**PROTOCOL AMENDMENT #5**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes

X Scientific changes (IRB approval)

___ Therapy changes (IRB approval)

___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

***Editorial, administrative changes***

- Decrease accrual to 90 (section 7.2)
- Remove any mention of Rex from the protocol (will no longer be opening at that site)
- Updated contact info for co-investigators

***THE ATTACHED VERSION DATED 01/15/21 INCORPORATES THE ABOVE REVISION***

**ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL**

**PROTOCOL AMENDMENT #4**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes

__ Scientific changes (IRB approval)

___ Therapy changes (IRB approval)

___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

***Editorial, administrative changes***

- PI change from Kyle Wang to Colette Shen

***THE ATTACHED VERSION DATED 08/28//2020 INCORPORATES THE ABOVE REVISION***

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**PROTOCOL AMENDMENT #3**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes

X Scientific changes (IRB approval)

___ Therapy changes (IRB approval)

___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

***Editorial, administrative changes***

- Listed existing co-investigators not already identified on the protocol (cover pages)
- Page numbers updated (table of contents)
- Registration procedures updated (section 8.3)
- Updated data management (section 7.4)

***Scientific changes***

- Accrual (section 7.2)

***THE ATTACHED VERSION DATED 03/05//2020 INCORPORATES THE ABOVE REVISION***

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**PROTOCOL AMENDMENT #2**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes

X Scientific changes (IRB approval)

___ Therapy changes (IRB approval)

X Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

***Editorial, administrative changes***

- Study personnel updated (cover pages)

***Scientific changes***

- Wording of treatment planning and delivery description updated to provide additional clarification/details (section 4.3.6)
- Additional assessments for patient treatment with steroids, narcotics, anticholinergics, and systemic therapy at various time points (section 4.3.10 & section 5.1)

***Eligibility changes***

- Narrowed treatment dose and fractionation range permitted for enrollment (section 3.1.1)
- Allowance to use of MRI-based planning simulation (section 3.2.1)
- Exclusion criterion added to explicitly state exclusion of pregnant patients (section 3.2.6)

***THE ATTACHED VERSION DATED 03/08/2019 INCORPORATES THE ABOVE REVISIONS***

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**PROTOCOL AMENDMENT #1**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

**AMENDMENT INCORPORATES (check all that apply):**

___ Editorial, administrative changes

___ Scientific changes (IRB approval)

___ Therapy changes (IRB approval)

X Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

***Eligibility changes***

- Time frame for prior RT exclusion criterion modified from within the last year to any time within the patient's life (section 3.1.2)

***THE ATTACHED VERSION DATED 08/29/2018 INCORPORATES THE ABOVE REVISIONS***

**ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL**

**LCCC 1802: Randomized Trial of Parotid Sparing Whole Brain Radiation**

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**Sponsor:**
Lineberger Comprehensive Cancer Center

**Funding Source:**
Department of Radiation Oncology

**Other Participating Institutions**:
University of Michigan, Ann Arbor, MI
Wake Forest University, Winston-Salem, NC

**Signature Page**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

**Principal Investigator (PI) Name**: Colette Shen, MD, PhD

**PI Signature:** *via IRBIS certification*

**Protocol Version Date:** 1/15/21

## TABLE OF CONTENTS

**1.0 BACKGROUND AND RATIONALE ..... 1**

**1.1** Study Synopsis ..... 1

**1.2** Background ..... 1

**1.3** Purpose and Rationale ..... 4

**2.0 STUDY OBJECTIVES/AIMS AND ENDPOINTS/OUTCOMES ..... 5**

**2.1** Primary Objective ..... 5

**2.2** Secondary Objectives ..... 5

**2.3** Exploratory Objective ..... 6

**2.4** Endpoints ..... 6

**3.0 PATIENT ELIGIBILITY ..... 6**

**3.1** Inclusion Criteria ..... 6

**3.2** Exclusion Criteria ..... 7

**4.0 STUDY PLAN ..... 8**

**4.1** Schema ..... 8

**4.2** Duration of Study ..... 9

**4.3** Study Details ..... 9

**4.4** Expected Risks ..... 15

**4.5** Removal of Patients from Protocol ..... 16

**5.0 TIME AND EVENTS TABLE ..... 16**

**5.1** Time and Events Table ..... 16

**6.0 UNANTICIPATED PROBLEMS ..... 16**

**6.1** Definition ..... 16

**6.2** Reporting ..... 17

**6.3 Monitoring and Oversight....17**
**STATISTICAL CONSIDERATIONS....17**

**7.1** Study Design....17

**7.2** Sample Size and Accrual....17

**7.3** Data Analysis Plans....18

**7.4** Data Management/Audit....18

**8.0 STUDY MANAGEMENT....19**

**8.1** Institutional Review Board (IRB) Approval and Consent....19

**8.2** Required Documentation....19

**8.3** Registration Procedures....19

**8.4** Adherence to the Protocol....19

**8.5** Amendments to the Protocol....21

**8.6** Record Retention....21

**8.7** Obligations of Investigators....21

**9.0 REFERENCES....22**

**10.0 APPENDIX....23**

# 1.0 BACKGROUND AND RATIONALE

## 1.1 Study Synopsis

The parotids have not been historically considered an organ at risk / avoidance structure and are not routinely delineated for whole brain radiation (WBRT) planning, despite receiving incidental dose [1] using standard fields. For this reason, we evaluated patient reported xerostomia in an ongoing prospective observational trial (LCCC 1540: Prospective Evaluation of Patient Reported Xerostomia After Whole Brain Radiation). At an interim analysis of LCCC 1540 with accrual at 90% of the goal, we found a clinically-meaningful rate of xerostomia following routine WBRT. Furthermore, the incidence/severity appeared to be related to parotid dose. The goal of this follow-up study is to investigate whether parotid sparing WBRT can reduce or prevent patient reported xerostomia. The study design will principally be a prospective randomized trial where patients are randomized to receive parotid sparing WBRT vs. standard WBRT where the parotids are not avoided. We will evaluate the xerostomia scores (using the University of Michigan Xerostomia Questionnaire [2]) of patients treated in each arm. Patients who refuse randomization will be offered enrollment in an observational arm to follow their symptoms of xerostomia for secondary analysis. This will be a multi-site study, with patients also enrolling at High Point Regional Health, High Point, North Carolina, as well as possibly other sites and institutions. We anticipate a total accrual of approximately 90 patients (45 in each interventional arm) with a goal of 62 evaluable patients reaching the primary 1 month post-RT endpoint.

## 1.2 Background

### 1.2.1 Salivary Gland Toxicity in Head and Neck Cancer

It is well known that radiotherapy for head and neck cancer is associated with significant and sometimes permanent dry mouth. Numerous studies have demonstrated that the degree of parotid gland exposure is related to the severity of xerostomia [2-5]. These studies have led to a national consensus guideline regarding minimization of parotid doses (e.g., mean bilateral parotid dose should be $\leq$ 25 Gy) [6]. Due to these guidelines, it is now standard to delineate the parotid glands and to use conformal treatment techniques such as intensity-modulated radiation therapy to minimize incidental irradiation to these organs in patients being treated for head and neck cancer.

### 1.2.2 Whole Brain Radiation – Background and Quality of Life

Whole brain radiation is commonly used for patients with multiple brain metastases. The prognosis of most patients who require whole brain radiation is poor, with many not living beyond six months [7]. Quality of life is thus of paramount importance in this population. Numerous prospective studies have reported on the well-known side effects of fatigue, alopecia, and neurocognitive decline following WBRT. This is balanced with the potential improvement in quality of life due to control of CNS disease [8-10]. While patients do occasionally complain of dry mouth following whole brain radiation, no prior studies have systematically assessed the frequency or severity of dry mouth in these patients, though one older case series did report several cases of parotitis following WBRT [11]. We believe that these symptoms are related to

incidental irradiation of the parotids, and that simple adjustments to the traditional RT fields can mitigate this toxicity.

### 1.2.3 Whole Brain Radiation – Standard Approach, Organs at Risk, and Parotid Dose

Due to the poor prognosis for most patients receiving whole brain radiation, and because typical total doses used for whole brain radiation are in the range of 20-35 Gy (vs. 60-70 Gy for patients with head and neck cancer), the parotids have not traditionally been considered an organ at risk in patients receiving whole brain radiation. Historically, whole brain radiation fields were designed based on the anatomy as seen on planning skull radiographs, and this 'standard approach' has not changed in several decades. While sophisticated computer-based techniques readily enable the consideration of 3D anatomy (e.g. from CT and/or MRI) in the treatment planning process, these newer approaches have not been applied in patients receiving whole brain radiation. The accepted standard WBRT field includes roughly 5-10mm of margin inferiorly around the cribiform plate and inferior skull, as well as coverage of the entire C1 and sometimes C2 vertebral bodies. For the purposes of WBRT, no standard normal tissues are delineated for avoidance, though the lenses are often delineated at the discretion of the treating physician.

As such, the location of the parotid glands is not considered during planning for whole brain radiation, and there are presently no dose/volume limits for the parotids. For example, in patients receiving whole brain radiation on the nationwide RTOG 0933 trial using hippocampal sparing intensity-modulated radiation, only the hippocampus, eyes, and lenses were required to be delineated with set dose limits. [12] In patients receiving whole brain radiation on other protocols, such as N107C, [13] no organs at risk are required to be delineated. Thus, the risk of radiation-associated parotid injury is not appreciated.

Nonetheless, the parotids do, in fact, receive substantial radiation dose during whole brain radiation For instance, several dosimetric studies report mean parotid doses of 10 to 20 Gy. [1, 14, 15] However, prior to LCCC 1540 there have been no studies that have reported the clinical impact of this parotid exposure. Several lines of evidence suggest that incidental parotid irradiation may cause meaningful toxicity in patients receiving whole brain radiation:

1. Gradual dose response: Though the recommended parotid "dose limit" for patients with head and neck cancer is 20-25 Gy, there is a gradual dose response, and it is recommended that parotid dose is kept as low as possible (e.g. << 20 Gy) to minimize xerostomia. Thus, mean parotid doses in the 10-20 Gy range (as is reported with whole brain radiation) may cause toxicity.
2. Acute vs. late toxicity: Parotid dose guidelines in patients with head and neck cancer are based on late (e.g. ≥1 year post-RT) toxicity. Patients generally suffer greater acute toxicities during RT, [16] or at shorter time intervals (e.g., 1-6 months) post-RT, with some recovery of salivary function at later time points. These acute toxicities are what matter most to patients receiving whole brain radiation; given their poor prognoses, few will survive long enough for later (e.g. ≥1 year post-radiation) salivary recovery.

3. Higher doses per fraction and shorter overall radiation treatment times: Though parotid doses during whole brain radiation are lower than for head and neck cancer, whole brain radiation is delivered in larger doses per fraction (2.5-3.0 Gy per fraction as opposed to 1.8-2.0 Gy per fraction for head and neck cancer) and in a shorter treatment time (e.g. 2-3 weeks as opposed to 7 weeks for head and neck cancer). Higher doses per fraction and shorter treatment intervals are both associated with increased risks of toxicity.

### 1.2.5 Preliminary Results of LCCC 1540: Prospective Evaluation of Patient Reported Xerostomia After Whole Brain Radiation

These hypotheses culminated in the design of LCCC 1540. We used the validated University of Michigan Xerostomia Questionnaire [2] and a "bother score" questionnaire to assess patient-reported xerostomia after standard whole brain radiation, in which the parotid glands were not prospectively delineated. The parotids were, however, retrospectively delineated to assess impact of parotid dose on xerostomia. Like other reports, the parotid glands received mean doses of roughly 17 Gy. However, LCCC 1540 provided the first data on the actual clinical significance of this incidental exposure. In an interim analysis with accrual at 90% of the goal, xerostomia was common, sometimes severe, and often persisted to the last post-RT assessment. Further, parotid doses were strongly correlated with xerostomia, consistent with our original hypothesis. These novel data have important implications for quality of life and perhaps even nutritional status in this vulnerable patient population, and were accepted for oral presentation this year at two national conferences (ACRO 2017 and ASTRO 2017).

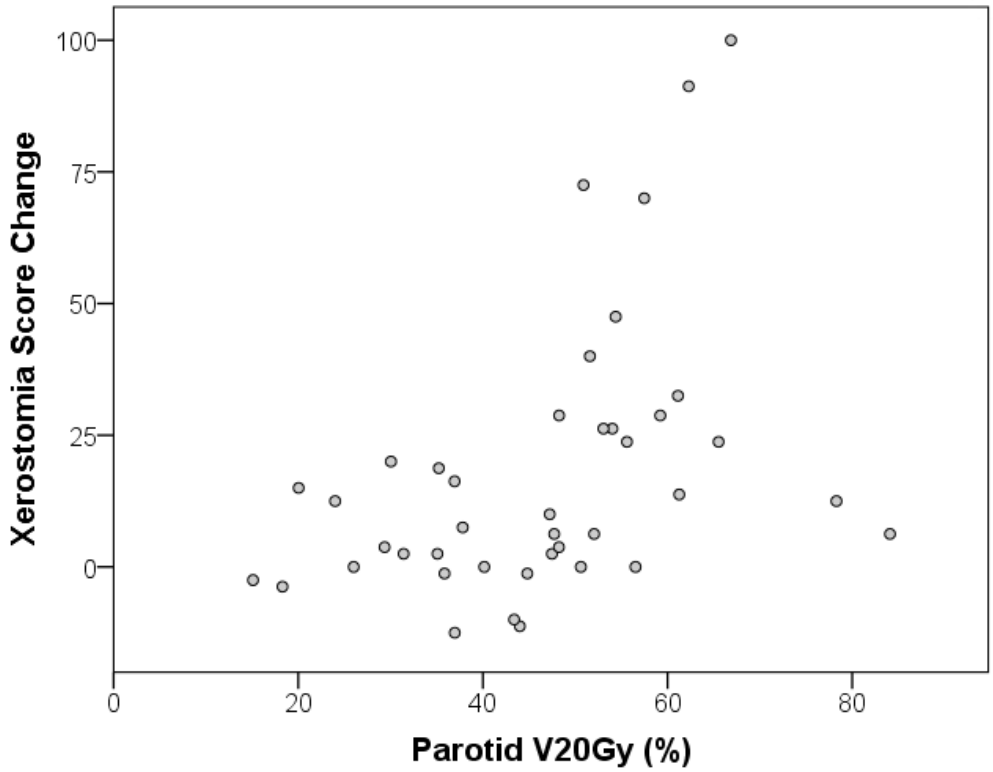


**Figure 1. LCCC 1540:** Change in xerostomia score (y-axis) plotted against parotid dose (x-axis) for all 41 patients reaching the 1 month post-RT primary endpoint. Parotid doses were significantly correlated with xerostomia (p=0.005). (Parotid V20Gy: % of the bilateral parotid glands receiving at least 20 Gy).

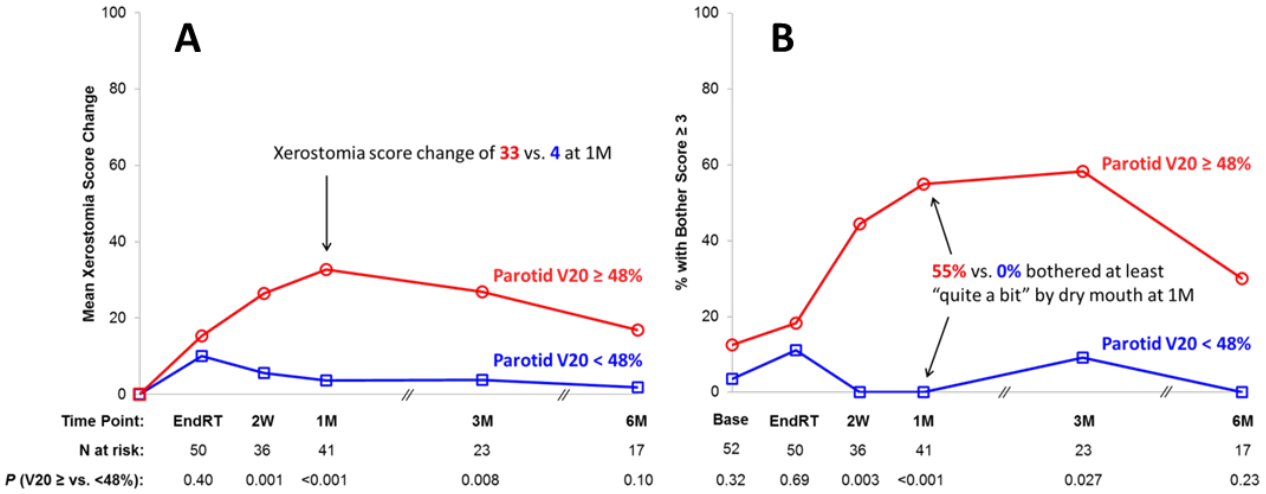



**Figure 2. LCCC 1540:** Mean xerostomia score change (A) and bother (B) were significantly worse in patients with higher parotid dose at most time points. (Parotid V20: % of the bilateral parotid glands receiving at least 20 Gy).

These are the first data demonstrating that dry mouth is a toxicity of WBRT and have implications on field design during treatment planning.

### 1.3 Purpose and Rationale

Given that the results of LCCC 1540 show a relationship between parotid dose and toxicity, it is our new hypothesis that prospective delineation of the parotids and minimization of dose to the parotids can provide clinically meaningful reductions in xerostomia while still adequately treating the brain. This is supported by a secondary analysis of LCCC 1540, where we assessed whether new radiation plans designed retrospectively to avoid the parotids could meaningfully reduce dose to the parotids while simultaneously maintaining adequate coverage of the brain. For the original (and delivered plans), the median parotid mean dose was 17 Gy and median parotid V20Gy was 48%. With systematic re-planning to reduce parotid exposure, the median parotid mean dose was reduced to 8 Gy and the median parotid V20Gy was reduced to 14%. This reduction in parotid dose did not appear to come at significant expense to brain coverage: the volume of brain receiving 95% of the prescription dose was 99.86% for the parotid sparing plans, vs. 99.99% for the original plans (Example, Figure 3).

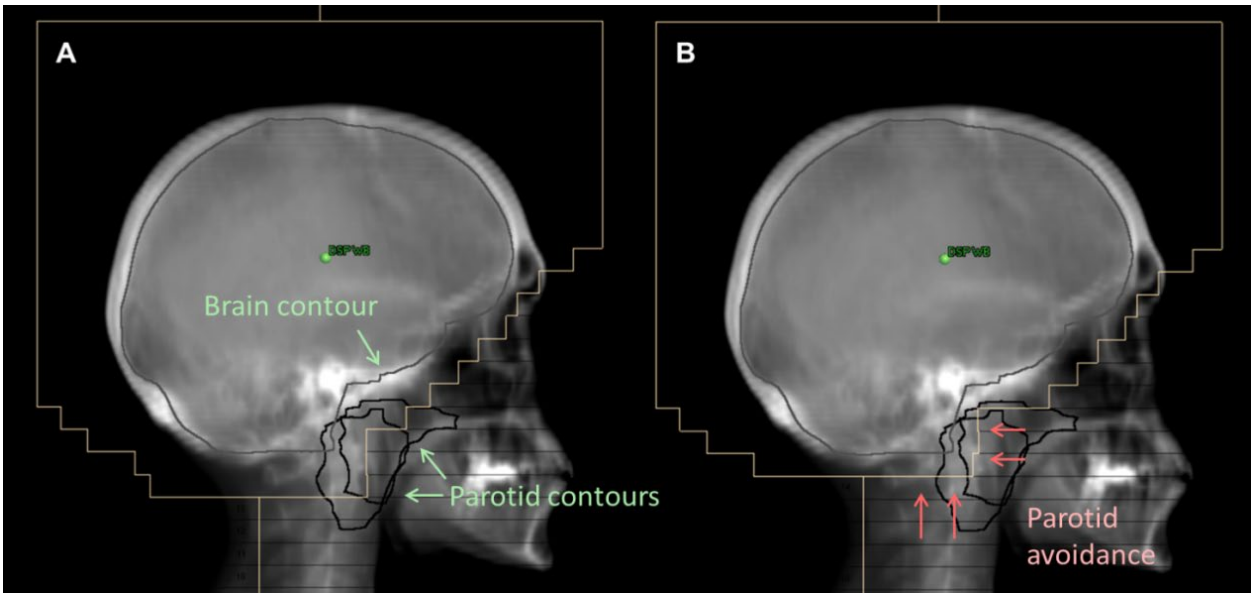



**Figure 3. Panel A:** Radiation fields for a patient receiving whole brain RT on LCCC 1540 with persistent severe post-RT xerostomia. The parotids were not prospectively delineated and received a mean dose of 20 Gy. Panel B: Alternative plan with fields designed to reduce parotid exposure resulting in a mean parotid dose of only 11 Gy. The volume of brain covered by 95% of prescription dose was 99.98% for the original, vs. 99.65% for the re-plan (thus parotid sparing does not significantly compromise target coverage).

The results of LCCC 1540 have introduced an evolving standard of care in our department. Because coverage of the brain does not appear to be compromised with the use of parotid sparing (see Figure 3, above), several physicians who are familiar with data from LCCC 1540 have already started utilizing parotid sparing WBRT fields *off trial* to attempt to reduce toxicity. Others, on the other hand, prefer to continue to use standard WBRT without parotid avoidance given the preliminary nature of the available data and the hypothetical risk of marginal failure either in the inferior brain or upper cervical vertebrae. To investigate the hypothesis that parotid sparing provides a clinical benefit in a safe manner, we will randomize patients *on trial* to receive either parotid sparing WBRT vs. standard WBRT. If our hypothesis is correct, then the severity of xerostomia will be lower in patients randomized to parotid sparing.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objective

To assess whether the use of parotid sparing WBRT fields results in decreased xerostomia compared to standard WBRT fields (where the parotids are not avoided) *in randomized patients.*

### 2.2 Secondary Objectives

Secondary objective #1: To assess whether the use of parotid sparing WBRT fields results in an increase in marginal tumor relapses in the region of the blocked parotid glands *in randomized patients*.

Secondary objective #2: To assess whether the use of parotid sparing WBRT fields results in decreased xerostomia *in all patients, including randomized patients and patients who refused randomization but consented for the observational arm*.

### 2.3 Exploratory Objectives

[redacted]

### 2.4 Endpoints

Primary endpoint: The primary endpoint will be the proportion of patients experiencing clinically significant xerostomia (defined as a ≥15 point increase in composite University of Michigan Xerostomia Questionnaire score [2]) *in randomized patients* from baseline to 1 month post-treatment.

Secondary endpoint #1: Freedom from marginal relapse, including CNS relapse in the inferior brain (defined as within 1 cm of the block edge overlying the blocked parotids), and the rate of upper cervical spine relapse (defined as relapses in the C1 or C2 vertebrae).

Secondary endpoint #2: Xerostomia (defined as a ≥15 point increase) at 1 month based on the use of standard vs. parotid sparing fields *in all patients, including randomized and non-randomized patients*.

Exploratory endpoint: [redacted]

Exploratory endpoint #2: [redacted].

## 3.0 PATIENT ELIGIBILIY

### 3.1 Inclusion Criteria

The subject must meet all of the following inclusion criteria to participate in this study:

**3.1.1** Patients to be treated with WBRT using 3-dimensional conformal RT in 10-15 fractions to a total dose of 30-35 Gy for any diagnosis other than elective treatment of potentially subclinical intracranial disease.

**3.1.2** No prior radiation that would have exposed the parotids to a significant (estimated >10 Gy mean parotid dose) level of radiation. Patients receiving prior stereotactic radiosurgery for brain metastasis are eligible for inclusion in this trial as this form of radiation is highly conformal and exposes the parotids to minimal (estimated <1 Gy) radiation.

- Patients enrolling on the observational arm may have started their current course of whole brain radiation therapy within 5 days prior to completing the baseline screening questionnaire and consenting to study.

**3.1.3** Greater than or equal to 18 years of age (no upper age limit).

**3.1.4** Raw xerostomia score < 40 / 80 on the initial screening xerostomia questionnaire. This is calculated by adding up the values from questions 1-8.

**3.1.5** Initial xerostomia questionnaire and informed consent obtained within the required time frame (≤ 30 days before RT start for interventional arm; ≤ 5 days after RT start for observational arm).

### 3.2 Exclusion Criteria

The subject may be excluded or withdrawn from the study if any of the following apply:

**3.2.1** Patients receiving WBRT without the use of a CT or MRI-based planning simulation.

**3.2.2** Patients receiving WBRT with the use of intensity-modulated radiation therapy.

**3.2.3** Patient receiving WBRT as elective treatment of potentially subclinical intracranial disease (e.g., WBRT for prophylactic cranial irradiation of small cell lung cancer).

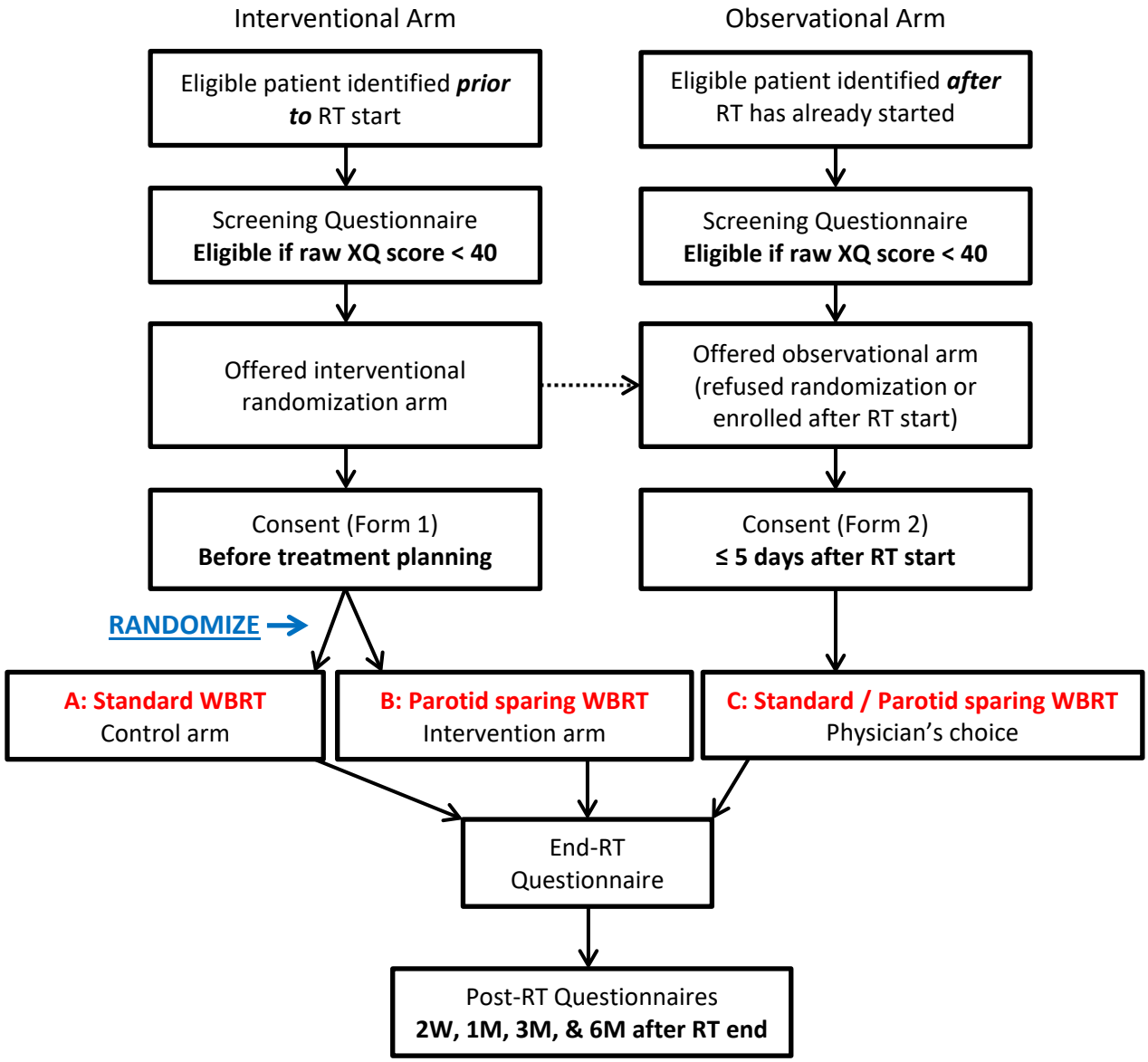
**3.2.4** Physically unable to communicate by paper or phone to complete the study survey.

**3.2.5** Prisoners.

**3.2.6** Pregnant women.

# 4.0 STUDY PLAN

## 4.1 Schema




Note: Due to the expedited nature of many whole brain radiation treatment plans, we anticipate identifying many subjects after treatment has already begun. Because of this, we will offer these individuals enrollment on an observational arm of this study. Additionally, if participants do not wish to participate in the interventional arm of this study, they will be approached for the observational arm. See Section 4.3 for more details.

## 4.2 Duration of Study

The anticipated accrual period is around 3-5 years.

### 4.3 Study Details

This is primarily a two-arm, single-blind, randomized study of parotid sparing WBRT, with a third observational arm of patients who were identified after radiation had already started or who refused randomization but were willing to be followed for quality of life assessment. The primary purpose of this study is to compare the proportion of patients experiencing significant xerostomia in patients randomized to parotid sparing vs. standard WBRT. Patients receiving WBRT often receive treatment in urgent situations, making pre-treatment randomization logistically challenging. Therefore, the observational arm serves to increase the number of eligible patients and allows for comparison of xerostomia in all patients receiving parotid sparing vs. standard WBRT, but who were unable to be approached in time for randomization. Patients enrolling on the randomization arms will be consented and enrolled prior to treatment. Patients enrolling on the observational arm may enroll up to 5 days after initiation of treatment. Post-treatment surveys will be collected up to 6 months post-RT. We therefore anticipate that patients' active participation will last approximately 6 months. Chart abstraction will take place for up to 1 year post-RT for assessment of secondary endpoint #1: freedom from marginal relapse.

#### 4.3.1 Screening for Eligibility and Registration Details

Patients identified as qualifying for the trial will be divided into those who were identified prior to radiation start vs. those identified after radiation start. Patients interested in participating will complete an anonymous screening baseline xerostomia questionnaire identical to the primary study assessment (see Section 4.3.9, below). Patients scoring ≥ 40 pts on the screening xerostomia questionnaire are ineligible. Patients scoring < 40 / 80 will be eligible and offered enrollment on the study. Questionnaires completed by patients who are found to be ineligible or who decline to enroll on the study will be destroyed. Questionnaires completed by patients who consent to the trial will be assigned patient information (de-anonymized) and serve as their baseline quality of life data.

Patients identified prior to radiation start will be offered enrollment into the randomization arms (Consent form 1, arms A and B), with the observation arm (Consent form 2, arm C) offered to those who refuse randomization. Patients identified after radiation has already started, but within 5 days of the first day of radiation, will be offered enrollment into the observational arm (Consent form 2, arm C).

#### 4.3.2 Randomization Details

Patients who agree to be randomized will be assigned to one of the following treatment groups using block randomization. A randomization list will be designed by the statistician. Patients will be randomized after informed consent is obtained, and before treatment begins. A list of randomized assignments will be provided to each site prior to enrollment of participants to facilitate ease of trial administration. This is done because of the often urgent nature of whole

brain cases and the necessity of clinicians knowing the randomized assignment before treatment planning.

Arm A: Standard WBRT (Control)
Arm B: Parotid sparing WBRT (Intervention)

### 4.3.3 Blinding

This will be a single-blind study, where all enrolled patients are blinded to the type of WBRT fields used in their treatment in order to minimize reporting bias between the study arms.

### 4.3.4 CT simulation

Patients on all study arms will routinely undergo a CT scan for treatment planning. Immobilization is achieved with an aquaplast mask form fitted on the patient's face and locked on to the table. Prior to the CT scan, a "scout X-ray" is taken to ensure the patient is in an acceptable position. A CT scan is then obtained through the treatment area, and including the entire neck. These images are used to create the radiation treatment plan. The planning CT scan is then transferred the treatment planning software program. 3D conformal radiation plans will then be created for each patient.

### 4.3.5 Treatment Planning and Delivery – Arm A: Standard WBRT (Control Arm)

Patients randomized to the control arm will receive standard WBRT without delineation or avoidance of the parotid glands, as per typical practice (see Figure 4, below). Patients must be enrolled prior to treatment. Laterally arranged beams will be designed based on digitally reconstructed skull radiographs. A 5-10 mm margin is used around the cribiform plate and skull base, with inferior extension of the field to cover the entirety of the C1 and/or C2 vertebra, with at least a 2mm margin anterior to the vertebral bodies. The parotids will *not* be delineated for avoidance, and delineation of other organs at risk or the brain is optional, consistent with most national studies utilizing WBRT (see section 1.2.3). All treatment plans are monitored for quality assurance at departmental meetings in which radiation fields are presented for peer review. Weekly X-ray films are taken to verify the accuracy of patient set up on actual treatment days. The initial treatment will not proceed without physician verification of accurate patient set up.

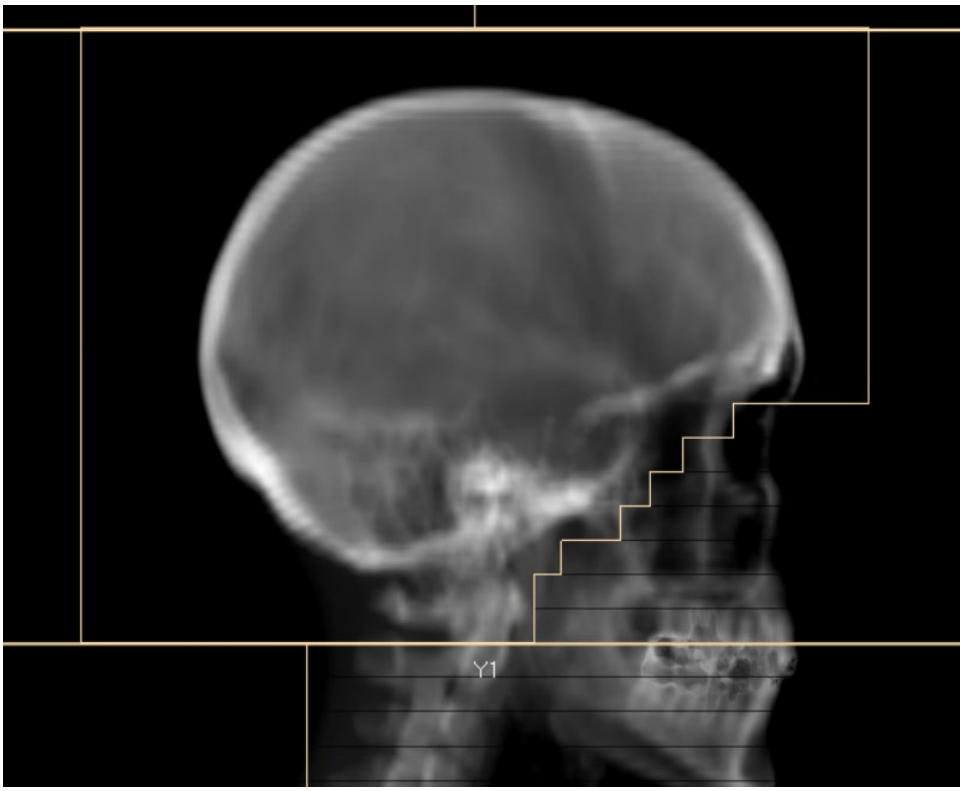



**Figure 4. Control arm (Standard WBRT).** Example of a laterally arranged treatment field for standard WBRT used in the control arm, where a small margin is provided around the inferior skull border. The C1 vertebra is covered with a small anterior margin. No organs at risk are standardly delineated, though providers may opt to delineate the lens and orbits for avoidance, or the brain to ensure coverage.

### 4.3.6 Treatment Planning and Delivery – Arm B: Parotid sparing WBRT (Intervention Arm)

Patients randomized to the intervention arm will receive parotid sparing WBRT (see Figure 5, below). Patients must be enrolled prior to treatment.

- The left parotid will be delineated and named **Parotid_Lt**
- The right parotid will be delineated and named **Parotid_Rt**
- The **Parotid_Lt** and **Parotid_Rt** structures will be combined and named **Parotids_Bilateral** for use in planning and dosimetric analysis.
- The **brain** will be delineated to the level of the foramen magnum, marked by the superior dens (see Figure 6, below), to ensure adequate target coverage.
- Laterally arranged beams will be designed based on both digitally reconstructed skull radiographs and CT anatomy. Radiation fields will be altered to minimize overlap with the **Parotids_Bilateral** contour, while maintaining around a 1cm margin around the brain contour. All treatment plans are monitored for quality assurance at departmental meetings in which radiation fields are presented for peer review. Weekly X-ray films are taken to verify the accuracy of patient set up on actual treatment days.

Based on the results of the replanning analysis from LCCC 1540, 87% of patients were able to achieve a bilateral parotid V20Gy <25% while maintaining a 1cm margin around the brain, and the range of replanned bilateral parotid V20Gy was 1-35%. Thus, there will be a **goal to limit the Parotids_Bilateral V20Gy to <25%, and lower if possible.** The following table summarizes the dose constraints of the parotid-sparing arm:

| **Parotid-sparing WBRT arm dose constraints (for Parotids_Bilateral)** | |
|---|---|
| Goal | V20Gy < 25% |
| Minor deviation | V20Gy ≥ 25% to < 35% |
| Major deviation | V20Gy ≥ 35% |

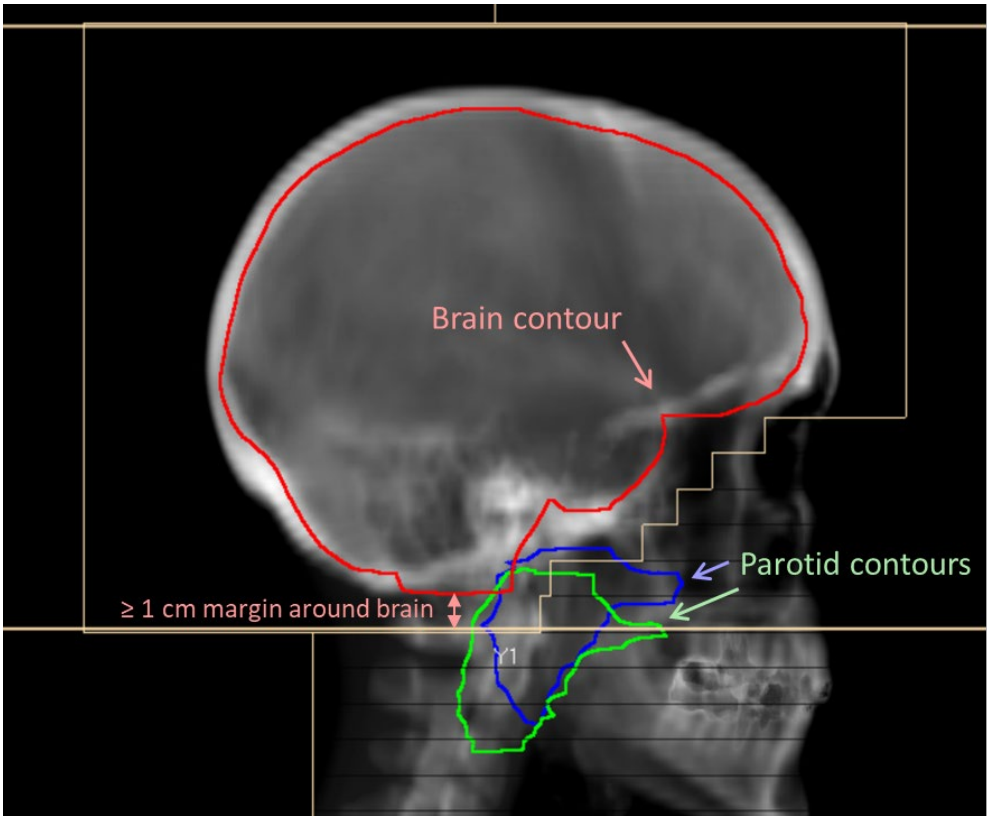



**Figure 5. Intervention arm (Parotid sparing WBRT).** Example of a laterally arranged treatment field for parotid sparing WBRT used in the intervention arm. Cervical vertebrae are no longer considered in treatment planning. The parotids and brain must be delineated. Ensuring around a 1 cm margin around the brain contour, the treatment field is altered to minimize overlap with the parotid glands.

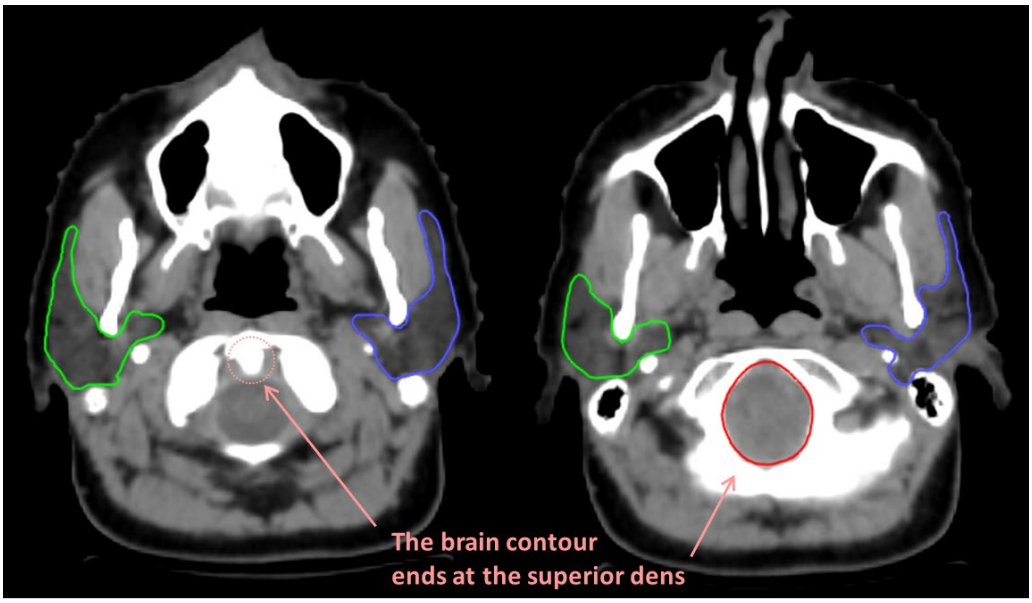



**Figure 6. Intervention arm (Parotid sparing WBRT).** Contouring of the parotids (green, blue) and brain (red). The brain contour extends inferiorly to the most superior point of the dens of the C2 vertebra (dotted circle).

### 4.3.7 Treatment Planning and Delivery – Arm C: Observational arm (WBRT protocol not specified)

Patients who decline randomization but consent to the observational arm will receive WBRT without the use of the above treatment planning guidelines. WBRT will be delivered using standard or parotid sparing fields, per treating physician preference. Patients may also enroll on this arm after initiation of WBRT, as long as the baseline questionnaire is completed within 5 days of initiation of treatment. These patients will complete the protocol-specified study assessments at the same time points as randomized patients.

### 4.3.8 Treatment Planning and Delivery – Quality Assurance

Given that whole brain radiation is often delivered in situations of medical urgency, there will be no requirement for the PI or primary site to approve treatment plans before initiation of radiation. However, to ensure delivery of radiation as intended, *a digitally reconstructed radiograph containing the treatment field and any delineated organs at risk or targets will be sent to the study coordinator for the first four randomized patients at each non-primary site participating in the protocol.* If the treatment plans are not found to be adequate, the Principal Investigator will hold a meeting with the pertinent sites to discuss requested corrections for future patients. Patients who received the incorrect treatment (per randomization) will not be analyzed as part of the primary endpoint.

### 4.3.9 Main Study Assessment: Xerostomia Questionnaire

Patients in this study will be asked to complete the Xerostomia Questionnaire and two additional supplemental survey questions at baseline (prior to radiation in randomized patients and within 5

days of radiation initiation in patients refusing randomization but consenting for the observation arm), at the end of radiation (on or within 5 days after the final day of radiation), then at two weeks (+/- 5 days) and one, three, and six months (+/- 7 days) after radiation completion, for a total of six planned surveys. This survey may be administered by phone or by email, vs. in person if the patient has an appointment at the appropriate time point necessary for clinical follow-up. This survey also acts as the screening questionnaire completed by patients prior to enrollment, and counts as the baseline questionnaire for those consenting to enrollment.

The full survey (see appendix) will consist of the validated University of Michigan Xerostomia Questionnaire (questions 1-8) and two additional questions related to dry mouth, (questions 9-10). Questions 1-8 will be answered on a Likert scale ranging from 0 (least bothersome) to 10 (most bothersome), summed, and linearly converted to a scale from 0-100. Questions 9-10 will be answered on a Likert scale with four responses: Not at all, a little, quite a bit, and very much. Questions 9-10 are designed to quantify the overall importance of dry mouth symptoms to each patient, and were adapted from the validated EORTC QLQ-H&N35 head and neck specific questionnaire [17].

### 4.3.10 Other Assessments

At the initial / baseline assessment, patients' Eastern Cooperative Oncology Group (ECOG) performance status will be recorded. Relevant demographic and clinical data will be abstracted from the medical record as part of this study. For patients randomized to standard WBRT, the parotids will be delineated retrospectively for dosimetric analysis. For patients randomized to parotid sparing WBRT, the parotids are prospectively delineated and dosimetric data prospectively collected.

For the purposes of assessing factors potentially confounding the measurement of dry mouth, we will prospectively record at the baseline assessment whether patients are taking different classes of medications. At the end of RT time point. We will record whether the patients required steroids at any point during radiation. At the 1 month time point, we will also record whether the patient has received systemic therapy (including chemotherapy) after WBRT. The details of these assessments are found in section 5.1 (Time and Events Table).

### 4.3.11 Follow Up

Follow up for the purposes of this study is limited to the administration of surveys up to six months post-radiation, which is the last planned questionnaire. Participation in this study will not impact the actual clinical follow-up schedule of patients receiving WBRT, which is based on the discretion of the treating radiation oncologist. Although a secondary endpoint is the rate of marginal relapse around the blocked parotid glands, this will be assessed using data obtained as part of standard of care follow-up of these patients. No additional visits or protocol-specified imaging will be required, as this would unnecessarily burden these palliatively treated patients, given the minimal expectation that a meaningful difference in tumor control exists (see section below on expected risks).

## 4.4 Expected Risks

Patients randomized to standard WBRT will not be subject to any risks specific to participation in this trial; these patients receive standard treatment and simply complete the study assessment at post-treatment time points. Several theoretic risks warrant mention for patients randomized to parotid sparing WBRT:

1. By delineating and minimizing dose to the parotids, the target (brain) could receive a lower dose, which could place the patient at higher risk of inferior brain relapse.
2. By omitting coverage of C1/C2, patients may develop bony metastases in this location which may be more difficult to treat with radiation in the future, given the abutment of the prior parotid sparing field.

For the following reasons, these risks are minimal:

1. The standard field arrangements of WBRT covering the upper cervical vertebrae have become standard practice with the advent of CT-based planning. Prior to CT-based planning, WBRT was delivered with an angled rectangular field splitting the cervical vertebrae. With the use of CT-based planning, WBRT fields became horizontal, and coverage of the cervical vertebrae was added to provide an additional margin around the foramen magnum. However, our preliminary analysis of LCCC 1540 and other studies [15, 18] show that coverage of brain is minimally affected with alterations to the field to maximize sparing of the parotids. Some of these studies have done this by omitting the upper cervical vertebrae and others have simply reduced the field borders in areas overlapping with the parotids. Therefore, target coverage is not expected to be compromised.

2. Regardless of any reductions in field size and the negligible impact on dose to the brain described above, whole brain radiation is essentially treatment of mostly subclinical disease in addition to areas of actual brain metastases. However, the field of radiation oncology as a whole has generally accepted that treatment of subclinical disease in the brain is not strictly necessary. This is demonstrated by the increasing use of stereotactic radiosurgery for multiple brain metastases with *no* elective brain treatment; it is generally accepted that if these patients develop new brain metastases they can be salvaged with additional stereotactic radiosurgery. Therefore, a small margin reduction with the goal of improving patient quality of life in a population with limited life expectancy should be acceptable and entail minimal excess risk.

3. For the same reason as above, omission of the C1/C2 vertebrae should also be of minimal significance. Given the overall poor prognosis of patients receiving WBRT, the rate of significant marginal bony relapses adjacent to the inferior WBRT field is expected to be extremely low. Furthermore, with the advent of stereotactic radiosurgery, any such relapses would still be safely treatable with definitive or palliative intent.

4. Finally, the willingness of many physicians and several institutions [1, 18-20] to adopt parotid sparing WBRT as their *current standard* is a testament to the generally low risk involved.

**4.5 Removal of Patients from Protocol**

Patients will be informed that they can request to withdraw from participation in this study at any time. If a patient withdraws from the study, they will no longer be contacted for the purposes of collecting data related to this study.

# 5.0 TIME AND EVENTS TABLE

## 5.1 Time and Events Table

| | Pre-study / Baseline[1] | Radiation | End-RT[2] | 2 Weeks Post-RT[3] | 1 Month Post-RT[4] | 3 Months Post-RT[4] | 6 Months Post-RT[4] |
|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | |
| Xerostomia Questionnaire | x | | x | x | x | x | x |
| ECOG Performance Status Assessment | x | | | | | | |
| Steroid Assessment[5] | x | | x | | | | |
| Narcotic Assessment[6] | x | | | | | | |
| Anticholinergic Assessment[7] | x | | | | | | |
| Systemic Therapy Assessment[8] | | | | | x | | |
| Quality Assurance (1st 4 pts per site) | | | x | | | | |
| Medical Record Abstraction | | Continuously throughout study | | | | | |

1. For randomized group this should be completed before treatment start, but no more than 30 days before treatment start. The observational arm should within 30 days of treatment start and up to 5 days after the first fraction of radiation is delivered.
2. This should be completed on the last day of treatment or up to 5 days after treatment end.
3. +/- 5 days
4. +/- 7 days
5. Is the patient on or has the patient been prescribed a steroid medication (eg, dexamethasone, methylprednisolone, or prednisone)? (Yes vs. No)
6. Is the patient on or has the patient been prescribed a narcotic medication (eg, hydrocodone, oxycodone, morphine, dilaudid, or fentanyl)? (Yes vs. No)
7. Is the patient on or has the patient been prescribed an anticholinergic medication on the following list? (Yes vs. No)
    a. Amitriptyline (Elavil)

b. Meclizine (Antivert)
c. Prochlorperazine (Compazine)
d. Scopolamine (Transderm Scop)
e. Hydroxyzine (Atarax)
f. Benztropine (Cogentin)
g. Chlorpromazine (Thorazine)
h. Olanzapine (Zyprexa)
i. Quetiapine (Seroquel)
j. Dicyclomine (Bentyl)
k. Atropine (Donnatal)
l. Oxybutynin (Ditropan)
m. Solifenacin (Vesicare)
n. Tolterodine (Detrol)
o. Cyclobenzaprine (Flexeril)

8. Has the patient received any systemic chemotherapy, immunotherapy, or targeted therapy between WBRT and the time of the 1M assessment? (Yes vs. No)

# 6.0 UNANTICIPATED PROBLEMS

## 6.1. Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

## 6.2. Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 6.1 must be reported to the UNC IRB using the IRB's web-based reporting system.

## 6.3 Monitoring and Oversight

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC) as required. This will include UNC and affiliate sites.

Meetings/teleconferences will be held at a frequency dependent upon study accrual and in consultation with the study Biostatistician. At these meetings, the research team will discuss all

issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc. and the team will produce summaries or minutes of these meetings.

# 7.0 STATISTICAL CONSIDERATIONS

## 7.1 Study Design / Study Endpoints

This is a prospective two arm randomized trial in which patients will complete the xerostomia questionnaire at six time points, including baseline and five post-radiation time points. The primary study endpoint is the change in composite xerostomia score (on a scale of 0-100, converted from the xerostomia questionnaire that is on a scale from 0-80; this conversion is made by adding up the values from questions 1-8 and dividing by 0.8, thus converting an 80 point scale into a 100 point scale) between baseline and 1 month. The xerostomia score change will be assessed using two methods: 1. Proportion of patients with a minimally clinically important difference and 2. Mean change. In LCCC 1540 (at n=41), the mean xerostomia score change from baseline to 1 month was 17.8, with a standard deviation of 26.0. The minimally clinically important difference is commonly defined as ½ of the standard deviation. For sample size calculations, we will therefore define a ≥15 point xerostomia score increase as a minimally clinically important difference.

## 7.2 Sample Size and Accrual

In LCCC 1540 (at n=41), the proportion of patients experiencing a ≥15 point xerostomia score increase was 42% (95% CI 26-57%). Setting the null hypothesis proportion of patients experiencing ≥15 point xerostomia score increase at 42% and an alternative proportion of 14%, 31 patients in each group are needed for 80% power to detect this difference using a two group chi-square test with a one-sided significance of 0.05.

In order to have 62 patients with both baseline and one month post-treatment surveys, we will target our enrollment for this study at 90 patients, given the patterns of patient attrition observed in LCCC 1540 and early enrollment to this study (assuming 70% completion rate). To obtain this target accrual, we anticipate an accrual period of roughly 3-5 years. This number is based on extrapolated accrual rates from LCCC 1540, which accrued 100 patients over roughly 2 years and the anticipated expansion of this study to other academic centers.

## 7.3 Data Analysis Plans

The primary data analysis plan is to compare the proportion of patients in each randomization arm experiencing a ≥15 point xerostomia score increase between baseline and 1 month, with the use of a two group chi-square test. As sample size allows, linear mixed effects models will be explored to evaluate changes over time including all repeated measurements. It is anticipated that a significant number of enrolled patients will be unable to complete the 3 month (estimated 40% response rate) and 6 month (estimated 20% response rate) post-radiation questionnaires due to disease morbidity and mortality, so modeling may be limited to the earlier time points. In such a

scenario with significant patient dropout, separate analyses will be performed for patients with vs. without long term follow up.

Descriptive statistics will be provided for all scores at all time-points and to summarize the patient population. Secondary data analyses will estimate the time to marginal relapse (defined as within 1 cm of the block edge overlying the blocked parotids) and the time to upper cervical spine relapse (defined as relapses in the C1 or C2 vertebrae) in each randomization arm using the Kaplan Meier method. A log rank test will be used to compare these time to event outcomes. Furthermore, the above analyses exploring xerostomia will also be conducted in all patients (including those who refused randomization but consented for the observational arm).

A linear regression model will be used to further explore the dosimetric relationship between parotid dose and xerostomia, to supplement data from LCCC 1540.

### 7.4 Data Management/Audit

The University of North Carolina will serve as the coordinating center for this trial. All data will be collected, entered, and maintained in a database on secure servers at the University of North Carolina at Chapel Hill. Questionnaires will be collected via Qualtrics and each site will be responsible for ensuring all questionnaires are entered into Qualtrics. Outside sites, including the University of Michigan andWake Forest University(High Point Regional Health), will send any other data via secure email to the University of North Carolina at Chapel Hill. All data will be pooled at UNC where personnel there will coordinate and manage data for quality control assurance and integrity. Data analysis will take place at UNC as well. Accrual data will be collected and entered into OnCore®. As an investigator-initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee.

## 8.0 STUDY MANAGEMENT

### 8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

### 8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

### 8.3 Registration Procedures

A list of all enrolled patients will be maintained in OnCore by the study coordinators at the University of North Carolina at Chapel Hill. Upon enrollment, affiliate sites should send UNC a copy of the signed informed consent and HIPAA documents, signed eligibility checklist, and baseline/screening questionnaire. Additional patient information may also be requested by the UNC coordinator to complete registration. For the randomized group, eligibility criteria must be confirmed with the UNC study coordinator before the start of treatment. For the observational group, eligibility must be confirmed with the UNC coordinator within 5 days of treatment start.

### 8.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

#### 8.4.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change. Affiliate site for this study are relying on UNC's IRB and should follow the same procedures for emergency modifications.

#### 8.4.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

#### 8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

**Protocol Deviations:** UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

**Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO):** Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 0) must be reported by the Study Coordinator using the IRB's web-based reporting system.

### 8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

### 8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory

documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### 8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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# 10.0 APPENDIX

**Dry Mouth Questionnaire**

For questions 1 to 8, please circle a number from zero to ten, with zero representing no symptoms and ten representing the worst symptoms.

1. Rate your difficulty in talking due to dryness.

   0 1 2 3 4 5 6 7 8 9 10

2. Rate your difficulty in chewing due to dryness.

   0 1 2 3 4 5 6 7 8 9 10

3. Rate your difficulty in swallowing solid food due to dryness.

   0 1 2 3 4 5 6 7 8 9 10

4. Rate the frequency of your sleeping problems due to dryness.

   0 1 2 3 4 5 6 7 8 9 10

5. Rate your mouth or throat dryness when eating food.

   0 1 2 3 4 5 6 7 8 9 10

6. Rate your mouth or throat dryness while not eating.

   0 1 2 3 4 5 6 7 8 9 10

7. Rate the frequency of sipping liquids to aid swallowing food.

   0 1 2 3 4 5 6 7 8 9 10

8. Rate the frequency of sipping liquids for oral comfort when not eating.

   0 1 2 3 4 5 6 7 8 9 10

For questions 9 and 10, please circle the answer that best represents how much your symptoms bother you.

9. How much does dryness bother you when you are eating?

   Not at all A little Quite a bit Very much

10. How much does dryness bother you when you are not eating?

    Not at all A little Quite a bit Very much