Taste Dysfunction Following Radiotherapy to the Head and Neck: A Systematic Review

ABSTRACT

BACKGROUND: An intact sense of taste provides pleasure, supports sustenance and alerts the body to toxins. Head and neck cancer (HNC) patients who receive radiotherapy (RT) are high-risk for developing radiation-induced taste dysfunction. Advances in RT offer opportunities for taste-preserving strategies by reducing dose to the gustatory organs-at-risk.

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

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 seen in ~25% of patients. Taste dysfunction was associated with sequalae including weight loss and reduced quality-of-life (QoL). Taste dysfunction was more common when the oral cavity, and specifically the anterior two-thirds of the tongue, was irradiated, suggesting a dose constraint for taste preservation might be feasible. Proton beam therapy and customised bite blocks reduced dose to the gustatory field and subsequent loss of taste.

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 is limited. 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

HIGHLIGHTS

Taste dysfunction is common, affecting 70-90% of people during radiotherapy with bitter and salt taste qualities affected most severely.

Taste dysfunction typically recovers partially post-radiotherapy but usually there is lingering dysfunction months to years after radiotherapy.

Minimising radiotherapy dose to the oral cavity and, specifically, the anterior two-thirds of the tongue is likely to reduce the risk of taste dysfunction.

Proton beam therapy and bite blocks may help to achieve this risk reduction.

Taste dysfunction is associated with a number of clinically important sequelae, including weight loss, xerostomia and reduced quality of life.

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 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 HPV-positive squamous cell carcinoma of the oropharynx.

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).

Further advances in the delivery of RT using proton beam therapy (PBT), for the first time offers an exciting opportunity to review the literature and summarise what is currently understood regarding dysgeusia following RT to the head and neck; in particular, 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 is feasible.

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.

3. Methods

We conducted a search of Medline, EMBASE and Pubmed for articles reporting on HNC; RT; and taste. Searches were conducted on 10th February 2020. Relevant systematic reviews identified by the search were checked for primary studies meeting inclusion criteria. The search was designed with a modified PICO(S) framework – focusing on the population of people with HNC, the intervention of RT and taste-related outcomes. Study design and comparators were not used to limit the search. 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 done at any time-point following RT.

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 (8). In this meta-analysis the proportion selected from each individual study was that closest to the conclusion of radiotherapy. 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).

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 (9) and the second had no structured protocol (10).

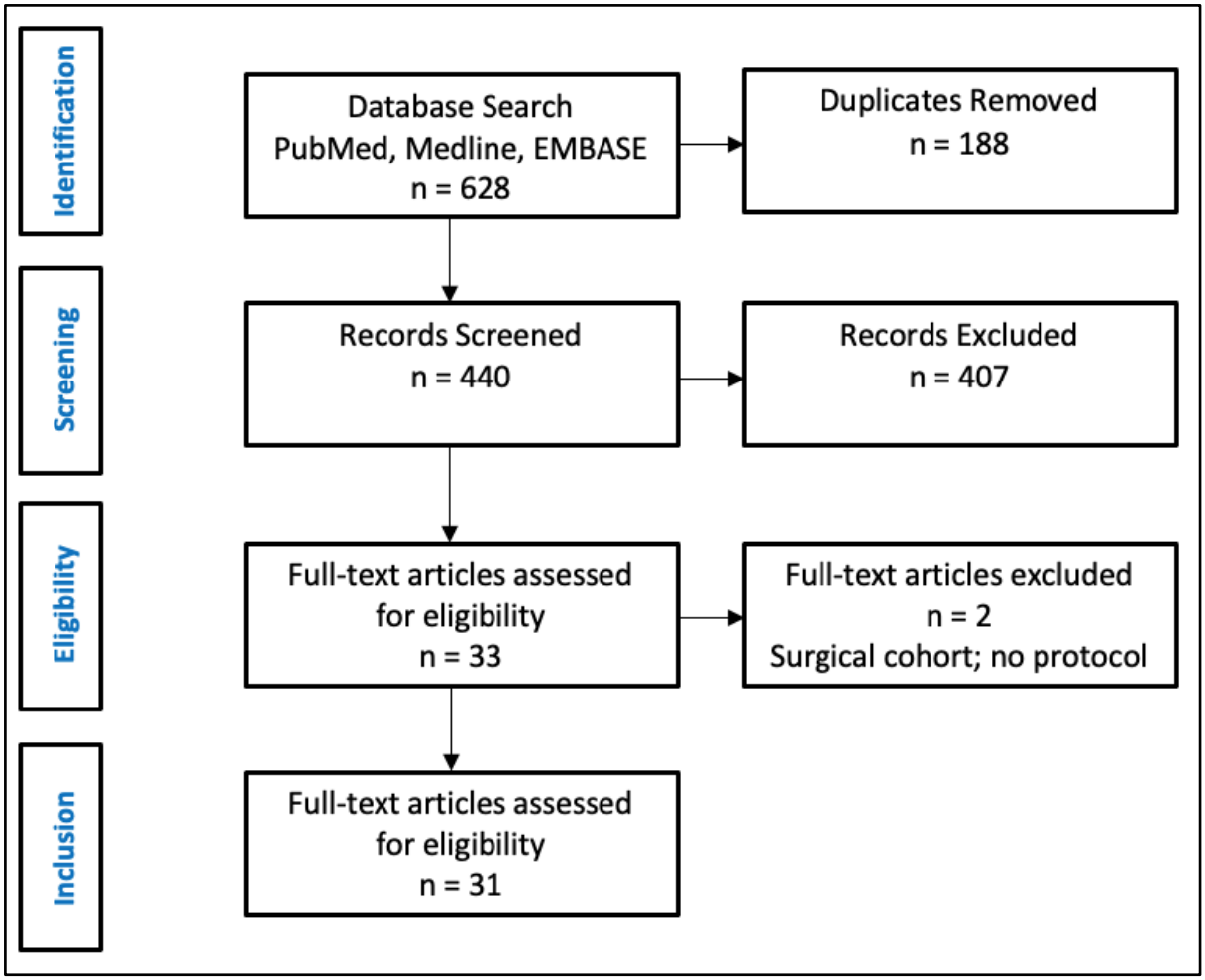


Figure 1. PRISMA Flow Diagram: Search outcomes for 'Taste Function Following Radiotherapy to the Head and Neck: A Systematic Review'

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, patient-reported outcome measures (PROMs) (either via a structured validated questionnaire or, frequently with older studies, with little information about reporting) and clinician-reported outcomes (CROs). 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.

Outcome Measures

Gustatory function was measured using both objective and subjective methods.

Objective Measures Used

Objective methods in this review often used chemo-sensory 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 (11). 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 (11,12).

Four studies used filter paper strips (13,14) or filter paper discs (15,16) which, similar to solution-based testing, present ascending concentrations of the basic taste qualities to assess both detection and recognition thresholds.

Two studies used electrogustometry (EGM) which involves delivering electrical stimuli with ascending amplitude and documenting the threshold at which participants can detect any sensation of taste (13,17).

Table 1 summarises the objective measures 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 (18–20).

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) (21).

In later decades, studies started using the European Organisation for Research and Treatment of Cancer Head and Neck Questionnaire (EORTC-HNQ) (22–24) which assesses a range of toxicities following treatment for HNC, including sense of smell and taste (25). 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 (26).

Two recent studies (27,28) 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 (29).

The common terminology criteria for adverse events (CTCAE) was used as a clinician-reported objective assessment for dysgeusia in 3 recent studies (27,30,31). This tool is simplistic and categorises patients into groups based on whether dysgeusia has led to dietary changes or not.

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

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 (1) **1978**	USA	CS / PC	27	2D-RT	OC, OP, NP, HP, L, HL, SG	PROM OM
Mossman (2) **1979**	USA	PC	51	2D-RT (photons vs neutrons)	LP, OC, ON, OP, SG, other	PROM OM
Mossman (3) **1982a**	USA	CS	13	2D-RT	OP, OC, HP, L, SG, NP	PROM OM
Mossman (4) **1982b**	USA	PC	84	2D-RT (photons vs neutrons)	LP, OC, OP, ON, SG, other	PROM OM
Mossman (5) **1986**	USA	PC / CS	75	2D-RT	A variety of head and neck sites	OM
Schwartz (6) **1993**	USA	CS	38	2D-RT	OC, OP, NP, SG, CN, neck, healthy controls	PROM OM
Fernando (7) **1995**	UK	PC	26	Conventional	L, OC, OP, HP, SC, E	CRO PROM OM
Maes (8) **2002**	Belgium	CS	73	Conventional	OP, OC, HP, SG, NP, other	PROM OM
Zheng (9) **2002**	Japan	PC	40	Conventional (atypical treatment schedule)	HP, L, NP, OP	OM
Shi (10) **2004**	Japan	PC	30	Conventional (atypical treatment schedule)	L, HP, OP, NP, OC, NV	PROM OM
Just (11) **2005**	Germany	PC	24	Not specified	HP, OP, L, SG	OM
Sandow (12) **2006**	USA	PC	13	Conventional	Unclear (OP and SG)	OM
Yamashita (13) **2006a**	Japan	PC	118	Conventional	L, HP, OP, OC, NP, SC, NC, N, lymphoma, other	OM
Yamashita (14) **2006b**	Japan	PC	51	Conventional	NP, OP, HP, other	OM

Kamprad (15) **2008**	Germany	PC	104	3D conformal	Cancer of the head and neck	OM
Mirza (16) **2008**	USA	PC	25	2D-RT	OP, NP, L, SG and other cancer site controls	OM Microscopy
Yamashita (17) **2009**	Japan	PC	52	Conventional	NP, OP, HP, other	OM
Baharvand (18) **2013**	Iran	PC	22	2D-RT	OC, OP, NP, HP, SG, SC	PROM OM
McLaughlin (19) **2013**	USA	CS	92	Not specified	OC, P, L, SC, other	PROM OM
Pavlidis (20) **2015**	Germany	PC	20	2D-RT	HP, L, OP, SG	OM Microscopy
Riva (21) **2015**	Italy	RC	60	2D-RT, IMRT	NPC and healthy controls	PROM OM
Romesser (22) **2016**	USA	PC	41	IMRT, PBT	SG	CRO
Sapir (23) **2016**	USA	PC	73	IMRT	OP	PROM
Negi (24) **2017**	India	PC	30	3D-Conformal RT	OC, OP, NP, HP, L	OM
Ihara (25) **2018**	USA	PC	30	Not specified	NP, OP, OC, L, SG, HP, UP	OM
Jin (26) **2018**	China	PC	114	IMRT	OC, NP, SG, L, O, T, NS, Ly, HP, other	PROM
Barbosa da Silva (27) **2019**	Brazil	PC	56	Conventional	OP, OC, HP, NP, SG	PROM OM
Chen (28) **2019**	Taiwan	PC	88	IMRT	OC, NP, OP, HP, L, other	PROM
Dragan (29) **2019**	Belgium	RC	106	IMRT	OC, OP, L, HP	CRO
Feng (30) **2019**	China	PC	60	IMRT	MS, OC, ON, Ly	CRO
Martini (31) **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

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 (32,33). One very early paper reported baseline dysgeusia rates as high as 96-100% (18). 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 (34,35).

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% (21,26–28,32). Those studies that used validated patient-reported questionnaires reported consistent prevalence of around 13-19% (26,28).

While studies went on to assess the impact of possible risk factors (for example smoking, tumour site) on taste dysfunction post-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 (15,16,18,21,33,35–37). 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 post-completion of RT (27,28). 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 (18,22,24,27,28,31,32,38,39), while that of objective acute dysfunction ranged from 52-100% (22,26,32,33,37,40,41). The only two studies that showed substantially lower rates of acute dysfunction either used a customised bite block (0% acute taste loss) (30) or used PBT (5.6% acute taste loss) (31). The most commonly reported peak prevalence was around 70-

90% (18,21,22,28,32,38). The results of the meta-analysis (figure 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 certain percentage experienced worsening function to the extent it could be considered important 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 (27,28). Studies which assessed objective taste dysfunction either during or shortly after radiation found signs of recovery at 2-4 weeks post-treatment (33,40,42). Two studies suggested that recovery is seen in latter weeks of radiation (16,36), 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 (36).

In terms of the extent of recovery, in some studies all participants had recovered taste function within 3-6 months post-completion of RT (27,35,36,39). However, in other studies, there was evidence of persistent taste dysfunction ranging from 23-50%, 1-2 years post-completion of treatment (15,26,32,34).

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 (7,14,23,24,44,45). At 2-3 years, the prevalence of subjective taste dysfunction was 23-53% (14,23,24). 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 (7,18,22,32,33,38,42), although these findings were not universal (34,39,43). Two studies looked specifically at umami and found that it was affected at lower radiation doses (21) and took longer to recover than other qualities (16).

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 fungiform papillae density is highest, was associated with objective acute (36) and late (15,42) taste impairment. Zheng et al (36) 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 (15). 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 oral cavity 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 (33). 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 (40). Lastly, Sapir et al found an association between dose to the oral cavity or anterior tongue ($p<0.05$) and late subjective taste dysfunction (26). This effect persisted following multivariate analysis with adjustment for time after treatment, age, sex and within-subject correlation for both oral cavity ($p=0.005$) 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 oral cavity (39). There were some suggestions the group with direct oral cavity 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 (46). 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 post-completion of RT (26). In 2019, Chen et al reported a mean dose of >50 Gy to the oral cavity was found to be significantly associated with late subjective taste impairment (median follow-up 27 months) (23).

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 (18,20).

One study compared IMRT with conventional RT and found no benefit in terms of patient-reported taste dysfunction. In fact, IMRT was associated with worse ($p<0.05$) objective taste dysfunction for sweet, bitter and salty taste qualities (14).

The only study that looked at the effects of PBT was a small non-randomised cohort comparison in patients with salivary gland tumours (31), which showed that the PBT group received a statistically significantly lower mean dose to the oral cavity 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 (30). Customised blocks were suitable for any patient undergoing radiation involving the nasal cavity, 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 (24). However, on the whole, chemotherapy was mostly found to have no statistically significant impact on taste dysfunction (15,16,22,37,39,45). In one very small study, chemotherapy actually appeared to have a protective effect (47), 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 (23).

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 (22). The following factors, when assessed, were typically found to have no association with taste dysfunction – age, gender, education, smoking, alcohol or prior surgery (22,23,39,40,42,44). 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 (28,45), diminished appetite (32), xerostomia (26) and quality of life (QoL) (22).

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 (28). 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) (45). 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 (32).

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 radiotherapy induced dysgeusia but did not report a comparison group who received radiotherapy but did not develop dysgeusia. As such it is difficult to determine the specific contribution of the single toxicity (22).

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 (32). Satisfaction with care was negatively associated with umami dysfunction in one Japanese study (21). 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 post-RT (13). Typically, these included cells with a longer shape, without nuclei or with multiple nuclei. Videomicroscopy at tissue level also showed a decrease in pore count from pre-treatment to post-treatment (34) and greater alterations in morphology and vascularisation of fungiform papillae (47).

Table 3: Summary of key outcomes from studies included				
Author Year	**Outcomes Measured**	**Time Points**	**Duration of FU post-RT**	**Key Findings**
Mossman (1) **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 (2) **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 (3) **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 (4) **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 (5) **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 (6) **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 (7) **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 (8) **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 (9) **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 (10) **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 (11) **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 (12) **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 (13) **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 (14) **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 (15) **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 (16) **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 (17) **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 (18) **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 (19) **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 (20) **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 (21) **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 (22) **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 (23) **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 (24) **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 (25) **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 (26) **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 da Silva (27) **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 (28) **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 (29) **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 (30) **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 (31) **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;				

5. Discussion and conclusions

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 oral cavity 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 sequelae, including weight loss, xerostomia and reduced QoL

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 oral cavity or in those with nasopharyngeal carcinoma 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 (48).

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 is safe and oncological outcomes are not compromised (49). 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. This is particularly important in the treatment of a unilateral target volumes although with careful application of dose constraints to the contralateral oral cavity OAR, risk of inadvertent toxicity could be mitigated (50).

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 (51), taste testing tablets (52) and non-edible taste strips (12), which were extended to include umami strips (53), and more recently taste strips to detect those patients with low gustatory thresholds and high gustatory sensitivity (54).

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.

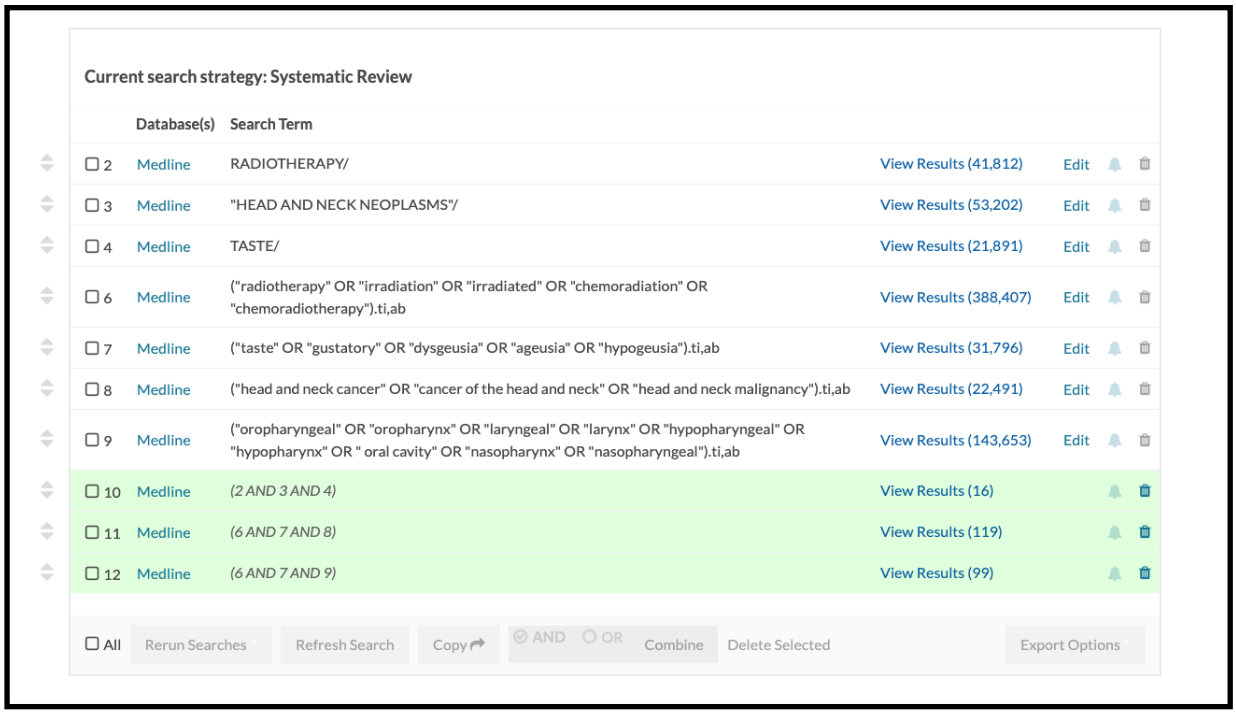
The only PBT study included showed remarkably low doses to the gustatory field and, with this, comparably low rates of taste dysfunction. Unfortunately, the study only looked at acute (within 90 days of start of RT) and CROs (by CTCAE, Grade 2+) which may have poorer sensitivity compared with PROMs or 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. oral cavity; whole tongue; anterior two-thirds of the tongue).

Appendix



Current search strategy: Systematic Review

	Database(s)	Search Term		
2	Medline	RADIOTHERAPY/	View Results (41,812)	Edit
3	Medline	"HEAD AND NECK NEOPLASMS"/	View Results (53,202)	Edit
4	Medline	TASTE/	View Results (21,891)	Edit
6	Medline	("radiotherapy" OR "irradiation" OR "irradiated" OR "chemoradiation" OR "chemoradiotherapy").ti,ab	View Results (388,407)	Edit
7	Medline	("taste" OR "gustatory" OR "dysgeusia" OR "ageusia" OR "hypogeusia").ti,ab	View Results (31,796)	Edit
8	Medline	("head and neck cancer" OR "cancer of the head and neck" OR "head and neck malignancy").ti,ab	View Results (22,491)	Edit
9	Medline	("oropharyngeal" OR "oropharynx" OR "laryngeal" OR "larynx" OR "hypopharyngeal" OR "hypopharynx" OR " oral cavity" OR "nasopharynx" OR "nasopharyngeal").ti,ab	View Results (143,653)	Edit
10	Medline	*(2 AND 3 AND 4)*	View Results (16)	
11	Medline	*(6 AND 7 AND 8)*	View Results (119)	
12	Medline	*(6 AND 7 AND 9)*	View Results (99)	

All | Rerun Searches | Refresh Search | Copy | AND OR | Combine | Delete Selected | Export Options

Appendix A. Example search strategy

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Disclosure

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