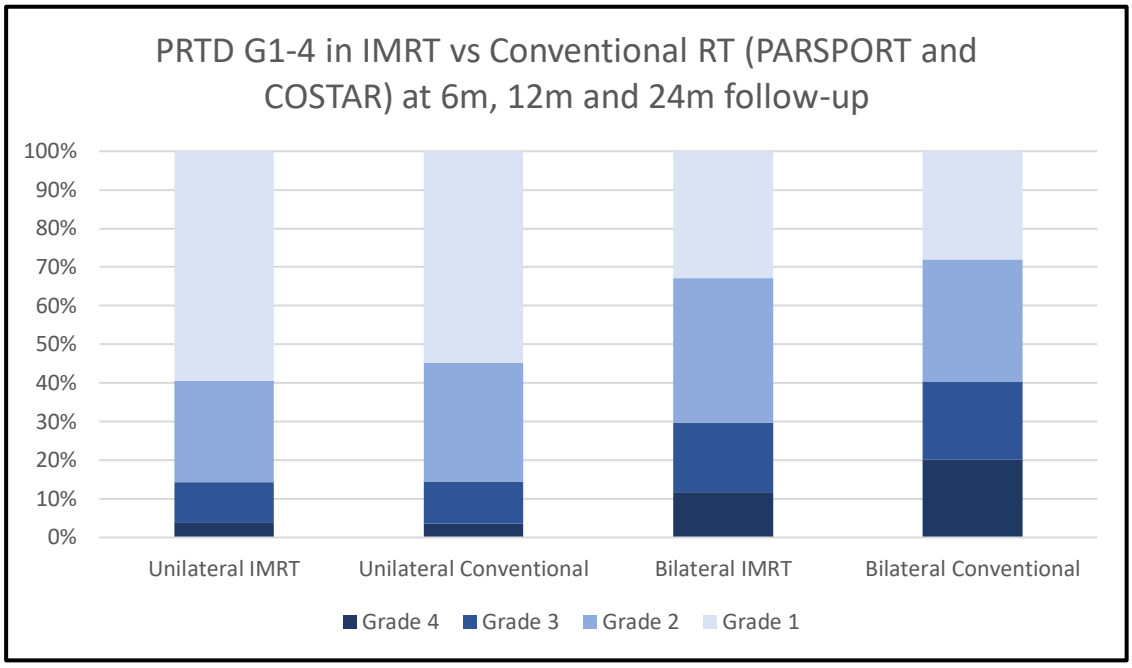


Figure 3-12: PRTD reported at 6m, 12m or 24m in IMRT versus Conventional Radiotherapy in those treated with bilateral (PARSPORT) or unilateral (COSTAR) radiotherapy

3.7 Discussion

This is the first study, including just under 200 patients, to compare taste outcomes in bilateral versus unilateral RT. The peak prevalence of G3+PRTD following bilateral RT (PARSPORT) was 52% with similar rates seen at 3m and 6m after completion of treatment. In the cohort treated with unilateral RT (COSTAR), peak prevalence was 30% at 6m. In both studies these were the first time points where patient reported outcomes following completion of treatment were collected. Previous studies have shown that the highest prevalence of dysfunction is seen immediately after completion of RT (57,58) and it is therefore likely that rates of acute toxicity were higher in the initial post treatment phase.

The prevalence of G3+PRSD was lower, peaking at 23% in PARSPORT at 12m and 12% in COSTAR at 6m. The nature of the dysfunction (hyposmia versus hyperosmia) cannot be determined from the HNQ35 which only asks patients to select to what extent they have a problem, rather than a description of the problem itself. The nature of patient reported taste and smell dysfunction will be explored in more detail in chapter 5 and 6.

The primary objective of this analysis was to compare the rates of gustatory toxicity in both studies with a hypothesis that rates would be higher in those treated with bilateral RT. Prevalence of G3+PRTD was indeed, consistently higher in those treated with bilateral RT within the PARSPORT study and this was statistically significant at all comparable timepoints (0m, p=0.01; 6m, p=0.02; 12m, p=0.01; 24m, p=0.004). Although the prevalence of G3+PRSD was also higher in those treated with bilateral RT, the differences were not statistically significant.

The difference in rates of taste and smell dysfunction between the groups is not wholly due to the laterality of the RT received as there were higher rates of G3+PRTD in PARSPORT even at baseline. It is possible this difference was due to other discrepancies between the patient characteristics. PARSPORT patients had oropharyngeal and hypopharyngeal tumours (as opposed to salivary gland); a higher proportion of advanced stage disease and 74% had received neo-adjuvant chemotherapy (as opposed to 0% in COSTAR). Although not reported, the proportion of patients with SCC of the head and neck (patients from the PARSPORT study) who smoke and drink alcohol is very likely to have been higher than in the COSTAR cohort, which had a higher number of women and tumour types not associated with a prior smoking and alcohol intake. It is interesting though, that G3+PRX was the only statistically significant predictor for baseline G3+PRTD in the PARSPORT cohort when you consider that the entire COSTAR population had undergone a prior parotidectomy. Despite this, in COSTAR only 9% of patients had G3+PRX at baseline, compared with 18% in PARSPORT. Predictors of baseline G3+PRTD and its relationship to subsequent toxicity following RT will be explored further in chapter 4.

At a number of time points in both studies, G3+PRSD and G3+PRX either showed a linear dependence or strong and statistically significant association with G3+PRTD. It is difficult to decipher whether these are associated toxicities or whether there is a causal relationship, but it likely to be combination of the two. Appreciation of flavour is certainly modulated by an intact sense of smell and it is feasible that in those with significant xerostomia there is difficulty in chemical stimuli making effective contact with the taste papillae.

Both PARSPORT and COSTAR used the LENT/SOMA tool to collect CRO for late toxicity. The rates of clinically relevant taste dysfunction between the use of CROs and PROs was inconsistent. Taking G3+PRTD as the reference standard, the sensitivity of the LENT/SOMA to detect clinically relevant taste dysfunction was 0.36 at 6m, 0.14 at 12mand 0.05 at 24m. Specificity was between 0.75 and 0.96. This suggests that even within the context of a multicentre phase 3 trial, clinicians are consistently under-reporting clinically relevant PRTD and potentially other toxicities too. This discordance has been documented elsewhere and the problem is likely to be inherent in any observer-based toxicity assessment (91). It is also interesting that over time the assessment tool was progressively less sensitive suggesting increased clinician bias or a move away from toxicity as the focus in longer term follow up.

Several studies have commented on the relationship between toxicity and dose to the anterior portion of the tongue (46,66,72). A sample of randomly selected RT plans from each study were reviewed to compare the mean doses (Gy) to the oral cavity, whole tongue, anterior 2/3 and posterior 1/3 of the tongue in each arm of each study. Mean doses (Gy) to, and volume of, the gustatory field irradiated were higher in PARSPORT than in COSTAR. Whole oral cavity doses in PARSPORT were estimated to be 64-65 Gy (IMRT-arm) and 54-60 Gy (conventional-arm). Within COSTAR doses were lower at 33-38 Gy (IMRT-arm) and 38-39 Gy (conventional-arm). Within PARSPORT doses to the anterior 2/3 of the tongue were estimated to be 64-66 Gy (IMRT-arm) and 46-62 Gy (conventional arm) and within COSTAR, 24-31Gy (IMRT-arm) and 27-33 Gy (conventional arm). It is possible these differences in dose to the gustatory field are at least partially responsible for the differences in prevalence of G3+PRTD although the sample size for dosimetry analysis was very small.

It is interesting to note that in PARSPORT, the mean dose (Gy) to the gustatory field was higher in those treated with IMRT. It has been shown previously that in patients with nasopharyngeal carcinoma, IMRT can result in lower olfactory and gustatory scores and it is important that clinical oncologists consider how techniques such as IMRT and VMAT may cause higher rates of G3+PRTD through inadvertent redistribution of dose throughout the gustatory field (45).

The mean change in GHS scores were similar between studies with no statistically significant difference at any time point (6m, 12m and 24 months). A sub-group analysis of the PARSPORT study showed that GHS scores were consistently higher (better) in those without G3+PRTD. The magnitude of this difference was clinically important at 18m and 24m, but the effect was not statistically significant.

Strengths of this study include the quality of data available derived from two large, randomised studies, the longitudinal analysis of smell and taste function by both PROs and CROs and an estimation of dose delivered to the gustatory field in each cohort.

Unfortunately, however, there were considerable limitations that require acknowledgement. The groups compared differed considerably in their baseline characteristics. It was clear that a proportion of patients in both studies had taste dysfunction at baseline not attributable to RT and in addition, patients were analysed as a group rather than tracking individual patients longitudinally to look at change in function from before-during-after RT. It was unclear in the PARSPORT cohort whether the baseline questionnaire was completed prior to, or following, induction chemotherapy which may have impacted on self-reporting of baseline taste dysfunction. The dosimetry analysis was small, and the patients selected were not case matched to control for confounders.

3.8 Conclusion

The prevalence of late G3+PRTD is higher in those treated with bilateral versus unilateral RT to the head and neck. Additionally, those having bilateral RT are more likely to develop G3+PRSD at some point during their treatment or during the 2 subsequent years of follow up. There is a strong association between G3+PRSD and G3+PRTD and it is likely that G3+PRX is also a contributing or associated factor. Baseline G3+PRTD is present in those with oropharyngeal / hypopharyngeal tumours and to a lesser extent those with salivary gland

tumours, which may be an important predictor of dysfunction up to 6m after RT. Those receiving bilateral RT receive higher doses to the gustatory field than those receiving unilateral radiation and the relationship between dose and gustatory dysfunction should be the focus of ongoing research to develop or estimate a RT planning dose constraint for taste. There was no difference in the prevalence of G3+PRTD in those treated with conventional versus IMRT. In this study, clinician reporting using the LENT/SOMA was not a sensitive tool for detecting clinically relevant G3+PRTD (using the EORTC-HNQ35) with a significant underreporting of the prevalence of taste dysfunction. Ideally future studies should combine objective chemosensory testing and prioritise the use of PROs for toxicity outcomes in taste research.

I decided that it would be useful to validate these findings in a larger dataset such as the HN5000 study and to explore the relationship between dose to the gustatory field and gustatory outcomes in a cross-sectional or better still, prospective setting. These studies are presented in the next 3 chapters (chapters 4, 5 and 6).

Chapter 4 – Gustatory Function Following Treatment for Head and Neck Cancer: Results from HN5000, a prospective observational cohort of people with head and neck cancer.

4.1 Background

The HN5000 study was large multicentre (UK) cohort study including 5511 people with HNC (92). This observational study combined the collection of biological samples and clinical data with patient-reported outcomes in a single cohort study to provide a large database for translational and prognostic research in the field. The full study protocol has been published elsewhere (92), but in brief the study included people with a newly diagnosed head and neck cancer and collected patient, treatment and outcome data at baseline, 4m, 12m months and 3 years.

As discussed in chapter 2 and chapter 3, patients frequently complain of taste dysfunction following completion of treatment and in the months and years that follow. However, there are no large prospective studies reporting the prevalence of PRTD at baseline and the first year of follow up. Data from the HN5000 study offers unique insight into this commonly reported, yet relatively under-researched toxicity.

4.2 Aims and Objectives

4.2.1 Primary Objectives

To describe the prevalence of patient-reported taste and smell dysfunction in entire HN5000 cohort at baseline.

To report the prevalence of PRTD and PRSD in those treated with radical RT or chemoradiotherapy (CRT) at 4m and 12m follow up.

4.2.2 Secondary Objectives

At baseline

- To present a breakdown of the prevalence of PRTD and PRSD in entire cohort by
    - Tumour site, stage, age, sex, smoking status, alcohol consumption, co-morbidities, smell dysfunction, xerostomia, HPV status (in oropharyngeal carcinoma (OPC))
- To perform a univariate and multivariate analysis to demonstrate potential risk factors for baseline dysfunction.

At 4 months

- To present a breakdown of prevalence of PRTD and PRSD in those treated with **primary RT or CRT** by
    - Tumour site, stage, age, sex, smoking status, alcohol consumption, co-morbidities, xerostomia, HPV status (in OPC), baseline taste or smell dysfunction, concomitant chemotherapy
- To perform a univariate and multivariate analysis to demonstrate potential risk factors for dysfunction at 4m.

At 12 months

- To present a breakdown of prevalence of patient-reported taste and smell dysfunction in those treated with **primary RT or CRT** by
    - Tumour site, stage, treatment modality, age, sex, smoking status, alcohol consumption, co-morbidities, smell dysfunction, xerostomia, HPV status (in OPC), baseline taste or smell dysfunction
- To perform a univariate and multivariate analysis to demonstrate potential risk factors for dysfunction at 12m.

All time points

- To explore the downstream effects of PRTD in the entire cohort
    - Explore the association between PRTD and body mass index (BMI)
    - Explore the association between PRTD and overall QoL using the GHS.

4.3 Methods

4.3.1 Primary End Point Measure

G3+PRTD was defined as those reporting grade 3 or worse (‘quite a bit’ or ‘very much’) problems with their sense of taste as per the EORTC-HNQ35 (55).

4.3.2 Secondary End Points

G3+PRX was defined as those reporting grade 3 or worse xerostomia per the EORTC-HNNQ35.

G3+PRSD was defined as those reporting grade 3 or worse problems with their sense of smell per the EORTC-HNNQ35.

Overall QoL was assessed as per the GHS from the EORTC QLQ-C30 v3.0.

BMI was used to assess the nutritional down-stream effects of G3+PRTD.

4.3.3 Co-variates

The following were used as co-variates for univariate and multivariate analysis.

Age - in years

Sex - Male or Female

Co-morbidities – Nil, Mild / Moderate, Severe

At baseline: smoking status – Current / Former / Never

At 4m and 12m: smoking status – Current / Former, Never

Current alcohol intake – Yes / No

Tumour subsite – OC / OPC / NPC / Hypopharyngeal carcinoma (HPC) / Laryngeal carcinoma (LC) / Thyroid cancer (TC) / NC / Sinus cavity tumours (SCT) / Unknown Primary (UP) / SG / Other

Stage – I, II / III, IV as per TNM 7th edition
In OPC: HPV status – Positive / Negative
Chemotherapy – Yes / No

4.3.4 Statistical Analysis Plan

Descriptive statistics were used to capture key characteristics of the study cohort. Fisher's exact test was used to compare proportions for dichotomous outcomes. Paired t-tests were used to compare mean values between groups for continuous outcomes. Univariate and multivariate logistic regression was used to investigate the association between potential predictors and PRTD and PRSD. All statistical tests were performed using STATA v14.0 (93).

4.3.5 Missing Data

This large cohort study included 5404 patients, of which 4009 responded with baseline data regarding gustatory function. At 4m there was follow up data for 3295 people and at 12m, there was data for 2792. There was a significant proportion of missing data and it was important to consider from the outset how this might affect planned analysis. To overcome this, the sample population (responders) was analysed to assess whether it was representative of the initial whole cohort (responders and non-responders) – see table 40.

At baseline, all the patient characteristics in the responders were representative of the whole population, except for HPV positive malignancies and patients with no comorbidities. Those with HPV positive OPC were over-represented in the responder population compared to the entire cohort and patients with moderate or severe comorbidities were under-represented.

At 4 months, there was a higher response from those who had undergone surgery alone, likely due to this group having undergone a single modality treatment with a comparatively quicker recovery prior to the 4m follow up assessment, therefore making them more likely to respond. There was a lower proportion of responders with stage III/IV disease, a 'current smoker' status at

baseline, moderate co-morbidities and those undergoing no treatment, likely reflecting poorer survival in these groups. Interestingly, the proportion of patients with severe co-morbidities was similar.

At 12m, again, factors associated with a better prognosis were more prevalent in responders than the whole population (HPV positive status in OPC, stage I disease, having OPC and no co-morbidities). In contrast there was a lower proportion of patients who were current smokers at diagnosis with stage 4 disease, HPC, SCT, moderate or severe co-morbidities, those treated with RT alone and those treated with palliative intent (chemotherapy or no treatment at all).

Overall, the fluctuations in patient characteristics analysed were deemed acceptable with changes consistent with what one would expect in clinical practice. For the purposes of this analysis, it was not felt necessary to impute data and instead to consider the effect of missing data in relevant predictors during the subsequent analyses.

	BASELINE	**Whole population**	**Baseline Responders**	**P (responders vs whole population)**
Age	Mean	60.81	60.66	0.56
	SD	11.83	11.8	
	Range (years)	18-85	18-95	
Sex	Male	3928 (72.7%)	2876 (71.7%)	0.2912
	Female	1474 (27.3%)	1133 (28.3%)	0.05
Smoking	Current	747 (19.5%)	715 (19.3%)	0.08
	Former	2138 (55.9%)	2072 (55.8%)	0.87
	Never	941 (24.6%)	925 (24.9%)	0.05
HPV	HPV Positive	1340 (29.5%)	1065 (30.8%)	0.01
	HPV Negative	3201 (70.5%)	2392 (69.2%)	0.16

Stage	I	1187 (22.0%)	923 (23.0%)	0.11
	II	894 (16.5%)	649 (16.2%)	0.55
	III	707 (13.1%)	530 (13.2%)	0.79
	IV	2366 (43.8%)	1712 (42.7%)	0.17
	Unknown	250 (4.6%)	195 (4.9%)	0.48
Sub-site	Oral Cavity	1288 (23.8%)	953 (23.8%)	0.97
	Oropharynx	1896 (35.1%)	1405 (35.1%)	0.94
	Nasopharynx	124 (2.3%)	86 (2.1%)	0.51
	Hypopharynx	237 (4.4%)	164 (4.1%)	0.34
	Larynx	1065 (19.7%)	786 (19.6%)	0.88
	Thyroid	261 (4.8%)	209 (5.2%)	0.22
	Nasal Cavity	61 (1.1%)	46 (1.2%)	0.77
	Sinuses	40 (0.7%)	24 (0.6%)	0.44
	Unknown Primary	204 (3.8%)	160 (4%)	0.53
	Salivary Gland	208 (3.8%)	161 (4%)	0.47
	Other	20 (0.4%)	15 (0.4%)	0.80
Co-morbidities	Nil	2295 (43.4%)	1787 (45.6%)	0.0008
	Mild	1781 (33.7%)	1323 (33.7%)	0.9976
	Moderate	953 (18.0%)	645 (16.4%)	<0.0001
	Severe	255 (4.8%)	168 (4.3%)	0.0037
	4 Months	**Whole population n=5404**	**4 M Responders n=3295**	**P (responders vs whole population)**
Age	Mean	60.81	61	0.45
	SD	11.83	11.6	
	Range (years)	18-95	19-95	
Sex	Male	3928 (72.7%)	2363 (71.7%)	0.20

	Female	1474 (27.3%)	931 (28.3%)	
Smoking (at baseline)	Current	747 (19.5%)	209 (16.9%)	0.02
	Former	2138 (55.9%)	751 (60.7%)	0.03
	Never	941 (24.6%)	277 (22.4%)	0.09
HPV	Positive	1340 (29.5%)	883 (31.1%)	0.06
	Negative	3201 (70.5%)	1958 (68.9%)	
Stage I/II vs III/IV	I/II	2081 (40.4%)	1339 (42.6%)	0.01
	III/IV	3073 (59.6%)	1802 (57.4%)	
Sub-site	Oral Cavity	1288 (23.8%)	805 (24.4%)	0.40
	Oropharynx	1896 (35.1%)	1154 (35.0%)	0.93
	Nasopharynx	124 (2.3%)	68 (2.1%)	0.37
	Hypopharynx	237 (4.4%)	128 (3.9%)	0.15
	Larynx	1065 (19.7%)	641 (19.5%)	0.72
	Thyroid	261 (4.8%)	170 (5.2%)	0.33
	Nasal Cavity	61 (1.1%)	36 (1.1%)	0.97
	Sinuses	40 (0.7%)	22 (0.7%)	0.82
	Unknown Primary	204 (3.8%)	132 (4.0%)	0.54
	Salivary Gland	208 (3.8%)	130 (4.0%)	0.66
	Other	20 (0.4%)	9 (0.3%)	0.36
Co-morbidities (at baseline)	Nil	2295 (43.4%)	1503 (46.6%)	0.04
	Mild	1781 (33.7%)	1090 (33.8%)	0.9
	Moderate	953 (18.04%)	513 (15.9%)	0.01

	Severe	255 (4.3%)	122 (3.8%)	0.9
Treatment	Surgery	1839 (34.1)	1189 (36.1%)	0.01
	CRT	1536 (28.4%)	939 (28.5%)	0.90
	RT	1067 (19.7%)	605 (18.3%)	0.05
	S+RT	561 (10.4%)	331 (10.1%)	0.51
	S+CRT	315 (5.8%)	195 (5.9%)	0.77
	S+C	15 (0.3%)	9 (0.3%)	0.78
	C	54 (1.0%)	24 (0.7%)	0.12
	No treatment	17 (0.3%)	3 (0.1%)	0.03
	12 Months	**Whole population n=5404**	**12M Responders n=2792**	***P (responders vs whole population)***
Age	Mean	60.81	61	0.46
	SD	11.83	11.42	
	Range (years)	18-95	28-94	
Sex	Male	3928 (72.7%)	1995 (71.4%)	0.14
	Female	1474 (27.3%)	797 (28.6%)	
Smoking (at baseline)	Current	747 (19.5%)	169 (15.5%)	<0.001
	Former	2138 (55.9%)	657 (60.4%)	0.02
	Never	941 (24.6%)	262 (24.1%)	0.9
HPV	Positive	1340 (29.5%)	823 (33.8%)	<0.001
	Negative	3201 (70.5%)	1613 (66.2%)	
Stage	I	1187 (22.0%)	675 (24.2%)	0.005
	II	894 (16.5%)	463 (16.6%)	>0.99
	III	707 (13.1%)	390 (14.0%)	0.16

	IV	2366 (43.8%)	1127 (40.4%)	0.0003
	Unknown	250 (4.6%)	137 (4.9%)	0.40
Sub-site	Oral Cavity	1288 (23.8%)	634 (22.7%)	0.18
	Oropharynx	1896 (35.1%)	1047 (37.5%)	0.008
	Nasopharynx	124 (2.3%)	69 (2.5%)	0.55
	Hypopharynx	237 (4.4%)	83 (3.0%)	0.0002
	Larynx	1065 (19.7%)	539 (19.3%)	0.60
	Thyroid	261 (4.8%)	141 (5.1%)	0.54
	Nasal Cavity	61 (1.1%)	30 (1.1%)	0.90
	Sinuses	40 (0.7%)	10 (0.4%)	0.03
	Unknown Primary	204 (3.8%)	118 (4.2%)	0.24
	Salivary Gland	208 (3.8%)	112 (4.0%)	0.56
	Other	20 (0.4%)	9 (0.3%)	0.52
Co-morbidities (at baseline)	Nil	2295 (43.4%)	1297 (47.4%)	0.02
	Mild	1781 (33.7%)	937 (34.2%)	0.9
	Moderate	953 (18.0%)	415 (15.2%)	0.0012
	Severe	255 (4.3%)	90 (3.3%)	0.02
Treatment	Surgery	1839 (34.3%)	992 (35.5%)	0.09
	CRT	1536 (28.4%)	837 (30.0%)	0.07
	RT	1067 (19.4%)	498 (17.9%)	0.01
	S+RT	561 (10.4%)	284 (10.2%)	0.72
	S+CRT	315 (5.8%)	163 (5.8%)	0.99

	S+C	15 (0.3%)	6 (0.2%)	0.52
	C	54 (1%)	12 (0.4%)	0.003
	No treatment	17 (0.3%)	0 (0.0%)	0.003

Table 40: Patient characteristics of baseline responders versus the entire HN5000 cohort using two sampled test for equality of proportions with continuity correction.

4.4 Results

The patients in the HN5000 cohort were typical of those seen in clinical research with a mean age of 60.8 years, more men than women, a higher proportion of stage III/IV disease and mostly had OC, OPC and LC

HN5000 – Patient, Tumour and Treatment Characteristics	
Total Number of Patients	5404
Mean age at study entry (years)	60.8 years (range 18-95; SD 11.8)
Male	3928 (72.7%)
Female	1474 (27.3%)
Smoking Status	
Current smoker	747 (13.8%)
Former smoker	2138 (39.6%)
Never smoker	941 (17.4%)
Missing	1578 (29.2%)
HPV status in Oropharyngeal Carcinoma	
Positive	1156 (59.2%)
Negative	479 (24.5%)
Unknown	318 (16.3%)
Treatment Intent	
Radical	5198 (96.2%)
Palliative / supportive	191 (3.5%)
Not specified / missing	15 (0.3%)

Table 41: Patient, tumour and treatment characteristics of the entire HN5000 cohort

Further details of tumour site by stage of disease and tumour site by subsequent treatment modality are below (table 42 and 43).

Site	Stage I	Stage II	Stage III	Stage IV	Missing	Total
Oral Cavity	432	290	103	458	5	1288
	33.5%	22.5%	8.1%	35.6%	0.4%	-
Oropharynx	83	184	268	1353	8	1896
	4.4%	9.7%	14.1%	71.4%	0.4%	-
Larynx	436	272	174	182	1	1065
	40.9%	25.5%	16.3%	17.1%	0.1%	-
Thyroid	125	32	46	53	5	261
	47.9%	12.3%	17.6%	20.3%	1.9%	-
Hypopharynx	14	36	34	153	0	237
	5.9%	15.2%	14.3%	64.6%	0.0%	-
Salivary Gland	71	35	25	71	6	208
	34.1%	16.8%	12.0%	34.1%	2.9%	-
Unknown Primary	0	0	0	0	204	204
	0.0%	0.0%	0.0%	0.0%	100.0%	-
Nasopharynx	8	27	46	42	1	124
	6.5%	21.8%	37.1%	33.9%	0.8%	-
Nasal Cavity	18	16	7	20	0	61
	29.5%	26.2%	11.5%	32.8%	0.0%	-
Sinuses	0	2	4	34	0	40
	0.0%	5.0%	10.0%	85.0%	0.0%	-
Other	0	0	0	0	20	20
	0.0%	0.0%	0.0%	0.0%	100.0%	-
Total	1187	894	707	2366	250	5404
	22.0%	16.5%	13.1%	43.8%	4.6%	-

Table 42: HN5000 cohort categorised by tumour site and stage

Site	S	S + RT	S + CRT	RT	CRT	S + Ch	Ch	Nil
Oral Cavity	951	160	42	70	55	3	5	2
	73.8%	12.4%	3.3%	5.4%	4.3%	0.2%	0.4%	0.2%
Oropharynx	185	182	7	261	1022	7	25	5
	10.9%	10.7%	0.4%	15.4%	60.3%	0.4%	1.5%	0.3%
Larynx	235	72	12	585	154	1	3	3
	22.1%	6.8%	1.1%	54.9%	14.5%	0.1%	0.3%	0.3%
Thyroid	235	19	1	6	0	0	0	0
	90.0%	7.3%	0.4%	2.3%	0.0%	0.0%	0.0%	0.0%
Hypopharynx	26	14	10	67	102	2	11	5
	11.0%	5.9%	4.2%	28.3%	43.0%	0.8%	4.6%	2.1%
Salivary Gland	129	59	5	12	2	0	0	1
	62.0%	28.4%	2.4%	5.8%	1.0%	0.0%	0.0%	0.5%
Unknown Primary	37	28	22	27	85	0	5	0
	18.1%	13.7%	10.8%	13.2%	41.7%	0.0%	2.5%	0.0%
Nasopharynx	3	1	6	14	97	1	2	0
	2.4%	0.8%	4.8%	11.3%	78.2%	0.8%	1.6%	0.0%
Nasal Cavity	18	13	4	14	9	1	2	0
	29.5%	21.3%	6.6%	23.0%	14.8%	1.6%	3.3%	0.0%
Sinuses	12	11	4	5	7	0	1	0
	30.0%	27.5%	10.0%	12.5%	17.5%	0.0%	2.5%	0.0%
Other	8	2	0	6	3	0	0	1
	40.0%	10.0%	0.0%	30.0%	15.0%	0.0%	0.0%	5.0%
Total receiving each treatment	1839	561	315	1067	1536	15	54	17
	34.0%	10.4%	5.8%	19.7%	28.4%	0.3%	1.0%	0.3%

Table 43: Summary of treatment received by tumour group (S, surgery; S+RT, surgery plus radiotherapy; S+CRT, surgery plus chemoradiotherapy; RT, radiotherapy alone; CRT, chemoradiotherapy; S+Ch, surgery plus chemotherapy; Ch, chemotherapy; Nil, no treatment)

4.4.1 Gustatory Outcomes at baseline, 4m and 12m

The prevalence of G3+PRTD at baseline, 4m and 12m was 11%, 45% and 31% respectively. Extending taste dysfunction to include any degree of loss (G2+PRTD), then prevalence of taste dysfunction was 31%, 70% and 60%. The

rate of G3+PRSD was lower with 6% at baseline, 17% at 4mand 12% at 12m (tables 44-45, figure 4-1).

HN35 Q44: Taste	Baseline n = 4013	%	4 months n = 3286	%	12 months n = 2790	%
1 = Not at all	2787	69%	974	30%	1127	40%
2 = A little	790	20%	823	25%	811	29%
3 = Quite a bit	271	7%	569	17%	446	16%
4 = Very much	165	4%	920	28%	406	15%
Grade 3+	436	11%	1489	45%	852	31%
Grade 2+	1226	31%	2312	70%	1663	60%

Table 44: Proportion of patients (entire HN5000 cohort) with patient reported taste dysfunction at baseline, 4 months and 12 months post treatment for head and neck cancer

HN35 Q43: Smell	Baseline n = 4009	%	4 months n = 3295	%	12 months n = 2792	%
1 = Not at all	3258	81%	2075	63%	1933	69%
2 = A little	492	12%	674	20%	511	18%
3 = Quite a bit	134	3%	269	8%	157	6%
4 = Very much	125	3%	277	8%	191	7%
Grade 3+	259	6%	546	17%	348	12%

Table 45: Proportion of patients (entire HN5000 cohort) with patient reported smell dysfunction at baseline, 4 months and 12 months post treatment for head and neck cancer

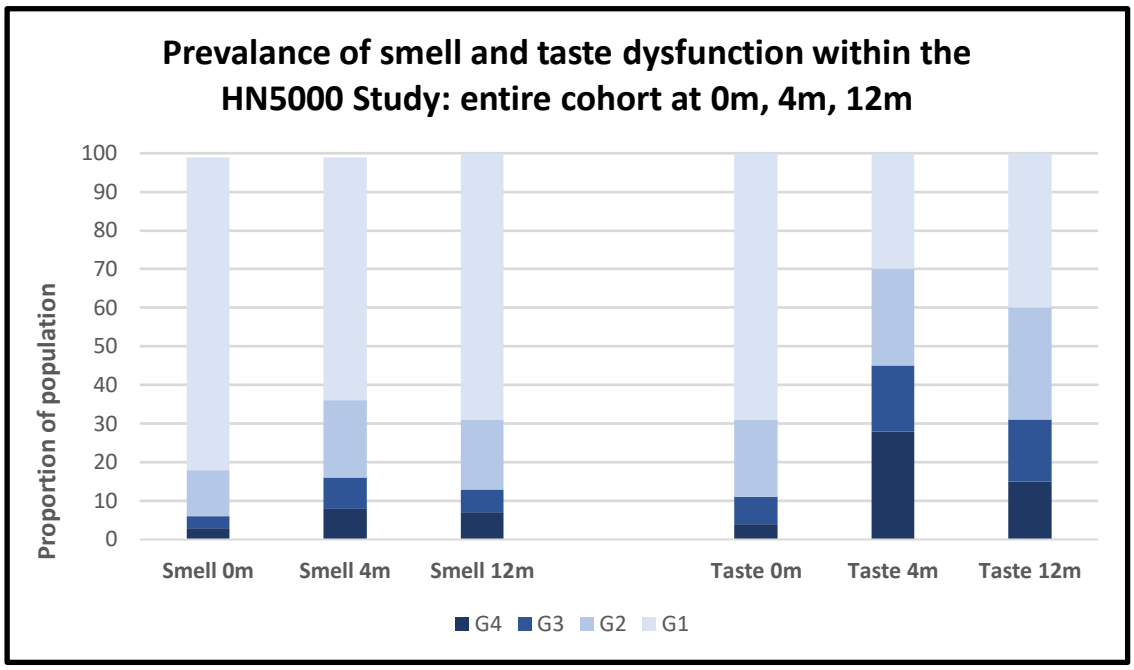


Figure 4-1: Graph showing prevalence of smell and taste dysfunction in all patients within the HN5000 cohort at baseline, 4m and 12m following treatment.

4.4.2 Gustatory outcomes at baseline (entire cohort)

Prevalence of baseline G3+PRTD and G3+PRSD by tumour site, stage, sex, age, HPV status in OPC, smoking and alcohol status, co-morbidities, baseline G3+PRX and baseline G3+PRSD are presented in tables 46-63. Univariate analysis using logistic regression identified statistically significant associations (table 64 and figures 4-2 and 4-3).

4.4.2.1 Taste

Tumours sites associated with increased risk of baseline G3+PRTD were tumour sites involving the nasal cavity (p=0.03), nasopharynx (p=0.0001) and sinus cavity (0.007). Tumour sites including larynx (p<0.001), thyroid (p=0.003) and salivary gland (p=0.009) were associated with reduced risk of baseline G3+PRTD. Alcohol consumption was also associated with reduced prevalence of G3+PRTD (p=0.001). Other factors also associated with baseline dysfunction were advanced stage (p<0.001), current smoker (p=0.002), moderate/severe

co-morbidities (p<0.001), baseline G3+PRX (p<0.0001) and baseline G3+PRSD (p<0.001).

Tumour Site	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Oral Cavity	623 (65.3%)	214 (22.4%)	72 (7.6%)	45 (4.7%)	**117 (12.3%)**
Oropharynx	948 (67.4%)	292 (20.8%)	109 (7.8%)	58 (4.1%)	**167 (11.9%)**
Nasopharynx	53 (61.6%)	14 (16.3%)	9 (10.5%)	10 (11.6%)	**19 (22.1%)**
Hypopharynx	97 (59.9%)	42 (25.9%)	14 (8.6%)	9 (5.6%)	**23 (14.2%)**
Larynx	617 (78.2%)	116 (14.7%)	37 (4.7%)	19 (2.4%)	**56 (7.1%)**
Thyroid	172 (82.7%)	27 (13.0%)	5 (2.4%)	4 (1.9%)	**9 (4.3%)**
Nasal Cavity	27 (57.5%)	10 (21.3%)	6 (12.8%)	4 (8.5%)	**10 (21.3%)**
Sinuses	13 (54.2%)	4 (16.7%)	4 (16.7%)	3 (12.5%)	**7 (29.2%)**
Unknown Primary	103 (64.4%)	37 (23.1%)	12 (7.5%)	8 (5.0%)	**20 (12.5%)**
Salivary Gland	122 (75.8%)	32 (19.9%)	2 (1.2%)	5 (3.1%)	**7 (4.4%)**
Other	12 (80.0%)	2 (13.3%)	1 (6.7%)	0 (0%)	**1 (6.7%)**
Total	**2787 (69.5%)**	**790 (19.7%)**	**271 (6.8%)**	**165 (4.1%)**	**436 (10.9%)**

Table 46: Prevalence breakdown of PRTD at baseline by primary tumour site

Stage	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
I	711 (76.8%)	149 (16.1%)	40 (4.3%)	26 (2.8%)	**66 (7.1%)**
II	466 (71.5%)	122 (18.7%)	42 (6.4%)	22 (3.4%)	**64 (9.8%)**
III	368 (69.7%)	97 (18.4%)	39 (7.4%)	24 (4.6%)	**63 (11.9%)**
IV	1111 (64.9%)	381 (22.3%)	135 (7.9%)	85 (5.0%)	**220 (12.9%)**
Unknown	131 (67.2%)	41 (21.0%)	15 (7.7%)	8 (4.1%)	**23 (11.8%)**

Table 47: Prevalence breakdown of PRTD at baseline by disease stage

Sex	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Male	2037 (70.7%)	544 (18.9%)	192 (6.7%)	109 (3.8%)	**301 (10.4%)**
Female	750 (66.3%)	246 (21.8%)	79 (7.0%)	56 (5.0%)	**135 (11.9%)**

Table 48: Prevalence breakdown of PRTD at baseline by sex

Age	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
60 and under	1309 (67.3%)	412 (21.3%)	141 (7.3%)	84 (4.3%)	**225 (11.6%)**
Over 60	1478 (71.5%)	378 (18.3%)	130 (6.3%)	81 (3.9%)	**211 (10.2%)**

Table 49: Prevalence breakdown of PRTD at baseline by age (above or below 60 years)

HPV in OPC	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Positive	632 (70.5%)	169 (18.9%)	59 (6.6%)	36 (4.0%)	**95 (10.6%)**
Negative	191 (60.6%)	79 (25.1%)	30 (9.5%)	15 (4.8%)	**45 (14.3%)**
Unknown	125 (63.8%)	44 (22.5%)	20 (10.2%)	7 (3.6%)	**27 (13.8%)**

Table 50: Prevalence breakdown of PRTD at baseline by HPV status in oropharyngeal patients only

Smoking	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Current	442 (61.6%)	174 (24.2%)	63 (8.8%)	39 (5.4%)	**102 (14.2%)**
Former	1470 (70.9%)	392 (18.9%)	133 (6.4%)	78 (3.8%)	**216 (10.2%)**
Never	683 (73.8%)	155 (16.8%)	53 (5.7%)	34 (3.7%)	**87 (9.4%)**
Missing	192 (64.7%)	69 (23.2%)	22 (7.4%)	14 (4.7%)	**36 (12.1%)**

Table 51: Prevalence breakdown of PRTD at baseline by smoking status

Alcohol	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Yes	1884 (71.3%)	513 (19.4%)	162 (6.1%)	83 (3.1%)	**245 (9.3%)**
No	712 (67.0%)	214 (20.2%)	79 (7.4%)	57 (5.4%)	**136 (12.8%)**
Missing	191 (61.8%)	63 (20.4%)	30 (9.7%)	25 (8.1%)	**55 (17.8%)**

Table 52: Prevalence breakdown of PRTD at baseline by alcohol status

Co-morbidities	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Nil	1303 (72.8%)	330 (18.4%)	99 (5.5%)	58 (3.2%)	**157 (8.8%)**
Mild	904 (68.2%)	276 (20.9%)	94 (7.1%)	50 (3.8%)	**144 (10.9%)**
Moderate	414 (64.3%)	126 (19.6%)	61 (9.5%)	43 (6.7%)	**104 (16.2%)**
Severe	101 (59.8%)	42 (24.9%)	14 (8.3%)	12 (7.1%)	**26 (15.4%)**
Missing	65 (75.6%)	16 (18.6%)	3 (3.5%)	2 (2.3%)	**5 (5.8%)**

Table 53: Prevalence breakdown of PRTD at baseline by co-morbidity status

Xerostomia	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	2479 (75.7%)	593 (18.1%)	141 (4.3%)	62 (1.9%)	**103 (6.2%)**
G3/4	298 (41.1%)	196 (27.0%)	129 (17.8%)	103 (14.2%)	**232 (32.0%)**

Table 54: Prevalence breakdown of PRTD at baseline by PRX

PRSD	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	2739 (73.2%)	734 (19.6%)	181 (4.8%)	88 (2.4%)	**269 (7.2%)**
G3/4	41 (15.8%)	53 (20.5%)	90 (34.8%)	75 (29.0%)	**165 (63.7%)**

Table 55: Prevalence breakdown of PRTD at baseline by PRSD

4.4.2.2 Smell

Tumour sites associated with G3+PRSD were NPC (p<0.001); HPC (p=0.02), nasal cavity (p<0.001) and sinus cavity (p<0.001); OPC was associated with reduced risk (p=0.05). Other factors associated with G3+PRSD was being a current smoker (p<0.001), moderate/severe co-morbidities (p<0.001) and G3+PRX (p<0.001); the consumption of alcohol (p=0.02) and being a former smoker (p=0.01) were associated with reduced risk.

Tumour Site	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Oral Cavity	790 (82.9%)	108 (11.3%)	20 (2.1%)	35 (3.7%)	**55 (5.8%)**
Oropharynx	1153 (82.1%)	176 (12.5%)	46 (3.3%)	30 (2.1%)	**76 (5.4%)**
Nasopharynx	59 (68.6%)	13 (15.1%)	7 (8.1%)	7 (8.1%)	**14 (16.3%)**
Hypopharynx	117 (71.3%)	29 (17.7%)	9 (5.5%)	9 (5.5%)	**18 (11.0%)**
Larynx	651 (82.8%)	89 (11.3%)	28 (3.6%)	18 (2.3%)	**46 (5.9%)**
Thyroid	189 (90.4%)	12 (5.7%)	4 (1.9%)	4 (1.9%)	**8 (3.8%)**
Nasal Cavity	16 (34.8%)	12 (26.1%)	8 (17.4%)	10 (21.7%)	**18 (39.1%)**
Sinuses	10 (41.7%)	6 (25.0%)	2 (8.3%)	6 (25.0%)	**8 (33.3%)**
Unknown Primary	121 (75.6%)	30 (18.8%)	6 (3.8%)	3 (1.9%)	**9 (5.6%)**
Salivary Gland	140 (87.0%)	15 (9.3%)	3 (1.9%)	3 (1.9%)	**6 (3.7%)**
Other	12 (80.0%)	2 (13.3%)	1 (6.7%)	0 (0.0%)	**1 (6.7%)**
Total	**3258**	**492**	**134**	**125**	**4009**

Table 56: Prevalence breakdown of PRSD at baseline by primary tumour site

Stage	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
I	787 (85.3%)	92 (10.0%)	22 (2.4%)	22 (2.4%)	**44 (4.8%)**
II	527 (81.2%)	89 (13.7%)	13 (2.0%)	20 (3.1%)	**33 (5.1%)**
III	435 (82.1%)	60 (11.3%)	19 (3.58%)	16 (3.0%)	**35 (6.6%)**
IV	1358 (79.3%)	219 (12.8%)	72 (4.2%)	63 (3.7%)	**135 (7.9%)**
Unknown	151 (77.4%)	32 (16.4%)	8 (4.1%)	4 (2.1%)	**12 (6.2%)**

Table 57: Prevalence breakdown of PRSD at baseline by disease stage

Sex	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Male	2339 (81.3%)	360 (12.5%)	101 (3.5%)	76 (2.6%)	**177 (6.2%)**
Female	919 (81.1%)	132 (11.7%)	33 (2.9%)	49 (4.3%)	**82 (7.2%)**

Table 58: Prevalence breakdown of PRSD at baseline by sex

Age	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
60 and under	1585 (81.5%)	237 (12.2%)	59 (3.0%)	63 (3.2%)	**122 (6.3%)**
Over 60	1673 (81.0%)	255 (12.3%)	75 (3.6%)	62 (3.0%)	**137 (6.6%)**

Table 59: Prevalence breakdown of PRSD at baseline by age (above or below 60 years)

HPV in OPC	G1 smell	G2 smell	G3 smell	G4 smell	G3+
Positive	763 (85.2%)	94 (10.5%)	22 (2.5%)	17 (1.9%)	**39 (4.4%)**
Negative	238 (75.6%)	56 (17.8%)	13 (4.1%)	8 (2.5%)	**21 (6.7%)**
Unknown	152 (78.4%)	26 (13.4%)	11 (5.7%)	5 (2.6%)	**16 (8.3%)**

Table 60: Prevalence breakdown of PRSD at baseline by HPV status in oropharyngeal patients only

Smoking	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Current	521 (72.9%)	126 (17.6%)	33 (4.6%)	35 (4.9%)	**68 (9.5%)**
Former	1701 (82.1%)	257 (12.4%)	60 (2.9%)	54 (2.6%)	**114 (5.5%)**
Never	794 (85.8%)	75 (8.1%)	29 (3.1%)	27 (2.9%)	**56 (6.1%)**
Missing	242 (81.5%)	34 (11.5%)	12 (4.0%)	9 (3.0%)	**21 (7.1%)**

Table 61: Prevalence breakdown of PRSD dysfunction at baseline by smoking status

Alcohol	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Yes	2170 (82.2%)	324 (12.3%)	75 (2.8%)	70 (2.7%)	**145 (5.5%)**
No	855 (80.6%)	126 (11.9%)	42 (4.0%)	38 (3.%)	**80 (7.5%)**
Missing	233 (75.4%)	42 (13.6%)	17 (5.5%)	17 (5.5%)	**34 (11.0%)**

Table 62: Prevalence breakdown of PRSD at baseline by alcohol status

Co-morbidities	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Nil	1517 (84.5%)	184 (10.3%)	52 (2.9%)	34 (1.9%)	**86 (4.8%)**
Mild	1055 (84.9%)	184 (13.9%)	41 (3.1%)	43 (3.3%)	**84 (6.4%)**
Moderate	498 (77.2%)	81 (12.6%)	27 (4.2%)	39 (6.1%)	**66 (10.2%)**
Severe	122 (72.6%)	30 (17.9%)	10 (6.0%)	6 (3.6%)	**16 (9.5%)**
Missing	66 (76.7%)	13 (15.1%)	4 (4.7%)	3 (3.5%)	**7 (8.1%)**

Table 63: Prevalence breakdown of PRSD at baseline by co-morbidity status

	Univariate analysis at baseline					
	Grade 3+ Taste			**Grade 3+ Smell**		
Variable	**OR**	**CI 95%**	**P**	**OR**	**CI 95%**	**P**
Tumour Site						
Oral Cavity vs others	1.20	0.96-1.50	0.11	0.86	0.63-1.16	0.32
Oropharynx vs others	1.17	0.95-1.44	0.13	0.76	0.57-0.99	0.05

Nasopharynx vs others	2.38	1.42-4.01	0.001	2.92	1.62-5.25	<0.001
Hypopharynx vs others	1.38	0.88-2.17	0.17	1.84	1.11-3.06	0.02
Larynx vs others	0.57	0.43-0.77	<0.001	0.88	0.63-1.22	0.44
Thyroid vs others	0.36	0.18-0.70	0.003	0.56	0.27-1.15	0.12
Nasal Cavity vs others	2.25	1.11-4.55	0.03	9.93	5.41-18.20	<0.001
Sinuses vs others	3.42	1.41-8.29	0.007	7.44	3.15-17.55	<0.001
Unknown Primary vs others	1.18	0.73-1.90	0.50	0.86	0.44-1.70	0.66
Salivary Gland vs others	0.36	0.17-0.78	0.009	0.55	0.24-1.25	0.16
Mucosal Cavity vs Not	1.82	1.44-2.31	<0.001	1.20	0.91-1.58	0.20
Stage						
III/IV vs I/II	1.61	1.29-2.00	<0.001	1.59	1.21-2.10	0.001
Sex						
Female vs Male	1.16	0.94-1.44	0.17	1.19	0.91-1.56	0.21
Age						
>60	0.87	0.71-1.06	0.17	1.06	0.82-1.36	0.64
HPV in OPC						
Positive vs Negative	0.71	0.49-1.04	0.08	1.13	0.88-1.45	0.35
Smoking status						
Current vs others	1.47	1.15-1.86	0.002	1.71	1.28-2.28	<0.001
Former vs others	0.86	0.71-1.05	0.15	0.72	0.56-0.93	0.011
Never vs others	0.82	0.64-1.04	0.10	0.91	0.67-1.24	0.57
Alcohol status						
Yes or no	0.69	0.56-0.87	0.001	0.71	0.54-0.95	0.02
Co-morbidities						
III/IV vs I/II	1.8	1.44-2.25	<0.001	1.91	1.45-2.82	<0.001
Xerostomia						
G1/2 vs G3/4	7.11	5.75-8.78	<0.001	3.92	3.02-5.09	<0.001
Smell Dysfunction						
G1/2 vs G3/4	22.66	17.09-30.05	<0.001			

Table 64: Univariate analysis to find predictors of patient reported smell and taste dysfunction at baseline prior to treatment for head and neck cancer

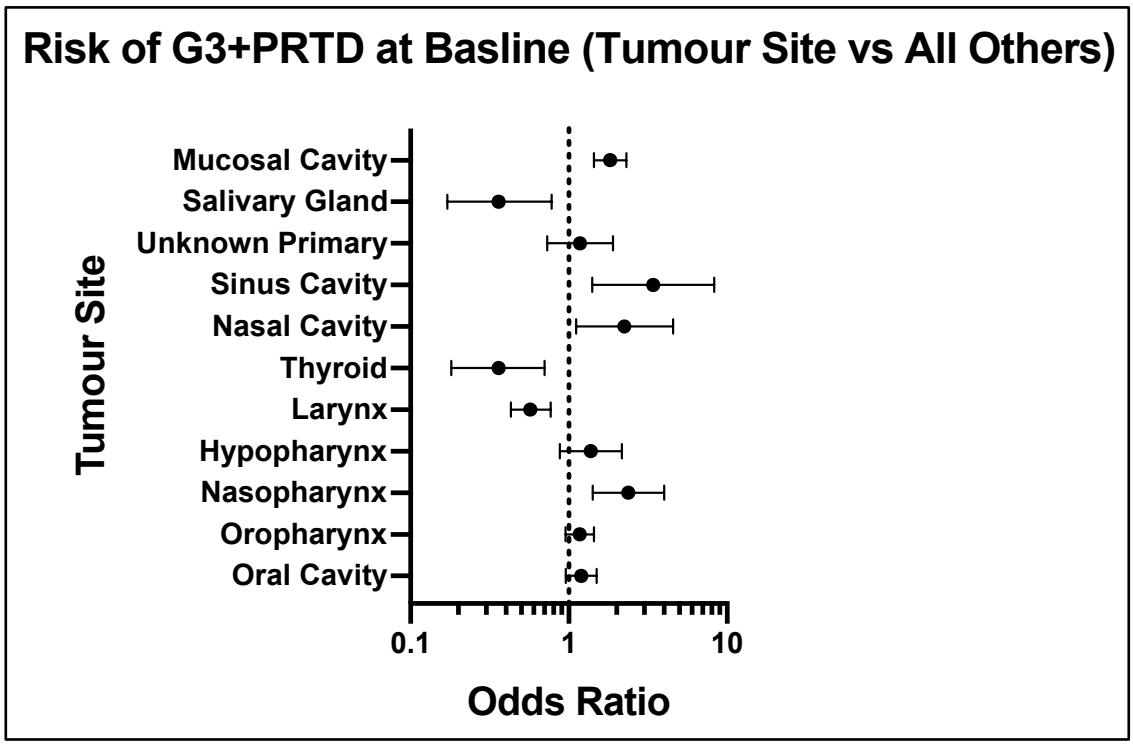


Figure 4-2: Forest plot showing risk of G3+PRTD at baseline by each tumour site versus all others

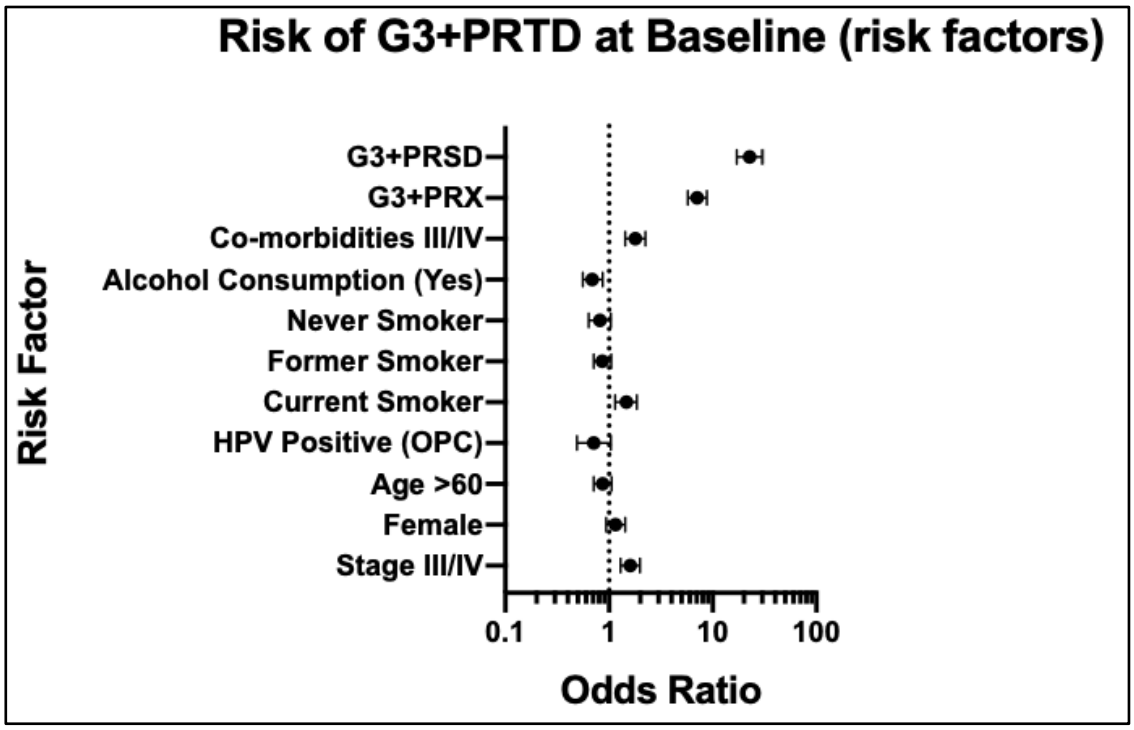


Figure 4-3: Forest plot showing risk of G3+PRTD at baseline by patient related risk factors

4.4.2.3 Multivariate analysis for baseline taste dysfunction

Association between risk factors and taste dysfunction was explored further using a multivariate analysis. In this analysis, tumour sites were grouped into those involving the OC or pharynx (OC, OPC, HPC, NPC and NC) versus tumours outside the mucosal cavity (TC, SGT, LC, SCT and UP). Other clinically relevant confounders were included in the multivariate analysis. Mucosal involvement (p<0.0001), stage III/IV disease (p=0.002), moderate to severe co-morbidities (p<0.0001), being a current smoker (p=0.009) and being female (<0.007) all conferred increased risk of baseline G3+PRTD. Odds ratios with 95% confidence intervals are presented below (table 65 and figure 4-4).

	Multivariate			Univariate	
Variable	**OR**	**CI95%**	**p value**	**OR**	**p value**
Mucosal cavity involvement	2.00	1.51 to 2.69	<0.0001	1.82	<0.001
Stage 3 or 4 disease	1.46	1.15 to 1.86	0.002	1.61	<0.001
Comorbidities	1.99	1.56 to 2.54	<0.0001	1.80	<0.001
Smoker	1.40	1.08 to 1.80	0.009	1.47	0.002
Female	1.39	1.09 to 1.76	0.007	1.16	0.17
Age >60	0.83	0.66 to 1.04	0.10	0.87	0.17

Table 65: Multivariate analysis for predicting baseline PRTD in the HN5000 cohort

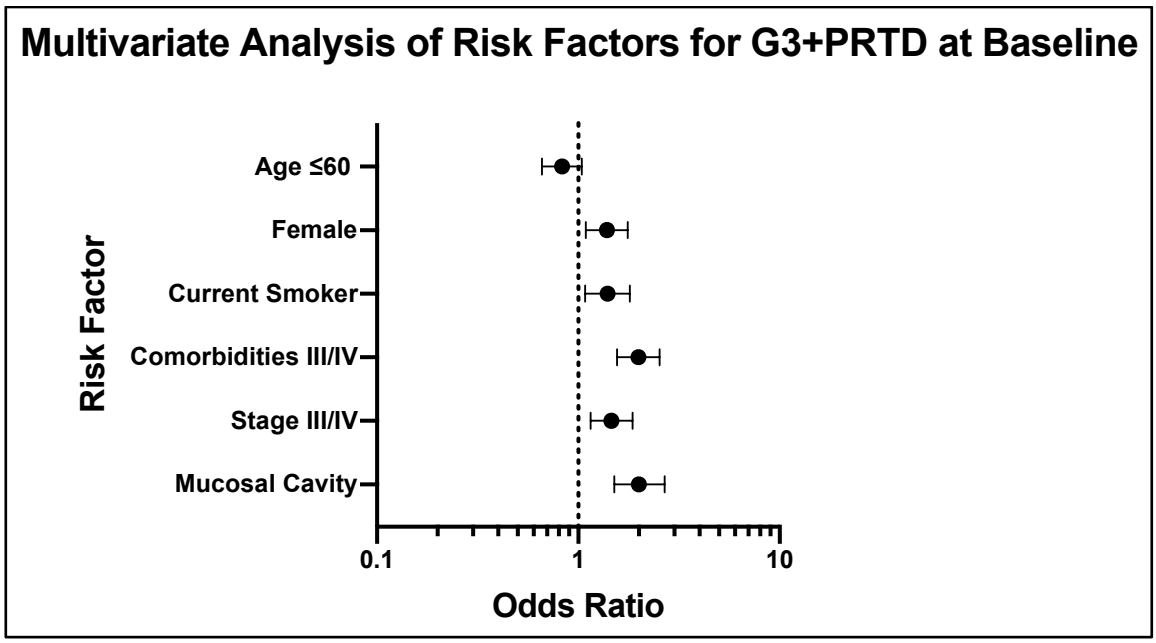


Figure 4-4: Forest plot showing multivariate analysis of risk factors for G3+PRTD at baseline

4.4.3 Gustatory outcomes at 4 months in those treated with RT / CRT (2377 patients)

4.4.3.1 Methods

A subgroup of patients treated with radical RT or CRT was extracted to analyse outcomes across the range of tumour sites commonly treated with RT (OPC, LC, HPC, NPC and UP). Tumour sites conventionally treated with surgery followed by adjuvant RT where necessary (e.g. OC, SGT, SCT, TC), were not included for this analysis.

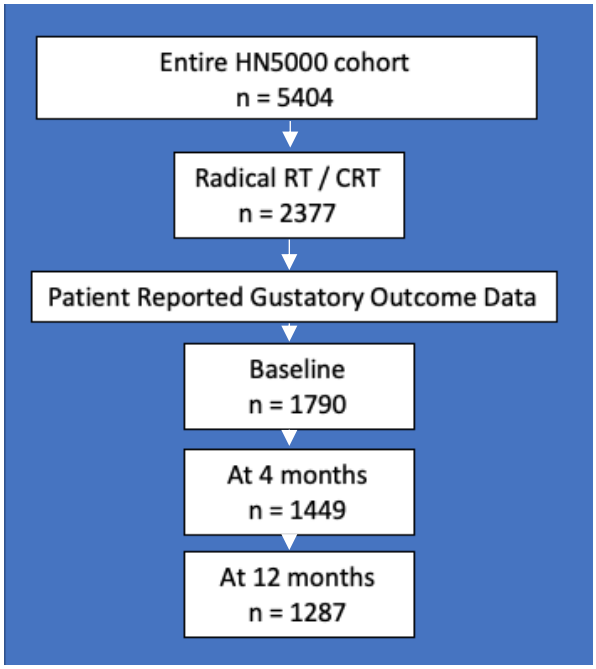


Figure 4-5: Flow chart of captured gustatory data throughout HN5000 follow up

4.4.3.2 Results

2377 patients were treated with radical RT or CRT. The average age of this cohort was 60.9 years (SD 10.2) with more men (82.2%) than women (17.8%). The majority of patients were treated for OPC (of which 60.4% were HPV positive) or laryngeal carcinomas. Almost half of patients had stage 4 disease (tables 66-68).

HN5000 – Patient, Tumour and Treatment Characteristics	
Total Number of Patients	2377
Mean age at study entry (years)	60.9 years (range 20-95; SD 10.2)
Male	1954 (82.2%)
Female	423 (17.8%)
Smoking Status	
Current smoker	156 (14.1%)
Former / never smoker	953 (85.9%)
Missing	1268 (53.3%)
HPV status in Oropharyngeal Carcinoma	
Positive	761 (60.4%)
Negative	294 (23.3%)
Unknown	205 (16.3%)
Treatment Intent	
Radical	2377 (100%)

Table 66: Patient, tumour and treatment characteristics of those treated with RT/CRT with radical intent from HN5000 cohort

Site	Stage I	Stage II	Stage III	Stage IV	Missing	Total
Oropharynx	34	111	175	937	3	1260
	2.7%	8.8%	13.9%	74.4%	0.2%	-
Larynx	303	230	137	71	0	741
	40.1%	31.0%	18.5%	9.6%	0%	-
Hypopharynx	11	29	25	97	0	162
	6.8%	17.9%	15.4%	59.9%	0%	-
Unknown Primary	0	0	0	0	108	108
	0%	0%	0%	0%	100%	-
Nasopharynx	8	24	42	32	0	106
	7.6%	22.6%	39.6%	30.2%	0%	-
Total	356	394	379	1137	111	2377
	15.0%	16.6%	15.9%	47.8%	4.6%	-

Table 67: Tumour site and stage (CRT/RT group)

Site	RT n = 895	%	CRT n = 1482	%
Oropharynx	227	18.0%	1033	82.0%
Larynx	581	32.7%	160	21.6%
Hypopharynx	53	32.7%	109	67.3%
Unknown Primary	22	20.4%	86	79.6%
Nasopharynx	12	11.3%	94	88.7%
Total n = 2377	**895**		**1482**	

Table 68: Treatment modality by tumour site for those treated with CRT or RT alone

4.4.3.2.1 Baseline dysfunction by tumour site (CRT/RT sub-group)

Rates of G3+PRTD and G3+PRSD were consistent with those seen in the entire HN5000 cohort (see table 69 and 70).

Tumour Site	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3 +
Oropharynx	646 (67.0%)	207 (21.5%)	70 (7.3%)	41 (4.3%)	**111 (11.6%)**
Larynx	441 (79.8%)	80 (14.5%)	21 (3.8%)	11 (2.0%)	**32 (5.8%)**
Hypopharynx	70 (62.0%)	28 (24.8%)	10 (8.9%)	5 (4.4%)	**15 (13.3%)**
Unknown Primary	54 (62.07%)	20 (23.0%)	6 (6.9%)	7 (8.1%)	**13 (15.0%)**
Nasopharynx	48 (65.8%)	12 (16.4%)	7 (9.6%)	5 (4.4%)	**12 (14%)**
ALL	1259 (70.3%)	347 (19.4%)	114 (6.4%)	70 (3.9%)	**184 (10.3%)**

Table 69: Prevalence of patient reported taste dysfunction by tumours site at baseline months in those treated with CRT or RT alone

Tumour Site	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3 +
Oropharynx	784 (81.2%)	124 (12.9%)	33 (3.4%)	24 (2.5%)	**57 (5.9%)**
Larynx	458 (83.1%)	70 (12.7%)	15 (2.7%)	8 (1.5%)	**23 (4.2%)**
Hypopharynx	86 (76.1%)	17 (15.0%)	7 (6.2%)	3 (2.7%)	**10 (8.9%)**
Unknown Primary	61 (70.1%)	19 (21.8%)	4 (4.6%)	3 (3.5%)	**7 (8.1%)**
Nasopharynx	54 (74.0%)	10 (13.7%)	5 (6.9%)	4 (5.5%)	**9 (12.4%)**
ALL	1443 (80.7%)	240 (13.4%)	64 (3.6%)	42 (2.4%)	**106 (6.0%)**

Table 70: Prevalence of patient reported smell dysfunction by tumours site at baseline months in those treated with CRT or RT alone

4.4.3.2.2 Taste

Figure 4-6 shows the prevalence of grade 1-4 taste dysfunction at 4m in this subgroup as a whole and subdivided by tumour subsite. Grade 3+PRTD was present in 54.2% of patients. Rates were highest in those treated for NPC, UP or OPC with much lower rates seen in those treated for LC Only 19.5% of patients reported normal taste function (table 71).

Tumour Site	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3 +
Oropharynx	60 (7.7%)	215 (27.7%)	183 (23.6%)	318 (41.0%)	**501 (64.6%)**
Larynx	207 (45.9%)	119 (26.4%)	56 (12.4%)	69 (15.3%)	**125 (27.7%)**
Hypopharynx	11 (12.6%)	23 (26.4%)	23 (36.4%)	30 (34.5%)	**53 (60.9%)**
Unknown Primary	3 (4.1%)	13 (17.6%)	19 (25.7%)	39 (52.7%)	**58 (78.4%)**
Nasopharynx	2 (3.3%)	10 (16.4%)	14 (23.0%)	35 (57.4%)	**49 (80.3%)**
ALL	283 (19.5%)	380 (26.2%)	295 (20.4%)	491 (33.9%)	**786 (54.2%)**

Table 71: Prevalence of patient reported taste dysfunction by tumours site at 4m in those treated with CRT or RT alone

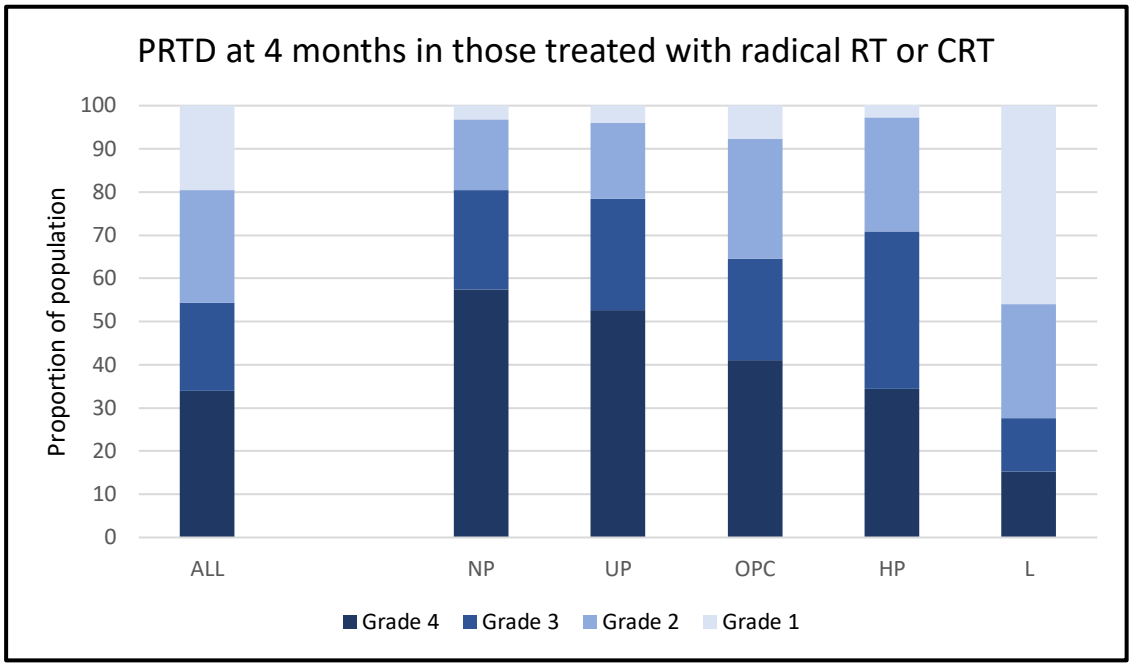


Figure 4-6: Rates of PRTD at 4m in those treated with radical RT or CRT

4.4.3.2.3 Smell

G3+PRSD was far less prevalent than G3+PRTD with only 15.9% reporting clinically relevant dysfunction. Once again, rates were highest (32.8%) in those treated for NPC (table 72 and figure 4-7).

Tumour Site	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3 +
Oropharynx	447 (57.5%)	203 (26.1%)	68 (8.8%)	59 (7.6%)	**127 (16.3%)**
Larynx	317 (69.8%)	88 (19.4%)	27 (6.0%)	22 (4.9%)	**49 (10.8%)**
Hypopharynx	45 (50.0%)	24 (26.7%)	16 (17.8%)	5 (5.6%)	**21 (23.3%)**
Unknown Primary	35 (47.3%)	25 (33.8%)	8 (10.8%)	6 (8.1%)	**14 (19.9%)**
Nasopharynx	25 (41.0%)	16 (26.2%)	8 (13.1%)	12 (19.7%)	**20 (32.8%)**
ALL	869 (59.7%)	356 (24.5%)	127 (8.7%)	104 (7.1%)	**231 (15.9%)**

Table 72: Prevalence of patient reported smell dysfunction by tumours site at 4m in those treated with CRT or RT alone

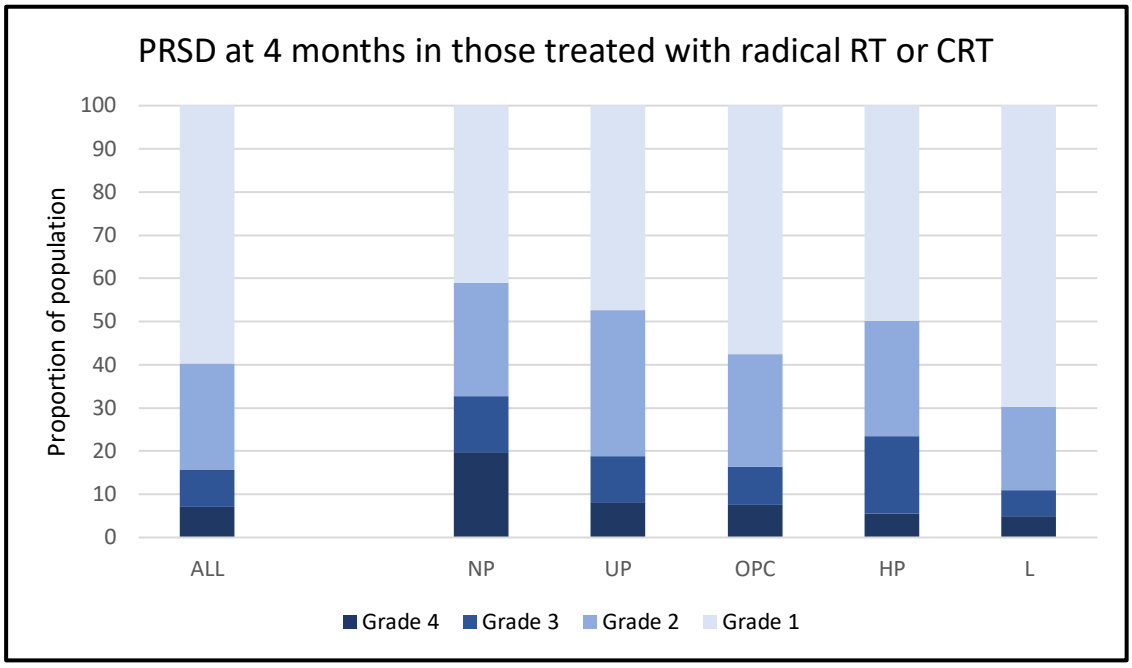


Figure 4-7: Rates of PRTD and PRSD at 4m in those treated with radical RT or CRT

The prevalence of PRTD and PRSD by stage, sex, age, HPV status in OPC, smoking/alcohol status, comorbidities, presence of xerostomia and use of concurrent chemotherapy are presented in tables 73-91. Univariate analysis using logistic regression was completed to look for statistically significant associations (see table 92 and figure 4-7). For the purposes of this analysis OPC and UP were analysed together as it is likely they will have been treated with the same approach.

4.4.3.2.4 Taste

People treated for OPC/UP and NPC were associated with an increased risk of G3+PRTD (odds ratio 3.15 for OPC/UP, 3.61 for NPC, p<0.0001). Conversely treatment for LC was associated with a reduced risk of G3+PRTD (odds ratio 0.20, p<0.0001). Other factors associated with increased risk of G3+PRTD were the use of concurrent chemotherapy (odds ratio 4.51, p<0.0001), stage 3 or 4 disease (odds ratio 4.67, p<0.0001), G3+PRX (odds ratio 6.58, p<0.0001), G3+PRSD (odds ratio 32.14, p<0.0001) and G3+PRTD at baseline prior to treatment (odds ratio 2.46, p<0.0001). Other factors associated with reduced

prevalence of G3+PRTD were age >60 (odds ratio 0.64, p<0.0001) and the consumption of alcohol (odds ratio 0.64, p<0.0001).

Chemo	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Yes	71 (7.7%)	228 (24.8%)	212 (23.1%)	407 (44.3%)	**619 (67.4%)**
No	212 (39.9%)	152 (28.6%)	83 (15.6%)	84 (15.8%)	**167 (31.4%)**

Table 73: Prevalence of patient PRTD in those treated with or without concurrent chemotherapy at 4m in those treated with primary CRT or RT alone

Stage	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
I	127 (56.0%)	56 (24.7%)	21 (9.3%)	23 (10.1%)	**44 (19.4%)**
II	72 (31.0%)	73 (31.5%)	39 (16.8%)	48 (20.7%)	**87 (37.5%)**
III	35 (14.2%)	66 (26.8%)	59 (24.0%)	86 (35.0%)	**145 (59.0%)**
IV	46 (6.9%)	172 (25.8%)	156 (23.4%)	294 (44.0%)	**450 (67.4%)**

Table 74: Prevalence of PRTD by stage at 4m in those treated with primary CRT or RT alone

Sex	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Male	248 (21.0%)	307 (26.0%)	242 (20.5%)	383 (32.5%)	**625 (53.0%)**
Female	35 (13.0%)	73 (27.1%)	53 (19.7%)	108 (40.2%)	**161 (59.9%)**

Table 75: Prevalence of PRTD by sex at 4m in those treated with primary CRT or RT alone

Age	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
60 and under	82 (13.0%)	168 (26.6%)	128 (20.3%)	253 (40.1%)	**381 (60.4%)**
Over 60	201 (24.6%)	212 (25.9%)	167 (20.4%)	238 (29.1%)	**405 (49.5%)**

Table 76: Prevalence of PRTD by age (above or below 60 years) at 4m in those treated with primary CRT or RT alone

HPV in OPC	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Positive	41 (8.2%)	139 (27.7%)	124 (24.7%)	198 (39.4%)	**322 (64.1%)**
Negative	11 (6.4%)	43 (25.2%)	35 (20.5%)	82 (48.0%)	**117 (68.5%)**

Table 77: Prevalence of PRTD by HPV status in those with OPC at 4m in those treated with primary CRT or RT alone

Smoking	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Current	31 (20.0%)	44 (28.4%)	33 (21.3%)	47 (30.3%)	**80 (51.4%)**
Former / Never	181 (19.3%)	247 (26.3%)	184 (19.6%)	328 (34.9%)	**512 (54.5%)**

Table 78: Prevalence of PRTD by smoking status at 4m in those treated with primary CRT or RT alone

Alcohol	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Yes	144 (22.6%)	185 (29.0%)	136 (21.4%)	172 (27.0%)	**308 (48.4%)**
No	106 (15.7%)	167 (24.8%)	130 (19.3%)	271 (40.2%)	**401 (59.5%)**

Table 79: Prevalence of PRTD by alcohol status at 4m in those treated with primary CRT or RT alone

Co-morbidities	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Nil	113 (16.9%)	179 (26.7%)	141 (21.0%)	237 (35.4%)	**378 (56.4%)**
Mild	109 (22.2%)	123 (25.0%)	94 (19.1%)	166 (33.7%)	**260 (52.8%)**
Moderate	52 (23.7%)	56 (25.6%)	41 (18.7%)	70 (32.0%)	**111 50.7%)**
Severe	8 (14.8%)	20 (37.0%)	14 (25.9%)	12 (22.2%)	**26 (48.1%)**

Table 80: Prevalence of PRTD by baseline co-morbidities at 4m in those treated with primary CRT or RT alone

Xerostomia	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	199 (41.8%)	158 (33.2%)	64 (13.5%)	55 (11.6%)	**119 (25.1%)**
G3/4	84 (8.7%)	220 (22.7%)	231 (23.8%)	436 (44.9%)	**667 (68.7%)**

Table 81: Prevalence of PRTD with or without xerostomia at 4m in those treated with primary CRT or RT alone

G3 Smell	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	282 (23.2%)	373 (30.6%)	242 (19.9%)	321 (26.4%)	**563 (46.3%)**
G3/4	1 (0.4%)	7 (3.1%)	53 (23.1%)	168 (73.4%)	**221 (96.5%)**

Table 82: Prevalence of PRTD with or without smell dysfunction at 4m in those treated with primary CRT or RT alone

4.4.3.2.5 Smell

G3+PRSD was more prevalent in those treated for NPC (odds ratio 2.74, p<0.0001) and HPC (odds ratio 1.68, p=0.05). Once again treatment for LC was associated with reduced risk of G3+PRSD (odds ratio 0.55, p=0.0004). Other factors associated with increased risk included the use of concurrent chemotherapy (odds ratio 1.84, p<0.0001), stage 3 or 4 disease (odds ratio 2.28, p<0.0001), moderate or severe comorbidities (odds ratio 1.49, p=0.02) and G3+PRX (odds ratio 3.54, p<0.0001). Factors associated with reduced prevalence of G3+PRSD were HPV positive status in OPC (odds ratio 0.49, p=0.001) and the consumption of alcohol (odds ratio 0.56, p<0.0001).

Chemo	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Yes	515 (55.8%)	236 (25.6%)	92 (10.0%)	80 (8.7%)	**172 (18.7%)**
No	354 (66.4%)	120 (22.5%)	35 (6.6%)	24 (4.5%)	**59 (11.1%)**

Table 83: Prevalence of PRSD in those treated with or without concurrent chemotherapy at 4m in those treated with primary CRT or RT alone

Stage	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
I	171 (74.7%)	44 (19.2%)	10 (4.4%)	4 (1.8%)	**14 (6.6%)**
II	150 (64.4%)	54 (23.2%)	17 (7.3%)	12 (5.2%)	**29 (12.5%)**
III	143 (57.4%)	59 (23.7%)	25 (10.0%)	22 (8.8%)	**47 (18.8%)**
IV	369 (55.2%)	173 (25.9%)	67 (10.0%)	60 (9.0%)	**127 (19.0%)**

Table 84: Prevalence of PRSD by stage at 4m in those treated with primary CRT or RT alone

Sex	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Male	692 **(58.3%)**	304 **(25.6%)**	105 **(8.6%)**	86 **(7.3%)**	**191 (15.9%)**
Female	177 (65.8%)	52 (19.3%)	22 (8.2%)	18 (6.7%)	**40 (14.9%)**

Table 85: Prevalence of PRSD by sex at 4m in those treated with primary CRT or RT alone

Age	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
60 and under	383 (60.3%)	154 (24.3%)	50 (7.9%)	48 7.6%)	**98 (15.5%)**
Over 60	486 (59.2%)	202 (24.6%)	77 (9.4%)	56 (6.8%)	**133 (16.2%)**

Table 86: Prevalence of PRSD by age (above or below 60 years) at 4m in those treated with primary CRT or RT alone

HPV in OPC	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Positive	313 (62.2%)	119 (23.7%)	36 (7.2%)	35 (7.0%)	**71 (14.2%)**
Negative	75 (43.6%)	54 (31.4%)	24 (14.0%)	19 (11.1%)	**43 (25.1%)**

Table 87: Prevalence of PRSD by HPV status in those with OPC at 4m in those treated with primary CRT or RT alone

Smoking	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Current	82 (52.9%)	40 (25.8%)	21 (13.6%)	12 (7.7%)	**33 21.3%)**
Former / Never	562 (59.5%)	234 (24.8%)	79 (8.4%)	70 (7.4%)	**149 (15.8%)**

Table 88: Prevalence of PRSD by smoking status at 4m in those treated with primary CRT or RT alone

Alcohol	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Yes	394 (61.8%)	169 (26.5%)	44 (6.9%)	31 (4.9%)	**75 (11.8%)**
No	394 (58.0%)	156 (22.9%)	68 (10.0%)	62 (9.1%)	**130 (19.1%)**

Table 89: Prevalence of PRSD by alcohol status at 4m in those treated with primary CRT or RT alone

Co-morbidities	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Nil	421 (62.4%)	159 (23.6%)	50 (7.4%)	45 (6.7%)	**95 (14.1%)**
Mild	302 (61.0%)	115 (23.2%)	42 (8.5%)	36 (7.3%)	**78 (15.8%)**
Moderate	116 (53.2%)	58 (26.6%)	26 (11.9%)	18 8.3%)	**44 (20.2%)**
Severe	24 (44.4%)	18 (33.3%)	8 (14.8%)	4 (7.4%)	**12 (22.2%)**

Table 90: Prevalence of PRSD by baseline co-morbidities at 4m in those treated with primary CRT or RT alone

Xerostomia	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
G1/2	349 (72.9%)	97 (20.3%)	21 (4.4%)	12 (2.5%)	**33 (6.9%)**
G3/4	520 (53.3%)	257 (26.4%)	106 (10.9%)	92 (9.4%)	**198 (20.3%)**

Table 91: Prevalence of PRSD with or without xerostomia at 4m in those treated with primary CRT or RT alone

	Univariate analysis – 4m					
	Grade 3+ Taste			**Grade 3+ Smell**		
Variable	**OR**	**CI 95%**	**P**	**OR**	**CI 95%**	**P**
Tumour Site						
Oropharynx / UP vs others	3.15	2.53 to 3.91	<0.0001	1.14	0.85 to 1.52	0.38
Larynx vs others	0.20	0.15 to 0.25	<0.0001	0.55	0.39 to 0.76	<0.0001
Hypopharynx vs others	1.34	0.86 to 2.10	0.20	1.68	0.98 to 2.74	0.05
Nasopharynx vs others	3.61	1.97 to 7.16	<0.0001	2.74	1.54 to 4.71	<0.0001
Treatment						
CRT vs RT alone	4.51	3.59 to 5.68	<0.0001	1.84	1.34 to 2.53	<0.0001

Stage						
III/IV vs I/II	4.67	3.66 to 5.96	<0.0001	2.28	1.60 to 3.25	<0.0001
Sex						
Female vs male	0.91	0.63 to 1.32	0.62	0.91	0.62 to 1.32	0.62
Age						
Age >60 vs <60 years	0.64	0.52 to 0.79	<0.0001	1.06	0.79 to 1.41	0.69
HPV in OPC						
Positive vs Negative	0.83	0.57 to 1.20	0.31	0.49	0.32 to 0.76	0.001
Smoking status at 4 months						
Current vs former / never	1.12	0.80 to 1.58	0.51	0.69	0.45 to 1.06	0.09
Alcohol Status						
Yes vs No	0.64	0.51 to 0.79	<0.0001	0.56	0.41 to 0.77	<0.0001
Co-morbidities at baseline						
III/IV vs I/II	0.83	0.64 to 1.08	0.16	1.49	1.07 to 2.09	0.02
Xerostomia at 4 months						
G3/4 vs G1/2	6.58	5.14 to 8.43	<0.0001	3.44	2.34 to 5.07	<0.0001
Smell Dysfunction at baseline						
G3/4 vs G1/2				7.40	4.47 to 12.2	<0.0001
Smell Dysfunction at 4 months						
G3/4 vs G1/2	32.14	15.73 to 65.7	<0.0001			
Taste Dysfunction at baseline						
G3/4 at 0m	2.46	1.59 to 3.80	<0.0001			

Table 92: Univariate analysis to determine association between patient and treatment related factors and PRTD or PRSD at 4m in patients treated with radical RT/CRT in OPC/UP, L, HP and NP tumours

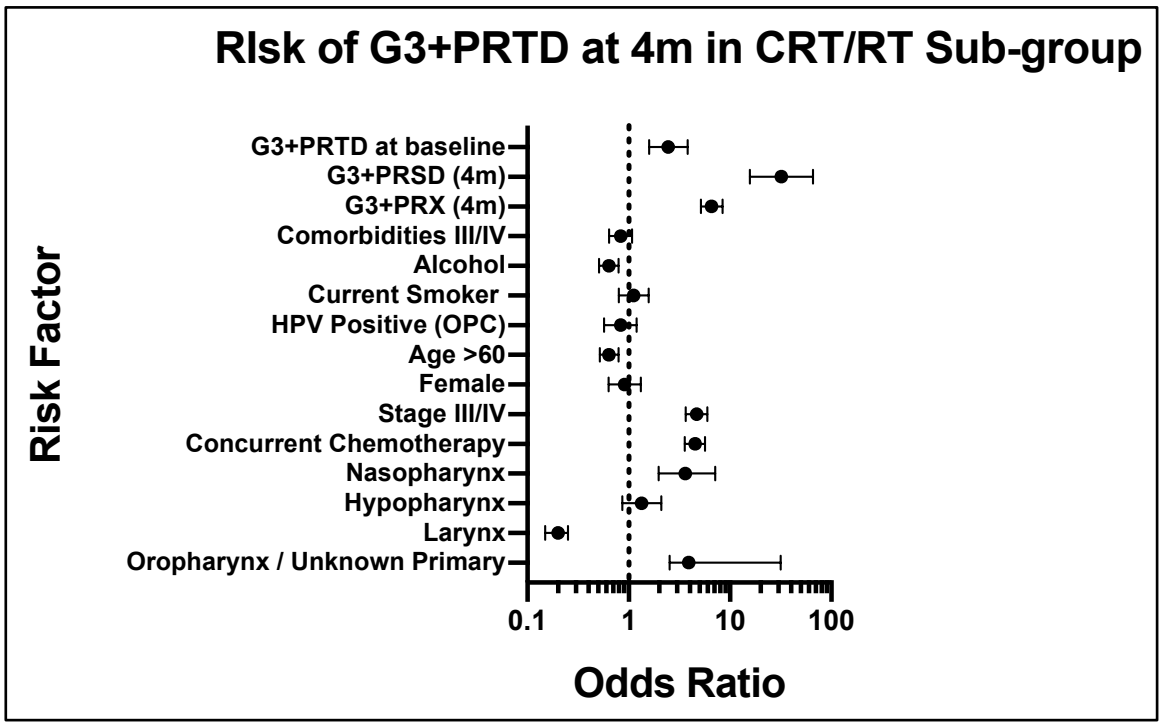


Figure 4-8: Forrest plot showing risk of G3+PRTD at 4m in those treated with CRT or RT

4.4.3.3 Multivariate analysis for taste dysfunction in those treated with CRT and RT at 4 months.

With adjustment for age, stage, and use of concurrent chemotherapy the odds ratio for G3+PRTD at 4m in those with OPC/UP versus other tumour groups was 1.49 (p=0.003). For LC the odds ratio 0.40 (p=<0.0001) and in NPC the odds ratio 3.62 (p=<0.0001). The odds ratio for developing G3+PRTD in those with HPC compared to all other tumours sites was not statistically significant on either univariate or multivariate analysis.

Variable	OR	CI 95%	P
Oropharyngeal / UP vs others	1.49	1.14 to 1.94	0.003
Larynx vs others	0.40	0.30 to 0.54	<0.0001
Nasopharynx vs others	3.62	1.90 to 7.42	0.0002
Hypopharynx vs others	1.19	0.75 to 1.93	0.47

Table 93: Multivariate analyses to determine the association between tumour site treated with radical RT/CT and G3+PRTD adjusted for age, stage and concurrent chemotherapy

A further multivariate analysis was completed to explore the effect of concurrent chemotherapy. When adjusted for age and stage of disease, the use of concurrent chemotherapy remained an independent statistically significant predictor of PRTD at 4 months (table 94).

Variable	OR	CI 95%	P
Age>60	1.02	0.80 to 1.30	0.89
Stage 3 or 4 disease	2.41	1.74 to 3.33	<0.0001
Concurrent chemotherapy	2.62	1.90 to 3.62	<0.0001

Table 94: Multivariate analysis to determine the association between concurrent chemotherapy and G3+PRTD at 4m when adjusted for age and stage

4.4.4 Gustatory outcomes at 12 months in those treated with RT or CRT.

A description of the cohort of patients treated with RT or CRT has been previously described. The same subgroup was analysed at 12m to capture the prevalence of late gustatory toxicity.

At 12m gustatory outcome data was available for 1287 patients. The prevalence of G3+PRTD ranged from 14.43% in those treated for LC to 54.70% in those with NPC (figure 4-9). The overall prevalence across this subgroup was 36.91% (table 95) which was slightly higher than the prevalence seen in the entire HN5000 cohort of 31% (see table 46). Rates of G3+PRTD and G3+PRSD by tumour site, stage, sex, age, HPV status in OPC, smoking/alcohol status, comorbidities, presence of xerostomia and use of concurrent chemotherapy are presented (tables 95-114).

Univariate analysis using logistic regression was completed to look for statistically significant associations (table 115).

4.4.4.1.1 Taste

For the purposes of this analysis OPC and UP were again analysed together. Factors associated with increased risk of G3+PRTD were OPC/UP (odds ratio

2.96, p<0.0001), NPC (odds ratio 2.15, p=0.003), concurrent chemotherapy (odds ratio 2.88, p<0.0001), stage III/IV disease (odds ratio 3.27, p<0.0001), being female (odds ratio 1.53, p=0.003), co-existing G3+PRX (odds ratio 6.32, p<0.0001), co-existing G3+PRSD (odds ratio 14.18, p<0.0001) and baseline G3+PRTD (odds ratio 3.14, p<0.0001). Factors associated with reduced risk of G3+PRTD were similar to those seen at 4m and included LC (odds ratio 0.19, p<0.0001), age >60 years (odds ratio 0.63, p<0.0001) and consumption of alcohol (odds ratio 0.55, p<0.0001).

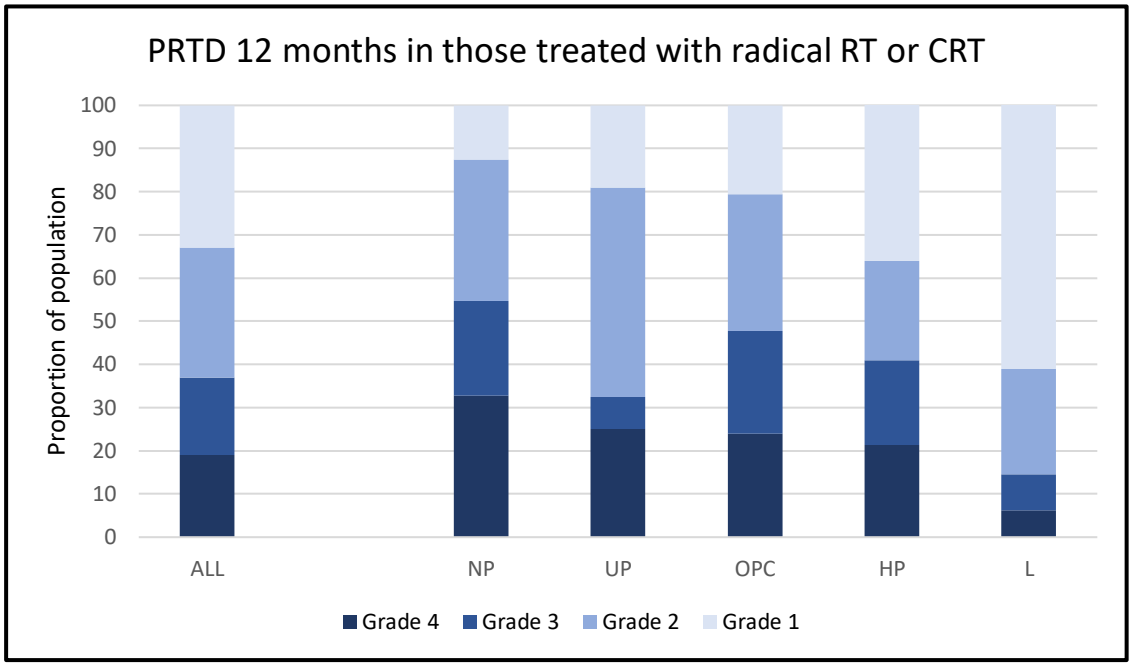


Figure 4-9: Rates of PRTD and PRSD at 12m in those treated with radical RT or CRT

Tumour Site	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3 +
Oropharynx	145 (20.5%)	224 (31.7%)	168 (23.8%)	169 (23.9%)	**337 (47.7%)**
Larynx	237 (61.1%)	95 (24.5%)	32 (8.3%)	24 (6.2%)	**56 (14.4%)**
Hypopharynx	22 (36.1%)	14 (23.0%)	12 (19.7%)	13 (21.3%)	**25 (41.0%)**
Unknown Primary	13 (19.1%)	33 (48.5%)	5 (7.4%)	17 (25.0%)	**23 (33.8%)**
Nasopharynx	8 (12.5%)	21 (32.8%)	14 (21.9%)	21 (32.8%)	**35 (54.7%)**
ALL	425 (33.0%)	387 (30.1%)	231 (18.0%)	244 (19.0%)	**475 (36.9%)**

Table 95: Prevalence of PRTD by tumours site at 12m in those treated with CRT or RT alone

Chemo	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Yes	183 (22.0%)	274 (33.0%)	176 (21.2%)	198 (23.8%)	**374 (45.0%)**
No	242 (53.1%)	113 (24.8%)	55 (12.1%)	46 (10.1%)	**103 (22.2%)**

Table 96: Prevalence of PRTD in those treated with or without concurrent chemotherapy at 12m in those treated with primary CRT or RT alone

Stage	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
I	133 (66.5%)	40 (20.0%	15 (7.5%)	12 (6.0%)	**27 (13.5%)**
II	84 (42.0%)	62 (31.0%)	25 (12.5%)	29 (14.5%)	**54 (27.0%)**
III	64 (28.7%)	68 (30.5%)	53 (23.8%)	38 (17.0%)	**91 (40.8%)**
IV	131 (22.0%)	184 (30.9%)	133 (22.4%)	147 (24.7%)	**280 (47.1%)**

Table 97: Prevalence of PRTD by stage at 12m in those treated with primary CRT or RT alone

Sex	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Male	360 (34.9%)	312 (30.2%)	176 (17.1%)	184 (17.8%)	**360 (34.9%)**
Female	65 (25.5%)	75 (29.4%)	55 (21.6%)	60 (23.5%)	**115 (45.1%)**

Table 98: Prevalence of PRTD by sex at 12m in those treated with primary CRT or RT alone

Age	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
60 and under	140 (24.5%)	186 (32.6%)	117 (20.5%)	128 (22.4%)	**245 (42.9%)**
Over 60	285 (39.8%)	201 (28.1%)	114 (15.9%)	116 (16.2%)	**228 (32.1%)**

Table 99: Prevalence of PRTD by age (above or below 60 years) at 12m in those treated with primary CRT or RT alone

HPV in OPC	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Positive	27 (20.0%)	41 (30.4%)	34 (25.2%)	33 (24.4%)	**67 (46.6%)**
Negative	106 (21.9%)	155 (32.0%)	114 (23.5%)	110 (22.7%)	**224 (46.2%)**

Table 100: Prevalence of PRTD by HPV status in those with OPC at 12m in those treated with primary CRT or RT alone

Smoking	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Current	30 (25.0%)	33 (27.5%)	30 (25.0%)	27 (22.5%)	**57 (47.5%)**
Former / Never	294 (32.7%)	273 (30.4%)	152 (16.9%)	179 (19.9%)	**331 (38.9%)**

Table 101: Prevalence of PRTD by smoking status at 12m in those treated with primary CRT or RT alone

Alcohol	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Yes	261 (37.4%)	220 (31.5%)	113 (16.2%)	104 (14.9%)	**217 (31.1%)**
No	115 (25.6%)	132 (29.3%)	88 (19.6%)	115 (25.6%)	**203 (45.1%)**

Table 102: Prevalence of PRTD by alcohol status at 12m in those treated with primary CRT or RT alone

Co-morbidities	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
Nil	191 (31.4%)	190 (31.2%)	117 (19.2%)	111 (18.2%	**228 (28.4%)**
Mild	149 (33.7%)	127 (28.7%)	82 (18.6%)	84 (19.0%)	**166 (37.6%)**
Moderate	67 (35.3%)	55 (29.0%)	24 (12.6%)	44 (23.2%)	**66 (35.8%)**
Severe	15 (42.9%)	11 (31.4%)	6 (17.1%)	3 (8.6%)	**9 (25.7%)**

Table 103: Prevalence of PRTD by baseline co-morbidities at 12m in those treated with primary CRT or RT alone

Xerostomia	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	217 (57.9%)	93 (24.8%)	44 (11.7%)	21 (5.6%)	**65 (17.3%)**
G3/4	162 (22.6%)	230 (32.1%)	149 (20.8%)	176 (24.6%)	**325 (45.4%)**

Table 104: Prevalence of PRTD with or without xerostomia at 12m in those treated with primary CRT or RT alone

G3 Smell	G1 taste	G2 taste	G3 taste	G4 taste	Grade 3+
G1/2	363 (39.0%)	283 (30.4%)	145 (15.6%)	140 (15.0%)	**285 (30.6%)**
G3/4	16 (9.9%)	41 (25.3%)	48 (29.6%)	57 (35.2%)	**105 (64.8%)**

Table 105: Prevalence of PRTD with or without smell dysfunction at 12m in those treated with primary CRT or RT alone

4.4.4.1.2 Smell

On univariate analysis G3+PRSD was statistically significantly associated with being treated for NPC (odds ratio 2.22, p=0.009), HPC (odds ratio 2.20, p=0.01) and consumption of alcohol (odds ratio 0.62, p=0.008).

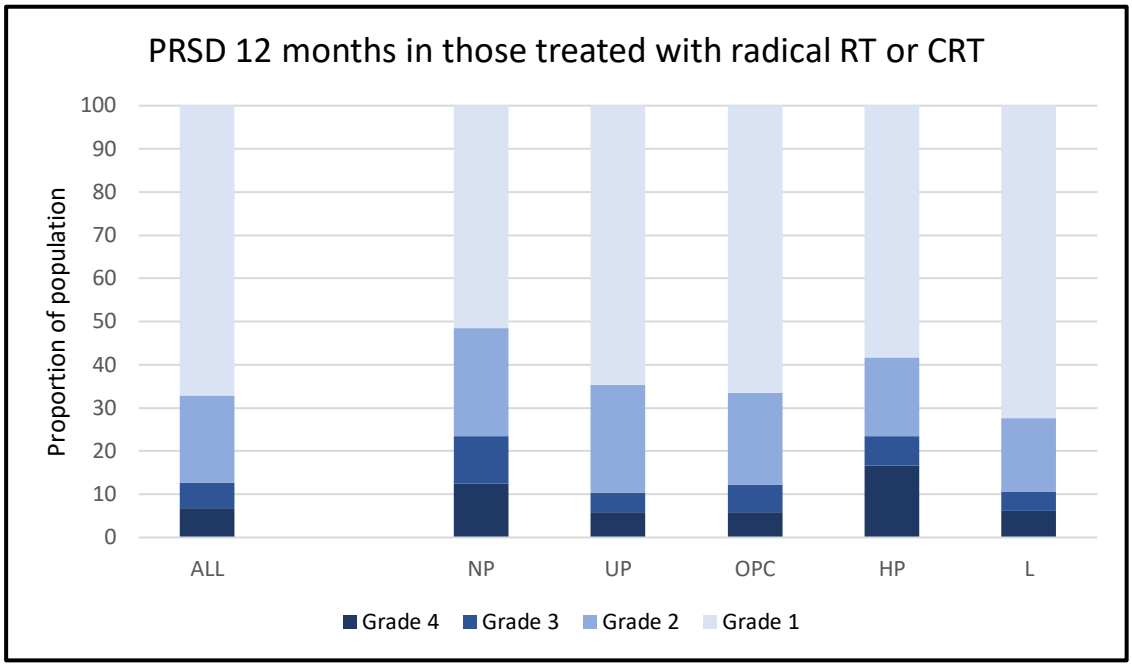


Figure 4-10: Rates of PRTD and PRSD at 12m in those treated with radical RT or CRT

Tumour Site	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3 +
Oropharynx	471 (66.6%)	150 (21.2%)	45 (6.4%)	41 (5.8%)	**86 (12.2%)**
Larynx	281 (72.4%)	66 (17.0%)	17 (4.4%)	24 (6.2%)	**41 (10.6%)**
Hypopharynx	35 (58.3%)	11 (18.3%)	4 (6.7%)	10 (16.7%)	**14 (23.3%)**
Unknown Primary	44 (64.7%)	17 (25.0%)	3 (4.4%)	4 (5.9%)	**7 (10.3%)**
Nasopharynx	33 (51.6%)	16 (25.0%)	7 (10.9%)	8 (12.5%)	**15 (23.4%)**
ALL	864 (67.1%)	260 (20.2%)	76 (5.9%)	87 (6.8%)	**163 (12.7%)**

Table 106: Prevalence of PRSD by tumours site at 12m in those treated with CRT or RT alone

Chemo	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Yes	538 (64.9%)	182 (22.0%)	51 (6.2%)	58 (7.0%)	**109 (13.2%)**
No	326 (71.1%)	78 (17.0%	25 (5.5%)	29 (6.3%)	**54 (11.8%)**

Table 107: Prevalence of PRSD in those treated with or without concurrent chemotherapy at 12m in those treated with primary CRT or RT alone

Stage	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
I	152 (76.0%)	27 (13.5%)	11 (5.5%)	10 (5.0%)	**21 (10.5%)**
II	143 (70.8%)	34 (16.8%)	10 (5.0%)	15 (7.4%)	**25 (12.4%)**
III	141 (63.8%)	46 (20.8%)	20 (9.1%)	14 (6.3%)	**34 (15.4%)**
IV	383 (64.4%)	136 (22.9%)	32 (5.4%)	44 (7.4%)	**76 (12.8%)**

Table 108: Prevalence of PRSD by stage at 12m in those treated with primary CRT or RT alone

Sex	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Male	702 (68.0%)	203 (19.7%)	62 (6.0%)	65 (6.3%)	**127 (12.3%)**
Female	162 (63.5%)	57 (22.4%)	14 (5.5%)	22 (8.6%)	**36 (14.1%)**

Table 109: Prevalence of PRSD by sex at 12m in those treated with primary CRT or RT alone

Age	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
60 and under	377 (66.0%)	119 (20.8%)	34 (6.0%)	41 (7.2%)	**75 (13.2%)**
Over 60	487 (68.0%)	141 (19.7%)	42 (5.9%)	46 (6.4%)	**88 (12.3%)**

Table 110: Prevalence of PRSD by age (above or below 60 years) at 12m in those treated with primary CRT or RT alone

HPV in OPC	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Positive	83 (61.5%)	31 (23.0%)	10 (7.4%)	11 (8.2%)	**22 (15.6%)**
Negative	337 (69.3%)	96 (19.8%)	28 (5.8%)	25 (5.1%)	**53 (10.9%)**

Table 111: Prevalence of PRSD by HPV status in those with OPC at 12m in those treated with primary CRT or RT alone

Smoking	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Current	69 (58.0%)	33 (27.7%)	10 (8.4%)	7 (5.9%)	**17 (14.3%)**
Former / Never	601 (66.9%)	172 (19.2%)	61 (6.8%)	64 (7.1%)	**125 (13.9%)**

Table 112: Prevalence of PRSD by smoking status at 12m in those treated with primary CRT or RT alone

Alcohol	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Yes	489 (70.1%)	140 (20.1%)	33 (4.7%)	36 (5.2%)	**69 (9.9%)**
No	294 (65.2%)	89 (19.7%)	30 (6.7%)	38 (8.4%)	**68 (15.1%)**

Table 113: Prevalence of PRSD by alcohol status at 12m in those treated with primary CRT or RT alone

Co-morbidities	G1 smell	G2 smell	G3 smell	G4 smell	Grade 3+
Nil	426 (69.8%)	118 (19.3%)	33 (5.4%)	33 (5.4%)	**66 (10.8%)**
Mild	287 (65.1%)	91 (20.6%)	25 (5.7%)	38 (8.6%)	**63 (14.3%)**
Moderate	124 (65.3%)	37 (19.5%)	15 (7.9%)	14 (7.4%)	**29 (15.3%)**
Severe	23 (65.7%)	7 (20.0%)	3 (8.6%)	2 (5.7%)	**5 (14.3%)**

Table 114: Prevalence of PRSD by baseline co-morbidities at 12m in those treated with primary CRT or RT alone

	Univariate analysis – 12M					
	Grade 3+ Taste			Grade 3+ Smell		
Variable	**OR**	**CI 95%**	**P**	**OR**	**CI 95%**	**P**
Tumour Site						
Oropharynx / UP	2.96	2.30 to 3.80	<0.0001	0.86	0.62 to 1.20	0.38
Larynx	0.19	0.14 to 0.26	<0.0001	0.75	0.51 to 1.09	0.14
Hypopharynx	1.20	0.70 to 2.02	0.50	2.20	1.14 to 4.00	0.01
Nasopharynx	2.15	1.30 to 3.56	0.003	2.22	1.18 to 3.97	0.009
Treatment						
CRT vs RT alone	2.88	2.22 to 3.73	<0.0001	1.13	0.80 to 1.60	0.48
Stage						
III/IV vs I/II	3.27	2.47 to 4.33	<0.0001	1.21	0.83 to 1.74	0.32
Sex						
Female vs male	1.53	1.16 to 2.02	0.003	1.17	0.79 to 1.74	0.44
Age						
Age >60	0.63	0.50 to 0.79	<0.0001	0.93	0.67 to 1.29	0.65
HPV in OPC						
Positive vs Negative	0.87	0.59 to 1.28	0.48	0.66	0.38 to 1.15	0.14
Smoking status at 12 months						
Former/never vs current	0.65	0.44 to 0.95	0.03	0.97	0.56 to 1.68	0.91
Alcohol Status						
Yes	0.55	0.43 to 0.70	<0.0001	0.62	0.43 to 0.88	0.008
Co-morbidities						
III/IV vs I/II	0.87	0.64 to 1.17	0.36	1.27	0.85 tp 1.91	0.25
Xerostomia at 12 months						
G3/4	6.32	4.77 to 8.38	<0.0001			
Smell Dysfunction at 12 months						
G3/4	14.18	8.96 to 22.45	<0.0001			
Taste Dysfunction at baseline						
G3/4 at 0m	3.14	2.03 to 4.86	<0.0001			

Table 115: Univariate analysis to determine association between patient and treatment related factors and PRTD or PRSD at 12m in patients treated with radical RT/CRT in OPC/UP, L, HP and NP tumours

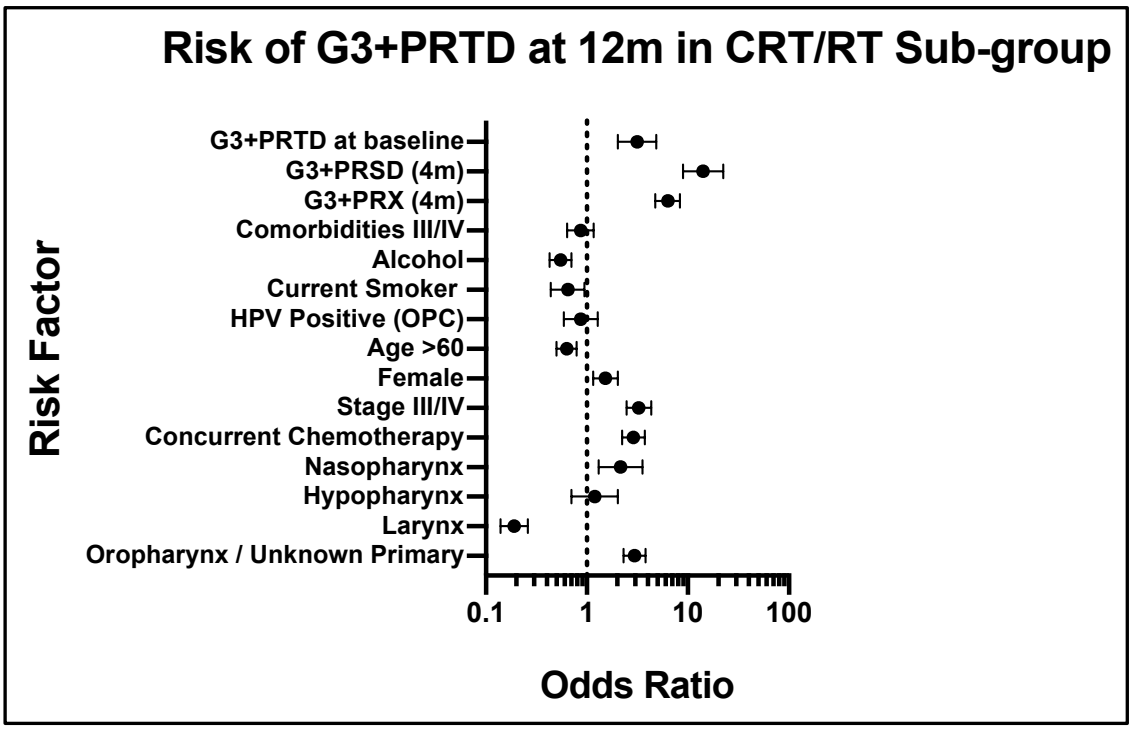


Figure 4-11: Forest plot showing risk of G3+PRTD at 12m in those treated with CRT or RT

4.4.4.2 Multivariate analysis for taste dysfunction in those treated with CRT and RT at 12 months.

With adjustment for age, stage and concurrent chemotherapy, the odds ratio for G3+PRTD at 12m in those with OPC/UP versus other tumour sites was 1.99 (p=<0.0001). For LC the odds ratio was 0.26 (p=<0.0001) and in NPC 2.11 (p=0.03). The odds ratio for G3+PRTD in those with HPC was not statistically significant either on univariate or multivariate analysis.

Variable	OR	CI 95%	P
Oropharyngeal / UP vs others	1.99	1.47 to 2.68	<0.0001
Larynx vs others	0.26	0.18 to 0.37	<0.0001
Nasopharynx vs others	2.11	1.24 to 3.59	0.006
Hypopharynx vs others	1.15	0.67 to 1.98	0.61

Table 116: Multivariate analyses to determine the association between tumour site and G3+PRTD when adjusted for age, stage and concurrent chemotherapy

4.4.4.3 Concurrent chemotherapy

A further multivariate analysis was completed to explore the effect of concurrent chemotherapy. When adjusted for age and stage of disease, the use of concurrent chemotherapy remained an independent statistically significant predictor of G3+PRTD at 12m (table 117) though appears to have less of an effect than seen at 4m (table 95).

Variable	OR	CI 95%	P
Age >60	0.77	0.60 to 0.98	0.04
Stage 3 or 4 disease	2.13	1.46 to 3.12	<0.0001
Concurrent chemotherapy	1.69	1.17 to 2.44	0.005

Table 117: Multivariate analysis to determine the association between concurrent chemotherapy and PRTD at 12m when adjusted for age and stage.

Figure 4-10 compares the odds ratios for developing G3+PRTD at 4m and 12m by in each tumour site (versus all others). The relative effect of each tumour site may evolve over time with the negative association of being in the laryngeal group and positive association of being in the oropharynx group strengthening, while the association in the nasopharynx group may weaken.

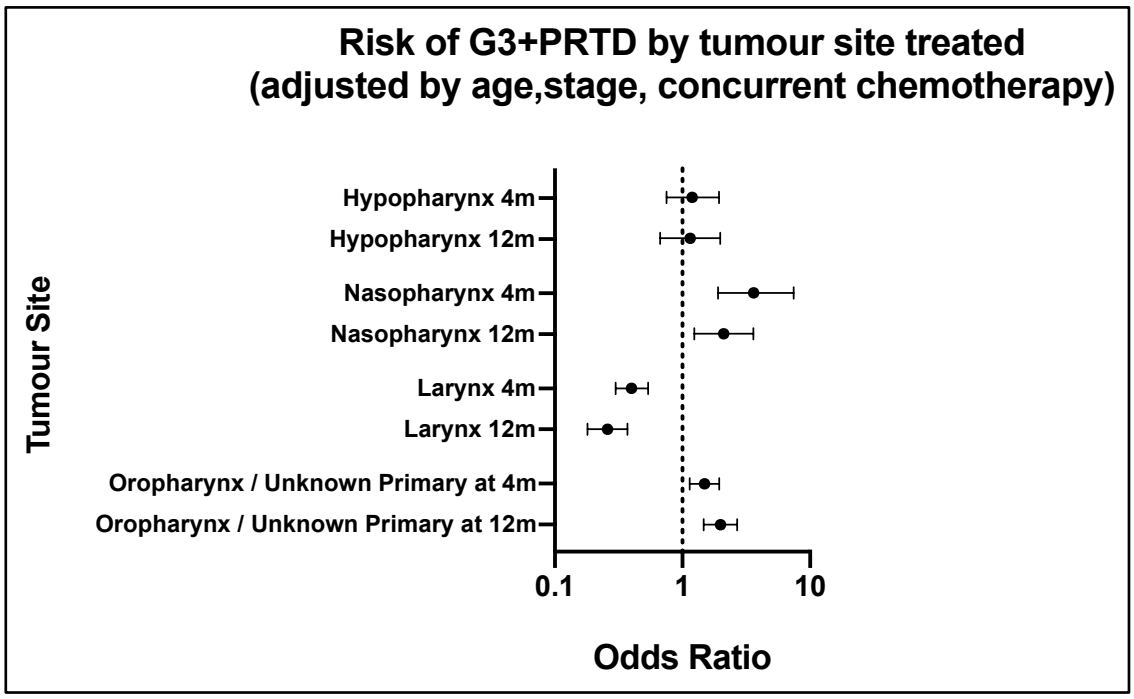


Figure 4-12: Forest plot showing risk of G3+PRTD by tumour site when adjusted for age, stage and use of concurrent chemotherapy at 4m and 12m follow up

4.4.5 Down-stream effects of PRTD

4.4.5.1 Global health scores – entire cohort

The HNQ35 questionnaire asks patients to rank their overall QoL, generating a GHS. The mean GHS in those with G3+PRTD was compared with those without at each time point. For this analysis the entire HN5000 cohort was included. GHS scores were consistently higher (better) in those without G3+PRTD ($p<0.0001$) and the magnitude of this effect was large and would be considered clinically significant with a difference in score of >10 points (90) (table 118).

	0m	4m	12m
G3/4 PRTD	47.29 (SD 27.8)	50.89 (SD 24.7)	59.59 (SD 25.7)
G1/2 PRTD	68.32 (SD 23.8)	68.68 (SD 22.8)	74.55 (SD 21.7)
Difference	21.03	17.79	15.0
P value	<0.0001	<0.0001	<0.0001

Table 118: Mean GHS in those with or without PRTD at 0m, 4m and 12m following treatment for HNC (two sample t test with equal variance).

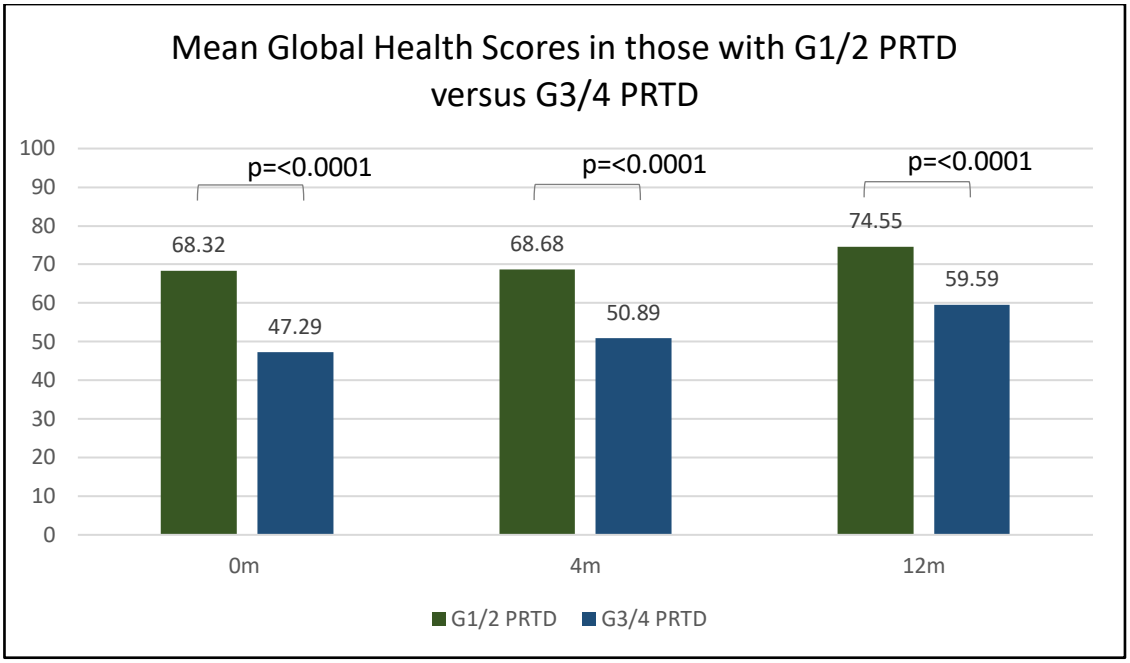


Figure 4-13: Bar chart showing mean GHS scores in those with G1/2 PRTD versus G3/4 PRTD (entire cohort) at baseline, 4m and 12m following treatment for HNC

4.4.5.2 BMI – entire cohort

The mean BMI was also compared in those with or without G3+PRTD at each time point. People with G3+PRTD had lower BMI at baseline, 4m and 12m and this was statistically significant at 4m and 12m (p<0.0001) (see table 119). The mean change in BMI was also compared between those with or without G3+PRTD. There was a larger reduction in BMI in those with PRTD at both 4m and 12m and this was statistically significant (p<0.0001) (see table 120 and figure 4-12).

	0m	**4m**	**12m**
G3/4 PRTD	25.61 (SD 5.52)	24.20 (SD 4.63)	23.81 (SD 4.59)
G1/2 PRTD	26.61 (SD 5.26)	25.44 (SD 4.95)	25.51 (SD 5.34)
Difference	1.00	1.24	1.70
P value	Not significant	<0.0001	<0.0001

Table 119: Mean BMI in those with or without PRTD at 0m, 4m and 12m following treatment for HNC

	4m	12m
G3/4 PRTD	-2.47 (SD 3.00)	-3.07 (SD 3.44)
G1/2 PRTD	-1.12 (SD 3.00)	-1.35 (SD 3.86)
P value	<0.0001	<0.0001

Table 120: Mean change in BMI from baseline in those with or without PRTD at 4m and 12m following treatment for HNC

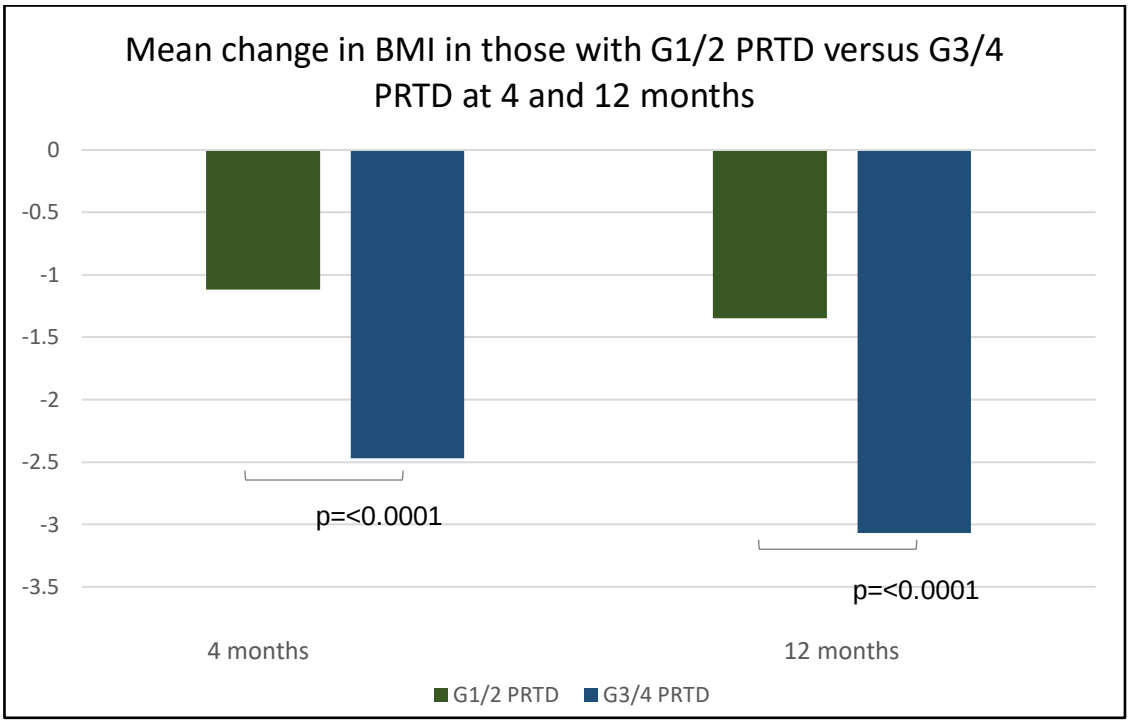


Figure 4-14: Mean change in BMI in those with G1/2 PRTD versus G3/4 PRTD at 4m and 12m post completion of treatment for HNC (entire HN5000 cohort)

4.5 Discussion and Conclusions

This is the largest prospective analysis of gustatory function in people diagnosed with HNC treated with RT or CRT. It is also the largest dataset reporting baseline dysfunction in treatment-naïve patients with HNC.

There is often a broad and likely incorrect assumption that baseline function at diagnosis is normal however this analysis has shown that 11% of the HN5000 entire cohort had G3+PRTD at baseline, with only 69% reporting entirely normal

(Grade 1) function. G3+PRSD was also present in 6% of patients with 81% reporting normal function.

Patients with tumours that might affect smell function (NC, OPC, SCT) were more likely to have baseline G3+PRTD. Advanced stage disease, being a current smoker, having moderate/severe comorbidities and coexisting baseline G3+PRSD and xerostomia were all statistically associated with baseline dysfunction also.

When adjusted for confounders tumours involving the mucosa of the upper aerodigestive tract, stage III/IV disease, moderate to severe comorbidities, being a current smoker and being female all remained statistically significant. It is likely therefore that where there is baseline dysfunction related to the presence of a tumour there may be scope for improvement following treatment of the primary disease. Disregarding primary tumour site, the two factors most associated with G3+PRTD were co-existing G3+PRSD and G3+PRX.

Analysis at 4m and 12m focused on gustatory outcomes in those treated with radical intent with RT or CRT. Data was collected 4m and 12m following joining the study therefore the timing of the survey relative to completion of RT will have varied slightly dependent on the treating centre. Regardless, the 4m data is representative of acute toxicity outcomes at a time where nutritional, physical and social recovery is paramount.

Over half (54.2%) of the patients at 4m reported G3+PRTD with higher rates seen in those with OPC, HPC, UP and NPC. For comparison the prevalence of G3+PRTD in the entire HN5000 cohort at 4m was 45% though is it is difficult to make a direct comparison when it is likely that those having surgery alone will have had a good period of recovery and those having surgery with adjuvant therapy were likely still completing their treatment.

Prevalence of G3+PRTD in those with OPC, UP, HPC and NPC ranged from 64.6% to 80.3% with a much lower rate of 27.7% seen in patients treated for LC. While in the HN5000 cohort, RT dosimetry data was not available, the differing

prevalence of taste dysfunction at the variety of tumour sites analysed can be taken as a proxy for dose delivered to the OAR. In this case the reduced prevalence of PRTD in those treated for LC, suggested a strong relationship between less RT dose to the gustatory field and minimal toxicity. I.e., small fields used in treating LC led to less dose to the gustatory OAR and less PRTD; and large treatment volumes for NPC result in higher doses to the gustatory OAR and higher rates of PRTD. Prevalence of G3+PRSD was 15.9% amongst the RT/CRT group overall, with higher rates seen in those treated for NPC (32.8%).

Advanced stage disease was strongly associated with G3+PRTD at 4m and 12m likely reflecting the relationship between size of volume irradiated and dose to the gustatory field. The proportion of patients with G3+PRTD was also consistently higher in those who had received concurrent chemotherapy. Concurrent chemotherapy is only given in stage III/IV disease (in suitable patients under age 70 years), and it is difficult to quantify the additional risk associated with concurrent platinum. Multivariate analysis suggested that at 4m concurrent chemotherapy when adjusted for stage and age remained an independent risk factor for G3+PRTD (odds ratio 2.62, $p<0.0001$). This effect appeared to persist and was statistically significant at 12m albeit with a slightly lower odds ratio (odds ratio 1.69, $p=0.005$).

Overall, outcomes at 12m showed some recovery of both G3+PRTD and G3+PRSD. Rates of G3+PRTD had fallen from 54.2% to 36.9% and rates of G3+PRSD from 15.9% to 12.7%. The proportion of patients with normal function (Grade 1) was significantly less than at baseline (70.3% at baseline versus only 33% at 12 months) suggesting that although severe toxicity improves, a new residual level of dysfunction albeit mild grade 2 PRTD, becomes the new normal for many patients.

Factors statistically associated with G3+PRTD at 12m on univariate analysis were very similar to those seen at 4m and included OPC/UP and NPC tumours, use of concurrent chemotherapy, advanced stage disease and being female. In particular co-existing G3+PRSD and G3+PRX were both strongly associated with G3+PRTD.

The effect of smoking and alcohol on gustatory function was not clear with the consumption of alcohol consistently associated with a reduced prevalence of G3+PRTD. There is no suggestion that the consumption of alcohol has a protective effect, and this analysis would in no way advocate this conclusion given alcohol consumption is a known risk factor for HNSCC. A more plausible explanation for this finding is that alcohol consumption is a reflection of the behaviour adopted by those with intact taste function. In the early weeks during and after RT, alcohol can be a strong irritant to the oral mucosa and in the longer term may not be as palatable in those with treatment related taste dysfunction. Current smoking status was associated with increased prevalence of G3+PRTD as baseline but there was no statistically significant association at 4m. At 12m being a former/never smoker was protective (odd ratio 0.65, p=0.03).

Age was also puzzling. It is known that with increasing age, the acuity of the senses can decline. It would therefore be reasonable to expect age >60 to be associated with increased risk of G3+PRTD however this was not observed in this analysis. At all time points, age >60 was associated with a reduced risk of G3+PRTD. This may be because older patients already have reduced taste function and therefore the relative change is less pronounced. Alternatively, the significance of being <60 years may be confounded by the fact that only those <70 years are treated with concurrent chemotherapy which in and of itself was shown to be an independent risk factor for G3+PRTD.

For the vast majority of people, eating is one of life's simple pleasures and difficulty enjoying meals after radical CRT or RT to the head and neck is often the focus of discussion at follow up for years after treatment. The effect of taste dysfunction on overall QoL (as measured using the HNQ35 global health score) showed that overall QoL was consistently better in those without G3+PRTD at all time points ($p<0.0001$) with absolute differences in score of >10 suggesting both statistical and clinical significance (90). An individual's response to the GHS question will be determined by a number of health and treatment related factors and it was not within the scope of this analysis to explore the relative impact that taste dysfunction has on overall QoL. It is fairly intuitive however, that preserving

the ability to taste food will for the vast majority be considered a positive outcome.

The reduction in BMI, was consistently greater in those with G3+PRTD at both 4m and 12m ($p<0.0001$) supporting the theory that taste impairment leads to nutritional deficits which have been associated with poor survival outcomes. Remarkably, for a patient cohort that typically struggles with maintaining nutritional intake during and after treatment, the mean BMI for the group was in the upper end of normal; though lower than the average BMI for adults within the UK which in 2018 was 27.5 (for both men and women) (94).

In terms of informing patients from the outset regarding the probability of gustatory dysfunction, it is likely that just over 5 in 10 will have G3+PRTD and almost 2 in 10 will develop G3+PRSD at 4m (sub-acutely). When adjusted for stage, age and sex, there is additional risk for those with OPC/UP (odds ratio 1.66) and in particular those with NPC (odds ratio 5.07). Conversely the risk will be significantly less in those with LC (odds ratio 0.35).

At 12m the probability is slightly lower at just under 4 in 10 for G3+PRTD and just over 1 in 10 for G3+PRSD. With adjustments for stage, age and sex, there is additional risk for those with OPC/UP (odds ratio 2.09) and now to a lesser extent than at 4 months in those with NPC (odds ratio 2.13). Risk is considerably lower for those with LC (odds ratio 0.27).

Strengths of the study include the use of a large prospective dataset focusing on patient reported outcomes and an approach to analysis that generated clinically meaningful outcomes to allow the clinical oncologist to identify at risk groups within their treatment population. The results also support a relationship between dose to the gustatory field and likelihood of toxicity prompting further research to develop a dose constraint for preservation of taste.

The survey used has limitations in that the question posed is whether or not patients have problems with their sense of taste, or sense of smell etc. It does not allow an opportunity to explore the nature of the perceived problem which is

often a presumed deficit but could also include heightened sensitivity / function or phantogeusia. There are no validated surveys that assess PRTD in patients undergoing radiotherapy; it would be useful to standardise this to optimise collection of taste data in the future. The study also lacked any objective assessment of gustatory function with chemosensory testing.

The analysis may have underestimated the effect of comorbidity status on outcomes as the proportion of participants with severe co-morbidities reduced over time. A closer look at survival data may inform whether this data is truly missing or whether it can be disregarded, and the population remains representative of the natural history of the analysed cohort.

As this is retrospective cohort analysis it is difficult to determine whether or not any of the observed associations truly represent causative relationships. G3+PRSD and G3+PRX were selected as two toxicities that have a rational causal link with G3+PRTD but there may be many other factors that contribute (consistency and composition of saliva; a deficit in tactile function of the tongue; oral pain; secretions to name a few).

The following two chapters will build upon the results from this large prospective dataset and will combine patient reported outcomes with objective chemosensory testing whilst analysing detailed dosimetry data to try and develop a constraint for preservation of taste following RT to the head and neck.

Chapter 5 – Gustatory Function 12 months following completion of radiotherapy to the head and neck: A Cross-Sectional Study

5.1 Background

This cross-sectional study was designed to capture gustatory outcomes 12m following completion of RT to the head and neck.

As previously discussed in chapter 2 (a systematic review of gustatory outcomes following radiotherapy to the head and neck), there are few studies from the IMRT era that use both objective and subjective gustatory assessments to capture late toxicity for HNC patients treated with RT.

The majority of studies demonstrate evidence of recovery of function or recovery to baseline function 3-6m after RT (66,69). There is evidence however that up to 50% of patients 1-2 years following treatment with RT continue to have subjective taste loss. This study protocol was developed to assess taste outcomes at 12m in our own treated cohort at The Royal Marsden.

5.2 Aims and Objectives

5.2.1 Primary Objective

To investigate the association between RT dose to the gustatory field and PRTD 12m following RT or CRT to the head and neck.

5.2.2 Secondary and Exploratory Objectives

To describe the prevalence of PRTD and objective hypogeusia in patients 12m following RT to the head and neck.

To escribe the prevalence of PRSD and objective hyposmia in patients 12m following RT to the head and neck.

To explore the agreement between PRTD and PRSD and objective chemosensory testing.

To investigate the association between RT dose and objective hypogeusia, 12m following RT or CRT to the head and neck.

To explore patient and treatment-related predictors for PRTD and objective hypogeusia, 12m following RT or CRT to the head and neck.

To compare changes in BMI scores in those with and without taste dysfunction 12m following RT and chemo-RT to the head and neck.

To compare QoL scores in those with and without taste dysfunction 12m following RT and CRT to the head and neck.

5.3 Methods

5.3.1 Recruitment

Consecutive patients who were approaching their 12m follow up since completion of RT were invited to participate in the study. We aimed to recruit a minimum of 52 patients. Between September 2018 and February 2020, 73 patients were enrolled in the study.

5.3.2 Inclusion Criteria

Patient were required to be age 18 years or more, 12m (+/- 4 weeks) post completion of unilateral or bilateral RT or concurrent CRT to the head and neck region using either a conformal or IMRT planning technique. There were no restrictions on tumour sub-site, tumour histology or radiotherapy dose and fractionation

5.3.3 Exclusion Criteria

Patients were excluded if they had a pre-existing olfactory or gustatory disorder, had radiological or clinical involvement of the facial nerve, chorda tympani, glossopharyngeal nerve, lingual nerve, greater petrosal nerve or geniculate ganglion. Patients who had undergone a total or partial glossectomy were also excluded having had the target organ-at-risk removed.

5.3.4 Primary End Point

For the purposes of the primary objective, mean RT dose (Gy) to the anterior two-thirds of the whole tongue was estimated. PROs were dichotomised by the presence or absence of clinically significant dysfunction (Grade 3 or 4) using Question 9 from the UW-QOL v4.0.

5.3.5 Secondary End Points

PRTD was defined as stated in the primary end point measure above.

Objective chemosensory taste testing generated a taste score between 0-16. Patients were categorised as hypogeusic (score 0-8) or normogeusic (9-16).

To investigate the pattern of objective hypogeusia, individual scores of 0-4 were generated for each taste quality (sweet, sour, salty, bitter).

Using olfactory identification testing patients were initially categorised as normosmic, hyposmic or anosmic. Scores were then adjusted for age and sex to determine whether an individual's score fell below the 10^{th} centile of the wider population representing hyposmia (95).

Self-reported taste and smell changes were also collated from the Taste and Smell Survey.

To investigate dosimetric predictors, dose volume histogram (DVH) data was generated to quantify RT dose to gustatory regions of interest (ROI), including but not limited to, mean doses (Gy) to the whole oral cavity, whole tongue, anterior two thirds of the tongue, posterior third of the tongue, the surface of the anterior two thirds of the tongue and the surface of the whole tongue.

Potential patient and treatment related predictors investigated were age, sex, smoking status, alcohol status, stage of primary tumour, xerostomia, use of induction and concurrent chemotherapy. Xerostomia was defined as grade 3 or 4 dry mouth as per Q10 from the UWQOL v4.0 questionnaire (96).

QoL was assessed using the UW-QOL v4.0 survey (96).

Change in weight was assessed using height and weight to determine BMI prior to RT and at 12m follow up.

5.3.6 Procedures

Patients were first asked to complete the UWQOL Questionnaire and the Taste and Smell Survey. A short consultation also allowed an opportunity to discuss gustatory changes and document other radiation toxicity outcomes using CTCAE v5.0 and the Subjective Total Taste Acuity (STTA) assessment.

Objective chemosensory testing for smell was completed using the Burghart Sniffin sticks. Each of the 12 pens represents an every-day scent. The pen was held approximately 2cm from the patients nose where they were asked to smell the pen intensively for 2-3 seconds. An answer card with four options was presented and patients were required to choose one correct answer (forced-choice method). Scores were broadly categorised as normosmia (score of 10-12), hyposmia (score of 6-9) and anosmia (score 0-5). Scores were adjusted for age and sex to determine those who fell within the lowest 10^{th} centile of the normative values representing abnormal smell identification scores.

Following testing of olfactory function, whole mouth gustatory function was assessed using validated taste strips (Burghart; Wedel, Germany). Filter paper test strips are impregnated at one end with $2cm^2$ of either sweet, sour, salty or bitter taste solutions in four concentrations:

Sweet taste: 0.05, 0.1, 0.2 or 0.4g/mL sucrose

Sour taste: 0.05, 0.09, 0.165 or 0.3g/mL citric acid

Salty taste: 0.016, 0.04, 0.1 or 0.25g/mL sodium chloride

Bitter taste: 0.0004, 0.0009, 0.0024 or 0.006 g/mL quinine hydrochloride

Individual strips were placed on the tongue and patients asked to close their mouth in order to assess whole mouth taste function. Patients were asked to identify the taste stimuli as either sweet, sour, salty or bitter. Scores for individual taste qualities ranged from 0-4 and an overall taste score ranged from 0-16. Patients were asked to rinse their mouth with tap water prior the application of each taste strip. Strips were presented in ascending concentration though the order of quality assessed varied and was selected at random.

Normative mean values, reproducibility and validity of the taste strips have been established and published previously (92). The 10^{th} percentile is used to distinguish normogeusic (scores 9-16) from hypogeusic (scores 0-8) patients (see table 121).

Table 121. Normative values derived from healthy volunteers for taste strips					
Percentile	**Sweet**	**Sour**	**Salty**	**Bitter**	**Total Score**
5^{th}	2.0	1.5	1.0	1.0	8.5
10^{th}	2.0	2.0	2.0	1.0	9.0
50^{th}	4.0	3.0	3.0	3.0	13.0
90^{th}	4.0	4.0	4.0	3.0	15.0
95^{th}	4.0	4.0	4.0	4.0	15.0

Table 121: Normative values for taste strips derived from healthy volunteers

Gustatory ROI were outlined retrospectively on the RT plans delivered to the patient 12 months prior to inclusion in the study. ROI were the whole oral cavity (A), whole tongue (B), posterior third tongue (C), anterior two thirds of the tongue (D), superior 2cm whole tongue (E) and superior 2cm anterior two thirds of the tongue (F) (see figure 5-1). Mean dose (Gy) to each ROI was generated.

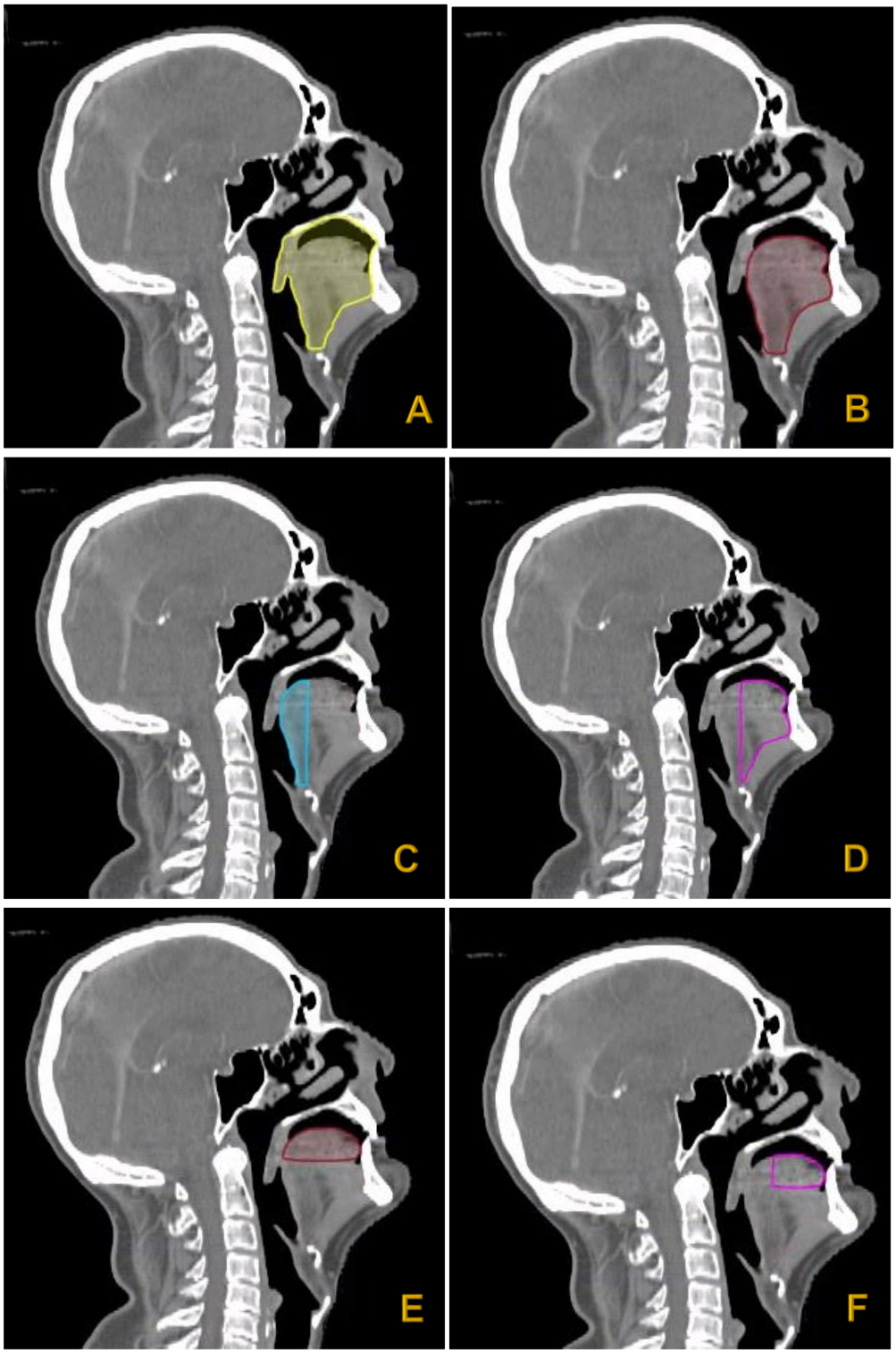


Figure 5-1: Regions of interest (potential gustatory organs-at-risk) for dosimetry analysis. A = extended oral cavity; B = whole tongue; C = posterior third tongue; D = anterior two-thirds of the tongue; E = superior 2cm of whole tongue; F = superior 2cm anterior two-thirds of the tongue

5.4 Analysis

5.4.1 Sample size

We expected to observe a mean difference in radiation dose of 20 Gy to the anterior tongue between two groups of patients with clinically significant and clinically insignificant taste dysfunction, with the SDs of 25 Gy and 17.5 Gy for the clinically significant and clinically insignificant groups, respectively. Using two sample t-test (for independent groups) with unequal variance, two-sided test, and alpha error of 5%, a sample size of 52 would provide 90% power.

5.4.2 Statistical analysis

Descriptive statistics were used to capture the key characteristics of the study cohort. Fisher's exact test was used to compare proportions for dichotomous outcomes. Paired t-tests were used to compare mean values between groups for continuous outcomes while ANOVA was used assess for group effects (for example in the taste quality analysis). Diagnostic test accuracy outcomes (sensitivity, specificity) were calculated to compare the performance of objective and subjective measures for defining taste dysfunction. Univariate and multivariate logistic regression was used to investigate the association between potential predictors and PRTD/objective taste dysfunction. All statistical tests were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. No adjustments for multiple testing were made, however results were interpreted accordingly.

5.5 Results

5.5.1 Patient and treatment characteristics

Patient demographics, tumour and treatment characteristics are summarised in table 122. The average age was 64 years with the majority of people (77%) having stage III/IV disease (TNM 7th edition). Approximately half the cohort received concurrent chemotherapy and half were treated for OPC. Almost all patients were treated with IMRT and 27% had RT in the post-operative setting. Only 1 person reported being current smoker.

Cross-Sectional Study – Patient, Tumour and Treatment Characteristics	
Total Number of Patients	73
Median age at study entry (years)	64 years (range 33-81; SD 10.1)
Male	60 (82%)
Female	13 (18%)
Smoking Status	
Current smoker	1 (%)
Ex-smoker	35 (48%)
Non-smoker	24 (33%)
Not disclosed	13 (18%)
Tumour Site	
Oropharynx	41 (56.2%)
Larynx	8 (11.0%)
Neck	7 (9.6%)
Nasopharynx	5 (6.8%)
Oral Cavity	4 (5.4%)
Salivary Gland	2 (2.7%)
Skin	2 (2.7%)
Hypopharynx	1 (1.4%)
Base of skull	1 (1.4%)
Unknown primary	1 (1.4%)
Sinus cavity	1 (1.4%)
Tumour Histology	
Squamous cell carcinoma	61 (83.6%)
Nasopharyngeal carcinoma	4 (5.5%)
Follicular Lymphoma	2 (2.7%)
Hodgkin's Lymphoma	1 (1.4%)
Other	5 (6.8%)

P16 Status in Oropharyngeal Tumours	
P16 positive OPC	38 (92.7%)
P16 negative OPC	3 (7.3%)
Tumour stage	
TX	1 (1.4%)
T0	7 (9.6%)
T1	19 (26.0%)
T2	23 (31.5%)
T3	12 (16.4%)
T4	8 (11.0%)
N/A (lymphoma staging)	3 (4.1%)
Nodal stage	
Positive	50 (68.5%)
Negative	20 (27.4%)
N/A (lymphoma staging)	3 (4.1%)
AJCC* stage (TNM 7th edition)	
I and II	17 (23.3%)
III and IV	56 (76.7%)
Treatment	
Radiotherapy	15 (20.5%)
Post op radiotherapy	18 (24.7%)
Chemoradiotherapy	38 (52.1%)
Post op chemoradiotherapy	2 (2.7%)
Neoadjuvant systemic therapy	
Yes	6 (8.2%)
No	67 (91.8%)
Concomitant chemotherapy	
Yes	40 (54.8%)
No	33 (45.2%)
Planning technique	
VMAT	56 (76.7%)
IMRT	3 (4.1%)
Conventional	14 (19.2%)

Table 122: Cross-Sectional Study - Patient, tumour and treatment characteristics

5.5.2 UW-QOL Outcomes

As part of the UW-QOL questionnaire patients are asked to select up to three domain issues that were the most important to them over the preceding 7 days. Table 123 summarises the results and shows that the three most commonly selected issues were saliva (47.2%), swallow (37.5%) and taste (33.3%).

UW-QOL	N of patients choosing the domain	% of patients choosing the domain	Rank Order
Saliva	34	47.2%	1
Swallow	27	37.5%	2
Taste	24	33.3%	3
Chewing	18	25.0%	4
Activity	11	15.3%	5
Speech	6	8.3%	6=
Appearance	6	8.3%	6=
Shoulder	6	8.3%	6=
Anxiety	6	6.9%	6=
Mood	6	8.3%	6=
Recreation	5	8.3%	11
Pain	4	5.6%	12

Table 123: Domain importance rating using the UW-QOL questionnaire 12m after RT (mean responses per patient = 2.1)

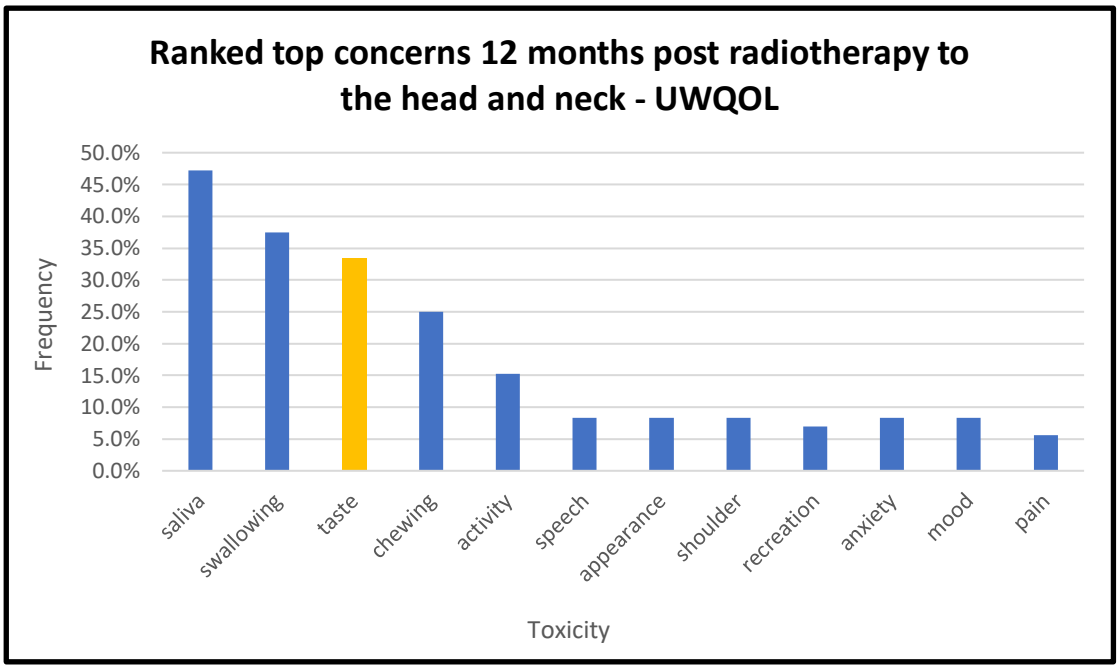


Table 124: Ranked top concerns 12m after RT to the head and neck as per the UWQOL questionnaire.

5.5.3 Patterns of taste and smell dysfunction

5.5.3.1 Patient reported outcomes – taste

Table 125 summaries the prevalence of grade 1-4 PRTD in the entire cohort and in the OPC sub-group. Overall, 33.3% of patients who returned their surveys within the study reported G3+PRTD. In total, 77.7% reported some level of dysfunction with only 22.2% reporting that they could taste all food normally. OPC represented over half of the cohort and in this subgroup the prevalence of G3+PRTD was slightly higher at 42.9% (p=0.04) with any degree of dysfunction reported by 84.4%.

PRTD in ALL patients						
	Grade 1 **Can taste all foods**	**Grade 2** **Can taste most foods**	**Grade 3** **Can taste some foods**	**Grade 4** **Can taste no foods**	**G3+**	**Total**
ALL	16 22.2%	32 44.4%	22 30.6%	2 2.8%	24 33.3%	72
PRTD in OPC Sub-group						
OPC	5 12.2%	17 41.5%	17 41.5%	1 2.4%	18 42.9%	41

Table 125: PRTD by grade in all patients and in OPC sub-group.

5.5.3.2 Objective chemosensory scores – taste

Objective hypogeusia using taste strip testing was seen in almost half of all patients (49.3%). Here the rates of objective hypogeusia were no different between the OPC subgroup and the entire cohort (p=0.81).

Rates of objective hypogeusia in ALL patients - n (%)			
	Normal function	**Hypogeusia**	**Total**
ALL	37 (50.7%)	36 (49.3%)	73
Rates of objective hypogeusia in OPC Sub-group			
OPC	20 (48.8%)	21 (51.2%)	41

Table 126: Rates of objective hypogeusia in all patients and in OPC subgroup.

The mean taste score for the entire cohort was poor at 7.49 out of a possible score of 16 (standard deviation 3.78). Hypogeusia is defined by a score falling within the 10th centile of the normal population (see section 5.3.6 procedures). Scores were broken down by taste quality with sour and bitter showing the greatest degree of dysfunction (p=0.0001).

	Overall Score (0-16)	Sweet (0-4)	Sour (0-4)	Salty (0-4)	Bitter (0-4)
Mean	7.49	2.36	1.71	2.01	1.41
SD	3.78	1.27	1.10	1.34	1.41
ANOVA p value		p=0.0001			

Table 127: Breakdown of taste scores by taste quality in entire cohort.

5.5.3.3 Patient reported outcomes – smell

When asked whether they had noticed any changes in their sense of smell (as per question 2 from the taste and smell survey) 30.6% of participants responded yes.

Q2. Patient reported changes in sense of smell	Yes	No
n	22	50
%	30.6%	69.4%

Table 128: Patient reported smell outcomes using the taste and smell survey Q2.

A further question in the survey asked patients to state whether their sense of smell was stronger, as strong, weaker or that they could not smell at all compared with their sense of smell prior to treatment for HNC. In total 23.6% (n = 17) reported any change and within this group almost half (8/17) specifically described in the free text option that they experienced a stronger or heightened sense of smell.

Q16. Compared to before you were treated for HNC, is your sense of smell…	Stronger	As Strong	Weaker	Cannot smell at all
n	8	55	7	2*
%	11.1%	76.4%	9.7%	2.8%

Table 129: Patient reported smell outcomes using the taste and smell survey Q12. *one patient had olfactory neuroblastoma and the other was post laryngectomy

5.5.3.4 Objective chemosensory scores – smell

With objective olfactory identification testing, patients were first categorised as having either normosmia (score 11-12, 46.5%), hyposmia (score 7-10, 46.5%) or anosmia (score <7, 6.9%). There are known differences in olfactory function based on age and sex. Therefore, olfactory scores were then compared with age and sex norms and patients were categorised into either above or below their 10th centile (table 130). 14.1% of patients were below the 10th centile for their age and sex bracket suggesting a higher proportion of patients with smell dysfunction than would be expected in the normal population.

Categorisation	Normosmia	Hyposmia	Anosmia
n	33	33	5
%	46.5%	46.5%	6.9%

Table 130: Categorisation of smell function (71 patients, unadjusted for age/sex)

Below 10th centile on objective testing in all patients				
	Yes – n (%)		No – n (%)	
ALL	10	(14.1%)	61	(85.9%)

Table 131: Objective hyposmia in all patients

5.5.4 Patient reported taste/smell dysfunction versus objective chemosensory testing

On univariate analysis there was a statistically significant association between objective hypogeusia and PRTD confirming there is a relationship between these two measures.

	Odds Ratio	95% CI	p value
Hypogeusia	3.05	1.12 to 8.88	0.03

Table 132: Univariate analysis demonstrating association between objective hypogeusia and patient reported taste dysfunction

Using PRTD as the reference standard the sensitivity of objective testing was 0.67 and the specificity was 0.60 suggesting some degree of overlap between these two testing modalities.

	TP	TN	FP	FN	Total	Sensitivity	Specificity
12m	16	29	19	8	72	0.67	0.60

Table 133: Sensitivity and specificity of objective hypogeusia testing to detect clinically relevant patient reported taste dysfunction

Similarly, there was a statistically significant association between patients reporting a weaker of sense of smell and objective hyposmia. However, the sensitivity of objective odour identification testing to capture patient reported smell dysfunction was only 0.56. To some extent this is to be expected as odour identification testing does not measure odour intensity as experienced by the patient.

	Odds Ratio	95% CI	p value
Objective hyposmia	14.25	2.58 to 86.88	0.002

Table 134: Univariate analysis demonstrating association between objective hyposmia and PRSD (using question 12)

	TP	TN	FP	FN	Total	Sensitivity	Specificity
12m	5	57	4	4	70	0.56	0.93

Table 135: Sensitivity and specificity of objective hyposmia testing to detect clinically relevant PRSD (using question 12)

5.5.5 Relationship between dose to gustatory field and taste dysfunction

Mean doses to the gustatory field for each tumour group within the study are tabulated below (see table 136). As one would anticipate, tumour sites in proximity to the tongue have higher mean doses to the gustatory field. Tumours further away, such as the HPC and LC received the lowest doses.

Mean dose to oral cavity, whole tongue, anterior two-thirds tongue, surface of whole tongue, surface of anterior two-thirds tongue					
	Oral cavity	**Whole tongue**	**Whole tongue surface**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**
OPC n=41	51.1 (SD 11.2)	51.4 (SD 10.5)	42.6 (SD 12.8)	44.6 (SD 10.6)	37.9 (SD 12.0)
OC n=4	51.6 (SD 5.6)	55.3 (SD 3.5)	54.8 (SD 7.0)	56.4 (SD 4.0)	55.6 (SD 6.1)
L n=8	13.23 (SD 15.9)	13.7 (SD 16.3)	5.3 (SD 8.4)	8.9 (SD 11.7)	4.4 (SD 6.9)
NPC n=5	43.9 (SD 14.8)	42.3 (SD 14.9)	42.3 (SD 14.5)	35.3 (SD 12.6)	36.3 (SD 13.0)
HP n=1	28.7	27.8	17.5	20.9	15.4
SG n=2	30.0 (SD 5.9)	29.2 (SD 4.9)	26.0 (SD 1.8)	23.9 (SD 0.1)	23.6 (SD 0.3)
SC n=1	6.7	2.7	3.3	2.9	3.9
Skin n=2	27.0 (SD 3.2)	26.9 (SD 3.1)	25.5 (SD 2.7)	25.7 (SD 0.3)	25.4 (3.6)
UP n=1	41.0	41.5	42.8	40.7	41.7
Neck n=7	18.60 (SD 15.9)	17.6 (SD 16.8)	12.1 (15.7)	14.9 (SD 15.5)	10.9 (SD 13.9)
BOS n=1	3.9	1.	-	2.3	5.7

Table 136: Mean dose (Gy) to oral cavity, whole tongue, anterior two-thirds tongue, surface of whole tongue, surface of anterior two-thirds tongue (OPC, oropharynx; OC, oral cavity; L, larynx; NPC, nasopharynx; HP, hypopharynx; SG, salivary gland; SC, sinus cavity; Skin, skin; UP, unknown primary; Neck, neck; BOS, base of skull)

As part of the primary objective the mean dose to the anterior two-thirds of the tongue in those with, or without G3+PRTD was compared. The doses received by these two groups are presented in table 137. There was a statistically significant difference between the mean dose at the OC (p=0.008), whole tongue (p=0.007) and anterior two-thirds of the tongue (p=0.013) between the two groups.

	Mean Dose (Gy) and SD				
	Oral cavity	**Whole tongue**	**Whole tongue surface**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**
G3+PRTD	49.2 SD 14.1	49.6 SD 14.1	40.3 SD 17.4	43.1 SD 14.6	36.0 SD 16.6
No PRTD	36.7 SD 20.0	36.78 SD 20.2	31.2 SD 19.2	32.0 SD 18.6	28.7 SD 17.9
p value	0.008	0.007	0.06	0.013	0.09

Table 137: Mean doses to gustatory OAR / gustatory field in those with or without PRTD (excluding patient with olfactory neuroblastoma where PRTD was related to anosmia).

The analysis was repeated using a lower threshold for PRTD to explore doses received by those reporting completely normal function. The mean dose to the anterior two-thirds of the tongue in patients reporting completely normal taste function was 20.98 Gy versus 39.88Gy (p=0.0001) in those with any degree of dysfunction (G2+). Again, there were statistically significant differences in the doses at the 3 regions of interest as for the primary analysis and in addition there were significant differences at the whole tongue surface and anterior two-thirds tongue surface.

	Mean Dose (Gy) and SD				
	Oral cavity	**Whole tongue**	**Whole tongue surface**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**
Any degree PRTD	45.0 SD 16.1	45.4 SD 16.5	38.7 SD 16.7	39.9 SD 15.9	34.9 SD 16.1
No PRTD	26.4 SD 22.0	25.9 SD 21.0	20.20 SD 19.7	21.0 SD 18.1	17.5 SD 16.8
p value	0.0004	0.0002	0.0004	0.0001	0.0003

Table 138: Mean doses to gustatory OAR / gustatory field in those with or without PRTD or any degree (excluding patient with olfactory neuroblastoma where PRTD was related to anosmia).

The same analysis was repeated using objective chemosensory testing to define hypogeusia. Once again there were statistically significant differences between the mean doses to all the gustatory ROI except for whole tongue surface (see table 139).

	Mean Dose (Gy) and SD				
	Oral cavity	**Whole tongue**	**Whole tongue surface**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**
Hypogeusia	44.4 SD 17.3	44.4 SD 17.6	36.9 SD 18.8	39.7 SD 17.5	33.9 SD 18.0
Normogeusia	33.6 SD 21.1	33.9 SD 21.5	28.6 SD 19.2	27.6 SD 17.5	25.0 SD 16.5
p value	0.02	0.03	0.08	0.006	0.04

Table 139: Mean doses to gustatory OAR / gustatory field in those with or without objective hypogeusia with objective chemosensory testing.

The objective chemosensory scores for each patient were plotted against dose received to the anterior two thirds of the tongue (see figure 5-2). Those scores above the red line indicate normogeusia, those below, hypogeusia. The green line indicates the 50th centile of normative data. Whilst there is a clustering of people with hypogeusia at higher doses it is clear there are still many patients who are hypogeusic having received even very low doses to the gustatory field.

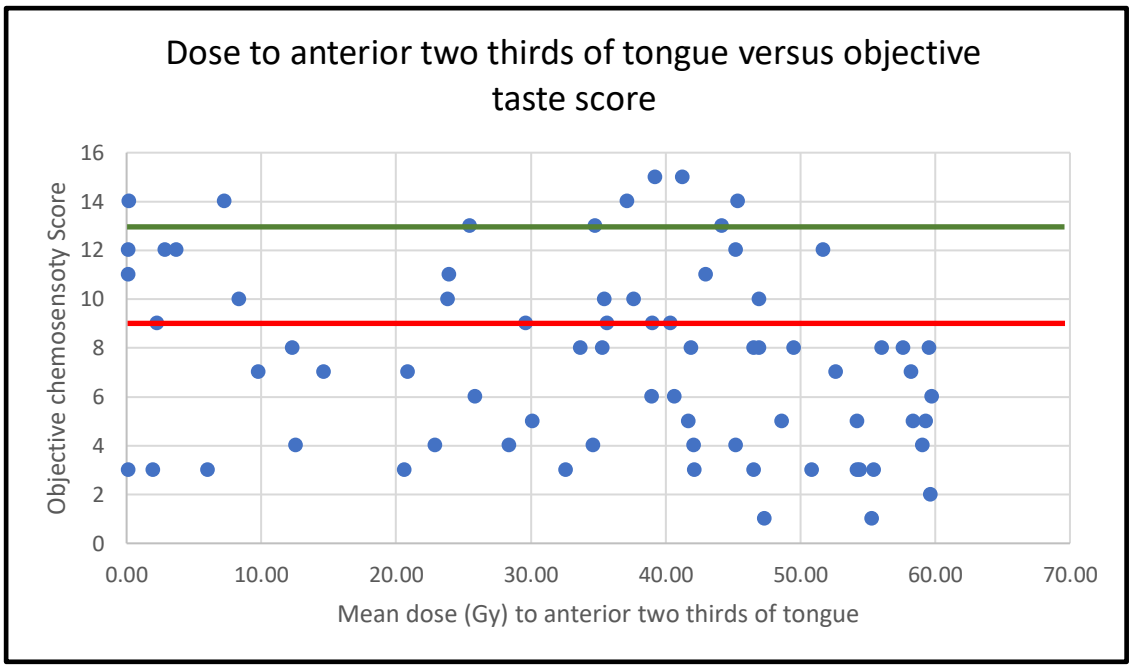


Figure 5-2: Scatterplot of objective chemosensory scores against dose to the anterior two thirds of the tongue (red line indicates threshold for objective hypogeusia defined by lowest 10% of normal population; green line indicates the median score (50th centile) for the normal population)

In order to inform potential dose constraints that could be applied to radiotherapy planning, the proportion of patients with G3+PRTD was calculated in those receiving 0-20Gy, 20-30Gy, 30Gy-50Gy or 50Gy+ to the anterior two-thirds of the tongue, representing very low, low, moderate and high radiotherapy doses. This was repeated for any degree of PRTD (tables 140-141). In general, there was an apparent dose dependent effect with increasing prevalence of subjective taste dysfunction (either by G3+ or G2+ cut-off) with increasing dose category to the anterior two thirds of the tongue. The effect became significant for 50+ Gy vs 0-20 Gy in the G3+ analysis and at the 30-50 Gy vs 0-20 Gy comparison in the G2+ analysis. However as for the objective hypogeusia analysis above, there were still cases of taste dysfunction even in the lowest dose category (14.3% G3+ PRTD and 42.9% G2+ PRTD in the 0-20 Gy category).

Proportion of patients with G3+PRTD by mean dose to anterior two thirds tongue				
	0-20 Gy	**20-30 Gy**	**30-50 Gy**	**50+ Gy**
N =	2/14	2/9	11/32	8/15
% of patients with G3+PRTD	14.3%	22.2%	34.4%	53.3%
p value	Reference	>0.99	0.29	0.05

Table 140: Proportion of patients with G3+PRTD by dose to the anterior two thirds of the tongue

Proportion of patients with G2+PRTD by mean dose to anterior two thirds tongue				
	0-20 Gy	**20-30 Gy**	**30-50 Gy**	**50+ Gy**
N =	6/14	7/9	26/32	15/15
% of patients with G2+PRTD (any degree of loss)	42.9%	77.8%	81.3%	100.0%
p value	Reference	0.20	0.02	0.0007

Table 141: Proportion of patients with G2+PRTD by dose to the anterior two thirds of the tongue

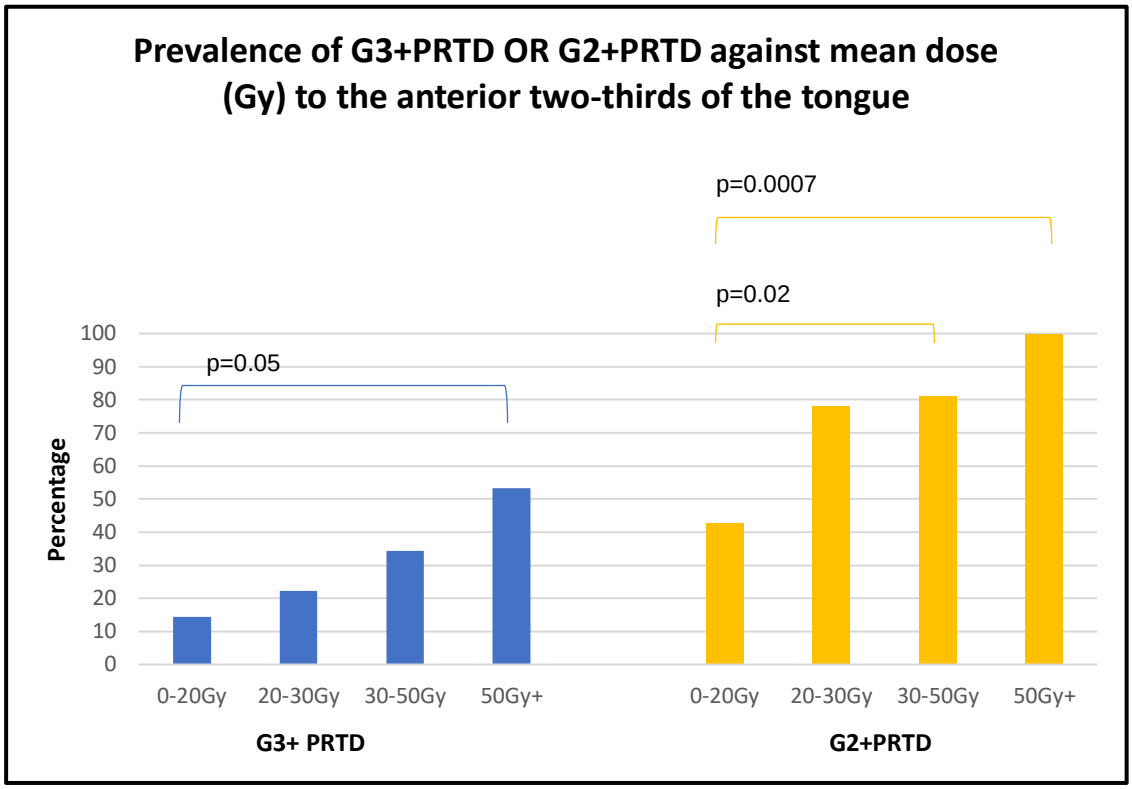


Figure 5-3: Proportion of patients with G2+PRTD OR G3+PRTD against mean dose to the anterior two thirds of the tongue

This analysis was repeated using objective taste scores to determine the proportion of patients with hypogeusia in each dose band. Again, those receiving highest doses (50 Gy+) were most likely to be hypogeusic (94.1%). Although for this objective analysis there was less of a trend and no difference between those receiving moderate or low doses.

Proportion of patients with objective hypogeusia by mean dose to anterior two thirds tongue				
	0-20 Gy	**20-30 Gy**	**30-50 Gy**	**50+ Gy**
N =	7/14	5/9	18/32	16/17
% of patients with hypogeusia	50.0%	55.6%	56.3%	94.1%
p value		>0.99	0.76	0.01

Table 142: Mean objective chemosensory taste scores by mean dose to the anterior two thirds of the tongue

5.5.6 Factors associated with taste dysfunction

Univariate analysis was undertaken to determine patient and treatment related factors associated with taste dysfunction at 12m. G3+PRX, PRSD (using question 12) and objective hyposmia were all statistically significantly associated with G3+PRTD. There was also a borderline significant association (p=0.05) with concurrent chemotherapy and dose to anterior two thirds of the tongue (per 1 Gy increase). When adjusted for stage, use of concurrent chemotherapy was no longer statistically significant (adjusted OR 2.56; CI 0.84 to 8.51; p=0.11). When adjusted for stage, use of chemotherapy and post-operative status, dose to the anterior two thirds of the tongue was no longer statistically significant suggesting a multifactorial aetiology leading to late toxicity.

Univariate analysis – 12m Taste (patient reported)			
Variable	**OR**	**CI95%**	**p value**
Age >60	0.37	0.13 to 1.03	0.06
Male	1.15	0.33 to 4.68	0.83
Alcohol >21 units / week	0.48	0.02 to 3.68	0.53
Stage 3/4	2.33	0.65 to 11.10	0.23
PORT	0.58	0.92 to 1.76	0.36
Dose to anterior two thirds tongue	1.03	1.00 to 1.07	0.05
G3 Xerostomia (UWQOL)	5.90	2.08 to 18.32	0.001
Concurrent chemotherapy	2.87	1.04 to 8.61	0.05
PRSD (Q12 TSS)	9.47	2.06 to 67.93	0.008
Objective hyposmia	19.69	3.17 to 383.1	0.007

Table 143: Univariate analysis to look for factors associated with G3+PRTD

A univariate analysis was also performed to look for variables associated with objective taste dysfunction. For objective taste dysfunction, dose to anterior two thirds tongue was the only strongly significant predictor although being male was borderline significant. Dose remained a statistically significant predictor (adjusted OR 1.04; CI 1.01 to 1.08; p-0.02) in a multivariate analysis including chemotherapy, stage III/IV and PORT as potential clinical confounders.

Univariate analysis – 12m Taste (objective)			
Variable	**OR**	**CI95%**	**P**
Age >60	1.55	0.59 to 4.15	0.89
Male	4.07	1.12 to 19.54	0.05
Alcohol >21 units / week	1.43	0.21 to 11.73	0.71
G3 Xerostomia (UWQOL)	1.24	0.48 to 3.17	0.66
Concurrent chemotherapy	2.08	0.82 to 5.42	0.19
PRSD (Q12 TSS)	0.48	0.10 to 2.00	0.33
Stage 3/4	2.30	0.72 to 8.15	0.17
PORT	1.04	0.37 to 2.93	0.94
Objective hyposmia	1.47	0.36 to 6.46	0.59
Dose to anterior two thirds tongue	1.04	1.01 to 1.07	0.009

Table 144: Univariate analysis for objective hypogeusia using chemosensory testing

5.5.7 Heightened sense of smell

As noted previously, unexpectedly 47% of patients self-reporting changes in their sense of smell were actually describing a *heightened* sense of smell (hyperosmia). To explore this finding further a univariate analysis was performed to look for associated factors. The only statistically significant variable was objective hypogeusia (p=0.05). There was also a trend towards significance in those self-reporting PRTD (p=0.08).

Univariate analysis – 12m heightened smell (patient reported)			
Variable	**OR**	**CI95%**	**P**
Objective hypogeusia	8.69	1.43 to 167.2	0.05
PRTD	3.95	0.88 to 20.85	0.08
Age >60	0.51	0.11 to 2.34	0.37
Male	1.59	0.25 to 31.05	0.68
Concurrent chemotherapy	0.81	0.18 to 3.67	0.77
Dose to anterior two thirds tongue	1.04	0.98 to 1.13	0.21

Table 145: Univariate analysis for heightened sense of smell (patient reported) 12 months following RT to the head and neck

5.5.8 Downstream effects of taste dysfunction

All patients within the study were treated at RMH and baseline height and weight were available for all patients. Mean BMI and mean change in BMI (pre radiation versus 12m post completion of treatment) in those with and without either PRTD or objective hypogeusia were compared (see table 146). By both objective and subjective definitions, patients with taste dysfunction had lower BMIs and a greater reduction in BMI following treatment although these differences did not reach statistical significance.

5.5.8.1 Changes in BMI

	Mean BMI (SD)	**Mean change in BMI (SD)**
PRTD	23.7 (SD 2.9)	-2.8 (SD 3.8)
No PRTD	25.8 (SD 6.1)	-0.2 (SD 5.2)
p-value	0.15	0.06
	Mean BMI (SD)	**Mean change in BMI (SD)**
Hypogeusia	24.8 (SD 3.4)	-1.7 (SD 3.4)
Normogeusia	25.6 (SD 7.6)	0.04 (SD 6.8)
p-value	0.55	0.21

Table 146: BMI in those with or without PRTD and those with or without objective hypogeusia

5.5.8.2 Overall Quality of Life

Similarly, overall QoL scores were worse in those with either subjective or objective taste dysfunction (compared to those with no dysfunction) however again this was not statistically significant. This was better analysed for significance in a much larger cohort (see chapter 4).

	Quality of Life Scores at 12m post RT
PRTD	70.8
No PRTD	72.5
p-value	0.7
	Quality of Life Scores at 12m post RT
Hypogeusia	70.7
Normogeusia	74.1
p-value	0.4

Table 147: Overall QoL scores in those with or without PRTD and those with or without objective hypogeusia

5.6 Discussion

Seventy-three patients were included in this cross-sectional analysis to determine the prevalence and pattern of subjective and objective gustatory dysfunction 12m following completion of RT for HNC.

The patient characteristics were generally representative of a typical head and neck cohort with a median age of 64, predominantly male with just over 50% of patients having OPC. There was a high proportion of patients with HPV positive tumours in the OPC group likely due to the general expansion in this patient cohort and their relatively good prognosis. The majority of patients (76.7%) were treated for stage III or stage IV disease (TNM7) with 54.8% receiving concurrent chemotherapy. The study had intended to consider the effect of smoking on gustatory outcomes however encouragingly only 1 patient remained a current smoker, so this was not possible.

The toxicity profile of treatment in this cohort was consistent with previous research (97). Despite the use of parotid-sparing IMRT patients still rank lack of saliva as the most important toxicity domain 12m following RT. Swallow was the next most commonly reported problem followed closely by taste. With an anticipated move towards pharyngeal constrictor sparing IMRT (98), it is plausible that taste will only increase in importance with no current randomised studies attempting to research this unmet need.

Subjective taste dysfunction was common. Any degree of PRTD was seen in 77.7% of patients (33.3% G3+). A breakdown by tumour subsite showed that in the OPC group, rates of PRTD were higher at 84.4% (42.9% G3+) suggesting a relationship between PRTD and dose to the gustatory field. The prevalence of PRTD in non-OPC tumour sites was only 19.4%.

The prevalence of objective hypogeusia using chemosensory testing was high at 49.3%. The pattern of taste loss between each of the taste qualities has been reported on previously. Typically bitter and salt qualities are affected the most with sweet often found to be relatively well preserved (7,48,52,62,63,68,72). Consistent with these findings, in this analysis the mean taste scores for sweet were higher (2.36) than mean scores for bitter (1.41) and salt (2.01) though sour scores were also low (1.71). It is not within the scope of this study to report on the potential underlying mechanisms of injury to individual taste receptors on a cellular level. However, it is interesting to note that the normative values (see table 110) for taste function show that even in healthy volunteers, sweet quality scores may be relatively well preserved compared to bitter in those with total taste scores in lower centiles. It would therefore appear that the pattern of taste loss seen here post-radiation is consistent with the pattern of natural variability in taste function. It is therefore unlikely that radiation induced taste dysfunction has a differential impact on each taste quality however, this could be investigated more effectively in a prospective longitudinal study (chapter 6).

Data from the Taste and Smell Survey gave some new insight into patient reported smell dysfunction 12m after RT. Again, about a third (30.6%) of patients self-reported that they had noticed a change in their sense of smell however almost half of these people felt that their sense of smell was stronger compared to their sense of smell prior to RT. This was unexpected and is a previously unreported phenomenon. Univariate analysis showed a statistically significant association between objective hypogeusia and patient reported heightened sense of smell ($p=0.05$). Cross modal neuroplasticity, whereby one sense compensates for loss of another, is a well described phenomenon (99). This is potentially the first documentation of this effect in the context of loss of gustatory function following RT to the head and neck. It would be interesting to see in a

longitudinal study how this relationship evolves over time, for instance if the heightened sense of smell develops after the onset of acute taste dysfunction and on a timescale consistent with neuroplasticity. The actual prevalence of a weaker sense of smell was low at 12.5%. Indeed, on objective chemosensory odour identification testing, when adjusted for age and sex, smell scores were normal in the vast majority with only 14.1% below their 10th centile (i.e., only a few percent over what would be expected to be seen in the normal population). This highlights one of the limitations of this study, in that it lacked a control group for comparison.

The relationship between subjective patient reported outcomes and objective chemosensory testing was analysed. Univariate analysis confirmed a statistically significant association between hypogeusia and PRTD (odds ratio 3.05, p=0.03) though the sensitivity of objective testing to capture those with PRTD was low at 0.67. If studies solely rely on objective testing to define participants who have taste dysfunction, they are likely missing approximately a third of people in their sample who consider themselves to have taste dysfunction. The mechanism of PRTD is complex and not a simple correlate of one's ability to detect sweet, sour, salty and bitter qualities. One patient within the study demonstrated this perfectly. Despite having no sense of flavour secondary to complete anosmia following surgery for an olfactory neuroblastoma, this patient was able to sense sweet, sour, salty and bitter tastes with relative ease.

The study included patients with a variety of tumour subsites to understand the effect of dose to the gustatory field and taste dysfunction. This has been relatively under-researched thus far but is of great interest in an era when technological advances and the use the proton beam therapy may enable further modulation of RT dose to meet tighter constraints to minimise toxicity. Some studies have suggested that the anterior two-thirds of the tongue may be an important site to spare if taste dysfunction is to be minimised (46,66,72). Indeed, sparing of the anterior two-thirds of the tongue is feasible as this region is only ever a target in the case of oral cavity tumours. In this study mean doses to this important gustatory region, packed densely with fungiform papillae, ranged from

2.2 Gy to 44 Gy. The mean dose to the anterior two-thirds of the tongue in those with G3+PRTD was statistically significantly (p=0.01) higher (43.1 Gy) than in those without G3+PRTD (32.0 Gy). When the effect of dose was considered on a broader definition of PRTD (now including those with any degree of self-reported taste dysfunction) the difference in dose between groups was more pronounced (39.9 Gy PRTD versus 21.0 Gy no PRTD) and this was also statistically significant (p=0.0001). There was a similar relationship between the mean dose to the anterior two thirds of the tongue and objective hypogeusia (39.7 Gy hypogeusia versus 27.6 Gy normogeusia, p=0.006). When grouped into very low (0-20 Gy), low (20-30 Gy), moderate (30-50 Gy) and high (50+ Gy) dose bands, prevalence of PRTD and objective hypogeusia was generally higher in higher dose bands and a dose response relationship was seen. The effect appeared dose dependent for PRTD whereas for objective hypogeusia there was a step change at the 50+ Gy cut-off. Overall, it appeared that higher doses to the anterior two-thirds of the tongue were associated with subjective and objective taste dysfunction. However, it is important to note that there were still patients with subjective and objective taste dysfunction who had received very low doses to the anterior two-thirds of the tongue. Without longitudinal data it is not possible to determine to what extent this represents pre-existing dysfunction or in fact radiation toxicity even at very low doses to this gustatory ROI.

Alongside dose, other patient and treatment related factors that might contribute to taste dysfunction were analysed. On univariate analysis G3+PRX, G3+PRSD and objective hyposmia were all statistically significantly associated. These relationships are plausibly causal but more likely describe interplay between clinically related toxicities. Moreover, neither G3+PRSD, G3PRX or objective hyposmia were associated with objective hypogeusia suggesting there is a large subjective component at play. Dose to the anterior two thirds of the tongue and concurrent chemotherapy were borderline significant though this latter effect might be partially driven by differences in age and stage, both of which determine whether a patient receives concurrent chemotherapy. Indeed, the effect was not significant when stage was included alongside chemotherapy in multivariate analysis. There was no longer a statistically significant association between

dose and PRTD when adjusted for clinically relevant confounders. This highlights the multifactorial nature of taste dysfunction and could question the singular impact of dose however it is worth noting that in the univariate analysis of factors associated with objective taste dysfunction, dose to the anterior two thirds of the tongue was the only significant factor and remained significant on multivariate analysis (p=0.02).

An intact sense of taste provides pleasure and supports sustenance, and it is therefore important to consider the down-stream effects of taste dysfunction. Overall QoL scores and changes in BMI were compared in those with or without PRTD or objective hypogeusia. Both BMI scores and overall QoL scores were higher in those without taste dysfunction though this was not statistically significant, however this study was not powered to detect differences in these outcomes.

5.7 Conclusion

Taste dysfunction remains a significant toxicity following RT to the head and neck even with modern conformal RT techniques. Across all tumour sites a third of patients complain of dysfunction with even higher rates seen in those receiving treatment within the gustatory field. The pattern of taste loss is consistent with previous research but also consistent with that of the normal population suggesting further research to understand how radiation might differentially affect individual taste receptor cells is required. Although a relationship was present, the consistency between subjective and objective measures was poor and gustatory research must continue to collect data using a combination of objective and patient reported end points to fully capture the prevalence of dysfunction. The presence of hyperosmia in this cross-sectional cohort was an interesting finding and serves as a reminder that ‘problems with’ or ‘changes in’ should not be presumed to represent a deficit in function. It is an interesting phenomenon and warrants further research. There was a clear relationship between dose to the anterior two thirds of the tongue and taste dysfunction both using objective and subjective measures. Although this study was unable to clearly determine a constraint to avoid taste loss, it is clear that

doses to the gustatory field must be kept to a minimum and even then, this is unlikely to be sufficient to prevent taste dysfunction altogether. In addition, the implementation of a constraint to the anterior two thirds of the tongue may prove challenging in particular for cancers involving the oropharynx, oral cavity or those requiring level 1b nodal irradiation.

Chapter 6 – Gustatory function following radiotherapy to the head and neck: A prospective study

6.1 Background

Chapter 3 started to look at the potential relationship between dose to the gustatory field and PROs. It was evident that baseline dysfunction was a potential predictor of subsequent dysfunction.

Chapter 4 again highlighted the prevalence of taste dysfunction at baseline and using tumour site as a surrogate, suggested there is a dose dependent relationship for patient reported taste dysfunction following RT at 4m and 12m.

Chapter 5 gave insight into the prevalence of objective and subjective gustatory dysfunction 12m following RT though lacked baseline and longitudinal data to understand the pattern of loss and recovery and its relationship to dose.

This study was developed to capture objective and subjective gustatory outcomes over time in the context of dose to gustatory regions of interest.

6.2 Aims and objectives

6.2.1 Primary Objective

To demonstrate the association between RT dose and PRTD at 6m following RT or CRT for HNC.

6.2.2 Secondary Objectives

To demonstrate the association between RT dose and objective chemosensory testing, 6m following RT or CRT to the head and neck.

To demonstrate other dosimetric predictors for PRTD and objective hypogeusia, 6m following RT or CRT to the head and neck.

To demonstrate patient and treatment-related predictors for PRTD and objective hypogeusia, 6m following RT or CRT to the head and neck.

To investigate the association between PRTD or objective hypogeusia and BMI.

To investigate the association between PRTD and overall QoL, 6m following RT or CRT to the head and neck.

6.2.3 Exploratory Objectives

To investigate the loss and recovery of PRTD and objective hypogeusia over time and its relationship to RT dose.

To investigate the pattern of objective hypogeusia affecting each taste quality (sweet, sour, salty, bitter) and the pattern of recovery over time.

To investigate the association between FPD and PRTD and objective hypogeusia at all measured time points.

To assess whether there is a relationship between dose to the anterior two thirds of the tongue and loss of FPD following RT or CRT, 6m and 12m following RT or CRT.

6.3 Methods

6.3.1 Recruitment

55 patients were recruited between 2nd October 2018 and 26th June 2019. All new patients presenting to clinic for radical treatment were offered a patient information sheet with a follow up phone call to organise pre-RT study consent and assessment should they agree to participate. Those patients who reached

12m of follow up were also enrolled into the cross-sectional study to increase power for analysis.

6.3.2 Inclusion Criteria

Patient were required to be age 18 years or more and due to commence RT or concurrent CRT to the head and neck region using either a conformal or IMRT planning technique. There were no restrictions on tumour sub-site, tumour histology or RT dose and fractionation

6.3.3 Exclusion Criteria

Patients were excluded if they had undergone previous RT; had pre-existing olfactory or gustatory disorder or had radiological or clinical involvement of the facial nerve, chorda tympani, glossopharyngeal nerve, lingual nerve, greater petrosal nerve or geniculate ganglion. Patients who had undergone a total or partial glossectomy were also excluded having had the target OAR removed.

6.3.4 Primary Endpoint

Based on the findings in chapter 5, for the purposes of the primary objective, mean RT dose (Gy) to the anterior two-thirds of the whole tongue was used. PROs were dichotomised by the presence or absence of clinically significant taste dysfunction (Grade 3 or 4) using Question 9 from the UW-QOL questionnaire v4.0 (96).

6.3.5 Secondary Endpoints

PRTD was defined as per the primary end point measure.

Objective chemosensory taste testing generated a taste score between 0-16. Patients were categorised as hypogeusic (score 0-8) or normogeusic (9-16).

To investigate the pattern of objective hypogeusia, individual scores of 0-4 were generated for each taste quality (sweet, sour, salty, bitter).

Using chemosensory testing patients were categorised as normosmic, hyposmic or anosmic. Scores were then adjusted for age and sex to determine whether an individual's score fell below the 10^{th} centile of the wider population.

Self-reported taste and smell changes were collated from the Taste and Smell Survey.

To investigate dosimetric predictors, DVH data was generated to quantify RT dose to gustatory ROI, including but not limited to, mean dose (Gy) to the OC, whole tongue, anterior two thirds of the tongue, posterior third of the tongue, surface of the anterior two thirds of the tongue and surface of the whole tongue.

Potential patient and treatment related predictors investigated were age, sex, smoking status, alcohol status, stage of primary tumour, xerostomia use of induction and concurrent chemotherapy. Xerostomia was defined as grade 3 or 4 dry mouth as per Q10 from the UWQOL questionnaire v4.0 (96).

QoL was assessed using the UW-QOL v4.0 survey (96).

Change in weight was assessed using height and weight to determine BMI.

6.3.6 Exploratory Endpoints

FPD was counted manually and measured number per cm^2.

6.3.7 Procedures

Patients were invited to have their FPD calculated at baseline and at subsequent follow up. The anterior portion of the tongue was stained with household blue food colouring and then photographed to obtain high resolution images. A scale was included in the photograph. FPD was manually counted by two independent operators trained in FPD analysis.

For all other procedures, the approach was consistent with the cross-sectional cohort except in this cohort assessments were done at baseline, end of treatment, 2m and 6m follow up). For further details see section 5.3.6

6.4 Analysis

6.4.1 Sample size

We expected to observe a mean difference in radiation dose of 20 Gy to the anterior tongue between two groups of patients with clinically significant and clinically insignificant taste dysfunction, with the SDs of 25 Gy and 17.5 Gy for the clinically significant and clinically insignificant groups, respectively. Using two sample t-test (for independent groups) with unequal variance, two-sided test, and alpha error of 5%, a sample size of 52 would provide 90% power.

6.4.2 Statistical analysis

Descriptive statistics were used to capture the key characteristics of the study cohort. Fisher's exact test was used to compare proportions for dichotomous outcomes. Paired t-tests were used to compare mean values between groups for continuous outcomes. Univariate and multivariate logistic regression was used to investigate the association between potential predictors and PRTD/objective taste dysfunction. All statistical tests were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Toxicity curves were produced in **R** Core Team (2013). **R**: A language and environment for statistical computing. **R** Foundation for Statistical Computing, Vienna, Austria. URL http://www.**R**-project.org/. No adjustments for multiple testing were made, however results were interpreted accordingly.

6.5 Results

6.5.1 Patient and treatment characteristics

Patient, tumour and treatment characteristics are summarised below (see table 148). The cohort included a variety of patients receiving RT to the head and neck including 6 patients with lymphoma and 2 with benign pathology (pleomorphic adenoma of the parotid and paraganglioma). Median age was 60 years, the largest group was represented by those with OPC and those with squamous cell carcinomas.

Prospective Study – Patient, Tumour and Treatment Characteristics	
Total Number of Patients	55
Median age at study entry (years)	60.3 (range 34.9 – 81.5, SD 10.6)
Male	42 (76.4%)
Female	13 (23.6%)
Smoking Status	
Current smoker	6 (10.9%)
Ex-smoker	25 (45.5%)
Non-smoker	22 (40.0%)
Not disclosed	2 (3.55)
Tumour Site	
Oropharynx	26 (47.3%)
Salivary Gland	6 (10.9%)
Larynx	5 (9.1%)
Neck	3 (5.5%)
Nasopharynx	3 (5.5%)
Skin	3 (5.5%)
Oral Cavity	2 (3.6%)
Hypopharynx	2 (3.6%)
Base of skull	1 (1.8%)
Unknown primary	1 (1.8%)
Sinus cavity	1 (1.8%)
Thyroid	1 (1.8%)
Nasal Vestibule	1 (1.8%)
Tumour Histology	
Squamous cell carcinoma	37 (67.3%)
Nasopharyngeal carcinoma	3 (5.5%)
Lymphoma (HL, FL, MCL, DLBCL)	6 (10.9%)

Pleomorphic adenoma	2 (3.6%)
Other	7 (12.7%)
P16 status (in 26 oropharyngeal patients)	
P16 positive	17 (65.4%)
P16 negative / unknown	9 (34.6%)
Tumour stage	
T0	1 (1.8%)
T1	9 (16.4%)
T2	19 (34.5%)
T3	10 (18.2%)
T4	8 (14.5%)
N/A (lymphoma staging / benign)	8 (14.5%)
Nodal stage	
Positive	30 (54.4%)
Negative	19 (34.5%)
N/A (lymphoma staging)	6 (10.9%)
AJCC stage (TNM 7th edition)	
1 and 2	19 (34.5%)
3 and 4	24 (43.6%)
N/A (benign)	2 (3.6%)
Treatment	
Radiotherapy	16 (29.1%)
Post op radiotherapy	12 (21.8%)
Chemoradiotherapy	23 (41.8%)
Post op chemoradiotherapy	3 (5.5%)
No treatment	1 (1.8%)
Neoadjuvant systemic therapy	
Yes	5 (9.1%)
No	50 (90.9%)
Concomitant chemotherapy	
Yes	26 (48.1%)
No	28 (51.9%)
Planning technique	
VMAT	48 (88.9%)
Conventional	6 (11.1%)

Table 148: Prospective Study - Patient, tumour and treatment characteristics

6.5.2 UW-QOL Outcomes

Between baseline and 6m follow up, 64.2% (34/53) of patients included taste in one of their top three concerns using the UWQOL tool at one or more time-points.

The percentage of patients choosing taste as one of their three top concerns was 16.7% at baseline, 56.4% at the end of RT, 40.5% at 2 months follow up and 23.4% at 6m follow up. In terms of relative importance of symptoms taste was ranked 6th at baseline, 1st at end of radiotherapy, 2nd at 2m follow up and 3rd at 6m (see tables 149-152).

UW-QOL	N of patients choosing the domain (n with data = 42)	% of patients choosing the domain	Rank Order
Anxiety	17	40.5%	1
Pain	12	28.6%	2
Swallow	11	26.2%	3
Mood	9	21.4%	4
Activity	8	19.0%	5
Taste	7	16.7%	6 =
Appearance	7	16.7%	6 =
Chewing	6	14.3%	8 =
Shoulder	6	14.3%	8 =
Speech	5	11.9%	10
Recreation	4	9.5%	11
Saliva	0	0.0%	12

Table 149: Domain importance rating using the UW-QOL questionnaire at baseline (mean responses per patient 2.19)

UW-QOL	N of patients choosing the domain (n with data = 40)	% of patients choosing the domain	Rank Order
Taste	22	56.4%	1
Swallow	17	43.6%	2
Pain	16	41.0%	3
Saliva	14	35.9%	4
Speech	7	17.9%	5
Mood	6	15.4%	6
Appearance	4	10.3%	7
Activity	3	7.7%	8 =
Anxiety	3	7.7%	8 =
Recreation	3	7.7%	8 =
Chewing	2	5.1%	11 =
Shoulder	2	5.1%	11 =

Table 150: Domain importance rating using the UW-QOL questionnaire at end of RT (mean responses per patient 2.54)

UW-QOL	N of patients choosing the domain (n with data = 42)	% of patients choosing the domain	Rank Order
Saliva	18	42.9%	1
Taste	17	40.5%	2
Swallow	15	35.7%	3
Activity	13	31.0%	4
Pain	10	23.8%	5
Mood	6	14.3%	6 =
Shoulder	6	14.3%	6 =
Chewing	5	11.9%	8 =
Anxiety	5	11.9%	8 =
Recreation	4	9.5%	10 =
Appearance	4	9.5%	10 =
Speech	2	4.8%	12

Table 151: Domain importance rating using the UW-QOL questionnaire at 2m follow up (mean responses per patient 2.5)

UW-QOL	N of patients choosing the domain (n with data = 48)	% of patients choosing the domain	Rank Order
Saliva	26	55.3%	1
Swallow	17	36.2%	2
Taste	11	23.4%	3
Activity	10	21.3%	4
Pain	7	14.9%	5
Chewing	5	10.6%	6 =
Speech	5	10.6%	6 =
Appearance	5	10.6%	6 =
Anxiety	5	10.6%	6 =
Mood	4	8.5%	10
Shoulder	3	6.4%	11
Recreation	0	0.0%	12

Table 152: Domain importance rating using the UW-QOL questionnaire at 6m follow up (mean responses per patient 2.09)

6.5.3 Taste dysfunction over time

6.5.3.1 Patient reported outcomes

The prevalence of G3+PRTD was 8.9% at baseline, rising to 82.5% at the end of RT, 45.2% at 2m falling to 35.4% at 6m. 12m follow up data was captured for a small proportion of patients (n=18, 34.6% of the total cohort) prior to the Covid-19 pandemic. At this time point, 11.1% were reporting G3+PRTD, relatively consistent with baseline. However, the proportion of patients with entirely normal taste function (Grade 1) was 71.1% at baseline but only 33.3% at 6m and 38.9% at 12m (table 153 and figure 6-1).

UW-QOL Q9 (taste)	0m n = 45	End of RT n = 40	2m n = 42	6m n = 48	12m n = 18
Grade 1 (normal)	32 (71.1%)	2 (5.0%)	7 (16.7%)	16 (33.3%)	7 (38.9%)
Grade 2 (can taste some foods)	9 (20.0%)	5 (12.5%)	16 (38.1%)	15 (31.3%)	9 (50.0%)
Grade 3 (can taste most foods)	4 (8.9%)	14 (35.0%)	15 (35.7%)	16 (33.3%)	2 (11.1%)
Grade 4 (can taste no foods)	0 (0.0%)	19 (47.5%)	4 (9.5%)	1 (2.1%)	0 (0.0%)
Grade 3+	4 (8.9%)	33 (82.5%)	19 (45.2%)	17 (35.4%)	2 (11.1%)
p value (G3+ vs not, 0m as reference)	Reference	0.0001	0.0002	0.003	1.00
Grade 2+	13 (28.9%)	38 (95.0%)	35 (83.3%)	32 (66.7%)	11 (61.1%)

Table 153: PRTD over time (Q9. UWQOL)

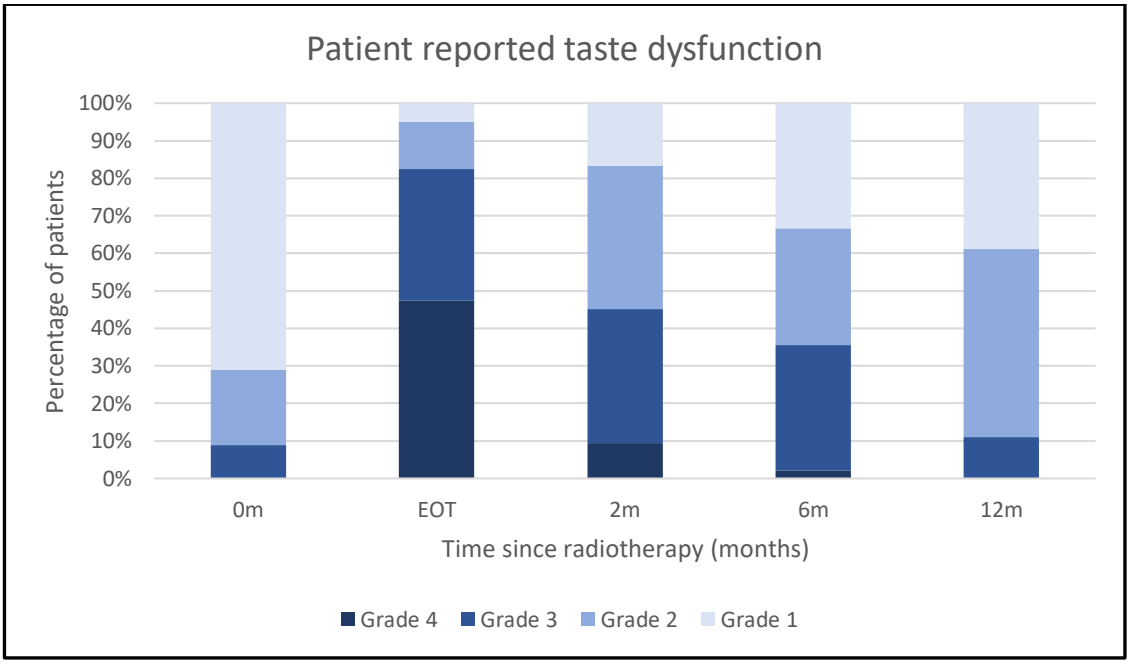


Figure 6-1: PRTD over time (Q9. UWQOL)

6.5.3.2 Objective outcomes

Chemosensory taste testing showed that almost a third (30.8%) of patients have objective hypogeusia at baseline. This rose to 87.2% at the end of RT and fell to 48.7% at 2m and back to baseline prevalence of 30.8% at 6m (table 154 and figure 6-2). It is worth noting that attrition changes in sample size aside, the patients who were hypogeusic at 6m were not necessarily those that were hypogeusic at baseline, indeed of the 30.8% who were hypogeusic at baseline, 53.3% (8/15) were normogeusic at 6m.

Objective Testing	**0m n = 52**	**End of RT n = 39**	**2m n = 39**	**6m n = 39**	**12m n = 18**
Normogeusia	36 (69.2%)	5 (12.8%)	20 (51.3%)	27 (69.2%)	10 (55.6%)
Hypogeusia	16 (30.8%)	34 (87.2%)	19 (48.7%)	12 (30.8%)	8 (44.4%)
p values	Reference	0.0001	0.09	1.0	0.39

Table 154: Objective hypogeusia over time using chemosensory testing

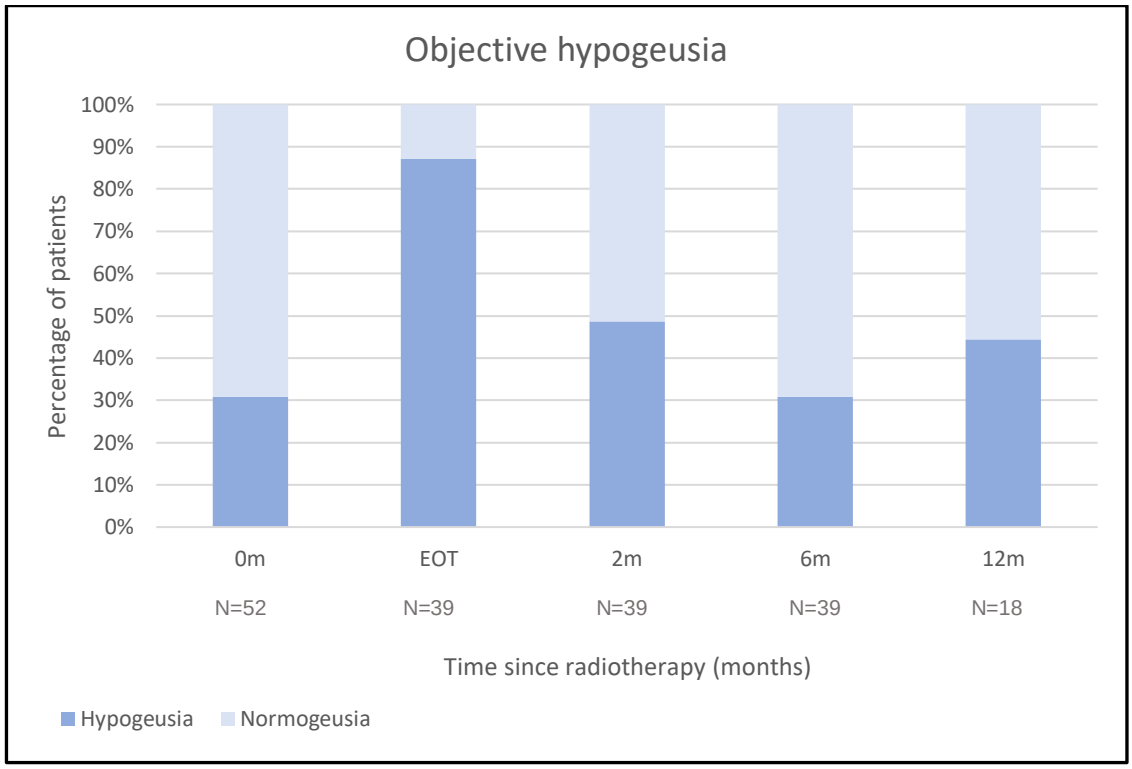


Figure 6-2: Objective hypogeusia (chemosensory testing) over time

The mean taste scores at each time point for the entire cohort are presented in table 162. The mean score for the group (10.02) was normogeusic (scores greater than 8) at baseline. By the end of radiation there was a statistically significant decrease in mean scores (4.79) into the hypogeusic range. This persisted at 2m post treatment (p=0.01) but had recovered by 6m. At 12m data was only collected for 18 patients but there was a small subsequent decline in function.

Objective Testing	**0m n = 52**	**End of RT n = 39**	**2m n = 39**	**6m n = 39**	**12m n = 18**
Mean Overall Score	10.02	4.79	8.36	10.2	9.33
Standard Deviation	3.23	3.89	3.96	3.10	2.85
Range	3-15	0-14	2-16	3-16	4-15
p value (vs baseline)		<0.0001	0.01	0.27	0.86
ANOVA p value for group effects		p = <0.0001			

Table 155: Mean scores for entire cohort over time (chemosensory taste testing)

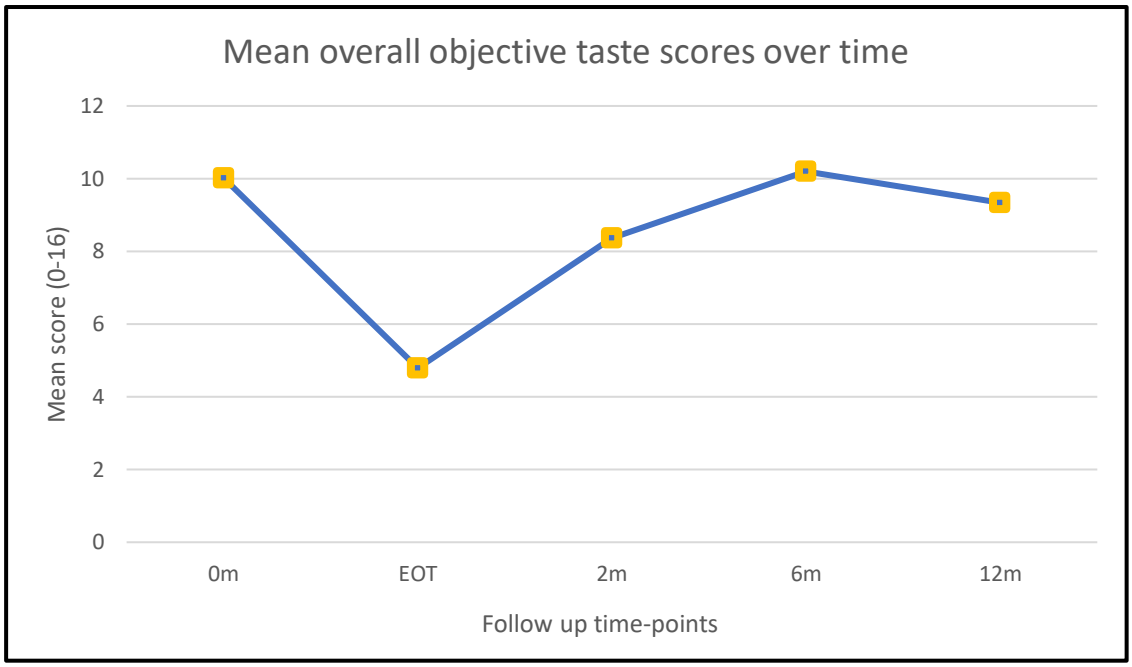


Figure 6-3: Mean overall taste scores using chemosensory testing over time

6.5.3.3 Differential loss and recovery of individual taste qualities

All four basic taste qualities showed a statistically significant decline in function between baseline and at the end of RT. This decline persisted for sweet, sour and salt but not bitter at 2m follow up. At 6m there was no statistically significant difference from baseline for any individual taste quality (table 156 and figures 6-4 and 6-5).

Objective Testing	**0m n = 52**	**End of RT n = 39**	**2m n = 39**	**6m n = 39**	**12m n = 18**
Sweet Score	**3.08**	**1.58**	**2.51**	**3.2**	**3.17**
Standard Deviation	1.03	1.65	1.17	0.94	0.79
p value (vs 0m)		<0.0001	0.04	0.18	0.37
Sour Score	**2.21**	**1.00**	**1.82**	**2.4**	**1.89**
Standard Deviation	1.07	0.92	1.07	1.07	1.08
p value (vs 0m)		<0.0001	0.07	0.29	>0.99
Salt Score	**2.56**	**1.23**	**2.08**	**2.3**	**2.5**
Standard Deviation	1.21	1.31	1.18	1.21	1.29
p value (vs 0m)		<0.0001	0.02	0.32	0.38
Bitter Score	**2.17**	**1.05**	**1.95**	**2.4**	**1.78**
Standard Deviation	1.52	1.45	1.61	1.42	1.44
p value (vs 0m)		<0.0001	0.49	0.17	0.68

Table 156: Mean scores for individual taste quality over time

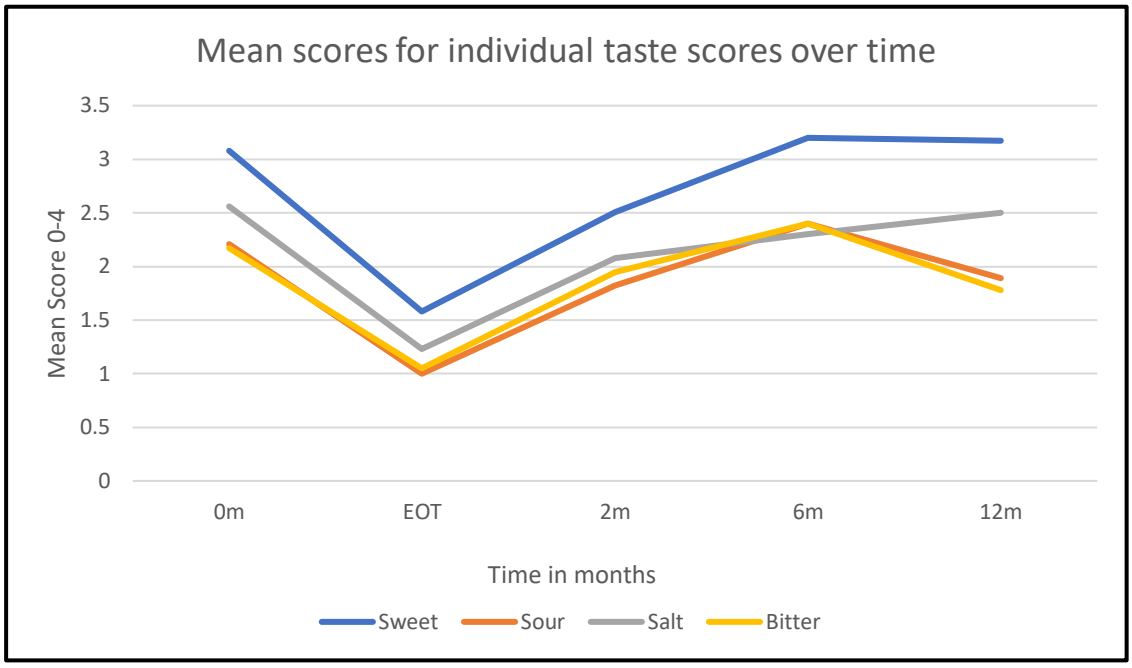


Figure 6-4: Mean scores for individual taste scores over time

6.5.4 Smell dysfunction over time

6.5.4.1 Patient reported outcomes – smell

Patient reported changes in sense of smell followed a similar trajectory to taste (table 157), with a small proportion reported at baseline (13.2%) rising to 57.5% at EOT, falling to 38.1% by 2m and further again by 6m (31.3%). In the limited data captured at 12m this decreased further to 11.1%.

TSS Q2. Patient reported changes in sense of smell										
	0m n = 43		EOT n = 40		2m n = 42		6m n = 48		12m n = 18	
	Y	N	Y	N	Y	N	Y	N	Y	N
n	5	38	23	17	16	26	15	33	2	16
%	13.2%	88.4%	57.5%	42.5%	38.1%	61.9%	31.3%	68.8%	11.1%	88.9%

Table 157: Patient reported smell outcomes using the taste and smell survey Q2

As reported in the cross-sectional analysis (chapter 5), the nature of smell dysfunction was explored. Table 158 and 159 show that of the patients reporting changes in their sense of smell a significant proportion were reporting a stronger / heightened experience, 56.5% at the EOT, 64.3% at 2m and 50% at 6m.

TSS Q12. Compared to before your treatment, is your sense of smell…								
	Stronger		Weaker		As strong		Cannot smell at all	
	n	%	n	%	n	%	n	%
0m	1	2.3%	4	9.3%	37	86.0%	1	2.3%
EOT	13	32.5%	8	20.0%	17	42.5%	2	5.0%
2m	9	21.4%	3	7.1%	28	66.7%	2	4.8%
6m	7	14.6%	6	12.5%	34	70.8%	1	2.1%
12m	0	0.0%	1	5.6%	17	94.4%	0	0.0%

Table 158: Patient reported smell outcomes using the taste and smell survey Q12

TSS Q12. In those with altered sense of smell from Q12				
	Stronger / Heightened		Weaker / Cannot Smell	
	n	%	n	%
0m	1	16.7%	5	83.3%
EOT	13	56.5%	10	43.5%
2m	9	64.3%	5	35.7%
6m	7	50.0%	7	50.0%
12m	0	0.0%	1	100.0%

Table 159: Proportion of patients with heightened sense of smell in those with patient reported altered sense of smell

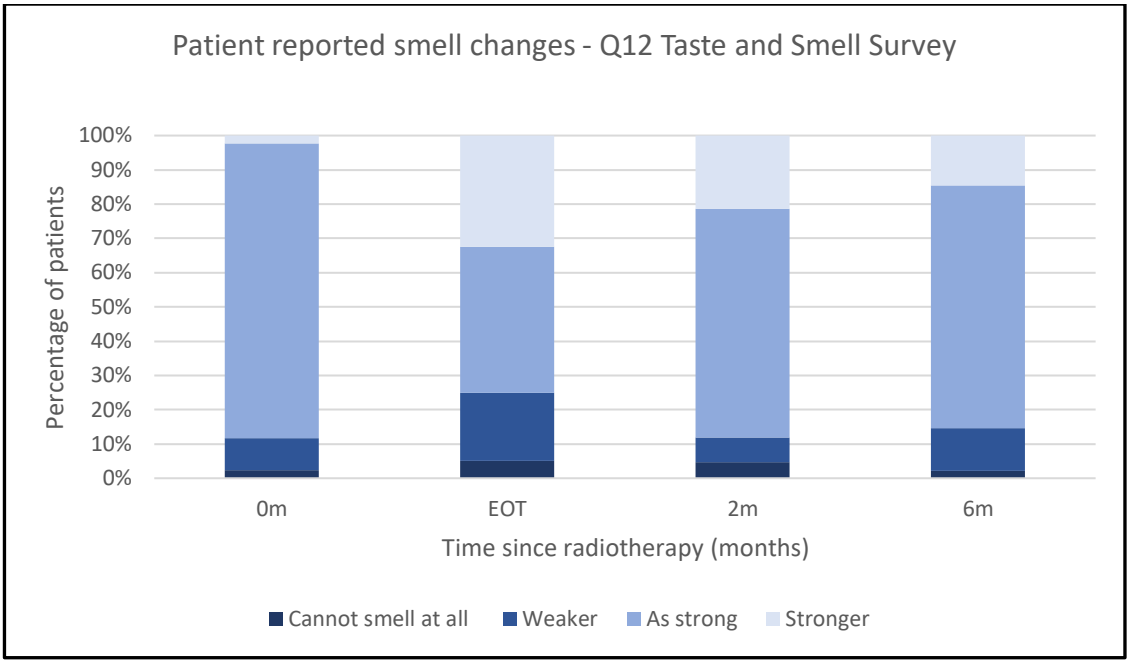


Figure 6-5: Patient reported smell changes as per Q12. Taste and Smell Survey

6.5.4.2 Objective outcomes – smell

Objective smell scores on average improved following RT. At baseline the mean score was 9.9, rising to 10.2 at EOT (p=0.05), 10.6 at 2m (p=0.04) and 10 at 6m (not significant). Consistent with these findings the proportion of people classified as normosmic increased from 54.9% at baseline to 61.8% at EOT (not significant) and generally remained high. The percentage of patients with smell scores below the age and sex adjusted 10th centile was 9.8% at baseline (as expected) though this number decreased to 2.9% at EOT, 0% at 2m and 6.3% at 6m. This was statistically significant at EOT (p=0.04).

	0m n = 51	EOT n = 34	2m n = 35	6m n = 32	12m n = 18
Smell Score (0-12)	9.9	10.2	10.6	10.0	10.4
SD	2.3	2.3	1.1	2.7	1.5
Range	0-12	0-12	8-12	0-12	7-12
p value (paired t 0m)	reference	0.05	0.04	0.7	0.8
Classification					
Normosmia	54.9%	61.8%	51.4%	63.0%	55.6%
Hyposmia	42.3%	35.3%	48.6%	34.3%	44.4%
Anosmia	2.0%	2.9%	0%	3.1%	0%
p value (paired t 0m)	reference	0.3	0.5	0.7	0.7
Adjustment for age / sex					
Normal	90.2%	97.1%	100%	93.8%	100%
Below 10th centile	9.8%	2.9%	0%	6.3%	0%
p value (paired t 0m)	reference	0.04	0.08	0.32	0.33

Table 160: Smell scores over time (raw score, classification from score, adjustment for age and sex)

6.5.5 Relationship between dose to gustatory field and taste dysfunction

6.5.5.1 Outcomes at 6 months follow up (primary end point)

Although the mean dose to each gustatory ROI was higher in those with G3+PRTD, there was no statistically significant difference between the groups for any ROI for this primary end point. The effect was similar when objective hypogeusia was used to define groups. However the difference was statistically significant for every ROI when a lower threshold for subjective PRTD (G2+PRTD) was used (table 161).

	Mean Dose (Gy) and SD				
	EOC	**Whole tongue**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**	**Whole tongue surface**
PRTD (G3+)	36.6 SD 14.5	36.8 SD 14.1	27.5 SD 11.7	23.3 SD 12.1	27.5 SD 14.5
No PRTD	28.8 SD 19.3	28.3 SD 19.3	24.1 SD 17.8	19.7 SD 15.8	21.9 SD 16.2
p value	0.15	0.12	0.48	0.44	0.28
PRTD (G2+)	38.1 SD 14.8	38. SD 14.8	30.6 SD 13.7	25.2 SD 12.9	28.0 SD 14.2
No PRTD	18.6 SD 17.1	17.8 SD 16.4	14.6 SD 14.6	12.6 SD 14.3	15.8 SD 15.8
p value	0.0002	<0.0001	0.0005	0.005	0.02
Hypogeusia	35.5 SD 19.0	35.6 SD 19.4	28.6 SD 16.5	24.3 SD 15.5	28.4 SD 16.7
Normogeusia	30.6 SD 16.9	30.3 SD 16.8	24.1 SD 15.0	20.9 SD 14.9	23.8 SD 15.0
p value	0.42	0.39	0.42	0.53	0.45

Table 161: Mean dose to the gustatory ROI in those with or without G3+PRTD; G2+ PRTD and objective hypogeusia at 6m

6.5.5.2 Outcomes at EOT and 2 months follow up

At the EOT the mean dose to each ROI was higher in those with G3+PRTD and this was statistically significant. Similarly mean doses were higher in those with objective hypogeusia and this was statistically significant across all ROI. Differences in dose between G2+PRTD and no PRTD were not significant, though there were only 2 patients in the no PRTD group at this time point (table 162).

At 2m the mean doses in those with either G2+PRTD or G3+PRTD were higher than those without and this was statistically significant across all ROI except for the whole tongue surface in those with or without G3+PRTD. Unlike at the other time points, the mean doses to each ROI were the same or higher in those with normogeusia than hypogeusia with no statistically significant difference across groups (table 163).

	Mean Dose (Gy) and SD				
	EOC	**Whole tongue**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**	**Whole tongue surface**
PRTD (G3+)	33.9 SD 15.8	33.3 SD 16.2	27.2 SD 14.7	21.6 SD 13.7	23.2 SD 14.0
No PRTD	7.5 SD 7.9	7.6 SD 8.0	5.5 SD 4.7	3.9 SD 2.5	5.2 SD 3.0
p value	0.0001	0.0002	0.0005	0.002	0.008
PRTD (G2+)	30.5 SD 17.4	30.0 SD 17.5	24.4 SD 15.5	19.1 SD 14.1	20.9 SD 14.5
No PRTD	5.1 SD 2.0	4.9 SD 2.6	3.9 SD 2.8	3.6 SD 3.7	6.8 SD 0.0
p value	0.05	0.05	0.07	0.14	0.34
Hypogeusia	31.3 SD 17.4	31.3 SD 17.4	25.1 SD 14.9	19.7 SD 12.5	22.2 SD 13.2
Normogeusia	16.9 SD 14.70	16.2 SD 14.76	10.2 SD 8.98	7.0 SD 6.90	10.3 SD 8.33
p value	0.09	0.07	0.04	0.03	0.09

Table 162**: Mean dose to the gustatory ROI in those with or without G3+PRTD; G2+ PRTD and objective hypogeusia at EOT**

	Mean Dose (Gy) and SD				
	EOC	**Whole tongue**	**Anterior two-thirds tongue**	**Anterior two-thirds tongue surface**	**Whole tongue surface**
PRTD (G3+)	35.9 SD 13.7	36.1 SD 14.3	28.2 SD 12.5	24.1 SD 12.4	26.0 SD 13.2
No PRTD	23.3 17.4	23.0 SD 17.0	18.5 SD 14.3	14.8 SD 13.5	18.2 SD 14.8
p value	0.01	0.01	0.03	0.03	0.11
PRTD (G2+)	33.0 SD 15.3	32.8 SD 15.6	26.2 SD 13.1	22.2 SD 13.0	24.9 SD 13.6
No PRTD	8.8 SD 7.6	9.3 SD 7.6	6.2 SD 4.3	4.4 SD 2.9	5.4 SD 2.7
p value	0.0002	0.0004	0.0003	0.001	0.001
Hypogeusia	32.3 SD 17.5	33.0 SD 17.5	26.5 SD 14.6	22.9 SD 14.4	25.2 SD 15.0
Normogeusia	34.2 SD 18.5	33.1 SD 18.6	27.3 SD 16.2	22.9 SD 15.2	27.7 SD 16.3
p value	0.8	>0.99	0.9	>0.99	0.6

Table 163: Mean dose to the gustatory ROI in those with or without G3+PRTD; G2+ PRTD and objective hypogeusia at 2m follow up

6.5.5.3 Changes over time by dose band

Patients were grouped by dose received to the anterior two thirds of the tongue to see if there was an appreciable difference in the loss and recovery of objective and subjective taste dysfunction by dose (table 164 and 165). Clinically relevant dose bands were selected as follows; low dose (0-20 Gy), moderate dose (20.1-40 Gy) and high dose (40.1 Gy+).

Proportion of patients with G3+PRTD by mean dose to anterior two thirds tongue (dose banded 0-20Gy, 20-40Gy, 40Gy+)					
	0m	**EOT**	**2m**	**6m**	**12m**
0-20Gy	2/20 10%	14/21 67%	7/21 33%	5/21 24%	0/6 0%
reference					
20-40Gy	1/16 6%	12/12 100%	8/14 57%	9/16 56%	1/8 13%
p value	1.00	0.03	0.19	0.09	>0.99
40Gy +	1/9 11%	7/7 100%	4/7 57%	3/8 38%	1/4 25%
p value	1.00	0.14	0.38	0.65	0.40

Table 164: Proportion of patients with G3+PRTD by mean dose to the anterior two thirds of the tongue

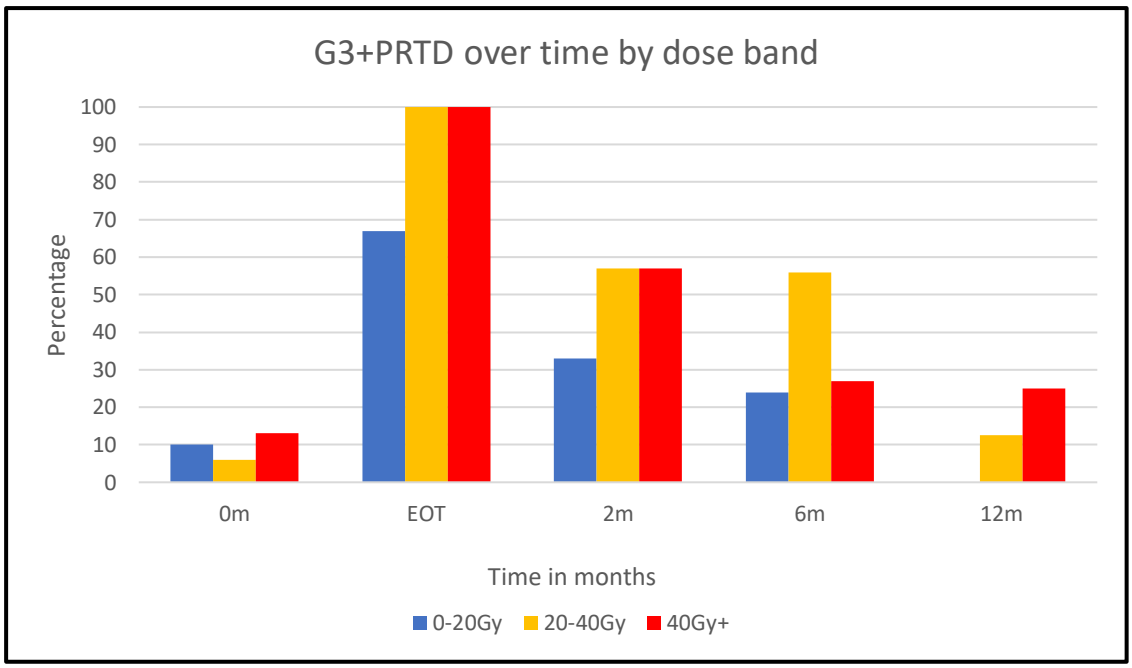


Figure 6-6: Proportion of patients with G3+PRTD over time by dose band

Mean taste scores by mean dose to the anterior two thirds tongue (dose banded 0-20Gy, 20-40Gy, 40Gy+)					
Mean Score	**0m**	**EOT**	**2m**	**6m**	**12m**
0-20Gy	10.8 SD 2.9	7.2 SD 3.7	9.6 SD 3.9	10.4 SD 2.0	10.8 SD 2.3
reference					
20-40Gy	9.4 SD 3.3	2.2 SD 2.3	6.6 SD 4.2	10 SD 3.9	8.6 SD 3.5
p value	0.2	0.0002	0.06	0.7	0.2
40Gy +	9.6 SD 3.6	2.6 SD 2.2	8.7 SD 3.3	10.11 SD 3.7	8.5 SD 1.0
p value	0.3	0.005	0.6	0.8	0.1

Table 165: Mean taste scores by mean dose to the anterior two thirds (dose banded 0-20 Gy, 20-40 Gy and 40+ Gy)

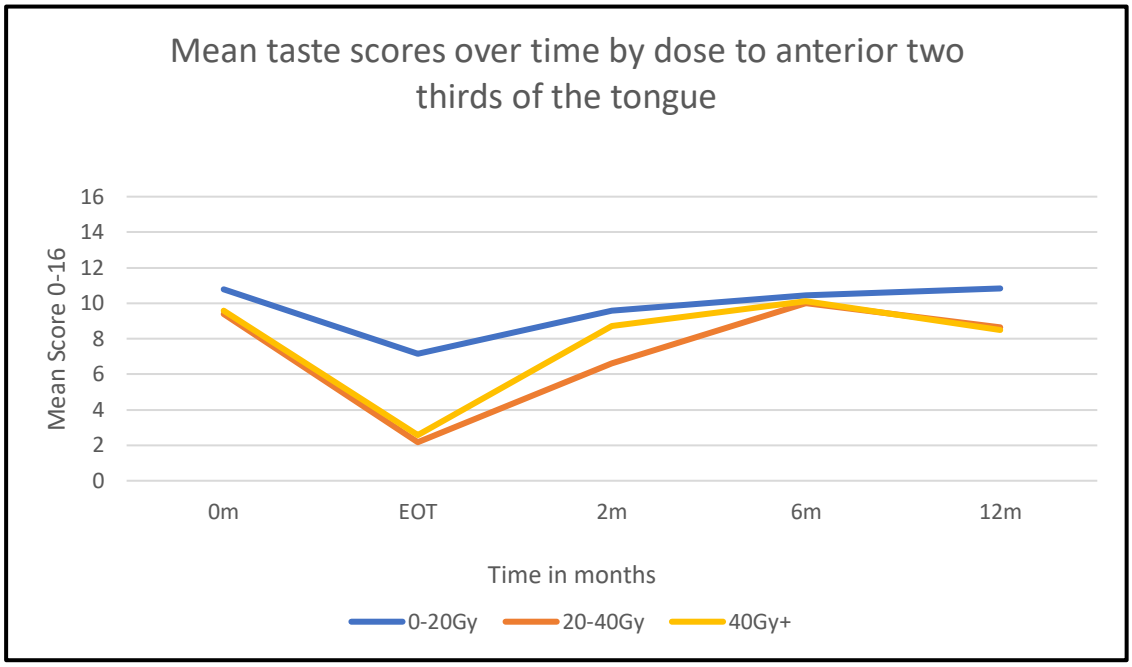


Figure 6-7: Mean taste scores (objective chemosensory testing) over time by dose received to anterior two thirds of the tongue

Proportion of patients with objective hypogeusia by mean dose to anterior two thirds tongue (dose banded 0-20Gy, 20-40Gy, 40Gy+)					
	0m	**EOT**	**2m**	**6m**	**12m**
0-20Gy	4/22 (18%)	15/20 (75%)	6/16 (38%)	4/16 (25%)	1/6 (17%)
reference					
20-40Gy	7/16 (44%)	12/12 (100%)	9/13 (69%)	4/14 (29%)	4/8 (50%)
p value	0.15	0.13	0.14	1.0	0.30
40Gy +	5/12 (42%)	7/7 (100%)	4/10 (40%)	4/9 (44%)	3/4 (75%)
p value	0.22	0.28	1.0	0.49	0.19

Table 166: Proportion of patients with objective hypogeusia by mean dose to anterior two thirds tongue (dose banded 0-20Gy, 20-40Gy, 40Gy+)

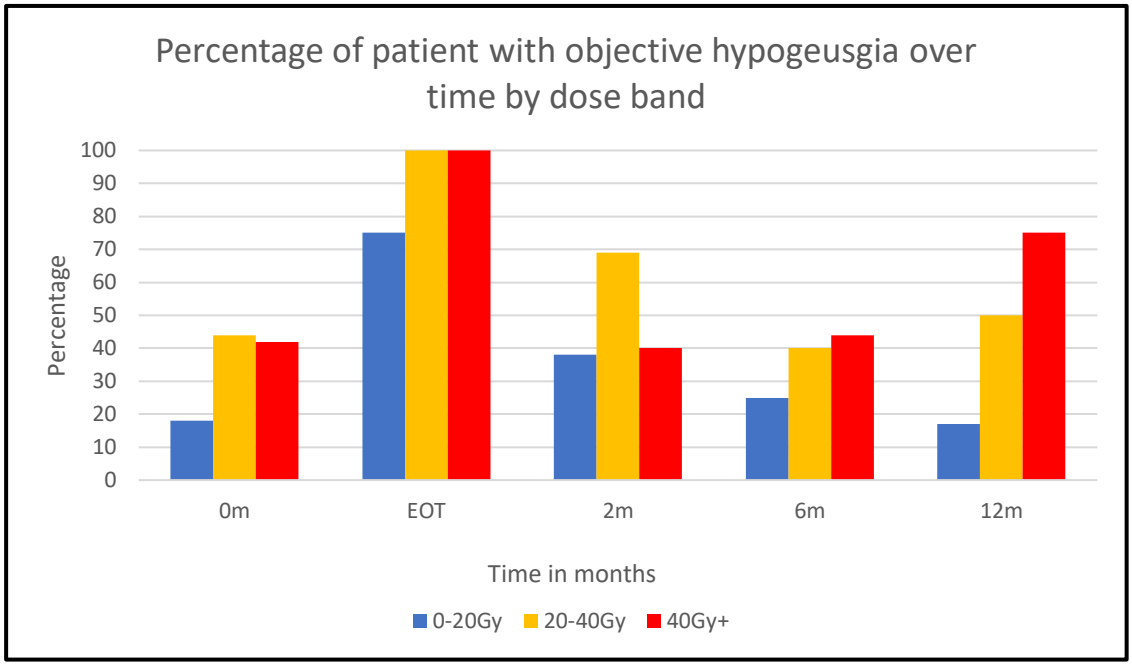


Figure 6-8: Proportion of patients with objective hypogeusia over time by dose band

6.5.6 Factors associated with taste dysfunction at 6 months

6.5.6.1 Subjective, univariate, 6 months follow up

Grade 3+PRX was associated with G3+PRTD (p=0.04) as was the use of concurrent chemotherapy (p=0.03). When included in a multivariate analysis

adjusting for age and stage (results not reported), the association of concurrent chemotherapy was no longer statistically significant.

Dose to the anterior two thirds of the tongue when analysed per additional Gy, was not significantly associated with G3+PRTD. To explore whether very low doses were associated with reduced risk of G3+PRTD, dose <20 Gy versus >20 Gy to the anterior tongue was assessed on univariate analysis. Very low doses appear protective with an odds ratio of 0.18 (p=0.04). However, when included in a multivariate analysis adjusting for potentially relevant clinical confounding factors (stage of disease, use of chemotherapy and post-operative status) very low doses <20 Gy were no longer statistically significant.

Univariate analysis – 6-months PRTD			
Variable	**OR**	**CI95%**	**P**
Age >60	0.71	0.21 to 2.37	0.58
Male	1.33	0.35 to 5.70	0.68
G3 Xerostomia 6m	3.86	1.10 to 14.40	0.04
PRSD (Q2 TSS)	0.88	0.23 to 3.11	0.84
Stage 3/4	6.55	1.07 to 126.9	0.09
PORT	0.45	0.09 to 1.78	0.28
Concurrent chemotherapy	3.85	1.14 to 14.19	0.03
PRTD 0m	2.36	0.26 to 21.83	0.42
Dose to anterior two thirds tongue	1.02	0.98 to 1.06	0.45
Dose <20Gy to anterior two thirds tongue	0.18	0.03 to 0.81	0.04

Table 167: Univariate analysis for G3+ PRTD at 6m

6.5.6.2 Objective, univariate, 6 months follow up

The same analysis was performed using objective measures obtained within the study. The only factor associated with objective hypogeusia was age >60 years (odds ratio 2.5; p=0.02)

Univariate analysis – 6-month hypogeusia			
Variable	**OR**	**CI95%**	**P**
Age >60	2.5	0.63 to 11.31	0.02
Male	1.43	0.27 to 10.94	0.69
Stage III/IV	0.24	0.05 to 1.15	0.077
Concurrent chemotherapy	2.38	0.60 to 10.07	0.22
G3 Xerostomia 6m	1.19	0.26 to 5.03	0.82
Hypogeusia 0m	3.33	0.82 to 14.52	0.10
Below 10th centile 6m	1.73	0.06 to 46.66	0.71
Hyposmia / Anosmia 6m	1.33	0.30 to 5.85	0.71
PORT	0.34	0.05 to 1.64	0.22
Dose to anterior two thirds tongue	1.02	0.97 to 1.07	0.51
Dose <20 Gy to anterior two thirds tongue	0.79	0.15 to 3.52	0.77

Table 168: Univariate analysis for objective hypogeusia at 6m

6.5.7 Downstream effects of taste dysfunction over time

6.5.7.1 Change in BMI

People who had G3+PRTD had a greater reduction in BMI from baseline to EOT (p=0.003), 2m (p=0.02) and 6m (0.004) compared with those without. There was a contrast when taste dysfunction was measured objectively. People who had objective hypogeusia tended to have a smaller reduction in BMI than those who were normogeusic, although this was only statistically significant at 2 months (p=0.04).

	Mean BMI (SD)	**Mean change in BMI from baseline (SD)**
G3/4 PRTD	23.8 (4.0)	-1.9 (1.4)
G1/2 PRTD	22.7 (3.3)	-0.02 (0.5)
p-value	0.52	0.003
	Mean BMI (SD)	**Mean change in BMI from baseline (SD)**
Hypogeusia	23.5 (3.60)	-1.6 (1.4)
Normogeusia	27.1 (6.19)	-2.1 (2.3)
p-value	0.07	0.51

Table 169: Mean BMI and mean change in BMI in those with and without G3+PRTD at EOT.

	Mean BMI (SD)	Mean change in BMI from baseline (SD)
G3/4 PRTD	23.9 (4.8)	-3.1 (1.9)
G1/2 PRTD	21.6 (3.2)	-1.4 (1.6)
p-value	0.14	0.02
	Mean BMI (SD)	**Mean change in BMI from baseline (SD)**
Hypogeusia	23.1 (4.0)	-1.98 (1.5)
Normogeusia	22.8 (4.3)	-3.60 (2.6)
p-value	0.82	0.04

Table 170: Mean BMI and mean change in BMI in those with and without G3+PRTD at 2m follow up.

	Mean BMI (SD)	Mean change in BMI from baseline (SD)
G3/4 PRTD	22.6 (4.1)	-4.6 (2.4)
G1/2 PRTD	22.7 (3.6)	-1.8 (2.7)
p-value	0.90	0.004
	Mean BMI (SD)	**Mean change in BMI from baseline (SD)**
Hypogeusia	23.8 (3.1)	-2.4 (2.5)
Normogeusia	22.9 (3.6)	-3.1 (3.0)
p-value	0.51	0.51

Table 171: Mean BMI and mean change in BMI in those with and without G3+PRTD at 6m follow up.

6.5.7.2 Quality of Life

QoL scores from question 16 (how would you rate your overall QoL in the past 7 days) of the UWQOL v4.0 were calculated for those with or without G3+PRTD and those with or without objective hypogeusia at each time point within the study. Overall QoL scores were consistently lower in those with G3+PRTD though this was only statically significant at baseline. Overall QoL scores in those with objective hypogeusia were more variable, appearing lower than those with normogeusia at baseline; equivalent at the EOT and at 2m and higher at 6m (table 172).

	Quality of Life Scores at 0m (SD)
G3/4 PRTD	40.0 (20.0)
G1/2 PRTD	67.4 (20.0)
p-value	0.03
	Quality of Life Scores at 0m (SD)
Hypogeusia	58.2 (22.7)
Normogeusia	68.6 (20.0)
p-value	0.17

Table 172: Mean QoL scores in those with and without subjective or objective taste dysfunction at baseline.

	Quality of Life Scores at EOT (SD)
Grade 3/4 PRTD	45.33 (25.69)
Grade 1/2 PRTD	65.71 (27.60)
p-value	0.07
	Quality of Life Scores at EOT (SD)
Hypogeusia	50 (26.68)
Normogeusia	50 (25.82)
p-value	>0.99

Table 173: Mean quality of life scores in those with and without subjective or objective taste dysfunction at EOT.

	Quality of Life Scores at 2M (SD)
Grade 3/4 PRTD	50.59 (18.86)
Grade 1/2 PRTD	62.50 (17.70)
p-value	0.07
	Quality of Life Scores at 2M (SD)
Hypogeusia	56.67 (19.70)
Normogeusia	56.00 (18.82)
p-value	0.92

Table 174: Mean quality of life scores in those with and without subjective or objective taste dysfunction at 2-months follow up.

	Quality of Life Scores at 6M (SD)
Grade 3/4 PRTD	60.00 (23.45)
Grade 1/2 PRTD	68.00 (22.03)
p-value	0.25
	Quality of Life Scores at 6M (SD)
Hypogeusia	70.00 (23.35)
Normogeusia	61.54 (22.57)
p-value	0.30

Table 175: Mean quality of life scores in those with and without subjective or objective taste dysfunction at 6-months follow up.

6.6 Discussion

Consistent with all previous research in this area and earlier chapters, in this longitudinal cohort study taste was an important concern for people, with the concern being highly ranked at EOT and at 2m and 6m of follow-up.

A proportion of people in the cohort had clinically significant G3+PRTD and objective hypogeusia at baseline, although relatively few (8.9% and 30.8% respectively) compared with the maximum number at the end of RT (82.5% and 87.2%).

G3+PRTD persisted in 35.4% at 6 months in this prospective cohort, consistent with the cross-sectional results of 33.3% at 12m. Preliminary 12m data from this cohort suggests some further recovery although this should be interpreted with caution given the sample size. Even if G3+PRTD rates return close to baseline in the longer term, there was a substantial decrease in the proportion of people with normal (G1) taste function. Given that at 12m taste dysfunction remains the 3rd highest ranked toxicity and is frequently reported by patients in the clinic setting, it is likely that any degree of dysfunction (G2+) has clinical significance to the patient.

Although data was limited in this cohort at 12m, there was some evidence of longer-term decline with overall continuous objective scores falling between 6m (10.2) to 12m (9.33, p=non-significant). This would also be more consistent with

the same objective measure taken at 12m (7.49) in the cross-sectional cohort study (chapter 5, section 5.5.3.2).

The results of the systematic review (chapter 2) in general found that bitter and salt were the most affected qualities. In this study, all 4 taste qualities were affected in this study, with statistically significant reductions from baseline to EOT. Interestingly it appeared that of the 4 taste qualities, bitter was the quickest to recover as the other 3 were still significantly lower at 2m. However, this is likely due to bitter being the worst scoring quality at baseline of the 4 therefore requiring the least absolute recovery to approximate baseline.

People reported similar subjective changes in smell function to taste, with a peak in reported changes in smell at EOT (57.5%) and fewer reporting a change by 6m (31.3%). However consistent with the cross-sectional cohort study (chapter 5), there were some people within the group of those reporting a change, whose sense of smell was getting stronger. This was reflected in the objective measures with an improvement in the mean continuous objective scores from baseline to EOT that persisted to 6m follow-up. It is possible that performance on objective testing may have improved over time as people became more familiar with the testing method, but this could not explain the subjective reports of a heightened sense of smell. As previously alluded to in chapter 5, this heightened sense of smell in the context of a taste deficit may reflect an element of cross-modal neuroplasticity. The gustatory senses are closely intertwined, and it is plausible that over our lifetime there are in built compensatory mechanisms that with loss of taste the sense of smell is enhanced to help stimulate nutritional intake whilst maintaining the ability to detect potentially harmful toxins.

On average, people with G3+PRTD at 6m had received higher doses to each of the gustatory ROI compared to those without G3+PRTD. However, unlike in the cross-sectional analysis (chapter 5), this was not statistically significant. The effect was similar for those with or without objective hypogeusia. Further analysis dichotomising patient outcomes into those with or without any degree

of taste dysfunction (G2+PRTD) showed a greater difference in doses received reaching statistical significance for all gustatory ROI.

The relationship between dose and taste dysfunction was more pronounced at the EOT and at 2m follow up. Those without G3+PRTD at EOT, on average received only 5.48 Gy to the anterior two thirds of the tongue. At 2m the equivalent dose was 18.49 Gy. One of the aims of this work was to identify dose constraints which might minimise the likelihood of taste dysfunction. This evidence suggests this may be achievable with a suggested gustatory dose constraint of 0-20 Gy either using photons or better still radiation techniques which specifically reduce low-dose radiation toxicities such as PBT.

There is currently no established specific gustatory OAR so in this analysis the effect of dose was assessed at 5 candidate anatomical sites based broadly on taste bud distribution (OC, whole tongue, anterior two-thirds tongue, anterior two-thirds tongue surface and whole tongue surface). Each OAR candidate performed equally well though this was likely because the study was not powered to detect differences between such closely related datasets. Typically for each outcome timepoint combination, the effect of dose was similar at all 5 ROIs. Previous literature has tended to focus on the anterior two thirds of the tongue and for further analysis here, this has been used as a proxy.

In order to investigate the possibility of dose constraints further, the frequency of taste dysfunction by clinically relevant dose bands at the anterior two thirds of the tongue; low dose (0-20 Gy), moderate dose (20.1-40 Gy) and high dose (40.1 Gy+) was assessed for G3+PRTD, objective hypogeusia and mean taste score. For all analyses the 0-20 Gy group of patients tended to have less dysfunction or better taste scores (e.g., 67% with G3+ PRTD at EOT compared with 100% in the 20.1-40 Gy group, p=0.03) however there were still a number of patients even in this low dose group experiencing dysfunction in the medium-term follow-up (e.g. 33% with G3+PRTD at 2m). While data at 12m was sparse (as noted previously), there was a suggestion that the low dose group performed particularly well comparatively at this longer time point.

A logistic regression was performed to look for statistically significant factors that could inform clinicians and their patients regarding risk of persistent G3+PRTD at 6m. The majority of factors assessed were not associated with G3+PRTD. Those that were on univariate analysis (G3+PRX and concurrent chemotherapy), were no longer significant when potential clinical confounders including age, stage and post-operative status were taken into account though this may partly be driven by sample size.

The same analysis was performed this time looking at factors associated with objective hypogeusia. Interestingly the results were distinct, again reaffirming that these two tests measure different aspects of taste dysfunction. The only significant factor was age >60 ($p=0.02$) with an odds ratio of 2.5 in the opposite direction to its non-sig effect for subjective dysfunction (odds ratio 0.71, $p=0.58$). It is likely that this study has demonstrated age associated decline in objective taste function but not one that translates into a subjective complaint.

Those with subjective taste dysfunction had a greater reduction in BMI compared to those without, supporting the hypothesis that taste dysfunction has important sequelae in this case being associated with greater weight loss which in turn has been associated with poorer outcomes (100). Rather unexpectedly if anything, the inverse was seen in those with or without objective taste dysfunction, though the relationship was weaker. This is further support for the use of PROMs in taste research as they appear to more strongly dictate important down-stream effects. A similar pattern was seen when comparing overall QoL in those with or without subjective or objective taste dysfunction although results were not statistically significant. This is not surprising given the multi-factorial nature of overall QoL measures and the small sample size.

There were a number of limitations that require acknowledgement. Although longitudinal data was collected, patients were analysed as a whole group with dichotomised outcomes. If sample size allowed, it would be optimal to disregard those with baseline dysfunction and/or to track the change in function over time. The objective data was collected by a single investigator which resulted in a lack of inter- and intra-observer variability. Inevitably there was also a proportion of

missing data for certain data items are various timepoints which will have impacted results. As always, a control arm would have isolated the effect of RT more effectively.

6.7 Conclusion

As per previous chapters, taste dysfunction was shown to be a highly ranked toxicity affecting over a third of patients 6m following completion of treatment. The prospective nature of this study allowed for a more thorough analysis of dysfunction across taste qualities (all were affected similarly) and the impact of dose (where a general relationship was observed, keeping dose at the anterior two thirds of the tongue below 20 Gy may reduce if not completely prevent dysfunction). Dose aside, in a cohort of this size, it is difficult to use other clinical characteristics to predict which patients may suffer from taste dysfunction, although concurrent chemotherapy and xerostomia may be associated. Subjective taste dysfunction itself appears to be linked to a tendency to lose more weight during and after treatment, confirming once again the tangible impact of this adverse effect, psychosocial considerations aside.

Chapter 7 – Thesis Discussion and Conclusions

In chapter 2 relevant data from 30 studies was pooled to summarise relevant research in the published literature to date. There was limited prospective data and the data that had been collected was so heterogenous in design making meta-analysis challenging, with a high degree of residual inconsistency despite separating into objective and subjective outcomes. Research spanning 30 years included a variety of objective and subjective measures with very little research into the relationship between dose to the gustatory field and taste function following RT to the head and neck.

In chapter 3 and chapter 4, large data sets were sourced to look for patient and treatment related predictors of dysfunction. For chapters 5 and 6, two new studies were developed, set-up and completed, to specifically explore the relationship between dose to the gustatory field and taste outcomes. Gaps within the literature identified in chapter 2, generated themes for the research and discussion throughout this thesis, the outcomes of which are summarised below.

7.1.1 Prevalence prior to treatment in HNC population

Previous studies (as discussed in chapter 2) agreed that a measurable deficit in taste acuity is present in people with HNC prior to radiation though the prevalence was variable. PRTD using validated questionnaires was reported in 13-19% (56,58). Across the datasets analysed for this thesis the prevalence of G3+PRTD at baseline was also variable - 17% in PARSPORT (40% G2+PRTD); 4% in COSTAR (16% G2+PRTD); 11% in HN5000 (31% G2+PRTD); 9% in our prospective study (29% G2+PRTD). The HN5000 dataset included patient reported outcomes from over 4000 patients in the UK, collected in the last 10 years and as such should probably be considered the most reliable and relevant estimate of prevalence for current UK clinical oncologists. Multivariate analysis of the HN5000 dataset showed that baseline dysfunction was associated with tumours involving the mucosal cavity, stage III/IV disease, co-morbidities, current smoker and being female. The strongest association was related to the underlying tumour site and is therefore likely that active mucosal disease itself

significantly contributes to PRTD. Arguably this is a modifiable risk factor with treatment of the primary disease. With this awareness of tumour related baseline dysfunction in mind, the aim post-treatment should be beyond just preserving baseline function and in fact be to improve taste function to its pre-disease state if possible.

7.1.2 PRO vs CRO

In all datasets presented, study outcomes were separated into patient reported, clinician reported or objective. In chapter 3 subjective PROs were compared with objective CROs. There was certainly a correlation between these assessments as one would hope, however a closer analysis showed a poor sensitivity of the CROs to detect PROs. This was consistent across both the PARSPORT and COSTAR datasets and the sensitivity in both studies declined with time demonstrating operator bias. In chapters 5 and 6 PROs were compared with objective chemosensory testing. As expected, there was an association between these two measures, but results showed that the assessments cannot be used interchangeably. For example, in chapter 5 (cross sectional study) one participant with an olfactory neuroblastoma demonstrated that despite having complete anosmia and therefore no ability to sense flavour, she could identify the four basic taste qualities on objective testing with relative ease. This nicely highlighted that the process of sensing whether something is sweet, or sour is very different to the complex processes that facilitate the interpretation and experience of flavour. Gustatory research should aim to use a combination of outcome measures with emphasis on using PROMs, these are after all by definition the most important to patients themselves. A survey specific to gustatory research that explores the nuances of taste is yet to be developed but in the interim the UWQOL or EORTC HNQ surveys both offer suitable options validated for use in the head and neck population. Consistency amongst researchers to enable pooling of data would overcome the difficulties with heterogeneity seen in research to date. As discussed in chapter 2 the vast array of approaches used by researchers in terms of outcome measurement (including inconsistency in timing, cut-off, subjective vs objective, continuous vs

dichotomous) makes meta-analysis and comparison across studies challenging if not impossible.

7.1.3 Clinically relevant dysfunction

From the outset it was difficult to know what represented clinically relevant dysfunction. The UW-QOL and EORTC HNQ35 questionnaires were both validated surveys for collecting toxicity data in HNC patients however neither offered specific cut off values or thresholds for clinically significant toxicity for individual symptoms scales. Combining objective and subjective measures offered the opportunity to explore minimally important differences but as discussed it quickly became obvious that the objective and subjective measures are not interchangeable and assess quite different abilities / experiences. Having interviewed over a hundred patients during data collection for chapter 5 and 6, it also became clear that grading toxicity is difficult. It would be far easier in future research for outcomes to be dichotomised – a forced choice approach whereby participants are asked to commit to whether their taste is normal, or not. In support of this in chapter 5 and 6, taste was a highly ranked toxicity (3rd only after problems with saliva and swallow) but the rates of G3+PRTD were relatively low. Rates of G2+PRTD were more in keeping with the level of importance seen in the ranking of toxicities and aligned with the level of PRTD expressed informally by patients in the clinic setting.

7.1.4 Downstream effects

It is clear that taste dysfunction is a significant toxicity for patients and ranks highly in importance both during and after treatment. In all datasets we showed a strong relationship between PRTD and overall QoL, and BMI. This was best demonstrated with statistical significance seen in chapter 4 (HN5000) where GHSs differed by 15-21 points (10 being clinically significant) between those with or without G3+PRTD ($p<0.0001$). Similarly, the average BMI in those with G3+PRTD was lower (<0.0001) at both 4m and 12m follow up. Due to the observational and non-randomised nature of these datasets it is not possible to say definitively whether the taste dysfunction specifically causes worse quality

of life or is just associated. It stands to reason that if a person generally has a worse quality of life, they are more likely to rate any specific function of theirs (including taste) as poorer. In future studies if treatment strategies are compared that may reduce taste dysfunction, for example potentially using proton beam therapy to spare the G-OAR, it will be fascinating to see if reducing taste dysfunction alone leads to improvements in global QoL measures.

7.1.5 Relationship with dose to gustatory field

In chapter 3 a higher prevalence of G3+PRTD in those receiving bilateral RT versus unilateral RT was found. Although there were differences between the groups analysed and the rates of baseline dysfunction, it was clear that there was a relationship between volume of the gustatory field irradiated and PRTD. In chapter 4 tumour site was used as a surrogate for dose to the gustatory field, with the assumption that RT planning techniques employed are fairly standardised across the UK. This analysis showed clearly the protective effect of lower doses to the gustatory field, particularly in those with LC where dose to the OC is minimal. Higher likelihood of PRTD was seen in those with tumours in proximity to the gustatory field, in particular in OPC and NPC. In chapter 5 (cross sectional study) a dose dependent relationship was seen with the lowest prevalence of PRTD seen in those receiving 0-20 Gy to the anterior two thirds of the tongue (selected ROI/OAR). Objective dysgeusia was almost universally present in those who had previously received 50+ Gy to the anterior two thirds of the tongue with much lower rates around 50-60% in those with low to moderate doses. In Chapter 6 (prospective study) again those patients receiving 0-20 Gy saw the lowest rates of PRTD and objective hypogeusia. Dose was plotted against probability of G3+PRTD showing increasing risk with increasing dose at all time points assessed. It is worth noting that while keeping dose low was good, it was not a guarantee of no dysfunction.

7.1.6 Associated factors

In all datasets, alongside taste dysfunction, olfactory outcomes were explored and within chapters 5 and 6, objective chemosensory smell function data was

collected. Smell dysfunction was consistently associated with PRTD. Initially in chapter 3 and 4 this was assumed to be a linked deficit i.e., a smell deficit causing or contributing to a taste deficit. Further exploration of the nature of smell dysfunction in chapters 5 and 6 revealed that a large proportion of patients reporting smell dysfunction were reporting a heightened sense of smell. Although previously unreported, this could feasibly represent cross modal neuroplasticity where one sense compensates for the deficit of another. Smell and taste are so closely intertwined, and both serve to support sustenance and avoid ingestions of toxin. It is likely that there are in built compensatory mechanisms that come in to play following RT to the gustatory field. If unable to detect toxins (or detect sweet and fatty foods to support calorific intake), then smell function steps in to provide secondary protection and function. Smell dysfunction was far more prevalent in those with NC or NPC. It is known that acute nasal congestion caused by either tumour or acute mucosal inflammation from RT will cause loss of smell and affect patient reported taste outcomes. However, for the remainder of patients, there is little to suggest that striving to improve smell function will improve taste outcomes. Xerostomia was also consistently associated with dysfunction. There is a theoretical rationale that lack of saliva leads to the inability for chemical stimuli to adequately reach the taste receptors within the taste buds though none of our datasets can go further than supporting an association and cannot confirm a causal relationship. As a caution against over-interpreting associated toxicities, there was also a strong association between xerostomia and smell dysfunction where there is no obvious biologically plausible causal link. Concurrent platinum-based chemotherapy was a consistent risk factor for taste dysfunction and in the HN5000 cohort it remained a statistically significant predictor of dysfunction when adjusted for age and stage of disease though, as might be expected, this effect reduced between 4m and 12m follow up. This is a fascinating and newly reported effect that will aid clinicians when consenting patients for concurrent platinum-based therapy.

7.1.7 Developing a constraint

It has been clearly shown that minimising dose to the gustatory field will reduce the risk of both PRTD and objective hypogeusia. In chapters 5 and 6 toxicity outcomes were analysed against dose to a selection of clinically relevant gustatory ROI. On the whole they all performed equally well but in agreement with previous research it would seem reasonable to assume the anterior two thirds of the tongue to be the clinically relevant target given this is home to the majority of the FFP. A recent paper has published a tongue contouring protocol (101) however this requires further refinement to select the most clinically relevant ROI for planning purposes. Outcomes from this research would support the use of the anterior two thirds of the tongue as the target OAR. In particular the majority of HNC are OPC whereby the posterior third of the tongue is often target but the anterior portion is almost universally not. Achieving ultra-low doses to the anterior portion is therefore technically achievable and will according to data from this thesis, preserve function without risking compromise to the PTV. Data from chapters 5 and 6 (and chapter 4 should tumour site be taken as a surrogate for dose) would advocate doses less than 20 Gy which for some patients may be achievable with IMRT using photons. However with PBT this constraint, or even lower, may be more readily achieved. Tongue motion will need some consideration. As part of this work, a small tongue motion analysis was completed. Eleven patients who underwent weekly cone-beam CTs (CBCTs) over the course of 6 weeks of RT were included for analysis. The whole tongue was contoured retrospectively on the planning CT and then again on a minimum of 5 CBCTs taken throughout the 6-week course of radiation. The variation in centre of mass in the x, y and z axis and dice similarity coefficients (DSC) were analysed. The largest deviation in the x axis (left to right movement of the tongue) was 0.43cm, in the y axis (anterior to posterior) was 0.66cm and in the z axis (superior to inferior) was 0.77cm showing potential for significant movement. The mean misalignment over the course of 6 weeks for all patients combined however was 0.08cm (SD 0.04) in the x axis, 0.17 (SD 0.12) in the y axis and 0.20 (SD 0.09) in the z axis. The dice similarity co-efficient (DSC) between the planning CT and CBCT ranged from 0.76 to 0.92 but on average across all scans at all time points, was 0.86. Overall, this small analysis

suggested that there is potential for large variations in tongue position and motion management will need further consideration particularly when using IMPT where small changes in positioning of both target and OAR can lead to significant dosimetric uncertainties.

7.1.8 Future research

Going forward a combination of PROMs (preferably using dichotomised outcomes) should be prioritised, with supplementary objective chemosensory testing where feasible but with caution that these measures are not interchangeable. In addition, a gold standard for assessing both objective and subjective testing should be agreed to allow for greater consistency in comparisons and collaboration across studies and research groups. The EORTC HNQ35 may have practical advantages given is has been used in the largest available dataset although methodologically the UWQOL questionnaire may be preferable given more precise wording relating to taste function. An interesting future project would be the development of a validated and consensus approved taste specific questionnaire for research in this field. CRO measures in this research were shown to be poor and did not capture patient reported toxicity and would be not recommended as a tool to reliably detect clinically relevant taste dysfunction.

Ideally further studies would include a control arm, include baseline testing and monitor change in function longitudinally rather than assessment of an entire group at various timepoints. Acute taste dysfunction is inevitable even at very low doses and the focus should be on assessing recovery or preservation of function at 6 months and 12 months.

The target OAR should be the anterior two thirds of the tongue with a target constraint of 0-20 Gy to minimise the risk of taste dysfunction. A protocol to contour the anterior two thirds of the tongue would need to be developed and approved by clinicians within the field, to ensure consistency in research and in clinical practice. For the purposes of this research the whole tongue was

contoured using the surface of tongue as the superior border; the hyoid as the inferior border; the mandible as the anterior border superiorly and the digastric muscles as the anterior border inferiorly and the soft palate as the posterior border superiorly and the aerodigestive tract inferiorly. The anterior two thirds of the tongue was then defined in the mid sagittal plane of the whole tongue, by measuring two thirds posteriorly from the mid mandible and then intersecting at this point with a vertical division from the superior tongue, down to the hyoid. This was a pragmatic a reproducible approach for the purposes of this thesis but standardisation and implementation in day to day practice is required.

A dose constraint of <20 Gy to the anterior two thirds of the tongue will be difficult to achieve with 3D conformal RT or IMRT particularly for tumours involving the oropharynx, oral cavity or those sites requiring level 1b nodal irradiation. Even if plans can be optimised to meet this constraint there may well be re-distribution of dose to other head and neck OAR and prioritisation of minimising various toxicities will need balancing carefully. Further planning studies would explore what is achievable and also demonstrate how the redistribution of dose might impact other important OAR. The benefits of PBT for patients with OPC is currently being evaluated in the TORPEDO study although not specifically regarding taste (102). Using the spread-bragg peak (SOPB) to achieve superficial deposition of high dose with PBT would reduce dose to the gustatory OAR in some patients, for example those with parotid tumours (figure 7-1).

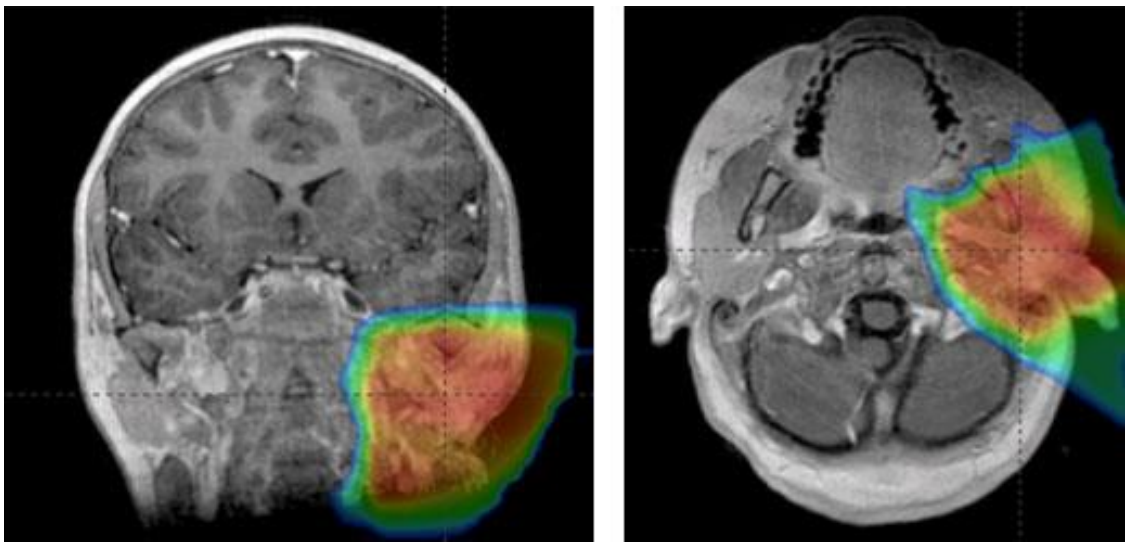


Figure 7-1: Proton beam therapy for parotid carcinoma (103).

A PBT study with commission through evaluation (CtE) is being developed for salivary gland tumours requiring post-operative RT (see appendix 1) where doses of less than 5 Gy to the anterior tongue would be easily achieved as seen in previous proton beam research (61). The expectation is that radiation induced taste dysfunction will be eliminated in this group entirely and pave the way for further tumour sites to follow.

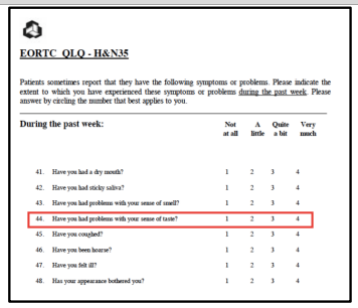
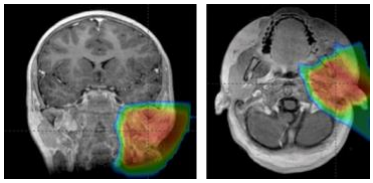
Chapter 8 - Appendices

8.1 Appendix 1

Call for proposals for Proton Beam Therapy (PBT) Clinical Trial ideas

Please kindly refrain from sending the entire proposal / protocol and keep to a page limit of 5 pages. Please send your completed form to ctrad@ncri.org.uk

Researcher details	
Researcher(s)	Professor Chris Nutting, Professor Emma Hall, **Dr Lucinda Gunn**
Institution(s)	Head and Neck Research Unit - The Royal Marsden NHS Foundation Trust Clinical Trials and Statistical Unit - The Institute of Cancer Research (ICR-CTSU)
Study overview	
Title of study	Taste function following intensity modulated proton beam radiotherapy for salivary gland tumours
Disease area	Radiotherapy for Salivary Gland Tumours
What is the scientific question?	Does intensity modulated proton beam therapy (IMPT) reduce taste loss compared to intensity modulated radiotherapy (IMRT) using photons.
Background and hypothesis	Taste loss following radiotherapy (RT) to the head and neck is common, affecting 70-90% of patients. In salivary gland tumours approximately 63% of patients report abnormal taste 6 months after treatment and toxicity can persist long term (data from COSTAR). Surgery and post-operative radiotherapy (PORT) is the standard of care for the majority of malignant salivary gland tumours. The toxicity profile seen following treatment has been well studied in the COSTAR study which randomised patients to either 3D conventional RT or IMRT for parotid tumours. Current RT techniques including IMRT, lead to the unnecessary irradiation of the oral cavity and with it, the taste cells and receptors necessary for taste function. Intensity modulated proton beam therapy (IMPT) restricts dose to the intended target providing the opportunity to spare the oral cavity. We hypothesise that IMPT will reduce dose to the tongue and oral cavity compared to IMRT and in doing so will reduce, if not eliminate, patient reported taste dysfunction
Pilot data and planning studies	State of the art IMRT outcome data for parotid tumours is available from COSTAR, including patient reported taste toxicity as per the EORTC QLQ HNQ35 module (see figure 1 below). Data held by the ICR-CTSU show the following incidence of patient reported taste dysfunction i.e. the proportion of patients answering “a little”, “quite a bit” or “very much” to the H&N35 question “have you had problems with your sense of taste”: 59% at 6 months; 53% at 12 months.

Study overview cont.	
Pilot data and planning studies	 EORTC QLQ - H&N35 Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you. During the past week: Not at all / A little / Quite a bit / Very much 41. Have you had a dry mouth? 1 2 3 4 42. Have you had sticky saliva? 1 2 3 4 43. Have you had problems with your sense of smell? 1 2 3 4 44. Have you had problems with your sense of taste? 1 2 3 4 45. Have you coughed? 1 2 3 4 46. Have you been hoarse? 1 2 3 4 47. Have you felt ill? 1 2 3 4 48. Has your appearance bothered you? 1 2 3 4 **Figure 1: Extract from EORTC-HNQ35 Questionnaire.** The dosimetric advantages of using proton beam therapy (PBT) for salivary gland tumours has been reported in two small studies. A small retrospective study compared pencil beam scanning (PBS) proton therapy against IMRT for parotid gland tumours (Swisher-McClure et al 2018). Although the study only included 8 patients, PBS proton therapy significantly reduced the mean dose to the oral cavity (0.58 Gy vs 13.48 Gy). Prior to this a small study reported toxicity outcomes in 41 patients treated with ipsilateral irradiation for major salivary gland or cutaneous squamous cell carcinoma (SCC). Twenty-three underwent IMRT and 18 were treated with PBT (Romesser et al 2016). Similar dosimetric advantages were observed. In particular mean oral cavity doses with IMRT were 20.6 Gy vs 0.94 Gy with PBT. The rates of grade 2 or greater acute dysgeusia (assessed as per CTCAE v4.0) were 65.2% in the IMRT group vs 5.6% in the PBT group (p=<0.001).  **Figure 2: Proton beam therapy for a parotid tumour (Floridaproton.org)**
Development of Trial Concept	
Research Groups (RGs)	☐ Have you presented or discussed the trial concept with the relevant NCRI Research Group(s)? - No, not yet
CTRad	☐ Have you discussed the trial concept with the relevant CTRad Workstream or received other CTRad input? - Yes: Informal advice from Professor Emma Hall and Professor Chris Nutting
PBT Centre Involvement	☐ Have you discussed your proposal with a UK PBT Centre? ☐ Have you involved a member of a UK PBT Centre in its development? - No, not yet

Development of Trial Concept cont.	
Future leaders	• Have you identified a trainee interested in clinical trials to be involved in your study? - Yes (research fellow to Professor Nutting)
International landscape	• What trials are planned/running internationally in the disease area you plan to study? Is there scope for international collaboration? - This is novel research - There are no registered randomised control trials or non-randomised studies comparing taste specific outcomes in IMPT versus IMRT in salivary gland tumours.
Trial Design	
Trial phase	Phase II / Commissioning through evaluation proposal
Trial design	Intensity modulated proton beam therapy (IMPT) versus intensity modulated photon therapy (IMRT) for salivary gland tumours – a case matched analysis. Non-randomised, multicentre study The IMPT group would be a prospective cohort of patients with salivary gland tumours requiring radiotherapy. We will aim to recruit a convenience sample of 100 patients. We will analyse the data of this cohort for prevalence of taste dysfunction (see endpoints below). We will also compare a matched subset of 37 patients from this cohort in a 1:1 ratio with the 37 patients from the IMRT COSTAR arm with available taste outcome and quality of life data. Patients will be matched on age, sex, T and N stage. New patient requiring post-operative radiotherapy for salivary gland tumour **PBT arm** Data from COSTAR **IMRT arm** Baseline questionnaire data 3-month questionnaire data 6-month questionnaire data **PRIMARY ENDPOINT ANALYSIS** 9-month questionnaire data 12-month, 24-month questionnaire data 12-month, 24-month PFS and OS data **SECONDARY ENDPOINT ANALYSES**

Trial Design cont.	
Trial design	To reduce confounding in the comparison with COSTAR, all questionnaires would ideally be posted to patients at home with paid postage to return once filled in. Electronic "delivery" of patient-reported outcomes and integration of data collection with routine data collection at the proton centres will be further discussed and agreed.
Eligibility	As per COSTAR but to also include salivary gland tumours of the submandibular gland. **Main Inclusion criteria:** Age >18 years; WHO PS 0-1; Histologically confirmed major salivary gland tumour pT1-4, N0-3, M0 requiring post-operative adjuvant radiotherapy. **Main Exclusion criteria:** Previous head and neck radiotherapy; Pre-existing gustatory dysfunction (anosmia, ageusia); Need for chemotherapy
Primary end point	Patient reported taste dysfunction at 6 months following completion of radiotherapy. Patient reported taste dysfunction will be defined as "a little", "quite a bit" or "very much" problems with your sense of taste as per the EORTC QLQ H&N43 questionnaire Note that the EORTC H&N43 module is selected for consistency with ongoing data collection for H&N patients undergoing proton therapy. Q45 on the H&N43 is identical to Q44 on H&N35 used in COSTAR.
Secondary end points	Describe the key secondary end points • Patient reported taste dysfunction at 12 and 24 months • Other patient reported toxicities at 6, 12 and 24 months following completion of radiotherapy as per EORTC HNQ43. • Overall QoL at 6, 12 and 24 months • PFS at 6, 12 and 24 months
Sample size	• What is the proposed sample size? - 100 IMPT patients • Summarise the statistical basis of the sample size and concept(s) used - Total sample size of patients undergoing IMPT should be sufficient to provide informative non-comparative data (e.g. prevalence of taste dysfunction in that group). With 100 patients, the proportion of patients reporting taste dysfunction could be estimates to within +/-8%. - In addition, this should provide a sufficiently representative sample to allow for matched 1:1 analysis with the 37 patients from the COSTAR IMRT arm with taste and quality of life outcomes. - Prevalence of taste dysfunction with IMRT arm is 59% at 6 months (COSTAR). It is reasonable to expect that IMPT could reduce that by 50%. A 1:1 comparison with 37 patients in each arm will be adequately powered (alpha 0.05, beta 0.2) to detect a difference between the groups if the prevalence of taste dysfunction in the IMPT arm is approximately 27%
Clinical Trial Unit	• Are you working with a Clinical Trial Unit? If so, which one? - Yes, ICR-CTSU • What statistical advice have you received? - Statistical input from Professor Emma Hall

Trial Design cont.	
Proposed source(s) of funding	• Which funder(s) are you considering? - Commissioning through evaluation (CTE)
Estimate of funding required	• Have you performed cost estimates of your proposed study? - No
Patient and public involvement	
Lay summary up to 200 words (Required)	This study aims to reduce loss of taste after radiotherapy for salivary gland tumours. Loss of taste is really common for people having radiotherapy to the head and neck. This study will tell us whether a new type of radiotherapy (proton beam therapy) is better at preventing loss of taste than the current radiotherapy used. All patients will be offered radiotherapy using proton beam therapy. Patients will need to fill in a questionnaire before starting radiotherapy and again at 3, 6, 12, and 24 months after treatment. We will compare the results with the known rates of taste loss seen with the current standard radiotherapy. Patients with salivary gland tumours who require radiotherapy will be invited to participate and can be referred from any centre in the UK, however the radiotherapy can only be delivered in London or Manchester. The treatment schedule is the same as for standard radiotherapy (daily treatment Monday to Friday over 6 weeks). All questionnaires will be posted to patients at home with paid postage to return once filled in. The trial will treat 100 patients and give them access to a new type of radiotherapy that may help preserve their sense of taste.
Outline of patient and public involvement	• Has patient input to the proposal/trial design been sought? - Yes – we are in discussion with NCRI H&N PPI group. - Dr Gunn has interviewed over 70 patients regarding taste dysfunction during and after RT to the head and neck with universal enthusiasm from patients regarding further research to reduce toxicity. • Is there a plan for PPI involvement in trial design and trial management? - Yes. Patient representative(s) will be invited to join the protocol development group. Links to the TORPEdO trial team at ICR-CTSU and TORPEdO TMG will ensure PPI input to this study benefits from the experience in the RCT setting. Consideration will be given to expanding the role of the PPI subgroup of the TORPEdO TMG (perhaps to a H&N proton studies PPI group) to achieve this.
Intervention & comparison	
RT Quality Assurance	
RTTQA	• Have you discussed your proposed study with the RTTQA group? - Yes; Liz Miles RTTQA Lead

Translational research	
	[Visit http://ctrad.ncri.org.uk/research-support/biomarker-support-network to access CTRad's biomarker and translational research advice]
Have you had translational / biomarker input? If so, from whom?	
Outline of any associated radiobiology, radiogenomics, biomarkers, physics or imaging related research	

General information about your proposal status	
Has the proposal already been submitted for funding? If so, where?	No
If the answer to the previous question is yes, please provide relevant dates and the outcome:	N/A
If the proposal has not been submitted for funding, would you say the proposal is almost ready for funding, can be submitted within 6 months, or at a very preliminary stage?	☒ Almost ready for funding ☐ Can be submitted within 6 months ☐ At a very preliminary stage

Benefits from this PBT clinical trial workshop	
How can we help?	Please list up to three items • Review of endpoints and rationale for non-randomised study in this rare cancer setting • Link to PBT centre • Streamlining data collection with PCOU
What are the challenges?	Please list up to three items • •

Chapter 9 - References

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