A feasibility study to investigate taste changes and their association with genes and dietary behaviour in patients with head and neck cancer

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Summary:

Patients undergoing treatment for head and neck squamous cell cancer (HNSCC) experience significant changes in or loss of taste, often leading to poor oral intake, weight loss and malnutrition, which impacts treatment outcomes and quality of life. The degree of changes in taste and recovery times differ between individuals with the causes not fully understood. This project aims to assess the feasibility of the proposed study design to determine a patient's individual taste status at baseline and how treatment impacts on their taste and dietary behaviour post treatment. This data will be used to inform a larger study to identify possible genetic markers for these individual variations.

Introduction

Patients with head and neck squamous cell cancer (HNSCC) receiving radiotherapy and/or chemotherapy often experience loss or alteration of taste (Ackerman, Laszlo, Provisor, & Yu, 2018). This altered taste can affect patients' oral intake so severely that it has been reported as a primary reason for requirement of tube feeding (Brown et al., 2017). Taste recovery post treatment varies and can take up to 6 months, although for some the taste changes can be long lasting (Negi et al., 2017). A patient's recovery time of different taste modalities (i.e. sweetness and bitterness) also varies (Deshpande et al., 2018; Irune, Dwivedi, Nutting, & Harrington, 2014; Nolden, Hwang, Boltong, & Reed, 2019). It is unknown what causes these individual variations.

An individual's inborn "taster status" is primarily determined by genetic variation within the bitter taste receptor gene *TAS2R38*, which determines the ability to perceive a specific bitter substance phenylthiocarbamide (PTC) (Bufe et al., 2005). Approximately 30% of the population find PTC tasteless ("non-tasters"), whereas the remaining find it extremely bitter ("tasters" or "supertasters") (Hwang et al., 2016). This taster status has been shown to affect the perception and consumption of food in healthy populations (Tepper, 2008). However, the association of the genetically predisposed taster status with the changes in taste and diet experienced by cancer patients has never been investigated. By understanding the role of genetics in influencing taste changes in this population, dietary counselling and interventions can be targeted more appropriately to support optimal nutrition outcomes.

This study will be the first to investigate changes in taste perception and their association with genes and dietary intake. Feasibility data from this study will enable future identification of novel predictors for taste alterations through larger studies. If we demonstrate an association between taster status and taste or dietary changes after cancer treatment, taster status could be integrated into pre-treatment screening, as it is a phenotype that can be easily determined by taste response to PTC or *TAS2R38* genotype. This will help guide clinicians on how to prepare patients for side effects in relation to taste and the impact this may have on their nutrition, as well as provide additional data to inform decision-making around the insertion of prophylactic feeding tubes pre-treatment.

The expected outcomes from this study will be to demonstrate the feasibility of the study design and procedures to inform a full-scale study with funding being sought from larger project grant applications. The impact of this research will assist both patients with HNSCC and their healthcare professionals. Loss or altered taste perception adversely impact patients' dietary intake, nutritional status and quality of life, with malnutrition adversely impacting on clinical outcomes and survival (Ackerman et al., 2018). Understanding the consequences of taste changes post treatment will help to assist patients to prepare for these treatment side effects, inform interventions and thus improve quality of life in survivorship.

As the largest cancer care service in Queensland, the Metro North Hospital and Health Service (MNHHS) provides care to: the MNHHS population (accounting for approximately 75% of patients), a regional population catchment, as well as further afield for highly complex cases (i.e. throughout QLD, northern NSW and the NT). Head and neck cancers are one of the key tumour streams managed by MNHHS with >600 patients attending the Combined Head and Neck Clinic per year.

In addition, HPV-associated oropharyngeal HNSCC incidence continues to rise, and thus the side effects and dysgeusia from cancer treatment will continue to affect an increasingly younger population (Mahal et al., 2019).

Local research at the Royal Brisbane and Women's Hospital (RBWH) has demonstrated that 86% of patients undergoing radiotherapy experience significant taste changes during treatment, with one third still experiencing dysgeusia three months post treatment and beyond (Moroney et al., 2017). Taste alterations have also been found to be one of the main reasons patients commence tube feeding, reported by 45-53% in weeks 2-3, and by 16-22% in weeks 6-7 (Brown et al., 2017). Anecdotal clinical experience has found that one of the most common questions patients ask health professionals is "When will my taste come back?". This is difficult to answer given the lack of evidence and individual variations that occur. Thus, this research will help to understand taste changes and recovery time post cancer treatment to help inform patient expectations and target interventions, as well as help to explain why different people are affected by taste alterations in different ways, as there may be a genetic pre-disposition.

Aims

1) To assess the feasibility of the proposed study design including: feasibility of recruitment, consent and retention; fidelity to study procedures; acceptability of assessment tools; and period of follow-up required (by determining the proportion of patients whose taste returns to normal during study period).
2) To explore preliminary outcomes by describing changes in different taste modalities in patients with HNSCC post-treatment and how these may impact on dietary intake and nutritional status
3) To explore if there is any potential relationship between pre-treatment taste function or the genetically predisposed "taster status" and changes in taste post treatment and/or dietary intake and nutritional status

Method

Study Design

The study design is a prospective longitudinal observational cohort study. Patients meeting the eligibility criteria will be sequentially identified during the study period for recruitment into the study. All outcomes will be quantitative measures and collected prospectively by the research team.

Subjects/Patients

Study population: The study population will include patients with oral cavity, oropharyngeal or hypopharyngeal HNSCC planned to receive curative intent definitive radiotherapy or chemoradiotherapy at RBWH. Patients will be identified from the Combined Head and Neck Cancer multidisciplinary clinic at the RBWH during the planned study period January 2021 to June 2021.

Recruitment: Potential patients will be identified from the weekly clinic list for the Combined Head & Neck Clinic at RBWH and their oncologist will be notified. At pre-treatment radiation or medical oncology outpatient appointments (approx. 2-4 weeks pre-treatment) the

participant information consent form (PICF) will be provided by the oncologist to all patients eligible for the study. The Research Assistant will subsequently contact the patient by phone to determine if the patient is interested in the study and/or to answer any questions. If the patient would like to proceed the research assistant will obtain written consent.

Inclusion: All patients aged > 18 years undergoing curative intent definitive radiotherapy or chemoradiotherapy (unilateral or bilateral) for oral cavity, oropharyngeal or hypopharyngeal HNSCC at RBWH who can provide written informed consent. Participants will also need to have appropriate technology (e.g. computer/tablet/smart phone with internet connection) to support telehealth sessions and completion of the online dietary assessments.

Exclusion: Age <18, unable to communicate in English, inability to provide written informed consent, sensory (taste) dysfunction of other medical causes (including history of traumatic brain injury, history of neurological disorders, history of middle ear surgery/infection) and current smoker.

Sample size: As this is a pilot feasibility study no formal sample size calculation will be completed. Patients that consent to participate within the six months recruitment period will be included. With over 600 patients attending this clinic per year, there are usually at least four patients per week who are expected to meet the inclusion criteria. Based on a conservative 50% consent rate from these eligible patients, we would expect to recruit approximately 2 patients/week and therefore achieve a practicable target of approximately 50 patients over a 6-month period. This will be adequate to assess feasibility of the proposed study.

Measurements

Anthropometry & Nutritional Status: Weight will be measured using standard digital weighing scales (kg); height will be measured using a stadiometer (m), and nutritional status will be assessed using a validated nutrition assessment tool (Patient Generated Subjective Global Assessment - PGSGA).(Jager-Wittenaar & Ottery, 2017).

Taste & Taster Status: Taste perception will be collected using the Monell Flavor Quiz,(Douglas et al., 2018) which contains taste stimuli of sucralose (sweet), sodium chloride (salty), citric acid (sour), and PTC (bitter). Participants will be instructed to rate their perceived intensity and liking on a seven-point scale as well as completing a self-assessment about their sensory responses using an online questionnaire (www.monell.org). Patients' taster status will be determined by their taste scores of PTC.

Dietary intake: Dietary data (including any enteral nutrition intake) will be collected using the Automated Self-Administered 24-hour Recall (ASA24-2016 Australia) to determine total energy intake and macronutrient intakes.(Subar et al., 2012).

Dysgeusia toxicity: Graded using CTCAE v5 (2017)

Acceptability of Assessment tools: This will be assessed using a 0-10 Likert type scale measuring how easy each assessment is to complete.

Interventions / Procedures

All patients will undergo a taste assessment using the Monell Flavor Quiz kits from the Monell Chemical Senses Center (USA) (www.monell.org), following the procedures modified from Douglas et al (2018) outlined below.

This test will be completed a four timepoints – baseline, and then at 1-, 3- and 6-months post radiotherapy treatment completion. Considering the current COVID situation, the taste test will be semi self-administered by patients at home with assistance and guidance from the research assistant via telehealth or virtual clinic appointment methods.

Psychophysical Taste Testing - Taste Test Administration

1. Provide participants with 4 boxes of taste test kits.
2. At the beginning of each test, instruct participants to prepare a bottle/glass of water and an empty cup. Preferably use the same brand of bottled water throughout the duration of all four test tests.
3. Confirm that the patient is comfortable to proceed with the taste test, as they may still be experiencing side effects from treatment that will make it difficult to tolerate oral intake. Inform the participant that they can stop at any point in the testing procedures if they are not comfortable.
4. Instruct participants to go to web page of the online questionnaire via tablet or desktop/Laptop. An individualized link will be provided to each participant via provided email address.
5. Instruct participants that they will be asked to rate both the intensity and quality (e.g., salty, sour, bitter, sweet, or no flavour) of each tastant. Also, inform participants they may not experience all qualities.
6. Explain the testing procedure, as follows:
    a. Rinse your mouth twice with water and spit it out in the empty cup.
    b. Pour all of sample 1 into your mouth and hold it there for 5 seconds before spitting the solution into the cup. Do not gargle or swallow the solution.
    c. Rate the sample's perceived intensity on a scale of 1 to 7, from "Like water" to "Strongest imaginable" and choose a single quality to describe the taste from a list of options including Salty, Sour, Bitter, Sweet, and No Taste.
    d. Afterward, rinse your mouth with water twice before proceeding to the next sample
7. Observe the subject tasting and rating sample 1 (water). If the rating deviates from "Like water" reiterate the questionnaire instructions before allowing the test to proceed.
8. Ensure participants fully finish the questionnaire by checking that the “completion web page” shows up at the end of the testing

Endpoints

Primary Outcome - Feasibility:

- recruitment rates (number of patients consented/number of patients screened)
- consent rates (number of patients consented/number of patients eligible)
- reasons for consent failure
- retention rates

- reasons for attrition
- fidelity to the study procedures
    - ability to complete the online self-administered dietary recall at each timepoint
    - ability to complete the taste testing procedures at each timepoint
    - ability to conduct semi self-administered taste test at home
    - proportion of nutrition assessments (weight and PG-SGA) completed face to face versus at home/virtual clinics
- reasons for non-fidelity to the study procedures
- acceptability of outcome assessment tools used

Secondary Outcomes - Clinical:

- Prevalence of taster status ("taster" vs "non-taster")
- Pre-treatment taste perception scores
- Taste outcomes
    - Changes in taste perception (for each taste modality), including the difference in taste scores between the baseline and a given time point.
    - Taste recovery time (for each taste modality), where the recovery time is defined as the number of days required for taste scores to return to the baseline scores after radiotherapy completion. Maximum follow up period will be 6 months post radiation completion.
    - Proportion of patients whose taste does not recover in 6 months post radiation completion to determine if a longer period of follow up is required in a larger study
- Nutrition outcomes
    - Changes in Dietary intake (Energy kcal/day and macronutrients g/day), including % differences in dietary intake between the baseline and a given time point
    - Weight change (kg and % weight loss), between baseline and a given time point
    - Nutritional status change (PGSGA category), between baseline and a given time point
    - Nutritional risk change (PGSGA score), between baseline and a given time point
- Clinical outcomes
    - Completion rates of prescribed radiotherapy dose
    - Completion rates of prescribed chemotherapy regimen
    - Dysgeusia toxicity grades at each timepoint

Study plan

Recruitment

Potential patients will be identified from the weekly clinic list for the Combined Head & Neck Clinic at RBWH and their Oncologist will be notified. At pre-treatment Radiation or Medical Oncology outpatient appointments (approx. 2-4 weeks pre-treatment), the participant information consent form (PICF) will be provided by the treating Oncologist to all patients eligible for the study. The Research Assistant will subsequently contact the patient by phone to determine if the patient is interested in the study and/or to answer any questions. If the patient would like to proceed the research assistant will obtain verbal consent and then arrange an initial appointment to complete baseline assessments where written consent will also be obtained.

Pre-treatment/Baseline

- Patients who consent to participate in the study will meet with the Research Assistant at a suitable/convenient time prior to their treatment commencement (or on Day 1 of treatment if not feasible prior to then)
- Height and weight will be measured by the Research Assistant
- Nutritional status will be assessed by the Research Assistant using the PG-SGA which involves an interview with the patient to discuss weight history, diet intake, nutrition impact symptoms, functional level and completion of a physical assessment of fat/muscle stores.
- Dysgeusia toxicity will be assessed by the Research Assistant using the CTCAE
- Dietary intake will be completed by the patient using the online Automated Self-Administered 24-hour Recall (ASA24-2016 Australia)
- Taste testing will also be completed by self-administration at home with assistance from the Research Assistant following procedures outlined previously. Prior to completing the taste assessments, the Research Assistant will ensure the patient is comfortable to proceed with the assessment, as they may still be experiencing side effects from their cancer or their treatment that may prevent them from tolerating anything orally.
- Acceptability of outcome assessment tools used will be completed with assistance from the Research Assistant
- Demographic and clinical data from the medical chart including; age, sex, primary cancer site, TNM stage, P16 status, histology, treatment details (including any previous surgery and the chemotherapy and radiotherapy prescriptions – including the planned radiation dose to the parotid salivary glands and tongue)

1-month post radiotherapy

- All outcomes will be re-assessed as above including; weight, PGSGA, 24-hour recall, dysgeusia toxicity grade, taste testing and acceptability of outcome assessment tools
- Radiotherapy and chemotherapy treatment compliance will also be recorded from medical chart
- Radiotherapy dose received to the tongue and the parotid salivary glands will be recorded from medical chart
- Total chemotherapy dose received

3-months post radiotherapy

- All outcomes will be re-assessed as above including; weight, PGSGA, 24-hour recall, dysgeusia toxicity grade, taste testing and acceptability of outcome assessment tools

6-months post radiotherapy

- All outcomes will be re-assessed as above including; weight, PGSGA, 24-hour recall, dysgeusia toxicity grade, taste testing and acceptability of outcome assessment tools

Wherever possible the appointments for the study outcome assessments will be completed face to face for anthropometric measurements and via video communication tools for taste measurements, with appointments coordinated alongside any existing medical appointments at the hospital.

To ensure high levels of inter- and intra-rater reliability, the trained dietetic research assistant will be responsible for both the baseline measures at recruitment and the outcome measures at each of the follow up timepoints (1-, 3- and 6-months post radiotherapy completion).

Data analysis

Raw data collected on paper forms will be stored in a lockable cabinet in the Department of Nutrition and Dietetics with access only by the named researchers carrying out data entry and analysis. This and other relevant data from electronic hospital files will be entered into REDCap (hosted on secure Queensland Health servers), to which only the named researchers will have access by unique username and password. This database will be set up using specific user permissions. Taste data collected via the online questionnaire will be automatically entered into REDCap hosted at the University of Pennsylvania with access only by named researchers carrying out data analysis. At the end of data analysis, all data will be deidentified and stored as per RBWH established data management protocols. Data analysis will be performed using an appropriate statistical package such as SPSS, R or Stata.

Descriptive statistics and narrative reporting will be used to describe feasibility outcomes. Analyses will be done separately for each taste modality (sweet, bitter, sour, salty) for the comparison of the changes in taste perception over time and for the recovery time between modalities. To investigate the effect of pre-treatment taste and taster status on post-treatment changes in taste, descriptive and bivariate analyses will be performed on pre-treatment taste scores with changes in taste perception, dietary intake and recovery time. Any large effects of taster status may suggest a genetic influence on post-treatment changes in taste perception. Statistical modelling such as mixed effects models for changes in taste perception and survival analysis for recovery time may be considered depending on final sample size achieved during the recruitment period. Covariates of age, sex and other clinical values of interest (e.g. enteral nutrition intake, radiation dosage to parotids, addition of concurrent chemotherapy, P16 status etc.) will be considered for all analyses to adjust for any confounding effects.

Ethical Issues

This research will be reviewed by the Royal Brisbane and Women's Hospital Human Research Ethics Committee. Any adverse events will be immediately reported to the HREC.

The Research Assistant undertaking recruitment and assessment will be independent to the patients' healthcare team and will not be involved in the decision-making or care of the patient during their oncology treatment. The patients' decisions to participate or not participate in the study will not affect the care that they receive at the RBWH.

The Taste Test kits are purchased through the Monell Center, USA, who are an independent, non-profit scientific institute dedicated to interdisciplinary basic research on the senses of taste and smell. The Research Team have no conflicts of interest to declare in the use of this equipment.

It is acknowledged that measuring taste using a whole mouth method may be challenging in this population due to side effects of the cancer or treatments in the mouth and throat, however this risk will be mitigated by ensuring the patient is comfortable to proceed at each timepoint. Any concerns raised by the patient during the study assessment appointments in relation to their medical condition will be escalated to their treating team for appropriate medical management.

The selection of patients will be open to all patients meeting eligibility criteria and will not be biased. All patients will receive a Patient Information and Consent Form (PICF) to outline the study details and information and they will be given ample opportunity to ask questions before deciding whether to participate or not. Informed consent will be completed verbally over the phone and subsequently written consent will be obtained at their baseline assessment appointment.

The management and storage of data will be completed as per the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007) guidelines. Participant confidentiality will be assured with all consenting patients assigned a unique identify code that will be recorded in a separate password protected database with any other identifiable information and saved on secure Queensland Health servers. All data entered onto the ASA24 system does not contain any identifying information. Each participant is provided with a username and encrypted password for access to the system. All data will be deidentified for analysis and publications/report writing/presentations.

Participation in the study is entirely voluntary and patients will not receive any payment or reward for participation. If study appointments are scheduled on days they are not scheduled to be at the hospital for other routine medical appointments, they will be offered car parking vouchers.

Resource Requirements

Schedule of Research Plan

	July 2020	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	March 2021	April 2021	May 2021	June 2021
Literature review												
Protocol & Ethics												
Recruitment												
1 month												
3 months												
6 months												

	July 2021	Aug 2021	Sept 2021	Oct 2021	Nov 2021	Dec 2021	Jan 2022	Feb 2022	March 2022	April 2022	May 2022	June 2022
Recruitment												
1 month												
3 months												
6 months												
Data Analysis												
Write Up												

Research Funding

Resource	**Details**	**Estimated Cost**
0.2FTE HP3 6 months Dietitian Backfill for PI	Literature review, study development, ethics and governance applications	$11,568
0.2FTE HP3 12 months Dietitian Backfill for PI or RA	Recruitment and assessment of Patients	$23,136
0.2FTE HP3 6 months Dietitian Backfill for PI	Analysis and write up	$11,568
Consumer fees	Research design meeting attendance	$ 500
Participant costs	Car parking for visits at 1- and 6-months when unlikely to have other hospital appointments (2 per patient for 1.5hrs = $36)	$1,800
Administration costs	Mailing taste kits and dietary questionnaires if required and phone call costs and/or stationary to coordinate appointments	$1,000
Monell Flavor Quiz kits)	4 kits per patient ($37AUD each) = 200 total plus shipping fees	$7,300 $ 500
TOTAL		**$57,372**

Supervision

As this study is part of a RBWH Post-Doctoral Research Fellowship – supervision to the Principal Investigator will be provided by two members of the research team – A/Prof Brett Hughes and A/Prof Judy Bauer. Bi-monthly meetings will be arranged to monitor and support progress. Quarterly updates will also be provided to the Executive Director of Research at RWBH.

Dissemination of findings

A summary of the research findings will be offered and provided to all research study participants if they indicate an interest in the results when they consent to participate.

The research findings will be presented to key stakeholders at the RBWH which will include: the multidisciplinary members of the Combined Head and Neck Clinic; as well as other interested staff groups in the health sector through in-service programs (e.g. nursing staff, dietitians, and other allied health professionals working in Cancer Care Services), and wider community groups such as the Cancer Council Queensland Head and Neck Cancer Patient Support Group.

The research findings will be presented at suitable local and national forums (e.g. annual Herston Health Care Symposium, Cancer Care Services Research Forums and Annual Symposium), and abstracts submitted to relevant national conferences such as the Australia & New Zealand Head and Neck Cancer Society and the Clinical Oncological Society of Australia. The results of this study are also planned to be published in a peer-reviewed journal.

This will be the first study examining the influence of taste changes on dietary intake among patients with head and neck cancer and the role of taster status. As a pilot study, the results will inform the design of larger, fully powered trials to investigate the potential role of genetics in pre-determining taste outcomes during cancer treatment.

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