RADIATION THERAPY ONCOLOGY GROUP

RTOG 0933

A PHASE II TRIAL OF HIPPOCAMPAL AVOIDANCE DURING WHOLE BRAIN RADIOTHERAPY FOR BRAIN METASTASES

Study Chairs
Co-Principal Investigator/Radiation Oncology Co-Chair
Minesh P. Mehta, MD
Northwestern University
Department of Radiation Oncology
676 N St Clair, Suite 1820
Chicago IL 60611
312-926-3120/FAX 312-926-6524
mmehtha@nmff.org

Co-Principal Investigator/Radiation Oncology Co-Chair
Vinai Gondi, MD
University of Wisconsin
600 Highland Avenue, K4/B100-0600
Madison, WI 53792
608-263-8500/FAX 608-263-9167
gondi@humonc.wisc.edu

Quality of Life Co-Chair
Benjamin Corn, MD
Tel Aviv Medical Center
Institute for Radiotherapy
6 Weizman Street
Tel Aviv, Israel 64239
011-972-3-694-7285/FAX 011-972-3-697-7284
bencom@tasmc.health.gov.il

Neuropsychology Co-Chair
Chip Caine, PhD
Neuroscience Clinic
Intermountain Medical Center
5171 Cottonwood Street, 8th Floor
Murray, UT 84107
801-507-9835/FAX: 801-507-9801
Chip.Caine@imail.org

Neurosurgery Co-Chair
Andrew Kanner, MD
Tel Aviv Sourasky Medical Center
Tel Aviv University
6 Weizman Street
Tel Aviv, Israel 64239
011-972-3-6974075/FAX 011-972-3-6974860
andrewk@tasmc.health.gov.il

Medical Physics Co-Chair
Wolfgang Tome, PhD
University of Wisconsin, Medical Physics
Box 3684 Clinical Science Center-K4
600 Highland Avenue, Madison WI 53792
608-263-8510/FAX 608-263-9167
tome@humonc.wisc.edu

Neuroradiology Co-Chair
Howard Rowley, MD
University of Wisconsin, Radiology
Box 3252 Clinical Science Center-E3
600 Highland Avenue, Madison WI 53792
608-263-9179/FAX 608-262-5839
hrowley@uwhealth.org

Senior Statistician
Stephanie Shook, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19013
215-574-0850/FAX 215-928-0153
sshook@acr.org

Document History

<table>
<thead>
<tr>
<th>Version/Update Date</th>
<th>Broadcast Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update</td>
<td>March 31, 2011</td>
</tr>
<tr>
<td>Activation</td>
<td>March 31, 2011</td>
</tr>
</tbody>
</table>

RTOG Headquarters
1-800-227-5463, ext. 4189

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

RTOG 0933
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 - Sample Consent Form
Appendix II - Study Parameters
Appendix III - Performance Status Scoring
Appendix IV - RTOG RPA Classification System
Appendix V - Administrative Procedures for Neurocognitive Test Battery
Appendix VI - Certification Worksheet for Test Administrator
Appendix VII - RTOG Blood Collection Instructions
Appendix VIII - Recommended Approach to Using Helical Tomotherapy or LINAC-Based IMRT Planning

RTOG 0933
A PHASE II TRIAL OF HIPPOCAMPAL AVOIDANCE DURING WHOLE BRAIN RADIOTHERAPY FOR BRAIN METASTASES

SCHEMA

For Patients with MRI Evidence of Brain Metastasis Within 1 Month Prior to Registration

<table>
<thead>
<tr>
<th>Register</th>
<th>Within 2 Weeks Prior to Treatment Start</th>
<th>Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 3D SPGR MRI with Fused CT Simulation(^2)</td>
<td>WBRT with Hippocampal Avoidance using IMRT (30 Gy in 10 Fractions)</td>
</tr>
<tr>
<td></td>
<td>2. Neurocognitive Function Testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Quality of Life Assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Rapid Central Review of Hippocampal Contours and HA-WBRT Treatment Plan(^3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Institutions must be credentialed by the RTOG prior to enrolling patients (See Section 5.0).

\(^2\)Three-dimensional spoiled gradient (SPGR) axial MRI scan with standard axial and coronal fluid attenuation inversion recovery (FLAIR), axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequence acquisitions with a 1.25 mm axial slice thickness must be fused to a non-contrast CT scan of the entire head region with a 1.25 mm axial slice thickness. An immobilization device such as an Aquaplast mask over the head must be used during CT simulation and during whole-brain radiotherapy, but not during the MRI scan.

\(^3\)Prior to treatment, all hippocampal contours and HA-WBRT treatment plans will be rapidly reviewed centrally for protocol compliance. Permission to treat or request for revision will returned to the investigator within 3 business days. Resubmission of revised treatment plans will not be required unless requested, in which case rapid central review will be completed in 3 additional business days.

**Patient Population:** (See Section 3.0 for Eligibility)
At least one radiologically diagnosed brain metastasis associated with a histologically proven diagnosis of a non-hematopoietic malignancy other than small cell lung cancer and germ cell malignancy. Patients must be classified as RTOG RPA class I or RPA class II

**Required Sample Size:** 102
RTOG Institution # __________

RTOG ELIGIBILITY CHECKLIST (3/31/11)

Case # __________ (page 1 of 3)

______(Y) 1. Is there evidence of at least one brain metastasis on a gadolinium contrast-enhanced MRI within 30 days prior to study entry?

______(Y)/N 2. Is there pathologic/histological/cytologic proof of a diagnosis of a non-hematopoietic malignancy within 5 years of study entry?

______(Y) 3. Does the patient have measurable brain metastasis outside a 5-mm margin around either hippocampus?

______(N) 4. Does the patient have a history of a prior small cell lung cancer and/or germ cell malignancy?

______(N/NA) 5. If the patient has NSCLC-associated brain metastases, is there radiographic evidence of ≥2 sites of extracranial metastases?

______(N) 6. Does the patient have MRI evidence of leptomeningeal metastases?

______(N) 7. Does the patient have radiographic evidence of hydrocephalus?

______(N) 8. Is there a history of, or plan for, treatment of brain metastasis with stereotactic radiosurgery or surgical resection? (Note: These treatment options are permitted at relapse.)

______(N) 9. Will the patient receive chemotherapy and/or targeted therapies during whole-brain radiotherapy or during the subsequent 7 days?

______(N) 10. Does the patient have a history of prior radiation therapy to the brain?

______(Y) 11. Is the patient ≥18 years of age?

______(Y) 12. Does the patient fall into RTOG Recursive Partition Analysis (RPA) class I or II? (See Appendix IV)

______(Y) 13. Does the patient have a Karnofsky Performance Score ≥70? (See Appendix III)

______(Y) 14. Does the patient have stable systemic disease (i.e., no evidence of systemic disease progression ≥3 months prior to study entry)? This eligibility requirement does not pertain to patients who have brain metastases at initial presentation, as these patients are eligible and do not need to demonstrate 3 months of stable scans.

______(Y)(N/A) 15. If an open biopsy of the brain metastasis was performed, was the biopsy done at least 1 week prior to registration? This requirement does not apply to stereotactic biopsies.

______(N) 16. Does the patient have a contraindication to MR imaging such as implanted metal devices or foreign bodies, severe claustrophobia?

______(N) 17. Does the patient have a creatinine level > 1.4 mg/dl drawn ≤28 days prior to study entry?

Continued on next page
18. Does the patient have any of the following severe, active co-morbidities?
   - Unstable angina, and/or congestive heart failure requiring hospitalization within the last 6 months
   - Transmural myocardial infarction within the last 6 months
   - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
   - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
   - Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
   - Uncontrolled, clinically significant cardiac arrhythmias

19. If the patient is a woman of childbearing potential, has a negative, qualitative serum pregnancy test been documented within two weeks prior to registration?

20. If the patient is of childbearing potential, has the patient agreed to practice effective methods of contraception?

21. Does the patient speak English?

22. Has the patient signed a study-specific informed consent form prior to study entry?

23. Were a history and physical performed within 28 days of study entry?

The following questions will be asked at Study Registration:

PRIOR TO REGISTRATION ALL OF THE FOLLOWING MUST BE COMPLETED:
1. IMRT CREDENTIALING
2. HIPPOCAMPAL CONTOURING CREDENTIALING
3. HA-WBRT TREATMENT PLANNING CREDENTIALING
4. NEUROCOGNITIVE CREDENTIALING

1. Institutional person randomizing this case
2. Has the Eligibility Checklist been completed?
3. In the opinion of the investigator, is the patient eligible
4. Date informed consent signed
5. Participant Initials (First Middle Last)
6. Verifying Physician
7. Patient ID

(Continued on the next page)
RTOG Institution # __

RTOG ELIGIBILITY CHECKLIST (3/31/11)

Case # ____________ (page 3 of 3)

8. Date of Birth
9. Race
10. Ethnicity
11. Gender
12. Country of Residence
13. Zip Code (U.S. Residents)
14. Method of Payment
15. Any care at a VA or Military hospital?
16. Calendar Base Date
17. Randomization date

(Y/N) 18. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

(Y/N) 19. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

(Y/N) 20. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

(Y/N) 21. Did the patient agree to participate in the quality of life component?

_________ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____________
3. Not approved by institutional IRB
4. Tool not available in patient’s language
5. Other reason: specify_________________

(Y) 22. Was hippocampal contouring done by or verified by a credentialed physician?

Physicians Name______________________

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________ Date ________________________

RTOG 0933
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 (Sundström 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). Recent work from our group has shown that NCF and quality of life are correlated in patients with brain metastases receiving WBRT (Li 2008). We found that deterioration in NCF preceded self-reported quality of life decline by up to 153 days. Hence, there is a sequential association between NCF decline and deterioration in self-reported quality of life for patients with brain metastasis. The results of our study 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 1-4 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, our research group recently published a detailed analysis 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 4 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 and our 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 (Sakat 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 therefore, propose to use conformal avoidance of the hippocampal region during whole brain radiotherapy (HA-WBRT) 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 HA-WBRT may delay or reduce the onset, frequency, and/or severity of NCF decline, as measured with clinical neurocognitive tools.

1.3 Feasibility of Hippocampal Avoidance During WBRT

HA-WBRT 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). Recently, our group demonstrated the capability of helical tomotherapy to conformally avoid the hippocampus, and still deliver radiosurgical-quality dose distributions to multiple metastases and a homogeneous dose distribution to the whole brain—all in a single treatment plan (Gutierrez 2007). Our institution and other institutions have also demonstrated the feasibility of HA-WBRT utilizing LINAC-based IMRT delivery systems broadly available at multiple academic and community radiation oncology practices (Gondi 2010a; Hsu 2009).

Given the challenges of hippocampal contouring and HA-WBRT treatment planning, participation in a credentialing process will be required for study participation by treating physicians and institutions. Credentialing will involve anatomic contouring on fused head MRI and CT images and HA-WBRT treatment planning according to pre-specified dosimetric criteria. These will be reviewed centrally by study investigators. An institution will be permitted to accrue patients to this phase II study once at least one treating physician at that institution is successfully credentialed. An institution that chooses to accrue patients from more than one treating physician must separately obtain successful credentialing for each treating physician. In addition, to enable quality assurance of patients treated with HA-WBRT on this phase II study, pretreatment central review of all hippocampal contours and HA-WBRT treatment plans will be planned and
recommended revisions will be communicated to the treating physician and institution. The credentialing and pretreatment reviews will be facilitated by the established resources available through the Advanced Technology Consortium (ATC).

Avoiding the hippocampus poses the risk of attenuating the benefit of WBRT due to increased metastatic disease within the hippocampal conformal avoidance region. We recently investigated the magnitude of this risk by 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%. Since this publication, we have reviewed 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, we conclude that 91% of newly diagnosed patients will be eligible for HA-WBRT. 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 HA-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 HA-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 HA-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.

1.4 Neurocognitive Function Assessment

According to Meyers and Brown (2006), for a neurocognitive test battery to be useful in clinical research it should fulfill the following 6 criteria:

a) It should be brief in order to reduce patient and clinical burden.
b) It should have alternate forms of the tests in order to reduce practice effects and therefore allow for repeated test administration.
c) It should have good psychometric properties such as validity, reliability, and population norms so that true changes in NCF above fluctuations due to situational factors can be detected.
d) It should be sensitive to changes in cognitive function.
e) It should be highly standardized and easy to administer so that no specialized psychological training is necessary in order to be able to administer the test battery.
f) Most patients should be able to complete the neurocognitive tests, even patients with significant neurocognitive problems, in order to reduce the likelihood of selection bias.

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.

In addition to HVLT-R, the RTOG seeks to expand its NCF assessment tools to include those that are computer based, culturally neutral, and less costly and that do not require proficiency in English. This inclusion would enable RTOG to broaden trial accrual to include patients from community cancer programs and international centers. We have chosen to partner with CogState, a global provider of cognitive testing products and services, with customers including 5 of the leading top 10 pharmaceutical companies and multiple major universities. CogState neurocognitive tests utilize computer-based technology and culturally neutral stimuli to detect cognitive change in subjects.

CogState computerized neurocognitive tests have an extensive literature base of more than 50 peer-reviewed publications, including breast cancer (Vardy 2006); clinical trials of benzodiazepines (Collie 2007); and patients with cognitive impairment due to mild traumatic brain injury, schizophrenia, and AIDS dementia complex (Maruff 2009).

For the present protocol, we will be using 2 tests from the CogState neurocognitive battery, comparing performance on those tests with that of HVLT-R during at baseline and at the 2-, 4-, and 12-month follow-up visits. Similar in design to HVLT-R, the International Shopping List Task (ISLT) is a 16-word 3-trial verbal list-learning test. The ISLT has the capability of using culturally specific verbal stimuli: food items that are easily obtained in local markets, stores or supermarkets in the region in which testing takes place. This format helps to minimize between-culture disparities for test content (Lim 2009). The ISLT includes both immediate (3 minutes to complete) and delayed (1 minute to complete) recall components, separated by a 20-minute delay. To minimize interaction effects between two similar verbal list-learning tasks (HVLT-R and ISLT), during each of the 4 visits where both are administered, administration of each will be separated by a break. At each visit, the HVLT-R will be administered prior to the ISLT administration, with the sole exception being the 2-month visit. To allow for comparisons between the two tests while addressing possible carry-over effects, ISLT will be administered prior (in counterbalanced form) to the HVLT-R at 2 months.

The second CogState test, the One Card Learning Test, is a continuous recognition measure of visuo-perceptual learning and memory that uses culturally universal stimuli in the form of standard playing cards, presented one at time, as stimuli. No oral response is required; instructions are minimal (Have you seen this card before in this task?) and available in multiple languages. Continuous visual recognition learning formats are used often in research, and require subjects to differentiate between repeated (i.e., learned) and novel stimuli (Maruff, 2009).

Prior to initiation of treatment, all patients will undergo baseline NCF testing using this test battery (see table below). 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, every 2 months for 6
months and then every 3 months until death or until 2 years after HA-WBRT, whichever comes first. To minimize NCF noncompliance with further NCF testing, the CogState tests will only be administered at baseline, 2 months, 4 months, and 12 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.

**Test Battery for Neurocognitive Function**

<table>
<thead>
<tr>
<th>Neurocognitive Parameter Measured</th>
<th>Test(^{1})</th>
<th>Time to Administer (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory/verbal learning and memory</td>
<td>Hopkins Verbal Learning Test-Revised(^{^\wedge})</td>
<td>5</td>
</tr>
<tr>
<td>Auditory/verbal learning and memory</td>
<td>International Shopping List Test(^{*})</td>
<td>4</td>
</tr>
<tr>
<td>Visuo-perceptual and -spatial learning and memory</td>
<td>One Card Learning Test(^{*})</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>17</strong>(^{^*})</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)The HVLT-R is the only neurocognitive test administered during visits 4, 5, and 7-10. 
\(^{*}\)Computerized NCF Tests. 
\(^{^*}\)Total time shown is actual subject test involvement time for visits 1-3, and visit 6, excluding 2 periods of time between immediate and delayed recall. For HVLT-R, the delay is 20 minutes. For ISLT, the delay also is 20 minutes, but the One Card Learning Test is administered during that interval.

### 1.5 Quality of Life Assessment

Quality of life will be assessed using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Barthel Index of Activities of Daily Living (ADLs).

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](http://www.facit.org/translation/licensure.aspx).

The Barthel Index of ADLs is a self-report instrument designed to assess a patient’s ability to carry out ADLs as reported by the patients, their families, or their caregivers. Direct testing of the patient is not needed, as information can be derived from families or caregivers. The Barthel Index score ranges from 0 to 20, with 20 corresponding to a normal functional status. Completion of the Barthel Index takes approximately 5-10 minutes.

**Test Battery for Quality of Life Assessment**

<table>
<thead>
<tr>
<th>Quality of Life Parameter Measured</th>
<th>Test(^{1})</th>
<th>Time to Administer (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (self-report)</td>
<td>Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR)</td>
<td>5</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>Barthel Index</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>10</strong></td>
<td></td>
</tr>
</tbody>
</table>

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 2
months for 6 months and then every 3 months until death. Quality of life assessments will be scored centrally by a blinded reviewer to avoid potential bias.

### 1.6 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 from our group and others 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. We and others have demonstrated the dosimetric capabilities of IMRT to conformally avoid the hippocampus without detriment to the radiation dose the remaining brain receives. 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 HA-WBRT will provide a net gain in this endpoint.

In this phase II study, we plan to treat patients with brain metastases with HA-WBRT. To assess the utility of HA-WBRT, 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) 4 months after hippocampal avoidance during whole-brain radiotherapy (HA-WBRT) for brain metastasis.

#### 2.2 Secondary Objectives

2.2.1 Evaluate auditory and visual learning and memory, as assessed by 2 CogState tests (International Shopping List Test and One Card Learning Test), after HA-WBRT for brain metastasis.

2.2.2 Compare psychometric properties of the 2 CogState tests to the HVLT-R for the assessment of memory decline after HA-WBRT for brain metastases.

2.2.3 Evaluate health-related quality of life [as assessed by the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Barthel Index of Activities of Daily Living (ADLs)] after HA-WBRT for brain metastasis.

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

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

2.2.6 Evaluate adverse events according to CTCAE criteria.

2.2.7 Evaluate predictive biomarkers of cognitive function.

### 3.0 PATIENT SELECTION

**NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.**

#### 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 within 5 years of registration. If the original histologic proof of malignancy is greater than 5 years, then pathological (i.e., more recent) confirmation is required (e.g., from a systemic metastasis or brain metastasis).
3.1.2 Patients with measurable brain metastasis outside a 5-mm margin around either hippocampus on gadolinium contrast enhanced MRI obtained within 30 days prior to registration.

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 (see Appendix IV)

3.1.6 Patients must have stable systemic disease (i.e., no evidence of systemic disease progression ≥3 months prior to study entry). Patients who have brain metastases at initial presentation are eligible and do not need to demonstrate 3 months of stable scans.

3.1.7 If an open biopsy is performed, the patient must be at least 1 week post-biopsy. This requirement is not necessary for stereotactic biopsies.

3.1.8 Age ≥ 18 years

3.1.9 Karnofsky performance status ≥ 70

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

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

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

3.1.13 Patients must be English speaking

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with leptomeningeal metastases

3.2.2 Patients with measurable brain metastasis resulting from small cell lung cancer and germ cell malignancy

3.2.3 Patients with NSCLC-associated brain metastases with ≥ 2 sites of extracranial metastases

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

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 Severe, active co-morbidity, defined as follows:

3.2.8.1 Unstable angina, and/or congestive heart failure requiring hospitalization within the last 6 months

3.2.8.2 Transmural myocardial infarction within the last 6 months

3.2.8.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.8.4 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects

3.2.8.5 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

3.2.8.6 Uncontrolled, clinically significant cardiac arrhythmias

3.2.8.7 Radiologic evidence of hydrocephalus

3.2.9 Women of childbearing potential and male participants who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the radiation treatment involved in this study may be significantly teratogenic.

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 Patients with a single brain metastasis must be reviewed by their treating physician to determine whether they would be eligible for surgery, stereotactic radiosurgery, or other radiotherapy boost that may benefit the patient. If these treatments are pursued, the patient is not eligible for this protocol.

4.1.2 All sites are required to administer the following neurocognitive assessments within 2 weeks prior to starting whole-brain radiotherapy with hippocampal avoidance (HA-WBRT): Hopkins Verbal Learning Test-Revised, One Card Learning Test, and International Shopping List Test (See Appendix V for order of test administration in conjunction with other pretreatment assessments.)
4.1.3 All sites with patients opting to participate in the quality of life portion of the study (see Section 11 and Appendix II) are required to administer the quality of life assessments 2 weeks prior to starting HA-WBRT: the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Barthel Index of Activities of Daily Living (ADLs). (See Appendix V for order of test administration in conjunction with other pretreatment assessments.)

4.1.4 Scans and ITC Submission Management Aspects Prior to HA-WBRT: See Section 6.0 for details.

4.2 Highly Recommended Evaluations/Management

4.2.1 Re-staging to confirm stability of systemic disease evaluated clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for Neurocognitive Function Testing (3/31/11)
Institutions must meet certification requirements for administering neurocognitive assessments.

See Appendix V for certification requirements.

Note: To facilitate neurocognitive function testing, laptops are available for distribution to sites meeting certain conditions. See the “RTOG 0933 Laptop Agreement Form” on the RTOG website in the miscellaneous column next to the protocol-specific materials.

See also the “CogState: How To Get Started” summary on the RTOG website in the miscellaneous column next to the protocol-specific materials.

5.2 Pre-Registration Requirements for IMRT Treatment Approach
5.2.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select “Credentialing” and “Credentialing Status Inquiry.” An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.2 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Physician-Specific Credentialing for MRI/CT Fusion and Hippocampal Contours

5.3.1 In order to be eligible to enroll patients onto this trial, treating physicians and institutions must be credentialed for hippocampal contouring and HA-WBRT treatment planning. At each institution, treating physicians interested in enrolling patients on this trial will need to successfully complete a “Dry-Run” QA test. The “Dry-Run” QA test first involves downloading 3D-SPGR MRI and non-contrast head CT images from one sample patient available from the ITC. The sample patient will be selected from a test group of 5 patients imaged at the University of Wisconsin but not enrolled on this study. Treating physicians must then create a fusion of the 3D-SPGR MRI and CT image sets, manually generate hippocampal contours (using contouring instructions specified on www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx), expand these three-dimensionally into hippocampal avoidance zones (see Section 6.1 for pre-defined criteria), and develop an HA-WBRT treatment plan (see Section 6.1 for pre-specified dosimetric parameters).
for that particular patient. The fused MRI-CT image set with associated hippocampal contours and the HA-WBRT treatment plan with associated dose-volume histogram must be returned electronically for central review. Hippocampal contours will be reviewed centrally by the Neuroradiology Study Chair; HA-WBRT treatment plans will be reviewed by the PI, New Investigator Co-Chair and the Medical Physics Co-Chair. Instructive feedback will be provided to each site and treating physician. CT-MRI fusion requirements can be found at http://atc.wustl.edu/protocols/rtog/0933/CT-MRI-fusion.pdf.

5.3.2 Fusion of the 3D-SPGR MRI and non-contrast head CT and hippocampal contours will be reviewed centrally by the Neuroradiology Study Chair. Using the Hausdorff distance, hippocampal contours will be volumetrically compared to a set of contours previously defined by the Neuroradiology Study Chair and approved by the PI. Instructive feedback will be provided electronically.

5.3.2.1 The physician will be credentialed to accrue patients to this trial if:
1) No corrections of the MRI/CT fusion are requested; AND
2) The Hausdorff distance is ≤ 7 mm.

5.3.3.2 If either of these criteria is not met, the physician will be asked to partake in the “Dry-Run” QA test again using a second image set provided by the ITC.

5.3.3.3 An institution may choose to have more than one attending physician credentialed in MRI/CT fusion and contouring as long as each person is separately credentialed. If the institution has already been credentialed for HA-WBRT IMRT planning, credentialing for the additional attending physician will involve only MRI/CT fusion and generation of hippocampal contours and hippocampal avoidance zones, and not HA-WBRT IMRT planning, UNLESS requested by the PI, New Investigator Co-Chair and Medical Physics Co-Chair.

5.4 **Institution-specific Credentialing for HA-WBRT IMRT Planning**

HA-WBRT treatment plans will be reviewed centrally by the PI, New Investigator Co-Chair and the Medical Physics Co-Chair. Instructive feedback will be provided electronically to each site and treating physician.

5.4.1 The institution will be credentialed to accrue patients to this trial if:
1) Hippocampus: Dose to 100% of the hippocampal volume (D100%) ≤ 10 Gy AND Maximum dose ≤ 17 Gy AND
2) PTV: Volume receiving 30 Gy or higher (V30) ≥ 90% Dose to 2% of the PTV (D2%) ≤ 40 Gy

5.4.2 If any of these criteria is not met, the institution will receive images from a second randomly selected patient with MRI-CT fusion already created and contours already included in order to repeat the treatment-planning process.

5.4.3 Each institution and treating physician will have 3 test opportunities to become credentialed. If credentialing is not attained after 3 attempts, 2 possible approaches will be available:

5.4.3.1 If the problem is primarily dosimetric in nature and not contour related, that institution will be asked to pursue independent testing and development of its treatment technologies until the dosimetric parameters are met and may then reapply for an additional case.

5.4.3.2 If the problem is primarily with fusion and/or contouring, the institution may reapply for an additional case, by designating a separate clinical investigator.

5.5 **Regulatory Pre-Registration Requirements**

5.5.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf, prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.5.2 **Pre-Registration Requirements FOR CANADIAN INSTITUTIONS**

Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.
5.5.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.5.3.1 For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx.

5.5.3.2 For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219 and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Logon" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

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

RAPID REVIEWS ARE REQUIRED. SEE SECTION 6.7 FOR DETAILS.
6.1 **Dose Specifications**

6.1.1 Prescription dose will be according to the following specifications:

6.1.1.1 The whole brain planning target volume (PTV) (whole brain clinical target volume excluding the hippocampal avoidance regions) will receive 30 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 dose is prescribed such that 95% of the whole brain PTV is covered by the prescription dose.

6.1.1.3 Maximum dose to 2% of the PTV (D2%) is 37.5 Gy, and minimum dose to 98% of the PTV (D98%) is 25 Gy.

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 or tomotherapy) 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 6MV or greater must be used, with a minimum source-axis distance of 100 cm. The exception is the use of the helical tomotherapy unit that has a source-axis distance of 85 cm.

6.2.3 For a recommended approach to using helical tomotherapy or LINAC-based IMRT planning, please see Appendix VIII.

6.2.4 **3D-SPGR MRI**

Three-dimensional spoiled gradient (SPGR) axial MRI scan with standard axial and coronal fluid attenuation inversion recovery (FLAIR), axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequence acquisitions with a 1.25 mm axial slice thickness will be required to allow for accurate contouring of the hippocampus. These imaging sequences should be obtained within two weeks prior to initiating treatment with the patient in the supine position. Immobilization devices used for CT simulation and daily radiation treatments need not be used when obtaining these imaging sequences, but an attempt should be made to image the patient in as close to the same plane as the CT simulation as possible to facilitate fusion of the MRI and CT images.

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. 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 axial 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 prior to initiating treatment.

6.3.3 **MRI-CT Fusion**

The 3D-SPGR MRI (see Section 6.2.4) and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

6.4 **Target Volumes**

6.4.1 The Clinical Target Volume (CTV) 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 Planning Target Volume (PTV) is defined as the CTV excluding the hippocampal avoidance regions (see Section 6.5.2).

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 specified on [http://www.rtog.org//corelab//contouringatlases//hippocampalsparing.aspx](http://www.rtog.org//corelab//contouringatlases//hippocampalsparing.aspx).

6.5.2 Hippocampal avoidance regions will be generated by three-dimensionally expanding the hippocampal contours by 5 mm.
6.5.3 The lenses, orbits, optic nerves, and optic chiasm 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. Dose to any point within the optic nerves or optic chiasm can not exceed 37.5 Gy.

6.5.4 For a recommended approach to using helical tomotherapy or LINAC-based IMRT planning, please see Appendix VIII.

6.6 Documentation Requirements
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. These films will not be collected but should be held by the institution and available for review if requested.

6.7 Radiation Therapy Rapid Quality Assurance Reviews for Rapid Review Cases

NOTE: PRIOR TO DELIVERING ANY PROTOCOL TREATMENT, all hippocampal contours and HA-WBRT treatment plans must be reviewed centrally, with permission to treat or request for revision returned to the treating physician and institution within 3 business days. HA-WBRT treatment cannot be initiated until permission has been granted.

6.7.1 The Co-Principal Investigators, Minesh Mehta, MD, and Vinai Gondi, MD; and Medical Physics Co-Chair, Wolfgang Tome, PhD, will remotely perform an RT Quality Assurance Rapid Review for each case from each site before the start of treatment. Complete data, including the fused 3D-SPGR MRI/planning CT image set with hippocampal contours and hippocampal avoidance regions and associated treatment plan with dose-volume histogram, must be received through the ITC before Rapid Central Review is initiated. CT-MRI fusion requirements can be found at http://atc.wustl.edu/protocols/rtog/0933/CT-MRI-fusion.pdf.

6.7.2 Once a treating physician and institution have enrolled at least 3 patients in a row with no unacceptable deviations, they may enroll further patients without rapid central review. However, submission of final treatment plan and contours is required to allow for final quality assurance analysis.

6.7.3 Rapid Review Process
6.7.3.1 Unacceptable Deviations
6.7.3.1.1 Unacceptable deviations involving MRI/CT fusion and/or hippocampal contouring: Using electronic and/or telephone feedback provided directly to the treating physician, institutions will be required to modify MRI/CT fusion and/or hippocampal contouring and repeat the HA-WBRT IMRT planning. Resubmission of the new treatment plan with revised contours does not require a rapid review to occur prior to HA-WBRT initiation UNLESS requested by the Co-Principal Investigators, Minesh Mehta and Vinai Gondi. This determination will be made at the time that unacceptable deviations are communicated to the treating physician. Once the revised HA-WBRT IMRT plan has been generated with the revised contours and submitted to the ITC, the institution will receive permission to treat. The final treatment plan and contours will have a final quality assurance analysis.

6.7.3.1.2 Unacceptable deviations involving HA-WBRT IMRT planning: Using electronic and/or telephone feedback provided by the Medical Physics Chair, Wolfgang Tome, institutions will be required to repeat the HA-WBRT IMRT planning. If unacceptable deviations of fusion and/or contours are also found (see Section 6.7.3.1.1), revised HA-WBRT treatment planning must incorporate the contours and/or fusion feedback provided directly to the treating physician. Resubmission of the new treatment plan with revised contours does not require a rapid review to occur prior to HA-WBRT initiation UNLESS requested by the Medical Physics Chair. This determination will be made at the time that unacceptable deviations are communicated to the institution. Once the revised HA-WBRT IMRT plan has been generated with the revised contours and submitted to the ITC, the institution will receive permission to treat. The final treatment plan and contours will have a final quality assurance analysis.

6.7.4 Final Quality Assurance Analysis
6.7.4.1 All final treatment plans and contours will be reviewed centrally after initiation of HA-WBRT.
6.7.4.2 If unacceptable deviations of MRI/CT fusion, hippocampal contours, and/or HA-WBRT IMRT planning are found on final quality assurance analysis, that patient will be rendered invaluable on final data analysis.
6.7.4.3 If a patient has an unscheduled break exceeding 3 normally scheduled treatment days, this unacceptable deviation must be reported to the Principle Investigator, Minesh Mehta, and the patient will be considered inevaluable on final data analysis.

### 6.8 Compliance Criteria and Critical Structure Constraints

<table>
<thead>
<tr>
<th>Treatment Component</th>
<th>Parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI/CT Fusion and Contouring</td>
<td>MRI-CT fusion</td>
<td>No corrections to MRI/CT fusion requested</td>
<td>No corrections to MRI/CT fusion requested</td>
<td>Corrections to MRI/CT fusion requested</td>
</tr>
<tr>
<td></td>
<td>Hippocampal Contouring</td>
<td>≤ 2 mm deviation using the Hausdorff distance*</td>
<td>&gt; 2, ≤ 7 mm deviation using the Hausdorff distance*</td>
<td>&gt; 7 mm deviation using the Hausdorff distance*</td>
</tr>
<tr>
<td>HA-WBRT IMRT Planning</td>
<td>PTV</td>
<td>D2% ≤ 37.5 Gy D98% ≥ 25 Gy</td>
<td>D2% &gt; 37.5 Gy, ≤ 40 Gy D98% &lt; 25 Gy</td>
<td>V30 ≤ 90% D2% &gt; 40 Gy</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>D100% ≤ 9 Gy Maximum dose ≤ 16 Gy</td>
<td>D100% &gt; 10 Gy Maximum dose &gt; 17 Gy</td>
<td>D100% &gt; 10 Gy Maximum dose &gt; 17 Gy</td>
</tr>
<tr>
<td></td>
<td>Optic Nerves and Chiasm</td>
<td>Maximum dose ≤ 37.5 Gy</td>
<td>Maximum dose ≤ 37.5 Gy</td>
<td>Maximum dose &gt; 37.5 Gy</td>
</tr>
<tr>
<td>Unscheduled Break Days</td>
<td>0 break days</td>
<td>1-3 break days</td>
<td>&gt; 3 break days</td>
<td></td>
</tr>
</tbody>
</table>

* To assess the Hausdorff distance, the Co-Principal Investigators, Minesh Mehta and Vinai Gondi, 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 3 normally scheduled treatment days, the treatment will be considered an unacceptable deviation from the protocol. This should be reported to the Principal Investigator, Minesh Mehta, and the patient will be considered inevaluable on final data analysis.

### 6.10 Radiation Therapy Adverse Events

6.10.1 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.

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

6.10.3 If significant increase in reaction of the normal tissue occurs, the site should report it on the appropriate CRF and notify the study Principal Investigator, Minesh Mehta, MD.

### 6.11 Radiation Adverse Event Reporting

6.11.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]
**Definition of an SAE:** 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.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

**AdEERS Reporting Requirements**

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

**Adverse Events (AEs) and Serious Adverse Events (SAEs)** that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/pls ql/gadeers_main$_.startup](https://webapps.ctep.nci.nih.gov/openapps/pls ql/gadeers_main$_.startup)). Use the patient’s case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS must also be reported to RTOG on the AE case report form (see Section 12.1). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.
CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Unrelated Unlikely</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible Probable Definite</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td></td>
<td>24 Hour: 5 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Unrelated Unlikely</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible Probable Definite</td>
<td>10 Calendar Days</td>
<td>Not required</td>
<td>Not required</td>
<td>Not Required</td>
</tr>
<tr>
<td></td>
<td>24 Hour: 5 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.
All supporting source documentation being faxed to NCI must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

6.11.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.0 DRUG THERAPY
Not applicable to this study.

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
9.1 Non-Permitted
Chemotherapy or targeted therapies during WBRT or over the subsequent 7 days

10.0 TISSUE/SPECIMEN SUBMISSION
NOTE: Patients must be offered the opportunity to participate in the correlative specimen collection component of the study.
- If the patient consents to participate in the specimen component of the study, the site is required to submit the patient’s specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

10.1 Specimen Submission
The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. The RTOG encourages participants in protocol studies to consent to the banking of their specimens. The RTOG Biospecimen Resource provides specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, serum, plasma, and whole blood (strongly recommended) will be submitted to the RTOG Biospecimen Resource for the translational research portion of this protocol and for banking for future studies.

10.2 Specimen Collection for Translational Research and Banking for Future Studies (strongly recommended)
10.2.1 Translational Component Rationale
Our understanding of the biochemical and genotypic factors of neurocognitive decline after cranial irradiation is limited. The ultimate objective of this translational research is to determine whether certain patients may be predisposed to radiation-induced neurocognitive decline based on either genetic or epigenetic factors or serum markers. Much of the hypotheses generated thus far (e.g., ApoE4 genotyping) have arisen from the wide body of literature on Alzheimer’s and other forms of dementia. However, the complex nature and evolving understanding of
neurocognition leaves open the possibility of other factors playing a role. As a result, we recommend that serum, plasma and whole blood be collected on patients prior to start of HA-WBRT and at 4 months after HA-WBRT (primary endpoint). A portion of these samples will be used to test the hypotheses described in Section 10.2.1; the remainder will be stored at RTOG headquarters for future investigational research.

### 10.2.1.1 Apolipoprotein E Genotyping

Through its lipid transport function, ApoE is an important factor in remodeling and repairing neurons in response to injury or stress (Mahley 1988; Mahley 2006). In the nervous system, non-neuronal cell types, most notably astroglia (Mouchel 1995; Pitas 1987) and microglia (Nakai 1996), are the primary producers of ApoE, while neurons preferentially express the receptors for ApoE (Wolf 1992). There are 3 isoforms of ApoE, ApoE2, ApoE3, and ApoE4, which differ from each other only by single amino acid substitutions at positions 112 and 158 (Rall 1982a; Rall 1982b; Weisgraber 1981). ApoE4 has been implicated preclinically in reduced neurite outgrowth (Nathan 1994) and clinically in atherosclerosis, Alzheimer's disease, and impaired cognitive function even in “normal” individuals (Mahley 2006; Farrer 1997; Cosentino 2008; Schultz 2008). ApoE4 is the largest known genetic risk factor for late-onset Alzheimer's disease in a variety of ethnic groups. For instance, Caucasian and Japanese carriers of 2 ApoE4 alleles have between 10 and 30 times the risk of developing AD by 75 years of age, as compared to those not carrying any ApoE4 alleles. It is estimated that 40% to 80% of Alzheimer's disease patients have at least one copy of the 4 allele (Farrer 1997), with a dose-dependent effect on age of onset (Farrer 1997) and rate of cognitive decline (Cosentino 2008). APOE4 allele status has also been associated with subtle impairments in cognition in “normal” individuals. In this study, 626 male twins in their 50s were tested for APOE4 allele status as well as verbal and visuospatial episodic memory using the Wechsler Memory Scale Logical Memory subset, consisting of 2 stories read to participants for immediate and delayed recall. Compared to individuals without the APOE4 allele, carriers of the APOE4 allele had small but significant memory deficits in the sixth decade of life despite showing no signs of preclinical dementia (Schultz 2008).

Preclinical and clinical studies have demonstrated an association between APOE4 and the hippocampus. In one study, neurogenesis in the hippocampal dentate gyrus was studied in transgenic mice expressing APOE4 or APOE3 in the setting of environmental stimulation. Environmental stimulation was noted to increase neurogenesis in the dentate gyrus of apoE3-transgenic and wild-type mice, but trigger apoptosis in the dentate gyrus of APOE4-transgenic mice. These effects were specific to the hippocampal dentate gyrus and were not observed in the subventricular zone, where neurogenesis was unaffected by either environmental stimulation or apoE genotype (Levi 2007). In addition, Villasana and colleagues (2008) irradiated APOE2-, APOE3-, and APOE4-transgenic mice and assessed hippocampal-dependent spatial learning and memory tasks. Irradiated APOE4-transgenic mice performed poorly on hippocampal-dependent tasks relative to sham-irradiated APOE4-transgenic mice or all other transgenic mice. These preclinical data seem to suggest that APOE4 plays a critical role in neurogenesis within the hippocampal dentate gyrus (the site of memory-specific neural stem cells) and hippocampal-dependent memory function following cranial irradiation (Villasana 2008).

In clinical studies, hippocampal atrophy rates have been demonstrated to be sensitive markers of early Alzheimer’s dementia and predictive of cognitive decline. In this setting, APOE4 allele status has been linked with rates of progressive hippocampal atrophy. In one study by Mori and colleagues (2002), 55 patients with probable Alzheimer’s disease were followed with serial annual MRI scans. The status of the APOE4 allele significantly correlated with the rate of hippocampal atrophy, implicating APOE4 allele status as relevant to the progression of hippocampal atrophy in the setting of Alzheimer’s dementia. Van der Pol and colleagues analyzed serial MRI data in 323 patients with mild cognitive impairment prospectively over a 2-year period. They observed a strong correlation between the baseline APOE4 allele status and subsequent accelerated rates of hippocampal atrophy as well (van de Pol 2007).

To our knowledge, APOE4 allele status has not been examined previously in the setting of neurocognitive decline after WBRT. The ongoing RTOG 0614 study comparing WBRT with
or without memantine in patients with brain metastases will be the first to do so. RTOG 0614, however, does not involve hippocampal avoidance during WBRT. Given preclinical and clinical evidence of a possible association between APOE4 and the hippocampus, we hypothesize that APOE4 allele status may negatively influence the ability of hippocampal avoidance to preserve neurocognitive function after WBRT. That is, patients with one or more APOE4 alleles may represent a subpopulation that is predisposed to benefit less, or not at all, from hippocampal avoidance during WBRT. Therefore, we intend to collect whole blood on patients enrolled on RTOG 0933. Using whole blood cells, we intend to conduct APOE4 genotyping, the results of which will not be shared with the patient, and correlate these data with prospectively analyzed neurocognitive function (NCF) outcomes.

25% to 30% of the general population is estimated to have one or more APOE4 alleles. We anticipate similar allelic prevalence amongst this trial’s population of patients with brain metastases. With a target accrual of 90 patients and an anticipated death rate of 40% at 4 months (the time of our primary endpoint), we predict that approximately 14 to 16 patients will have one or more APOE4 alleles and remain eligible for analysis of our primary endpoint of delayed recall at 4 months. Such a sample size should provide exploratory observations to determine whether analysis of APOE4 genotype should be included in future studies of hippocampal avoidance during cranial irradiation.

10.2.2 Specimen Collection Schedule
- Serum, plasma, and whole blood must be collected prior to HA-WBRT.
- Serum and plasma must also be collected 4 months after HA-WBRT.

10.2.3 The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the RTOG protocol number, the patient’s case number, and method of storage, for example, stored at -20°C, must be included.

Please refer to Appendix VII for plasma, serum, and whole blood collection details.

10.2.4 Storage Conditions
Store at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada: Mon-Tues).

OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only- Canada: Mon-Tues).

OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada: Mon-Tues).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.2.5 Shipping Address
Submit materials to:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu
### Specimen Collection Summary

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum: 5-10 mL of whole blood in 2 red-top tubes - centrifuge and aliquot</td>
<td>1) Prior to HA-WBRT 2) 4 months after HA-WBRT</td>
<td>Frozen serum samples containing 0.5 mL per aliquot in 5 to 10 1 mL cryovials</td>
<td>Serum sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>Plasma: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top)-centrifuge and aliquot</td>
<td>1) Prior to HA-WBRT 2) 4 months after HA-WBRT</td>
<td>Frozen plasma samples containing 0.5 mL per aliquot in 5 to 10 1 mL cryovials</td>
<td>Plasma sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) - mix and aliquot.</td>
<td>1) Prior to HA-WBRT. NOTE: If site is unable to collect the whole blood pre-tx, then it is acceptable to collect it at another time point, but this must be noted on the STF.</td>
<td>Frozen whole blood samples containing 1.0 ml per aliquot in 3 to 5 1 ml cryovials</td>
<td>Whole blood sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>

### Reimbursement

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement & Case Credit Schedule found on the RTOG Web site [http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323](http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution’s summary report with the institution’s regular case reimbursement.

### Confidentiality/Storage


10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it or destroyed.

### Patient Assessments

#### Study Parameters

See Appendix II.

#### Neurocognitive Evaluation (3/31/11)

Note: To facilitate neurocognitive function testing, laptops are available for distribution to sites meeting certain conditions. See the “RTOG 0933 Laptop Agreement Form” on the RTOG website in the miscellaneous column next to the protocol-specific materials.
See also the “CogState: How To Get Started” summary on the RTOG website in the miscellaneous column next to the protocol-specific materials.

11.2.1 Certification

See Appendix V for pre-registration examiner certification requirements.

11.2.2 Summary of Required Neurocognitive Tests for All Patients

Three required 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).

See Appendix V for order of test administration in conjunction with other study assessments.

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 The One Card Learning Test (OCLT)

The OCLT is a test of visuoperceptual learning and memory, where standard playing cards display in the center of the screen one at a time, and the subject presses one mouse button if the card was presented previously and the other mouse button if it was not. Eighty-eight items are presented, in 8 trials of 11. Learning and memory are operationally defined as the ability to discriminate between previously presented and novel (i.e., distractors) information. Recognition paradigms are especially useful for assessing encoding and storage of newly learned information (Delis 2000).

11.2.2.3 International Shopping List Test (ISLT)

Similar in design to HVLT-R, the International Shopping List Task (ISLT) is a 16-word 3-trial verbal list-learning test. The ISLT has the capability of using culturally specific verbal stimuli: food items that are easily obtained in local markets, stores or supermarkets in the region in which testing takes place. This format helps to minimize between-culture disparities for test content (Lim 2009). The ISLT includes both immediate (3 minutes to complete) and delayed (1 minute to complete) recall components, separated by a 20-minute delay.

HVLT-R will be administered at baseline, every 2 months for 6 months, and every 3 months until death or until 2 years after HA-WBRT. To minimize NCF testing noncompliance with longer follow-up, the ISLT and OCLT will only be administered at baseline and at the 2-, 4-, and 12-month visits. To minimize interaction effects between two similar verbal list-learning tasks (HVLT-R and ISLT), during each of the 4 visits where both are administered, administration of each will be separated by a break. At each visit, the HVLT-R will be administered prior to ISLT, with the sole exception being the 2-month visit. To allow for comparisons between the two tests while addressing possible carry-over effects, ISLT will be administered (in counterbalanced form) prior to the HVLT-R at 2 months. See Appendix V for the administration schedule.

11.3 Quality of Life Evaluation

NOTE: Patients must be offered the opportunity to participate in the quality of life component of the study. For consenting patients, see Appendices I and II.

Quality of life will be assessed using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Barthel Index of Activities of Daily Living (ADLs). Quality of life assessments will be scored centrally by a blinded reviewer to avoid potential bias.

See Appendix V for order of test administration in conjunction with other study assessments.
11.3.1 FACT-BR
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 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.

11.3.2 Barthel Index of Activities of Daily Living (ADL)
The Barthel Index of ADLs is a self-report instrument designed to assess a patient’s ability to carry out ADLs as reported by the patients, their families, or their caregivers. Direct testing of the patient is not needed, as information can be derived from families or caregivers. The Barthel Index score ranges from 0 to 20, with 20 corresponding to a normal functional status. Completion of the Barthel Index takes approximately 5-10 minutes.

11.4 Administration of Neurocognitive and Quality of Life Evaluations
11.4.1 Timing
11.4.1.1 Prior to initiation of treatment, all patients will undergo baseline neurocognitive 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 the HVLT-R neurocognitive testing and quality of life evaluation (FACT-BR and ADL) every 2 months for the first 6 months and then every 3 months until death or until 2 years after HA-WBRT, whichever comes first. The CogState neurocognitive tests (ISLT and OCLT) will be administered at baseline and 2, 4, and 12 months after completion of radiotherapy.
11.4.1.2 The examiner is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a FACT-BR or ADL question, they will be informed that they can skip that question.
11.4.1.3 Examiners will give patients a short break if the patient appears fatigued or otherwise in need of a few-minutes break.
11.4.2 Administration Approach
See Appendix V.

11.5 Measurement of Response
Patients will undergo gadolinium contrast-enhanced brain MRI prior to study entry (the 3D-SPGR MRI obtained for hippocampal contouring can be used for this purpose), every 2 months for the first 6 months, and every 3 months thereafter until death or until 2 years after HA-WBRT, whichever comes first.
11.5.1 Criteria for CNS Progression
11.5.1.1 Assessment
The treating radiation oncology will measure and calculate the bidimensional product for each of the 1-3 largest brain metastases identified at baseline. 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) of any new brain metastases will be recorded on all follow-up forms. The appearance (yes/no) of any new brain metastases within the hippocampal avoidance region (the hippocampus plus 5 mm) will be recorded on all follow-up forms.
11.5.1.2 Definition of CNS Progression
CNS progression will be defined as a defined increase (see below) in perpendicular bidimensional tumor area for any of the 1-3 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 bidimensional 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.

11.5.1.3 **Central Review of CNS Progression**
The brain MRI demonstrating CNS progression must be submitted for central review (See Section 12).

11.6 **Criteria for Discontinuation of Protocol Treatment**
11.6.1 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, and RTOG Headquarters data management must be notified.

11.6.2 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

Data should be submitted to:
RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Evaluation Summary Form (HVLT-R) (CS)</td>
<td>Submit only the cover page from the CS form. Retain the test forms in the study chart for source documentation.</td>
</tr>
<tr>
<td>CogState Database (ISLT and OCLT) (NP)</td>
<td></td>
</tr>
<tr>
<td>Barthel Index of Activities of Daily Living (PQ)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy: FACT-Br (FA)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>2, 4, and 6 months after WBRT is completed; thereafter, every 3 months for 2 years after WBRT is completed</td>
</tr>
<tr>
<td>Neurocognitive Evaluation Summary Form (HVLT-R) (CS)</td>
<td>Submit only the cover page from the CS form. Retain the test forms in the study chart for source documentation.</td>
</tr>
<tr>
<td>Barthel Index of Activities of Daily Living (PQ)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy: FACT-Br (FA)</td>
<td></td>
</tr>
<tr>
<td>CogState Database (ISLT and OCLT) (NP)</td>
<td>2, 4 and 12 months after WBRT is completed</td>
</tr>
<tr>
<td>Progression MRI Scan &amp; Report</td>
<td>Within 1 week of scan date</td>
</tr>
</tbody>
</table>

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>†Digital Data Submission – Treatment Plan submitted via SFTP account exported from treatment planning machine by Physicist</td>
<td></td>
</tr>
<tr>
<td>Digital data submission includes the following:</td>
<td></td>
</tr>
</tbody>
</table>
• CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3)
• Digital beam geometry for initial and boost beam sets
• Doses for initial and boost sets of concurrently treated beams
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)

Planning MRI Scan (the scan used to delineate the target volumes for planning. If more than 1 series is submitted digitally, specify on the DDSI form which one was used for planning)

Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)

Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)

NOTE: Sites must notify ITC via e-mail (itc@castor.wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.

Final Dosimetry Information
Radiotherapy Form (T1) [copy to HQ and ITC]
Daily Treatment Record (T5) [copy to HQ and ITC]
Modified digital patient data as required through consultation with Image-Guided Therapy QA Center

†Available on the ATC web site, http://atc.wustl.edu/
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

12.2.1 Digital Data Submission to ITC
Digital data submission may be accomplished using media or the Internet.
For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to: itc@castor.wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Delayed recall, 4 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 Endpoints
13.1.2.1 Auditory and visual learning and memory as measured by the International Shopping List Test and One Card Learning Test (CogState)
13.1.2.2 Quality of life as measured by the Functional Assessment of Cancer Therapy-Brain (FACT-Br) and the Barthel Index of Activities of Daily Living (ADL)
13.1.2.3 Time to radiographic progression
13.1.2.4 Overall survival
13.1.2.5 Adverse events based on CTCAE criteria
13.1.2.6 ApoE4 genotype and other potentially predictive biomarkers of cognitive function

13.2 Sample Size

This study looks to establish the use of IMRT for HA-WBRT in a multi-institutional setting. Each institution must be credentialed by the RTOG prior to registering the first patient (See Section 5.0). The primary endpoint will be delayed recall, as measured by the change in HVLT-R delayed recall score from the start of treatment to 4 months after the start of treatment.

The sample size calculations will address the specific primary hypothesis that HA-WBRT reduces decline in delayed recall (from baseline to 4 months). We do not expect improvement in delayed recall; at best, we anticipate a preservation of delayed recall. Data from the WBRT-alone arm (n=85) of the PCI-P-120-9801 phase III trial indicate that the mean relative loss in HVLT-R delayed recall score at 4 months was 30%, with a standard deviation of 41%. We anticipate that HA-WBRT will have better delayed recall functioning at 4 months than WBRT alone. Detecting a 15% average relative loss due to HA-WBRT suggests a 50% relative improvement over previous results (see table below). The null and alternative hypotheses are:

\[ H_0: \Delta \text{HVLT-R} > 0.15 \text{ vs. } H_a: \Delta \text{HVLT-R} \leq 0.15 \]

\( \Delta \text{HVLT-R} \) is the mean of relative decline between baseline and 4 month after treatment in this patient population. For patient individual \( i \), the relative decline is calculated as follows: \( \Delta \text{HVLT-R}_i = (\text{HVLT-R}_i^0 - \text{HVLT-R}_i^4) / \text{HVLT-R}_i^0 \), where \( \text{HVLT-R}_i^0 \) and \( \text{HVLT-R}_i^4 \) denotes individual patient score at baseline and 4 month after treatment, respectively.

Based on the Wilcoxon Signed Rank Test, with alpha=0.05 (one-sided), a total of 51 analyzable patients would ensure 80% statistical power to detect a 15% average relative loss in delayed recall at 4 months. Assuming a death rate of 40% prior to 4 months (based on the PCI-P-120-9801 trial) and a 10% inevaluable rate (due to unacceptable protocol deviations noted on final quality assurance analysis) the target sample size will be 102 registered patients. Promising results would provide evidence to support a future phase III randomized trial to definitively compare decline in delayed recall between WBRT alone and HA-WBRT.

<table>
<thead>
<tr>
<th>Expected Cognitive Loss (from baseline to 4 months) with HA-WBRT (( \Delta \text{HVLT-R} ))</th>
<th>Relative Improvement over WBRT</th>
<th>Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>10%</td>
<td>67%</td>
<td>224</td>
</tr>
<tr>
<td>15%</td>
<td>50%</td>
<td>102</td>
</tr>
<tr>
<td>20%</td>
<td>33%</td>
<td>60</td>
</tr>
<tr>
<td>25%</td>
<td>17%</td>
<td>40</td>
</tr>
<tr>
<td>30%</td>
<td>0%</td>
<td>30</td>
</tr>
</tbody>
</table>
*Assumes 40% death rate prior to month 4 and 10% inevaluable rate; alpha=0.05, 1-sided
Wilcoxon Signed Rank Test

13.3 Patient Accrual
RTOG 0614 is a phase III symptom management trial with a neurocognitive endpoint comparing WBRT with or without memantine. This trial closed in July 2010 and accrued approximately 20 patients per month (total accrual 554, CCOP accrual 58, target accrual 536). RTOG 0933 excludes patients with small cell lung cancer and germ cell malignancy. Given the widespread availability of IMRT technology and eagerness of patients to mitigate neurocognitive toxicity, we anticipate a high level of interest from both CCOP and academic institutions. No accrual is expected during the first 3 months of trial activation as institutions obtain IRB approval and complete credentialing requirements. A total accrual of 5 patients is expected during the next 3 months. Monthly accrual is then expected to reach 5 patients per month, based on previous RTOG trials, for a total accrual period of 26 months. The Co-Principal Investigators’ institutions are limited to 20% of the total accrual (approximately 21 patients out of the targeted 102 patients can come from these institutions combined). The RTOG Data Safety and Monitoring Board (DSMB) will evaluate patient safety semiannually.

13.4 Analysis Plan
13.4.1 Primary Endpoint
The primary endpoint is delayed recall, as determined by the decline in HVLT-R delayed recall score from the start of treatment to 4 months after the start of treatment.

It is anticipated that up to 10% of patients may be inevaluable due to unacceptable protocol deviations noted on final quality assurance analysis (see Section 6.7.4). It is also anticipated that up to 40% of patients may die prior to the 4 month assessment and will not be included in the analysis. Although missing and incomplete assessments should be minimized due to current improved data collection methods, some patients alive at 4 months may not be assessed. Sensitivity analyses will be conducted to determine the impact of the latter exclusion.

Previous results of WBRT alone resulted in a mean decline cognitive loss at 4 months of 30%. We hypothesize that the use of HA-WBRT will reduce the decline in delayed recall at 4 months to 15% (from baseline). Descriptive statistics of the actual change scores will also be provided. The mean (median) change score and standard deviations (quartiles) will be reported. Treatment will be tested using the one-sided Wilcoxon Signed Rank Test with a significance level of 0.05. The general linear mixed effects model will be used to evaluate the effects of histology, RPA class, and other covariates of interest on delayed recall.

13.4.2 Secondary Endpoints
13.4.2.1 Cognitive Function
Given the use of the HVLT-R in prior trials evaluating HA-WBRT, HVLT-R remains the primary endpoint. Other cognitive test batteries normally administered with the HVLT-R in RTOG trials will be replaced with the International Shopping List Test (auditory/verbal learning and memory) and the One Card Learning Test (visuoperceptual learning and memory). To minimize interaction effects between two similar verbal list-learning tasks (HVLT-R and ISLT), administration of these tests will be separated during each of the 4 visits (baseline and 2, 4, and 12 months) by a break. At each visit, the HVLT-R will be administered prior to the ISLT administration, with the sole exception being the 2-month visit. To allow for comparisons between the two tests while addressing possible carry-over effects, ISLT will be administered (in counterbalanced form) prior to the HVLT-R at 2 months. The OCLT will always be administered with the ISLT, during the period between immediate and delayed recall. The mean decline in cognition at 4 months will be evaluated similar to the analysis of the primary endpoint. Additionally, the relationship between the change from baseline through 12 months in the HVLT-R, ISLT, and OCLT will be evaluated using Spearman correlation coefficients.

13.4.2.2 Quality of Life
Patients will complete assessments at 2, 4, and 6 months from the start of treatment and then quarterly until death. The Functional Assessment of Cancer Therapy-Brain (FACT-Br,
version 4) includes the four domains on the general FACT—physical well-being (7 items), social well-being (7 items), emotional well-being (6 items), functional well-being (7 items)—and the 23-item brain subscale. Patient scores on the FACT-Br range from 0 to 92 with lower scores indicating declining quality of life. The Barthel Index of Activities of Daily Living (ADL) is a 10-item assessment. Patient scores on the ADL range from 0 to 20 with lower scores indicating declining functional status. For each questionnaire, the general linear mixed effects model will be used to determine the impact of neurocognitive decline on overall trends in quality of life adjusted for histology, RPA class, and other covariates of interest.

13.4.2.3 Radiographic Progression
Patients will have MRI assessments at 2, 4 and 6 months from the start of treatment and then quarterly until death. 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 histology, RPA class, and other covariates of interest on time to radiographic progression.

13.4.2.4 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 histology, RPA class, and other covariates of interest on survival.

13.4.2.5 Adverse Events
Adverse events will be reported according the CTCAE criteria.

13.4.2.6 Translational Research Analyses
The feasibility of proposed translational studies will be assessed following completion of accrual and sample collection. Serum, plasma, and whole blood will be collected for tissue banking and exploratory analyses as detailed in Section 10.0. Because of the anticipated limited number of evaluable patients, all analyses will be exploratory. The impact of apoE4 allele status on cognitive decline after WBRT is being evaluated in RTOG 0614. If feasible, specimens from patients treated with WBRT plus placebo will be used. Of current interest is the impact of apoE4 allele status on cognitive decline (Section 10.2.1.1) after HA-WBRT. In determining the predictive value of apoE4, case subjects are patients that experience cognitive decline after treatment. Control subjects are patients that maintain cognitive function. In determining the predictive value of apoE4, the case/control comparison will be done within each treatment group (HA-WBRT/WBRT plus placebo). Promising findings will inform a definitive hypothesis on the predictive value of apoE4 in the phase III trial comparison of HA-WBRT to WBRT. In determining the impact of apoE4, the odds ratio for cognitive decline and corresponding 95% confidence intervals will be estimated using conditional logistic regression models. At the time of data maturity, the specific assays used will be addressed and further specific aims with appropriate statistical considerations will be developed.

13.5 Interim Reports to Monitor the Study Progress
The RTOG Data Safety and Monitoring Board (DSMB) will monitor the study for safety and feasibility. Interim reports will be prepared semiannually until the primary efficacy analysis has been accepted for presentation or publication. These reports will contain the following, at a minimum: patient accrual rate and projected completion date for accrual phase; total institution accrual; patient exclusions and reasons for exclusion; pretreatment characteristics for eligible patients; patient compliance with baseline quality of life assessments; frequency and severity of adverse events. The interim reports will not contain treatment results with respect to the primary or secondary endpoints.

In addition, adverse events for this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means.

13.6 Reporting the Initial Treatment Results
The primary hypothesis of this study is to determine the efficacy of HA-WBRT for preserving delayed recall. This final analysis will occur after 51 evaluable patients have been followed for at least 4 months following the start of treatment. It will include tabulation of all cases entered
and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis will be evaluated using the one-sample Wilcoxon signed rank test as specified in the analysis plan. Also, where feasible, treatment evaluation with respect to all endpoints will be compared within each racial and ethnic category.

### 13.7 Gender and Minorities

**Projected Distribution of Gender and Minorities**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>43</td>
<td>53</td>
<td>96</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td><strong>46</strong></td>
<td><strong>56</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>White</td>
<td>38</td>
<td>48</td>
<td>86</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>46</strong></td>
<td><strong>56</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>
REFERENCES


Rall SC, Jr., Weisgraber KH, Mahley RW. Human apolipoprotein E. The complete amino acid sequence. J Biol Chem 1982;257:4171-4178.b


This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have cancer that has spread to the brain.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, avoiding the hippocampus has on memory and thinking in participants receiving whole-brain radiotherapy. The hippocampus is a brain structure that is important for memory. Doctors hope that avoiding the hippocampus will be effective in preventing memory loss and deterioration of thinking ability after whole-brain radiotherapy, although there is no proof of this yet. In this study, you will get whole-brain radiotherapy with the hippocampus shielded from high doses of radiation. At this time, avoidance of the hippocampus during whole-brain radiotherapy is experimental and only offered through this clinical trial.

How many people will take part in the study?

About 102 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical and neurologic examination to evaluate the tumor
- Blood test to confirm you are not pregnant (if applicable)
- Blood test to confirm your kidneys are working properly
- An MRI of the brain with contrast.

You will need to answer questions measuring your memory and thinking that take about 20 minutes to complete.

All of these tests and procedures can be performed on an outpatient basis; no hospitalization is necessary.
In some patients with cancer that has spread to the brain, chemotherapy is used in addition to radiation therapy. If you and your doctors decide you should receive chemotherapy during the two weeks of radiation therapy and for 7 days following completion of radiation therapy, you will not be able to receive treatment on this study.

In some patients with cancer that has spread to the brain, surgery and/or radiosurgery is used in addition to whole-brain radiotherapy. If you and your doctors decide you should receive surgery and/or radiosurgery, you will not be able to receive treatment on this study. But, if the cancer comes back in the brain and you and your doctors decide you should receive surgery and/or radiosurgery at that time, you will be able to do so on this study.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- A radiotherapy planning CT scan with the creation of a mask placed over your head to keep your head in place during each radiation treatment.
- A physical examination every 2 months for the first 6 months and every 3 months for the next 18 months after whole-brain radiotherapy.
- An MRI of the brain every 2 months for the first 6 months and every 3 months for the next 18 months after whole-brain radiotherapy.

All of these tests and procedures can be performed on an outpatient basis; no hospitalization is necessary.

You will need these tests to see how the study is affecting your memory.

- A 20-minute testing session asking you to answer questions and follow a few directions. This will occur every 2 months for the first 6 months and every 3 months for the next 18 months after whole-brain radiotherapy. At 2 months, 4 months, and 12 months after whole-brain radiotherapy, there will be another 20-minute testing session to measure other components of your memory.

If you chose to enter the study, you will receive whole-brain radiotherapy daily Monday through Friday for about 2 weeks.

When you are finished with the whole-brain radiotherapy, you will continue to follow with your doctor for regular exams, tests or procedures that are part of regular cancer care. You will be followed as long as you live or until you do not wish to participate in the study.

How long will I be in the study?

You will be receiving whole-brain radiotherapy for approximately 2 weeks. After you are finished with whole-brain radiotherapy, the study doctor will ask you to visit the office for follow-up exams every 2 months for the first 6 months and every 3 months for the next 18 months after whole-brain radiotherapy.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from whole-brain radiotherapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.
**What side effects or risks can I expect from being in the study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop the whole-brain radiotherapy. In some cases, side effects can be serious, long lasting, or may never go away. As with any experimental study, there also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

**Risks and side effects related to the whole-brain radiotherapy include those which are:**

**Likely**
- Hair loss, which may be permanent
- Dry mouth and/or change in taste
- Headaches
- Nausea and/or vomiting
- Scalp reddening or tanning and irritation (Your skin will be examined once a week during radiation therapy)
- Memory loss, which can occur in the first few months after whole-brain radiotherapy and may be permanent
- Tiredness

**Less Likely**
- Temporary worsening of tumor-like symptoms such as seizures or weakness
- Drainage of clear fluid from the ears or plugging of the ears with decreased hearing
- Behavioral change and/or increased sleepiness (occurring four to ten weeks after radiotherapy is complete and lasting for several days up to two weeks)
- Cataracts and eye damage with the possibility of impaired vision

**Rare but serious**
- Severe local damage to or death of normal brain tissue, which may require surgery to remove
- Hardening of the arteries in the brain, which may lead to strokes
- A second new cancer caused by radiation, in the brain or nearby organs
- Eye damage with the possibility of permanent blindness

**Risks and side effects related to avoiding the hippocampus during whole-brain radiotherapy include those which are:**

**Less Likely but serious**
- The development of cancer in or near the hippocampus

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the radiation therapy in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. Doctors hope that avoiding the hippocampus during whole-brain radiotherapy will be equally useful against cancer but cause less side effects compared to the usual treatment; however, there is no proof of this yet. We do know that the information from this study will help
doctors learn more about avoiding the hippocampus during whole-brain radiotherapy as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Radiation Therapy Oncology Group (RTOG)

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, ___________________ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at ___________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.
What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This “quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete two questionnaires prior to treatment and every 2 months for 6 months and every 3 months for the next 18 months after treatment. Each questionnaire takes about 5 minutes to fill out.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out these questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES     NO
Consent Form for Use of Blood for Research

About Using Blood for Research

As a result of your participation in this trial, you will have blood tests performed before you start treatment. We would like to keep for future research about three tablespoons of blood taken at that time. In addition, we would collect for future research about three tablespoons of blood approximately 4 months after you’ve completed treatment on the study.

If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm.

Your blood may be helpful for research. The research that may be done is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood. Then any blood that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your tissue and specimens are used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.

No matter what you decide to do, it will not affect your care.

1. My blood may be kept for use in research to learn about, prevent, or treat cancer.
2. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   Yes   No

3. Someone may contact me in the future to ask me to take part in more research.
   Yes   No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

   1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

   • For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
   • For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ______________________________

Date _____________________________________
## APPENDIX II

### STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 5 yrs prior to registration</td>
<td>Within 28 days prior to registration</td>
</tr>
<tr>
<td>Histo/cyto eval</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>History/physical</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event eval</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3D-SPGR MRI</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Head CT simulation scan</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>HA-WBRT treatment plans</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gadolinium contrast-enhanced brain MRI</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>HVLT-R</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CogState</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Quality of life testing (for consenting pts)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serum, plasma, whole blood collection for banking/translational research (for consenting pts)</td>
<td></td>
<td>Prior to HA-WBRT</td>
</tr>
</tbody>
</table>
APPENDIX III

KARNOFSKY PERFORMANCE SCALE

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

Patients with KPS $\leq 60$ (Zubrod $\geq 2$) OR uncontrolled primary malignancy are class III and not eligible for this study. (controlled primary malignancy is defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy during the previous 3 months or longer).

**Class I:** age $< 65$ years AND no extra-cranial metastases;

**Class II:** For this study defined as all eligible patients which do not fall into Class I. (Patients $\geq 65$ years OR extra-cranial metastases)
CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

EXAMINER CERTIFICATION FOR RTOG 0933

Institutions must meet certification requirements for administering neurocognitive assessments. This appendix describes the procedures in detail.

For HVLT-R and the 2 CogState tests, upon review and successful completion of the Neurocognitive Certification, Dr. Caine will notify the certified administrator that the administrator has successfully completed certification requirements.

Summary of certification procedures:
- a) Test administrator candidates review 0933 neurocognitive tests instruction manual.
- b) Candidates self-administer the HVLT-R and CogState tests, as if they were a subject.
- c) Candidates complete quiz and fax or email quiz to the Neuropsychology Co-Chair, Chip Caine, PhD.
- d) Dr. Caine grades the quiz and emails candidate pass/fail feedback. The quiz is "open book," so candidates may review the manual while taking the quiz.
- e) Dr. Caine will notify candidates of certification. Test administrators are now ready to administer tests to study subjects.

ALTERNATE TEST FORMS/VERSIONS

The HVLT-R is a paper-and-pen test that requires use of individual test forms with differing content. Each test administration session requires use of the appropriate test form, as shown below.

<table>
<thead>
<tr>
<th>TEST</th>
<th>² Within 2 weeks prior to registration</th>
<th>2 mos after HA-WBRT</th>
<th>4 mos after HA-WBRT</th>
<th>6 mos after HA-WBRT</th>
<th>9 mos after HA-WBRT</th>
<th>12 mos after HA-WBRT</th>
<th>15 mos after HA-WBRT</th>
<th>Every 3 months for 2 years after HA-WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R</td>
<td>Form 1</td>
<td>Form 2</td>
<td>Form 3</td>
<td>Form 4</td>
<td>Form 5</td>
<td>Form 6</td>
<td>Form 1</td>
<td>Continue to alternate in order</td>
</tr>
</tbody>
</table>

The CogState test software automatically adjusts each administration so that patients receive alternate forms of the tests.

TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

Additional comments:
1. Testing must be completed in one session. Test instructions must be followed verbatim (test instruction scripts for each of the 3 tests are provided in the neurocognitive tests manual) with every patient at every study visit. Responses should be completed in black pen.
2. Tests should be administered in the following order to every patient:

Visit 1: Baseline Visit
1) HVLT-R immediate recall.
2) HVLT-R immediate recognition,
3) Quality of Life (QOL) questionnaires (for consenting patients).
4) Blood specimen acquisition (for consenting patients).
5) HVLT-R delayed recall. Time interval between HVLT-R immediate and delayed recall should be about 20 minutes.
6) Announce that HVLT-R is complete. (Subjects will no longer be tested on the HVLT-R words.) Ask subject to take a short break of about 5 minutes. Log into the CogState system.
7) ISLT immediate recall.
8) OCLT.
9) Physician history and physical. (Results of the patient’s MRI scans are not to be discussed until completion of ISLT delayed recall.)
10) ISLT delayed recall. Time interval between ISLT immediate and delayed recall should be about 20 minutes.

**Visit 2: 2 Months**
1) Log into the CogState system.
2) ISLT immediate recall.
3) OCLT.
4) QOL questionnaires (for consenting patients).
5) ISLT delayed recall. Time interval between ISLT immediate and delayed recall should be about 20 minutes.
6) Announce that ISLT is complete. (Subjects will no longer be tested on the ISLT words.) Ask subject to take a short break of about 5 minutes.
7) HVLT-R immediate recall.
8) HVLT-R immediate recognition.
9) Physician history and physical. (Results of the patient’s MRI scans are not to be discussed until completion of ISLT delayed recall.)
10) HVLT-R delayed recall. Time interval between HVLT-R immediate and delayed recall should be about 20 minutes.

**Visit 3: 4 Months**
Same sequence as Baseline Visit (HVLT-R completed first, followed by ISLT and OCLT).

**Visits 4-5: 6 and 9 Months**
1) HVLT-R immediate recall.
2) HVLT-R immediate recognition.
3) QOL questionnaires (for consenting patients).
4) Blood specimen acquisition (for consenting patients).
5) HVLT-R delayed recall. Time interval between HVLT-R immediate and delayed recall should be about 20 minutes.

**Visit 6: 12 Mons**
Same sequence as Baseline Visit (HVLT-R completed first, followed by ISLT and OCLT).

**Visits 7-10: 15, 18, 21, and 24 Months.**
1) HVLT-R immediate recall.
2) HVLT-R immediate recognition.
3) QOL questionnaires (for consenting patients).
4) Blood specimen acquisition (for consenting patients).
5) HVLT-R delayed recall. Time interval between HVLT-R immediate and delayed recall should be about 20 minutes.

3. For those subjects who are not participating in QOL assessment, it is very important that they engage in visual review of written material provided by test administrators for about 10 minutes during the 20-minute interval between immediate and delayed recall (of either HVLT-R or ISLT). Mimicking the activities of those subjects who complete the QOL questionnaires helps ensure that all subjects are cognitively processing verbal material unrelated to the test content during the interval between immediate and delayed recall, thereby helping to minimize any advantage at delayed recall for non-QOL questionnaire participants, which might include covertly self-rehearsing the words learned at immediate recall.

4. Follow the instructions on the Forms Packet Index before submission of forms to RTOG.
5. Please keep all original test forms. Results remain on file at the institution as source documentation pending request for submission by RTOG or a study chair. In the event of questions, contact Dr. Caine (see contact information on front page of protocol).
6. HVLT-R 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. CogState test results are uploaded directly to a database.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her cooperation.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the Neurocognitive Evaluation Summary Form (CS).

TEST ADMINISTRATION PROCEDURE

HVLT-R instructions script

HVLT-R Part A – Immediate Recall: Trial 1

Say, 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.

Say, OK. Now tell me as many of those words as you can remember.

Check off the words the subject recalls on the form.

If a word is said that is not in the list, write that word on the form but say nothing to the subject about the word not being on the list.

There is no time limit for each recall trial. If, after about 15 seconds, the subject has not recalled any words, provide a single prompt, such as, Anything Else? or See if you can think of any more.

If not, administer trial 2 immediately.

HVLT-R Part A – Immediate Recall: Trial 2

Say, 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.

Say, OK. Now tell me as many of those words as you can remember.
Check off the words the subject recalls on the form.

If a word is said that is not in the list, write that word on the form but say nothing to the subject about the word not being on the list.

There is no time limit for each recall trial. If, after about 15 seconds, the subject has not recalled any words, provide a single prompt, such as, Anything Else? or See if you can think of any more.

If not, administer trial 3 immediately.

HVLT-R Part A – Immediate Recall: Trial 3

Say, 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.

Say, OK. Now tell me as many of those words as you can remember.

Check off the words the subject recalls on the form.

If a word is said that is not in the list, write that word on the form but say nothing to the subject about the word not being on the list.

There is no time limit for each recall trial. If, after about 15 seconds, the subject has not recalled any words, provide a single prompt, such as, Anything Else? or See if you can think of any more.

Record the time on your clock in the designated space on the HVLT-R form (HVLT-R Immediate Recall Stop Time). It is important that RTOG has a precise measurement of when Immediate Recall ends and Delayed Recall Begins. This interval should be 20 minutes.

HVLT-R Part B – Immediate Recognition

DO NOT READ THE WORD LIST AGAIN.

Say, 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?

Read the words from the top of the columns down.

Check either the “Y” (Yes) or “N” (No) box next to each word to indicate the subject's response.

Guessing is allowed.

Record the time on your clock in the designated space on the HVLT-R form (HVLT-R Immediate Recall Stop Time). It is important that RTOG has a precise measurement of when Immediate Recall ends and Delayed Recall Begins. This interval should be 20 minutes.

HVLT-R Part C – Delayed Recall

When ready to begin HVLT-R Delayed Recall, record the time on your clock in the designated space on the HVLT-R form (HVLT-R Delayed Recall Start Time). It is important that RTOG has a precise measurement of when Immediate Recall ends and Delayed Recall Begins.

DO NOT READ THE WORD LIST AGAIN.
Say, *Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember.*

*Check off the words the subject recalls on the form.*

If a word is said that is not in the list, *write that word on the form* but say nothing to the subject about the word not being on the list.

There is no time limit for each recall trial. If, after about 15 seconds, the subject has not recalled any words, provide a single prompt, such as, *Anything Else? or See if you can think of any more.*

HVLT-R administration is now complete.

**Completing the Neurocognitive Evaluation Summary Form (CS)**

After the subject is dismissed, complete all sections of the CS, transferring data from the HVLT-R test form.

For Immediate Recall, add the number of words recalled from the three trials (0-36) and write this number in the appropriate section of the CS.

For Immediate Recognition, add the number of UPPER CASE words answered with “Yes” to obtain a value from 0-12. Next, add the number of LOWER CASE words answered with “Yes” to obtain a value of 0-12. Subtract the second value (the number of lower case words answered with “yes”) to obtain the score for Delayed Recall. Write this number in the appropriate section of the CS.

For Delayed Recall, write the number of words recalled for that trial only (0-12) in the appropriate section of the CS.


**CogState tests instructions script**

**International Shopping List Test (ISLT): Immediate Recall**

⚠️ **Important**

For ISLT, the computer screen must *never* face the subject. *Turn the screen so that it faces you.* The subject must never view the words to be learned as you read them aloud, or the words as they are recalled.

Say, *In this task, I am going to read you a shopping list. I would like you to remember as many items from this list as possible. Are you ready to start?*

*Read aloud each shopping list item as it appears on the screen.* After the last item is presented, a new screen appears, and you will use this screen to enter the words recalled by the subject.

*Read aloud the instructions at the top of the screen.* Say, *Tell me as many of the items on the shopping list as you can remember.*

*Click Enter* to begin recording the subject’s responses. As the subject recalls words, *click the appropriate buttons on the screen.*
If the subject says a word that was not on the list, click the Other Word button. If the subject repeats a word, click the appropriate button again, clicking each time the subject says a word that was recalled previously in that same trial. If you make a mistake, click the Undo Last button.

Each recall period lasts 60 seconds. If time remains and the subject has not recalled all the words from the list, say, Anything Else?

When the subject is finished or the timer reaches zero, click the Continue button.

Say, I am going to read you the same shopping list. Try and remember as many items as you can. Are you ready to start?

Read aloud each shopping item as it appears on the screen. After the last item is presented, a new screen appears, and you will use this screen to enter the words recalled by the subject.

Read aloud the instructions at the top of the screen. Say, Tell me as many of the items on the shopping list as you can remember.

Click Enter to begin recording the subject’s responses. As the subject recalls words, click the appropriate buttons on the screen.

If the subject says a word that was not on the list, click the Other Word button. If the subject repeats a word, click the appropriate button again, clicking each time the subject says a word that was recalled previously in that same trial. If you make a mistake, click the Undo Last button.

Each recall period lasts 60 seconds. If time remains and the subject has not recalled all the words from the list, say, Anything Else?

When the subject is finished or the timer reaches zero, click the Continue button.

Say, I am going to read you the same shopping list. Try and remember as many items as you can. Are you ready to start?

Read aloud each shopping item as it appears on the screen. After the last item is presented, a new screen appears, and you will use this screen to enter the words recalled by the subject.

Read aloud the instructions at the top of the screen. Say, Tell me as many of the items on the shopping list as you can remember.

Click Enter to begin recording the subject’s responses. As the subject recalls words, click the appropriate buttons on the screen.

If the subject says a word that was not on the list, click the Other Word button. If the subject repeats a word, click the appropriate button again, clicking each time the subject says a word that was recalled previously in that same trial. If you make a mistake, click the Undo Last button.

Each recall period lasts 60 seconds. If time remains and the subject has not recalled all the words from the list, say, Anything Else?

When the subject is finished or the timer reaches zero, click the Continue button.

The Learning (immediate recall) portion of the ISLT is complete. The subject receives a cheer.

DO NOT INFORM THE SUBJECT THERE WILL BE A SUBSEQUENT RECALL TRIAL.

There should be a 20-minute delay before administering the Delayed Recall portion of ISLT.

One Card Learning Test (OCLT)
**Important**

OCLT begins automatically. Administer OCLT during the interval between ISLT Immediate Recall and ISLT Delayed Recall.

Turn the computer screen so that it faces the subject. Ensure that the screen is positioned so that it is directly in front of the subject (not angled to the side) and at a comfortable distance from the subject. Adjust the screen pitch if necessary.

Before OCLT begins, a screen appears that allows the subject to practice entering “yes” and “no” responses via the mouse. The left mouse button is always “no” and the right mouse button is always “yes,” regardless of the hand used. Ensure that the subject understands by practicing clicking the proper buttons several times.

Click Enter to begin OCLT.

The instructions appear on the screen. The subject should read them silently as you read them aloud.

Say, *Have you seen this card before in this task? You are now going to do a practice*. You will need to use both the “Yes” and “No” buttons for this task. *In this task, a playing card will appear face-down in the center of the screen and then turn face-up. As soon as a card turns face-up decide if you have seen it before in this task. Only a few of the face-up cards will repeat during the task. If you have seen the card before in this task, press the “Yes” button. If you have not seen the card before in this task, press the “No” button. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after the card turns face-up.*

Click Enter to begin the practice items.

When the practice items are complete, the instructions for the scored or “real” portion of the test appear.

Say, *Have you seen this card before in this task? Cards seen in the practice are not used again. You are now going to do the real test.*

Click Enter to begin the scored items.

If the subject appears confused, offer a single prompt. Say, *Have you seen this card before in this task?*

When presentation of items is complete, OCLT ends automatically. The subject receives a cheer.

**There should be a 20-minute delay between ISLT Immediate Recall and ISLT Delayed Recall.**

The CogState software will help you keep track of the time by displaying a digital clock that shows the time elapsed since ISLT Immediate Recall finished. A message appears onscreen as well: “When timer reaches 20 minutes, turn screen around and administer ISLT DR.”

To fill the remainder of the 20 minutes since ISLT Immediate Recall finished—OCLT doesn’t take the full 20 minutes—you should now allow the subject to engage in specified study activity. (To determine what the subject should do, see page 20; the activity depends on whether this is visit 1, 2, or 3).

When 20 minutes has elapsed, click Enter.

You’ll see a STOP sign. The STOP sign appears in case the subject happens to click Enter, before you’re ready to administer ISLT Delayed Recall.
Important

Turn the computer screen so that it once again faces you.

For ISLT, the computer screen must never face the subject, including when recalling words.

Click Enter to remove the STOP sign and administer ISLT Delayed Recall.

International Shopping List Test (ISLT): Delayed Recall

Say, Now we are going to go back to the shopping list I read to you earlier. I need you to try and remember the items on this list and tell me what they were. Are you ready to start?

Click Enter to begin recording the subject’s responses. As the subject recalls words, click the appropriate buttons on the screen.

If the subject says a word that was not on the list, click the Other Word button. If the subject repeats a word, click the appropriate button again, clicking each time the subject says a word that was recalled previously in that same trial. If you make a mistake, click the Undo Last button.

Each recall period lasts 60 seconds. If time remains and the subject has not recalled all the words from the list, say, Anything Else?

When the subject is finished or the timer reaches zero, click the Continue button.

The subject receives a cheer.

The CogState tests are complete.

© 2009 CogState Limited. (The above instructions script was edited slightly for clarity.)
CERTIFICATION WORKSHEET FOR NEUROCOGNITIVE TEST ADMINISTRATOR

RTOG 0933

This worksheet must be completed and signed by the test administrator (ie, nurse, research associate, physician) requesting certification and must then be submitted to Dr. Caine prior to registering any patients on RTOG 0933.

1. Have you reviewed the RTOG Study 0933 HVLT-R and CogState tests: Information for Test Administrators manual thoroughly?
2. Have you self-administered each of the three tests?
3. Have you completed the Study 0933 neurocognitive tests quiz?
4. Have you sought satisfactory clarification of any questions you may have?
5. Do you believe you are ready to serve as a test administrator for RTOG 0933?
6. I have completed the full certification to perform the Neurocognitive Battery for RTOG 0424, 0534, 0614, 0825, or 0834?

_________________________ Date of completion.

(Please Print)
Name of test administrator: ____________________________________________
Institution number/name: ______________________________________________
Telephone number of test administrator: _________________________________
Fax number of test administrator: _____________________________________
E-mail address of test administrator: ________________________________

_________________________________________ ____________________________
Signature of test administrator Date

If you have questions regarding certification, please contact Dr. Caine (see contact information on front page of protocol).

RTOG 0933 Test Administrator or Research Associate: Once this worksheet is complete, please attach the 0933 Neurocognitive Tests Training Quiz and send to Chip Caine, PhD. Please scan and email to chip.caine@imail.org or fax to 801.507.9801.

Dr. Caine will e-mail the reviewed form, indicating his decision (via the box below) to CTSU, CTSURegOffice@ecogchair.org and to RTOG HQ, 0933cogstate@acr.org.

(For Dr. Caine’s Use Only)
☐ Reviewed and approved
☐ Reviewed and not approved: Dr. Caine also will contact the site

_________________________ ____________________________
Chip Caine, PhD Date
Neuropsychology Co-Chair
APPENDIX VII

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or blood:

Kit contents:
- Two Red Top tubes for serum
- One Purple Top EDTA tube for plasma
- One Purple Top EDTA tube for Whole Blood
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

Serum: Red Top Tube

Label as many 1ml cryovials (5 to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred, but room temperature is acceptable if done within 2 hours of draw- please note if done at RT on STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma: Purple Top EDTA tube #1

Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date/time, time point collected and clearly mark cryovials “plasma”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes 4°C (preferred, but room temperature is acceptable if done within 2 hours of draw- please note if done at RT on STF.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.
Whole Blood for DNA: Purple Top EDTA tube #2

- Using 3 to 5 or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “blood”.

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials labeled “blood” as possible (3-5), clearly mark the tubes with date/time of collection and time point collected.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
4. Store blood samples frozen until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Freezing

- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

Storage

- Store at -80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
    - OR:
      - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
    - OR:
      - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice from breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

Shipping Address:
FedEx/UPS/Courier address (all courier packages & frozen samples)
RTOG Biospecimen Resource
UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact # 415.476.7864
APPENDIX VIII

RECOMMENDED APPROACH TO USING HELICAL TOMOTHERAPY OR LINAC-BASED IMRT PLANNING

NOTE: The following IMRT planning approaches have been found to meet the dosimetric requirements set forth in Section 6.0 of the protocol. Participating institutions are welcome to use these approaches as a starting point, to refine these approaches, or to develop their own approach, as long as they meet the dosimetric constraints outlined in Section 6.0.

Helical Tomotherapy

- Optimize plans such that 96% of the whole brain PTV receives the prescription dose of 30 Gy in 10 fractions
- Utilize the following planning parameters: 1.05cm field width, 0.215 pitch, and 3.0 modulation factor.
- Directionally block the eyes and lenses
- Use the following inverse-planning algorithm constraints:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Helical Tomotherapy Plan Criteria</th>
<th>Penalty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain PTV</td>
<td>Max Dose: 30 Gy</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>30 Gy to ≥96%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Max Dose: 6 Gy</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>3 Gy to ≤20%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hippocampal Avoidance</td>
<td>Max Dose: 30 Gy</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Volume</td>
<td>20 Gy to ≤20%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Eyes*</td>
<td>Max Dose: 8 Gy</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>5 Gy to ≤20%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lenses*</td>
<td>Max Dose: 3 Gy</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

*Directionally block the eyes and lenses.

LINAC-based IMRT Involving Static Gantry Angles

- Optimize plans such that 92% of the whole brain PTV receives the prescription dose of 30 Gy in 10 fractions
- Utilize one of the following beam and gantry angle arrangements:

<table>
<thead>
<tr>
<th>Beam</th>
<th>IEC Scale Couch Angle (°)</th>
<th>IEC Scale Gantry Angle (°)</th>
<th>Varian Scale Couch Angle (°)</th>
<th>Varian Scale Gantry Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>160</td>
<td>270</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>100</td>
<td>270</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>40</td>
<td>270</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>61</td>
<td>208</td>
<td>119</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>127</td>
<td>196</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>354</td>
<td>98</td>
<td>174</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>344</td>
<td>233</td>
<td>164</td>
<td>307</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>262</td>
<td>186</td>
<td>278</td>
</tr>
<tr>
<td>9</td>
<td>332</td>
<td>299</td>
<td>152</td>
<td>241</td>
</tr>
</tbody>
</table>
Beam arrangement 2:

<table>
<thead>
<tr>
<th>Beam</th>
<th>IEC Scale Couch Angle (°)</th>
<th>IEC Scale Gantry Angle (°)</th>
<th>Varian Scale Couch Angle (°)</th>
<th>Varian Scale Gantry Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>320</td>
<td>30</td>
<td>140</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>330</td>
<td>310</td>
<td>150</td>
<td>230</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>180</td>
<td>225</td>
<td>360</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>104</td>
<td>190</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>49</td>
<td>196</td>
<td>131</td>
</tr>
<tr>
<td>6</td>
<td>276</td>
<td>9</td>
<td>96</td>
<td>171</td>
</tr>
<tr>
<td>7</td>
<td>330</td>
<td>265</td>
<td>150</td>
<td>275</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>317</td>
<td>196</td>
<td>223</td>
</tr>
<tr>
<td>9</td>
<td>270</td>
<td>319</td>
<td>90</td>
<td>221</td>
</tr>
</tbody>
</table>

- Use the following inverse-planning algorithm constraints:

<table>
<thead>
<tr>
<th>Structure</th>
<th>LINAC-Based IMRT Plan Criteria</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain PTV</td>
<td>Max Dose: 34 Gy</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Min Dose: 32 Gy</td>
<td>100</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Max Dose: 11 Gy</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9 Gy to ≤40%</td>
<td>10</td>
</tr>
<tr>
<td>Hippocampal Avoidance Volume</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eyes*</td>
<td>Max Dose: 7 Gy</td>
<td>5</td>
</tr>
<tr>
<td>Lenses*</td>
<td>Max Dose: 5 Gy</td>
<td>5</td>
</tr>
</tbody>
</table>