Official title: Phase II Trial of Hippocampal-Avoiding Whole Brain Irradiation With Simultaneous Integrated Boost for Treatment of Brain Metastases

NCT number*:* NCT01414738

eIRB approval date: Version 8.0, 07/30/2014

Phase II trial of Hippocampal-Avoiding Whole Brain Irradiation with Simultaneous Integrated Boost for Treatment of Brain Metastases

University of Texas Southwestern Medical Center

Principal Investigator (P.I.): Robert Timmerman, M.D.
Department of Radiation Oncology

Co Investigators: Hak Choy, M.D.
Kevin Choe, M.D., Ph.D.
Ramzi Abdulrahman, M.D.
Dan Garwood, M.D.
Puneeth Iyengar, M.D., Ph.D.
Jeffrey Meyer, M.D.
Lucien Nedzi, M.D.
David Pistenmaa, M.D., Ph.D.
Ann Spangler, M.D.
Department of Radiation Oncology

Jonathan Dowell, M.D.
David Gerber, M.D.
Randall Hughes, M.D.
Joan Schiller, M.D.
Department of Internal Medicine
Division of Hematology-Oncology

Tony Whitworth, M.D.
Christopher Madden, M.D.
Department of Neurosurgery

C. Monro Cullum, Ph.D.
Division of Clinical Psychology

Version	Date
1	4/28/2011
2	8/17/2011
3	1/16/2012
4	7/19/2012
5	8/20/2012
6	11/13/2012
7	05/06/2013
8	05/14/2014

INDEX

Schema

Eligibility Checklist

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations/Management

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Tissue/Specimen Submission

11.0 Patient Assessments

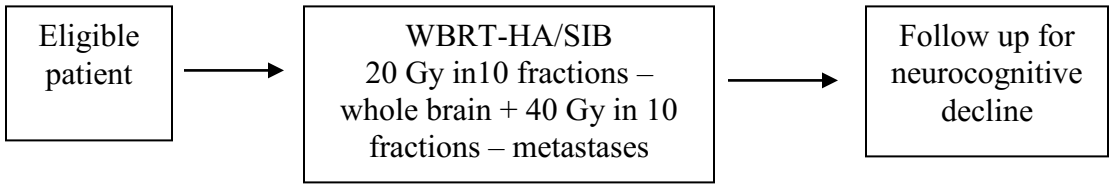
12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I	Study Parameter Table/Study Calendar
Appendix II	Follow-up Radiographic Assessment Form
Appendix III	Neurocognitive Function Assessment
Appendix IV	Performance Status Scoring
Appendix V	RTOG RPA Classification System

SCHEMA



Patient Population: (See Section 3.0 for Eligibility)

1. Pathologically proven diagnosis of a non-hematopoietic malignancy other than small cell lung cancer and germ cell malignancy.
2. Patients with less than 9 discrete metastases on MRI.
3. Measurable brain metastasis outside a 5-mm margin around either hippocampus
4. Have not been treated with SRS or surgical resection.
5. Patients with progressive brain metastases beyond a brain lesion previously treated with radiosurgery are eligible so long as at least 3 months has transpired from the radiosurgery procedure prior to registration.
6. RTOG RPA class I or II
7. Life expectancy of at least 3 months
8. Age ≥ 18 years
9. Karnofsky performance status ≥ 70
10. Two or fewer sites of uncontrolled or untreated sites of extracranial metastases
11. No active pulmonary, gastrointestinal, genitourinary or other serious infection at time of enrollment

Required sample size: 102

ELIGIBILITY CHECKLIST

(page 1 of 2)

Patient Initials _____ Case # _____

_____(Y) 1. Does the patient have a pathologically confirmed diagnosis of a non-hematopoietic malignancy other than small cell lung or germ cell cancer?

_____(Y) 2. Does the patient have measurable brain metastases outside a 5-mm margin around either hippocampus?

_____(N) 3. Has the patient been treated with SRS or surgical resection?

_____(Y) 4. Has the patient had a history/physical examination within 28 prior to registration?

_____(Y) 5. Does the patient fall into RTOG RPA class I or II?

_____(Y) 6. Does the patient have a life expectancy of at least 3 months?

_____(Y) 7. Is the patient 18 years or older?

_____(Y) 8. Does the patient have a KPS of 70 or greater?

_____(Y) 9. Did the patient provide study-specific informed consent prior to any protocol-specified procedure(s)?

_____(Y/NA) 10. If female, was there a negative serum or urine pregnancy test performed prior to treatment for women of childbearing potential?

_____(N) 12. Does the patient have more than 9 discrete metastases on the MRI?

_____(N) 13. Does the patient have leptomeningeal metastases?

_____(N) 14. Is there a plan for chemotherapy or targeted therapies during WBRT or over the subsequent 7 days?

_____(N) 15. Does the patient have a contraindication to MRI such as implanted metal devices or foreign bodies, severe claustrophobia and unable to receive gadolinium contrast agents?

_____(N) 16. Does the patient have serum creatinine > 1.4 mg/dl ≤ 28 days prior to study entry?

_____(N) 17. Is the patient planning to undergo radiosurgery to any CNS lesion or planning to have surgical resection of all of their CNS lesions?

_____(Y) 18. Does the patient have 2 or fewer sites of uncontrolled or untreated extracranial gross disease?

_____(N) 19. Does the patient have an active pulmonary, gastrointestinal, genitourinary or other serious infection at time of enrollment?

_____(Y) 20. For patients with progressive brain metastases beyond a brain lesion previously treated with radiosurgery, has at least 3 months transpired from the radiosurgery procedure?

ELIGIBILITY CHECKLIST

(page 2 of 2)

Patient Initials _____ Case # _____

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed

_____ 5. Patient's Initials (First Middle Last) [If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Date of Birth

_____ 8. Race

_____ 9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 10. Gender

_____ 17. Registration date

Completed by _____ Date _____

Investigator Signature _____ Date _____

1.0 INTRODUCTION

1.1 Neurocognitive Effects of Whole-Brain Radiotherapy (WBRT)

Whole-brain radiotherapy (WBRT) is the most widely used treatment option for patients with multiple brain metastases (Sundstrom 1998). In addition to providing rapid palliation of neurologic symptoms and improved local control as an adjuvant to resection or radiosurgery, WBRT also prolongs time to neurocognitive function (NCF) decline (Aoyama 2007). As such, NCF and quality of life are correlated in patients with brain metastases receiving WBRT, with deterioration in NCF preceding self-reported quality of life decline by up to 153 days. (Li 2008). Hence, there is a sequential association between NCF decline and deterioration in self-reported quality of life for patients with brain metastasis. These results demonstrate that delaying NCF decline results in net clinical benefit important for preserving quality of life for patients with brain metastasis.

However, NCF decline can also be a sequela of WBRT; the time course of this varies based on the specific domains being measured. There is a component of early neurocognitive decline, within the first 1-3 months, which primarily reflects memory. Long-term serious and permanent adverse effects, including cognitive deterioration in other domains and cerebellar dysfunction, have also been described (Roman 1995). DeAngelis et al. (1989) suggested that as many as 11% of long-term brain metastases survivors (>12 months) treated with WBRT develop severe dementia, especially with the use of larger dose-per-fraction schedules. The analysis of WBRT-induced NCF decline can be confounded by two effects: 1) patients with brain metastases tend to have reduced NCF at the time of presentation, and 2) disease progression will negatively skew population distributions of NCF scores.

In an attempt to disentangle these confounding effects, a detailed analysis was published of the time course of NCF decline in eight prospectively measured domains in 208 brain metastases patients treated with 30 Gy of WBRT (Li 2007). NCF, assessed by tests of memory, executive function, and fine motor coordination, was correlated with metastasis volume regression as measured by magnetic resonance imaging. NCF and survival were compared in 135 patients evaluable at 2 months with tumor shrinkage less than (poor responders) and greater than (good responders) the population median. The mean NCF scores and brain metastasis volume at 4 and 15 months were compared. Good responders experienced significantly improved survival (unidirectional $p = 0.03$). For all tests, the median time to NCF deterioration was longer in the good than in the poor responders, with statistical significance seen for executive and fine motor functions. In long-term survivors, defined as patients surviving more than 15 months, tumor shrinkage was significantly correlated with preservation of executive function and fine motor coordination ($r = 0.68$-0.88). These findings support two important possibilities. First, achieving local control with WBRT was integral to both improving survival and preserving certain NCF domains. Second, an intriguing exception to these findings was memory function, specifically recall and delayed recall as assessed with the Hopkins Verbal Learning Test (HVLT-R). These NCF domains appeared to have a weaker association with tumor reduction and were the most susceptible to early decline, even in patients with non-progressing brain metastases, implying the selective effect of WBRT in preserving certain domains over others and the differential sensitivity of certain domains to radiation effects.

Further evidence of the early susceptibility of memory function to WBRT was recently demonstrated by Chang and colleagues (2009). They reported a single-institution phase III trial of stereotactic radiosurgery (SRS) with or without WBRT in patients with one to

three brain metastases, with the principal objective of comparing NCF decline between the two arms. Utilizing HVLT-R as a neurocognitive metric for learning and memory, they defined NCF decline as a >5 point drop 3 months from baseline. Their study was halted early due to an interim observation of a two-fold increase in the mean probability of NCF decline (49%, SRS+WBRT, vs 23%, SRS alone). Similar findings were reported by Welzel et al. (2008), who observed a decline in verbal memory function, as assessed by the Auditory Verbal Learning Test (AVLT) 6 to 8 weeks after the completion of WBRT for brain metastases. The sum of these findings suggest that, although achievement of macroscopic lesion control is an important treatment aim, strategies meant to preserve memory-related NCF warrant further investigation.

1.2 Rationale for Hippocampal Avoidance During WBRT

Emerging evidence suggests that the pathogenesis of radiation-induced NCF deficit may involve radiation-induced injury to proliferating neuronal progenitor cells in the subgranular zone of the hippocampi (Mizumatsu 2003; Raber 2004). It has been found that relatively small doses of radiation cause apoptosis in the subgranular zone of young rats and mice (Mizumatsu 2003; Ferrer 1993; Nagai 2000). On the other hand, little to no apoptosis is observed in other areas of the cerebrum (Nagai 2000). In particular, it has been noted that irradiation causes a sharp and prolonged decline in neurogenesis in the subgranular zone (Ferrer 1993; Nagai 2000; Abayomi 1996; Madsen 2003; Monje 2002; Peissner 1999; Tada 2000). Clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the cognitive decline of patients. In particular, deficits in learning, memory, and spatial processing observed in patients who have received WBRT are thought to be related to hippocampal injury (Roman 1995; Abayomi 1996). Moreover, irradiation of the hippocampus has been associated with pronounced cognitive impairment in the learning and memory domain in patients receiving radiation therapy for nasopharyngeal tumors (Lee 1989; Leung 1992), maxillary tumors (Sakata 1993), pituitary tumors (Grattan-Smith 1992), and base of skull tumors (Meyers 2000). Preliminary results from a recent MD Anderson study of low-grade or anaplastic brain tumors treated with radiotherapy have observed a dose-response phenomenon, wherein the maximum radiation dose to the left hippocampus was correlated with subsequent decline in learning ($p = 0.014$) and delayed recall ($p = 0.01$) (Mahajan 2007).

Monje and colleagues (2002) found that radiation injury to the hippocampus in Fisher 344 rats leads to structural alterations of the microenvironment of the "stem cell niche" of the hippocampus that regulates progenitor-cell fate; one consequence of this is decreased neurogenesis. Monje and colleagues (2003) went on to show that neurogenesis is inhibited by inflammation in the area surrounding the stem or progenitor cells. This inhibition occurred whether the inflammation was induced by radiation injury or by bacterial lipopolysaccharide. Hence, inflammatory injury of the hippocampus putatively represents a possible mechanism for the domain-wise differential benefit in NCF, as well as the temporal sequence of events, following WBRT.

We propose to use conformal avoidance of the hippocampal region during whole brain radiotherapy to reduce the dose to the hippocampi, thereby putatively limiting the radiation-induced inflammation of the hippocampal region and subsequent alteration of the microenvironment of the neural progenitor cells. We hypothesize that avoidance of the hippocampal region with WBRT may delay or reduce the onset, frequency, and/or severity of NCF decline, as measured with clinical neurocognitive tools.

1.3 Rationale for Integrated Boost During WBRT

Randomized trials involving WBRT with or without Stereotactic Radiosurgery (SRS) (Andrews 2004, Kondziolka 1999) in patients with multiple brain metastases have been published, and demonstrate improved local control for patients receiving SRS in addition to WBRT. Randomized trials involving SRS +/- WBRT in patients with multiple brain metastases show that the addition of WBRT reduces the risk of intracranial relapse (Aoyama 2007) at the expense of decreased neurocognition (Chang 2009).
Intensity modulation can be utilized to deliver a dose of radiation to the whole brain to control microsopic disease while simultaneous delivering a boost of radiation all radiographically evident brain metastases. Additionally, intensity modulated radiation therapy (IMRT) can be utilized to spare the structures responsible for memory-related neurocognition. The technical feasibility of this approach has been reported for a variety of flavors of intensity modulation, including helical tomotherapy (Rodrigues 2010, Gutierrez 2007), as well as volumetric modulated arc therapy (Lagerwaard 2009, Hsu 2010). Boost doses comparable to radiosurgery are generally achievable, with the possibility of delineation and avoidance of the hippocampal regions thought to be related to radiation-induced neurocognitive decline. There is a logistic advantage to the simultaneous integrated boost in that it can be administered in a single course of radiotherapy rather than a combination of conventionally fractionated radiotherapy and radiosurgery. Additionally, the treatment can be administered with linear accelerators that are common in most community-practice settings. There is a dosimetric advantage as well, in that the composite plan can be fully optimized to achieve a relatively homogenous whole brain dose, a steep gradient for the radiographically evident disease, and adequate hippocampal sparing, all at once.

1.4 Feasibility of Hippocampal Avoidance and Integrated Boost During WBRT

In general, hippocampal avoidance poses important challenges in conformally avoiding the centrally located hippocampus with its unique anatomic shape, while allowing for uniform dose delivery to the remainder of the brain. In a recent dosimetric analyses of 30 Gy in 10 fractions prescribed to the whole brain, intensity-modulated radiotherapy (IMRT) allowed for the delivery of highly conformal dose distributions, maintaining the hippocampal volume receiving 10 Gy or higher (V10) to less than 50% and the maximum dose to the hippocampus to less than 16 Gy (Gondi 2010a). Coupling hippocampal avoidance with a more heterogenous plan than delivers a higher volume to radiographically evident disease has also been demonstrated in a single treatment plan (Gutierrez 2007). Multiple institutions have also demonstrated the feasibility of WBRT with hippocampal avoidance utilizing LINAC-based IMRT delivery systems broadly available at multiple academic and community radiation oncology practices (Gondi 2010a). Incorporating an integrated boost into a WBRT with hippocampal avoidance has been demonstrated as well (Hsu 2010).

Avoiding the hippocampus poses the risk of attenuating the benefit of WBRT due to increased metastatic disease within the hippocampal conformal avoidance region. The magnitude of this risk has been reported in a study reviewing the MR images of 100 patients, 98 of whom received WBRT with or without SRS boost (Ghia 2007). T1-weighted, three-dimensional spoiled gradient, post-contrast axial MRI images with a 1.25 mm slice thickness, obtained prior to radiotherapy, were reviewed. In the 100 patients, 272 metastases were identified and analyzed. Out of the 272 metastases, 3.3% were within 5 mm of the hippocampi (n=9); 4.4% of metastases were between 5 to 10 mm from the hippocampi (n=11); and 6.3% of metastases lay between 10 and 15 mm from the hippocampi (n=17). Of all metastases, 86.4% were greater than 15 mm from the hippocampi (n=235). However, none of the metastases lay within the hippocampi. The upper 95% confidence limit for the risk of finding a metastatic lesion within 5 mm of the hippocampi at the time of presentation was 15.2%. An update of this study reported on an additional 271 patients with up to 10 brain metastases (Gondi 2010b). Of these

patients, 1133 brain metastases were identified. Thirty-two patients had at least one brain metastasis within 5 mm of the hippocampi at the time of presentation. This yielded an incidence of 8.6%, allowing for the tightening of the estimated upper 95% confidence limit to 11.5%. From this, it can be concluded that 91% of newly diagnosed patients will be eligible for the WBRT that avoids the hippocampus. Patients who present with perihippocampal or hippocampal brain metastases will not be eligible for this protocol.

Although response rates after WBRT without hippocampal avoidance vary, complete or partial responses have been documented in more than 60% of patients in randomized controlled studies conducted by the RTOG, with intracranial disease control observed in approximately 50% of patients at 6 months (Khuntia 2006). It is currently not possible to provide a direct estimate of the risk of developing a metastasis after hippocampal avoidance WBRT, since such a comprehensive data set does not exist. However, if we assume that the risk of developing subsequent brain metastasis in the hippocampal avoidance region scales in the same proportion as that at presentation, from our data on the distribution of brain metastases relative to the hippocampus at presentation, we can conclude that a patient treated with hippocampal WBRT will derive 91.4% of the relative benefit of WBRT in terms of radiographically evident intracranial lesions, with a lower 95% confidence limit of 88.5% (Gondi 2010b). As the overall aim is to improve the interval to NCF decline, we hypothesize that hippocampal avoidance WBRT will provide a net gain in this endpoint. Furthermore, the modest increase in risk of intracranial progression with hippocampal avoidance may be partially compensated by the possibility of salvage with radiosurgery. Should salvage SRS be indicated for a perihippocampal recurrence, we expect that, given the very steep radiation dose falloff with SRS, some but not all of the benefit of hippocampal avoidance will be lost.

1.5 Neurocognitive Function Assessment

To assess our primary endpoint, we have chosen to use the Hopkins Verbal Learning Test (HVLT-R) test that has been used and validated in the phase III trial of motexafin gadolinium for patients with brain metastases. In this trial, compliance with NCF testing was 87% to 98% at baseline and 77% to 87% at 6 months (Meyers 2004). Our reasons for using this particular NCF test include: 1) its ease of use, 2) our institutional experience with its administration, and 3) its validation by RTOG for use in a prior multi-institution study. In RTOG 0018, a phase II trial to evaluate the feasibility of neurocognitive testing of brain metastasis patients receiving WBRT in the cooperative group setting, compliance was >90% prior to WBRT, >84% at the completion of WBRT, and >78% at one month after WBRT. Most non-compliance was attributed to patient-related factors such as decline in performance status (Regine 2004).

The version of the HVLT-R used in the phase III trial of motexafin gadolinium for patients with brain metastases, which for consistency and study comparability will be used in the present study, incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) with 4 words drawn from 3 semantic categories, which differ across the 6 forms. The test involves memorizing a list of 12 targets for 3 consecutive trials (immediate recall), identifying the 12 targets from a list of semantically related or unrelated items (immediate recognition), and recalling the 12 targets after a 20-minute delay (delayed recall). Raw scores are derived for total recall, delayed recall, retention (percentage retained), and a recognition discrimination index. Each patient will serve as his/her own control, as the difference in scores obtained at baseline and at pre-specified post-treatment intervals will be calculated.

Prior to initiation of treatment, all patients will undergo baseline NCF testing using a test battery consisting of the HVLT-R, Trail Making Test (TMT), Controlled Word Association Test (COWAT), and Mini-Mental Status Examination (MMSE). At that time, history regarding level of education reached will also be obtained. After

completion of radiotherapy, all patients will undergo this neurocognitive test battery, conducted by trained and certified nurses or clinical research associates, at 3, 6, 9, 12, and 24 months. In the analysis of NCF decline, each patient will serve as his/her own control, as NCF for each test at each follow-up time point will be compared to baseline NCF.

1.6 Fatigue Assessment and Quality of Life Assessment

Fatigue will be assessed using the Multidimensional Fatigue Inventory (MFI-20).

The MFI-20 is a multidimensional, self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. A subscore from 4 to 20 is reported for each dimension, with 20 corresponding to maximal fatigue.

Within 2 weeks prior to WBRT-HA/SIB, all patients will undergo a baseline fatigue assessment. After completion of WBRT-HA/SIB, all patients will undergo fatigue assessments at 3, 6, 9, 12, and 24 months.

Quality of life will be assessed using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Euroqol EQ-5D .The FACT-BR is a multidimensional, self-report quality of life instrument specifically designed and validated for use with brain malignancy patients. It is written at the 4th grade reading level and can be completed in 5-10 minutes with little or no assistance in patients who are not neurologically incapacitated. It measures quality of life related to symptoms or problems across 5 scales: physical well-being (7 items); social/family well-being (7 items);emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Items are rated on a 5-point scale: 0-"not at all", 1- "a little bit", 2-"somewhat", 3-"quite a bit" and 4-"very much". FACT-BR is self-administered and does not require pre-certification. It has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at:
http://www.facit.org/translation/licensure.aspx.

Quality of Life Assessments

Quality of Life Assesment	Test	Time to Administer
Quality of Life (self reported)	Functional Assesment of Cancer Therapy with Brain Subscale	5
Utility	EQ-5DL (self reported)	3
	Total Time	8

Within 2 weeks prior to HA-WBRT, all patients will undergo a baseline quality of life assessment. After completion of HA-WBRT, all patients will undergo quality of life assessments every 3 months for 12 months and then at 24 months until death. Quality of life assessments will be scored centrally by a blinded reviewer to avoid potential bias.

1.7 Summary and Historical Control

In summary, preclinical and clinical evidence suggests that radiation dose received by the hippocampus during WBRT may play a role in radiation-induced neurocognitive decline. Although neurocognitive assessment in patients receiving WBRT can be confounded by intracranial metastatic disease, analyses suggest a differential sensitivity of various neurocognitive domains, such as delayed recall, to WBRT. This provides the rationale to explore the clinical feasibility of hippocampal avoidance during WBRT. The dosimetric capabilities of IMRT to conformally avoid the hippocampus without detriment to the

radiation dose the remaining brain receives has been demonstrated, as well. Through retrospective analyses, we have also estimated the theoretical risk of perihippocampal disease progression with hippocampal avoidance. Given the overall aim of prolonging neurocognitive decline, and the possibility of salvaging hippocampal and perihippocampal recurrences with radiosurgery, we hypothesize that WBRT with HA and SIB (WBRT-HA/SIB) will provide a net gain in this endpoint.

In this phase II study, we plan to treat patients with brain metastases with WBRT-HA/SIB. To assess the utility of WBRT-HA/SIB, a comparison of these endpoints with historical data of WBRT without hippocampal avoidance will be necessary to determine whether a phase III prospective randomized trial of WBRT with and without hippocampal avoidance would be warranted, and if so, what statistical considerations would be needed. We plan to utilize data from the control arm (WBRT alone) of a recent phase III trial (PCI-P120-9801) of motexafin gadolinium and WBRT (30 Gy/10 fractions) versus WBRT alone in 401 patients with brain metastasis (PI: Mehta) (Mehta 2003; Mehta 2002). These phase III data serve as a particularly useful control for our phase II study, given the similarities in inclusion criteria and study design.

2.0 OBJECTIVES

2.1 Primary Objective

Evaluate delayed recall as assessed by the Hopkins Verbal Learning Test-Revised (HVTL-R) 3 months after whole-brain radiotherapy modified as outlined (WBRT-HA/SIB) for brain metastases.

2.2 Secondary Objectives

2.2.1 Evaluate time to neurocognitive failure as measured by cognitive decline on a battery of tests: the HVLT-R for free recall, delayed recall, and delayed recognition; the Controlled Word Association Test (COWAT); the Trail Making Test Parts A and B (TMT); the Medical Outcomes Scale-Cognitive Functioning Subscale (MOS); and the Mini-Mental Status Examination (MMSE) after WBRT-HA/SIB for brain metastases

2.2.2 Evaluate fatigue, as assessed by the Multidimensional Fatigue Inventory (MFI-20) after WBRT-HA/SIB for brain metastases.

2.2.3 Evaluate local control within the brain

2.2.3.1 Evaluate local control of brain metastases treated with integrated boost

2.2.3.2 Evaluate local control within the region of brain within the CTV receiving 20 Gy.

2.2.3.3 Evaluate local control within the hippocampal regions.

2.2.4 Evaluate time to radiographic progression after WBRT-HA/SIB for brain metastasis.

2.2.5 Evaluate overall survival after WBRT-HA/SIB for brain metastasis.

2.2.6 Evaluate adverse events according to CTCAE criteria.

2.2.7 Evaluate health-related quality of life [as assessed by the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Euroqol EQ-5D before and after (WBRT-HA/SIB)

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of a non-hematopoietic malignancy other than small cell lung cancer and germ cell malignancy.. Direct biopsy of CNS lesions is not necessarily required although could constitute an allowed site of tissue confirmation as medically prudent. Patients who have been disease free for more than 5 years prior to the appearance of CNS metastases should undergo repeat biopsy of either a systemic metastasis or the CNS metastases to confirm the recurrent malignancy.

3.1.2 Patients with measurable brain metastasis outside a 5-mm margin around either hippocampus

3.1.3 Patients with measurable brain metastasis who have not been or will not be treated with SRS or surgical resection (Note: These treatment options are only permitted at relapse)

3.1.4 History/physical examination within 28 days prior to registration

3.1.5 Patients must fall into RTOG recursive partitioning analysis (RPA) class I or II

3.1.6 Patients must have a life expectancy of at least 3 months.

3.1.7 Age ≥ 18 years

3.1.8 Karnofsky performance status ≥ 70

3.1.9 Patients must provide study-specific informed consent prior to study entry

3.1.10 Women of childbearing potential and male participants must practice adequate contraception

3.1.11 Women of childbearing potential must have a negative, qualitative serum pregnancy test ≤2 weeks prior to study entry

3.1.12 Patients who had radiosurgery > 3 months prior to registration are eligible

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with greater than 9 discrete metastases on MRI.

3.2.2 Patients with leptomeningeal metastases

3.2.3 Patients with measurable brain metastasis not resulting from small cell lung cancer and germ cell malignancy

3.2.4 Plan for chemotherapy or targeted therapies during WBRT or over the subsequent 7 days

3.2.5 Contraindication to MR imaging such as implanted metal devices or foreign bodies, severe claustrophobia AND patients unable to receive gadolinium contrast agents

3.2.6 Serum creatinine > 1.4 mg/dl ≤ 28 days prior to study entry

3.2.7 Prior radiation therapy to the brain

3.2.8 Patients planning to undergo radiosurgery to any CNS lesion OR patients planning to have surgical resection of ALL of their CNS lesions

3.2.9 Patients with more than 2 (i.e., 3 or greater) uncontrolled or untreated extracranial sites of gross disease

3.2.10 Evidence of an active pulmonary, gastrointestinal, genitourinary, or other serious infection at time of enrollment.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 Neurocognitive assessments within 2 weeks before starting modified whole-brain radiotherapy (WBRT-HA/SIB): HVLT-R, COWAT, TMT, MOS, MMSE.

4.1.2 Fatigue assessment within 2 weeks before starting WBRT-HA/SIB: the Multidimensional Fatigue Inventory (MFI-20).

4.1.3 Scans Prior to WBRT-HA/SIB: See Section 6.0 for details.

4.1.4 Subjects will be screened for renal impairment prior to administration of gadolinium-based contrast agents (GBCA) as it is routinely done in the Radiology Department at UT Southwestern. A creatinine determination 28 days prior to the research MRI examination must be available to calculate an eGFR. An eGFR calculation may be repeated closer to the MRI appointment if the patient's medical condition has changed. An eGFR ≥45 mL/min/1.73m2 is considered acceptable for administration of a standard weight-based dose of GBCA for research purposes.

5.0 REGISTRATION PROCEDURES

5.1 Procedures

5.1.1 Enrolling investigator must review eligibility checklist and sign/date at bottom that all criteria have been met.
5.1.2 FAX or carry the enrollment form to the Registrar
5.1.3 A unique patient participation ID will be assigned
5.1.4 Eligibility will be confirmed by CRO Personnel
5.1.5 Successful completion of preregistration activities will be confirmed by the CRO Personnel
5.1.6 Treatment assignments will be conveyed to the treating investigator

6.0 RADIATION THERAPY

Note: Intensity-Modulated RT (IMRT) is required. Acceptable IMRT modalities include LINAC-based IMRT involving static gantry angles or volumetric arc therapy (VMAT).

6.1 Dose Specifications (see target definitions below)

6.1.1 Prescription dose will be according to the following specifications:

6.1.1.1 The prescription for the whole brain planning target volume (PTVwb - whole brain clinical target volume excluding the hippocampal avoidance regions) is 20 Gy in 10 fractions. Treatment will be delivered once daily, 5 fractions per week, over 2 to 2.5 weeks. Breaks in treatment should be minimized.

6.1.1.2 The prescription dose for each metastasis planning target volume (PTV1, PTV2, etc.) is 40 Gy in 10 fractions as a simultaneous integrated boost.

6.1.1.3 Coverage is considered adequate when 95% of each of the PTVs is covered by the assigned prescription dose (D95% = prescription dose).

6.1.1.4 The minimum dose to 98% of each of the PTVs (D98%) is 80% of the assigned prescription dose.

6.2 Technical Factors

6.2.1 Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator) is required. The use of custom-made compensators or partial transmission blocks is also acceptable as long as dose specifications and constraints are satisfied.

6.2.2 A megavoltage beam of 4 MV or greater must be used, with a minimum source-axis distance of 80 cm.

6.2.3 MRI

T1 contrast enhanced images should be used for targeting of gross lesions. T2 images may also be used when they allow clear demarcation of the edge of the targeted tumor(s). These imaging sequences should be obtained within two weeks of initiating treatment.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patients will be immobilized in the supine position using an immobilization device such as an Aquaplast mask over the head. A pituitary board may be utilized to maximze the number of available vertex beams. Patients will be treated in the immobilization device.

6.3.2 A non-contrast treatment-planning CT scan of the entire head region with a 1.25 mm slice thickness will be required to define clinical and planning target volumes and hippocampal avoidance regions. The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. This should be obtained within 2 weeks of initiating treatment.

6.3.3 The MRI (see Section 6.2.3) and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

6.4 Target Volumes

6.4.1 The Whole Brain Clinical Target Volume (CTVwb) is defined as the whole brain parenchyma to C1 (if no posterior fossa metastasis) or C2 (if MRI evidence of posterior fossa metastasis).

6.4.2 The Whole Brain Planning Target Volume (PTVwb) is defined as the CTV excluding the hippocampal avoidance regions (see Section 6.5.2).

6.4.3 Each brain metastasis identified on MRI will be assigned a unique Clinical Target Volume identified by number (CTV1, CTV2, etc.)

6.4.4 Each metastasis Planning Target Volume (PTV1, PTV2, etc.) is defined as the corresponding CTV with a uniform 2 mm margin.

6.5 Critical Structures

6.5.1 Bilateral hippocampal contours will be manually generated on the fused 3D-SPGR MRI-planning CT image set by the treating physician according to contouring instructions.

6.5.2 Hippocampal avoidance regions will be generated by three-dimensionally expanding the hippocampal contours by 5 mm.

6.5.3 The lenses and orbits will be contoured as per the clinical experience of the treating physician. Care should be taken to minimize the dose to the lens and orbits.

6.6 Documentation Requirements

6.6.1 Verification orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films.

6.7 Final Quality Assurance Analysis

6.7.1 All final treatment plans and contours will be reviewed after initiation of WBRT-HA/SIB.

6.7.2 If unacceptable deviations of MRI/CT fusion, hippocampal contours, and/or WBRT-HA/SIB IMRT planning are found on final quality assurance analysis, that patient will be rendered inevaluable on final data analysis.

6.7.3 If a patient has an unscheduled break exceeding 3 normally scheduled treatment days, this unacceptable deviation must be reported to the Principle Investigator, and the patient will be considered inevaluable on final data analysis.

6.8 Compliance Criteria and Critical Structure Constraints

Treatment Component	**Parameter**	**Per Protocol**	**Variation Acceptable**	**Deviation Unacceptable**
Contouring	Hippocampal Contouring	≤ 2 mm deviation using the Hausdorff distance*	> 2, ≤ 7 mm deviation using the Hausdorff distance*	Neither per protocol or variation acceptable
Planning	PTV_{wb}	D_{95} ≥ 20 Gy; D_{98} ≥ 16 Gy	D_{95} ≥ 18 Gy; D_{98} ≥ 15 Gy	Neither per protocol or variation acceptable
	PTV_1, PTV_2, etc	D_{95} ≥ 40 Gy; D_{98} ≥ 30 Gy	D_{95} ≥ 37.5 Gy; D_{98} ≥ 28 Gy	Neither per protocol or variation acceptable
	Hippocampus	Maximum Dose ≤ 16 Gy	Maximum Dose ≤17 Gy	Maximum dose > 17 Gy
Unscheduled Break Days		0 break days	1-3 break days	> 3 break days

* To assess the Hausdorff distance, the Principal Investigator will remotely contour the "true" hippocampus on the submitted MRI/CT fusion, and a comparison will be made to the submitted contours.

6.9 Radiation Therapy Interruptions

6.9.1 Radiotherapy will be continued without interruption if at all possible.

6.9.2 If the sum total of radiotherapy interruptions exceeds -7 normally scheduled treatment days, the treatment will be considered an unacceptable deviation from the protocol. This should be reported to the Principal Investigator, and the patient will be considered inevaluable on final data analysis.

6.10 Radiation Therapy Adverse Events

6.10.1 Definition of an Adverse Event (AE)

6.10.1.1 Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

6.10.2 Definition of a Serious Adverse Event (SAE)

6.10.2.1 Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

6.10.3 Expected Adverse Events

6.10.3.1 Acute, ≤ 90 days from treatment start: Expected adverse events include hair loss, erythema of the scalp, head ache, nausea and vomiting, lethargy, and transient worsening of neurologic deficits. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

6.10.3.2 Late, > 90 days from treatment start: Possible adverse events include radiation necrosis, cognitive dysfunction, visual difficulties, accelerated atherosclerosis, and radiation-induced neoplasms.

6.10.4 Any adverse event equivalent to CTC V.4 grade 3, 4, or 5 or which precipitates hospitalization or prolongs an existing hospitalization must be reported regardless of designation (expected or unexpected) along with the attribution. This includes all deaths that occur within 30 days after the patient was discontinued from the study regardless of attribution AND any events that occur beyond 30 days and are considered probably related to treatment.

6.10.5 SAE reports must be completed (the CRF plus information describing the event, the grade, and the attribution) within 48 hours of the investigator's awareness of the occurrence of the event.

6.10.6 Attribution of an event can be categorized as:

- Not Related
- Possibly Related
- Probably Related
- Definitely Related

6.10.7 Adverse events (below grade 3) do not need to be submitted immediately. Rather, they should be documented in the Adverse Events Clinical Report Form (CRF) along with a brief description of the event, grade, and attribution).

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I.

11.2 Neurocognitive Evaluation

11.2.1 Summary of Required Neurocognitive Tests for All Patients

The tests will be used to assess neurocognitive function. These tests are to be administered by a certified examiner (a health care professional such as a physician, nurse or data manager certified to administer the tests)Certification from other RTOG/ECOG studies is acceptable,

11.2.2.1 Hopkins Verbal Learning Test (HVLT-R)

The HVLT-R incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) with 4 words drawn from 3 semantic categories, which differ across the 6 forms. The version used in RTOG 0933 involves memorizing a list of 12 targets for 3 consecutive trials (immediate recall), identifying the 12 targets from a list of semantically related or unrelated items (immediate recognition), and recalling the 12 targets after a 20-minute delay (delayed recall). Raw scores are derived for total recall, delayed recall, retention (percentage retained), and a recognition discrimination index. Each patient will serve as his/her own control, as the difference in scores obtained at baseline and at pre-specified post-treatment intervals will be calculated.

11.2.2.2 Trail Making Test (TMT)

This is a measure of visuospatial scanning, attention, sequencing, and speed Part A and executive function in Part B. Patients must "connect the dots" either in a numbered sequence or alternating letters and numbers. Generally Part A and Part B require less than 5 minutes, and Part A is discontinued at 3 minutes, Part B at 5 minutes, to reduce burden on patients with significant cognitive impairment.

11.2.2.3 Controlled Word Association Test (COWAT)

The patient produces as many words as possible in 1 min. (each) for a specific letter (C, F, L or P, R, W). Requires about 5 min to complete. Assesses language and executive/frontal skills.

11.2.2.4 Mini-Mental Status Examination (MMSE)

This is a brief, standardized tool to grade patients' global cognitive function.[61] The MMSE begins with an assessment of orientation to place and time. Next is a test of memory (immediate recall) by having the subject immediately repeat the names of 3 objects presented orally. Following this the patient subtracts sevens serially from 100. The subject is then asked to recall the three items previously repeated (delayed recall). The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a 3-step command, comprehension of written words, writing, and copying a drawing. The maximum score that can be obtained for the entire MMSE is 30 points. There is no specific training to perform MMSE as the questions and conduct are straightforward and this is not a validated metric like the others.

11.3 Fatigue Evaluation

Fatigue will be assessed using the Multidimensional Fatigue Inventory (MFI-20).

11.3.1 Summary of Required Fatigue Evaluations For All Patients

11.3.1.1 Multidimensional Fatigue Inventory (MFI-20)

The MFI-20 is a multidimensional, self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. A subscore from 4 to 20 is reported for each dimension, with 20 corresponding to maximal fatigue.

11.4 Quality of Life Assessments

11.4.1 Summary of Quality of Life Assessments

11.4.1.1 FACT-BR (Appendix VI)

The FACT-BR is a multidimensional, self-report QOL instrument specifically designed and validated for use with brain malignancy patients. It is written at the 4th grade reading level and can be completed in 5-10 minutes with little or no assistance in patients who are not neurologically incapacitated. It measures quality of life related to symptoms or problems across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Items are rated on a five-point scale: 0-"not at all", 1-"a little bit", 2-"somewhat", 3- "quite a bit" and 4-"very much". FACT-BR is self-administered and does not require precertification. It has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement. Form is available in English and Spanish.

11.4.1.2 EQ-5D (Appendix VII)

The EQ-5D health related quality of life questionnaire will be used as well. EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. . The US version of the EQ-5D will be used, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population. These utility scores are needed for cost-utility analysis (estimates of costs per "quality adjusted" life-year gained). Form is available in English and Spanish. This form can be completed in less than 5 minutes and is a two page questionnaire.

11.5 Administration of Neurocognitive, Fatigue, and Quality of Life Assessments

11.5.1 Timing

11.5.1.1 Prior to initiation of treatment, all patients will undergo baseline neurocognitive, fatigue, and quality of life testing using this test battery. At that time, history regarding level of education reached will also be obtained. After completion of radiotherapy, all patients will undergo neurocognitive and fatigue evaluation at 3, 6, 9, 12, and 24 months after WBRT-HA/SIB.

11.5.1.2 Examiners will give patients a short break if the patient appears fatigued or otherwise in need of a few-minutes break.

11.6 Measurement of Response

Patients will undergo brain MRI prior to study entry (the MRI obtained for hippocampal contouring can be used for this purpose) and every 3 months until death or until 2 years after WBRT-HA/SIB, whichever comes first.

11.6.1 Criteria for CNS Progression

11.6.1.1 Assessment

The the bidimensional product for each of the 1-3 largest brain metastases identified at baseline will be recorded. The bidimensional product is defined as the largest dimension multiplied by the second largest dimension that is perpendicular to it (the largest dimension). This value will be recorded on the baseline form and every subsequent follow-up form. The appearance (yes/no and number) of any new brain metastases within the whole brain minus the hipposcampal region will be recorded on all follow-up forms. The appearance (yes/no and number) of any new brain metastases within the hippocampal avoidance region (the hippocampus plus 5 mm) will be recorded on all follow-up forms.

Recurrences will be categorized as either within the hippocampal avoidance region or elsewhere within the brain. Therefore, there will be 3 kinds of local recurrences

reported: a) in the brain, b) in the hippocampal avoidance region, and c) elsewhere in the brain.

11.6.1.2 Definition of CNS Progression

CNS progression will be defined as a defined increase (see below) in perpendicular bidimensional tumor area for any of the tracked brain metastases, or the appearance of any new brain metastasis on a follow-up MRI.

For lesions < 1cm in maximum diameter, a minimum increase of 50% of perpendicular bi-dimensional treatment area will be necessary to score as progression. This caveat is included to account for potential variability in measurement, which will be most susceptible to proportionate errors at smaller sizes.

For lesions > 1cm in maximum diameter, the definition will use a 25% rule for change.

11.7 Criteria for Discontinuation of Protocol Treatment

11.7.1 Unacceptable adverse event to the patient (at the discretion of the treating physician)—Reasons for removal must be clearly documented on the appropriate case report form/flowsheet.

11.7.2 Interruption of treatment of >3 days

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol but the patient will be considered inevaluable.

12.0 DATA COLLECTION

Summary of Data Submission

Item	Due
Demographic Form Initial Evaluation Form Mini-Mental Status Exam Neurocognitive Evaluation Summary Form (HVLT-R, TMT, COWAT) Fatigue Evaluation Summary, FACT-BR, EQ-5D	Within 2 weeks of registration Before the first treatment
Follow-up Forms Mini-Mental Status Exam Neurocognitive Evaluation Summary Form (HVLT-R, TMT, COWAT) Fatigue Evaluation Summary Quality if life Assessments (FACT-BR, EQ-5D) Progression MRI Scan & Report	3, 6, 9, 12, and 24 months after radiotherapy is completed As above Within 1 week of scan date

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Delayed recall, 3 months from the start of treatment as measured by the Hopkins Verbal Learning Test-Revised for delayed recall (HVLT-R delayed recall)

13.1.2 Secondary Endpoint

13.1.2.1 Cognitive function includes the HVLT-R for free recall, and delayed recognition; the Controlled Word Association Test (COWAT); the Trail Making Test Parts A and B (TMT); the Medical Outcomes Scale-Cognitive Functioning Subscale (MOS); the Mini-Mental Status Examination (MMSE) after WBRT-HA/SIB for brain metastasis

13.1.2.2 Fatigue as measured by the Multidimensional Fatigue Inventory (MFI-20)

13.1.2.3 Time to radiographic progression

13.1.2.3 Overall survival

13.1.2.5 Adverse events based on CTCAE criteria

13.2 Sample Size

The primary endpoint will be delayed recall, as measured by the relative (percent) change in HVLT-R delayed recall score from the start of treatment to 3 months after the start of treatment.

The sample size calculation will address the specific primary hypothesis that WBRT-HA/SIB reduces decline in delayed recall (from baseline to 3 months). We do not expect improvement in delayed recall; at best, we anticipate a preservation of delayed recall. Data from a randomized trial showed that the decline in HVLT-R delayed recall score was 64% at 4 months for those getting whole brain radiation for brain metastases (Chang et al., 2009). We anticipate that WBRT-HA/SIB will have better delayed recall functioning at 3 months than WBRT alone. Detecting a 30% average relative loss due to WBRT-HA/SIB suggests a 50% relative improvement over previous results. The null and alterative hypotheses are:

H_0: ΔHVLT-R = 0.60 vs. H_A: ΔHVLT-R $\leq$ 0.30

ΔHVLT-R is the mean of relative decline between baseline and 3 month after treatment in this patient population. For patient individual i, the relative decline is calculated as follows: $\Delta HVLT\text{-}R_i = (HVLT\text{-}R_{i0} - HVLT\text{-}R_{i3}) / HVLT\text{-}R_{i0}$, where $HVLT\text{-}R_{i0}$ and $HVLT\text{-}R_{i3}$ denote individual patient scores at baseline and 3 months after treatment, respectively.

Initial sample size calculation:
Based on the one-sided one sample t-test, assuming a standard deviation of 41%, with alpha=0.05 (one-sided), a total of 9 analyzable patients would ensure 80% statistical power to detect a 30% average relative loss in delayed recall at 3 months. Assuming a death rate of 60% prior to 3 months and a 10% in-evaluable rate, the target sample size will be 34 registered patients.

Sample size re-estimation based on internal pilot study:
The internal pilot consists of 32 patients enrolled at baseline, among which 9 patients have complete information on HVLT-R delayed recall score at the start of treatment and 3 months after the start of treatment. For the 9 patients, the mean and standard error of relative (percent) change (decline) in HVLT-R delayed recall score is 31% and 51%. We re-estimate the required sample size using the updated standard error.

Based on the one-sided one sample t-test, assuming a standard deviation of 51%, with alpha=0.05 (one-sided), a total of 18 analyzable patients would ensure 80% statistical power to detect a 30% average relative loss in delayed recall at 3 months. Assuming a death rate of 60% prior to 3 months and a 10% in-evaluable rate, the target sample size will be 50 registered patients. Therefore, additional 18 patients need to be recruited at the second stage.

13.3 Analysis Plan

13.3.1 Primary Endpoint

The primary endpoint is delayed recall, as determined by the relative change in HVLT-R delayed recall score from the start of treatment to 3 months after the start of treatment. To test the null hypothesis H_0, the primary endpoint will be analyzed using the one-sided one sample t-Test with a significance level of 0.05.

13.3.2 Secondary Endpoints

13.3.2.1 *Cognitive Function and Fatigue*

All the secondary cognitive and fatigue endpoints will by analyzed similar to the primary endpoint. Additionally, the relationship between the change from baseline through 12 months in cognitive and fatigue endpoints will be evaluated using Spearman correlation coefficients.

13.3.2.2 *MFI*

Change in MFI domain scores from baseline to each post-baseline assessment point will be analyzed using mixed models for repeated measures.

13.3.2.3 *Radiographic Progression*

The Kaplan-Meier estimator will be used to determine the median time to radiographic progression for this patient population (along with 95% confidence intervals). The Cox proportional hazards regression model will be used to evaluate the effects of covariates of interest on time to radiographic progression.

Overall Survival

The Kaplan-Meier estimator will be used to determine the median time to death for this patient population (along with 95% confidence intervals). The Cox proportional hazards model will be used to evaluate the effects of covariates of interest on survival.

13.3.2.5 Adverse Events

Adverse events will be reported according the CTCAE criteria.

13.0 DATA SAFETY MONITORING PLAN

13.1 Purpose and Scope

13.1.1 The purpose of the Radiation Oncology Data and Safety Monitoring Plan is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants.

13.1.2 The Radiation Oncology DSMC is charged with developing, implementing, and maintaining the Data and Safety Monitoring Plan. The membership consists of a Medical Director of Clinical Research as well as representation from the following groups: clinical research, nursing, regulatory, pharmacy, physicists, radiation therapists, and faculty. Ad hoc members are contacted to participate as needed

13.2 Procedures

13.2.1 Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines.

All clinical trials are reviewed on monthly basis for enrollment. All local SAEs are reviewed by Radiation Oncology DSMC monthly for severity and attribution. For investigator-initiated trials, all SAEs at affiliated institutions are monitored as local SAEs. The principle investigator and study coordinator will present a study treatment summary and SAEs for review. Source documents will be available for the DSMC members during the review. NCI Common Toxicity Criteria Version 4 will be used for grading and attributing adverse events.

If the SAE occurs on a multi-institutional clinical trial coordinated by the Radiation Oncology Clinical Research Office, the Clinical Research Manager or primary coordinator ensures that all participating sites are notified of the event and resulting action, within one (1) working day of the determination.

REFERENCES

Abayomi OK. Pathogenesis of irradiation-induced cognitive dysfunction. ***Acta Oncol*** **1996;35:659-663.**

Andrews 2004. Whole Brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. ***Lancet*** **2004; 363:1665–1672.**

Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;68:1388-1395.

Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;10:1037-1044.

DeAngelis LM DJ, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989;39:789–796.

Ferrer I, Serrano T, Alcantara S, et al. X-ray-induced cell death in the developing hippocampal complex involves neurons and requires protein synthesis. *J Neuropathol Exp Neurol* 1993;52:370-378.

Fleming, T. One-Sample Multiple Testing Procedure for Phase II Clinical Trials. Biometrics. 38: 143-151, 1982.

Ghia A, Tome WA, Thomas S, et al. Distribution of brain metastases in relation to the hippocampus: implications for neurocognitive functional preservation. *Int J Radiat Oncol Biol Phys* 2007;68:971-977.

Gondi V, Tolakanahalli R, Mehta MP, et al. Hippocampal-sparing whole-brain radiotherapy: A "how-to" technique, utilizing helical tomotherapy and LINAC-based intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2010a**; Epub ahead of print.**

Gondi V, Tome WA, Marsh J, et al. Estimated of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: Safety profile for RTOG 0933. *Radiother Oncol* 2010b**;95:327-331.**

Grattan-Smith PJ, Morris JG, Shores EA, et al. Neuropsychological abnormalities in patients with pituitary tumours. *Acta Neurol Scand* 1992;86:626-631.

Gutierrez AN, Westerly DC, Tome WA, et al. Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. *Int J Radiat Oncol Biol Phys* 2007;69:589-597.

Hsu F, Carolan H, Nichol A, et al. Whole Brain Radiotherapy with Hippocampal Avoidance and Simultaneous Integrated Boost for 1-3 Brain Metastases: A Feasibility Study Using Volumetric Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys*; 76:1480-1485.

Khuntia D, Brown P, Li J, et al. Whole-brain radiotherapy in the management of brain metastasis. *J Clin Oncol* 2006;24:1295-1304.

Kondziolka, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999;45(2):427-34.

Lagerwaard, *et al.* Whole-Brain Radiotherapy with Simulataneous Integrated Boost to Multiple Brain Metastases Using Volumetric Modulated Arc Therapy. **.** *Int J Radiat Oncol Biol Phys 2009;* 75: 253-259.

Lee PW, Hung BK, Woo *EK, et al.* Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. *J Neurol Neurosurg Psychiatry* 1989;52:488-492.

Leung SF, Kreel L, Tsao SY. Asymptomatic temporal lobe injury after radiotherapy for nasopharyngeal carcinoma: incidence and determinants. *Br J Radiol* 1992;65:710-714.

Li J, Bentzen SM, Renschler M, et al. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007;25:1260-1266.

Li J, Bentzen SM, Renschler M, et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008;71:64-70.

Madsen TM, Kristjansen PE, Bolwig TG, et al. Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. *Neuroscience* 2003;119:635-642.

Mahajan A, Dong L, Prabhu S, et al. Application of deformable image registration to hippocampal doses and neurocognitive outcomes. Society of Neuro-Oncology. Vol 9. Dallas; 2007. p. 538.

Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol* 2003;21:2529-2536.

Mehta MP, Shapiro WR, Glantz MJ, et al. Lead-in phase to randomized trial of motexafin gadolinium and whole-brain radiation for patients with brain metastases: centralized assessment of magnetic resonance imaging, neurocognitive, and neurologic end points. *J Clin Oncol* 2002;20:3445-3453.

Meyers CA, Geara F, Wong PF, et al. Neurocognitive effects of therapeutic irradiation for base of skull tumors. *Int J Radiat Oncol Biol Phys* 2000;46:51-55.

Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* 2004;22:157-165.

Mizumatsu S, Monje ML, Morhardt DR, et al. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res* 2003 ;63 :4021-4027.

Monje ML, Mizumatsu S, Fike JR, et al. Irradiation induces neural precursor-cell dysfunction. *Nat Med* 2002;8:955-962.

Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 2003;302:1760-1765.

Nagai R, Tsunoda S, Hori Y, *et al.* Selective vulnerability to radiation in the hippocampal dentate granule cells. *Surg Neurol* 2000;53:503-506; discussion 506-507.

Peissner W, Kocher M, Treuer H, *et al.* Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. *Brain Res Mol Brain Res* 1999 ;71 :61-68.

Raber J, Rola R, LeFevour A, *et al.* Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res* 2004;162:39-47.

Regine WF, Schmitt FA, Scott CB, et al. Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of Radiation Therapy Oncology Group trial BR-0018. *Int J Radiat Oncol Biol Phys* 2004;58:1346-1352.

Rodrigues, et al. Phase I Trial of Simultaneous In-Field Boost With Helical Tomotherapy for Patients with One to Three Brain Metastases. *Int J Radiat Oncol Biol Phys* 2010 Jul 31. Epub ahead of print.

Roman DD SP. Neuropsychological effects of cranial radiation: Current knowledge and future directions. *Int J Radiat Oncol Biol Phys* 1995;31:983-998.

Sakata K, Aoki Y, Karasawa K, et al. Analysis of the results of combined therapy for maxillary carcinoma. *Cancer* 1993;71:2715-2722.

Sundstrom JT MH, Lertola KK, et al. Prognosis of patients treated for intracranial metastases with whole-brain irradiation. *Ann Med* 1998;30:296-299.

Tada E, Parent JM, Lowenstein DH, et al. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. *Neuroscience* 2000;99:33-41.

Welzel G, Fleckenstein K, Schaefer J, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *Int J Radiat Oncol Biol Phys* 2008;72:1311-1318.

APPENDIX I:

STUDY PARAMETER TABLE	**Pre-Treatment**			**Follow-Up**					
	Within 5 yrs prior to registration	Within 28 days prior to registration	Within 2 wks prior to registration	Before 1st treatment	3 mos after RT	4-6 mos after RT	9 mos after RT	12 mos after RT	24 mos after RT
Histo/cyto eval	X								
History/physical		X			X	X	X	X	X
Performance status		X			X	X	X	X	X
Serum creatinine		X							
Serum pregnancy test (if applicable)			X						
Adverse event eval					X	X	X	X	X
MRI with contrast and assessment		X			X	X	X	X	X
Head CT simulation scan				X					
HA/SIB-WBRT treatment planning				X					
Neurocognitive assessment				X	X	X	X	X	X
Fatigue assessment				X	X	X	X	X	X
Quality of Life Assessments				X	X	X	X	X	X

Appendix II:

Follow-up Radiographic Assessment

Date of MRI:

Patient Name:

Treated metastases

Lesion Number	Side (L,R,ML) & Location	d_{AP} (cm) (Ant-Pos)	d_{ML} (cm) (Med-Lat)	d_{SI} (cm) (Sup-Inf)	Bidimensional product[1]
First set of treated metastases					
1					
2					
3					
4					
5					
6					
7					
8					
9					

[1] Bidimensional product = largest dimension x second-largest dimension

New Brain Metastases outside the hippocampus? (yes/no)
Number

New Brain Metastases within the hippocampus? (yes/no)
Number

Appendix III:

Neurocognitive Function Assessments
Background Information and Test Instructions

There are three immediate recall responses, one delayed recall response, and one delayed recognition response in the HVLT-R. The response is the number of words the patient can recall out of 12 words for recall responses and the difference of the listed words correctly and incorrectly recalled for recognition response. The response from Trail Making Test, parts A & B is the time takes to finish each test less than 3 and 5 minutes, respectively. There are three responses for the COWAT, and each response is the number of words starting with a provided letter of the alphabet that the patient can produce in one minute.

Testing: General Information

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every assessment visit.
2. Tests should be administered in the following order to every patient and at each assessment visit: HVLTR Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. Follow the instructions on the Forms Packet Index before submitting the forms.
4. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
5. **Note**: Sites should keep all original test records, and test results must remain on file at the institution as source documentation pending request for submission by a Study Chair.
6. Patients should not be given copies of their tests to avoid learning the material between test administrations.
7. The HVLT-R and the COWAT have alternate forms or versions in order to reduce the effects of practice. See the test instructions below for the versions to be administered at pre-treatment and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

Before dismissing the patient, thank him/her for their cooperation. Remind the patient of their next appointment and that these tests will be repeated.

In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.

Testing: Specific Instructions
Note: Administer the tests in the following order to every patient at each assessment visit.

1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms (only the first 4 forms will be used in this study):
Part A - Free Recall: Complete the three learning trials first
Part B - Delayed Recall: Complete after Trail Making Tests and COWAT
Part C - Delayed Recognition: Complete after Delayed Recall

Part A – Free Recall: Trial 1
Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"*
• Read the words at the rate of one word every 2 seconds.

***Examiner: "OK. Now tell me as many of those words as you can remember*."**

• Check off the words the patient recalls on the form.
• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 2

Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."*

• Read the words at the rate of one word every 2 seconds.
• Check off the words the patient recalls on the form.
If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 3

Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."*

• Read the words at the rate of one word every 2 seconds.
• Check off the words the patient recalls on the form.
• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• **Do not tell the respondent that recall of the words will be tested later.**
• Record the time on the clock that you *complete* 'Part A – Free Recall' (for example, 1:00 p.m.) on the designated space on the HVLT-R form.

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample*:* Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a black pen and say:

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3), *3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.
The following explanations of mistakes serve as illustrations:
• ***This is where you start (point to number 1).***
• ***You skipped this circle (point to the circle omitted).***
• ***You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END.***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take

his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:
Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*
• Start timing as soon as the instruction is given to "begin"
• Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
• The patient must complete the test in **3 minutes** or less.
• **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**
• Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
• If the patient does not complete the test within **3 minutes** terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.

Part B – Sample: Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
Examiner*: "On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the end (*point to the circle marked END*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.
The following explanations of mistakes serve as illustrations:
• ***You started with the wrong circle. This is where you start (point to number 1)***
• ***You skipped this circle (point to the circle omitted)***
• ***You should go from number 1 (*point*) to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, until you reach the circle marked END (*point*).***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:

After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (***point***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the circle marked END (***point***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (***point to B***), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

• Start timing as soon as the instruction is given to "begin".

• Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred

• The patient must complete the test in **5 minutes** or less.

• **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**

• Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds.

• If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.

3. CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]

This test has three parts (letters) and two alternate forms.

Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' 'Eats,' and 'Eating.'*

"For example, if I say 's,' you could say 'sit,' 'shoe,' or 'show.' Can you think of other words beginning with the letter 's'?"

Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner*: "That is fine. Now I am going to give you another letter. Again, say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."*

"You will have a minute for each letter. The first letter is '___'" (see scoring sheet).

****Allow exactly one minute for each letter.****
• If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
• If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
• No extension on the time limit is made in the event that instructions are repeated.
• Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:
• The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
• Incorrect responses either should not be recorded or, if recorded, should be struck through with a line.
• If the patient provides more responses than there are lines on the record sheet, keep writing the responses *(or a "+")* elsewhere on the record sheet.
• Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form.

Comments on scoring:
• Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
• The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
• Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sadsadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger),* it would be counted as a correct answer.
• Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
• Slang terms are OK if they are in general use.
• Foreign words *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of English vocabulary *(for example, in general use or found in the dictionary).*
• If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF

4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall
• **DO NOT READ THE WORD LIST AGAIN.**
• Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 1:20 p.m.) on the designated space on the HVLT-R form.
• Administer 'Part B – Delayed Recall' **after** completing **all** Trail Making Tests and the COWAT. There should be at least **15 minutes** between 'Part A' and 'Part B'. If the time is too short, allow the patients to complete a questionnaire.

Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."*
• Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
• If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.

• If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
• If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"*

• Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
• Guessing is allowed.
• If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF.

The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 *(no list words identified and all non-list words identified)* to +12 *(all list words identified and no non-list words identified)*.

APPENDIX IV:

Performance Status Scoring

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).
5	Death (Karnofsky 0).

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX V

RTOG RPA Classification System

Class I: KPS ≥ 70 *(Zubrod 0-1)*;
Age < 65 years;
No extra-cranial metastases; and
Controlled primary malignancy*

Class II: KPS ≥ 70
Age ≥ 65;
Extra-cranial metastases
Controlled primary malignancy

Class III: KPS < 70

**Controlled primary malignancy is defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy during the previous 3 months or longer).*

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

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

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

GS7	I am satisfied with my sex life.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

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

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

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4

Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

APPENDIX VII – EQ-5D – form is available in English and Spanish
Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]