WHOLE BRAIN RADIATION THERAPY WITH SIMULTANEOUS BOOST TO GROSS METASTATIC TUMOR VOLUME USING VOLUMETRIC MODULATED ARC THERAPY (RAPIDARC)

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1.0 INTRODUCTION/BACKGROUND

Brain metastases are the most common adult intracranial tumor, occurring in approximately 10% to 30% of adult cancer patients, and represent an important cause of morbidity and mortality in this population.[1] The risk of developing brain metastases differs with different primary tumor histologies, with lung cancer accounting for approximately one half of all brain metastases.[2] The prognosis of patients with brain metastases is poor. The median survival time of untreated patients is approximately 1 month.[3] With treatment, the overall median survival time after diagnosis is approximately 4 months.[4] The RTOG recursive partitioning analysis (RPA) describes three prognostic classes, defined by age, Karnofsky Performance Score (KPS), and disease status.[5] The most widely used treatment for patients with multiple brain metastases is WBRT. The appropriate use of WBRT can provide rapid attenuation of many neurological symptoms, improve quality of life, extend median survival, and be especially beneficial in patients whose brain metastases are surgically inaccessible or when other medical considerations preclude surgery.[6,7] The use of adjuvant WBRT after resection or sterotactic radiosurgery (SRS) has been proven to be effective in terms of improving local control of brain metastases, and thus, the likelihood of neurological death is decreased.[8]

The majority of patients who achieve local tumor control die from progression of extracranial disease, whereas the cause of death is most often due to CNS disease in patients with recurrent brain metastases.[7,8] Currently, no consensus on the optimal radiation schedule for patients with brain metastases is established. Standard treatment regimens include dose fractionation schemes evaluated in the early RTOG studies and range from 20 Gy in 5 fractions to 40 Gy in 20 fractions. The exact regimen used is generally at the discretion of the treating physician and often depends upon issues such as the severity of CNS symptoms, the extent of systemic disease, and physician preference.

More recently, a phase III randomized study (RTOG 9508) found that the combination of WBRT and SRS boost was superior to WBRT alone in selected patients.[9] On this study, patients with a solitary brain metastases had an overall survival benefit when SRS was given. Furthermore, patients in the SRS group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months follow-up than were patients allocated WBRT alone. Intracranial disease control and use of steroids were also improved with SRS in patients with multiple brain metastasis.[9] While the benefits of improved local control gained by adding SRS to WBRT are clear, many factors continue to limit the use of SRS. This procedure is generally contraindicated in lesions larger than 3-4 cm in size. In addition, while multiple lesions can be treated with SRS, the procedure can quickly become unwieldy as the number of lesions increases and dosimetric considerations may also start to increase the risk of toxicity.

RapidArc (RA) (Varian Medical Systems, Palo Alto, CA) is a volumetric modulated arc technique that uses a single 358 degree rotation of the linear accelerator to deliver highly conformal intensity modulated three dimensional dose distributions. The combination of accurate and reproducible patient setup prior to treatment with a RA plan provides an alternative to conventional SRS by allowing for integration of the WBRT with fractionated SRS-like boost. A recent publication generated composite RA plans consisting of WBRT with an integrated boost to gross brain metastases. These RA plans were then measured in a solid water phantom. It was also clinically delivered in 3 patients. The generated plans demonstrated excellent PTV coverage with a steeper dose gradient outside of brain metastasis as well as higher conformity index than WBRT followed by SRS.[10] A similar experience was recently published describing WBRT with simultaneous infield boost using helical tomotherapy. Generated plans demonstrated similar target coverage with improved critical tissue sparing in patients with one to three metastatic brain metastases.[11] RapidArc delivery allows for giving differential, highly conformal, radiation doses to different portions of the brain. With conventional WBRT, the entire brain is treated to the "macroscopic disease dose" due to the inability with conventional fields to selectively deliver dose to specific areas of the brain. The conventional "macroscopic disease" dose is typically 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Several studies have indicated that patients at high risk of brain involvement, but without gross brain metastases, achieve high levels of intracranial control with lower "prophylactic disease" doses. The typical prophylactic cranial irradiation (PCI) dose for lung cancer is 25 Gy in 10 fractions. RTOG 0214 randomized patients with locally advanced non-small cell lung cancer status post definitive therapy to PCI or not.[12] These patients are known to be at high risk of brain metastases, up to 25% at 2 years. PCI reduced the 1 year incidence of brain metastases significantly from 18% to 8%. With RapidArc technology, the whole brain at risk could be given a reduced PCI dose, while the gross disease seen on MRI can be boosted with higher doses known to lead to better local control. We feel that the reduced whole brain dose allowed by this technique would lead to similar rates of distant brain control as conventional dosing, but with the possibility of reduced neurcognitive toxicity, as critical structures such as the white matter tracts and hippocampi will receive lower radiation doses.

Varian Medical Systems has notified and received clearance from the Food and Drug Administration (FDA) to use RapidArc in patient care. This technology is not considered an experimental device. The standard of care for patients with 1 – 4 brain metastases is currently WBRT with or without SRS boost. Patients with more than 4 brain metastases are typically eligible for WBRT only. With an integrated boost method, we believe that we can deliver increased dose to the gross disease, in a more convenient and time efficient manner, include patients who would not otherwise be SRS candidates, and spare more normal brain tissue, which may translate into improved local control and median survival. We believe that the risk:benefit ratio is favorable for patients who would be enrolled on this study due for several reasons: the current very poor prognosis of the condition, the use of an existing FDA approved technology, and the integration of a proven treatment into a more efficient regimen.

Given the limitations of the SRS boost technique, the purpose of our investigation is to evaluate an alternative strategy for giving WBRT with highly focal boost to gross visible lesions in patients with brain metastasis. In this study, we plan to assess the tolerability of using volumetric modulated arc therapy (RapidArc) on patients with brain metastasis to simultaneously treat the entire brain with a concomitant focal boost to grossly identified lesions on MRI scan to try to improve local control and reduce neurocognitive toxicities.

This previous version of this study was a phase I dose escalation trial giving 25 Gy in 10 fractions to the whole brain with simultaneous infield boost (SIB) to a total of 45 Gy in 10 fractions to gross brain metastatic disease. Prior to this, patients were enrolled onto one of two cohorts with whole brain dose of 30 Gy in 10 fractions with SIB to total of 45 Gy in 10 fractions to gross brain metastatic disease or whole brain dose of 37.5 Gy in 15 fractions with SIB to total of 52.5 Gy in 15 fractions to gross brain metastatic disease. A total of 12 patients have been previously enrolled on this trial. No patients have experienced a dose limiting toxicity (grade 3 or above) at least possibly due to study therapy. Also, no patients experienced local brain failure/progression at a site of treated metastatic brain disease. Based on this, we no longer feel that dose escalation to the gross brain disease is warranted and would proceed with a single arm pilot study treating patients with 25 Gy in 10 fractions to the whole brain with simultaneous infield boost (SIB) to a total of 45 Gy in 10 fractions to gross brain metastatic disease.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the feasibility of treating brain metastasis patients with whole brain radiation and simultaneous focal boost using an RA technique. (see Section 11.4)

2.1.2 To determine the locoregional control [at visible lesion(s) and new site(s)] in the brain of patients treated with a concomitant boost RA plan.

2.2 Secondary Objectives

2.2.1 To determine the overall survival of brain metastasis patients treated with such an RA plan.

2.2.2 To determine the progression-free survival of brain metastasis patients treated with such an RA plan.
2.2.3 To assess the long-term neurocognitive effects of this treatment using the Hopkins Verbal Learning Test–Revised (HVLT-R), Mini Mental Status Exam (MMSE) and Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS).
2.2.4 To assess quality of life (QOL) outcomes after this treatment using the quality of life questionnaire for the Functional Assessment of Cancer Therapy-Brain (FACT-Br).

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Pathologic proven diagnosis of solid tumor malignancy.
3.1.2 Age ≥ 18.
3.1.3 KPS ≥ 70.
3.1.4 Mini Mental Status Exam (MMSE) ≥ 18 prior to study entry.
3.1.5 RPA class I (KPS≥70, primary cancer controlled, age<65, metastases in brain only) or class II (lack of one or more of class I criteria) (see **Appendix A** for definitions).
3.1.6 One to ten brain metastatic lesions.

3.2 Exclusion Criteria

3.2.1 Previous whole brain radiation therapy
3.2.2 Previous radiosurgery to any currently progressive gross metastatic disease
3.2.3 Previous radiosurgery to any intracranial site within the prior 6 weeks
3.2.4 RPA class III (KPS<70, see **Appendix A**).
3.2.5 Radiosensitive (eg. small cell lung carcinomas, germ cell tumors, leukemias, or lymphomas) or unknown tumor histologies.
3.2.6 Concurrent chemotherapy (no chemotherapy starting 14 days before start of radiation
3.2.7 Evidence of leptomeningeal disease by MRI and/or CSF cytology.
3.2.8 Current pregnancy
3.2.9 No metastases to brain stem, midbrain, pons, or medulla or within 7 mm of the optic apparatus *(optic nerves and chiasm)*.

4.0 PRE-TREATMENT EVALUATION

4.1 MRI scan with and without contrast (at least 5mm resolution on T1 post-contrast imaging).
4.2 History and physical including a detailed neurologic exam.
4.3 Steroid and anti-convulsant doses must be documented.
4.4 Baseline MMSE.
4.5 Baseline neurocognitive function using the HVLT-R (memory).
4.6 Baseline neurocognitive function using MOS (self-report).
4.7 Baseline QOL assessment using FACT-Br.
4.8 Documentation of extent of systemic disease.
4.9 Pregnancy test in women of child bearing potential when there is clinical suspicion of pregnancy

5.0 REGISTRATION

This will be a single cohort pilot study. Safety of the chosen dose level has been shown based on the previous phase I dose escalation iteration of this study.

18 patients will be enrolled consecutively into this single arm pilot study.

6.0 RADIATION THERAPY

6.1 Localization, Simulation, and Immobilization

6.1.1 Patient immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A standard head-holding device involving a thermoplastic mask that is transparent to x-rays will be used to ensure adequate immobilization during therapy and daily reproducibility.

6.1.2 Simulation CT scan

At simulation, a non-contrasted CT scan with at least 1.25mm resolution will be obtained.

6.1.3 MRI scan

A post-contrast T1 MRI series with at least 5 mm resolution will be required for study entry. This image series will be fused/registered with the simulation CT scan using appropriate software.

6.1.4 Target definition

Target/tumor volumes will be contoured. Target volumes shall include the whole brain parenchyma inferiorly bordered by the foramen magnum with boost to gross metastatic tumor(s) as defined by the post-contrast T1 weighted MRI. The whole brain CTV will be expanded by 3 mm to create the whole brain PTV. Each metastatic tumor GTV will be expanded by 2 mm to obtain the planning target volumes (PTVs) for the boost targets.

6.1.5 Daily patient setup

Patients will be setup with daily on-board imaging guidance. This will involve obtaining orthogonal kV images prior to each treatment fraction and making appropriate adjustments to ensure treatment setup accuracy.

6.2 Technical Factors

6.2.1 X-ray energy

Treatment shall be delivered with megavoltage machines of energy ranging from 6MV up to and including 18 MV photons. Selection of the appropriate photon energy should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissues.

6.2.2 Hardware configuration

Treatment will be delivered via volumetric modulated arc therapy (Rapid Arc) with 1-3 arcs with rotations up to 358^{o}. Collimator will be turned at 45^{o} for the planning.

6.3 Dose specifications

6.3.1 Planning goals

Goal is to obtain 95% PTV coverage with the prescription dose with a Dmin to PTVs of 90% of the prescribed dose. Whole brain PTV will be prescribed 25 Gy. The boost PTV(s) will be prescribed according to the dose escalation scheme described below. In the optimization process, dose to the brain outside of the boost PTV should be minimized as much as possible while maintaining the dose prescription goals listed above.

6.3.2 Dose

This cohort is based on giving 25 Gy in 10 fractions to the whole brain** (see below). The efficacy and tolerability of this fractionation has also been established.

Group	Dose (to lesions)	SIB dose/fx	BED_{10}	BED_3	Patients
Brain dose	2.5 Gy x 10 fx		31.25	45.83	
** resection cavity	3 Gy x 10 fx	0.5 Gy SIB			
Cohort group	4.5 Gy x 10 fx	2 Gy SIB	65.25	112.5	18

Gy, Gray; fx, fraction; SIB, simultaneous in-field boost; BED_{10}, biologically equivalent dose for α/β of 10 (response of tumor, or early-reacting tissue); BED_3, biologically equivalent dose for α/β of 3 (response of late-reacting tissue).

** If a patient has had brain metastases resected that is part of the whole brain volume, then that resection cavity with a 2mm PTV expansion will be boosted to a total of 30 Gy in 10 fx with a 0.5 Gy SIB / fx over the whole brain 25 Gy in 10 fx baseline.

6.4 Critical Structures

Dose specification to be used in the treatment planning process to limit dose to critical structures are as follows: 1) the lens (<10 Gy), 2) globes (<30 Gy), 3) optic chiasm/nerves (<37 Gy), 4) brainstem (90% < 37 Gy), and 5) cervical spinal cord (<36 Gy)

6.5 Radiation Adverse Events

6.5.1 Acute (≤ 90 days from treatment start)

Expected adverse events include sore throat, hair loss, erythema of the scalp, headache, nausea and vomiting, lethargy, and transient worsening of neurological deficits. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

6.5.2 Late (> 90 days from treatment start)

Possible adverse events include radiation necrosis, cognitive dysfunction, visual difficulties, accelerated atherosclerosis, and radiation-induced neoplasms.

7.0 DRUG THERAPY

Corticosteroid and anti-convulsant use will be documented.

8.0 SURGERY

Not applicable to this protocol.

9.0 OTHER THERAPIES

Not applicable to this protocol.

10.0 PATHOLOGY

All patients will have a pathologically documented malignancy prior to initiating therapy.

11.0 PATIENT ASSESSMENTS

11.1 Neurocognitive Assessments

11.1.1 Tests to be administered

Cognitive Domain	Assessment
Memory	Hopkins Verbal Learning Test-Revised
Global Function	Mini-Mental Status Examination
Cognitive Function (self-report)	Medical Outcomes Cognitive Scale

11.1.2 Hopkins Verbal Learning Test- Revised (HVLT-R)

The patient learns 12 words read to them 3 times; free recall is tested after each learning trial. Delayed recall is evaluated after 20 minutes. Following the delayed recall trial, the patient completes a delayed recognition test to determine if an impairment of delayed recall is due to a retrieval deficit or to a consolidation deficit. Entire test requires about 5 minutes to complete.

11.1.3 Mini-Mental Status Examination (MMSE)

This is a brief, standardized tool to grade patients' global cognitive function. The MMSE begins with an assessment of orientation to place and time. Next is a test of memory (immediate recall) by having the subject immediately repeat the names of 3 objects presented orally. Following this, the patient subtracts sevens serially from 100. The subject is then asked to recall the three items previously repeated (delayed recall). The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a 3-step command, comprehension of written words, writing, and copying a drawing. The maximum score that can be obtained for the entire MMSE is 30 points.

11.1.4 Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS)(Self-report)

This 6-item, self-report measure is designed to measure day-to-day cognitive functioning of which the patient would be aware, including difficulty with problem-solving, slowed reaction times, forgetfulness, and concentration. Reliability and validity have been reported for patients with cancer. Scale is based on multiple choice questions asking about cognitive function where the item is present 1= all of the time to 6=none of the time. Scored in five steps (data cleaning, changing out of range values to missing, item re-calibration and skip pattern recording, reverse scoring of items so that the highest score reflects the best health state, transforming

scores linearly to a common metric with a range of 0-100, averaging across items in the same scale). Completion time is estimated to be less than 5 minutes.

11.1.5 Frequency of neurocognitive assessments

All tests will be given at baseline and at every follow-up for the first 6 months, then every 6 months thereafter (at 1, 3, 6, 12, 18, and 24 months). A window period of +/- 6 weeks will be allowed to correlate with each study time-point visit.

11.2 Quality of Life Evaluation

11.2.1 Functional Assessment of Cancer Therapy-Brain (FACT-Br)

This assessment is a commonly used instrument measuring general quality of life (QOL) reflecting symptoms or problems associated with brain malignancies 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). Patients rate all items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale.

11.2.2 Frequency of QOL assessment

The FACT-Br will be given at baseline and at every follow-up for the first 6 months, then every 6 months thereafter (at 1, 3, 6, 12, 18, and 24 months). A window period of +/- 6 weeks will be allowed to correlate with each study time-point visit.

11.3 Toxicity and Outcome Assessments

11.3.1 Imaging followup

Patients will undergo brain MRI prior to study entry and at 1 month, 3 months and every 3 months thereafter or when otherwise indicated (eg. at onset of clinical deterioration). A window period of +/- 6 weeks will be allowed to correlate with each study time-point MRI.

11.3.2 Brain metastasis size evaluation

The treating radiation oncologist will measure and calculate the volume for each brain metastasis identified as a contrast enhancing mass on MRI at baseline using radiation oncology treatment planning software. 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.

11.3.3 Lesion response evaluation

Each treated lesion will have a volumetric measurement made at each study imaging follow-up using the visit high resolution MRI scan and radiation oncology treatment planning software. Percentage change in volume from the original baseline volume will be calculated using the formula: [original volume – current volume] / original volume. Lesions with complete resolution will be noted as complete response (CR).

11.3.4 Definition of CNS progression

CNS progression will be defined as a > 25% increase in volume for any tracked brain metastasis, or the appearance of any new brain metastasis on a follow-up MRI. For lesions smaller than 1 cm in maximum diameter, a maximum increase of 50% in volume 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 greater than 1 cm lesions, the definition will use a 25% rule for change.

11.3.5 RTOG CNS toxicity determination

Neurologic/brain toxicity assessment will be made during treatment and at each follow up (1 month, 3 months, and every 3 months thereafter) (See **Appendix B** for definitions).

11.3.6 Adverse Events (AEs)

Any unfavorable and unintended sign, 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). These events will be recorded for each subject and is subject to review by the investigators and data safety monitoring committee (DSMC).

11.3.7 Serious Adverse Events (SAEs)

Any adverse event that results with any of the following outcomes:

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

Important medical events that may not result in death, be life threatening, or 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. These events will also be recorded for each subject and is subject to review by the investigators and data safety monitoring committee (DSMC). In addition, these events will be reported to the Emory University Institutional Review Board (IRB).

11.4 Feasibility Assessment

11.4.1 Criteria of feasibility

Treatment plans using the RapidArc treatment planning software to deliver simultaneous in-field boosts to gross metastatic lesions have been successfully generated in our department. Therefore, the main question of feasibility is regarding whether the treatment setup and delivery can be accomplished in a "reasonable" period of time. A typical treatment slot for conventional radiation therapy in our department is 15 minutes. We will define 2 treatment slots, or 30 minutes as a "reasonable" time for this treatment. Therefore, this treatment will considered feasible if the treatment setup/delivery time is <30 minutes in >90% of treatment fractions.

11.4.2 Feasibility data to be collected

Our departmental record-and-verify system will document the time when setup OBI images are first obtained and when the radiation treatment delivery is turned off for each treatment fraction. This time will be recorded for each treatment fraction. An additional 5 minutes will be added to this time to estimate the time required to setup a patient prior to the acquisition of the first OBI image plus the time from when the machine is turned off to when the patient is released from the treatment couch. This total time will need to be <30minutes for the treatment to be considered "reasonable."

12.0 DATA COLLECTION

12.1 Data Fields

The following data will be collected on each patient: name, date of birth, medical record number, tumor characteristics by pathology of surgical specimen, radiologic results, performance status, radiation and chemotherapy treatment parameters, clinical outcome including local and regional control, overall survival, treatment complications, neurocognitive assessments, and QOL assessments.

12.2 Criteria for patient to be considered off study

12.1.1 Local CNS disease progression.
12.1.2 Patient death.
12.1.3 Patient request to come off study.
12.1.4 Patient is discharged to hospice

12.3 Data Safety Monitoring

12.3.1 Data Safety Monitoring Committee (DSMC)

We will use the Winship Cancer Institute data safety monitoring committee chaired by Dr. Suresh Ramalingam as an independent review. As per WCI policy, the DSMC monitors all investigator initiated studies and cooperative group studies at Winship. Each qualifying study is reviewed at least once a year. Two of the first 5 patients enrolled to investigator-initiated studies and 10% of total accrual is reviewed.

Once a chart is monitored, the PI and the study coordinator are presented with the findings. They have a 2 week period to respond to the findings. A summary report is submitted to the DSMC for committee review. Any serious unanticipated problem is reported to the IRB with due notice to the PI.

Included in the review:
- Regulatory documents
- Patient eligibility
- Informed consent process
- Accuracy and timeliness of data
- Verification of source documents
- Toxicity assessment process

• Submission of SAEs

13.0 STATISTICAL CONSIDERATIONS

13.1 Study endpoints

13.1.1 Primary endpoints

- Feasibility – Measurement of the amount of time required for daily treatment
- Rates of toxicities
- Local brain control
- Regional brain control

13.1.2 Secondary Endpoints (to be compared with standard historical controls)

- Progression-free survival
- Overall Survival
- Neurocognitive effects
- QOL outcomes

13.2 Sample size

This will be a single cohort pilot study. Safety of the chosen dose level has been shown based on the previous phase I dose escalation iteration of this study.

18 patients will be enrolled consecutively into this single arm pilot study.

If a patient is not able to complete follow up to the toxicity assessment point of 4 months due to a toxicity judged not to be at least possibly related to therapy, then that patient will be replaced by the next patient enrolled.

13.3 Statistical Analysis

Descriptive statistics will be performed on the clinical and treatment factors on subjects on this study. Categorical data will be presented on frequency tables while continuous data will be presented as mean, standard deviation, median and range. Local control, regional brain control, progression-free survival and overall survival will be assessed using the Kaplan-Meier method with censoring as appropriate. Univariate and multivariate analysis will be performed with these endpoints to determine patient factors that may influence outcome. These curves will also be compared to previously published results as historical controls. The results of the neurocognitive and quality of life surveys/tests will be plotted for each patient to assess for a general trend over time. The trend over time can also analyzed by linear regression analysis. Each point in time can be compared with historical controls using a student's t-test to determine whether there is a significant difference in the survey/test scores in patients on our study versus historical results.

14.0 REFERENCES

1. Wen PY, Black PM, Loeffler JS: Cancer: Principles and Practice of Oncology (ed 6). In *Metastatic Brain Cancer* Edited by: DeVita V, Hellman S, Rosenberg SA. Philadelphia, PA, Lippincott, WIlliams, & Wilkins; 2001:2655-2670.
2. Zimm S, Wampler GL, Stablein D, *et al.*: Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. *Cancer* 1981, 48:384-394.
3. Sundstrom JT, Minn H, Lertola KK, *et al.*: Prognosis of patients treated for intracranial metastase with whole-brain irradiation. *Ann Med* 1998, 30:296-299.
4. Chao JH, Phillips R, Nickson JJ: Roentgenraytherapy of cerebral metastases. *Cancer* 1954, 7:682-689.
5. Gaspar L, Scott C, Rotman M, *et al.*: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997, 37:745-754.
6. Patchell RA, Regine WF: The rationale for adjuvant whole brain radiation therapy with radiosurgery in the treatment of single brain metastases. *Technol Cancer Res Treat* 2003, 2:111-115.
7. Arbit E, Wronski M, Burt M, Galicich JH: The treatment of patients with recurrent brain metastases:A retrospective analysis of 109 patients with nonsmall cell lung cancer. *Cancer* 1995, 76:765-773.
8. Wen PY, Loeffler JS: Management of brain metastases. *Oncology (Huntingt)* 1999, 13:941
9. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665–1672.
10. Lagerwaard F, Van der Hoorn E, Verbakel W, Senan S, *et al.* Whole-Brain Radiotherapy With Simultaneous Integrated Boost to Multiple Brain Metastases Using Volumetric Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys* 2009, 75: 253-259.
11. Bauman G, Yartsev S, Fisher B, Kron T, Laperriere N, Heydarian M, VanDyk J. Simultaneous infield boost with helical tomotherapy for patients with 1 to 3 brain metastases. Am J Clin Oncol. 2007 30:38-44.
12. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol. 2011 Jan 20;29(3):272-8. Epub 2010 Dec 6.

APPENDIX A

RTOG RPA Classification System

RPA Class I	All of the following criteria: KPS ≥ 70% Age < 65 years Absence of extracranial metastases Controlled primary cancer
RPA Class II	KPS ≥ 70% **and** One or more of the following criteria: Age > 65 years Presence of extracranial metastases Uncontrolled primary cancer
RPA Class III	KPS < 70%

APPENDIX B

CTCAE (Common Terminology Criteria for Adverse Events), version 4.02

The exact full criteria for toxicity assessment can be obtained at the NCI CTEP website at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf.

APPENDIX C – Evaluation Timeline

SEE BELOW

APPENDIX C - Timeline

Note:). A window period of +/- 6 weeks will be allowed to correlate with each study time-point and MRI visit.

	Baseline	1 month	4 months	7 months	10 months	13 months	16 months	19 months	22 months	25 months
H&P	X	X	X	X	X	X	X	X	X	X
Toxicity Assessment		X	X	X	X	X	X	X	X	X
MRI	X	X	X	X	X	X	X	X	X	X
HVLT-R	X	X	X	X		X		X		X
MMSE	X	X	X	X		X		X		X
MOS	X	X	X	X		X		X		X
FACT-Br	X	X	X	X		X		X		X
Imaging Response Evaluation		X	X	X	X	X	X	X	X	X