**Development and Validation of Dysgeusia Grading Scale
for Patients with Head and Neck Cancers
Treated with Intensity-Modulated Radiation Therapy: A Research Protocol**

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1. Background of the study

Head and neck cancers (HNC), which includes the lip, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx cancer, represent 5.3% of all new cancers worldwide in 2017. In terms of mortality, 507 000 deaths due to HNCs occurred, representing 5.3% of all cancer deaths. There was an observed decrease in the worldwide incidence of laryngeal and nasopharyngeal cancers in the past three decades. In contrast, incidence of oro/hypopharyngeal, lip, and oral cavity increased. This is attributable to the increasing incidence of Human Papilloma Virus (HPV)-associated HNC, in addition to previously established risk factors like tobacco smoking and alcohol consumption. [1]

Radiotherapy plays an integral role in the multimodality treatment of HNC, both in the early and locally advanced stage. However, delivering radiation dose accurately with minimal toxicity poses a great challenge. In the past few decades, several advanced radiotherapy techniques, including three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy, and stereotactic body radiotherapy (SBRT) have been developed to increase the conformal degree of target areas as well as the radiation dose, and to decrease the toxicity to normal organs. In the study of Van Gestel et.al [2] which administered IMRT in patients with early and locoregionally advanced HNC patients, IMRT resulted in acceptable acute toxicities like dermatitis, and mucositis. And after a median follow up of 18.7 months, late toxicities like xerostomia, fibrosis of the neck, dysphagia (1 patient needed a permanent feeding tube), and bone and teeth problems were observed. Of note, there was documented taste alteration in 14% of patients treated with IMRT.

Dysgeusia, a side effect of radiotherapy documented in various publications with differing incidence, is a generic term used to denote alteration in taste perception which can be described as any of the following: ageusia or the loss of taste functions of the tongue, cacogeusia which is the unpleasant taste that does not originate from food or beverage, hypogeusia means decreased ability to taste, parageusia or abnormal sense of taste, and phantogeusia which is the continuous abnormal taste in the mouth, usually bitter or metallic. [3] Rose-Ped et. al reported taste alteration in 90% of subjects who have undergone RT or chemoradiotherapy. Specifically, 54% suffered ageusia, 13% had hypogeusia and 33% had dysgeusia. [4] Similarly, Schwartz et al. reported a 93.3% prevalence rate of dysgeusia in irradiated HNC patients. Dysgeusia was reported to manifest prior to or as early as 3–4 weeks after starting RT. Furthermore, it can be precipitated by doses as low as 30 Gy. It is frequently reversible with noted taste improvements occurring as early as 8 weeks from the start of RT although it has been noted to persist beyond 1 year in some subjects and particularly after higher RT doses. [5]

Previous studies about severity of taste alteration employed objective measurements like solution- based testing (e.g. three- drop method, filter paper strips/ discs method) which employed 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). Several studies used electrogustometry (EGM) which involves delivering electrical stimuli with ascending amplitude and documenting the threshold at which participants can detect any sensation. Subjective measures were also used to document taste alterations. Example of which is 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). Another tool is the European Organization for Research and Treatment of Cancer Head and Neck Questionnaire which assesses a range of toxicities following treatment for HNC, including sense of smell and taste. The Common Terminology Criteria for Adverse Events (CTCAE) is a similar tool which is used as a clinician-reported objective assessment for categorizing patients into groups based on whether dysgeusia has led to dietary changes or not. Lastly, the Chemotherapy- induced Taste Alteration Survey (CiTAS) consisting of an 18-item scale assessing four dimensions of taste including decline in basic taste; discomfort, phantoguesia / parageusia and generalized alterations of taste.[6]

2. Objectives

2.1 General Objectives

The objective of this study is to develop and validate a dysgeusia grading scale to assess patients with head and neck cancers treated with IMRT.

2.2 Specific Objectives

Specifically, this study aims to:

1. Determine the validity of the Dysgeusia Grading Scale in terms of:
 - 1.1 Content validity
 - 1.2 Convergent validity using the CiTAS as reference scale.
 - 1.3 Divergent validity using MDASI- HN.
 - 1.4 Concurrent validity using the Xerostomia Inventory.
2. Determine the reliability of the Dysgeusia Grading Scale in terms of:
 - 2.1. Internal consistency (Cronbach's alpha)
 - 2.2. Test-retest reliability

3. Determine the sensitivity of the scale in terms of responsiveness which compares the scores before radiotherapy and after 15 fractions of radiotherapy.

4. Pilot test and including the factor loading by factor analysis

3. Ethical considerations

This study will be reviewed by the University of Santo Tomas Hospital-Research Ethics Committee (USTH-REC) for approval. It will be conducted in accordance with the applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice Guidelines (GCP), National Ethical Guidelines for Health and Health- Related Research 2017 (NEGHHR 2017).

3.1 Conflict of interest

Dr. Michael A. Mejia is an active consultant in the Benavides Cancer Institute Department of Radiation Oncology and serves as the chair of the Department of Radiation Oncology.

All investigators do not have commercial nor financial affiliations

3.2 Privacy and Confidentiality

All the data from the patients shall be kept private and confidential. Only the authors shall have access to the names of the patients and the data being presented. Subjects' names will be replaced by alphanumeric codes to protect their privacy. All soft copies of data will be stored in an external hard drive (password protected) dedicated for the study. Hardcopies of data will be stored in a locked cabinet dedicated for research inside Benavides Cancer Institute. All data will be for safekeeping for up to 5 years. If deemed to be no longer needed, data shall be

permanently deleted from the hard drive and hardcopies shall be shredded before disposal. The following identifiers of the individual will be removed:

(A) Names

(B) All geographic subdivisions smaller than a state, including street address, city, ZIP code

(D) Telephone or cellphone numbers

(F) Email addresses

3.3 Informed Consent Process

For face-to-face administration of the survey, invited participants will be given a printed consent form which is written in both English and Filipino incorporated in one form. If the face-to-face survey is conducted during the current pandemic, appropriate institutional safety protocols will be strictly observed. A physical copy of the Certificate of Consent will be signed by the investigator, participant, and impartial witness (i.e., companion of patient).

If a respondent will be unable to answer or submit the questionnaires personally, they have the option to answer and submit it through email provided that a consent form will be signed personally so that patients are well-informed and that their contact number will be used to track their completion of the questionnaires. An impartial witness should also be present.

For patients with visual or writing difficulties, their legally authorized representative or primary caregiver may give consent on their behalf should they be unable to. The principle of autonomy and respect for persons will be always observed during the study. Any participant that shows any expression of dissent will not be pressured to join. Investigators serve only as the study investigators and not

the participant's attending physician. Investigators are likewise prohibited from obtaining the consent of their own private patients.

4. Materials and Methods

4.1 Study Design

4.1.1. This is a psychometric, methodologic design study that assesses taste alteration in patients with head and neck cancers treated with IMRT using a newly- developed Dysgeusia Grading Scale that will be subsequently validated against the Chemotherapy- Induced Grading Scale (CiTAS), M. D. Anderson Symptom Inventory-Head and Neck Module (MDASI-HN) English or Filipino Version, and Xerostomia Inventory. This study comprises three phases: conceptualization phase, preliminary item evaluation phase, and scale refinement and field-testing phase.

Phase 1: Conceptualization and Questionnaire Development Phase

This phase involves identifying the construct to be measured, determining the type of scale, and development of an item pool that encompasses possible taste alteration experienced by patients undergoing radiotherapy. The item pool was generated after reviewing pertinent literature, theories, and available questionnaires for taste alteration used in previous studies assessing dysgeusia in cancer patients. A 31- item Dysgeusia Grading Scale was generated on a 4- point Likert scale with 1 corresponding to "not at all", and 4 corresponding to "very much".

Phase 2: Preliminary Item Evaluation Phase

During the second phase, the 31-item scale was evaluated by content experts composed of two radiation oncologists with specialization in head and neck cancers, two oncology nurses with expertise in managing cancer patients treated with radiotherapy, one professional chef who is knowledgeable about the complexity of taste perception and food preparation, and a nutritionist- dietician. The scale was evaluated using a 4-point Likert scale with 1 corresponding to “strongly correlated to the study” and 4 corresponding to “not correlated at all”. An item- content validity index (I-CVI) was done and items with I-CVI less than 0.78 were omitted. After initial evaluation, the number of items was reduced to 28 after items with low relevance was removed.

Another content validation will be done to the 28- item Dysgeusia Grading Scale. After evaluation, item- and scale- content validation indexes (I-CVI and S-CVI) will be computed. From there, items with low relevance will be removed and the scale will be revised according to the comments of the experts.

Phase 3: Scale Refinement, Pilot and Field-Testing Phase

The last phase of instrument development involves pilot testing of the proposed scale. The revised grading scale will be administered to a sample size corresponding to three times the total number of items of the scale. Respondents will be asked to answer the revised Dysgeusia Grading Scale, CiTAS, MDASI-HN, and Xerostomia Inventory. The results of CiTAS and MDASI- HN will be used to evaluate the convergent and divergent validity respectively, which are both components of construct validity and are used to evaluate internal consistency. Concurrent validity will be tested against the Xerostomia Inventory. Respondents will also be asked to

comment on the structure of the grading scale including the font size, style, and if they had trouble understanding certain items. A preliminary reliability score will be obtained from the pilot study.

In case of planned induction chemotherapy, baseline testing will be done before the first cycle of chemotherapy. The questionnaires will also be administered before the 1st session of radiotherapy, after the 15th day of radiotherapy, and on the last day of radiotherapy. Participants not treated with chemotherapy will not be required to answer the CiTAS. Sensitivity of the scale will be determined in terms of responsiveness which will require the participants to answer the Dysgeusia Grading Scale on the 15th session of radiotherapy since the onset of radiotherapy-induced taste alteration is approximately 2-4 weeks after the start of radiotherapy. While for the test-retest reliability, the Dysgeusia Grading Scale will be administered twice before the start of radiation treatment (i.e., during initial patient consultation and before start of the first radiotherapy session) with an interval of three to five days to minimize bias.

The revised Dysgeusia Grading Scale will then be subjected to field testing to a sample size corresponding to five to ten times the total number items of the scale. Respondents will also be asked to answer the other questionnaires following the same schedule in the pilot testing.

Questionnaires	Time				
	Before Induction Chemo	Initial Consultation	1 st Day of Radiotherapy	15 th Day of Radiotherapy	Last Day of Radiotherapy
Dysgeusia Grading Scale (25 participants for test- retest reliability)		/	/	/	/
Dysgeusia Grading Scale (with Induction Chemo)	/		/	/	/
Dysgeusia Grading Scale			/	/	/
CiTAS			/	/	/
MDASI-HN			/	/	/
Xerostomia Inventory			/	/	/

Table 1: Schedule of Questionnaire Administration for Pilot and Field Testing

4.2 Inclusion Criteria

4.2.1. 18 years and older

4.2.2. Patients with non-metastatic nasopharyngeal (Stage I-IVA) or oropharyngeal cancer (Stage I-III)

4.2.3 Treated with definitive radiotherapy with or without concurrent chemotherapy or induction chemotherapy

4.2.3. Undergoing IMRT (with or without chemotherapy)

4.2.4. Able to communicate and make decisions

4.4.5. Fluent in English (at least Grade 6 level)

4.5 Exclusion Criteria

4.5.1. Those who underwent tube feeding and total parenteral nutrition

4.5.2. Those with metastatic head and neck cancers who received palliative radiotherapy

4.5.3. Those who are unable to provide competent consent (e.g., patients with cognitive problems, unable to communicate)

4.5.4 Those with poor performance status (i.e., ECOG $\geq$ 3) who are more likely to have treatment interruptions due to intolerance to treatment.

4.6 Sampling Design and Size

The researchers will use purposive sampling to enroll head and neck cancer patients, specifically those with non-metastatic nasopharyngeal and oropharyngeal cancer treated using IMRT at the University of Santo Tomas Hospital. After content validation by experts, the revised Dysgeusia Grading Scale will be subjected to pilot testing and the sample size is three times the total number of items the scale. After data analysis of the pilot testing, the grading scale will be further revised, and field testing will be administered wherein the sample size is five to ten times the total number of items included in the final version of the Dysgeusia Grading Scale. For the test-retest reliability, the Dysgeusia Grading Scale will be administered twice (i.e. during initial patient consultation and before start of the first radiotherapy session) in 25 participants included in the field testing. The participants in the field testing will be subjected to simple random sampling to determine the 25 participants who will answer the scale twice.

4.7 Data Collection

Subjects will be asked to complete an informed consent form before answering the research instruments. If a respondent will be unable to answer or submit the

questionnaires personally, they have the option to answer and submit it through email provided that a consent form will be signed personally so that patients are well-informed and that their contact number will be used to track their completion of the questionnaires. The online questionnaires should be completed and submitted not more than 7 days after the last session of radiotherapy. Clinical information will be collected from their medical records.

4.8 Research instruments

4.8.1. Dysgeusia Grading Scale

A 31- item questionnaire was developed by the investigators encompassing taste alteration symptoms that may be experienced by patients treated with radiotherapy to the head and neck area. The item pool was generated after reviewing pertinent literature, theories, and available questionnaires for taste alteration used in previous studies assessing dysgeusia in cancer patients. Items are evaluated on a 4-point Likert scale with 1 corresponding to “not at all”, and 4 corresponding to “very much”.

4.8.2. Chemotherapy-induced Grading Scale

The Chemotherapy- induced Taste Alteration Survey (CiTAS) consists of an 18-item scale assessing four dimensions of taste including decline in basic taste; discomfort, phantoguesia / parageusia and generalized alterations of taste. This will be validated against the result of the Dysgeusia Grading Scale to determine the convergent validity.

4.8.3 M.D. Anderson Symptom Inventory-Head and Neck Module (MDASI-HN) English and Filipino Version

The M. D. Anderson Symptom Inventory–Head and Neck (MDASI-HN) module is a validated patient-reported outcome instrument that provides a brief measure of the symptom distress experienced by HNC patients because of their disease and/or treatment. The MDASI-HN includes questions that measure general cancer symptom burden, symptom burden specific to HNC, and the degree to which symptoms interfere with everyday life. The MDASI-HN is a 28-item questionnaire which is scored using a 0–10 response scale, with 0 indicating “not present” and 10, “as bad as you can imagine’. A Filipino version of this scale has been validated and this can be used by patients who are more comfortable in using this language.

4.8.4 Xerostomia Inventory

The Xerostomia Inventory (XI) is an 11-item summated rating scale which combines the responses to 11 individual items into a single continuous scale score which represents the severity of chronic xerostomia; higher scores represent more severe symptoms. Respondents will choose using a 5- point Likert Scale wherein 1 corresponds to “never” and 5 corresponds to “very often” [12].

4.9 Statistical/Data Analysis

Statistical analyses will be performed using STATA Statistical Software, Version 13, College Station, TX: StataCorp LP. A $p \leq 0.05$ will be considered significant. Descriptive statistics shall include mean and standard deviation, while inferential statistics will include basic item analysis, correlation analysis, and reliability analysis.

For the content validation of the Dysgeusia Grading Scale, an item- and scale content validity index will be computed using the formula of Lynn (1986). Basic item

analysis using Spearman's Rank-Order Correlation will be performed to evaluate inter-item correlations and those less 0.30 and greater than 0.70 (Polit & Beck, 2012) will be removed. Correlational analysis, on the other hand, will be conducted using Spearman's Rank-Order Correlation of the overall mean scores of the newly developed Dysgeusia Grading Scale with the mean scores of the Chemotherapy-Induced Grading Scale to estimate convergent validity and with the MDASI-HN to determine divergent validity (Daniel & Cross, 2013). Reliability analysis will be performed using Cronbach's alpha to determine the internal consistency of the Dysgeusia Grading Scale (Daniel & Cross, 2013).

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