A Phase II Randomized Sham-Controlled Trial with Allocation Concealment and Blinded Patients and Assessors, Investigating Hyperbaric Oxygen as a Radiation Sensitizer for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Study Sponsor

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Study Protocol

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1.0 List of Abbreviations and Definition of Terms

Abbreviation	Abbreviated Term
°C	Degrees Celsius
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AML	Acute Myeolid Leukemia
ANC	Absolute Neutrophil Count
AP	At Pressure
AS	At Surface
ATA	Atmospheres Absolute
BID	Twice per day
BUN	Blood Urea Nitrogen
C	Complication(s)
cc	Cubic Centimeter
CHT	Certified Hyperbaric Technologist
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical Target Volume
CTV-P	Clinical Target Volume-Primary
DNA	Deoxyribonucleic Acid
DSMB	Data Safety and Monitoring Board
DVH	Dose-Volume Histogram
EST	Eastern Standard Time (USA)
FAB	French-American-British
FACT	Functional Assessment of Cancer Therapy
FDA	Federal Drug Administration
GFR	Glomerula Filtration Rate
GTV	Gross Tumor Volume
Gy	Gray (Unit of Radiation Dose)
Gy/d	Gray Per Day (Daily Unit of Radiation Dose)
H & N	Head and Neck
HBO	Hyperbaric Oxygen
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
Hz	Hertz
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
IUD	Intrauterine Contraceptive Device
iv	Intravenous
K	Potassium
KPS	Karnofsky Performance Scale
LP	Left Pressure

LPI	Local Principal Investigator
LS	Left Surface
M	Distant Metastasis
MDS	Myelodysplastic Syndrome
mg	Milligram
Mg	Magnesium
mg/m^2	Milligram per Meter Squared
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N	Nodes
NCI	National Cancer Institute
O_2	Oxygen
OAR	Organ(s) at Risk
OPC	Oropharyngeal Cancer
P16	Tumor Suppressor Protein
PET	Positive Emission Tomography
pH	Logarithmic Scale of Acidity/Alkalinity
PHI	Protected Health Information
PLT	Platelet
pO_2	Pressure of Oxygen
psig	Pounds per Square Inch Gauge
PSS	Performance Status Scale
PTV	Planning Target Volume
RNA	Ribonucleic Acid
RT	Radiation Therapy
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SUV	Standardized Uptake Value
SWG	Study Working Group
T	Tumor
TTY	Text Telephone
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

2.0 Study Introduction and Rationale

The goal of this research is to address the question:

"Does the addition of hyperbaric oxygen to radiation and chemotherapy improve outcomes in locally advanced oropharyngeal and laryngeal squamous cell carcinoma?"

There is reason to believe that hyperbaric oxygen administered immediately prior to radiotherapy will prove beneficial for this cancer type and stage. The basis for this hypothesis is a review of several decades of published work, the conclusion of a recent (2018) Cochrane Review, and results of a Phase I trial. A summary of this body of work follows.

During the 1950's, several reports laid the groundwork for hyperbaric oxygen's potential as an effective radiation sensitizer. Gray and colleagues observed that curability of small animal tumors with radiotherapy was limited by the radio-resistance of the portion of cells that retain their reproductive integrity.[1] Tumor cell sensitivity to irradiation was seen to increase when tumor-bearing mice breathed oxygen under hyperbaric conditions. Gray's group further observed that radiobiological damage demonstrates dependence on the concentration of oxygen in the immediate vicinity of tumor cells at the time of radiation.[2] It became evident that many solid tumor cell populations exist within a wide range of oxygen tensions.[3] These findings were sufficiently encouraging to warrant a small clinical study to determine if this anticipated radio-sensitization effect could be demonstrated histologically.[4] A small diver recompression chamber was acquired from the Royal Navy and modified to accommodate a recessed acrylic window.[5]

The trial involved eight patients whose breast or lung tumor sites would lie directly below the window, above which a radiation delivery source was mounted. To assess any difference afforded by hyperbaric oxygen, tumors had to be large enough so they could addressed in two aspects. Irradiation of the inferior aspect occurred conventionally, with the superior aspect shielded. Shielding was then reversed and the superior aspect irradiated while patients breathed oxygen to 3.0 ATA.[4] Preliminary findings of increased tumor destruction secondary to hyperbaric oxygen exposure promoted investigators to treat another 35 patients in this manner. Despite their uniformly poor prognosis, the hyperbaric effect was again significant and outcomes were deemed "much better than anticipated".[6]

On the strength of this preliminary data there was widespread interest in hyperbaric radiation sensitization.[7,8,9,10] However, frustration at the lack of 'visibility' for other anatomic sites with these chamber types initially limited wider application. Industry responded by manufacturing purpose-built chambers

with increasing numbers of windows. By the early 1960's, a completely seamless acrylic hyperbaric chamber had been produced.

It eventually became apparent that hyperbaric oxygen's effectiveness was inconsistent across all tumor types (the concept of varying tumor hypoxic fraction was in its infancy). Quite probably, many of these cancers had already metastasized. Along with suggestions of a higher incidence of new primary tumors and rates of metastasis in hyperbaric oxygen irradiated patients, [11, 12] the testing of alternative sensitizers, and a lack of uniformity in radiation dosing (making comparisons difficult), interest in hyperbaric sensitization eventually began to wane. By the early 1970's, the hyperbaric chamber as a sensitizing agent had largely been abandoned.

Little more was heard of this sensitization technique until 1996, when Japanese neurosurgeons reported the results a small clinical trial investigating malignant gliomas.[13] Due to the evolution of targeted radiation delivery devices it was no longer possible to undertake concurrent hyperbaric oxygen and radiotherapy. This group, therefore, introduced a sequential approach, irradiating patients immediately upon exiting the chamber. They were encouraged enough by their findings to undertake, along with several other Japanese groups, additional brain tumor trials.

In 1997, Machin *et al*. summarized 30 years of the U.K.'s Medical Research Council sponsored trials of solid tumors, using modern statistical methodology.[14] When the five trials involving hyperbaric sensitization were re-analyzed, a clear survival advantage was evident in each of the two head and neck cancer trials, with mixed results in cancers of the cervix. In 1999, oncologists from Yale reported the results of a head and neck squamous cell carcinoma trial, conducted 20 years earlier.[15] Patients were randomized to receive radiotherapy conventionally or during hyperbaric oxygenation. Significant improvement in local control, and relapse free survival at five years was evident in the hyperbaric group.

In 2000, MR imaging demonstrated hyperbaric oxygen's ability to elevate implanted tumor oxygen levels in mice. This effect remained for 20-30 minutes after chamber decompression.[16] Malignant glioma oxygen responses to various conditions were measured via stereotactic CT guided implanted oxygen electrodes in 18 patients.[17] Hyperbaric, but not normobaric, oxygen significantly increased tumor oxygen tension, and this effect likewise remained for more than 20 minutes following patient removal from the chamber. This study had involved pre- and post-hyperbaric recordings. Becker and colleagues took this one step further and measured tumor oxygen response prior to and *during* hyperbaric oxygen exposure.[18] In seven head and neck SCC patients, mean baseline tumor pO_2 was 17 mmHg, increasing to 550 mmHg in a mean of 17 minutes of hyperbaric oxygen breathing.

Four clinical trials have further evaluated the sensitization potential of hyperbaric oxygen in malignant gliomas. This technique was considered feasible, held promise,[19] and involved minimal toxicity,[20,21] and modestly extended overall survival.[19,20,21,22]

A 2018 Cochrane Review concluded that '*given the findings of improved tumor control and mortality with the use of hyperbaric oxygen for patients with cancers of the head and neck…, there is a case for large randomized trials of high methodological vigor…'.*[23]

In contrast to earlier unsystematic reports, a 2003 meta-analysis failed to establish a causal relationship between hyperbaric oxygen therapy and *de novo* development of a tumor, established tumor growth, or an increase in the degree of metastases.[24]

Key messages from this body of work:

i. Radiation-resistance is largely a function of tumor tissue hypoxia
ii. Hyperbaric oxygen elevates SCC tumor oxygen tension in animals and man.
iii. In humans, SCC tumor oxygen tensions to peak at a mean of 17 minutes during hyperbaric oxygenation. They remain elevated for more than 15 minutes after exposure.
iv. Provision of hyperbaric oxygen has proven feasible and safe as a radiation sensitizer for both malignant brain tumors and HNSCC's.

In preparation for this Phase II trial, a Phase I 'dose escalation' study was undertaken.[25] Its purpose was to verify safety and tolerability of hyperbaric oxygen immediately prior to radiation therapy for oropharyngeal SCC. It also assessed the acute toxicity impact of hyperbaric oxygen delivered in different groups twice, three times, and five times weekly. With a mean follow-up of 19 months, five days per week hyperbaric dosing had not increased overall toxicity, and patient compliance was good. [25] Complete clinical response occurred in all patients who completed the protocol. One patient suffered bone and liver metastases. While this study was not designed to assess clinical outcomes, a subsequent report involving a minimum 61 months follow-up confirmed no late toxicities, with overall survival of 100%, zero local recurrence, and an 11% incidence of distant metastases.[26]

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3.0 Protocol Synopsis

Investigational Medicinal Product: Hyperbaric Oxygenation

Title of Study: Phase II Randomized Controlled, Double Blind Trial Investigating Hyperbaric Oxygen as a Radiation Sensitizer for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Chief Investigator: Richard Clarke

Study Sponsor: National Baromedical Services

Number of Study Centers: Minimum of ten

Main Objectives: To determine the benefit of hyperbaric oxygen administered immediately prior to radiation therapy. Study questions:

1. Effect on progression-free survival at two years*
2. Effect on an recurrence free survival at two years *
3. Effect on overall survival at two years
4. Incidence of acute toxicities
5. Incidence of acute hyperbaric complications
6. Incidence late radiation tissue injury at two years
7. Impact on quality of life
8. Protocol compliance

** Primary outcome measures*

Number of Patients to be Enrolled: 500, assuming a drop rate of 20% to 400 evaluable.

Participating centers will agree to identify all adult head and neck cancer patients as possible study participants. Once eligibility screening and informed consent has completed, patients will be randomized to Experimental or Sham-Control Groups. Each center will be encouraged to recruit 8-10 patients annually over approximately five years.

Duration of Treatment: Thirty-five hyperbaric chamber exposures will immediately precede each of the 35 radiation treatments.

4.0 Trial Registration

The trial is registered with the U.S. National Library of Medicine www.clinicaltrials.gov, **(NCT03843671)** and BioMed Central's International Standard for Randomized Controlled Trials www.isrctn.com **(ISRCTN93840508)**

5.0 Study Administration Structure

5.1 Investigators and Trial Centers

5.1.1 Chief Investigator

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5.1.2 Study Working Group

The Working Group will be responsible for day-to-day study management

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5.1.4 Independent Data Safety Monitoring Board

The Independent Data Safety Monitoring Board (DSMB) will be responsible for reviewing and assessing recruitment, interim monitoring of safety, trial conduct and external data.

The DSMB consists of an independent Radiation Oncologist, an independent Head and Neck Surgeon, an independent Hyperbaric Medicine Specialist, and an independent Biostatistician.

5.1.5 Data Safety Monitoring Board Members

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5.1.6 Local Principal Investigators

A Local Principal Investigator (LPI) will be appointed at each study center. The LPI will be responsible for all aspects of trial conduct at his/her participating center. LPI's will be provided with details on how and when to report serious Adverse Events to their local IRB and the Chief Investigator.

5.1.7 Potential Study Centers

Prisma Health Richland Hospital
Columbia, South Carolina USA
Co-LPI: D. Lindsie Cone, MD, UHM, FUHM
Co-LPI: Richard Clarke

Mayo Clinic
Rochester, Minnesota USA

LPI: Robert Foote, MD

Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire USA
LPI: Jay Buckey, MD

Hotel Dieu Hospital of Levis
Quebec City, Quebec, CANADA
LPI: Dominique Buteau, MD

Memorial Hermann Hospital
Houston, Texas, USA
LPI: pending

David Grant Medical Center
Travis Air Force Base
Fairfield, California, USA
LPI: pending

Wilford Hall Medical Facility
Lackland Air Force Base
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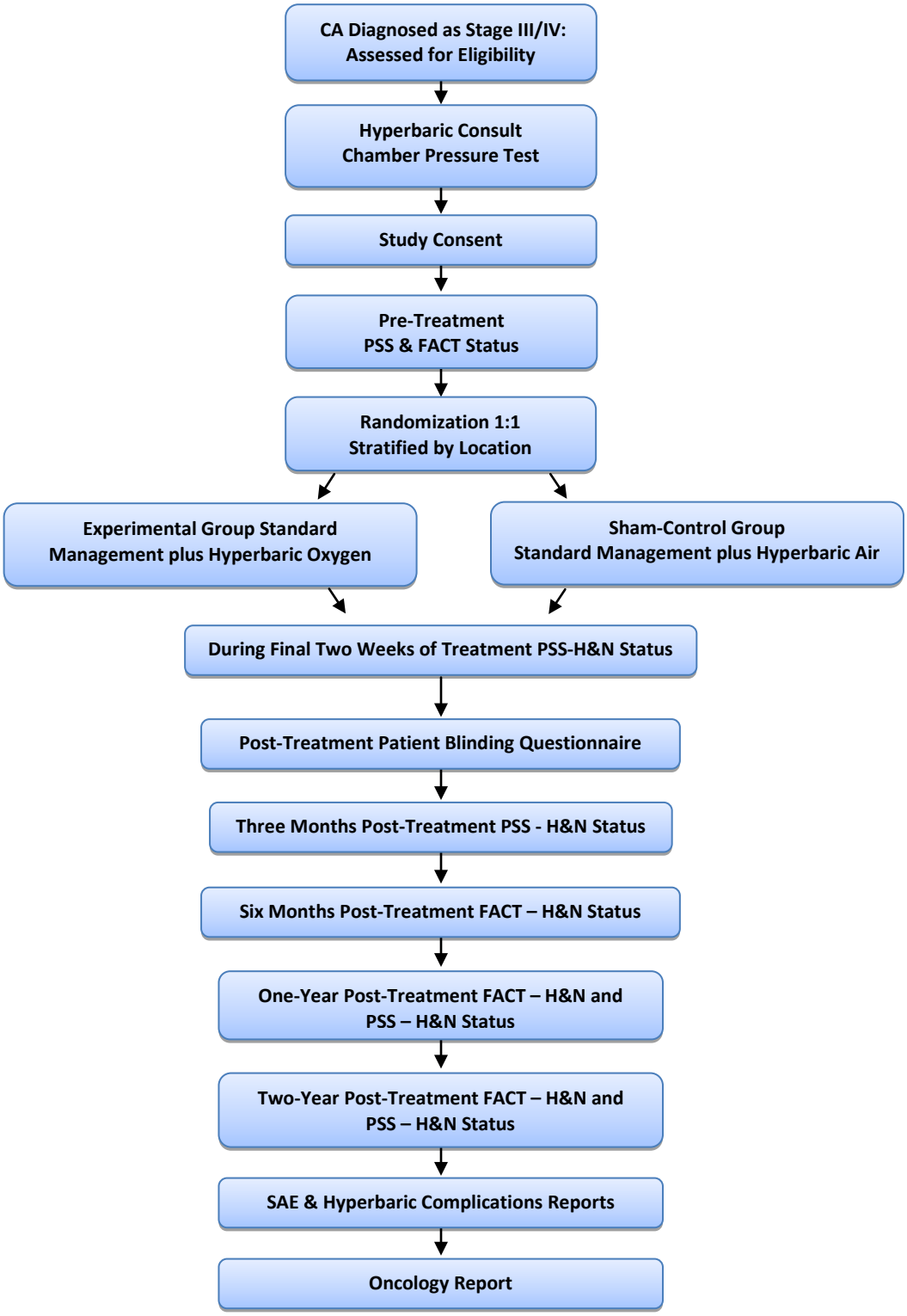
LPI: Michael Richards, MD, MC, USAF

Tobata Kyoritu Hospital
Kitakyushi, Japan
LPI: Takayuki Ohguri, MD, PhD

6.0 Investigation Plan

6.1 Study Design

6.1.1 Overall Design



6.2 Patient Monitoring and Criteria for Study Withdrawal

i. Each patient will be assessed for physical and psychological fitness by a physician credentialed in hyperbaric medicine.
ii. Patients will be assessed daily for inter-current illness prior to each chamber compression. Patients who develop inter-current upper respiratory infections during their treatment course who become unable to equalize middle ear pressure will be offered:
    a. Decongestant therapy: pseudoephedrine hydrochloride (Sudafed) 60mg, 8 hourly, orally, or Oxymetazoline (Afrin) nasal spray for acute middle ear equalization difficulties
    b. If a patient remains dependent upon those agents for more than five consecutive days he/she will be offered elective myringotomy/grommet insertion

Patients may withdraw from the trial for either of the following reasons:

i. Patient decision to discontinue treatment
ii. Intolerable adverse effects as judged by the hyperbaric physician or the patient
iii. Other reason(s), as determined by the LPI

If the patient is withdrawn from the trial, the reason for withdrawal will be noted in their medical record. The chief investigator should be notified of each/any withdrawal within 72 hours of its occurrence.

6.3 Interim Analysis and Data Safety Monitoring Board

Analysis of trial data by the DSMB is initially planned for 12-monthly intervals, to assess recruitment rates and toxicity.

A single formal interim analysis will be carried out when 200 patients have been recruited and followed for a mean of 12 months. The Peto stopping rule (for efficacy) will be implemented for the primary outcomes, (progression free survival at two years and overall survival at two years). A futility analysis will be conducted to determine if the trial is unlikely to achieve statistical significance. The futility analysis will be in the form of an estimate of conditional power comparing the two trial arms with respect to primary endpoints.

7.0 Institutional Review Board

7.1 Institutional Review Board Approval

The study protocol must be approved by the Institutional Review Board (IRB) at each the study center prior to any patient recruitment at that

center. A copy of that IRB approval document will be forwarded to the Chief Investigator.

Patients will be asked to consent that data are recorded, collected, processed and stored, and transferred to the Chief Investigator.

7.2 Patient Information and Informed Consent

The consent process is to be carried out by a medically qualified member of the research team. All patients will receive written and verbal information concerning the nature of the study, the known side effects that they may expect, and associated risks. This information will emphasize that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. All patients will be given the opportunity to ask questions and will be given sufficient time to consider before consenting.

Both the clinician taking consent and the patient must personally sign and date the form. The original copy of the signed Consent Form is to be retained by the Local Principal Investigator in their Study File. A copy will be placed in the participating patient's treatment record and a further copy of the signed Consent Form will be given to the participating patient.

Each patient's signed and dated informed consent to participate in the trial must be obtained **prior** to any trial related procedure and randomization being carried out.

8.0 Informed Consent Document

8.1 Study Title

A Phase II Trial of Hyperbaric Oxygen as a Radiation Sensitizer for Locally Advanced Squamous Cell Carcinoma of the Oropharynx or Larynx

8.2 Why Is This Study Being Done?

This research is being conducted because we do not know the best treatment for locally advanced squamous cell carcinomas of the oropharynx of larynx. These cancers have been treated with various combinations of surgery, radiation and chemotherapy. When the tumor is inoperable, radiation therapy, with or without chemotherapy, is used in the hope of curing the tumor.

Recently, studies have shown that cancer cells often have areas of low oxygen concentrations (relative degrees of hypoxia). Since radiation therapy and certain chemotherapy agents work better in the presence of oxygen, these low oxygen concentrations may explain why some cancer treatments have not been completely successful. The theory behind this

study is to give a high dose of oxygen to patients prior to radiation therapy in the hope of generating greater killing of cancer cells. Extra oxygen may also improve the effect of chemotherapy, but the main goal of this study is to administer extra oxygen just prior to radiation therapy with the intent to improve sensitivity of the tumor to radiation. The primary objective is to determine the efficacy (effectiveness) of hyperbaric oxygen given immediately prior to radiation in the treatment of your disease.

8.3 Why Are You Being Asked To Take Part?

You are being asked to participate in this research project because you have been diagnosed with squamous cell cancer of the oropharynx or larynx that has not spread to other parts of your body.

This is a research study. This study includes only people who choose to take part. Please take your time to make your decision and feel free to ask any questions you might have.

8.4 What Are Some Important Details About This Study?

Approximately 500 people will take part in this study at several participating centers.

You will remain in the study for the 6 to 8 weeks you are on active treatment for your cancer and then followed for two additional years. The purpose of this study is to determine whether giving hyperbaric oxygen just prior to radiation therapy will improve survival and limit any tumor progression) when added to standard therapy (radiation and chemotherapy) for squamous cell carcinoma of the oropharynx or larynx Prior to each of your prescribed radiation treatments, you will enter a hyperbaric chamber where you will spend approximately 40 minutes breathing either oxygen or air. You will be unaware which of these gases you are breathing. The physicians who will analyze the result of this research will also be unaware of your treatment allocation. This ‘blinding’ of patients and assessors is a well-established method to make accurate determinations about the potential benefit of various treatment options.

8.5 When Should You Not Take Part?

If you are not at least 18 years of age.
If you have received prior radiation or chemotherapy to treat your oropharyngeal cancer.
If you are unable to perform activities of daily living and are not able to perform self-care at least 70% of the time.
If you have any serious heart conditions such as irregular heart rate requiring medication, symptomatic angina (active chest pain), heart attack within the past six months, or a history of heart block.
If you have cancer that has spread somewhere else in your body other than in your oropharynx.
If you are diagnosed with a second primary cancer.

You are claustrophobic (fear of confinement in a small area).
If you are pregnant or breast-feeding.

8.6 What Is Involved In The Study?

If you enter in this study, your cancer will be treated in the following manner:

First, a chemotherapy drug called Cisplatin will be administered intravenously along with a course of radiation treatment targeted to the tumor in your oropharynx.

Cisplatin will be given every three weeks through a vein in your arm. Radiation will be given every weekday for seven weeks.

You will have a physical examination and a hyperbaric medicine focused history performed by
(Local hyperbaric physician inserted here)

A chest x-ray and/or a chest CT scan will be performed as routine work-up for your cancer evaluation. These reports may also be examined when evaluating your ability to safely tolerate the increased pressures used inside the hyperbaric chamber.

You will undergo a trial run in the hyperbaric chamber. The purpose of this is to ensure that you can comfortably accommodate the pressure changes that will occur within your ears. Although somewhat greater in magnitude, these changes are similar to those that occur while flying in a commercial aircraft or driving through the mountains. If this trial run presents undue ear equalization difficulty, your cancer surgeon will likely place ear ventilation tubes, a procedure common in children with persistent ear infections. When you have completed your radiation treatments, they will be removed. Placement of ear ventilation tubes may also become necessary during your course of treatment. Neither you nor your insurance company will be responsible for the cost of ventilation tube placement and removal.

If you agree to participate, you will sign this informed consent document in order to be registered as a study participant.

8.7 What Are The Risks Of The Study?

You should discuss any side effects that you may be experiencing with the research investigator and/or your regular doctor or healthcare provider while taking part in this study. Other drugs may be given to make side effects less serious and make you more comfortable. All patients taking part in the study will be observed for any side effects. However, doctors

do not know all the side effects that may occur. Side effects may be mild or very serious. Many side effects go away soon after you stop taking Cisplatin or receiving radiation. In some cases, side effects can be serious, long lasting, or may never go away.

Risks and side effects related to the administration of **Cisplatin** and **Radiation Therapy** include those, which are:

Likely (50 – 75%)

- Decreased white blood cells, which can lead to infection
- Decreased red blood cells (anemia), which may make you weak and tired
- Decreased platelets, which may increase the risk of bleeding
- Mouth and throat sores
- Nausea and/or vomiting
- Fatigue
- Temporary hair loss
- Weight loss
- Numbness of fingers and toes
- Ringing in the ears
- Hearing loss
- Loss of appetite or altered taste
- Tanning, redness, blistering or peeling of skin in the radiation treatment area
- Loss of teeth or cavities in the teeth if strict dental care is not followed
- Hardness and tightening of the skin and soft tissues of the face and neck
- Dryness of mouth
- Potential loss of fertility

Rare, not serious (5 – 10 %)

- Allergic reaction (facial swelling, sweating and difficulty breathing)
- Muscle cramps
- Rapid heart rate
- Loss of taste
- Restlessness
- Involuntary movement
- Blurred vision
- Difficulty in walking

Rare but serious (5 – 10 %)

- Kidney damage
- Liver damage
- Leukemia

Risks and side effects associated with the administration of **Hyperbaric Oxygen** (HBO) include those, which are:

Likely (3– 60%)

- Ear discomfort; ear pain (without injury)
- Manageable confinement anxiety (fear of small places)
- Reversible visual changes (short or far sightedness)

Rare, not serious (0.1 – 1%)

- Ear discomfort; ear pain (with injury)
- Ruptured ear drum
- Unmanageable confinement anxiety
- Sinus pain
- Central nervous system oxygen toxicity; involving one or more of the following:
  Nausea, sweating, anxiety, muscle twitching, visual changes, ringing in the ears, auditory hallucinations, seizure.

Rare, but serious (<1%)

- Lung damage
- Pulmonary edema
- Inner ear injury

In preparation for this study, a smaller study was conducted to better understand the potential for hyperbaric oxygen-related side effects. It used an identical hyperbaric oxygen dose to that planned for this study. No side effects that could be attributable to HBO therapy occurred. If any rare but serious complications do arise, you will be removed from the study. However, you will continue to receive standard care (radiation therapy and chemotherapy).

Reproductive risks: You should not become pregnant or father a baby while participating in this study because the drugs being used in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important for you to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. You may also have the potential of becoming sterile, which would prevent future childbearing.

You and your partner should use effective birth control during this study. Methods that protect more than 95 of 100 couples per year from pregnancy include male condoms plus added vaginal spermicide (to kill

sperm), the birth control patch, ring or pill. Methods that prevent pregnancy in more than 99 of 100 couples per year include total abstinence, male sterilization (vasectomy), female sterilization (tubal ligation), Norplant implants, injection contraceptives (Depo-Provera or Lunelle), or intrauterine contraceptives (IUD) (Paragard or Mirena). Be aware that emergency contraception is available within 72 hours of any situation where you think your method may have failed or you failed to use your method properly. Please contact the study investigator or your regular physician to obtain this.

Risks from Study Procedures:
A risk associated with allowing your data to be saved is the release of personal information from your study record. We will strive to protect your records so that your personal information, such as name address, social security number and phone number will remain private.

There may be other presently unknown side effects.

For more information about risks and side effects, please contact (**local oncology principal investigator name inserted here**)

8.8 Are There Benefits To Taking Part In The Study?

If you agree to take part in this study, there may or may not be a direct benefit to you. We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful. While doctors hope the use of Cisplatin and radiation in combination with hyperbaric oxygen will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We hope the information learned from this study will benefit other patients with oropharyngeal cancers in the future.

8.9 What Other Options Do You Have?

You can get treatment for your oropharyngeal cancer without being in this study. All of the treatment used in this study may be available at this center or at other close by locations.

Depending upon your treating physician's recommendations, you can receive:

- radiation treatment, with or without chemotherapy
- chemotherapy without radiation treatment
- treatment with other investigational therapies
- no treatment with supportive care (treatment for symptoms to make you feel better) only

You may choose not to participate in this research study.

Please talk to your regular doctor or health care provider about these and other options.

8.10 What About Confidentiality?

In conducting this research study, it may be necessary for the research team to send information about you and your health to persons in other organizations.

All protected health information will be maintained in strict confidence as required by law. However, your protected health information may be disclosed if required by law. Once your protected health information is disclosed for research, such as to the study sponsor, federal privacy laws may no longer protect the information.
This information may include what we call "protected health information (PHI)", which includes personal information about you. It will be shared with others only as described below:

Description of Your PHI to Be Disclosed	Organization and Person (or their title) Disclosing Your PHI	Organization and Person (or their title) Receiving Your PHI	Purpose of Disclosure
Name, age, SSN, chemotherapy, x-rays, physician records, lab reports, treatment records related to this study	Clinical research staff at your treatment facility	Richard Clarke, CHT Study lead investigator National Baromedical Services Nine Richland Medical Park, Suite 330 Columbia, SC 29203 USA Tel:+1.803.434.7101 Fax:+1.803.434.4354	Collection of data for research analysis and reporting

If you refuse to give your approval for your personal information to be shared as described in this consent form, you will not be able to participate in this study. However, your choice will not affect any medical benefits to which you are entitled.

By signing this consent form to participate in the study, you are allowing the research team to share PHI, as described in this consent form.

You have the right to cancel your approval for the sharing of PHI. If you cancel your approval, you will have to leave the study. All information collected about you before the date you cancelled will continue to be used.

To cancel your approval, you must notify **(local principal investigator name and contact information inserted here)**

Your approval for the sharing of personal information about you for this study does not expire at the end of the study.

You also have the right to review your research records, or someone you designate may review your research records on your behalf, once the study has ended unless prohibited by law.

Any research information in your medical record will become a permanent part of that document.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the National Cancer Institute, the Food and Drug Administration, and National Baromedical Services. Your identity and medical records and data related to this study will be kept confidential, except as required by law, and except for inspections by Agencies that regulate experimental drug studies, e.g. the Federal Drug Administration (FDA), members of the Institutional Review Board (IRB) or Ethics Committee, and **(name of local hyperbaric principal investigator inserted here).**

Information learned from this research may be used in reports, presentations and publications. None of these activities will personally identify you.

8.11 What Will Participation In The Study Cost Or Pay?

Doctors office visits, hospital visits, laboratory tests (blood work), chest scans, and other procedures required in this study are felt to be part of standard medical care for your condition and will be paid by you or your health insurance company. The cost of the hyperbaric chamber exposures will be provided to you at no cost, as will any necessary placement and removal of your ear ventilation tubes. You or your health insurance company will be responsible for all other costs related to your care.

The use of medications to help control side effects from your treatment could result in added costs. How much you will have to pay depends on whether or not you have health insurance and what costs your insurance plan will cover. If you do not have insurance, every effort will be made to assist with you with provision of medically necessary drug,

You will not be paid for taking part in this study.

8.12 What If You Get Injured?

In the case of injury or illness resulting from this study, emergency treatment is available and will be provided at a local medical facility at

their usual charge. Further medical care and/or hospitalisation resulting from this injury or illness, will be charged to you and/or your health insurance company.

No funds have been set aside to compensate you in the event of injury;

(**Participating hospital name inserted here**) will not provide free medical care for any sickness or injury resulting from being in this study.

Financial compensation for a research related injury or illness, lost wages, disability, or discomfort is not available. However, you do not waive any legal rights by signing this consent form.

8.13 What Are Your Rights As A Participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

We will tell you about any important new information that may affect your health, welfare, or willingness to stay in this study. The study doctor may decide to take you off this study if it is in the best interest of your health, if your condition worsens, should side effects become too severe, or new information becomes available that indicate this treatment is no longer in your best interest.

The study doctor may decide to take you off this study if your disease gets worse despite the treatment, if the side effects of the treatment become too dangerous for you, if new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding support.

State law may say that if you or anyone associated with the study is exposed to the other person's body fluids that might transmit the virus that causes AIDS or the Hepatitis B or C virus. The person whose body fluids were involved is deemed to have consented to testing for those viruses so that no further consent is necessary to test the person for these diseases, ***and*** those test results will be released to the person who was exposed and the health department, as required by state law.

8.14 Whom Do You Call If You Have Questions Or Problems?

For questions about the study, contact the investigator listed directly below (day or night):

(Insert local principal investigator contact information)

For questions about your rights as a research participant, contact a member of the Institutional Review Board through the Institutional Review Board office at **(local IRB contact number).** If you believe you have suffered an injury as a result of your participation in this study, you should contact **(contact determined by the local IRB office).**

8.15 Where Can You Get More Information?

You may call the National Cancer Institute's Cancer Information Service at +1–800–4–CANCER (+1–800–422–6237) or TTY: +1–800–332–8615

SIGNATURE			
You will get a copy of this signed form. You may also request more information from the study investigator. By signing your name on the line below, you agree to take part in this study and accept the risks.			
_____ Signature of Participant/LAR	_____ Typed or Printed Name	_____ Relationship to Subject	___/___ /___ MM/ DD/ YY
_____ Signature of Witness ☐ Witnessed Signature Only ☐ Witnessed Consent Process	_____ Typed or Printed Name		___/___ /___ MM/ DD/ YY

STATEMENT OF THE INVESTIGATOR OR APPROVED DESIGNEE	
I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised and have witnessed the above signature. I have explained all of the above to the study volunteer on the date stated on this consent form.	
_____ Signature of Investigator or Approved Designee	___ / ___ / ___ MM/ DD/ YY
_____ Printed Name of Investigator or Approved Designee	

NOTE: **The informed consent document may be modified if there are local IRB demands for are additional stipulations. It is unlikely that the Design Study Group will approve any relaxation of the informed consent process.**

9.0 Patient Eligibility Criteria

9.1 Eligibility Criteria

- Patients with histological or microscopic proof (from the primary tumor and/or lymph nodes) of invasive squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx or larynx (World Health Organization [WHO] type 1).
- Stage III or IV disease, M0
- Non-surgical candidate; for reasons of health or age (except biopsy)
- HPV (P16) negative for oropharyngeal cancers
- Life expectancy of at least 6 months and a Karnofsky performance status of ≥ 70 ***(Appendix II)***
- Age ≥ 18 years
- No distant metastatic disease
- No clinically significant heart disease:
    - No significant ventricular arrhythmia requiring medication with antiarrhythmic
    - No symptomatic coronary artery disease (angina)
    - No myocardial infarction within the last 6 months
    - No second or third degree heart block or bundle branch block or clinically significant conduction system abnormality
- Patients must sign a study-specific informed consent form

9.2 Exclusion Criteria

- Histology other than squamous cell carcinoma (for nasopharyngeal carcinoma, cannot be WHO type II or III).
- Evidence of metastasis (below the clavicle or distant) by clinical or radiographic means
- History of prior invasive malignancy, unless at least 5 years without evidence of recurrence (tumor-specific restaging)
- Prior resection of the primary tumor or lymph node, unless un-operated N2-N3 nodal disease or primary tumor remaining, respectively.
- Prior chemotherapy for head and neck cancer or radiotherapy to the head and neck
- Prior treatment with Bleomycin
- Creatinine clearance: measured or estimated GFR <40 ml/min.
- Patients with simultaneous primaries
- Pregnancy
- Participating in a conflicting protocol
- Pulmonary pathologies (risk of decompression-induced pulmonary barotrauma)
    - Current, untreated pneumothorax
    - Previous history of spontaneous pneumothorax
    - Previous history of intrathoracic surgery
    - History or evidence of pulmonary blebs or bullous lung disease

- Clinically significant chronic obstructive pulmonary disease:
  Associated with carbon dioxide retention
  Poorly controlled or associated with acute bronchospasm
- Where the hyperbaric physician deems the patient to have an otherwise unacceptable risk for hyperbaric chamber exposure

- Claustrophobia

10.0 Study Protocol and Patient Management

10.1 Objectives

10.1.1 Primary Outcomes Measures

a) Comparison of progression-free survival at two years between groups
   - *Local progression*
   - *Regional nodal metastasis*
   - *Distant metastasis*

b) Comparison of relapse-free survival at two years between groups

10.1.2 Secondary Outcomes Measures

a) Comparison of overall survival at two years between groups
b) Quality of life
c) Incidence of acute hyperbaric complications
d) Incidence and degree of acute radiation toxicity
e) Incidence and nature of late radiation tissue injury at two years
f) Protocol compliance

10.2 Study-Specific Pretreatment Evaluation

Hyperbaric medicine focused history and physical examination
Urine pregnancy screening for all pre-menopausal women
Order/review chest x-ray and/or thoracic CT scan where clinically indicated
Hyperbaric chamber pressure test on air to 2.0 ATA at 1.0 psig/minute. Hold for one to two minutes then 2.0 psig/minute decompression

Consider need for Tympanostomy tubes (if required, insert prior to radiation therapy planning whenever possible)

10.3 Registration Procedures

Patients are registered after evaluation and eligibility criteria are met by emailing or faxing form Appendix III A to:
National Baromedical Services:
dick.clarke@palmettohealth.org

Fax; +1.803.434.4354
Patients will have a study case number and randomization allocation assigned, and confirmed by email.

10.4 Treatment Schema

10.4.1 Study Type

A Phase II randomized, sham-controlled trial with allocation concealment, with both patient and assessor blinding.

10.4.2 Study Groups

Experimental Group: Standard care (chemo radiation), with radiation treatments immediately proceeded by hyperbaric oxygen exposure

Sham-Control Group: Standard care (chemo radiation), with radiation treatments immediately proceeded by 'sham' hyperbaric air exposure

11.0 Hyperbaric Dosing Protocol

11.1 Experimental Group

At 2.4 ATA for 30 minutes, breathing oxygen. This time period begins upon arrival at 2.4 ATA. Chamber oxygen percent is recorded every 15 minutes, in accordance with the Treatment Record ***Appendix III C (a)***

11.1.1 Chamber Compression Rate

Initial treatment at 1.0 – 1.5 psig/minute. If well tolerated, increase rate to 2.0 – 2.5 psig/minute for all subsequent treatments.

11.1.2 Chamber Decompression Rate

Decompression rate all treatments at 2.0-3.0 psig per minute; It is uncommon for patients to experience ear equalization difficulties during the decompression phase.

Interval between exiting chamber and RT "beam on" not to exceed 15 minutes. Alert receiving radiation technician for patient anticipated arrival time.

11.2 Sham-Control Group

1.1 ATA/1.5 psig, following sham procedure noted in **11.2.1,** for a total in-chamber time of 45 minutes, breathing air. This pressure represents the steady-state level while the control system is activated and pressure is

selected to zero (with oxygen/air flowing). Record the chamber oxygen percent every 15 minutes, in accordance with the Treatment Record ***Appendix III C (b)***

11.2.1 Patient Blinding Procedure

Every sham-control exposure will first involve compression to 1.34 ATA/5.0 psig for patient blinding purposes. Within 1-2 minutes of arrival at this pressure, begin a slow (1.0 psig/minute) decompression to 1.1 ATA /1.5 psi. Remain at this pressure for the balance of the 45 minutes.

Interval between exiting chamber and RT "beam on" not to exceed 15 minutes. Alert receiving radiation technician for patient anticipated arrival time.

Patients in each group must complete at least 24 (80%) of their first 30 treatments and at least 28 (80%) of all 35 treatments.

12.0 Radiation Therapy Protocol

12.1 Treatment Technology

IMRT using megavoltage photons is mandatory. Volumetric arc therapy or "step and shoot" techniques are both acceptable.

12.2 Immobilization and Simulation

All treatment volumes must be designed using CT-scan based simulation. The CT scan should utilize IV contrast unless contraindicated, and slice thickness should be 3 mm or less. Immobilization with a thermoplastic head, neck and shoulder mask is required. Bite blocks or customized oral prosthetic devices to displace the tongue, palate, or mandible may also be helpful. If the target volume includes oral tongue, a form of tongue immobilization is recommended.

12.3 Definition of Target Volumes and Margins

12.3.1 Gross Target Volume (GTV)

The GTV is defined as the gross primary and lymph node tumor volume as determined by a combination of physical and radiographic examination (CT, MRI, PET). Diagnostic or treatment planning CT, MRI and/or PET scans with image fusion also may be helpful in treatment planning, particularly if these scans can be performed with the same immobilization device as was used for the planning CT scan; of note, GTV border delineation should not rely entirely on PET given the uncertainty of relevant SUV cutoffs.

Primary GTV: The primary tumor GTV will be labeled as GTVp.

Nodal GTV: The nodal GTV will be labeled as GTVn. The nodal GTV should be defined as nodes that > 1 cm in short axis and/or those that are > 1.5 cm in long axis, a node of any size that has radiographic evidence of necrosis, or the presence of extra-nodal extension on radiographic imaging.

12.3.2 Clinical Treatment Volume (CTV)

The CTVs are intended to encompass areas at **risk** for microscopic disease in relation to the primary malignancy and involved nodes. In certain situations CTVs may be expanded beyond the study definitions to encompass areas deemed at high risk for malignant involvement (e.g. musculature directly involved by gross tumor). In general, CTVs associated with the primary malignancy should conform to consensus guidelines (Addendum 27.1). In general, CTVs encompassing nodal basins at risk for microscopic disease should conform to consensus guidelines (Gregoire 2014 PMID 24183870).

For the CTV70s associated with the primary and nodal GTVs a 3D isotropic expansion should be created, then altered to account for potential barriers to microscopic spread (e.g. air cavities bone, fascial planes).

Primary Tumor at High Risk for Subclinical Disease:

As modified from Addendum 25.1

GTV-P: delineated from clinical and imaging assessment. CTV-P1: CTV-P associated with the high dose prescription (70Gy); the CPT-P1 corresponds to the GTV-P and a 5 mm margin edited as for air, bones, etc.

Primary CTV at Intermediate Risk for subclinical disease:

As modified from Addendum 25.1

CTV-P2: CTV-P associated with the intermediate dose prescription (63 Gy); the CTV-P2 corresponds to the GTV-P and a 10 mm margin edited for air, bone, etc.

Primary CTV at Lower Risk for subclinical disease:

As modified from Addendum 25.1

CTV-P13; CTV-P associated with the low prescription (57 Gy); the CTV-P3 is the same volume as CTV-P2 or can be expanded to 5 mm from the CTV-P2 and edited for air, bone, etc. at the discretion of the treating physician.

Nodal CTVs at Lower Risk for subclinical disease:

Labeled as CTVn57: this treatment volume encompasses nodal levels without clinical or radio-graphical evidence of gross disease but considered at risk for microscopic spread. These may include the contralateral and/or ipsilateral neck considered at risk and electively treated (Levels II-V [plus Level I for oral cavity cancer]: for pharyngeal cancers, these include the retropharyngeal lymph node level

12.3.3 Planning Treatment Volumes (PTV)

These will be named PTV70, PTV63, and PTV57. These include the CTV plus a margin to compensate for various uncertainties, such as systematic treatment setup variables, organ and patient motion, and organ displacement. A minimum of 5 mm around the CTV is recommended in all directions, except where the CTV is immediately adjacent to the spinal cord or brainstem (in which case, the margin from CTV to PTV may be as small as 1-3 mm). The CTV to PTV expansion may be as small as 2mm if daily IGRT is performed and image-matching software confirms a mismatch of < 2 mm.

12.4 Definition of Organs at Risk

OAR's will be contoured according to the consensus statement referenced in the Addendum 27.2

12.5 Radiation Dose and Treatment Planning

12.5.1 Radiation Dose Prescription

A simultaneous integrated boost IMRT technique is mandatory. The strong preference is to treat the entire volume with IMRT. Radiotherapy will be delivered once daily over 35 fractions (seven weeks) using the following dose regimen:

a) Primary tumor and involved nodal PTVs, entitled PTV70: 2 Gy per fraction
b) Intermediate risk PTV, entitled PTV63: 1.8 per fraction
c) Elective nodal PTV, entitle PTV57 Gy: 1.63 Gy per fraction

The patient must receive at least three consecutive fractions (prior to any two-day interruption) at the start of radiotherapy. At the end of therapy, BID treatment (> 6 hour inter-fraction interval) remains an option in order to complete treatment on a Friday in order to avoid a two-day treatment interruption over a weekend with treatment completion on a Monday. Any such BID decision must take into account each respective patient's degree of toxicity, and tolerance.

Plan normalization should guarantee that at least 95% of the PTV is covered by the prescribed dose.

The maximum dose should not exceed 110% of the prescribed dose. However, for the lower dose electively treated PTVs, the maximum dose can be increased to a value that is 10% higher than the value of the high dose volume (70 Gy). This maximum dose is allowed to spill outside of the involved region into the 63 and 57 Gy region.

For all PTVs:

≥95% of the PTV should receive the prescribed dose.

≤10% of the PTV may receive ≥105% of the prescribed dose.

≤1% of the PTV may receive ≥110% of the prescribed dose.

≤1% of the PTV should receive ≤95% of the prescribed dose.

≤1-5% or ≤1 cc of the unspecified tissue outside of the PTV may receive ≥100 – 110% of the prescribed dose.

The following will be reported for all PTVs:

%PTV >110% of the prescribed dose

%PTV >115% of the prescribed dose,

PTV <95% of the prescribed dose

The minimum, mean and maximum dose to the PTV

12.5.2 Prioritization for IMRT Planning and Normal Tissue Constraints

Note: Max doses = maximum dose to 0.03 cc of the volume

All doses must be clearly documented

Priority	Name	Dose Constraints
1	Spinal Cord / Spin Cord + 0.5 cm	Max ≤ 48 Gy / Max ≤ 50 Gy
2	Brainstem / Brainstem + 0.3 cm	Max ≤ 50 Gy / Max ≤ 52 Gy
3	Optic Nerve/Chiasm	Max (or D0.01cc) <+50 for optic nerve and/or optic chiasm. Max (or D0.01cc) <=55Gy for optic nerve and/or optic chiasm prv.
4	PTV70	See 12.5.1
5	PTV63	See 12.5.1
6	PTV57	See 12.5.1

7	Parotid	Mean dose to at least one parotid gland to ≤26 Gy and/or ≥50% of either parotid <30 Gy and/or ≥20 cc combined volume of both parotids <20 Gy
8	Larynx	Mean dose ≤ 35 Gy and/or ≥50% ≤40 Gy and/or ≥67% ≤50 Gy and/or ≥90% ≤60 Gy for non-laryngeal and non-hypopharyngeal primaries
9	Submandibular Gland	Mean ≤ 39 Gy for contralateral gland if level Ib is not a target
10	Oral Cavity Avoid / Nasal Cavity Avoid / Paranasal Sinus Avoid	Mean dose ≤ 30 Gy and/or ≤20% ≥55 Gy and/or ≤1% ≥65 Gy
11	Petrous and mastoid bone (middle and inner ear including cochlea, semi-circular canals, ossicles, external canal and mastoid air cells)	Mean dose 30 Gy and ≤1% ≥45 Gy
12	Esophagus	Mean dose 30 Gy and ≤20% ≥40 Gy
13	Mandible	D1cc < 63 Gy
13	Retinas	Max 45 Gy
14	Lacrimal gland(s)	≤10 Gy
15	Lens	As low as reasonably possible

12.6 Radiation Therapy Interruptions

Radiotherapy interruptions or delays only will be permitted for Grade IV in-field mucous and/or skin toxicity. Radiotherapy can be interrupted for 3-5 days (systemic chemotherapy also should be held) until the reaction subsides to Grade III and radiotherapy (and chemotherapy) is resumed; however, every effort should be made to keep this treatment break as short as possible. The maximum radiotherapy treatment break should be 7 days. Total dose, number of fractions, elapsed days and treatment breaks should be carefully and clearly reported and recorded. Treatment interruptions may be compensated by weekend treatments or BID (>6 hours between fractions) treatments one day per week. Any treatment break(s) exceeding two treatment days for reasons other than toxicity will be considered a protocol deviation.

12.7 Radiation Therapy Protocol Compliance Criteria

12.7.1 Quality Assurance Reviews

Participation in radiation oncology studies must be in accordance with institutional medical quality guidelines. Below is an example evaluation tool.

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Overall Evaluation	**Radiotherapy Prolongation**	**Total Dose Variation; refers to PVT70**	**Spinal cord dose (volume 0.03 cc, or D0.01cc)**
Per protocol	< =1 day	See table below	<=45 Gy ≤ 48 Gy
Minor Variation (Acceptable)	<=5 days	See table below	> 45 Gy but ≤+48 Gy
Major Deviation (Unacceptable)	> 5 days	See table below	> 48 Gy could use ≤ 50 Gy

Dose (Gy)	**Per Prescription**	**Minor Variation (Acceptable)**
66.5	99%	97%
70	95%	95%
77	10%	20%
84	1%	4%

12.8 Radiation Toxicity

Reversible radiation mucositis is expected to develop in the majority of patients. This will commonly manifest as Grades I to III in severity. In those rare cases of Grade IV mucositis, radiation can be interrupted (see Section 6.6.1). Other common radiation toxicities include fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, hypogeusia, dysgeusia, dysphagia, and skin erythema and desquamation within the treatment volumes. If a feeding tube is placed for nutritional supplementation, this should be recorded. Less common long-term radiation toxicities include hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, laryngeal edema, cartilage necrosis and cervical fibrosis. Much less common radiation toxicities include mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in ***Appendix I***), and cervical myelopathy (< 1% with restriction of spinal cord dose to $\underline{\leq}$ 45 Gy).

12.9 Radiation Toxicity Reporting

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology

Criteria for Adverse Events (CTCAE) v 5.0. CTCAE is downloadable from the CTEP homepage (http://ctep.cancer.gov/reporting/ctc.html).

13.0 Chemotherapy Protocol

Chemotherapy will be given in any week that is anticipated to give radiation for more than three days. Systemic therapy with Cisplatin is to commence within 24 hours from the start of radiotherapy and be administered on Monday, Tuesday, or Wednesday. For patients starting radiotherapy on Wednesday, the systemic treatment should also start on Wednesday. To accommodate for holidays, the drug treatment may be advanced or delayed by one day and then the original schedule resumed for subsequent cycles. Systemic therapy is administered for radiation sensitization, and the intent is to deliver systemic therapy during radiotherapy. When radiotherapy concludes, the final dose of Cisplatin can be given up to one-week post radiation completion, as the radio-sensitizing effect will still be ongoing.

13.1 Radiation Plus Three Weekly Cisplatin

Cisplatin 100 mg/m2 IV every three (3) weeks

- Anti-emetics and Cisplatin hydration to be administered in accordance with institutional protocol.
- Creatinine clearance: measured or estimated GFR <40 ml/min. If >40 but <60, cisplatin should be stared at does level (-)1.

13.2 Suggested Supportive Measures

- Dolasetron 100 mg IV (or equivalent antiemetic) can be administered 30 minutes prior to delivery of cisplatin.
- Dexamethasone 20 mg IV can be administered 30 minutes prior to delivery of cisplatin.
- Patients should be adequately hydrated prior to receiving cisplatin. A recommended approach is 1 liter of sodium chloride 0.9% over 2 hours prior to treatment.
- Attention should be given to K+ and Mg++ levels, with replacement as needed and chemotherapy administered as long as the patient is stable.

13.3 Cisplatin (Cis-Diamminedichloroplatinum, DDP)

13.3.1 Formulation

Each vial contains 10 mg of cisplatin, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One

vial is reconstituted with 10 mL of sterile water. The pH range will be 3.5 to 4.5.

13.3.2 Storage and Preparation

The dry, unopened vials should be stored at refrigeration temperature (+4°C to +8°C). Reconstitution results in a solution stable for not more than one hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

13.3.3 Administration

Intravenous.

13.3.4 Pharmacology

The mechanism of action of cisplatin has not been clearly elucidated. However, the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that cisplatin binds to DNA and produces inter-strand cross-links. Also cisplatin is not phase sensitive and its cytotoxicity is similar in all phases of the cell cycle.

13.3.5 Side Effects and Toxicities

The major effects in humans have been renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range (4000 to 8000 Hz), nausea and vomiting, hyperuricemia, mild to moderate anemia, peripheral neuropathy, and electrolyte abnormalities, namely hypokalemia and hypomagnesemia.

13.3.6 Supplier

Commercially available. For further information, please see the package insert.

13.4 Dose Modifications

NOTE: Serum chemistries are to be monitored weekly during chemotherapy. It is expected that appropriate adjustments in electrolyte therapy will be addressed by the patient's attending physician.

13.4.1 Cisplatin Dose Levels

	Starting Dose	Dose Level -1	Dose Level -2
Cisplatin	100 mg/m2 (3 weekly)	75 mg/m2	50mg/m2

13.4.2 Dose Modifications for Hematologic Toxicity

NCI CTCAE Toxicity Grade (CTCAE v. 5.0)	Cisplatin Dose at Start of Subsequent Cycles of Therapy
Neutropenia	
ANC> 1000/mm3	Maintain dose level
500-999/mm3	Hold Dose for this week; if continues >7 days, decrease dose 1 level and resume when ANC >=1000 /mm3
<500/mm3	Hold Dose for this week; decrease dose 1 level if this level continues more than one week and resume when ANC >=1000/mm3
Thrombocytopenia	
> 75,000/mm3	Maintain dose level
50,000-74,999/mm3	Hold Dose for this week; if continues >7 days, decrease dose 1 level and resume when PLT >= 75,000/mm3
<50,000/mm3	Hold Dose for this week; decrease dose 1 level and resume when PLT >=75,000/mm3

13.4.3 Dose Modifications for Non-Hematologic Toxicity

NCI CTCAE Toxicity[a] Grade (CTCAE v. 5.0)	Cisplatin Dose[c]
Renal-serum Creatinine [b]	
≤ Grade 1	Maintain dose levels
Grade 2	Decrease by 1 dose level
≥ Grade 3	Hold drugs until ≤ grade 1, then decrease by one level
Nausea/Vomiting ≤ Grade 2 with maximal medical management ≥ Grade 3 with maximal medical management	 Maintain dose level Hold drug until ≤ grade 2
Other non-hematologic Toxicities [d]	
Neuropathy ≤ Grade 2 Grade 3-4	Decrease by 1 dose level Discontinue cisplatin
Other: Mucositis in RT field Grade 0-3 Grade 4	 Maintain dose levels Hold drug until ≤ grade 3
Rash, in RT field ≤ Grade 2 Grade 3 Grade 4	 Maintain dose levels Maintain dose levels Hold drug until ≤ grade 3
Rash, out of RT field ≤ Grade 2	 Maintain dose levels

Grade 3 Grade 4	Maintain dose levels Hold drug until ≤ grade 3
Grade 4 / Other	Hold drug until ≤ grade 1
Hypersensitivity	See Section 7.5.4

[a]For CTCAE Grade < 2 non-hematologic toxicity not described above, maintain dose level of drug.
[b]Choose one or the other study to assess renal function and base treatment decision.
[c]Dose levels are relative to the previous dose.
[d]For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician.

13.5 Duration of Treatment

13.5.1 Discontinuation from Protocol Treatment

Study therapy MUST be immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Termination of the study by the sponsor.
- Any clinical adverse event, laboratory abnormality or intercurrent illness, which, in the opinion of the investigator, indicates that continued treatment with all study therapy is not in the best interest of the subject.
- Pregnancy.
- Subject non-compliance with the protocol.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease)
- Progressive disease.
- Any clinical event requiring discontinuation from therapy as detailed in Section 7.5.

The reason(s) for discontinuation from protocol treatment should be documented in the patient's medical record and Case Report Form (CRF).

13.5.2 Treatment Compliance

Trained medical personnel will administer study therapy. Treatment compliance will be monitored by drug accountability, as well as recording treatment administration in the patient's medical record and Case Report Forms.

13.5.3 Modality Review

Participation in chemotherapy studies must be in accordance with institutional medical oncology quality control guidelines.

An example scoring mechanism is **per protocol**; **variation, acceptable**; **deviation unacceptable**; **not evaluable for chemotherapy review,** or, **incomplete chemotherapy**.

13.6 Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for grading of all treatment related adverse events. A copy of the CTCAE version 5.0 is downloadable from the CTEP home page ((http://ctep.cancer.gov/reporting/ctc.html). All appropriate treatment areas should have access to a copy of the CTCAE v5.0.

13.6.1 Adverse Events

STUDY AE PHONE NUMBER: (local IRB recommendation) (available 24 hours/day)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [*CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements, 2017*]

13.6.2 Serious Adverse Events

All SAEs that fit any one of the criteria in the SAE definition below must be reported to (local IRB recommendation) (SAE PHONE: (contact number); available 24 hours/day) within 24 hours of discovery of the event.

13.6.3 Definition of a Serious Adverse Event

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [*CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirement, 2017*]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller's contact information. A Data Manager will return the call the next business day requesting details of the event.
Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to **(local IRB recommendation)** via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) AML or MDS diagnosed during or subsequent to treatment in patients on NCI/CTEP sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification

13.6.4 Serious Adverse Event Reporting

In addition to the reporting requirements noted in Section 13.6.2, it is required that all SAE's be documented on the Serious Adverse Event Reporting Form, Appendix IV. This form should be completed and forwarded to the Chief Investigator within 48 hours of knowledge of a SAE.

14.0 Statistical Considerations

14.1 Introduction

This is a multicenter, parallel group randomized, sham-controlled clinical superiority trial conducted in a tertiary care setting.

14.2 Blinding

This is a double-blind trial. Outcomes assessors will be unaware of allocation, as will enrolled patients.

Assessor blinding occurs by limiting their access to the hyperbaric chamber facility. Further, under no circumstances should any un-blinded member of the research team discuss patient allocation with assessors and others who are required to remain blinded.

Blinding occurs by compressing both groups in the hyperbaric chamber. While degree of chamber pressure change differs between groups, patients are unable to discern this difference. Likewise, they will not sense differences in chamber oxygen concentration. Both groups will experience

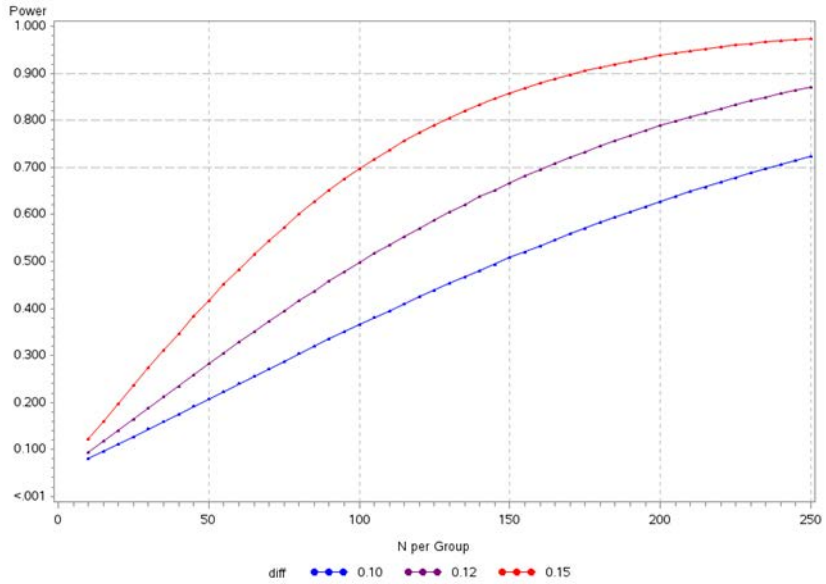
the warming sensation associated with compression and a corresponding cooling as the chamber is decompressed. Both groups will experience pressure imbalances across the tympanic membrane sufficient to prompt middle ear inflation. Chamber pressure gauges will not be visible to patients, nor too the analyzer readout of chamber oxygen percentage.

The integrity of the blinding process is vital to effective conduct of the trial.

14.3 Sample Size

In order to ensure the study involves appropriate sample size and power, 20 radiation, medical, surgical oncologists were polled, and 16 responded. (Appendix 26.0). Through this process, it was determined that the appropriate primary outcome was two-year disease free survival, the expected rate in the control group to be 55% and the minimum difference that was clinically important was 10% (i.e. 65% disease free two year survival). To detect this difference would require a sample size in excess of available resources, so a 15% difference became the basis for sample size.

Calculations are based on an assumption of proportional hazards, using survival analysis to test for different survival patterns in the experimental and sham-control groups. It is assumed that in the sham-control group, probability of survival is multiplied by .742 every year, which yields 55% progression free and relapse free survival (primary outcome measures) after two years. For the experimental group, probabilities of .806, .819, and .837 are used, which yield 65%, 67%, and 70% progression free survival after two years, resp. Power calculations, using a two-sided test at $\alpha = .05$, are summarized in the figure below, where the variable 'diff' is the difference in two-year progression free and relapse free survival between the two groups, expressed as a percent.



Minimum sample size (without and with assuming 20% attrition) needed to attain desired power.

Desired Power	Two-year survival in HBO		
	65%	67%	70%
.7	240 / 300	165 / 206	105 / 131
.8	305 / 381	210 / 263	130 / 163
.9	405 / 506	275 / 344	175 / 219

All values are **per group**, and before adjusting for attrition, have been rounded to the nearest multiple of five.

Based on these calculations, 200 subjects per group are required. Recruitment will therefore be 250 per group to allow for 20% attrition.

14.4 Missing Data

Potential for missing data will be closely monitored during the trial and its occurrence minimized by adopting the following strategy:

A CRF completion guideline document will be provided to each participating study center. A copy of the document is included herein as Section 25, Appendix VII. Data from the CRF will be entered into the study database as each milestone is reached. The database will to alert for incomplete data prior to allowing entry of any subsequent data.

An NBS clinical trial assistant will monitor the database and alert local principal investigators should missing data become apparent.

Analyses will be performed using all data available. If enough missing data raises concerns about bias, one of several possible imputation methods will be considered to accommodate this. The expectation is that the strategy described earlier will minimize the possibility of having to use such an approach. Any missing data due simply to loss to follow-up is accounted for in the survival analyses described in section 14.6.

14.5 Patient Accrual

Recruitment is planned for 100 patients per annum with each participating study center expected to contribute eight to ten patients annually. The duration of the patient recruitment is, therefore, likely to take approximately five years. An additional two years is required for assessment of outcome endpoints in all patients, extending the study period to approximately seven years. The trial will close after the last study patient follow-up visit is completed.

14.6 Statistical Analysis Plan

Descriptive statistics (means, medians, standard deviations, and IQRs for numeric variables, frequencies and proportions for categorical variables) will be calculated to describe the sample, both within and across locations.

The primary outcome is two-year progression free survival, with a secondary outcome of overall survival at two years. Both of these variables will be modeled using survival analysis, with the main independent variable being group (sham-control or experimental). This approach allows observations to be "censored" if the event of interest (point at which the patient shows disease progression or relapse for the primary outcomes, or dies for the secondary outcome) occurs after the study is completed and/or the patient is lost to follow-up. The model will also include a random location variable to allow for clustering (non-independence) among subjects treated at the same location. Adjustment for variables such as gender, race, and age will also occur.

An interim analysis will occur when 200 patients have been recruited and with a mean follow-op of 12 months, as noted in Section 6.3.

SAS 9 or higher will be used for all analyses.

14.7 Randomization

Randomization will be done separately at each center participating in the study. Within each center, subjects will be randomized using block randomization with randomly generated block sizes of either four or six subjects, with an equal number allocated to the experimental and sham-

control groups within each block. This assures that at any point in time, the overall number allocated to each group with be close to the desired 1:1 ratio.

Center randomization sequences will be computer generated using SAS, with the "seed" used to generate the random sequence unique to each center. Each local principal investigator will be provided with a series of 'A' or 'B' levels; a this point the LPI will randomly decide which of these letters represents the experimental group and which represents the sham-control group. This further helps blind those involved until finalization of results.

Each center will receive a randomization sequence in excess of the anticipated number of subjects to be recruited from that center. In the unlikely event that a center is able to recruit more subjects than have been initially randomized, another sequence will be obtained using a new seed.

15.0 Data Collection

15.1 Data Collection Forms

Data collection forms are located within **Appendix III**

15.2 Data Collection Reporting

Data collection forms are to be submitted to National Baromedical Services within 72 hours of completion of specific evaluations

15.3 DSMB Review

The Data Safety & Monitoring Board (DSMB) will review un-blinded study data at 50% patient recruitment with median follow-up of two years

DSMB is at liberty to request additional data reviews at any time

16.0 Completion of Patient Recruitment

16.1 Trail Completion Procedures

Local principal investigators will be informed when patient recruitment is to cease. This decision will be based primarily on achieving planned patient totals consistent with computed power analysis.

The DSMB may also recommend to the Chief Investigator that the trial be suspended or stopped prematurely. Examples expected to guide this recommendation include serious concerns about safety, serious concerns regarding study conduct and trial integrity, study objectives having been

achieved according to pre-established statistical guidelines, and estimation of futility.

17.0 Patient Blinding Survey

17.1 Patient Blinding Survey

Upon completion of the treatment protocol patients will undertake a 'blinding' survey. Its purpose is to assess the effectiveness of the measures that were in place to blind patients to their group allocation.

17.2 Rotation of Patient Blinding Forms

The survey asks patients if they thought they were aware of their group allocation. Answer choices are 'Hyperbaric oxygen' (experimental group), 'Sham / Control', or 'Don't know'. Patients are instructed not to guess. There are three such forms, titled as A, B and C. The difference in the forms is the order in which answer choices appear. This helps to avoid 'leading' patients to a particular choice. Rotate forms A, B and C with each consecutive patient.

18.0 Quality of Life

The Functional Assessment of Cancer Therapy (FACT) – Head & Neck cancer and the Performance Status Scale (PSS) for Head & Neck cancer will be conducted at the following time points: ***(Appendix III E)***

18.1 Functional Assessment Cancer Therapy: Head & Neck

- Pre-treatment
- 6 months after completing treatment
- 1 year after completing treatment
- 2 years after completing treatment

18.2 Performance Status Scale: Head & Neck

- Pre-treatment
- During the last two weeks of treatment
- 3 months after completing treatment
- 1 year after completing treatment
- 2 years after completing treatment

19.0 Appendix I: Management of Dental Problems in Irradiated Patients

Dental Care for Irradiated Patients

Goals for a dental care program include:
1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth which are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth
If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors
The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by:

1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program,

2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp.,

20.0 Appendix II: Karnofsky Performance Scale

100 Normal; no complaints; no evidence of disease

90 Able to carry on normal activity; minor signs or symptoms of disease

80 Normal activity with effort; some sign or symptoms of disease

70 Cares for self; unable to carry on normal activity or do active work

60 Requires occasional assistance, but is able to care for most personal needs

50 Requires considerable assistance and frequent medical care

40 Disabled; requires special care and assistance

30 Severely disabled; hospitalization is indicated, although death not imminent

20 Very sick; hospitalization necessary; active support treatment is necessary

10 Moribund; fatal processes progressing rapidly

0 Death

21.0 Appendix III: Data Collection Forms

21.1 Patient Eligibility Check

Page 1 of 2

Study center name

Pt. Study No.

_____ (Y) 1. Is there histologic confirmation of squamous cell cancer of the oral cavity, oropharynx, hypopharynx or larynx?

_____ (Y) 2. Is the tumor stage III or IV? *(N+: any T: N0: T3-4; M0) (Appendix II)*

_____ (N) 3. Any evidence of distant metastasis?

_____ (N) 4. Any evidence of simultaneous cancer, i.e., more than one cancer?

_____ (Y) 5. Is the patient's life expectancy at least 6 months?

_____ (N) 6. Any evidence of clinically significant heart disease *(see Section 2.1.6 for descriptions?)*

_____ (N) 7. Any history of prior chemotherapy?

_____ (N) 8. Any history of prior radiation therapy to the head or neck area?

_____ (N) 9. Except for diagnostic biopsy, has there been any surgery of the primary tumor or nodes?

_____ (Y/N) 10. Other than non-melanoma skin cancer, is there any history of a prior malignancy?

_____ (Y) *If **yes**, has the patient been continually cancer free for the past 5 years?*

_____ (≥ 18) 11. What is the patient's age?

_____ (N/NA) 12. Is the patient pregnant?

_____ (Y) 13. Has study-specific informed consent document been signed?

Patient Eligibility Check

_____ (Y) 1. Has the above study-specific Patient Eligibility Checklist been completed?

_____ (Y) 2. Is the patient eligible for this study?

_____ Patients Name

_____ Verifying Physician

_____ Radiation Oncologist

_____ Patient Study ID#

_____ Karnofsky Performance Status *(≥ 70) Appendix 1)*

_____ Birth Date

☐ Female ☐ Male Sex

_____ Race

_____ Treatment Start Date

Completed by: _____ _____
Date

The above Patient Eligibility Check form is to be submitted to National Baromedical Service at the time of patient registration

21.2 Cancer Related History

Date Diagnosed: _____

Tumor Type: _____

Tumor Location: _____

Tumor Stage

T	N	M
0	0	0
1	1	1
2	2	2
3	3	3
4	4	4

21.3 Hyperbaric Treatment Record

21.3.1 Experimental Group Treatment Record

2.4 ATA Oxygen x 30 mins

Patient Label

Patient Name: _____ Study No: _____

Date m/d/yyyy	TX #	ATA	O_2%	LS	AP	LP	AS	AS TO BEAM ON (Mins)	C	INIT.

LS= left surface AP= at pressure LP= left pressure AS=at surface C= Complications: record specifics in chart

21.3.2 Sham-Control Group Treatment Record

To 1.34 ATA/5psig (P1). Hold 1-2 min 1psig/min.
ascent to 1.1 ATA /1.5 psig (P2)
Total in-chamber time – 45 mins

Patient Label

Patient Name: Study No:

Date m/d/yyyy	TX #	ATA P2	O_2%	LS	AP1	AP2	LP2	AS	AS TO BEAM ON (Mins)	C	INIT.

LS= left service AP1= at pressure 1 AP2= at pressure 2 LP2= left pressure 2 AS= at surface C= Complications: record specifics in chart

21.3.3 Hyperbaric Oxygen Radiation "Beam On" Interval Record

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Day 1	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**
Day 2	**Day 2**	**Day 2**	**Day 2**	**Day 2**	**Day 2**	**Day 2**
Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**
Day 3	**Day 3**	**Day 3**	**Day 3**	**Day 3**	**Day 3**	**Day 3**
Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**
Day 4	**Day 4**	**Day 4**	**Day 4**	**Day 4**	**Day 4**	**Day 4**
Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**
Day 5	**Day 5**	**Day 5**	**Day 5**	**Day 5**	**Day 5**	**Day 5**
Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**	Date: Interval**

** Minutes

21.3.4 Functional Assessment Cancer Therapy: Head & Neck (Version 4)

Below is a list of statements that other people with your illness have said are import. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not At all**	**a little bit**	**some-what**	**quite a bit**	**very much**
GP1	I have a lack of energy ……	0	1	2	3	4
GP2	I have nausea ……0		1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family……0		1	2	3	4
GP4	I have pain ……0		1	2	3	4
GP5	I have bothered by side effects of treatment……	0	1	2	3	4
GP6	I feel ill ……	0	1	2	3	4
GP7	I am forced to spend time in bed……...0		1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not At all**	**a little bit**	**some-what**	**quite a bit**	**very much**
GS1	I feel close to my friends ……..0		1	2	3	4
GS2	I get emotional support from my family……0		1	2	3	4
GS3	I get support from my friends ……...0		1	2	3	4
GS4	My family has accepted my illness……0		1	2	3	4
GS5	I am satisfied with family communication about my illness…….……0		1	2	3	4
GS6	I feel close to my partner (or the person who is my main support) ……...……0		1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next secti*					
GS7	I am satisfied with my sex life……0		1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not At all**	**a little bit**	**some-what**	**quite a bit**	**very much**
GE1	I feel sad ……0	1	2	3	4	
GE2	I am satisfied with how I am coping with my illness……..0	1	2	3	4	
GE3	I am losing hope in the fight against my illness….0	1	2	3	4	
GE4	I feel nervous……..0	1	2	3	4	
GE5	I worry about dying……0	1	2	3	4	
GE6	I worry that my condition will get worse……0	1	2	3	4	

	FUNCTIONAL WELL-BEING	**Not At all**	**a little bit**	**some-what**	**quite a bit**	**very much**
GF1	I am able to work (include work at home) ……0	1	2	3	4	
GF2	My work(include work at home) is fulfilling……..0	1	2	3	4	
GF3	I am able to enjoy life ……...0	1	2	3	4	
GF4	I have accepted my illness…….0	1	2	3	4	
GF5	I am sleeping well……..0	1	2	3	4	
GF6	I am enjoying the things I usually do for fun…….0	1	2	3	4	
GF7	I am content with the quality of my life right now…0	1	2	3	4	

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	**Not At all**	**a little bit**	**some-what**	**quite a bit**	**very much**
H&N 1	I am able to eat the foods that I like……	0	1	2	3	4
H&N 2	My mouth is dry……	0	1	2	3	4
H&N 3	I have trouble breathing……	0	1	2	3	4
H&N 4	My voice has its usual quality and strength……..	0	1	2	3	4
H&N 5	I am able to eat as much food as I want……	0	1	2	3	4
H&N 6	I am unhappy with how my face and neck look……	0	1	2	3	4
H&N 7	I am swallow naturally and easily…….	0	1	2	3	4
H&N 8	I smoke cigarettes or other tobacco products……	0	1	2	3	4
H&N 9	I drink alcohol (e.g. beer, wine, etc.)…….	0	1	2	3	4
H&N 10	I am able to communicate with others……...	0	1	2	3	4
H&N 11	I can solid foods…….	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck……	0	1	2	3	4

21.3.5 Performance Status Scale for Head and Neck Cancer

Normalcy of Diet

Definition: A scale to rate the ability of a head and neck cancer patient to consume a normal diet that requires the ability to chew and swallow.	
Permissible Values	
(**Permissible Values)**	(**Value Meanings**)
100	Full diet (no restrictions)
90	Full diet (liquid assist)
80	All meat
70	Raw carrots, celery
60	Dry bread and crackers
50	Soft, chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft food requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

Understandability of Speech Rating

Definition: A scale to rate the ability of a head and neck cancer patient to speak in an understandable manner.	
Permissible Values	
(**Permissible Values)**	(**Value Meanings**)
100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

Public Eating Rating

Definition: A scale to rate the ability of a head and neck cancer patient to eat in public setting.	
Permissible Values	
(**Permissible Values)**	(**Value Meanings**)
100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less “messy” foods, e.g., liquids)
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone

21.3.6 Patient Follow-up Blinding Survey Form A

Pt. Name:_____ Study ID#:_____

You have recently completed a clinical trial that is investigating the role of hyperbaric oxygen therapy in the treatment of head and neck cancer. The trial involved a treatment arm and a sham / control arm. The trial was designed to prevent both you and your physicians from being aware of which arm you were randomly assigned to.

We would like to determine how effective we were in this "blinding" process. It would be helpful, therefore, if you could answer the two questions listed below.
Please try not to guess.

1. Circle or check which arm of the study you think you were assigned to?

    a) Hyperbaric oxygen
    b) Sham / control
    c) Don't know

2. If you answered a) or b) in the above question, what made you think that this was the correct answer?

Please do not discuss your answers to the above question with your treating doctors and allied health professionals.

Thank you.

21.3.7 Patient Follow-up Blinding Survey Form B

Pt. Name:_____ Pt. ID#:_____

You have recently completed a clinical trial that is investigating the role of hyperbaric oxygen therapy in the treatment of head and neck cancer. The trial involved a treatment arm and a sham / control arm. The trial was designed to prevent both you and your regular physicians from being aware of which arm you were randomly assigned to.

We would like to determine how effective we were in this "blinding" process. It would be helpful, therefore, if you could answer the two questions listed below.
Please try not to guess.

1. Circle or check which arm of the study you think you were assigned to?

   a) Don't know
   b) Sham / control
   c) Hyperbaric Oxygen

2. If you answered b) or c) in the above question, what made you think that this was the correct answer?

Please do not discuss your answers to the above question with your treating doctors and allied health professionals.

Thank you.

21.3.8 Patient Follow-up Blinding Survey Form C

Pt. Name: _____Pt. ID#:_____

You have recently completed a clinical trial that is investigating the role of hyperbaric oxygen therapy in the treatment of head and neck cancer. The trial involved a treatment arm and a sham / control arm. The trial was designed to prevent both you and your regular physicians from being aware of which arm you were randomly assigned to.

We would like to determine how effective we were in this "blinding" process. It would be helpful, therefore, if you could answer the two questions listed below.
Please try not to guess.

1. Circle or check which arm of the study you think you were assigned to?

   a) Sham / control
   b) Don't know
   c) Hyperbaric Oxygen

2. If you answered a) or c) in the above question, what made you think that this was the correct answer?

Please do not discuss your answers to the above question with your treating doctors and allied health professionals.

Thank you.

22.0 Appendix IV: Serious Adverse Event Reporting Form

A. Summary			
Report Type (check one)	☐ Initial Report	☐ Follow-up	☐ Final
Criteria for Definition of SAE (check one)			
☐ Subject died	☐ Life – threatening		
☐ Inpatient hospitalization or prolongation	☐ Persistent or significant disability		
☐ Medically important event	☐ Other: _____		
☐ Required intervention to prevent permanent impairment			
Study Location of SAE			
Date of SAE Awareness			
Start Date of SAE			
Stop Date of SAE *(or state if ongoing)*			
SAE Diagnosis			
Subject Initials			
Subject ID			
Was this an unexpected event:	☐ Yes ☐ No		
B. Narrative			
Please provide an account of the event and nature of the SAE. Mention any relevant lab data or diagnostic tests. Attach additional page(s) if needed.			
C. Intervention Type			
☐ None	☐ Withdrawn From Study		
☐ Treated with Medication (specify): _____	☐ Treated with Medical Device (specify): _____		
☐ Treated with Surgery (specify): _____	☐ Other: _____		
D. Relationship of Event to Study Participation			
☐ Unrelated (clearly not related to study participation)	☐ Possible (may be related to study participation)		
☐ Definite (clearly related to study participation)			
E. Any Additional Narrative			
F. Local Principal Investigator			
Name:		**Tel:**	
Email:		**Fax:**	
Signature:		**Date:**	

23.0 Appendix V: Oncology Outcomes Reporting Form

Pt. Name: _____ **Study ID No:** _____

Study Center: _____

a) Primary Outcomes Measures

Two Year Progression Free Survival ☐ Yes ☐ No Type: Check all that apply
- ☐ Local
- ☐ Regional Node Metastasis
- ☐ Distant Metastasis

Two Year Overall Survival ☐ Yes ☐ No

b) Secondary Outcomes Measures

Two Year Recurrence Free Survival ☐ Yes ☐ No

Quality of Life: FACT & PSS Forms Submitted ☐ Yes ☐ No

Acute Radiation Tissue Injury
- ☐ No greater than anticipated standard with chemo-radiation
- ☐ In excess of that anticipated with chemo-radiation

Notes:

Name: _____ _____
PRINT NAME SIGNATURE:

Date: _____

24.0 Appendix VI: Hyperbaric Complications Reporting Form

Pt. Name: _____ **Study ID No:** _____

Study Center: _____

c) Acute Complications

- ☐ None
- ☐ Ear Barotrauma: *if checked, Teed Scale**
  - ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
- ☐ Sinus Barotrauma
- ☐ Other Barotrauma: *describe* _____
- ☐ CNS Oxygen Toxicity
  - ☐ Seizure
  - ☐ Premonitory Event(s): *describe* _____
  - ☐ Confinement Anxiety
  - ☐ Myopia
  - ☐ Other: *describe* _____

***Teed Scale**

1. **Vascular congestion of tympanic membrane**
2. **Vascular congestion of tympanic membrane with superficial hemorrhage**
3. **Early retraction of tympanic membrane**
4. **Gross retraction of tympanic membrane, middle ear hemorrhage**
5. **Perforation**

d) Late Complications

- ☐ None
- ☐ Mandibular Osteoradionecrosis: *if checked, Notani Scale**
  - ☐ 1 ☐ 2 ☐ 3
- ☐ Soft Tissue Radionecrosis: *describe* _____
- ☐ Other: *describe* _____

e) Hyperbaric Protocol Compliance

- ☐ Compliant
- ☐ Compliance Shortcomings: *describe* _____

***Notani Scale**

1. **Confined to dento-alveolar bone**
2. **Limited to dento-alveolar bone or mandible above inferior dental canal, or both**
3. **Involving mandible below inferior dental canal, or pathologic fracture, or skin fistula**

Name: _____ _____

PRINT NAME SIGNATURE:

Date: _____

25.0 Appendix VII: Case Reporting Form

Pt. Name:		**Study ID No:**	
Study Center:		**Enrollment Date:**	

Pt. Eligibility Check Form Completed	☐ Yes	☐ No
Cancer Related History Form Completed	☐ Yes	☐ No
Pre-Treatment PSS Scale Completed	☐ Yes	☐ No
Pre-Treatment FACT Scale Completed	☐ Yes	☐ No
Hyperbaric Chamber Pressure Test Completed	☐ Yes	☐ No
Hyperbaric Chamber Treatment Record Up To Date	☐ Yes	☐ No
Hyperbaric Chamber-RT Interval Record Up To Date	☐ Yes	☐ No
Final Two Weeks of Treatment PSS Scale Completed	☐ Yes	☐ No
Final Two Weeks of Treatment FACT Scale Completed	☐ Yes	☐ No
Post Treatment Blinding Questionnaire Completed	☐ Yes	☐ No
Serious Adverse Even Reporting Form Completed	☐ Yes	☐ N/A
Oncology Outcomes Reporting Form Completed	☐ Yes	☐ No
Hyperbaric Complications Reporting Form Completed	☐ Yes	☐ N/A

Notes:

Name: _____ _____
PRINT NAME SIGNATURE:

Date: _____

26.0 Appendix VIII: Sample Size Polling Form

Phase II Trial of Hyperbaric Oxygen as a Radiation Sensitizer for Locally Advanced OPC (Stage III/IV Ø M) in HPV Negative Patients

1. Primary Outcome(s) Measure Preference

Check all that apply if you prefer more than a single outcome measure

- ☐ Recurrence free survival at two years
- ☐ Recurrence free survival at three years
- ☐ Progression free survival at two years
- ☐ Progression free survival at three years
- ☐ Overall survival at two years
- ☐ Overall survival at three years
- ☐ Other measure: _____

Comments:

2. What is the best estimate of outcome for your selection(s) based upon current standard practice?

_____ %

3. What is the smallest improvement in your selected outcome(s) measure that would be of clinical importance for patients and practitioners?

☐ 5% ☐ 10% ☐ 15% ☐ 20% ☐ 25%

☐ Other: _____

☐ Please check if you would like to receive a summation of responses :

Email:

Thank you!

Please return your responses to dick.clarke@palmettohealth.org

27.0 Addendums

27.1 Clinical Target Volume Expansions Consensus Statement

Gregoire V, Evans M, Le Quynh-Thu, *et al*. Delineation of the primary tumor Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC, CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. **Radiation and Oncology 2018;126:3-24.** Consensus statement included as Addendum I.

27.2 Organs at Risk Consensus Statement

Brouwer CL, Steenbakkers R, Bourhis J, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC, NRG Oncology and TROG consensus guidelines. **Radiation and Oncology 2015;117:83-90.** Full consensus statement included as Addendum II.