ISRCTN93840508 https://doi.org/10.1186/ISRCTN93840508

Hyperbaric radiation sensitization of head and neck cancers

Submission date 29/01/2019	**Recruitment status** Stopped	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 08/02/2019	**Overall study status** Stopped	
Last Edited 08/07/2022	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

The aim of this study is to determine if the addition of hyperbaric oxygen to radiotherapy and chemotherapy will increase tumor cell destruction and improve patient survival in cancers of the head and neck. The definition of hyperbaric oxygenation is the act of breathing oxygen while inside a pressurized chamber. There is reason to believe that this treatment goal is achievable if patients receive hyperbaric oxygen immediately prior to each radiation treatment. This is because radiation therapy's effectiveness is, in large part, a function of presence of oxygen throughout the tumor at the time of radiation. Different tumor types have varying degrees of poorly oxygenated cells. Some tumors have few such cells so any benefit from hyperbaric oxygen in the manner described would be unlikely. Others have greater degrees of poorly oxygenated cells. Medical professionals describe this phenomenon as "tumor hypoxic (low oxygen) fraction". The higher the fraction of hypoxic cells the greater a tumor's resistance to radiation treatment.

The tumor type selected for study in this research contains a relatively large 'hypoxic fraction'. Tumors with high hypoxic fractions are not only resistant to standard care (radiotherapy); they are also one reason why cancers spread to other parts of the body. This potential to spread complicates patient care and lowers survival. The more effective one can kill can all cancer cells the lower the likelihood cancer will spread. This 'radio-resistant' phenomenon has been known for more than 50 years. Cancer specialists have different drug therapies to either reduce tumor oxygen consumption or increase its delivery. None has proven effective enough to be included in today's medical standard of care.

Laboratory and human studies have demonstrated the ability of hyperbaric oxygen to increase tumor oxygen levels to the point of eliminating radio-resistance. This technique has used in preliminary studies of brain cancers, with only modest success. As malignant brain tumors are usually fatal, hyperbaric oxygen's impact has been limited to extending survival by weeks or perhaps months. It has not improved cure and overall survival.

The tumor type involved in this research, on the other hand, is survivable. Depending on several factors, survival rates range from 40-70%. Unlike brain tumors, then, a metric exists to measure any enhanced survival that this unique interventional technique may impart. The study will specifically investigate tumor grades with lower survival rates.

In preparation for this research, a Phase I 'safety' study was conducted. Patients with the same tumor type and degree of advancement underwent radiotherapy immediately preceded by

hyperbaric oxygen. The purpose was to determine if pre-radiation hyperbaric oxygen was technically feasible and safely tolerated. Both short and long-term results were very encouraging enough to prompt the current study.

Who can participate?
Patients age 18 and over with head and neck cancers

What does the study involve?
Participants are randomly allocated to be treated with either hyperbaric oxygen (experimental group) or hyperbaric air (sham group) immediately before each radiation treatment. Active treatment lasts for 7 weeks (35 daily radiation treatments Monday through Friday, each immediately preceded by a hyperbaric chamber exposure). Follow-ups occur at two weeks after radiation treatment / hyperbaric oxygen, then 3 months, 6 months, 1 year and a final follow-up at 2 years after radiation treatment.

What are the possible benefits and risks of participating?
The benefit is contributing to the advancement of medical science. The experimental group subjects might benefit to a greater extent from their cancer treatment, while the sham group will have the identical outcome expectations of cancer treatment than all others who are treated as current standard of care. Risks associated with participation are identical to those associated with the routine application of hyperbaric oxygen therapy, namely; confinement anxiety, ear sinus discomfort/pain, paranasal sinus pain, reversible myopia (experimental group only), central nervous system oxygen toxicity (experimental group only), pulmonary oedema (experimental group only).

Where is the study run from?
1. Prisma Health Richland Hospital (USA)
2. Dartmouth-Hitchcock Medical Center (USA)
3. The Mayo Clinic (USA)
4. Hotel Dieu Hospital of Levis (Canada)
5. Memorial Hospital Hermann (USA)
6. Wilford Hall Medical Facility (USA)
7. David Grant Medical Center(USA)

When is the study starting and how long is it expected to run for?
January 2019 to December 2024

Who is funding the study?
Presently investigator initiated and funded

Who is the main contact?
Richard Clarke
dick.clarke@prismahealth.org

Contact information

Type(s)
Scientific

Contact name
Mr Richard Clarke

ORCID ID
https://orcid.org/0000-0002-8292-2724

Contact details
9 Richland Medical Park, Suite 330
Columbia
United States of America
29203
+1 (0)803 434 7101
Dick.Clarke@PrismaHealth.org

Additional identifiers

ClinicalTrials.gov (NCT)
NCT03843671

Protocol serial number
NBS2019-02

Study information

Scientific Title
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 objectives
The additional of hyperbaric oxygen to chemo-radiotherapy will improve progression-free survival and overall survival versus chemo-radiotherapy alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Prisma Health Richland Hospital Institutional Review Board, 17/05/2019, ref: Pro00079382

Primary study design
Interventional

Study design
Multi-center randomized sham-controlled trial with allocation concealment and blinding of patients and assessors

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Stage 3 and Stage 4 squamous cell carcinoma of the oropharynx and larynx

Interventions
Randomization will be by location and in equal blocks of four randomly stratified as two experimental and two sham, per each block.

Treatment group: Hyperbaric oxygen at 2.4 atmospheres absolute for 30 minutes; radiation beam on within 15 minutes of exiting the hyperbaric chamber.
Sham group: Brief (several minute) air compression to and hold at 1.34 atmospheres absolute, then balance of 45 minutes at 1.1 atmospheres absolute; radiation beam on within 15 minutes of exiting the hyperbaric chamber.

Active treat phase is 7 weeks (35 daily RT treatments Monday through Friday, each immediately preceded by a hyperbaric chamber exposure). Follow-ups will occur at two weeks post-RT/HBO, then 3 months, 6 months, 1 year and a final follow-up at 2 years post-RT.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Hyperbaric oxygen

Primary outcome(s)
Progression-free survival (local progression; regional nodal metastasis; distant metastasis) and relapse-free survival at 2 years post-RT

Key secondary outcome(s)
1. Overall survival at 2 years post-RT
2. Incidence of acute hyperbaric complications assessed clinically by the hyperbaric physician during and upon completion of the HBO/RT course (7 weeks from its initiation)
3. Incidence and degree of acute radiation toxicity per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 upon completion of the RT/hyperbaric protocol (7 weeks from its initiation)
4. Incidence and degree of late radiation tissue injury at 2 years as above (CTCAE v 5.0) and clinical assessment by the hyperbaric physician
5. Protocol compliance, as per Section 12.7.1; assessed per Radiation Oncology Chair upon completion of the RT/hyperbaric protocol
6. Quality of life per Functional Assessment of Cancer Therapy (FACT): Head and Neck v 4.0, and Performance Status Scale (PSS) for Head and Neck Cancer at two weeks post-RT, then 3 and 6 months and 1 and 2 years post-RT/HBO

Completion date
31/12/2024

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 03/04/2019:
1. Histological and microscopic proof (from 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)
2. Stage III or IV disease, M0
3. Non-surgical candidate; for reasons of health or age (except biopsy)
4. HPV (P16) negative for oropharyngeal cancers only; added 27/06/2019: All other tumors independent of P16 status
5. Life expectancy of at least 6 months and a Karnofsky performance status of ≥ 70
6. Age ≥ 18 years
7. No distant metastatic disease
8. No clinically significant heart disease:
8.1. No significant ventricular arrhythmia requiring medication with antiarrhythmic
8.2. No symptomatic coronary artery disease (angina)
8.3. No myocardial infarction within the last 6 months
8.4. No second or third degree heart block or bundle branch block or clinically significant conduction system abnormality
9. Patient ability to sign a study-specific informed consent document

Previous participant inclusion criteria:
1. Histological and microscopic proof (from 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)
2. Stage III or IV disease, M0
3. Non-surgical candidate; for reasons of health or age (except biopsy)
4. HPV (P16) negative
5. Life expectancy of at least 6 months and a Karnofsky performance status of ≥ 70
6. Age ≥ 18 years
7. No distant metastatic disease
8. No clinically significant heart disease:
8.1. No significant ventricular arrhythmia requiring medication with antiarrhythmic
8.2. No symptomatic coronary artery disease (angina)
8.3. No myocardial infarction within the last 6 months
8.4. No second or third degree heart block or bundle branch block or clinically significant conduction system abnormality
9. Patient ability to sign a study-specific informed consent document

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Key exclusion criteria
1. Histology other than squamous cell carcinoma (for nasopharyngeal carcinoma, cannot be WHO type II or III)
2. Evidence of metastasis (below the clavicle or distant) by clinical or radiographic means
3. History of prior invasive malignancy, unless at least 5 years without evidence of recurrence (tumor-specific restaging)
4. Prior resection of the primary tumor or lymph node, unless un-operated N2-N3 nodal disease or primary tumor remaining, respectively.
5. Prior chemotherapy for head and neck cancer or radiotherapy to the head and neck
6. Prior treatment with Bleomycin
7. Creatinine clearance measured or estimated GFR <40 ml/min
8. Simultaneous primaries
9. Pregnancy
10. Participating in a conflicting protocol
11. Pulmonary pathologies (risk of decompression-induced pulmonary barotrauma):
11.1. Current, untreated pneumothorax
11.2. Previous history of spontaneous pneumothorax
11.3. Previous history of intra-thoracic surgery
12. History or evidence of pulmonary blebs or bullous lung disease
13. Clinically significant chronic obstructive pulmonary disease:
13.1. Associated with carbon dioxide retention
13.2. Poorly controlled or associated with acute bronchospasm
14. Where the hyperbaric physician deems the patient to have an otherwise unacceptable risk for hyperbaric chamber exposure

Date of first enrolment
01/07/2019

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

Canada

Japan

United States of America

Study participating centre
Prisma Health Richland Hospital
5 Richland Medical Park

Columbia
United States of America
29203

Study participating centre
Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon
United States of America
03756

Study participating centre
The Mayo Clinic
200 First Street SW
Rochester
United States of America
55905

Study participating centre
Hotel Dieu Hospital of Levis
143 Rue Wolf
Levis, Quebec City
Canada
G6V 3Z1

Study participating centre
Memorial Hospital Hermann
6411 Fannin Street
Houston
United States of America
77030

Study participating centre
Wilford Hall Medical Facility
1100 Wilford Hall Loop
San Antonio
United States of America
78236

Study participating centre
David Grant Medical Center
101 Bodin Circle
Fairfield
United States of America
94533

Study participating centre
Wm. Jennings Dorn VA Medical Center
6439 Garners Ferry Road
Columbia
United States of America
29209

Sponsor information

Organisation
National Baromedical Services

Funder(s)

Funder type
Other

Funder Name
Presently investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		25/02/2019	25/02/2019	No	No
Protocol file		03/04/2019	03/04/2019	No	No