A Phase II Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma: Radiotherapy vs. Trans-Oral Surgery (ORATOR II)

STUDY PROTOCOL

For summary of changes since activation, see end of protocol (Page 42)

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Protocol Date: June 1, 2020

PROTOCOL SIGNATURE PAGE

My signature below confirms that I have reviewed and approved this protocol, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local regulations

_____

Qualified Investigator (Please Print)

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Qualified Investigator Signature

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1.0 INTRODUCTION AND RATIONALE

1.1 Background

Oropharyngeal cancer (OPC) is the fastest-rising incident cancer in Canada, due to the rapidly increasing rates of oral infection with the human papillomavirus (HPV).[1] Treatment options for HPV-positive OPC can involve either a primary radiation therapy (RT) approach (± concomitant chemotherapy) or a primary surgical approach (± adjuvant therapy). These two treatment paradigms have different spectrums of toxicity.

Standard chemoradiation (70 Gy with high-dose cisplatin) incurs frequent swallowing dysfunction, mucositis, xerostomia, fibrosis, osteoradionecrosis, neutropenia, neurotoxicity and hearing loss.[2] Primary surgery can have rare serious consequences such as fatal hemorrhage, stroke, shoulder dysfunction and dysphagia.[3] Patients with HPV-related OPC have an excellent chance of survival, and therefore may have to deal with these sequelae of therapy for many decades. With excellent rates of cure, post-treatment quality of life (QOL) becomes of paramount importance.

Currently, there is no level I evidence to favour one treatment strategy over the other. Instead, treatment selection is largely driven by institutional and patient biases with the majority of patients in the United States receiving surgery (82% of T1-T2 disease[4]), while most patients receive primary RT in Canada. Given the dramatic rise in the incidence of HPV disease and the paucity of high-quality data comparing treatment options, the management of OPC is the most contentious issue in head and neck oncology.

In 2012 our group opened the ORATOR trial (**O**ropharyngeal squamous cell cancer – **RA**diotherapy versus **T**rans**O**ral **R**obotic Surgery).[5] This trial was the first, and only, trial worldwide to address this critical question of a primary RT vs. primary surgical approach in a randomized fashion. The trial included patients with OPC regardless of HPV status. The study was powered to identify a 10-point difference in swallowing quality of life using the MD Anderson Dysphagia Index (MDADI)[6] at 1 year after treatment, since preserved swallowing was suggested as the benefit of the primary surgical approach in place of RT. ORATOR completed accrual in June 2017, with results expected in late 2018.

While the results of the ORATOR study are highly anticipated in the head and neck oncology community, the philosophies of management of HPV-positive OPC have changed since the study was opened. The impact of HPV on outcomes has been so substantial that a different staging system has been created to better represent the different prognosis of these patients[7,8]. The oncology community is now focused on de-intensification of treatment in HPV-related OPCs, in an attempt to reduce adverse events while maintaining excellent oncologic outcomes. De-intensification trials focusing on a primary RT approach have opened that include arms that decrease the doses of primary RT (to 60 Gy, instead of 70 Gy) and eliminate systemic therapy (NRG-HN002). Trials focusing on a primary surgical approach have decreased the adjuvant RT dose to

50Gy (ECOG3311, NCT01898494). Although these studies were rapidly accruing and both have already completed accrual, they are years away from being reported due to the length of follow-up needed.

The goal of this randomized phase II treatment de-escalation study is to assess the safety of two potential treatment de-escalation approaches, comparing each to historical controls, and to provide a high level of evidence to guide the selection of treatment options for a potential subsequent phase III trial.

Addendum February 2019:

ORATOR2 was originally launched with a primary endpoint of progression-free survival (PFS). The results of the original ORATOR trial, which became available in February 2019, have indicated that overall survival (OS) would be a preferred endpoint for ORATOR2. Both arms in ORATOR showed excellent OS in p16-positive cancers (both >92% at 2 years). OS is preferred as the primary endpoint to evaluate de-escalation, since it was evident in ORATOR that progression events, whether local, regional, or distant, can be salvaged for cure with surgery, radiation, or systemic therapy including immunotherapy. Therefore, in Feb 2019, without knowledge of outcomes data from ORATOR2, this trial was amended to promote OS from a secondary to primary endpoint, and demote PFS to a secondary endpoint.

2.0 OBJECTIVES

To compare OS relative to historical controls for de-intensified primary radiotherapy [60 Gy ± chemotherapy] versus transoral surgery (TOS) and neck dissection [± adjuvant 50Gy radiotherapy] in patients with early T-stage HPV-positive squamous cell carcinoma of the oropharynx, and to compare progression-free survival, toxicity and quality of life (QOL) profiles.

Hypothesis: For patients with HPV-positive T1-2N0-2 oropharyngeal cancer, primary surgery with reduced dose adjuvant therapy and reduced dose primary radiation with weekly cisplatin (given based on advanced nodal disease) will achieve 2-year OS rates not less than 85%.

Primary Endpoint

- Overall Survival
    - Defined as time from randomization to death from any cause

Secondary endpoints:

- 2-year progression-free survival (comparison with historical controls)
    - Time from randomization to disease progression at any site or death

  Progression free survival events are defined as death from any cause, or first recurrence of tumor at any site (including local, regional, or distant). Second primary tumors (e.g. head and neck cancer at a different site, such as laryngeal cancer) will not be included as PFS events.

- 2-year OS and PFS comparisons between Arm 1 and Arm 2

- Dysphagia-Related QOL at 1-year post-treatment
    - Assessed with the MD Anderson Dysphagia Inventory (MDADI)

- Quality of life at other time points
    - Using the MD Anderson Dysphagia Inventory (MDADI), the EORTC QLQ-C30 and H&N35 scales, the Voice Handicap Index (VHI-10), the Neck Dissection Impairment Index (NDII), and the Patient Neurotoxicity Questionnaire (PNQ), EQ-5D-5L.

- Toxicity
    - Assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4

- Other functional measurements, including, measured by:
    - Feeding tube rate at 1-year

- CTC-AE Dysphagia scores
- Functional Oral Intake Score (FOIS) at 1-year

3.0 STUDY DESIGN

This study is designed to assess two potential treatment de-escalation approaches, comparing each to a historical control, with the potential goal of evaluating one or both compared to standard chemo-radiation in a subsequent phase III trial. The required sample size is 140 patients. Patients will be randomized between a RT-based approach (Arm 1) vs. a primary surgical approach (Arm 2) in a 1:1 ratio. Arm 1 of this trial is based on the chemoradiation arm of HN002, and Arm 2 is based on the treatment paradigm of ECOG-3311.

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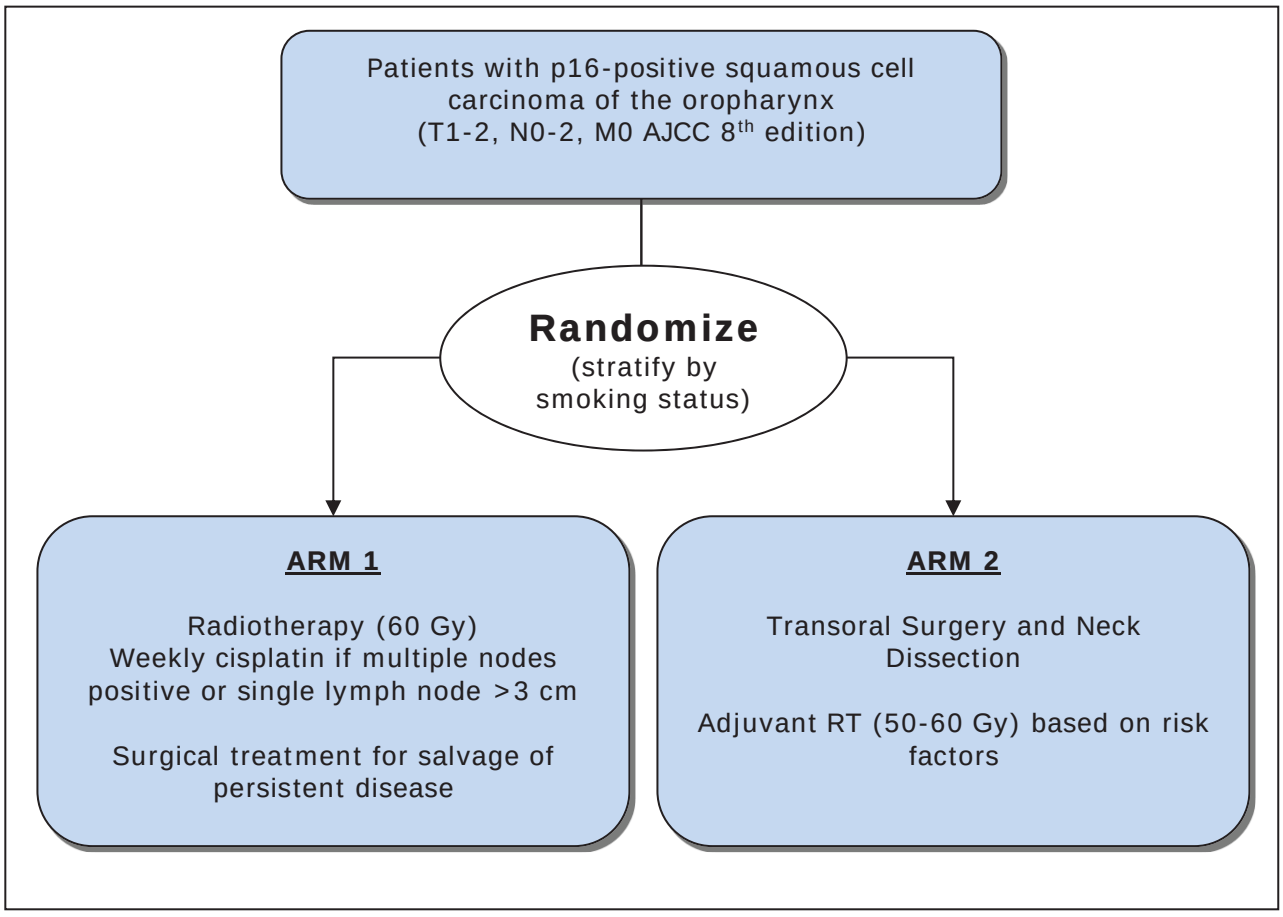

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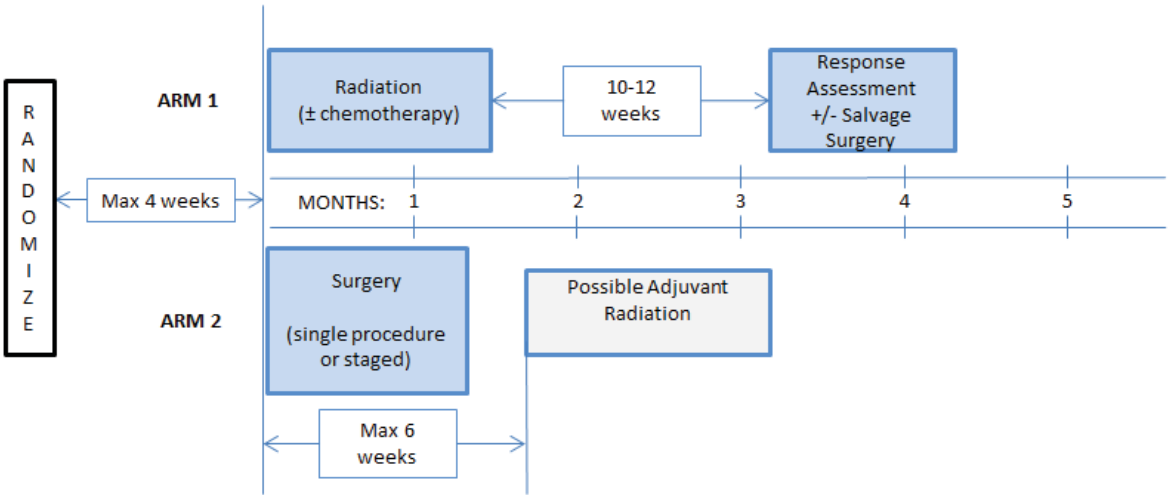


4.0 PATIENT SELECTION

4.1 Inclusion Criteria

- Age 18 or older
- Willing to provide informed consent
- ECOG performance status 0-2
- Histologically confirmed squamous cell carcinoma
- HPV-positive tumor, as determined by: positive p16 status, real-time PCR or *in-situ* hybridization. Central confirmation is not required.
- Primary tumor site in the oropharynx (includes tonsil, soft palate, base of tongue, walls of oropharynx)
- Eligible for curative intent treatment, with likely negative resection margins at surgery. For patients where adequate transoral access is in question, they will first undergo an examination under anesthesia prior to randomization to ensure adequate exposure can be obtained
- Smokers and non-smokers are included. Patients will be stratified by <10 pack years smoking history versus ≥ 10 pack years. Pack-years are calculated by multiplying the number of years smoked against the packs of cigarettes smoked per day. One pack is considered to contain 20 cigarettes.
- Tumor stage (AJCC 8th edition): T1 or T2
- Nodal stage (AJCC 8th edition): N0, N1 or N2
- For patients who may require chemotherapy (i.e. patients with multiple lymph nodes positive or a single node more than 3 cm in size, in any plane; see section 6): CBC/differential obtained within 4 weeks prior to randomization, with adequate bone marrow function, hepatic and renal function, as determined by the enrolling investigator
- Patient assessed by a radiation oncologist and surgeon
- Patient case presented at multidisciplinary tumor board prior to randomization. If not feasible, case can be discussed with the Principal Investigator

4.2 Exclusion Criteria

- Unambiguous clinical or radiological evidence of extranodal extension on pre-treatment imaging. This includes the presence of matted nodes, defined as 3 or more nodes that are abutting with loss of intervening fat planes.

- Serious medical comorbidities or other contraindications to radiotherapy, chemotherapy or surgery

- Prior history of head and neck cancer within 5 years

- Prior head and neck radiation at any time

- Metastatic disease

- Inability to attend full course of radiotherapy or follow-up visits

- Prior invasive malignant disease unless disease-free for at least 5 years or more, with the exception of non-melanoma skin cancer

- Pregnant or lactating women

5.0 PRE-TREATMENT EVALUATION

- History and physical examination by a radiation oncologist and head and neck surgeon within 8 weeks prior to randomization, including laryngopharyngoscopy.

- Documentation of smoking history

- Staging imaging within 12 weeks prior to randomization:

    - Contrast-enhanced CT of the neck and chest
      or
    - MRI of the neck with CT of the chest
      or
    - Whole body PET/CT

- Histological confirmation of squamous cell carcinoma

- p16 or HPV-positive tumor status, as defined above

- For patients where adequate transoral access is in question, they will first undergo an examination under anesthesia prior to randomization to ensure adequate exposure can be obtained

- CBC/differential, hepatic (AST, ALT, total bilirubin) and renal function testing (BUN and creatinine, or creatinine clearance) within 4 weeks prior to randomization, if chemotherapy would be required (see section 6)

- Pregnancy test for women of child-bearing age, within 2 weeks prior to randomization

- Dental evaluation before initiation of treatment

- Assessment of all baseline symptoms, including assessment of dysphagia, using CTC-AE version 4 within 2 weeks prior to randomization. Baseline dysphagia CTC-AE will be scored in all patients.

- Completion of QOL scoring prior to treatment initiation

- Blood sample for whole genome sequencing analysis prior to initiation of treatment (see section 12.2)

- Informed consents must be obtained prior to any study specific activities

Audiogram before initiation of treatment
- Functional Oral Intake Score documented before initiation of treatment

5.1 Randomization

The study will employ a 1:1 randomization between Arm 1 and Arm 2 (Figure 1) in a permutated block design. There will be one stratification factor: smoking status (<10 pack-years vs. ≥10 years).

5.2 Pre-requisites for non-LRCP patient enrolment into trial

5.2.1 For centres providing transoral surgery (TOS) on trial, the centre must confirm that any surgeon enrolling patients onto trial has completed at least 20 previous transoral robotic or laser oropharyngeal cases. In cases where more than one surgeon has participated in a previous operation, both attending surgeons are credited with that case. Operative notes and pathology reports must be provided and bleeding complications must be reported for those 10 cases. Surgeons approved under the ORATOR trial do not need re-approval for ORATOR2.

5.2.2 Prior to opening the study, each participating research centre will be required to complete mock radiotherapy treatment plans, to ensure that such plans are designed in compliance with the protocol. The principal investigators will provide pertinent CT datasets. There will be three such mock plans: one node-negative radical case, one node-positive radical

case, and one adjuvant case. Once these have been received and approved, the centre can be activated. Centers approved under the ORATOR trial do not need re-approval for ORATOR 2.

5.2.3 All participating centres will be issued a Site Activation Notification by the Central Office when all site regulatory documents have been received. No patient enrollment may occur before this notification is received.

5.3 Registration Procedure and Data Collection

5.3.1 Data Collection

All study data will be entered into REDCap, an electronic case report form database. De-identified supporting source documents will be uploaded directly into REDCap.

All radiation plans will be uploaded to the Quantitative Imaging for Personalized Cancer Medicine (https://technainstitute.com/qipcm/) for post-hoc quality assessment and correlation with outcomes.

5.3.2 Registration procedure

Study randomization is done through REDCap. When a new participant has signed the informed consent form and meets all eligibility criteria, follow the registration steps listed on the paper Enrollment Form.

If all eligibility criteria are met, the patient will be registered on study through REDCap and the randomization arm will be automatically assigned. You will receive an email confirmation through the REDCap notification system. Please ensure all relevant study team members are notified of the randomization arm.

6.0 TREATMENT PLAN

Initiation of treatment (Arm 1 and Arm 2) should occur within 4 weeks of randomization.

6.1 Radiotherapy

6.1.1 Technique, Immobilization and Localization

Intensity modulated radiotherapy (IMRT) will be used for all patients in this study. IMRT can be delivered using static-beam techniques or rotational techniques (e.g. Tomotherapy or Volumetric Modulated Arc Therapy [VMAT]).

All patients will be immobilized in a custom thermoplastic shell and will undergo a planning CT simulation encompassing the head and neck to below the clavicles, using a slice thickness of 3 mm or less. Contrast will be used (unless contra-indicated) for patients in Arm 1. For patients in both arms, the planning CT will be fused with other diagnostic imaging (e.g. MRI scans or pre-operative CT scans for patients in Arm 2) where necessary.

6.1.2 Dose/Fractionation and Principles of Radiation Treatment

ARM 1: Treatment in this arm is generally based on Arm 1 of NRG-HN002. Dose levels are as follows:

- **60 Gy in 30 fractions**: Gross Tumor and Involved Nodes
- **54 Gy in 30 fractions**: High risk subclinical areas.
- **48 Gy in 30 fractions**: Low-risk nodal areas

Radiation Alone in Arm 1: Accelerated over 5 weeks
Patients who are node-negative (N0), or have only a single node that is 3 cm or less in maximal diameter (in any plane) size will NOT receive chemotherapy. These patients will receive ACCELERATED radiotherapy where treatment is delivered over 5 weeks, with the sixth weekly fraction delivered on a weekday with a minimum 6 hour intrafraction interval, or on a Saturday. In patients >70 years of age, standard fractionation (daily, Mon-Fri over 6 weeks) can be used at the discretion of the radiation oncologist.

Concurrent Chemotherapy in Arm 1: Standard radiation fractionation over 6 weeks
Patients with multiple lymph nodes positive, or a single node more than 3 cm in size, in any plane, will receive concurrent chemotherapy. Chemotherapy will consist of cisplatin 40 mg/m^2 delivered weekly, for 6 cycles. For patients who are deemed unfit for weekly cisplatin, the dose and/or schedule can be modified, or cetuximab or weekly carboplatin AUC 1.5 can be used, at the discretion of the medical oncologist. When concurrent chemoradiation is delivered, radiation will be delivered daily, Mon-Fri, **over 6 weeks**.

In patients >70 years of age, chemotherapy may be omitted if the medical oncologist deems the patient to be unsuitable.

ARM 2 (if radiation required after surgery, see 6.2.1.3 below):

Patients with positive margins or extranodal extension (ENE) will receive a 6-week course of radiation as follows:

- **60 Gy in 30 fractions**: Area of positive margins or ENE

- **54 Gy in 30 fractions:** Operative bed, including primary tumor location and all dissected nodal levels (see 6.1.3 below)

- **48 Gy in 30 fractions**: Undissected areas considered to be at low-risk of harbouring microscopic disease.

Patients without positive margins or ENE will receive a 5-week course of radiation as follows:

- **50 Gy in 25 fractions:** Operative bed, including primary tumor location and all dissected nodal levels (see below)

- **45 Gy in 25 fractions**: Undissected areas considered to be at low-risk of harbouring microscopic disease.

Concurrent Chemotherapy is NOT used in Arm 2, except in the unlikely event that there is residual gross disease that could not be resected (see section 6.2.1.3 below).

In this trial, chemotherapy is NOT used for patients with extranodal extension or positive margins, since such patients, had they been treated with a primary RT approach instead of surgery, may have been enrolled on HN-002 and been treated with primary radiotherapy alone (60 Gy). In addition, retrospective surgical data do not support an OS benefit to the use of chemotherapy in HPV-positive patients with ENE.[9]

6.1.2.1 Unilateral vs. Bilateral Radiation

Unilateral radiation is RECOMMENDED if the following criteria are ALL met:

- tonsil primary
- <1 cm extension into the tongue base or palate
- no posterior pharyngeal wall extension
- no ECE
- N0, or only a single ipsilateral lymph node positive

Unilateral radiation is OPTIONAL if the following criteria are ALL met

- tonsil primary
- <1 cm extension into the tongue base or palate
- no posterior pharyngeal wall extension
- no ECE
- more than one ipsilateral lymph node positive, but are all less than 6 cm, and are all in level II.

In all other cases, BILATERAL radiation is MANDATORY

These criteria apply to all patients in Arm 1, and to patients in Arm 2 who require adjuvant radiotherapy (see 6.2.1.3 below). For the patients in Arm 2 who receive adjuvant

radiotherapy, these criteria are based on the pathological findings and intraoperative findings, not the pre-operative clinical findings.

6.1.3 Specific Radiotherapy Volume Definitions

Arm 1

The gross tumor volume (GTV) is defined as the tumor (labelled GTV_P) and any grossly involved nodes that are: >1.5 cm in long axis, >1 cm in short axis, necrotic, PET positive (where applicable) or biopsy-proven to contain carcinoma (labelled GTV_N). The two GTVs will be combined and a 5 mm expansion will be added to create the CTV60 (excluding natural boundaries of spread). A 5 mm expansion will again be added, to create the PTV60.

The CTV54 includes high risk subclinical areas. This includes:

- A 1 cm expansion on the GTV_P
- Any nodal level that contains a positive node.
- Any node <1 cm in short axis the radiation oncologist deems suspicious for harbouring disease. This node plus an additional 5 mm margin will be included in the CTV54.
- The first echelon draining nodal levels. This is nearly always level 2, but should include the lateral retropharyngeal nodes (RP) for soft palate and posterior pharyngeal wall extension.

A 5 mm expansion will be added to create the PTV 54.

The CTV48 includes low-risk nodal areas defined in 6.1.4 below.

Arm 2

Patients with ENE or positive margins (Dose levels of 60 Gy, 54 Gy and 48 Gy in 30 fractions over 6 weeks):

- The region of the positive margins and/or extra-nodal extension will be defined as the CTV60. The CTV54 will comprise the remainder of the tumor bed and any dissected neck nodal levels, with the CTV48 used for undissected nodal areas that must now be treated based on pathological results, if applicable.

- Treatment volumes must include nodal levels adjacent to areas containing involved nodes. For example, if there is a level II node positive, levels Ib and V must be included. RP nodes are to be included as per the guidelines in section 6.1.4. The contralateral neck is to be included as per the guidelines in section 6.1.2.1, and based on the pathologic findings, not the pre-operative clinical findings. In treating these volumes, a CTV54 will be used for dissected areas,

whereas a CTV48 will be used for any undissected areas that do not harbor a positive node.

Patients without ENE or positive margins (Dose levels of 50 Gy and 45 Gy in 25 fractions over 5 weeks)

- The CTV50 will be defined to include the entire tumor bed and the dissected neck nodal levels. The CTV45 used for undissected nodal areas that must now be treated based on pathological results, if applicable.

- Treatment volumes must include nodal levels adjacent to areas containing involved nodes. For example, if there is a level II node positive, levels Ib and V must be included. RP nodes are to be included as per the guidelines in 6.1.4. The contralateral neck is to be included as per the guidelines in 6.1.2.1, and based on the pathologic findings, not the pre-operative clinical findings.

In all cases, a 5 mm CTV to PTV expansion is to be used.

In the unlikely event of residual gross disease, the patient should then be treated adjuvantly using the dose fractionations in Arm 1. In the unlikely scenario where a patient is deemed to have highly aggressive disease (e.g. frank growth/progression during the post-surgical interval), the radiation oncologist may elect to treat with a standard (non-deescalated) dose of 70 Gy in 35 fractions.

6.1.4 Nodal levels to be treated for microscopic disease (CTV48 in Arm 1, CTV48 or CTV45 in Arm 2):

The areas below are to be included in the low-risk CTVs unless already included in the high-risk CTVs as defined above.

- Patients that are node negative:
    - Ipsilateral: II-IV. RP only if extension to posterior pharyngeal wall or soft palate
    - Contralateral (if treating, per requirements in 6.1.2.1 above): II-IV, RP only if extension to posterior pharyngeal wall or soft palate

- All patients with N1 (ipsilateral) nodal disease:
    - Ipsilateral: Ib, II-V, RP
    - Contralateral (if treating, per requirements in 6.1.2.1 above): II-IV, RP only if extension to posterior pharyngeal wall or soft palate

- All patients with N2 disease:
    - Ipsilateral and contralateral: Ib, II-V, RP

6.1.5 Dose Constraints

Target dose constraints are shown below, adapted from RTOG protocols 1016 (Arm 1) and 0920 (Arm 2), HN-002, ECOG-3311 and the NCIC-CTG HN6 protocol. Dose constraints are the same whether 25 or 30 fractions are delivered, as the radiobiological conversion factor is small.

Structure	Maximum dose for either Arm 1 or Arm 2
Spinal Cord	48 Gy point dose 45 Gy to 0.1 cc
Spinal Cord PRV (defined as spinal cord + 5 mm)	52 Gy to 0.1 cc
Brainstem	54 Gy point dose 50 Gy to 0.1 cc
Brainstem PRV (defined as brainstem + 5 mm)	60 Gy to 0.1 cc
Contralateral submandibular*	Mean < 39 Gy
Lips	Mean < 20 Gy
Oral Cavity*	Mean < 30 Gy
Parotid*	Mean < 26 Gy
Mandible*	Maximum < 66 Gy
Larynx*	Maximum <45 Gy
Pharyngeal Constrictor outside of PTVs*	Mean <40 Gy

**Maximum doses will often be exceeded if the PTV overlaps with, or is in close proximity to, these structures. For example, if the contralateral level IB nodal group is within one of the PTVs, then the contralateral submandibular gland dose will be higher than the dose listed here.*

6.1.5.1 Contouring definitions:

Spinal cord: from cranial-cervical junction to T3/4. A planning organ at risk volume (PRV) will be defined as the spinal cord + 5 mm in all directions.

Brainstem: from the top of the midbrain to the cranial-cervical junction. A planning organ at risk volume (PRV) will be defined as the spinal cord + 5 mm in all directions.

Lips: each should be contoured as a 2 cm structure in the cranio-caudal direction, and extend laterally to the commissures

Oral cavity: the anterior 2/3 of the tongue, floor of mouth, the buccal mucosa, and palate

Parotid glands: to be contoured bilaterally including the accessory lobes, not to overlap with the CTVs

Mandible: the entire mandible, including the coronoid and condyloid processes and excluding teeth, contoured on the bone window

Larynx: A triangular volume extending from the inferior aspect of the hyoid to the superior aspect of the cricoid, anteriorly to include the anterior commissure and posteriorly to include the arytenoids. It does not include the suprahyoid epiglottis.

Pharyngeal constrictors: defined as the posterior pharyngeal wall, extending from the level of the inferior pterygoid plates to the cricoid.

Bilateral submandibular glands: Both glands are to be contoured in their entirety, based on its appearance on CT.

6.1.6 Radiotherapy Planning

Intensity modulated radiotherapy (IMRT) will be used for all patients in this study. IMRT can be delivered using static-beam techniques or rotational techniques (e.g. Tomotherapy or Volumetric Modulated Arc Therapy [VMAT]).

Prior to enrolling patients, each centre will be given a sample CT dataset for contouring, planning and physics QA. Enrollment can begin once the plan and QA have been approved at the LRCP.

All plans will be normalized to ensure that 95% of each PTV is covered by 100% of the prescription dose for that volume. 99% of each PTV must receive at least 93% of the prescription dose. The maximum dose must be less than 115% of the highest prescription dose.

Priorities for planning:

1. Spinal cord
2. Brainstem
3. PTVs (in descending order of dose, with highest dose level being the highest priority)
4. Contralateral parotid gland
5. Larynx
6. Pharyngeal constrictors
7. Contralateral submandibular gland
8. Lips
9. Oral Cavity
10. Mandible
11. Ipsilateral parotid
12. Ipsilateral submandibular gland

6.1.7 Quality Assurance

In order to ensure patient safety and effective treatment delivery, a robust quality assurance protocol is incorporated. The following requirements must be completed for each patient:

- Prior to treatment, or within the first week of treatment, each radiotherapy plan will be discussed at head and neck quality assurance (QA) rounds.

- All dose delivery for intensity-modulated plans (including arc-based treatments) will be confirmed before treatment by physics staff.

- Cone-beam CT and/or orthogonal x-rays will be used on a daily basis to verify treatment positioning, as per institutional standard practice.

6.1.8 Salvage Surgery in Arm 1

Treatment response will be evaluated 10-12 weeks after completion of radiation therapy. This can be done using a CT scan, MRI and/or a PET-CT.

Treatment of residual disease at the site of the primary tumor will be determined by the treating physicians, and should include surgical salvage if feasible.

Management of residual enlarged lymph nodes in the neck should be guided by standard institutional practice. In general, for patients with residual enlarged nodes on CT, a PET-CT is preferred to confirm FDG avidity prior to neck dissection. If the PET-CT is negative in the setting of enlarged nodes on CT, then close interval follow-up with repeat CT every 2-3 months is recommended until the lymph nodes resolve.
If PET-CT is unavailable, any nodes > 1 cm in short axis should, at a minimum, be carefully followed with repeat CT every 2-3 months until the lymph nodes resolve, with neck dissection at the discretion of the treating physician.

Salvage surgery for the primary tumor or lymph nodes within 5 months of treatment will be considered part of the initial treatment package and scored as persistent disease, not as recurrence. Surgery beyond 5 months post-treatment will be scored as recurrence if malignancy is evident in the pathology specimen.

6.2.1 Surgery (Arm 2)

6.2.1.1 Transoral surgery (TOS) for the primary tumor

For patients with easily accessible oropharyngeal tumors as determined by the consulting surgeon, they will proceed directly to transoral surgery with either a transoral robotic surgery (TORS), transoral laser microsurgery (TLM) or bovie cautery approach at the surgeon's preference. For patients where adequate transoral access is in question, they will first undergo an examination under anesthesia **prior to randomization** to ensure adequate exposure can be obtained.

Surgical resection will be carried out with at least 1 cm margins. At the time of surgery circumferential margins will be taken and sent for frozen section analysis. The resection will proceed until negative margins are obtained if feasible. Wounds may be closed by primary closure, local flaps (i.e. buccal or palatal flaps) or allowed to heal by secondary intention at the discretion of the treating surgeons. Free flap and regional flaps are not allowed.

The learning curve for surgeons carrying out transoral oropharyngeal cancer resections has been demonstrated to be short for early-stage cases, with significant improvements in operative time after 20 cases (but not oncologic outcomes) as learning occurs.[10] Surgeons will be required to complete a "Surgical Credentialing Questionnaire" based closely on the ECOG 3311 credentialing criteria. This includes 1) being fellowship trained in head and neck surgical oncology, 2) having carried out at least 20 transoral oropharyngeal cancer resections as primary surgeon, 3) providing operative notes for 10 of those cases, 4) a minimum of 5 oropharyngeal resection in the last year and 5) perform at least 30 neck dissections per year.

Individual surgeons will be reviewed for surgical quality after every 5 surgical cases by the principal investigator (Nichols). Bleeding or positive margin rates of greater than 20% may result in exclusion from the trial at the discretion of the principal investigators. The occurrence of an oropharyngeal bleeding fatality or severe anoxic brain injury in the absence of a tracheostomy may also result in the exclusion of the centre from the trial.

If a positive or close margin is found on the final pathology from the transoral resection, an attempt to clear the margin transorally may be performed within four weeks of the original TORS resection. This can be done with or without the robot at the surgeon's discretion.

A tracheostomy is strongly recommended, but not mandatory, to provide airway protection due to swelling and bleeding.

Centres will be reviewed for surgical quality after 5, 10 and 15 surgical cases by the principal investigators. Bleeding or positive margin rates of greater than 20% may result in exclusion from the trial at the discretion of the principal investigators. The

occurrence of an oropharyngeal bleeding fatality or severe anoxic brain injury in the absence of a tracheostomy may also result in the exclusion of the centre from the trial.

A Surgeon Case Questionnaire will be completed to capture surgical details of each case (Appendix 3).

6.2.1.2 Neck Dissection

Patients will undergo standard selective neck dissections for the lymph node areas at risk at the time of transoral resection, or as a staged procedure within two weeks prior (not after) the primary site resection, at the discretion of the surgeon. At this time the lingual and facial branches of the external carotid artery must be ligated on the side ipsilateral to the primary tumor. Patients with tonsillar, lateral pharyngeal and lateral palate cancers, with <1 cm of palate or base of tongue extension, will undergo ipsilateral neck dissections only, while all other patients will undergo bilateral neck dissections. If levels 1 or 5 are involved they will be dissected, otherwise selective neck dissections will be limited to levels 2-4. For patients with positive margins at the primary site at the time of TORS, an attempt can be made to clear the positive margin transorally.

Pathology reporting of extranodal extension (ENE): The electronic case report forms must include a description of ENE using the same descriptors as the E3311 trial:

i) absent (node without metastasis or nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule)
ii) minimal (tumor extends ≤1 mm beyond the lymph node capsule)
iii) present - extensive (tumor extends >1 mm beyond the lymph node capsule (includes soft tissue metastasis)

6.2.1.3 Adjuvant Radiotherapy

In general, no more than 6 weeks should elapse between the date of surgery and the initiation of adjuvant therapy

Adjuvant radiotherapy is required for the following risk factors:

- Extranodal extension
- Positive margins or close resection margins (<3 mm)
- More than 1 lymph node positive, or any lymph node >3 cm in size on pathology
- Lymphovascular invasion
- pT3-4 disease

In situations where perineural invasion alone is present, without the other risk factors above, adjuvant RT is at the discretion of the treating physicians.

Radiotherapy prescriptions and planning details are outlined in section 6.1.

Concurrent chemoradiation will not be delivered in the adjuvant setting unless gross tumor is left behind at the primary site or in the neck AND the patient would have received chemotherapy had they been randomized to Arm 1, then chemotherapy should be delivered.

A post-hoc analysis of two previous RCTs identified an overall survival benefit of chemotherapy and radiation in the adjuvant setting for positive margins and extranodal extension[11,12]. However, these trials were carried out prior to the HPV era on an unselected population involving multiple aerodigestive sites (not just OPC). In addition, long-term follow-up at 10 years of demonstrated that this survival advantage no longer existed[13]. Large retrospective datasets from multiple institutions demonstrate no benefit for adjuvant chemotherapy for HPV-positive patients supporting our rationale for adjuvant therapy[14-16]. More compellingly, patients with ENE in the NRG HN002 study were not excluded and specific radiation doses prescribed in the protocol to treat these nodes. Thus, in the HN002 study schema patients with ENE could potentially receive only 60Gy (no chemo) in one arm, while these same patients would be treated with at least surgery and 60Gy RT in Arm 2 of our study.

6.2.1.4 Surgical Restaging

The AJCC 8th edition has a pathologically based staging system for HPV-positive patients treated with primary surgery that differs significantly from the clinically based staging system used for patients treated with primary radiation. All surgically treated patients will be separately restaged after the final pathology is available.

7.0 ADVERSE EVENTS

7.1 Definitions

Adverse Event (AE) or reaction is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Serious Adverse Event (SAE) or reaction as defined in the ICH Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A Section IIB includes any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization may be considered a serious adverse event, when, based upon medical and scientific judgment, they may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Unexpected adverse reaction is one that the nature and severity is not consistent with the applicable product information (e.g., Investigator's Brochure or Product Monograph, described in the REB/IRB approved research protocol or informed consent document), or occurs with more than expected frequency.

7.2 Causality (attribution)

An adverse event or reaction is considered **related** to the research intervention if there is a reasonable possibility that the reaction or event may have been caused by the research intervention (i.e. a causal relationship between the reaction and the research intervention cannot be ruled out by the investigator(s)).

The relationship of an AE to the study treatment (causality) will be described using the following definitions:

Unrelated: Any adverse event for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study treatment and the adverse event does not follow any previously documented pattern. The adverse event, after careful consideration by the investigator, is clearly and incontrovertibly due to causes other than the intervention.

Unlikely: Any adverse event for which the time relationship between the study treatment and the event suggests that a causal relationship is unlikely and/or the event is more likely due to the subject's clinical condition or other therapies concomitantly administered to the subject.

Possible: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The adverse event, after careful consideration by the investigator, is considered to be unlikely related but cannot be ruled out with certainty.

Probable: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The adverse event, after careful consideration by the investigator, is believed with a high degree of certainty to be related to the intervention.

Definitely Related: Any adverse event occurring within a timely manner after administration of the study treatment that is a known sequela of the intervention and follows a previously documented pattern but for which no other explanation is known. The adverse event is believed by the investigator to be incontrovertibly related to the intervention.

7.3 Severity

The severity of adverse events will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading scale (see (http://ctep.cancer.gov).

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening or disabling
Grade 5: Death

Note: The term "severe" is a measure of intensity: thus a severe adverse event is not necessarily **serious**. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

7.4 Immediately Reportable Adverse Events and Serious Adverse Event reporting

All Serious Adverse Events are to be reported to the Central Office within 24 hours of discovery and the SAE report form is to be completed in REDCap with all available information. The Central Office must be notified by email or telephone that a new SAE form has been entered in REDCap. All available source documentation should be uploaded with this report.

It is the responsibility of each local Principal Investigator to report all Serious Adverse Events to their REB as per local REB requirements.

The lead Principal Investigator will also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies).

7.4.1 Events or Outcomes Not Qualifying as SAEs

Any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to the disease under study or disease progression and is not possibly attributable to study treatment, are not reported as SAEs even though such event or outcome may meet the definition of SAE.

Events that are exempt from reporting as serious adverse events include:

• Events emerging during the study that is part of the natural progression of the underlying cancer (including disease-related deaths) unless more severe than expected or not possibly attributable to study treatment. For example, hospitalization for the evaluation or treatment of signs and symptoms of disease progression that are not possibly attributable to study treatment will not be reported as an SAE.

• Serious Adverse Events that occur more than 30 days after the final study treatment that are judged by the investigator to be unrelated to study treatment.

7.5 ADVERSE EVENT DOCUMENTATION

All Adverse Events that are judged to be **related** to one or more of the study treatments (surgery, radiation and/or chemotherapy) will be captured in REDCap. All events qualifying as an SAE will be reported and entered in REDCap, regardless of causality.

All Grade 3, 4 and 5 Adverse Events **and** all Serious Adverse Events (regardless of grade) require the start/stop date and a full assessment of causality to each study treatment (unrelated, unlikely, possibly, probably or definitely related) as judged by the treating investigator.

For any Grade 1 and Grade 2 adverse events judged to be related to one or more of the study treatments, start and stop dates are not required to be entered in the study database unless additional information is requested by the study sponsor or the Data and Safety Monitoring Committee.

8.0 SUBJECT DISCONTINUATION / WITHDRAWAL

Subjects may voluntarily discontinue participation in the study at any time. If a subject is removed from the study, the clinical and laboratory evaluations that would have been performed at the end of the study should be obtained. If a subject is removed because of an adverse event, they should remain under medical observation as long as deemed appropriate by the treating physician.

9.0 FOLLOW-UP EVALUATION AND ASSESSMENT OF EFFICACY

The follow-up schedule is shown in Appendix 1. Day 1 of follow-up will be the first day of radiotherapy (Arm 1) or the date of surgery (Arm 2); however, survival will be calculated from the date of randomization.

Arm 1: For patients receiving radiotherapy, they will be seen weekly during radiotherapy, and 4-6 weeks after radiotherapy, as part of routine care. A CT scan or MRI of the neck

or PET/CT will be carried out 10-12 weeks after completion of radiotherapy for assessment of residual disease for neck dissection, with a routine radiotherapy appointment approximately 2 weeks after the CT scan.

Arm 2: Patients will be seen approximately 2 weeks after completion of the neck dissection for routine post-operative assessment. Adjuvant radiotherapy, if required, shall begin within 6 weeks of surgery. Radiotherapy will be pre-booked to start within 6 weeks of the date of surgery to avoid unnecessary delays. During radiotherapy, routine visits will occur weekly during radiotherapy and 4-6 weeks afterward. For all patients in Arm 2, a return visit with the surgeon will occur at 3 months from the date of surgery.

Both arms: In addition to the above, patients will be seen at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months from first date of treatment. At each visit, a history and physical examination will be conducted (including laryngopharyngoscopy), and CTCAE toxicities recorded. Only toxicities that have been judged to be possibly, probably or definitely related to study treatments will be recorded in the case report form.

The quality of life questionnaires are to be completed every 6 months except for the Patient Neurotoxicity Questionnaire (PNQ) that will be completed one year post-treatment. It is preferred that the quality of life forms be completed during clinic visits, but they may also be completed by phone, mail or email if required.

One year post-randomization, an audiogram is required.

For patients in both arms, a CT of the neck, and chest, MRI of the neck with CT of the chest or whole body PET/CT will be done at 12 months. Additional imaging or laboratory investigations should be carried out at the discretion of the oncologist, based on findings in the history or physical, and additional treatment (e.g. salvage treatment) is at the discretion of the treating physicians.

During treatment, for patients receiving chemotherapy, blood tests will be performed as per standard of care and highest BUN and Creatinine values and lowest white blood cell, neutrophil and platelet counts will be recorded on the CRF. One year post-treatment, blood test to measure BUN, Creatinine, and CBC/Differential will be performed.

9.1 Disease Progression and New Primary

In the event of disease progression, the details of new or recurrent disease and treatment details will be captured in the case report form.
Audiogram, bloodwork and quality of life questionnaires should continue to be done according to the follow up schedule in Appendix 1.

All ongoing AEs at the time of progression should be followed until resolution.

Subsequent imaging after progression can be done at the discretion of the treating investigator.

9.2 Measurement of Outcomes

9.2.1. Survival outcomes: Overall survival will be measured as time from randomization until death from any cause, and progression-free survival as time to either progression or death, whichever occurs first. These outcomes will be reported using the Kaplan-Meier method.

9.2.2 Quality of life outcomes:
The MDADI, EORTC scales, NDII, and VHI-10 will be measured at baseline and at 6-month intervals. PNQ will be completed at 1 year post-treatment.

9.2.3. Economic assessment:
Utilities will be calculated from the EQ-5D-5L which will be administered at baseline and 6 month intervals. Quality adjusted life years (QALYs) will be assessed as the area under the preference-weighted survival curve. Overall costs of each treatment strategy will be abstracted from the available literature. The incremental cost effectiveness ratios (ICERs) between treatment arms will be compared through the standard method of ratio between differences in costs and QALYs. Point estimates for these differences can be derived from multivariable generalized estimating equations (GEE) or general linear model (GLM) analyses.

9.2.4 Toxicity outcomes
CTC-AE toxicities will be recorded during treatment and at every follow-up visit (3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months from the first date of treatment)

10.0 STATISTICS AND SAMPLE SIZE CALCULATION

10.1 Endpoints

See section 3.0

10.2 Stratification

There will be one stratification factor: smoking status (<10 pack-years vs. ≥10 years).

10.3 Sample Size

The 2-year OS in each arm, based on the results of ORATOR, is estimated to be 94%. A 2-year OS of <85% will be considered inadequate. In order to differentiate an OS of 94% vs 84% using a 1-sided one-sample binomial test, with 80% power and alpha of 0.05, with 10% dropout, 70 patients are needed in each arm (140 total).

10.4 Analysis Plan

Patients will be analyzed in the groups to which they are assigned (intention-to-treat). They will also be analyzed per protocol as a secondary analysis. Comparisons of OS with historical controls will be evaluated using a one-sided binomial test as described in section 10.3.A comparison of OS and PFS between the two groups will also be conducted, using the stratified log-rank test. With a sample size of 140 patients, we will have 80% power to detect a 10% superiority in OS in either arm (assuming baseline OS of 94% in whichever arm is superior), using a two-sided alpha of 0.05. An independent-sample t-test will be used to compare QOL scores at 1-year. The percent of each patients in each arm who experience a clinically significant QOL decline (10 points) will also be reported. Pre-planned subgroup analysis will occur based on the stratification variable. A Cox multivariable regression analysis will be used to determine baseline factors predictive of survival. For the secondary endpoints involving QOL scales, linear mixed effects models will be used; for the MDADI, NDII and VHI-10, the total scores will be compared between the two arms, whereas for the EORTC scales, each of the subscales (e.g. pain, swallowing, etc.) will be compared between the two arms. The PNQ scores (A to E) will be converted to a numerical score (0 to 4, respectively), and the mean scores in each group will be compared with a t-test. In addition, the proportion of patients reporting severe neurological dysfunction (D or E) will be compared with the Chi-Square Test, or Fisher's exact test, as appropriate. FOIS scores at 1-year will also be compared using the Chi-Square or Fisher’s exact test, as appropriate. Audiology reports will be centrally reviewed. CTC-AE toxicity (grade 2 or higher) will be compared between arms using the Chi-square or Fisher’s Exact Test, as appropriate.

The availability of data from the original ORATOR trial will allow for additional historical controls. A comparison will occur between HPV-positive patients in ORATOR (who were treated with more aggressive approaches) and ORATOR2 to assess differences in quality-of-life and time-to-event outcomes.

10.5 Data Safety Monitoring Committee

The DSMC, consisting of at least one radiation oncologist, one medical oncologist, and surgical oncologist not involved in the study, will meet bi-annually after study initiation to review toxicity outcomes. The DSMC can recommend modification of the trial based on toxicity outcomes.

After half of the patients are enrolled and followed for 6 months, one interim analysis will take place. For this interim analysis, OS at 2-years will be calculated for each arm. The DSMC may recommend cessation or modification of the trial if any of these two criteria are met:

1. The rate of grade 5 toxicity definitely related to treatment is >5% in either arm
2. The upper bound of the 95% confidence interval of OS at 2 years does not include 94%.

11.0 ETHICAL CONSIDERATIONS

The Principal Investigator will obtain ethical approval and clinical trial authorization by competent authorities according to local laws and regulations.

11.1 Institutional Review Board (IRB) / Research Ethics Board (REB)

The protocol (and any amendments), the informed consent form, and any other written information to be given to subjects will be reviewed and approved by a properly constituted Institutional Review Board (IRB)/Research Ethics Board (REB), operating in accordance with the current federal regulations (e.g., Canadian Food and Drug Regulations (C.05.001); US Code of Federal Regulations (21CFR part 56)), ICH GCP and local regulatory requirements. A letter to the investigator documenting the date of the approval of the protocol and informed consent form will be obtained from the IRB/REB prior to initiating the study. Any institution opening this study will obtain REB IRB/REB approval prior to local initiation.

11.2 Informed Consent

The written informed consent form is to be provided to potential study subjects should be approved by the IRB/REB and adhere to ICH GCP and the ethical principles that have their origin in the Declaration of Helsinki. The investigator is responsible for obtaining written informed consent from each subject, or if the subject is unable to provide informed consent, the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). The investigator should inform the subject, or the subject's legally acceptable representative, of all aspects of the study, including the potential risks and benefits involved. The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form should be given to the subject or the subject's legally acceptable representative. The process of obtaining informed consent should be documented in the patient source documents.

11.3 Confidentiality of Subject Records

The names and personal information of study participants will be held in strict confidence. All study records (CRFs, safety reports, correspondence, etc.) will only identify the subject by initials and the assigned study identification number. The data coordinator will maintain a confidential subject identification list (Master List) during the course of the study. Access to confidential information (i.e., source documents and patient records) is only permitted for direct subject management and for those involved in monitoring the conduct of the study (i.e., Sponsors, CRO's, representatives of the

IRB/REB, and regulatory agencies). The subject's name will not be used in any public report of the study.

12.0 BIOMARKER STUDIES

12.1 Human papillomavirus testing

P16 testing (which is an excellent surrogate marker of HPV status) is required for enrollment. This will be done through the routine pathology laboratories as per current routine clinical care.

The accompanying biomarker study will determine HPV status by real-time PCR, not for the purposes of randomization, but to confirm the accuracy of P16 results and also for subtyping of HPV strain. Pre-treatment formalin fixed paraffin embedded primary site biopsy specimens will be retrieved in 10 slides 8um thick from the FFPE blocks. DNA will be extracted from the specimens for HPV testing by real-time polymerase chain reaction (PCR).

12.2 Whole Genome Sequencing Analysis

DNA will be extracted either from formalin fixed specimens or preferably fresh tumor for patients undergoing transoral surgery as well as 10mL of venous blood drawn prior to the initiation of treatment. Specimens yielding DNA of adequate quantity and quality (>5µg, OD between 1.8 and 2.0) will be subjected to high-throughput sequencing and gene copy number.

All of the biomarker studies described in this section will be performed in Dr. Anthony Nichols' laboratory located at the London Regional Cancer Program, in London, Ontario.

APPENDIX 1 – FOLLOWUP SCHEDULE

Follow-up dates calculated from first day of treatment

Assessments: Year 1	Pre-Treatment	During Treatment	Month 3	Month 4	Month 6	Month 9	Month 12
Physical Exam, including laryngopharyngoscopy	X		X		X	X	X
Baseline Pre-Treatment Evaluations as listed in section 5.0	X						
Study Blood Collection	X						
QOL questionnaires MDADI, NDII, EORTC QLQ H&N 35 and C30, VHI-10, EQ-5D-5L	X				X		X
QOL questionnaire PNQ							X
CTCAE Toxicity Assessment	X	X	X		X	X	X
Functional Oral Intake Score	X						X
Audiogram	X						X
Bloodwork - See section 5.0 for complete list of tests (For chemotherapy patients only)	X	X					X
Surgeon Case Questionnaire (for Arm 2 patients only)		X					
Follow up CT neck, MRI neck or PET-CT to assess for residual nodes post RT (Arm 1 only)				X			
CT neck and chest, MRI neck and CT chest or PET/CT (both arms)							X

Assessment: Years 2-5	Month 15	Month 18	Month 21	Month 24 and every 6 months thereafter until 5 years
Physical exam, including laryngopharyngoscopy	X	X	X	X
QOL questionnaires MDADI, NDII, EORTC QLQ H&N 35 and C30, VHI-10, EQ-5D-5L		X		X
CTCAE Toxicity Assessment	X	X	X	X

APPENDIX 2 – Surgical Credentialing Questionnaire

Surgeon Credentialing Questionnaire

1. Please check the item that best describes the scope of your practice:
   ___ General Otolaryngology
   ___ Head and Neck Surgery without fellowship training
   ___ Head and Neck Surgery with fellowship training (≥ 1 year)

   Necessary criteria: Head and Neck Surgery with fellowship

2. Please estimate the number of neck dissections you perform per year. _____

   Minimal criteria: 30 neck dissections / year

3. Please estimate the number of transoral endoscopic surgical procedures you perform each year

   _____

   Minimal criteria: 20/year

4. Have you performed a minimum number of 20 cases of transoral excision for oropharyngeal carcinoma as the primary surgeon?

YES_____ NO_____

   Minimal criteria: 20 cases

5. Have you performed at least 5 transoral resections of oropharyngeal carcinoma in the past 12 months?

YES_____ NO_____

   Minimal criteria: 5 cases

6. Please contact study contact study coordinator Susan Archer to upload the operative notes and pathology reports for 10 transoral oropharyngeal cancer cases, including at least one tonsil and one tongue-base primary tumor.

7. If there are other surgeons at your institution who will be participating in this program, have they also completed one of these forms?

YES_____ NO_____

APPENDIX 3 – Surgeon Case Questionnaire

ORATOR case number:

Primary Site Resection

Primary tumour site:
Epicentre:

- Tonsil
- base of tongue
- soft palate
- lateral pharyngeal wall

Extension (select all that apply)

- Tonsil
- Base of tongue
- Soft palate
- Lateral pharyngeal wall
- Posterior pharyngeal wall
- Oral cavity
- Nasopharynx
- Hard palate
- Supraglottic larynx

Was a resident or fellow involved in the primary site resection? Yes/No
If yes, Who did the majority of the primary site resection?

- Consultant surgeon (s) (names)
    - 1
    - 2 (if applicable)
- resident
- fellow

Did you use frozen section analysis?

- Yes/No

If yes, were you able to clear the margins intraoperatively based on frozen sections?

- Yes/No

Did you take frozen sections from the:

- tumour specimen
- tumour bed
- both

Neck Dissections

Was a unilateral or bilateral neck dissection performed? Yes/No

If a bilateral neck dissection was performed, why?

- Clinically or radiographically positive contralateral nodes
- It was a base of tongue primary and I perform bilateral neck dissections for all base of tongue primaries
- It was a base of tongue primary approaching within 1cm of midline
- There was more than 1cm of base of tongue or palate extension of a primary from a site other than the base of tongue
- Other _____

Was an ipsilateral external carotid vessel ligation performed for bleeding prevention? Yes/No
If yes, which vessel(s)? select all that apply

- External carotid artery
- Facial artery
- Lingual artery
- Superior thyroid artery
- Ascending pharyngeal artery

If not, why was it not performed?

_____

Tracheotomy

Did you place a prophylactic tracheotomy?

- Yes/No

If so, why? (click all that apply)

- Improve access
- airway protections
- other _____

If a trach wasn't placed, what was your reason? Click all that apply:

- not needed for access
- low risk of bleeding
- I rarely/never place trachs for transoral oropharyngeal resections

Reconstruction

Did you perform any reconstruction? Click all that apply

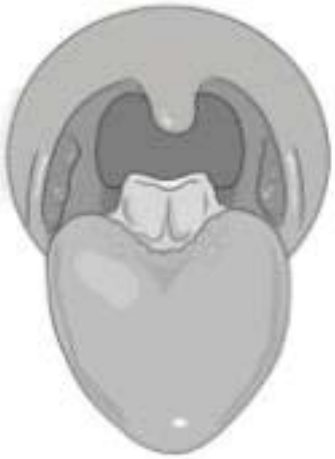
- Pharyngoplasty
- Local flap
    - Buccal flap
    - Buccal mucosal
    - Palatal island
    - Strap muscle
    - Platysma

- Other

Optional Drawing of the Resection

Print off the attached Oropharyngeal Cancer Template. Please indicate on the drawing the location of the tumour in black, the margins taken with the resection in red and the location of the circumferential margins taken in blue (if any).
Contact Anthony Nichols (anthony.nichols@lhsc.on.ca) with any questions.

Oropharyngeal Cancer Template



Margins

1) _____

2) _____

3) _____

4) _____

5) _____

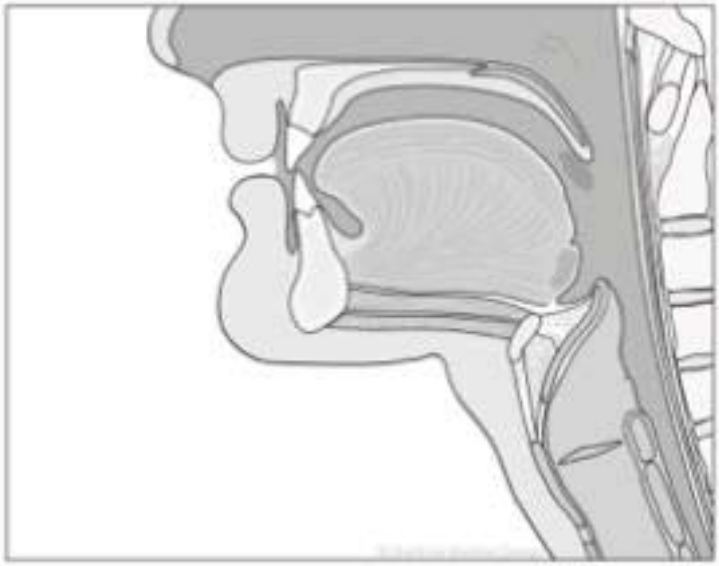
6) _____

7) _____

8) _____

9) _____

10) _____



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A Phase II Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma: Radiotherapy vs Trans-Oral Surgery (ORATOR II)

CTO Project ID: # 0905

Protocol Amendment – Rationale of Changes in Version 2.0, 01-June-2020

Summary of Protocol Changes:

Change #1	
Location	All pages
Original Wording	Version 1.3, March 15, 2019
Change	Version 2.0, June 1, 2020
Rationale	Protocol version control

Change #2	
Location	Section 4.0, page 10
Original Wording	• For patients who may require chemotherapy (i.e. patients with multiple lymph nodes positive or a single node more than 3 cm in size, in any plane; see section 6): CBC/differential obtained within 4 weeks prior to randomization, with adequate bone marrow function, hepatic, and renal function, defined as: Hemoglobin $\geq$ 80 g/L; Absolute neutrophil count $\geq 1.5 \times 10^9$ /L, platelets $\geq$ 100 $\times 10^9$/L; Bilirubin $\leq$ 35 umol/L; AST, ALT $\leq$ 3 x the upper limit of normal; serum creatinine $\leq$ 130 umol/L or creatinine clearance ≥ 50 ml/min
Change	• For patients who may require chemotherapy (i.e. patients with multiple lymph nodes positive or a single node more than 3 cm in size, in any plane; see section 6): CBC/differential obtained within 4 weeks prior to randomization, with adequate bone marrow function, hepatic and renal function, as determined by the enrolling investigator
Rationale	To allow investigators to enroll patients according to local standards for laboratory investigations

Change #3	
Location	Section 4.0, page 10
Original Wording	• Patient assessed at head and neck multidisciplinary clinic (with assessment by radiation oncologist and surgeon) and presented at multidisciplinary tumor board prior to randomization.
Amended Wording	• Patient assessed by a radiation oncologist and surgeon • Patient case presented at multidisciplinary tumor board prior to randomization. If not feasible, case can be discussed with the Principal Investigator
Rationale	Separated into two points for clarity

Change #4	
Location	Section 5.0 page 12
Original Wording	• Dental evaluation within 6 weeks prior to randomization
Amended Wording	• Dental evaluation before initiation of treatment
Rationale	To be in line with standard of care

Change #5	
Location	Section 5.0 page 12
Original Wording	Completion of QOL scoring within 2 weeks of randomization
Amended Wording	Completion of QOL scoring prior to treatment initiation
Rationale	To allow flexibility of QOL completion

Change #6	
Location	Section 5.2, page 12
Original Wording	Operative notes must be provided and bleeding complications must be reported for these 20 cases
Amended Wording	Operative notes and pathology reports must be provided and bleeding complications must be reported for those 10 cases.
Rationale	Credentialing requirements updated

Change #7	
Location	Section 5.3.2, page 13
Original Wording	1) Call the Central Office located at the London Regional Cancer Program at 519-685-8618. The Project Manager will assign a study number 2) Complete the Enrollment Form in REDCap, using the assigned study number. Upload the de-identified consent form and signed Eligibility Checklist 3) Notify the Central Office that the patient is ready for randomization 4) If the patient is eligible, the Central Office will issue an email confirming the patient has been registered and provide the randomization arm.
Amended Wording	Study randomization is done through REDCap. When a new participant has signed the informed consent form and meets all eligibility criteria, follow the registration steps listed on the paper Enrollment Form. If all eligibility criteria are met, the patient will be registered on study through REDCap and the randomization arm will be automatically assigned. You will receive an email confirmation through the REDCap notification system. Please ensure all relevant study team members are notified of the randomization arm.

Rationale	Operational change to the randomization process to support sites in different time zones

Change #8	
Location	Section 6.2.1.1, page 23
Original Wording	None
Amended Wording	A Surgeon Case Questionnaire will be completed to capture surgical details of each case (Appendix 3).
Rationale	Added to capture specific surgical details from the surgeon

Change #9	
Location	Section 7.4, page 26
Original Wording	Any grade 4 or 5 adverse reaction that is definitely, probably, or possibly the result of protocol treatment must be reported to the Principal Investigator and Central Office within 24 hours of discovery. Serious Adverse Events are to be reported to the Central Office within 24 hours of discovery. The SAE report form is to be completed with all available information and uploaded to the REDCap Serious Adverse Event page. The Central Office must be notified by email of telephone that a new SAE form has been uploaded into REDCap.
Amended Wording	All Serious Adverse Events are to be reported to the Central Office within 24 hours of discovery and the SAE report form is to be completed in REDCap with all available information. The Central Office must be notified by email or telephone that a new SAE form has been entered in REDCap. All available source documentation should be uploaded with this report.
Rationale	Administrative update to SAE handling

Change #10	
Location	Section 7.5, page 27
Original Wording	none
Amended Wording	**<u>7.5 ADVERSE EVENT DOCUMENTATION</u>** All Adverse Events that are judged to be **related** to one or more of the study treatments (surgery, radiation and/or chemotherapy) will be captured in REDCap. All events qualifying as an SAE will be reported and entered in REDCap, regardless of causality. All Grade 3, 4 and 5 Adverse Events **and** all Serious Adverse Events (regardless of grade) require the start/stop date and a full assessment of causality to each study treatment (unrelated, unlikely, possibly, probably or definitely related) as judged by the treating investigator. For any Grade 1 and Grade 2 adverse events judged to be related to one or more of the study treatments, start and stop dates are not required to be entered in the study database unless additional information is requested by the study sponsor or the Data and Safety Monitoring Committee.

Rationale	Administrative update on how AEs are captured in the database

Change #11	
Location	Section 9.0, page 27
Original Wording	The quality of life questionnaires are to be completed every 6 months except for the Patient Neurotoxicity Questionnaire (PNQ) that will be completed one year post-treatment. One year post-randomization, an audiogram is required.
Amended Wording	The quality of life questionnaires are to be completed every 6 months except for the Patient Neurotoxicity Questionnaire (PNQ) that will be completed one year post-treatment. It is preferred that quality of life forms to be completed at clinic visits, but they may also be completed by phone, mail or email if required. One year post-randomization, an audiogram is required
Rationale	Wording added to allow sites to complete QOLs in the way most convenient for the patient

Change #12	
Location	Section 10.4, page 30
Original Wording	Patients will be analyzed in the groups to which they are assigned (attention-to-treat).
Amended Wording	Patients will be analyzed in the groups to which they are assigned (attention-to-treat). They will also be analyzed per protocol as a secondary analysis.
Rationale	Additional details added to analysis plan

Change #13	
Location	Section 10.4, page 30
Original Wording	none
Amended Wording	CTC-AE toxicity (grade 2 or higher) will be compared between arms using the Chi-square or Fisher's Exact Test, as appropriate.
Rationale	Additional details added to analysis plan

Change #14	
Location	Appendix 1 – Follow Up Schedule
Amended Wording	**APPENDIX 1 – FOLLOWUP SCHEDULE** **Follow-up dates calculated from first day of treatment**

YEAR 1

Assessments ; Year 1	Pre-Treatment	During Treatment	Month 3	Month 4	Month 6	Month 9	Month 12
~~History and~~ Physical Exam, including laryngopharyngoscopy	X		X		X	X	X
Baseline Pre-Treatment Evaluations as listed in section 5.0	X						
Study Blood Collection	X						
QOL questionnaires MDADI, NDII, EORTC QLQ H&N 35 and C30, VHI-10, EQ-5D-5L	X				X		X
QOL questionnaire PNQ							X
CTCAE Toxicity Assessment	X	X	X		X	X	X
Functional Oral Intake Score	X						X
Audiogram~~, with CTCAE grade assessment~~	X						X
Bloodwork - See section 5.0 for complete list of tests (For chemotherapy patients only)	X	X					X
Surgeon Case Questionnaire (for Arm 2 patients only)		X					
Follow up CT neck, MRI neck or PET-CT to assess for residual nodes post RT (Arm 1 only)				X			
CT neck and chest, MRI neck and CT chest or PET/CT (both arms)							X

~~YEARS 2-5~~

Assessment; Years 2-5	Month 15	Month 18	Month 21	Month 24 and every 6 months thereafter until 5 years
Physical exam, including laryngopharyngoscopy	X	X	X	X
QOL questionnaires MDADI, NDII, EORTC QLQ H&N 35 and C30, VHI-10, EQ-5D-5L		X		X
CTCAE Toxicity Assessment	X	X	X	X

Rationale	Updated to reflect administrative changes to protocol

Change #15	
Location	Appendix 3, page 38
Original wording	None
Amended Wording	Surgeon case questionnaire added to protocol
Rationale	Added as appendix to reflect addition of surgeon questionnaire

A Phase II Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma: Radiotherapy vs Trans-Oral Surgery (ORATOR II)

CTO Project ID: # 0905

Protocol Amendment – Rationale of Changes in Version 1.3, March 15, 2019

Summary of Protocol Changes:

Change #1	
Location	All pages
Original Wording	Version 1.2, June 1, 2018
Change	Version 1.3, March 15, 2019
Rationale	Protocol version control

Change #2	
Location	Page 2
Original Wording	none
Change	Addition of investigator signature page
Rationale	Compliance with regulations

Change #3	
Location	Section 1.1, page 5
Original Wording	none
Amended Wording	**Addendum February 2019:** ORATOR2 was originally launched with a primary endpoint of progression-free survival (PFS). The results of the original ORATOR trial, which became available in February 2019, have indicated that overall survival (OS) would be a preferred endpoint for ORATOR2. Both arms in ORATOR showed excellent OS in p16-positive cancers (both >92% at 2 years). OS is preferred as the primary endpoint to evaluate de-escalation, since it was evidence in ORATOR that progression events, whether local, regional, or distant, can be salvaged for cure with surgery, radiation, or systemic therapy including immunotherapy. Therefore, in February 2019, without knowledge of outcomes data from ORATOR2, this trial was amended to promote OS from a secondary to primary endpoint, and demote PFS to a secondary endpoint.
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #4	
Location	Section 2.0 page 6
Original Wording	To compare progression free survival (PFS) relative to historical controls
Amended Wording	To compare ~~progression free survival (PFS)~~ **OS** relative to historical controls
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #5	
Location	Section 2.0, page 6
Original Wording	…will achieve a 2 year progression free survival (PFS) rate of >75%
Amended Wording	…will achieve ~~a~~ 2 year ~~progression free survival (PFS) rate of >75~~ **OS rates not less than 85**%
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #6	
Location	Section 2.0, page 6
Original Wording	• 2-year progression-free survival (comparison with historical controls) o Time from randomization to disease progression at any site or death Progression free survival events are defined as death from any cause, or first recurrence of tumor at any site (including local, regional, or distant). Second primary tumors (e.g. head and neck cancer at a different site, such as laryngeal cancer) will not be included as PFS events.
Amended Wording	• **Overall Survival** o **Defined as time from randomization to death from any cause** ~~• 2-year progression-free survival (comparison with historical controls)~~ ~~o Time from randomization to disease progression at any site or death~~ ~~Progression free survival events are defined as death from any cause, or first recurrence of tumor at any site (including local, regional, or distant). Second primary tumors (e.g. head and neck cancer at a different site, such as laryngeal cancer) will not be included as PFS events.~~
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #7	
Location	Section 2, page 6
Original Wording	none
Amended Wording	• 2-year progression-free survival (comparison with historical controls) ○ Time from randomization to disease progression at any site or death Progression free survival events are defined as death from any cause, or first recurrence of tumor at any site (including local, regional, or distant). Second primary tumors (e.g. head and neck cancer at a different site, such as laryngeal cancer) will not be included as PFS events.
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #8	
Location	Section 2.0, page 5
Original Wording	2 year progression free survival comparison between Arm 1 and Arm 2
Amended Wording	2 year ~~progression free survival~~ **OS and PFS** comparison**s** between Arm 1 and Arm 2
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #9	
Location	Section 2.0, page 6
Original Wording	• Overall Survival ○ Defined as time from randomization to death from any cause
Amended Wording	None, wording removed
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #10	
Location	Section 2.0, page 7
Original Wording	none
Amended Wording	Functional Oral Intake Score (FOIS) at 1 year
Rationale	Additional secondary outcome added

Change #11	
Location	Section 3.0, page 6
Original Wording	244
Amended Wording	140
Rationale	Sample size reduced based on ORATOR 1 interim results

Change #12	
Location	Section 5.0, page 12
Original Wording	none
Amended Wording	Functional Oral Intake Score documented before initiation of treatment
Rationale	To support secondary outcome

Change #13	
Location	Section 6.8.1, page 20
Original Wording	This can be done using a CT scan and/or a PET-CT
Amended Wording	This can be done using a CT scan, **MRI,** and/or a PET-CT
Rationale	MRI neck allowed to accommodate standard practices at all institutions

Change #14	
Location	Section 9.0, page 27
Original Wording	A CT scan of the neck or PET/CT will be carried out…
Amended Wording	A CT scan **or MRI** of the neck or PET/CT will be carried out…
Rationale	MRI neck allowed to accommodate standard practices at all institutions

Change #15	
Location	Section 9.2.1, page 28
Original Wording	none
Amended Wording	These outcomes will be reported using the Kaplan-Meier method
Rationale	Additional information analysis information provided

Change #16	
Location	Section 10.3, page 30
Original Wording	The 2-year PFS in this cohort is estimated to be approximately 85%, based on the results of CCTG HN6. If the 2-year PFS is <75%, then we will consider that unacceptable. PFS will be calculated using the Kaplan-Meier method. We will use a one-sample binomial test to test the 2-year PFS in each arm. We expect a 10% rate of drop-out after randomization. With 80% power and a one-sided type of error rate of 5%, we require 122 patients in each arm (total = 244 patients)
Amended Wording	**The 2-year OS in each arm, based on the results of ORATOR, is estimated to be 94%. A 2-year OS of <85% will be considered inadequate. In order to differentiate an OS of 94% vs 84% using a 1-sided one-sample binomial test, with 80% power and alpha of 0.05, with 10% dropout, 70 patients are needed in each arm (140 total).**
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #17	
Location	Section 10.4, page 30
Original Wording	Patients will be analyzed in the groups to which they are assigned (intention-to-treat). The primary endpoint will be evaluated using a one-sided binomial test. A comparison of PFS between the two groups will also be conducted, using the log-rank test. With a sample size of 244 patients, we will have >80% power to detect a 10% improvement in PFS, using a two-sided alpha of 0.05.
Amended Wording	Patients will be analyzed in the groups to which they are assigned (intention-to-treat). ~~The primary endpoint~~ **Comparisons of OS and PFS with historical controls** will be evaluated using a one-sided binomial test **(as described in section 10.3)**. A comparison of **OS and** PFS between the two groups will also be conducted, using the **stratified** log-rank test. With a sample size of ~~244~~ **140** patients, we will have ~~>~~80% power to detect a 10% ~~improvement~~ **superiority** in **OS in either arm (assuming baseline OS of 94% in whichever arm is superior)** ~~PFS~~, using a two-sided

	alpha of 0.05.
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #18	
Location	Section 10.4, page 30
Original Wording	none
Amended Wording	FOIS scores at 1 year will also be compared using the Chi-Squared or Fisher's exact test as appropriate. Audiology reports will be centrally reviewed.
Rationale	To support the new secondary outcome and analysis of audiology reports

Change #19	
Location	Section 10.5, page 30
Original Wording	After half of the patients are enrolled and followed for 6 months, one interim analysis will take place. For this interim analysis, PFS at 6 months will be calculated for each arm. The DSMC may recommend cessation or modification of the trial if any of these two criteria are met: 1. The rate of grade 5 toxicity is >5% in either arm 2. The upper bound of the 95% confidence interval of PFS at 6 months does not include 96%. This value was calculated to correspond to the anticipated 85% 2-year PFS, using an exponential survival curve.
Amended Wording	After half of the patients are enrolled and followed for 6 months, one interim analysis will take place. For this interim analysis, ~~PFS at 6 months~~ **OS at 2 years** will be calculated for each arm. The DSMC may recommend cessation or modification of the trial if any of these two criteria are met: 1. The rate of grade 5 toxicity **definitely related to treatment** is >5% in either arm 2. The upper bound of the 95% confidence interval of ~~PFS at 6 months~~ **OS at 2 years** does not include 9~~6~~**4**%. ~~This value was calculated to correspond to the anticipated 85% 2-year PFS, using an exponential survival curve.~~
Rationale	To support the change in Primary Endpoint to OS and Secondary Endpoint to PFS

Change #20	
Location	Appendix 1, page 35
Original Wording	Follow up CT neck or PET-CT to assess for residual nodes post RT (Arm 1 only)
Amended Wording	Follow up CT neck, **MRI neck or** PET-CT to assess for residual nodes post RT (Arm 1 only)
Rationale	MRI neck allowed to accommodate standard practices at all institutions

Change #21	
Location	Appendix 1, page 35
Original Wording	CT neck and chest or PET/CT (both arms)
Amended Wording	CT neck and chest, **MRI neck and CT chest**, or PET/CT (both arms)
Rationale	MRI neck allowed to accommodate standard practices at all institutions

Change #22	
Location	Appendix 1, page 35
Original Wording	none
Amended Wording	Functional Oral Intake Score added at baseline and 12 months

Rationale	For consistency with study procedures

Change #23	
Location	Appendix 2, pages 35-44
Original Wording	QOLs listed in appendix 2
Amended Wording	Removed QOLs
Rationale	To ensure centres use the approved QOLs with headings