A proof-of-principle study of hyperbaric oxygen as a radiosensitizer prior to stereotactic radiosurgery for brain metastases

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List of Abbreviations

ATA – Atmospheres absolute
DHMC – Dartmouth-Hitchcock Medical Center
EF-5- Hypoxia marker
HBO – Hyperbaric oxygen
HBOT- Hyperbaric oxygen therapy
HIF-1- Hypoxic inducible factor-1
NCCC – Norris Cotton Cancer Center
OER – Oxygen enhancement ratio
SCC- Squamous cell carcinoma
SRS – Stereotactic radiosurgery
WBRT – Whole Brain Radiation Therapy

Study Summary

Title	**Proof-of-principle study of hyperbaric oxygen (HBO) as a radiosensitizer prior to stereotactic radiosurgery (SRS) for brain metastases**
Short Title	HBO-SRS for brain metastases
Protocol Number	*D12129*
Phase	Proof of principle
Methodology	Open label
Study Duration	5 years
Study Center(s)	Single center (Radiation Oncology section of the NCCC at DHMC)
Objectives	To demonstrate that coordination of HBO with SRS treatments is feasible. To demonstrate that outcomes for patients treated with combination of HBO and SRS are non-inferior to historical controls.
Number of Subjects	20 evaluable participants
Diagnosis and Main Inclusion Criteria	Patients with brain metastases referred for SRS
Study Product, Dose, Route, Regimen	Hyperbaric oxygen given at 2.4 ATA for 30 minutes immediately prior to SRS
Duration of administration	HBOT for 30 minutes
Reference therapy	SRS without prior HBO
Statistical Methodology	Prospective Phase-I trial (“proof-of-principle”) with matched historical controls

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

1.1 Background

Hyperbaric oxygen (HBO) treatment, in which patients breathe 100% oxygen at a high ambient atmospheric pressure, is an appealing strategy for overcoming tumor hypoxia. HBO dramatically increases the oxygen dissolved in blood plasma, which in turn increases oxygen delivery to tissue.

Radiation therapy is the standard of care for the treatment of many malignancies, including brain metastases. Its mechanism of action includes interaction with dissolved molecular oxygen, formation of oxygen radicals, and consequent damage of nuclear DNA. For this reason, hypoxic tissues are less sensitive to radiation damage, both *in vitro* and *in vivo* (Figure 1, Figure 2). This increase in radiation sensitivity is quite profound: two- to three-fold between hypoxic and oxic tissues (an "oxygen-enhancement ratio" – OER – between 2 and 3) (Figure 1). In contrast, oxygen's radiation sensitizing effect flattens at higher pO2 levels, with little additional sensitization above pO2 levels of 20-30 mm Hg (Figure 3).

Figure 1. Oxygen enhances radiosensitivity of cells growing *in vitro.* From Hall 2012, page 88 [1].

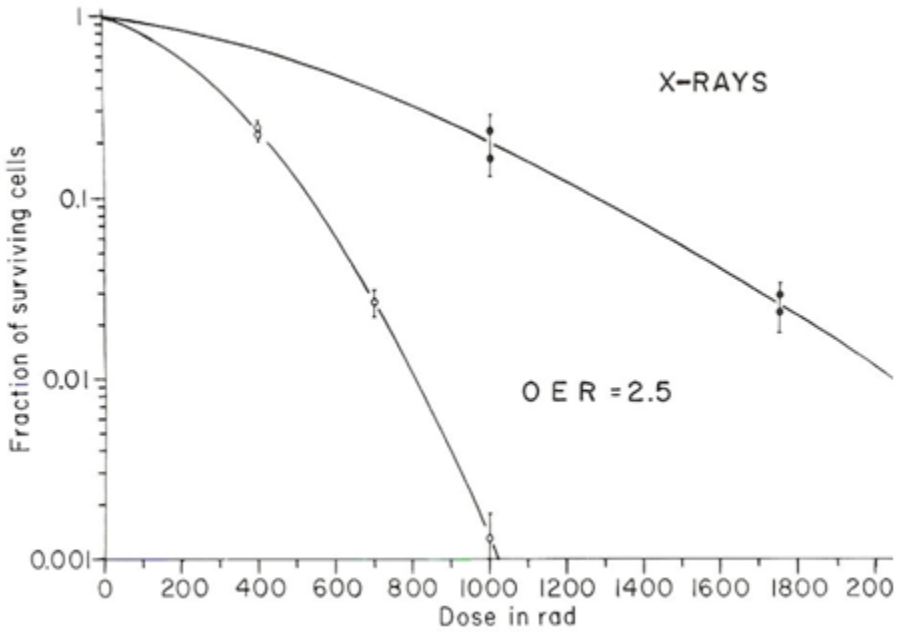


Figure 2. Oxygen enhances radiosensitivity of cells irradiated *in vivo.* The "Air Curve" represents data for cells from tumors irradiated in mice breathing air (a mix of hypoxic and oxic cells). The "Hypoxic Curve" represents data for cells from tumors irradiated in mice breathing pure nitrogen (all cells hypoxic). The "Oxic Curve" is for cells irradiated *in vitro* in oxygen (all cells oxic). From Hall 2012, page 95 (data courtesy of Dr. Sara Rockwell – see citations listed in Hall) [1].

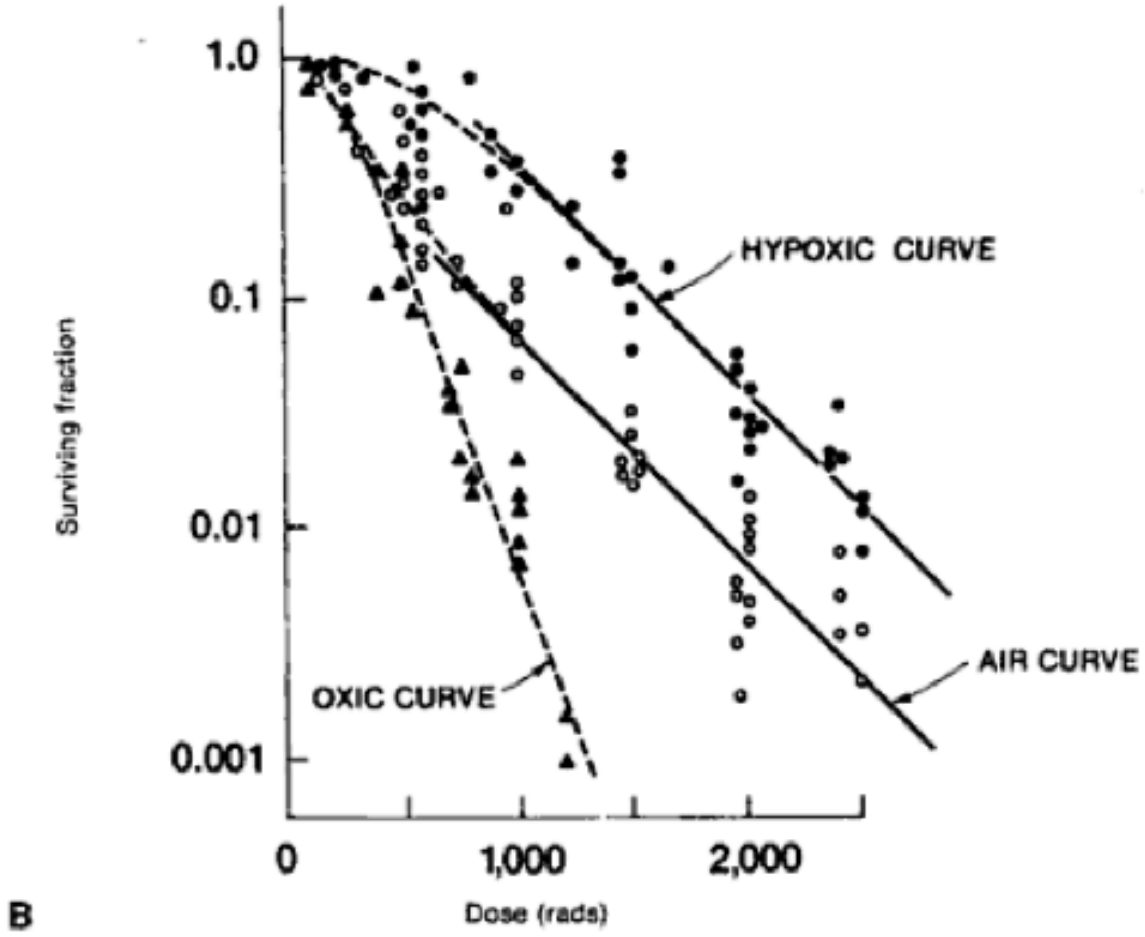
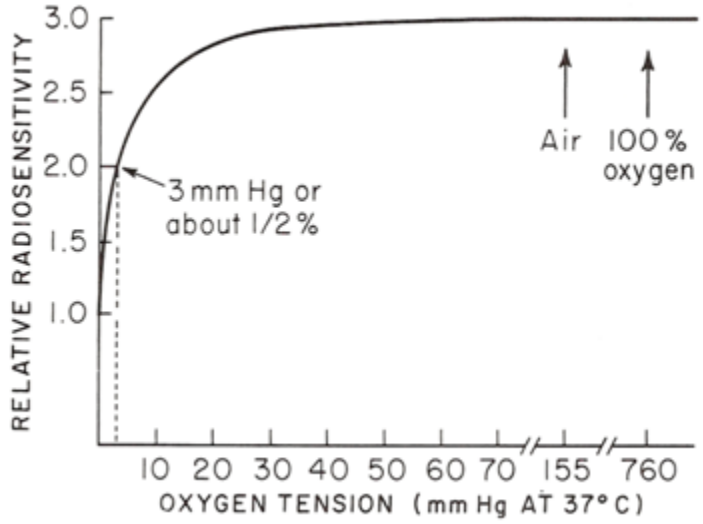


Figure 3. Dependence of radiosensitivity on oxygen concentration, as summarized by Eric Hall. Note that most of this change in radiosensitivity arises between 0 and 30 mm Hg. There is virtually no additional sensitization at p02 levels above 155 mm Hg (normal levels in air). From Hall 2012, page 90 [1].



Thus, HBO offers the potential advantage of increasing the radiation sensitivity of hypoxic tissues (e.g. tumors with poor blood supply) by raising their pO2 levels (even if only by a relatively small amount, increasing radiosensitivity disproportionately), while having little additional effect on surrounding normal tissues. These normal tissues have normal oxygenation and blood supply, so suffer little additional radiosensitivity if their pO2 levels are increased.

Experimental data support the potential radiosensitizing effect of HBO in intracranial tumors (characterized by large hypoxic fractions) while having little effect on normal tissues (with normal oxygen levels). Four clinical trials have evaluated the radio-sensitizing potential of hyperbaric oxygen in malignant gliomas. This technique was found to be feasible [2], involved minimal toxicity on normal tissues [3, 4], and improved outcomes [5, 6]. A recent review of hyperbaric oxygen as a radiosensitizer concluded, "… *given the findings of improved tumor control and mortality…, there is a case for large randomized trials of high methodological vigor…"* [7].

Although HBO has been studied in conjunction with XRT in the treatment of primary brain tumors, no prior study has examined the role of HBO in combination with XRT in the treatment of tumors ("secondary") metastatic to the brain. Furthermore, no prior study has studied HBO in conjunction with stereotactic radiosurgery (SRS).

Characterized by the delivery of millimeter-accurate, high-dose radiation therapy in a single fraction to a small volume of target tissue, SRS is the standard of care for the

treatment of small brain metastases. It is safe and efficacious in a wide variety of clinical situations. Local control rates at one year following SRS range from 50-90%, with tumor size a significant prognostic factor (Figures 4 and 5).

Figure 4. Kaplan-Meier analysis of freedom-from-local recurrence (LR) stratified by tumor size for a large population of patients with intact brain metastases treated with SRS [8].

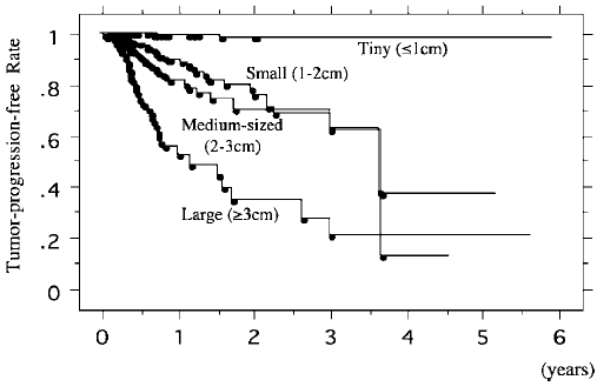


FIG. 1. Graph showing cumulative tumor progression–free survival curves, based on tumor size. The maximum lesion diameters are provided. The mean prescribed doses were 20.6 Gy in 8573 tiny, 20.3 Gy in 977 small, 19.2 Gy in 441 medium, and 15.7 Gy in 172 large lesions. The tumor control rates at 1 year were 99.5% in tiny, 92.6% in small, 87.3% in medium, and 65.5% in large lesions. Differences were statistically significant ($p < 0.0001$).

Figure 5. Kaplan-Meier analysis of freedom-from-local recurrence (LR) stratified by pre-operative tumor diameter at 3.0 cm: recent DHMC experience [9].

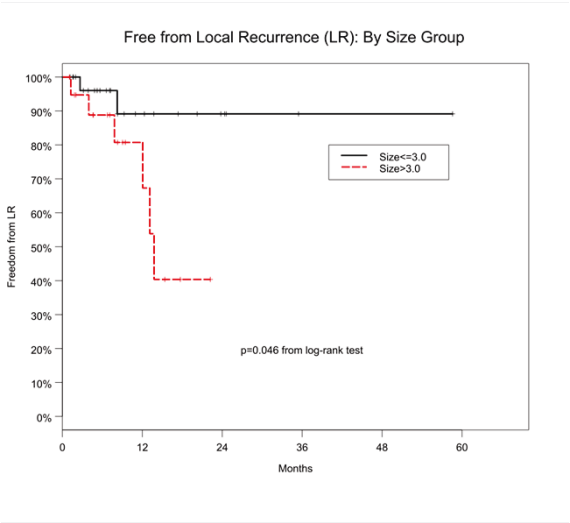


Table 1. One-year and two-year outcomes stratified by tumor size: recent DHMC experience [9].

Table 1 Incidence as a function of tumor size

	% for all subjects		% of subgroup with tumors below or above cutoff size of 3.0 cm				% of subgroup with tumors below or above cutoff size of 2.0 cm			
			Below or equal to 3.0 (n=29)		Above 3.0 (n=20)		Below or equal to 2.0 (n=15)		Above 2.0 (n=34)	
Parameter	1 y	2 y	1 y	2 y	1 y	2 y	1 y	2 y	1 y	2 y
Overall survival	52.5	31.7	51.3	36.0	55.0	30.0	69.2	49.5	46.6	25.1
Free of LR	85.5	66.9	89.1	89.1	80.7	40.4	100.0	100.0	79.2	51.3
Free of DR	43.8	24.4	50.0	36.4	35.6	8.9	81.8	65.5	31.5	10.5
Free of ICR	41.4	17.7	45.4	31.1	35.6	5.9	81.8	65.5	28.3	4.2
Free of WBRT	58.4	37.3	75.9	65.0	39.9	13.3	100.0	100.0	44.5	20.0

Abbreviations: DR = distant recurrence; ICR = intracranial recurrence (LR or DR); LR = local recurrence; WBRT = whole-brain RT.
Data show estimated 1- and 2-year percentages above and below 3.0 cm (median) and above and below 2.0-cm tumor diameter for the entire sample and for subgroups defined by tumor diameters.

In this trial we will use hyperbaric oxygen as a radiosensitizer prior to stereotactic radiosurgery (SRS) for brain metastases. We hypothesize that reducing tumor hypoxia with HBO will increase the sensitivity of these tumors to SRS, that this clinical benefit should increase with lesion size, and that no significant radiosensitizing effect of HBO will

arise in the surrounding normal brain tissues.

We postulate these hypotheses due to several well-known laboratory phenomena, as demonstrated in the research studies of Prof. Swartz (co-investigator on this project) and of other investigators:

- tumors are hypoxic;
- HBO increases tissue oxygenation;
- increasing pO2 levels above hypoxic levels (pO2 >3 mm Hg) increases radiosensitivity with an OER between 2 and 3;
- this OER effect flattens above 20-30 mm Hg (limiting toxicity in normal tissues).

Several clinical observations also support these hypotheses:

- SRS delivers dose with millimeter accuracy to target tissues, limiting normal tissue toxicity;
- efficacy of SRS for tumors metastatic to the brain decreases when treating larger metastases – for example, >30% local recurrence risk at one year after SRS for lesions >3 cm in diameter versus <20% for lesions <2 cm [8] (Figure 4);
- efficacy of SRS decreases when treating larger resected lesions – for example, DHMC experience demonstrated 51% local control rate observed at two years for resected lesions with diameters greater than 2.0 cm versus 100% local control rate observed for diameters less than 2.0 cm [9] (Table 1).

If effective, this innovative approach to the treatment of brain metastases may offer patients improved tumor control and quality of life without increased treatment risks.

1.2 Investigational Agent

⇨ Hyperbaric oxygen treatment given at 2.4 ATA for 30 minutes followed by radiation therapy

Hyperbaric oxygen is oxygen under pressure delivered within a specially designed chamber (hyperbaric chamber). During hyperbaric treatment the patient receives oxygen while resting supine inside the hyperbaric chamber. This increases the oxygen content of blood markedly, not by increasing hemoglobin saturation, since hemoglobin is already highly saturated breathing room air, but by increasing the oxygen dissolved in blood plasma. This increase in partial pressure of oxygen (pO2) in blood increases the pO2 commensurately within both normal and tumor tissues.

1.3 Preclinical Data

As discussed in Section 1.1, over the past five decades molecular oxygen has been proven to be a powerful modifier of cellular radiation sensitivity [10]. The cytotoxic effect of ionizing radiation is increased three-fold when irradiation is performed under well-oxygenated conditions compared to anoxic conditions (the “oxygen-enhancing ratio” or OER) [11].

1.4 Clinical Data

Recent reviews have summarized the use of hyperbaric oxygen as a radiation sensitizer [7, 12, 13].

Several investigators have demonstrated hypoxic regions within brain tumors of patients [14-16]. Likewise, many studies have demonstrated significant hypoxia within both primary and metastatic tumors in a wide variety of animal and human models.

HBO treatment addresses this issue. Intratumoral oxygen levels remain elevated for about 30 minutes after exposure to hyperbaric oxygen; however, intratumoral p02 in the presence of 100% normobaric oxygen does not increase either intra- or peritumoral p02 [17].

Older clinical studies of HBO as radiosensitizer demonstrated positive results. For example, in 1997 Machin and colleagues summarized 30 years of the U.K.'s Medical Research Council trials of solid tumors, an experience that included five trials comparing standard therapy in air against standard therapy in hyperbaric oxygen [18]. Of these five trials, two demonstrated highly significant advantages for patients receiving HBO (both studies in head-and-neck cancer), two did not demonstrate a significant survival advantage for HBO (one bladder and one cervix trial), and one demonstrated a strong trend for a survival advantage for HBO (also in cervical cancer patients). The authors concluded: "Thus, the five trials of HBO, when taken together, established a conclusive survival advantage over standard radiotherapy in air and give a pooled HR [hazard ratio] = 0.80 (95% CI 0.68-0.94)."

Conducted in the mid-1970s, a trial of 48 head-and-neck cancer patients at Yale-New Haven randomized subjects to receive radiotherapy with or without HBO [19]. Although interpretation of the results was severely limited due to several technical factors, including the use of large radiation fraction sizes (two fractions of 12.65 or 11.70 Gy, the former without HBO, the latter with HBO), long-term outcomes demonstrated a highly significant difference in complete clinical response with the addition of HBO (even in combination with the lower XRT dose): 21/25 in the HBO arm, 13/25 in the control arm. Long-term severe late complications were not significantly different between the two groups (though excessive in both arms, due to the large fraction sizes). This study exemplifies the difficulties of most early trials of HBO: poor radiotherapy techniques confounded potential improvements in outcomes [13].

More recent trials using hyperbaric oxygen prior to radiation therapy have shown promising results. In a non-randomized study in 1999, Koshi et al. demonstrated improved median survival in patients with high-grade gliomas who received hyperbaric oxygen prior to radiation compared to patients who were treated with standard radiation therapy and chemotherapy alone (24 months versus 12 months) [20]. Beppu et al. studied hyperbaric oxygen prior to radiation therapy in patients with malignant high-grade gliomas who were also treated with interferon-beta and nimustine hydrochloride. Progression-free survival in their patients with glioblastoma multiforme was 9.5 months, which compares favorably with the 6.9 months in a recent trial of temozolomide combined with radiation therapy [3].

Ogawa et al. recently published long-term follow up data from their successful Phase II trial which ran from 2000-2006 [6].

In a 2007 review of hyperbaric oxygen as a radiation sensitizer, Overgaard concluded, "…ample data exist to support a high level of evidence for the benefit of hypoxic modification [21]." In a recent meta-analysis of HBO in head-and-neck trials [11] Overgaard found the odds ratio between HBO and control treatments to be 0.46 (CI 0.33-0.64, p<0.001).

In a contemporary Phase-I multi-institutional trial studying the addition of HBO as radiosensitizer for the treatment of head-and-neck cancer, currently reported in abstract form [22], DHMC established a successful record for coordinating HBO with fully fractionated radiation delivery (average time from chamber to "beam on" of approximately 8 minutes), in conjunction with standard radiation doses delivered five days a week over seven weeks. No excess toxicity was observed among these patients.

Extending this experience, our current study will explore the safety of the novel combination of HBO followed by SRS for brain metastases.

1.5 Dose Rationale and Risk/Benefits.

Dose Rationale: Hyperbaric oxygen will be given at 2.4 ATA, the dose that was used previously in our phase I head and neck cancer study. This is the dose of oxygen generally used for the treatment of radiation complications. Also, this dose is consistent with the doses used in several previous studies, although this level is not as high as was used in some of the prior glioma studies (2.8 ATA). In short, this dose has been shown in our own work and that of others to be safe.

Risks: The main risks of hyperbaric oxygen therapy are barotrauma to the ear, claustrophobia, and oxygen-induced seizures. Ear barotrauma, if it occurs, is not life threatening and resolves with time. Patients with claustrophobia requiring treatment will be offered lorazepam to help with confinement anxiety and will have the opportunity to experience the hyperbaric chamber prior to the treatment day. Patients are at small risk for increased seizure activity since high oxygen levels can produce seizures, although usually at levels higher than planned for this study. For the level of oxygen used in this study (2.4 ATA) the incidence in the general population receiving HBOT is about 0.06% or 6 per 10,000 dives [23].

HBO may also contribute to the risk of radiation-related complications. In his review and meta-analysis of hypoxic modification of radiotherapy in head-and-neck cancer patients, Overgaard identifies eight trials that studied HBO in comparison to normal treatment controls. These showed a significant increase in the risk of radiation-related complications, with an odds ratio of 2.43 (CI 1.43-4.12, p<0.01). However, Overgaard hastens to add that the late tissue damage observed with HBO arose in trials where the radiation technique was – even absent HBO – known to have a relatively high likelihood of late toxicity; and the difference in some of the trials was further exacerbated by administering high doses per fraction in the HBO arm but conventional doses per fraction

in the control arm, further confounding the results. Overgaard concludes, "Consequently, there is no definitive evidence of any excess morbidity associated with the [HBO] hypoxic modification itself…" [11]

Risk/Benefit Summary: This is a study for patients with brain metastases. These patients are at significant risk for tumor recurrence. Treatment options for these patients are limited. The results of this investigation may provide information for improved treatment of other patients with this disease. Treatment with hyperbaric oxygen is safe, but nevertheless there is the very small risk for seizures and barotrauma to the ear. Also, the theoretical potential risk exists that the combination of HBO with radiation therapy may increase late tissue damage from radiation exposure – although there is no solid clinical evidence of this potential risk, while there is good radiobiological data that HBO does not contribute significantly to the radiation sensitivity of tissues that are already well-oxygenated, such as normal brain.

2 Study Design

2.1 General Design

This is a Proof of Principle study of hyperbaric oxygen as a radiation sensitizer prior to radiosurgery for brain metastases.

2.1.1 Study Objectives

Primary Objective: To demonstrate that coordination of HBO with SRS treatments is feasible.

Secondary Objective: To demonstrate that outcomes for HBO combined with SRS treatment are non-inferior to historical controls.

2.1.2 Study Flowchart

The duration of the study is 5 years. The study flowchart encompasses three sequential phases for each participant: (1) pre-treatment preparations for both HBO and SRS, (2) treatment with HBO immediately followed with SRS; (3) post-treatment follow-up including history and physical exam, brain MRI, and QOL instruments initially 4 to 6 weeks after treatment and then every 3 months for a minimum of 1 year. See Figure 6.

Figure 6. Study Flowchart

2.2 Primary Study Endpoints

Demonstrate that coordination of HBO with SRS treatments is feasible.
For HBO sensitization of SRS patients to be feasible, patients must receive radiation treatment within a time frame in which pO2 levels are meaningfully elevated. Since intratumoral oxygen levels within the brain remain elevated for about 30 minutes after exposure to hyperbaric oxygen [17], feasibility of HBO-SRS treatment requires that a patient at least begin SRS within 30 minutes of leaving the HBO chamber. Evaluation of the ability to achieve this goal will be the primary study endpoint. We will measure time from end of "dive" to start of SRS treatment. Goal will be to achieve "beam on" within 15 minutes of leaving the chamber. Total time for treatment to one isocenter (from first arc's beam-on to last arc's beam-off) using SRS in this study is estimated at 10 minutes (three SRS arcs, each 2 minutes, plus set-up time between the first and second and between the second and third arcs, each 2 minutes, totaling 10 minutes). We anticipate a learning-curve as HBO and therapy staff to develop skill sets for optimizing time across the various steps of the procedure:

- Leaving the HBO chamber
- Fitting the - VisionRT open face mask system
- Positioning the patient on the table
- Imaging the patient to confirm position
- Reviewing/approving images for treatment

2.3 Secondary Study Endpoints

Demonstrate that outcomes for HBO combined with SRS treatment are non-inferior to historical controls.
Secondary endpoints will include:

- Symptomatic treatment toxicity. Every patient who receives treatment on this protocol will be evaluated for solicited adverse events. "Solicited adverse events" are predefined side effects/medical occurrences identified by the PI and co-PIs to be potentially related to intracranial SRS and/or HBO treatments. These are enumerated in Attachment 14.6. These will be graded using the

Common Toxicity Criteria Adverse Events (CTCAE) v4.0 of the National Cancer Institute. These will be analyzed in one of two categories:
    - Acute toxicities
        - Neurological toxicities
        - Other toxicities
    - Chronic toxicities
        - Neurological toxicities
        - Other toxicities
- Radiographic evidence for radionecrosis/treatment effects in normal tissue, as defined by review/analysis by diagnostic radiologist of follow-up MRI imaging
- Incidence of whole brain radiation therapy (WBRT)
- Incidence of repeat SRS to the index site
- Incidence of repeat SRS to a distant site
- Local disease recurrence at the treatment site, as defined by review/analysis by diagnostic radiologist of follow-up MRI imaging
- Distant disease recurrence elsewhere in the brain, as defined by review/analysis by diagnostic radiologist of follow-up MRI imaging
- Overall survival

Radiographic MRI outcomes will be assessed by a diagnostic radiologist using standard criteria for radiation treatment effects and disease recurrence. Imaging sets will typically include T1-weighted sequences (with and without gadolinium), T2- and Flair-weighted sequences, and also perfusion, ADC ("apparent diffusion coefficient"), and spectroscopic imaging studies.

2.4 Further Exploratory Study Endpoints

- Quality of life measures (see attachments)
    - St. Louis University Mental Status Exam (SLUMS)
    - EORTC Quality of Life Questionnaire C-30
    - EORTC Quality of Life Questionnaire BN-20
- Serum markers for tissue apoptosis and for neuronal damage

Several different quality-of-life measures following radiation treatment of the brain have been validated in large-scale studies internationally. We will use the EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTC QLQ-C30/BN20), which has been employed in several RTOG and EORTC studies. (See Attachment 1.) As discussed in RTOG-0825 protocol documentation:

> "The EORTC QLQ C-30/BN-20 were developed and validated for use in this [brain cancer] patient population. The QLQ C-30 is a 30-item self-report questionnaire that has patients rate the items on a 4-point scale, with 1 "not at all" to 4 "very much." The instrument measures several domains, including physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, nausea and vomiting, and several single items (dyspnea, insomnia, anorexia, constipation,

diarrhea, and financial impact). The BN-20 consists of 4 scales comprised of multiple items (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). The combined instrument takes an average of 8 minutes to complete by patients with primary brain tumors [24]."

Several mental status examinations have been used in the literature, with the Mini-Mental State Exam (MMSE), dating back more than 30 years, being the most popular. However, the St. Louis University Mental Status (SLUMS) examination has been shown to be more sensitive than the MMSE for detecting mild dementia [25], and it is free for academic research use, while the MMSE requires a fee. Hence, we are employing the SLUMS exam in this study.

Serum markers for brain metastases responding to radiation treatment have not been demonstrated to date, nor have serum markers for radiation damage to normal brain tissue been documented. In this protocol we test two potential markers: S100β and NSE. Exploratory tests of serum markers will be performed following SRS-HBO using these markers found to be specific for neuronal damage.

Apoptosis after SRS has been shown to arise 6 hours after the procedure, to continue up to 48 hours, but to decline by 72 hours post-SRS [26]. S100 β and NSE are relatively specific for neurological injury and have been shown to be potentially useful serum markers of early hypoxic brain injury [27]. We hypothesize that these will be elevated following SRS (due to damage of normal brain tissue adjacent to tumor targets). We propose to test S100β and NSE levels 24-48 hours after the SRS treatment in a subgroup of patients who have separately consented to this portion of the study. We anticipate that such preliminary data may be of interest in their own right, and that they may also be useful for further analysis should a larger study be pursued subsequently of SRS and HBO treatments for patients with malignant brain lesions.

3 Subject Selection and Withdrawal

3.1 Inclusion Criteria

Patients meeting all the following criteria are eligible for this trial:

- Metastatic brain tumor referred to radiation oncology for treatment
- Size of the presenting metastatic lesion up to 5.0 cm diameter
- Age ≥ 18 years
- Patients must give informed consent indicating they are aware of the investigational nature of this treatment
- Karnofsky Performance Status ≥ 70% (Zubrod score 0 to 1)
- Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days to start of study therapy
- CBC and CMP within 30 days to start of study therapy

- Chest imaging (Chest Xray or Chest CT) within past 12 months, that does not show any contraindication to hyperbaric therapy (if patient has had any thoracic surgery or other significant event that might have affected the thorax such as trauma, pneumothorax, chest tube insertion, pleurodesis, or thoracentesis and has not had imaging since that event, then the imaging should be repeated).
- Neurosurgery Consult

3.2 Exclusion Criteria

Patients with the following conditions are not eligible to participate in this trial:

- Pregnant women or women of childbearing potential without adequate contraception. Contraception, which can include abstinence, is required since the last menstrual period until completion of SRS.
- Evidence of pneumothorax
    - Untreated pneumothorax risks tension pneumothorax during ascent in HBO chamber
- COPD with C02 retention
    - Such patients can develop respiratory depression as HBO reduces their hypoxemic drive
- Uncontrolled seizure disorder
    - Note that patients on adequate antiepileptic medications may receive HBO
- Claustrophobia resistant to medication
    - Pre-medication with anxiolytics is generally sufficient for almost all anxious patients undergoing HBO treatment
- History of middle ear surgery
    - Failure to equalize pressure in the middle ear can cause displacement of middle ear structures with consequent hearing loss
    - To clarify: placement of a tympanostomy tube is not a contraindication to HBO, and in fact may improve tolerability of the procedure
- History of bleomycin administration
    - HBO can exacerbate interstitial pneumonitis in such patients
- Current cis-platinum chemotherapy (i.e. therapeutic levels in the bloodstream at the time of HBO therapy)
    - HBO can increase cytotoxicity of cis-platinum
- Uncontrolled high blood pressure
    - HBO can increase systemic vascular resistance
- Unstable angina or myocardial infarction within the previous 3 months
    - Increased afterload due to HBO can increase myocardial workload
- Cardiac EF ≤ 35%
    - Pulmonary edema can arise with HBO in certain patients with severe heart failure
    - In patients with prior history of CHF, subsequent echocardiogram and ECG are required to establish EF>35%
- Treatment with disulfiram

    - Disulfiram inhibits superoxide dismutase and is not approved for use concomitantly with hyperbaric oxygen therapy
- Active drug/alcohol dependence or abuse
- Lack of adequate social support structures, e.g. homelessness
- Tumors with potential confounding results on serum marker studies
    - Small cell (neuroendocrine) carcinomas
    - Carcinoid tumors

3.3 Subject Recruitment and Screening

Subjects will be recruited from patients who are potential candidates for SRS treatment at DHMC for brain metastases. Such patients are referred to radiation oncology by practitioners at DHMC and by physicians at outlying hospitals.

The patient's first visit with radiation oncology will serve to screen the patient for most of the inclusion and exclusion criteria noted above. If the patient appears to be a candidate and wishes to enroll on the protocol, then he/she will be scheduled for a visit with the hyperbaric medicine service. At this visit the subject will be screened for any contraindications to hyperbaric oxygen therapy, and will be given a chance to visit the chamber.

3.4 Early Withdrawal of Subjects

3.4.1 When and How to Withdraw Subjects

Reasons for treatment discontinuation include:

- Subject request or withdrawal of consent
- Subject non-compliance with the protocol
- Life-threatening or unacceptable adverse events at time of SRS or HBO treatment, such as HBO-induced seizure
- Physician judgment in view of subject's inter-current illness or safety considerations
- Administrative decision to discontinue the study.

3.4.2 Data Collection and Follow-up for Withdrawn Subjects

The date and reason for subject discontinuation from the study will be recorded. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances. Withdrawal due to an adverse event will be distinguished from withdrawal from the study according to the definition of adverse event.

Despite the discontinuation, every effort will be made to complete the appropriate assessments. The patient will be followed using the standard follow-up procedures for patients who receive radiation therapy for brain metastases.

3.4.3 Replacement of withdrawn subjects

Patients withdrawn from the protocol as per Section 3.4.1 within one year of enrollment will not be deemed as counting towards the enrollment goal of twenty evaluable patients. Therefore, another patient (comparable in terms of resection status and tumor size) will be enrolled who may serve as a "substitute" for the withdrawn participant.

4 Study Intervention

4.1 Description

Hyperbaric oxygen given immediately preceding intracranial stereotactic radiosurgery

4.2 Treatment Regimen

Prior to the day of treatment, each patient will receive an orientation to the hyperbaric chambers located in the hyperbaric medicine department within radiation oncology. A "test drive" will be performed with the patient in the chamber with air rather than 100% oxygen. This will verify the patient's ability to equalize pressure in the middle ear and will assure that he or she is not claustrophobic. A small percentage of patients (estimated at 15%, based on prior experience) may be unable to achieve pressure equalization in the middle ear. These patients will be offered placement of a tympanostomy tube to facilitate HBO treatment and to enable continuation with the protocol, a simple procedure performed typically by a Physician's Assistant in DHMC's Section of Otolaryngology.

On the day of SRS, during HBO treatment the patient will receive oxygen under pressure while lying supine inside the hyperbaric chamber. HBO will be given at 2.4 ATA. Compression will occur at 3.77 feet/minute. The patient will stay at depth for 30 minutes. Decompression will be performed over a 5-minute time span.

Patients then will be transported from the HBO chamber via stretcher to the SRS treatment area while receiving 100% oxygen via non-rebreather face mask @15L/minute to help maintain oxygen saturation.

Patients then will receive radiosurgery for their metastases as detailed below (Section 5.3 – "SRS Treatment Visit").

A stopwatch will be used to document the time elapsed from when the patient exits the hyperbaric chamber to when he/she starts receiving SRS ("beam-on"). The goal of this time interval should be kept at ≤15 minutes. Elapsed time from leaving the hyperbaric chamber to completion of SRS will be recorded as well.

4.3 Acute HBO toxicity

We do not anticipate patients experiencing toxicities in conjunction with their HBO treatments. All will have undergone pre-screening for claustrophobia and barotrauma.

The likelihood of a seizure in conjunction with HBO treatment is less than one in a thousand (in the general population).

In the very unlikely event of a tonic-clonic seizure, the chamber will be brought to surface after air breaks and after tonic-clonic movements have subsided and regular respirations have resumed. Then the patient will be removed from the chamber and transported to the DHMC Emergency Department for further evaluation and management.

4.4 Prior and Concomitant Therapy

Patients will continue on the medications prescribed by their treating providers.

Patients who are taking anticonvulsants upon enrollment in the study will continue those medications as prescribed. Palliative and supportive care for disease-related symptoms will be offered to all subjects enrolling on this trial (which is our standard of care), and these will be continued as appropriate during the phases of this protocol. Details about interventions and concomitant medications will be collected.

Treatment with disulfiram is not allowed in this study since disulfiram inhibits superoxide dismutase. Patients should not receive cis-platinum chemotherapy just prior to their hyperbaric oxygen treatments.

5 Study Procedures (see attached table, Section 14.1)

5.1 Visit 1 – "Initial consultation visit"

At this "visit" the radiation oncologist screens potential patients, discusses risk/benefits of the study with eligible patients, and provides patients with information about the study. Patients will also have a consultation with neurosurgery. During this time the study consent will be completed (along with any further required screening procedures, including blood work). Although we are considering the consultations with radiation oncology and neurosurgery to be part of the same "visit," for logistical reasons the consultations with the radiation oncologist and neurosurgeon may take place on different days. Chest imaging is required (in preparation for HBO to exclude pulmonary contraindications) if the patient has not had ~~a~~ chest imaging in the prior year. We estimate 25% of patients will require ~~a~~ chest imaging, though it seems likely that in this heavily treated cancer population the number will in actuality be lower than this estimate.

Information collected at Visit 1
Inclusion /Exclusion criteria
History and Physical Examination
EORTC Quality of Life C-30 and BN20

Karnofsky/Zubrod Performance Status
St. Louis University Mental Status Exam
Complete Blood Count (within 30 days of SRS treatment)
Comprehensive Metabolic Profile (within 30 days of SRS treatment)
*Blood sample for biomarkers (pre-TX)
Review of prior MRI of the brain
Pathology confirmation
Pregnancy Test, if applicable (within 14 days of SRS treatment)
Chest imaging, if indicated

*If the patient is enrolled in the biomarker sub-study, a blood draw will be performed prior to the HBO and SRS treatments to test NSE and S100β levels.

5.2 Visit 2 – "Pretreatment visit"

At this "visit" the patient will have a consult for HBO treatment, and then will have a practice dive with air in the hyperbaric chamber. The patient will also have a radiotherapy-planning MRI, a fitting for the VisionRT open face mask system, and a CT-based simulation of the SRS treatment for radiation therapy treatment planning. Although these items are all considered part of the "pre-treatment visit," for logistical reasons some of the items may be scheduled on different days.

Information collected at Visit 2
HBO consult with "dry run"
RT-planning brain MRI
CT-based RT simulation (including fitting of - VisionRT open face mask)

5.3 Visit 3 – "SRS Treatment Visit"

At this visit the patients will undergo HBO treatment (as detailed in Section 4.2 above), followed by radiation therapy (SRS).

5.3.1 Principles:

Stereotactic radiosurgery (SRS) requires precise target definition using volumetric (3D conformal) techniques. Treatment delivery is accomplished with millimeter-precision through the combination of precise pre-treatment MRI imaging, accurate image co-registration of planning MRI scans and CT-simulation datasets, and precise frame-based treatment with image-guidance on the linear accelerator at time of treatment delivery.

5.3.2 Equipment:

Accelerator x-ray beams (photons) with nominal energy of at least 4 MV and not greater than 20 MV. The accelerator must have available cone-beam CT (CBCT) imaging capabilities to assure accurate set-up at the time of treatment delivery.

5.3.3 Protocol Volume Target Definitions:

All treatment planning will be based upon the following target definitions. Treatment will be prescribed to the PTV, which will be derived from the GTV, as follows:

5.3.4 Gross Tumor Volume (GTV):

This is the volume occupied by radiographically visible disease as per postoperative and pre-irradiation MRI. The T1-MR image with contrast is usually the optimal imaging study. Appropriate fusion of the MRI with the planning CT scan is required for accurate treatment delivery.

5.3.5 Planning Target Volume (PTV):

The PTV accounts for uncertainties in imaging, registration, and patient set-up, and also incorporates the potential for microscopic disease extension. For unresected metastases treated in the VisionRT open face mask, the additional margin from GTV to PTV will be 2 mm in all dimensions. For resected metastases treated in the VisionRT open face mask, the additional margin will be 3 mm in all dimensions.

5.3.6 Timing of Radiotherapy:

Radiation therapy will be delivered following the patient's exit from the HBO chamber. Every effort will be made to begin radiation treatment within 15 minutes of the patient's exit from the chamber. The time between exit from the chamber and beam-on will be recorded as part of the patient's treatment record.

5.3.7 Target Dose:

In general, the target dose to the margin of the PTV will be prescribed as per RTOG 90-05, which is considered the current standard of care [28]. However, the target dose may be modified to respect normal tissue tolerances (see below), as per clinical judgment of the prescribing radiation oncologist and the consulting neurosurgeon:

Target diameter	Dose to target margin
Up to 2.0 cm	20 Gy
2.1 – 3.0 cm	18 Gy
3.1 – 4.0 cm	15 Gy
4.1 – 5.0 cm	12 Gy

5.3.8 Normal Tissue Tolerance:

Dose prescriptions will take into account the tolerances of surrounding normal tissues, such as brainstem, optic nerves, optic chiasm, and motor cortex. Target dose to the margin of the PTV may be modified to avoid excess dose to such sensitive tissues, per the clinical judgments of the prescribing radiation oncologist and the consulting neurosurgeon.

5.3.9 Optional Blood Draw for Markers

If the patient is enrolled in the blood marker sub-study, a blood draw will be performed the day following the SRS treatment.

5.4 Follow-up visits

At each of these visits, the patient will undergo a follow-up MRI scan (with sequences including dynamic susceptibility contrast (DSC) perfusion, apparent diffusion coefficient ("ADC"), and single voxel proton MR spectroscopy if radionecrosis and/or local tumor recurrence is suspected on the standard MRI sequences) as well as history and physical exam with the radiation oncologist. Bloodwork will be drawn at the first follow-up visit (including CBC, CMP, and biomarkers (for participating patients only).

These visits will occur at the following intervals:
Optional follow-up visit for blood marker study – Day after SRS
First follow-up visit ("Visit 4") – 4-6 weeks after SRS;
Visits 5 through 12 – at 3-month intervals after the initial follow-up till the conclusion of the study (two years following SRS).

Further follow-ups (off-protocol) will continue as per standard of care:
Visits 13 through 15 – at 4-month intervals after Visit 12;
Visits 15 through 18 – at 6-month intervals after Visit 15;
Visits 19+ – annual follow-up visits after Visit 18.

Information collected at each follow-up visit
History and Physical Examination
EORTC QLQ C-30 and BN-20
St. Louis University Mental Status Exam
MRI of the brain
(Plus bloodwork drawn at Visit 4 including CBC, CMP, and biomarkers)

6 Statistical Plan

6.1 Statistical Methods

For the primary outcome variable of feasibility, the twenty evaluable patients will be analyzed on the basis of the amount of time required from leaving the HBO chamber to beginning SRS for the target lesion (T1).

The goal for each patient (as discussed in Section 2.2) is for T1 to be no greater than 15 minutes. In a Phase I trial of HBO treatment in coordination with fully fractionated head-neck cancer XRT, DHMC established a track-record of an average of only eight minutes from time of leaving the HBO chamber to "beam on" for this patient group [22]. However, set-up for SRS treatment is more complex, involving placement of a head-frame and performance of a CT-scan prior to SRS treatment. These may extend the time interval required for patient set-up after leaving the HBO chamber.

We anticipate a learning curve for the team members of this study. Therefore, stopping rules are as outlined in Section 7.4: no more than 20% of first ten patients treated within

30 minutes of HBO; and no more than 33% of first fifteen patients treated within 30 minutes of HBO.

The primary endpoint of feasibility is defined as having been achieved if more than 50% of the 20 evaluable patients start SRS treatment within 30 minutes of leaving the HBO tank: in other words, T1 is <=30 minutes for >50% of evaluable patients.

For the secondary endpoints, using Cox proportional hazards models, and Kaplan-Meier survival statistics, the overall group of 20 will be analyzed for event-free survival and compared against a matched set of patients from our institution (see below for methodology). This match will be based on tumor size, resection status, and histology-specific graded prognostic assessment (GPA). The GPA is a validated, widely accepted prognostic scale predictive of survival for patients presenting with brain metastases. Diagnosis-specific GPA calculation is based on published criteria including tumor histology, presence of systemic metastases, number of brain metastases, age, performance status, and breast-cancer specific molecular markers [29-31]. Further demographic and treatment data will also be collected, including: gender, subtotal resection versus gross total resection (if tumor resected), tumor diameter (prior to first treatment, whether surgery or SRS), SRS target volume (PTV), and prescribed dose to the PTV. The secondary outcome variables will be the first occurrence of the event of interest and also the time until the first occurrence of the event of interest. These events include: intracranial recurrence at SRS site, intracranial recurrence at a distant site, whole brain XRT, second SRS (classified as either local or distant), third SRS (classified as local or distant), radionecrosis at the SRS site, and death.

A retrospective database pertaining to Dartmouth-Hitchcock's experience with stereotactic radiosurgery in the treatment of brain metastases is being collected through Study 00030625 (PI Greg Russo, MD). Pertinent matching variables, along with demographic variables, treatment variables, and outcome variables for the control population are available on 00030625. The matching variables (histology, lesion size, resection status, and calculated GPA) will be used to identify a control population in the Study 00030625 that match 1:1 against the D12129 enrolled patient population.

Specifically, patients with similar tumor histologies will be matched against histologies found in the D12129 patient population, falling into one of six categories: (1) non-small cell lung cancer, (2) melanoma, (3) breast cancer, (4) renal cell cancer, (5) GI cancers, and (5) other histologies. Once a histologic match is identified, the patient is then matched by resection status (either unresected or resected). The third matching variable is then GPA. If an exact GPA match is not available in the 000030625 data base, then a patient with a higher GPA will be selected, with the control patient's GPA as near as possible to that of the corresponding D12129 patient (thereby, if anything, biasing the survival outcome data slightly against the D12129 data set). Lastly, the fourth matching variable is tumor size (i.e. maximum tumor diameter) at time of treatment (a categorical variable, either below or above 2.0 cm). If an exact match for the fourth variable is not available in the 000030625 data base, then size will be matched as closely as possible to the 2.0 cm cut-off from those patients available in this historical database. These

matching patients identified in 000030625 data base will serve as the control group for the D12129 study.

Once the control group patients have been selected, their data will be extracted from the 00030625 database in de-identified form. These data will be reviewed by an "honest broker" to assure proper de-identification and HIPAA compliance. These de-identified control group data will then be merged with the D12129 dataset. Analysis of this combined data base then will allow comparison of HBO-treated and control patients in terms of event-specific outcome parameters, with events including: death, local intracranial recurrence, distant intracranial recurrence, whole brain radiation therapy, and repeat SRS (either local or distant).

Exploratory variables will include QOL data and tumor markers. Comparisons for change in markers before versus after HBO-SRS treatment will be performed for the entire group of twenty patients. Also comparisons will be performed for subgroups (including comparisons of those with resections versus those without, and of those above 2.0 cm diameter versus those below).

Time line for completion of the study is 5 years. We anticipate accrual of the 20 patients in the first three years (0-36 months). Follow-up is anticipated to be a minimum of one to two years for each surviving patient (13-48 months). Manuscript preparations and submissions should occur in the fourth and fifth years (48-60 months).

6.2 Sample Size Determination

For the initial phase of this study we anticipate enrolling 20 patients (DHMC treats about 80-100 SRS patients yearly): 5 with resected lesions up to 2.0 cm (diameter), 5 with intact lesions up to 2.0 cm, 5 with resected lesions greater than 2.0 cm, and 5 with intact lesions greater than 2.0 cm. Based on a median event-free survival time of 6 months in the control group, a log-rank test with a one-sided significance level of 0.05 and a power of 0.80 can detect a relative risk of 0.39 or smaller. Thus, we have sufficient power to detect 61% increase in the risk of toxicity, recurrence or death.

6.3 Subject Population(s) for Analysis

The study population will be any subject enrolled in the study.

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Solicited Adverse Event
A **solicited adverse event** is any adverse event that has been identified by the PI or co-PIs as potentially related to intracranial SRS and/or HBO treatments. Occurrence and severity of all solicited adverse events will be catalogued for all D12129 patients. These are enumerated in Attachment 14.6.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that resulted in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All solicited adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious solicited adverse events***.

Adverse Event Reporting Period
The study period during which solicited adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment

follow-up. For this study, the study treatment follow-up is defined as the time following study treatment until the date of documented death, withdrawal of consent, or the end of the study, whichever occurs first.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as a solicited adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved solicited adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the solicited adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor will also be notified if the investigator becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any solicited adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as a serious adverse event if the condition meets the criteria for a solicited adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery will be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on solicited adverse events by specific questioning and, as appropriate, by examination. Information on all solicited adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. These will be graded using the Common Toxicity Criteria Adverse Events (CTCAE) v4.0 of the National Cancer Institute. Retrospective review of patient charts will be employed to assure accurate recording of solicited adverse events. Any additional solicited adverse events identified by such retrospective review will be incorporated into the data base and included in the analysis.

All solicited adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

Adverse events that will be reported are those that are:

- At least possibly related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 7.1).

The following information will be included in the adverse event report initial report:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued

- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.3.1 Investigator reporting: notifying the IRB

Serious adverse events will be reported to the Dartmouth-Hitchcock Health (D-HH) IRB as required per IRB and institutional policy.

7.4 Stopping Rules

An internal stopping rule is set in place whereby the study will be terminated if (1) feasibility appears unattainable, or (2) a significant number of patients experience a significant adverse event (SAE) as outlined above:

- Regarding the primary endpoint of feasibility, we anticipate a steep learning curve for treatment of patients on this trial. The overall goal is to begin SRS within 15 minutes of exiting the HBO chamber; however, it is known that oxygen levels remain elevated in the brain up to 30 minutes after HBO treatment. The following stopping rules will be applied:
    - Analysis after enrollment of first 10 patients demonstrates no more than two patients (20%) treated within 30 minutes of HBO chamber exit.
    - Analysis after enrollment of first 15 evaluable patients demonstrates no more than five patients (33%) treated within 30 minutes of HBO chamber exit.

- Regarding the secondary endpoint of noninferiority, every patient who receives treatment on this protocol will be evaluated at every patient encounter for adverse events. Toxicities will be graded using the Common Toxicity Criteria Adverse Events (CTCAE) v4.0 of the National Cancer Institute.
    - Overall incidence of adverse events in this study will be reviewed every three months.
    - At time of any such review, if more than 40% of enrolled patients (minimum of 5 patients) experience SAEs that are deemed likely related to the protocol treatment (HBO combined with SRS), then the study will be terminated (i.e. more than 2 out of 5 patients, or more than 4 out of 10 patients, for example).
    - Note that some SAEs are expected in this patient population, given the nature of the disease process that is being treated. The stopping rule of 40% was elected as representing an incidence level significantly higher than that expected routinely in this patient population.
- It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as quarterly review by the Norris Cotton Cancer Center Data and Safety Monitoring and Accrual Committee (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Participants will sign an authorization that includes the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Loss of patient confidentiality is a risk of participation. Study participant identities will be kept confidential except as required by law. Subjects' samples will be identified by code only (i.e. linked, but de-identified). Patient samples will be de-identified at the time and site of collection. Electronic case report forms, participant, and study information will be kept in the Velos eResearch password protected database. Additionally, documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location in the Office of Clinical Research at the Norris Cotton Cancer Center.

8.2 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be entered. If the item is not applicable to the individual case, "N/A" will be entered. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialed and dated.

ERRORS WILL NOT BE ERASED OR WHITED OUT. For clarification of illegible or uncertain entries, a clarification will be printed above the item, then initialed and dated.

8.4 Records Retention

Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored in Dartmouth College Records Management off-site storage. Documents are shredded on site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in the Velos eResearch password protected database indefinitely.

9 Study Monitoring, Auditing, and Inspecting

9.1 Safety and Data Monitoring

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information of all studies that have accrued participants. The DSMAC has the authority to suspend or terminate all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated by the DSMAC, that information will be forwarded to the D-HH IRB.

9.2 On-Site Monitoring

Clinical research monitoring will be conducted by appropriately trained staff of Dartmouth-Hitchcock Medical Center Clinical Trials Office or those of the OCR. This monitoring will include periodic assessment of the regulatory compliance, data quality, pharmacy records, and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator, Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

9.3 Auditing and Inspecting

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth Research compliance and quality assurance offices (The Dartmouth CTO). The investigator will permit study-related audits and inspections by the D-HH IRB, government regulatory bodies, and the Dartmouth compliance and quality assurance groups (CTO) of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted, reviewed and approved by the Dartmouth-Hitchcock Health (D-HH) IRB prior to conduct of the study or amendment. All subjects for this study will be provided an IRB-approved consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study is funded by the Norris Cotton Cancer Center Clinical Translational Research effort.

11.2 Conflict of Interest

The Conflict of Interest Policy on Human Subject Research for Dartmouth-Hitchcock Clinic, Mary Hitchcock Memorial Hospital and Dartmouth College found at http://www.dartmouth.edu/~cphs/docs/coi-hs-policy.pdf will be followed.

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information regarding the performance of the study, will be published or passed on to any third party without the consent of the study sponsor, Dr. Hartford.

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14 Attachments

14.1 Table summarizing study procedures/flowchart

Visit sequence	Type	Description	Data/Activities
#1	Initial consultation visit	Consults with radiation oncology and neurosurgery	H+P** Protocol screening (check inclusion/exclusion criteria, including pathology/radiology) Protocol consent Bloodwork (CBC, CMP, pregnancy test if indicated) Optional biomarker blood draw Chest imaging if indicated (per section 3.1)
#2	Pre-treatment visit	HBO and SRS preparation	Patient familiarized with HBO technique ("dry run" through the HBO chamber) RT-planning brain MRI VisionRT open face mask fitting CT-based simulation for SRS planning
#3	SRS treatment visit	HBO and SRS treatments	HBO SRS to brain metastases (beam-on goal within 15 minutes after leaving HBO decompression)
#4+	Follow-up visit	Follow-up visits – the first 4-6 weeks after SRS, then every 3 months for two years, then every 4 months for one year, then every 6 months for two years, then annually. Individuals in the substudy for biomarkers will have an additional follow-up the day after the SRS treatment visit.	H+P** Brain MRI Bloodwork at first follow-up visit (CBC, CMP) Optional biomarker blood draw

** Note: All history/physical exam evaluations will include vital signs, performance status, neurological exam, mini-mental status exam, and QOL assessments (EORTC Quality of Life C-30 and BCM20).

14.2 SAE Reporting Form

Please see SAE Reporting Form as detailed on the DHMC CPHS website: http://www.dartmouth.edu/~cphs/tosubmit/forms/.

14.3 HBO Treatment Protocol (including "dry run")

HBO Protocol

14.3.1
Prior to the first visit, any contraindications to hyperbaric treatment will be reviewed. Patients will be scheduled for a chest X-ray, if indicated.

14.3.2
During the first visit patients will have a hyperbaric focused history and physical, and the results of any imaging tests will be reviewed.

Patients will then have a familiarization dive in the chamber. Prior to entering the chamber the patients will have an otoscopic exam. Patients will be placed in the chamber, and the chamber will be pressurized with air to 2.4 ATA. The pressure will then be released. After the patients come out of the chamber they will then have another otoscopic exam.

Patients who have difficulty with equalizing the pressure within their ears will be offered pressure-equalization tubes.

14.3.3
On the treatment day, patients will come first to radiation oncology, where the procedure for the day will be reviewed. The patient will then return to hyperbarics to begin the hyperbaric treatment.

The patients will remove jewelry, watches and any other items that are not approved for use in the chamber (e.g. electronics, matches, lighters, metal objects, cigarettes, car keys, coins/money, batteries, watches, shoes, hand warmers, newspapers, books, magazines, loose medications, stockings, hearing aids). They will remove their street clothes and put on 100% cotton gowns provided by the hyperbaric center.

The chamber will be pressurized to 2.4 ATA at a compression rate (breathing oxygen) of approximately 1 – 3 psi per minute, depending on patient tolerance. The patient will receive hyperbaric oxygen for 30 minutes starting at the time the chamber reaches 2.4 ATA. The decompression rate will be approximately 2-3 psig/fsw per minute depending on patient tolerance. When the treatment is finished, the patient will be removed from the

chamber and transported to the radiation oncology suite via stretcher while receiving 100% non-rebreather face mask @ 15L/min to help maintain oxygen saturation.

The patient will have the Gill-Thomas-Cosman head frame or the VisionRT open face mask placed. Pre-treatment imaging studies then will be performed on the radiation therapy treatment unit, to assure accurate localization of the planned treatment. Stereotactic radiosurgery treatment may then proceed.

The goal for time from leaving the hyperbaric chamber to "beam-on" in the radiation oncology suite is anticipated to be ≤ 15 minutes.

14.4 Quality of Life Instruments

14.4.1 St. Louis University Mental Status (SLUMS) exam

VAMC
SLUMS EXAMINATION
Questions about this assessment tool? E-mail aging@slu.edu

Name_____ Age_____
Is the patient alert?_____ Level of education_____

__/1 (1) 1. What day of the week is it?
__/1 (1) 2. What is the year?
__/1 (1) 3. What state are we in?

4. Please remember these five objects. I will ask you what they are later.
Apple Pen Tie House Car

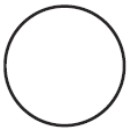
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
(1) How much did you spend?
__/3 (2) How much do you have left?

6. Please name as many animals as you can in one minute.
__/3 (0) 0-4 animals (1) 5-9 animals (2) 10-14 animals (3) 15+ animals

__/5 7. What were the five objects I asked you to remember? 1 point for each one correct.

8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
__/2 (0) 87 (1) 648 (1) 8537

9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
(2) Hour markers okay
__/4 (2) Time correct



(1) 10. Please place an X in the triangle.

__/2 (1) Which of the above figures is largest?

11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.
Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.
(2) What was the female's name? (2) What work did she do?
__/8 (2) When did she go back to work? (2) What state did she live in?

_____ TOTAL SCORE

SCORING

High School Education		Less than High School Education
27-30	Normal	25-30
21-26	Mild Neurocognitive Disorder	20-24
1-20	Dementia	1-19

CLINICIAN'S SIGNATURE DATE TIME

SH Tariq, N Tumosa, JT Chibnall, HM Perry III, and JE Morley. The Saint Louis University Mental Status (SLUMS) Examination for detecting mild cognitive impairment and dementia is more sensitive than the Mini-Mental Status Examination (MMSE) - A pilot study. *Am J Geriatr Psych* 14:900-10, 2006.

14.4.2 EORTC QLQ C-30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Used with permission.

14.4.3 EORTC QLQ BN-20

ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

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14.5 Description of Biomarker Assays

Blood samples will be examined for cellular, secreted, and molecular biomarker expression levels. Examples include:

14.5.1 S100β

S100β is a Ca^{++}-binding protein that is found in astrocytes, oligodendrocytes, and Schwann cells. In Europe it is being used as a screening tool for traumatic brain injury in Emergency Departments, although this usage has not yet been approved by the FDA in the US. It is thought to be a specific marker for neurological tissue injury. The ELISA test is commercially available. Testing will be performed through agreement with DartLab resource. One kit is estimated required per patient, which assumes serum storage (frozen at -70) of the first two patient samples until the third is collected in follow-up; therefore, serum storage will run about 4-6 weeks per patient.

14.5.2 Neuron-specific enolase (NSE)

NSE is a cytoplasmic glycolytic neuronal enzyme. Like S100β it is relatively specific for neurological tissue injury. NSE may also be found elevated in patients with carcinoid tumors or neuroendocrine tumors such as small cell lung cancer. Carcinoid tumors rarely metastasize to the brain and are excluded from this study. Likewise, small cell lung cancer patients are excluded from this protocol. ELISA test is commercially available. Testing will be performed through agreement with DartLab resource. One kit is estimated required per patient, which assumes serum storage (frozen at -70) of the first two patient samples until the third is collected in follow-up; therefore, serum storage will run about 6 weeks per patient.

14.6 Solicited Adverse Events

Nervous System Disorders
Akathisia
Amnesia
Aphonia
Arachnoiditis
Ataxia
Central Nervous system necrosis
Cognitive disturbance
Concentration impairment
Depressed level of consciousness
Dizziness
Dysarthria

Dysesthesia
Dysgeusia
Dysphasia
Encephalopathy
Facial muscle weakness
Headache
Hydrocephalus
Hypersomnia
Intracranial hemorrhage
Ischemia cerebrovascular
Leukoencephalopathy
Memory impairment
Meningismus
Neuralgia
Nystagmus
Paresthesia
Peripheral motor neuropathy
Peripheral sensory neuropathy
Presyncope
Seizure
Somnolence
Spasticity
Stroke
Syncope
Transient ischemic attacks
Tremor
Nervous system disorders – Other, specify

Cardiac Disorders
Heart failure

Gastrointestinal Disorders
Toothache

Psychiatric Disorders
Anxiety

Respiratory, Thoracic, and Mediastinal Disorders
Pneumothorax
Sinus pain

Ear and Labyrinth Disorders
Ear and labyrinth disorders - Other, specify: Barotrauma

Eye Disorders

Eye disorders - Other, specify