A Phase II Trial of Hippocampal-Sparing Prophylactic Cranial Irradiation (PCI) for Small Cell Lung Cancer (SCLC)

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TITLE: A Phase II Trial of Hippocampal-Sparing Prophylactic Cranial Irradiation (PCI) for Limited Stage Small Cell Lung Cancer (SCLC)

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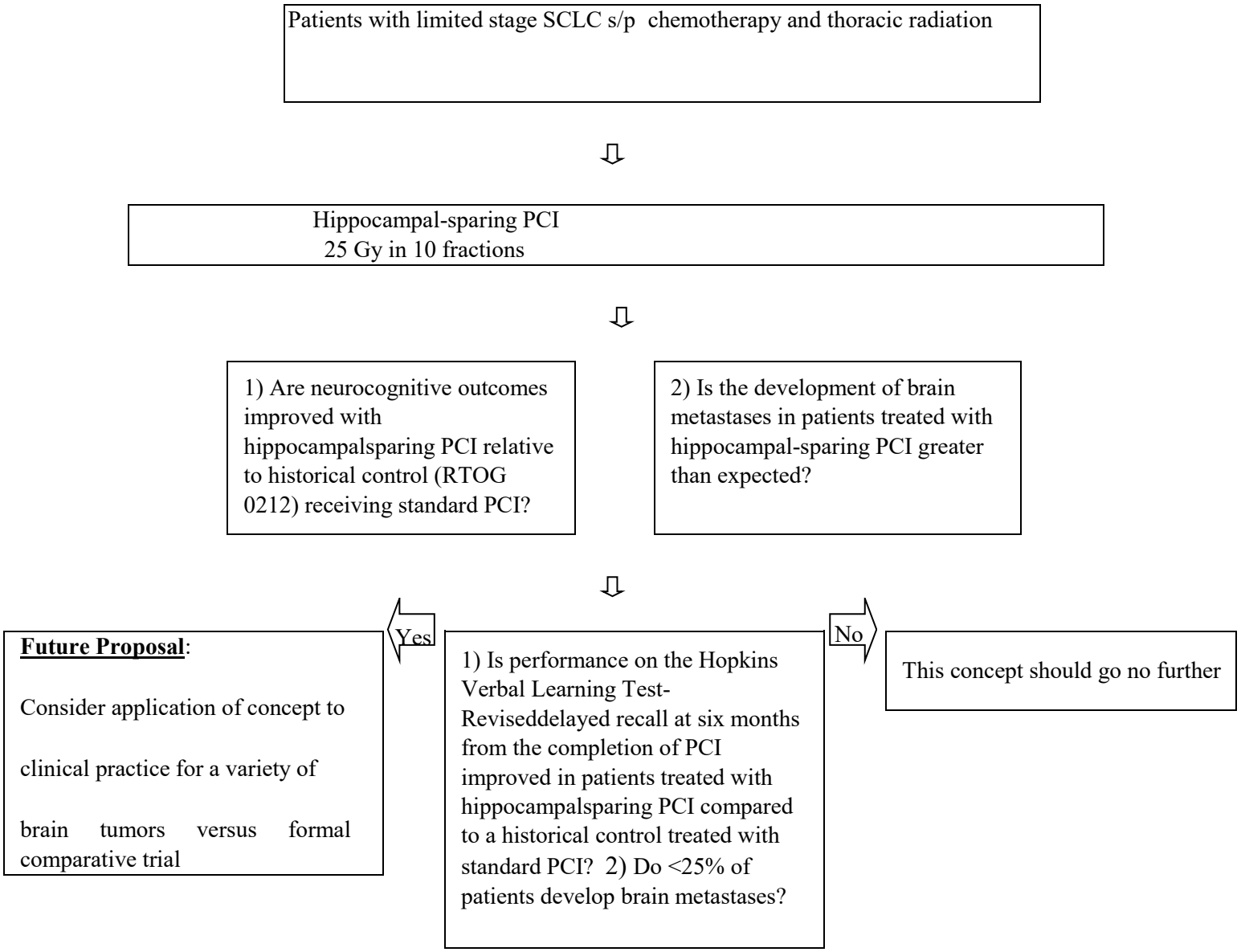
SCHEMA

Patient Eligibility:

- Histological or cytological evidence of small cell lung cancer (SCLC)
- Zubrod performance status of ≤ 1
- RTOG neurological function class of 1 or 2 (Appendix A)
- Limited disease with CR to chemotherapy and consolidative chest radiotherapy that was documented at least on standard chest X-rays within one month of study entry.
- No definitive evidence of brain metastases on brain MRI or CT scan at least one month before protocol entry.

Treatment Plan:



Required sample size: 125 patients

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1. OBJECTIVES

1.1 Primary Objectives

Evaluate performance on the Hopkins Verbal Learning Test-Revised for delayed recall (HVLT-R-delayed recall) at 6 months following hippocampal-sparing PCI relative to a historical control receiving standard PCI.

1.2 Secondary Objectives

1.2.1 Evaluate performance on HVLT-R delayed recall at 12 months following hippocampal-sparing PCI relative to historical control receiving standard PCI.

1.2.2 Evaluate composite cognitive function at 6 and 12 months following hippocampal-sparing PCI relative to a historical control receiving standard PCI

1.2.3 Evaluate quality of life following hippocampal-sparing PCI relative to a historical control receiving standard PCI.

1.2.4 Determine whether development of brain metastases following hippocampalsparing PCI is higher than expected.

1.2.5 Determine whether development of leptomeningeal carcinomatosis following hippocampal sparing PCI is higher than expected

1.2.6 Evaluate overall survival following hippocampal sparing PCI.

2. BACKGROUND

2.1 Study Disease and Rationale

The current standard of care for treatment of limited stage small cell lung cancer consists of chemotherapy plus thoracic irradiation (1), followed by prophylactic cranial irradiation (PCI). The recommendation for PCI is based on the results of a meta-analysis in patients with limited stage small cell lung cancer which demonstrated a 5.4% increase in overall survival with the addition of PCI to chemo-radiation therapy for the primary lung tumor (2).

Unfortunately, it is well documented that whole brain radiation therapy is associated with neurocognitive toxicity (3-7) and that there is a direct relationship between neurocognitive dysnfunction and worsening quality of life (8). This toxicity is particularly important in patients being treated with PCI for SCLC since they represent a potentially curable patient population who have a relatively high likelihood of surviving long enough to develop the long-term sequalae of therapy.

The precise mechanism of radiation induced neurotoxicity remains unclear and the effect is likely multi-factorial. However, emerging data suggests that radiation induced damage to neural progenitor cells within the hippocampus may play a role. Animal studies have shown that new neurons and glia are produced throughout adult life from neural stem cell precursors in the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus (9-11). These cells play an important role in injury repair within the central nervous system (12,13). Similarly, these cells migrate to the site of inflammation caused by irradiation or brain injury (13).

Multiple animal studies have shown that neural progenitor cells are extremely sensitive to radiation (14-17). Tada et al. showed that 2 Gy of radiation effectively killed proliferating cells in both the SVZ of the lateral ventricles (14) and the subgranular zone of the dentate gyrus (15). The anti-proliferative effects last for up to 15 months after a single radiation treatment (18) and are dose dependent (19,20). There is repair over time following low doses of radiation, suggesting likely recovery of cells with fractionation (14).

There is an association between radiation-induced neural progenitor cell impairment and neurocognitive decline after central nervous system irradiation in rodents. Cranial irradiation significantly decreases hippocampal neurogenesis and is associated with impaired performance of hippocampal-dependent tasks 19-22, indicating that newly born cells may be essential for normal hippocampal functioning.

Several studies suggest that neurogenic areas similar to those described in the rodent brain exist in the human brain as well. For example, Eriksson et al. (23) demonstrated that progenitor cells in the human dentate gyrus divide to form new neurons, while Sanai et al. (24) found that astrocytes in the human SVZ of the lateral ventricles divide in vivo and act as multipotent progenitor cells in vitro. Human studies have likewise demonstrated cognitive deficits following cranial irradiation, most notably in children (25-28). This decline includes diminished capability to learn and memorize new tasks and information, as well as a dramatic reduction in full-scale IQ (29).

Recent human studies have demonstrated that it is possible to use intensity modulated radiation therapy (IMRT) to reduce the radiation dose to the hippocampus during radiation therapy for brain tumors (30-32). In addition, preliminary data using a mouse model has suggested that NPC sparing radiation may allow improved survival of neural progenitor cells compared to conventional radiation treatment plans, at least at an early time point (33). Similarly, recent data from a prospective study in children treated with radiation therapy to the brain suggests an inverse relationship between radiation dose to the hippocampus and performance on neurocognitive testing (34), and a randomized trial comparing 25 Gy versus 36 Gy of PCI found that the risk of chronic neurotoxicity was significantly higher in the 36 Gy arm (35).

The purpose of this study is to evaluate performance on neurocognitive testing following hippocampal-sparing PCI relative to the historical experience of patients (RTOG 0212) who received standard PCI.

2.2 Correlative Studies Background

Correlative studies include a neurocognitive function test battery that has been validated in a multi-institutional phase III study by the Radiation Therapy Oncology Group (RTOG) in the context of brain metastases (36,37). The tests will be performed by a trained examiner. The tests utilized in this protocol are described briefly below:

2.2.1 **Mini Mental State Examination**

The Mini Mental State Examination (38) is designed to evaluate global function. It consists of six tasks designed to evaluate short-term memory retention and recall, attention, and language. The maximum score is 30. Scores fall into 4 categories:

- 24-30: "Normal" range
- 20-23: Mild cognitive impairment
- 10-19: Moderate cognitive impairment
- 0-9: Severe cognitive impairment

2.2.2 **Trail Making Test**

The Trail Making Test A is designed to evaluate visual motor scanning speed and the Trail Making Test B is designed to evaluate executive function (39,40). These tests require patients to connect circles in numerical (part A) or alternating numerical and alphabetical sequence (part B) within a timed interval of less than 5 minutes for each test. Results are reported as the number of seconds required to complete the task with higher scores reflecting higher degrees of impairment.

	Average	**Deficient**	**Rule of Thumb**
Trail A	29 seconds	>78 seconds	Most in 90 seconds
Trail B	75 seconds	>273 seconds	Most in 3 minutes

2.2.3 **Controlled Oral Word Association Test**

The Controlled Oral Word Association Test (COWAT) is designed to evaluate letter-cued verbal fluency. It requires patients to name words beginning with a specific letter with increasing associated activity, in three 1minute periods.

Scoring is based on the number of words named during the 1minute periods, with adjustments for education and age. Individual scores are categorized as intact, low average, borderline, deficient, or seriously deficient, based on their scores after these adjustments (41).

2.2.4 **Hopkins Verbal Learning Test-Revised**

The Hopkins Verbal Learning Test-Revised is designed to evaluate memory. It requires patients to memorize a list of 12 items for three consecutive tests (recall), to identify the same 12 items from a list of semantically related or unrelated items (recognition), and to recall the same 12 items after a 15minute delay (delayed recall). Scoring and interpretation are simple, and outlined in a professional manual (42).

2.2.5 **EORTC Quality of Life questionnaire (QLQ-C30) and the Brain Cancer Module 20**

The EORTC Quality of Life questionnaire (QLQ-C30, Appendix B) is a 30 item questionnaire designed for and validated in cancer patients. It consists of 9 multi-item scales—1 global scale, 5 functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (nausea, pain, fatigue). The remaining 6 questions are single items addressing other symptoms and financial impact. The Brain Cancer Module 20 (BN 20, Appendix C) is a 20 question addendum to QLQ-C30 designed specifically for patients with brain tumors. It assesses neurologic deficits, future uncertainty and disease and treatment related symptoms.

2.3 Additional Testing

The following tests will be administered to the subject after those outlined in Section 2.2 have been completed.

2.3.1 **Brief Visuospatial Memory Test-Revised**

The Brief Visuospatial Memory Test-Revised is designed to evaluate nonverbal/visuospatial learning and memory. It serves as a non-verbal analogue to the HVLT-R, and is generally more sensitive to right hippocampal functioning. It requires patients to learn a series of six figures printed on a page over the course of three exposure trials (immediate recall), recall those same six figures after a 15-20 minute delay (delayed recall), and identify the figures from among an equal number of foils (recognition). Scoring and interpretation are simple, and outlined in a professional manual (43).

2.3.2 **Category-cued verbal fluency**

The Category Fluency Test is designed to evaluate semantically-guided verbal generativity and is often administered in conjunction with the COWAT. It requires patients to name as many different category exemplars as they can in 2 60-second trials. Scoring involves tallying the number of acceptable words reported for the two trials and interpretation is simple and outlined in a professional manual (44).

2.3.3 **Brief Test of Attention**

The Brief Test of Attention is designed to evaluate auditory divided attention and can be used with individuals with visual and motor impairments that preclude tests requiring visual scanning or manual dexterity. It requires patients to count numbers or letters from lists read aloud consisting of both types of stimuli. The number of correctly monitored lists is tallied, with raw scores ranging from 0 to 20. Interpretation is simple and outlined in a professional manual (45).

2.3.4 **Hopkins Adult Reading Test**

The Hopkins Adult Reading Test is designed to evaluate pre-illness intellect. It requires patients read aloud a series of 35 printed, phonetically irregular words. The number of correctly pronounced words is tallied and entered into a formula along with demographic characteristics to estimate WAIS-III Full Scale IQ [(86.664 + 0.145(age) − 6.136(sex) − 8.642(race) + 0.564(educ) + 0.862 + 1.140(HART), when age is coded in years; sex is coded 1 (male) or 2 (female); race is coded 1 (non-black) or 2 (black); education is coded in years as the highest grade completed] (46).

2.3.5 **Perceptual Comparison Test**

The Perceptual Comparison Test is designed to evaluate mental processing speed. It requires patients make speeded same/different distinctions in response to pairs of letter strings and pairs of patterns over the course of two 90-second trials. Scoring involves tallying the number of correct responses across the two trials, with higher scores reflecting faster processing speed (47).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologic proof or unequivocal cytologic proof (fine needle aspiration, biopsy, or two positive sputa) of SCLC

3.1.2 Patients must have limited disease SCLC after clinical staging evaluation: clinical TNM stages I-IIIB (i.e., confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement) according to AJCC 1997 staging manual to be consistent with RTOG 0212

3.1.3 Patients must have completed all of their prescribed chemotherapy at least one week prior to study entry; the plan for PCI should be such that PCI begins no more than 240 days from the start of induction chemotherapy

3.1.4 Patients must have achieved a complete response to induction chemotherapy (+/- thoracic radiation therapy) assessed according to local habits (at least on a chest xray) at the time of study entry.

3.1.5 Patients may have started consolidative chest irradiation by the time of study entry.

3.1.6 Age ≥ 18 years.

3.1.7 Zubrod performance status ≤ 1

3.1.8 No definitive evidence of brain metastases on brain CT scan or brain MRI < 1 month prior to study entry

3.1.9 Neurological function class of 0-2 (Appendix A)

3.1.10 Patients of childbearing potential (male or female) must practice adequate contraception due to possible harmful effects of radiation and chemotherapy on an unborn child.

3.1.11 Neuropsychological tests will be performed by a trained examiner.

3.1.12 Long-term follow up must be possible.

3.1.13 Patients must sign a study-specific informed consent prior to study entry.

3.1.14 All patients must be informed of the investigational nature of this study and must be given written informed consent in accordance with institutional and federal guidelines.

3.1.15 If a woman is of child-bearing potential, a negative urine or serum pregnancy test must be demonstrated prior to treatment. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for up to 12 weeks following the study. Should a women become pregnant or suspect she is pregnant while participating in this study she should inform her treating physician immediately.

3.2 Exclusion Criteria

3.2.1 Patients receiving prior external beam irradiation to the head or neck, including any form of stereotactic irradiation

3.2.2 Radiographic evidence of brain metastases and/or ipsilateral lung metastases/malignant pleural effusion

3.2.3 Planned concurrent chemotherapy or antitumoral agent during PCI

3.2.4 Concomitant malignancy or malignancy within the past five years other than nonmelanomatous skin cancer or carcinoma *in situ* of the cervix

3.2.5 Patients with minimal pleural effusion evident on CXR; minimal pleural effusion visible on chest CT is allowed.

3.2.6 Patients with epilepsy requiring permanent oral medication

3.2.7 Patients must not have a serious medical or psychiatric illness that would, in the opinion of the investigator, prevent informed consent or completion of protocol treatment, and/or follow-up visits.

3.2.8 Patients may not take Memantine. This is the only eligibility criterion that has been added to those of RTOG 0212, since some physicians might now prescribe Memantine. This medication would not have been given at the time of enrollment on RTOG 0212 and its administration could confound the results of this study.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

Patients will be accrued from Johns Hopkins Medical Institutes. Contact information for the Principal Investigator is listed on the cover page.

To register the patient, the following documents must be completed and faxed or e-mailed to the Study Coordinator:

- Copy of operative note and pathology report
- Source documentation verifying eligibility
- Eligibility checklist
- Signed patient consent form
- HIPAA authorization form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number

5. TREATMENT PLAN

5.1 Radiation

5.1.1 Radiation Simulation and Prescription

Patients will be treated to a total dose of 25 Gy with a once daily fractionation schedule of 2.5 Gy per fraction, administered five days per week. All patients will undergo CT simulation. They will be treated in a supine position using an aquaplast mask system for immobilization.

5.1.2 Hippocampal sparing

The hippocampus will be defined according to the RTOG atlas. It will be contoured on the simulation CT scan using a coregistered MRI as a reference. A treatment plan will be generated in which the mean radiation dose to the true hippocampus avoidance region is < 8 Gy

5.1.3 Equipment, Radiation Technique, and Dosimetry

Patients will be treated using a megavoltage linear accelerator with nominal beam energy of 6 MV. At least 90% of the whole brain should receive 90% of the prescription dose.

5.1.4 Beam Verification

Either on-line cone beam CT guidance or weekly portal imaging will be used for precise patient setup.

5.1.5 Therapy Interruption

For radiation therapy interruptions of up to and including 14 days, irradiation should be completed to the full prescribed dose. On the last day, the total number of fractions and the reasons for interrupting therapy must be documented

If radiation therapy interruption goes beyond 14 days, the patient will be removed from the protocol treatment. Resumption and completion of treatment will then be at the discretion of the radiation oncologist in consultation with the principal investigator. All patients who initiate protocol treatment will be followed per the study calendar.

5.1.6 Risks of Radiation

Short term toxicities of radiation therapy include fatigue, alopecia, erythema or irritation of the skin, dry skin, headaches, worsening of current symptoms, edema of brain requiring steroids, ear pain or discomfort, damage to the baby if patient is or becomes pregnant, seizures, neurologic deficits depending on tumor location, edema of brain requiring surgery, death. Long term toxicities include memory loss, cataracts, edema of the brain requiring steroids, vision loss, hearing loss, necrosis of brain requiring surgery second tumor or cancer caused by radiation.

5.2 Duration of Follow Up

Patients will be followed until death or the time of data analysis. Follow-up visits may be performed at outside hospitals and records sent to Johns Hopkins. Patients will undergo neurocognitive and QOL testing at baseline and 6 months and 12 months following PCI. They will have brain MRI every six months for 2 years following completion of PCI. It is preferred that MRIs be performed at Johns Hopkins Hospital but they may also be performed at outside facilities as necessary for insurance, scheduling, or other reasons.

5.3 Criteria for Removal from Study

Patients will be removed from the study for the following reasons:

5.3.1 Unacceptable toxicity from therapy. Toxicity must be appropriately documented.

5.3.2 Development of intercurrent, non-cancer related illness that prevents either continuation of therapy or regular follow-up.

5.3.3 The patient may decide to discontinue enrollment in the protocol at any time and for any reason.

All reasons for discontinuation of treatment must be documented.

6. STUDY CALENDAR

Baseline evaluations are to be conducted within approximately 30 days prior to initiation of radiation therapy. Patients will be evaluated at least weekly during the course of radiation therapy. Note that the study calendar is based on the ideal subject. The schedule should be followed as closely as realistically possible, but may be modified due to problems such as scheduling delays, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events.

	Baseline[6]	**Radiation**		**Follow-Up**				
		Week 1	**Week 2**	**Mo 6 Post RT**	**Mo 12 Post RT**	**Mo 18 Post RT**	**Mo 24 Post RT**	**Every 6 months until patient death**
Demographics	X							
Medical history	X							
Physical Exam	X			X	X	X	X	X
Vital signs	X			X	X	X	X	X
Height & Weight	X							
Performance status	X	X	X	X	X	X	X	X
Neurocognitive testing[1]	X			X	X			
Acute toxicity[2]	X	X	X					
Late toxicity[3]	X			X	X	X	X	X
Brain MRI	X			X	X	X	X	
Chest X-ray	X							
CT Simulation[4]	X							
Quality of Life[5]	X			X	X			
Radiation		X	X					
Pregnancy test	X							

[1]Neurocognitive testing consists of the tests outlined in Section 2.2 and Section 2.3

[2]RTOG Acute Morbidity Scoring Criteria

[3]RTOG Late Morbidity Scoring Criteria

[4]CT simulation without contrast will be performed and coregistered with T1 weighted MRI. Fused MRI may be the diagnostic MRI used prior to study entry or a dedicated treatment planning MRI.

[5]EORTC Quality of Life Questionnaire (QLQ-C30), Brain Cancer Module 20 (BN20) [6]Within approximately 30 days prior to registration

7. MANAGEMENT OF TOXICITY

7.1 Acute Toxicity

Acute morbidity potentially associated with therapy will be monitored and recorded on the Radiation Oncology On-Treatment Evaluation Form for all patients from baseline to 90 days after completion of radiation therapy. Grading will be according to the RTOG Acute Morbidity Scoring Criteria as follows:

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No change over baseline	Faint erythema, epilation, dry desquamation, or decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate erythema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Eye	No change over baseline	Mild conjunctivitis with or without scleral injection, increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids and/or antibiotics, dry eye requiring artificial tears, iritis with photophobia	Severe keratitis with corneal ulceration, objective decrease in visual acuity or in visual fields, acute glaucoma, panopthalmitis	Loss of vision (unilateral or bilateral)
Ear	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged over baseline.	Moderate external otitis requiring topical medication, serous otitis media, hypoacusis on testing only	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, not drug related	Deafness

CNS	No change over baseline	Fully functional status with minor	Neurologic findings present sufficient to	Neurologic findings requiring hospitalization	Serious neurologic impairment which included
		neurologic findings, no medications needed	require home care. Nursing care may be required. Medications including steroids and/or antiseizure agents	for initial management	paralysis, coma, or seizures, despite medications. Hospitalization required

7.2 Late Toxicity

Late toxicity will be recorded on the Radiation Oncology Follow-up form at each follow-up visit greater than 90 days post completion of radiation therapy. Grading will be according to the RTOG Late Radiation Morbidity Scoring Schema as follows:

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	None	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangioectasia	Ulceration	Death directly related to late

Subcutaneous Tissue	None	Slight induration and loss of subcutaneous fat	Moderate fibrosis but asymptomatic. Slight field contracture. <10% linear reduction	Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement	Necrosis	radiation effect
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurologic findings at or below cord level treated	Mono-, para-, quadra-plegia	
Brain	None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headaches, severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures, paralysis, coma	
Eye	None	Asymptomatic cataract, minor corneal ulceration of keratitis	Symptomatic cataract, moderate corneal ulceration, minor retinopathy or glaucoma	Severe keratitis, severe, retinopathy or detachment, severe glaucoma	Panopthalmitis, blindness	

8. STATISTICAL CONSIDERATIONS

8.1 Study Design/Endpoints

8.1.1 **Study Design**

This is a single-arm phase II prospective study of patients with limited stage SCLC to evaluate neurocognitive outcomes following hippocampal-sparing PCI (25 Gy in 10 fractions) relative to a historical control receiving standard PCI (RTOG 0212 arm receiving 25 Gy in 10 fractions).

8.1.2 **Primary Endpoint**

The primary endpoint for this study is cognitive function, specifically memory, six months from the completion of PCI as measured by the HVLTR-delayed recall.

8.1.3 **Secondary Endpoints**

8.1.3.1 Cognitive function, specifically memory, at 12 months from PCI as measured by the HVLT-R delayed recall

8.1.3.2 A composite cognitive function endpoint using the validated Reliable Change Index (48,49) to include the Controlled Word Association Test (COWAT), the HVLT-R-delayed recall, the HVLT-R-trials 1-3 and Trail Making Tests part A and B (TMT)

8.1.3.3 Quality of Life (QOL) as measured using the EORTC Quality of Life Questionnaire (QLQ-C30) and Brain Cancer Module 20 (BN20) at baseline, 6 months, and 12 months

8.1.3.4 Development of brain metastases at 2 years following completion of radiation therapy will be coded as a binary variable (yes or no)

8.1.3.5 Development of leptomeningeal carcinomatosis at 2 years following completion of radiation therapy will be coded as a binary variable (yes or no)

8.1.3.6 Overall survival

8.2 Sample Size/Accrual Rate

8.2.1 **Sample Size**

The sample size calculations address the specific primary hypothesis that patients treated with hippocampal-sparing PCI for SCLC will not experience as much decline in neurocognitive function as reported for the historical control of RTOG 0212 receiving the same dose of conventional PCI. The clinically meaningful difference and associated standard deviation are based on the RTOG study and the work of Meyers et al. The latter reported a mean score in the HVLT-R delayed recall change in patients treated only with whole-brain radiation therapy of 0.87 (from 7.04 at baseline to 6.17 at 6 months), with a standard deviation of 3.19. In RTOG 0212, the average decline in HVLT memory at six months is 1.13 (sd=2.80). We expect patients receiving hippocampal-sparing PCI to experience a smaller decline in cognitive function from baseline to six months, compared to the historical control group. The

onesided statistical hypothesis test is as follows: H0: $\Delta\mu = 1$ vs. HA: $\Delta\mu < 1$, where $\Delta\mu$ is the mean change in HVLT scores from baseline to 6 months for patients receiving hippocampal-sparing PCI (baseline minus 6-month score). With change measured in 100 patients, we will have 90% power to detect a meaningful change (0.88 points less change in HVLT scores over 6 months, i.e., mean change of 0.12) in our treated group with a one-sided test at the 5% level of significance, assuming a standard deviation of around 3. Similarly, we will have 80% power with a one-sided 5% level test to detect a mean change of 0.75 (with standard deviation equal to 3). We will enroll 125 patients to allow for up to 20% of patients to be not evaluable at 6 months.

8.2.2 **Accrual**

We anticipate enrollment of approximately 2 patients per month to the protocol with accrual completed in approximately 5 years.

8.3 Stratification Factors

There will be no stratification factors upon initial enrollment in the protocol.

8.4 Statistical Methods of Analysis

The primary objective of this study is to evaluate change in cognitive function as measured by the HVLT-R-delayed recall. We will compare hippocampal-sparing PCI to the historical experience of patients who received standard PCI in RTOG 0212. Each patient will be assessed pre-therapy and post-therapy, with the change at 6 months being the primary endpoint. Patient scores on the HVLT-R delayed recall section are whole numbers, ranging from 0 to 12, with lower scores indicating declining cognitive function. The score itself refers to the number of words a patient can recall from a list of 12 words. Therefore, if a patient initially is able to recall 8 words pre-therapy and is, at 6 months, able to only recall 6 words, their change in score would be 2. The primary endpoint (change score) is the difference between the pre-therapy and post-therapy scores. A change score of zero indicates preserved cognitive function. Change scores from -1 to -12 indicated improved cognitive function and are not expected. Summary statistics of the change scores, such as means, medians, standard deviations, and ranges will be listed separately by treatment (sparing PCI and historical standard PCI groups). We hypothesize that change scores from pre-therapy to 6 months post-therapy is lower among patients receiving hippocampal-sparing PCI compared to the historical PCI group in the RTOG study. We will use the Wilcoxon Signed-Rank test to test the change in HVLT-R scores over six months, relative to the expectation based on the historical information, according to the statistical hypotheses given in the sample size section (Section 8.2.1).

The analysis of the secondary outcome of HVLT-R-delay score change at 12 months will be performed as described above for the primary outcome. In addition, we will examine if there appears to be a trend to increasing change score over time for the treatment groups.

The Reliable Change Index will measure meaningful change between baseline and 6 and 12 months for HVLT–R, Trail Making Test part A and B, COWAT. The Reliable Change Index is derived from the standard error of measurement (SEM) for each test in the battery. The SEM is calculated from the test–retest reliability (r) and the standard deviation of test scores (SD): SEM=sqrt[SD×(1-r)]. The standard error of the difference (SEdiff) is then calculated as SEdiff =sqrt[2×(SEM)^2]. For each test in the neurocognitve battery, the Reliable Change Index value will be determined *a priori* for that particular test to determine whether a change from baseline is clinically meaningful.

We will compute summary statistics and compare our patients to the historical controls based on tests that are appropriate for the type of data.

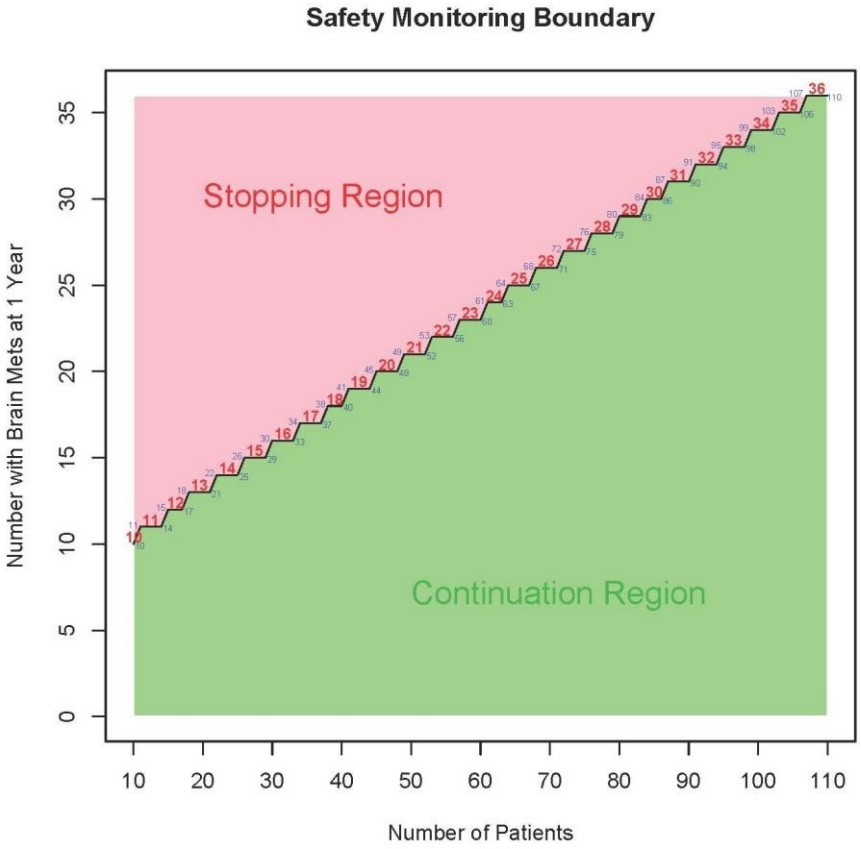
Quality of Life on our study will be assessed using EORTC Quality of Life questionnaire (QLQ-C30) and the Brain Cancer Module 20 (BN 20) pre-therapy, at 6 months, and at 12 months after therapy. For each module, summary statistics of the scores will be reported for each study time point. Change scores in quality of life from pre-therapy to post-therapy will be calculated and tested via paired t-tests for the hippocampal-sparing PCI treatment group. We may fit mixed-effect models to explore changes in quality of life assessments over time.

We will tabulate development of brain metastases within 0.5 mm of the hippocampus. We will report adverse events based on CTCAE v4.0 by frequency tables. We will test the proportion of patients who develop brain metastases via binomial test. Overall survival will be measured from the start of treatment to death or last followup. For subjects who alive or lost follow up at the end of study, overall survival will be censored at the last follow up date. Overall survival probabilities will be estimated via the Kaplan-Meier method; median survival and 95% confidence interval via Greenwood's formula for variance will be reported.

8.5 Safety Monitoring

We have included a formal statistical stopping rule for monitoring the occurrence of brain metastases. The article describing RTOG 0212 reported that the raw proportion of patients with brain metastases is 22% (29/131) at 1 year for the group getting 2.5 Gy in 10 fractions. We established a monitoring rule that will recommend considering stopping the study if there appears to be high probability that the risk of brain metastasis at 1 year is above 22%. Specifically, if the posterior probability that the risk exceeds 25% of brain metastasis by 1 year after treatment is 75% or greater (3:1 odds), then we will consider stopping the study. In this calculation, the number of patients with brain metastasis at 1 year is a binomial random variable. The prior

distribution for the risk of brain metastasis by 1 year is beta with parameters 29 & 102. Although we can apply the stopping rule calculation after every patient, we may monitor in batches of 10. The stopping rule is illustrated in the figure below.



9. ADVERSE EVENTS AND RECORDING

9.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding). In clinical trials, from the time of signing an informed consent, an AE may include an undesirable medical condition, occurring at any time, even if no trial treatment has been administered.

9.2 Radiation Related Adverse Events

All radiation related adverse events will be recorded on the local toxicity case report forms.

10. SERIOUS ADVERSE EVENTS (SAE) AND REPORTING

10.1 Serious Adverse Event

10.1.1 Definition of Serious Adverse Event

A serious adverse event is an AE occurring at any point during a clinical trial that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is a congenital abnormality or birth defect.
- Unexpected event that cause harm or place person at a greater risk of harm than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

10.2 SAE Reporting Guidelines for Johns Hopkins Hospital

All SAE, with the exception of death, must be reported to the Johns Hopkins Hospital Institutional Review Board (JH-IRB) within 10 working days of the principal investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention, must be reported to the JH-IRB within 3 working days of when the principal investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported to the JH-IRB within 10 working days from the time the principal investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the principal investigator does not have to report the death until the time of continuing review.

11. DATA AND SAFETY REPORTING/ REGULATORY CONSIDERATIONS

11.1 Data Quality Monitoring

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (09/22/2011). The Clinical Research Office QA Group will perform an audit at the

end of the first year and periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

In addition to the ongoing quality assurance evaluations for each individual at the time of treatment, there will be regular meetings between the principal investigator, a medical oncologist, and the study coordinator to assess the data quality. This meeting will occur annually and a monitoring report of the findings will be submitted to the Data Safety Monitoring Committee on an annual basis. Any protocol deviations or violations will be documented in the monitoring reports. The review will include: consent forms, eligibility criteria, protocol compliance, treatment administration, toxicity reports, response, regulatory compliance, case report forms (completeness as well as verifying that information coded on the case report forms are supported by source documents), and all other materials related to the trial. In addition, this trial will be audited annually by the central clinical research office at Johns Hopkins.

11.2 Data Safety Monitoring

All SAE's and major protocol deviations that occur at Johns Hopkins Hospital will be submitted to the Sidney Kimmel Comprehensive Cancer Center Data Monitoring Committee for review per Institutional guidelines. In addition, the overall study safety and potential activation of the study's early stopping rules will be assessed at the time of every SAE. The Data Safety Monitoring Committee with review this trial for safety annually.

11.3 Data Reporting

11.3.1 Method

Data will be collected on Case Report Forms (CRF's). These CRF's will be completed by the Study Coordinator. The CRF's for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the protocol. The Clinical Research Office (CRO) will audit this trial per their standards to ensure and verify that the protocol is being carried out according to plan as well as to verify that data included on subject CRF's are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the IRB of record for review.

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Appendix A:
RTOG Neurological Function Class

1 Able to work and perform normal activities. Neurological findings minor or absent.

2 Able to carry out normal activities with minimal difficulty. Neurological impairment does not require nursing care or hospitalization

3 Seriously limited in performing normal activities; requires nursing care or hospitalization. Patient confined to bed or wheelchair or with significant intellectual impairment.

4 Unable to perform even minimal normal activities. Requires hospitalization and/or constant nursing care. Patient unable to communicate or in coma.

Appendix B

Performance Status Criteria

ECOG/Zubrod Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix C

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix D

ENGLISH

EORTC QLQ - BN20

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

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

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