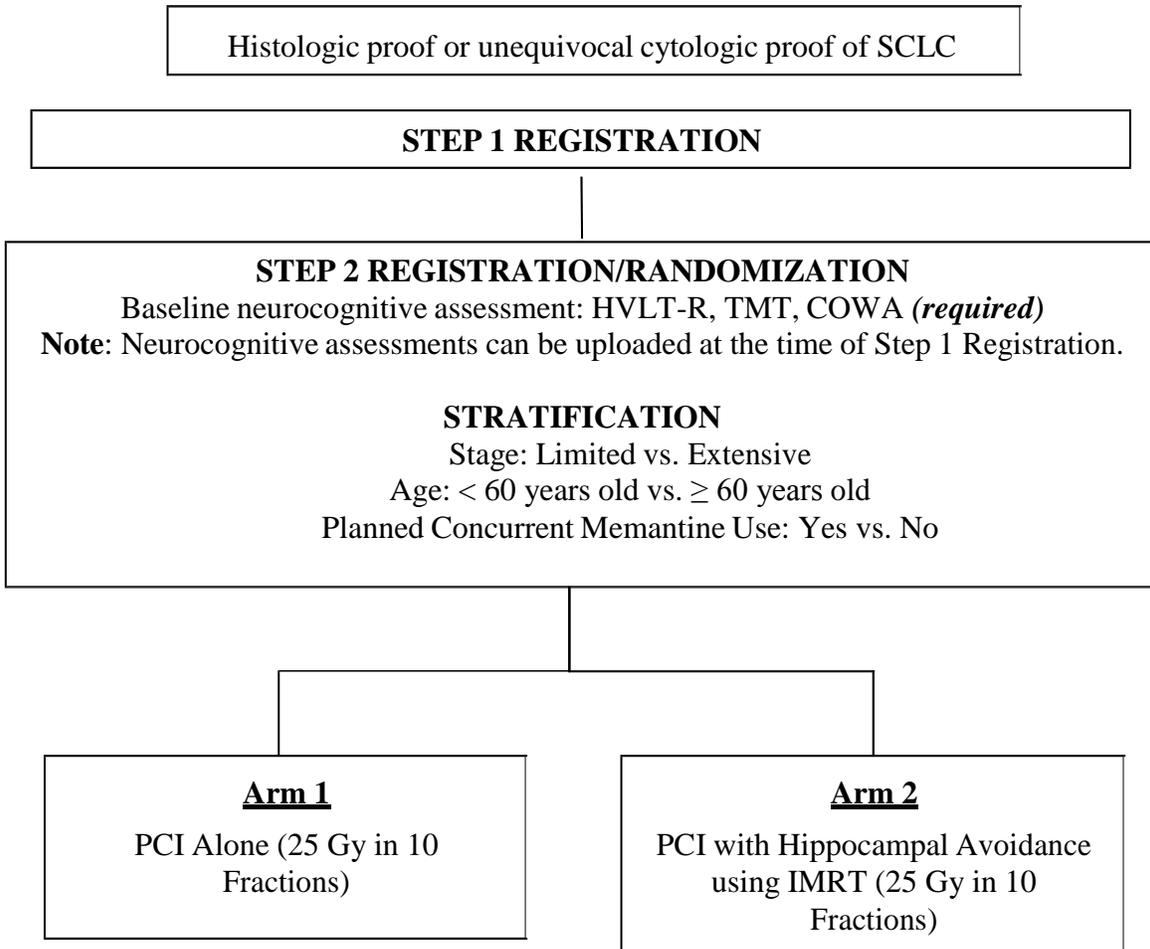


**NRG ONCOLOGY  
NRG-CC003**

**A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer**

**SCHEMA**



**NOTE:** If the trial proceeds to the phase III component, all patients enrolled on the randomized phase II component will be included in the primary and secondary endpoint analysis of the phase III component.

- 1) An overall sample size of 304 randomized SCLC patients for this phase IIR/III remains feasible;
- 2) The use of concurrent rather than historical controls permits more accurate comparison of both phase IIR and phase III endpoints;
- 3) The trial closure when the phase IIR component reaches accrual provides sufficient follow-up time to assess 12-month intracranial relapse risk before proceeding with the phase III component;
- 4) Utilization of the cognitive outcomes data from the phase IIR component to address the phase III primary and secondary endpoints limits overall sample size, while providing greater power for the phase III endpoints.

To remain consistent with the memory-specific toxicity of cranial irradiation observed in prior clinical trials and memory-specific benefits of hippocampal avoidance demonstrated in RTOG 0933, this proposed phase IIR/III study will utilize HVL-T-R, the same memory-specific measurement tool used in prior studies, as the primary endpoint of the phase III component.

HVL-T-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 test involves memorizing a list of 12 targets for 3 consecutive trials (immediate recall), recalling the 12 targets after a 20-minute delay (Delayed Recall), and then identifying the 12 targets from a list of semantically related or unrelated items (delayed recognition). Raw scores are derived for total recall, delayed recall, and a delayed recognition discrimination index. Each patient will serve as her/his own control, as the difference in HVL-T-R scores obtained at baseline and post-treatment intervals will be calculated with the Reliable Change Index (RCI) to define deterioration (Jacobsen 1991).

Other cognitive instruments, including the Controlled Oral Word Association (COWA) and the Trail Making Test (TMT) Parts A and B, also will be used to complement HVL-T-R in defining the secondary endpoint of time to cognitive failure. This battery of instruments has been selected based on accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general cognitive status, minimal practice effects, and brevity of the overall battery. Additionally, similar variations of this cognitive testing battery have been utilized in multiple cooperative group trials.

### 3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

**Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted.** For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the protocol title page). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the protocol title page).

#### 3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

- 3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
- 3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the therapy (PCI alone or PCI with hippocampal avoidance) part of the trial.
- 3.1.3 Submission of serum and whole blood is strongly encouraged for all patients. Samples will be submitted for banking for the translational research portion of this protocol and for future studies. (See Section 10 for further details).

#### 3.2 Eligibility Criteria

**A patient cannot be considered eligible for this study unless ALL of the following conditions are met.**

##### Prior to Step 1 Registration

- 3.2.1 Histologic proof or unequivocal cytologic proof (fine needle aspiration, biopsy or two positive sputa) of SCLC within 250 days prior to Step 1 registration;
- 3.2.2 Patients must be registered on study no earlier than 7 days and no later than 56 days prior to Step 1 registration after completing chemotherapy (+/- thoracic radiotherapy).
- 3.2.3 Patients must have a three-dimensional (3D), T1-weighted, spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan without and with gadolinium contrast-enhanced T1-weighted axial, coronal, and sagittal sequence acquisitions and standard T2-weighted axial and coronal fluid-attenuation inversion recovery (FLAIR) sequence acquisitions within 56 days of Step 1 registration. To yield acceptable image quality, the pre-contrast-enhanced should have a resolution of 1 x 1 x 1.2 mm and should follow the protocols established by the Alzheimer's Disease Neuroimaging Initiative (ADNI). Performance of this sequence at a 3 Tesla field strength is recommended. Vendor-specific versions of this sequence are available for download from the ADNI website, <http://www.adni-info.org/scientists/MRIProtocols.aspx>. Sites may contact the Imaging Co-Chair, Dr. Tammie Benzinger, for further information or assistance if needed. To yield acceptable image quality, the gadolinium contrast-enhanced T1-weighted scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. The associated coronal and sagittal sequences can be up to 2.5 mm in slice thickness. This imaging is considered

standard of care.

**Note:** The MRI study is mandatory irrespective of randomization to the experimental or control arm of this study.

- 3.2.4** Prior to chemotherapy +/- thoracic radiotherapy, patients must be defined as limited-stage or extensive-stage SCLC after clinical staging evaluation involving the following:
- History/physical examination;
  - CT of the chest and abdomen with contrast (does not have to be done if the patient has had a PET/CT scan prior to initiating chemotherapy or thoracic radiotherapy);
  - MRI of the brain prior to initiating chemotherapy or thoracic radiotherapy;
  - For patients without evidence of extensive-stage SCLC on chest and abdomen CT and brain MRI, a PET/CT or bone scan is required to confirm limited-stage SCLC.
- 3.2.5** After chemotherapy, patients must be restaged within 56 days prior to Step 1 registration using the same diagnostic work-up as required pre-chemotherapy (see Section 3.2.4). Repeat PET/CT or bone scan is not required. Patients must have:
- History/physical examination;
  - No CNS metastases (Repeat MRI required; see Section 3.2.3 for details);
  - Radiographic partial or complete response to chemotherapy in at least one disease site using RECIST criteria;
  - No progression in any site.
- 3.2.6** Zubrod performance status 0-2 within 30 days prior to Step 1 registration;
- 3.2.7** Age  $\geq 18$ ;
- 3.2.8** Women of childbearing potential must have a negative qualitative serum pregnancy test  $\leq 14$  days prior to Step 1 registration.
- 3.2.9** Patients who are primary English or French speakers are eligible.
- 3.2.10** Patients must sign a study-specific informed consent prior to study entry.

#### Prior to Step 2 Registration

- 3.2.11** The following baseline neurocognitive assessments must be completed and uploaded within 10 calendar days after Step 1 registration: HVLТ-R, TMT, and COWA. The neurocognitive assessments will be uploaded into the NRG Oncology RAVE System for evaluation by Dr. Wefel. Once the upload is complete, a notification will be sent to the site to proceed to Step 2. **Note:** Completed baseline neurocognitive assessments can be uploaded at the time of Step 1 registration.
- 3.2.12** Patients must have a baseline raw score greater than 2 on the HVLТ-R Delayed Recall to be determined by the Neurocognitive Co-Chair, Dr. Wefel.

### **3.3 Ineligibility Criteria**

*Patients with any of the following conditions are NOT eligible for this study.*

- 3.3.1** Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields;
- 3.3.2** Radiographic evidence of CNS metastases;
- 3.3.3** Radiographic evidence of hydrocephalus;
- 3.3.4** Planned concurrent chemotherapy or anti-tumor agent during PCI;
- 3.3.5** Concomitant invasive malignancy or invasive malignancy within the past five years other than non-melanomatous skin cancer; history of *in situ* carcinoma (e.g. ductal carcinoma *in situ* of breast, *in situ* carcinoma of the cervix, vulva or larynx) is permitted.
- 3.3.6** Contraindication to MR imaging, such as implanted metal devices or foreign bodies or

severe claustrophobia;

**3.3.7** Severe, active comorbidity, defined as follows:

- 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;
- HIV positive with CD4 count < 200 cells/microliter;
  - **Note:** Patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count  $\geq$  200 cells/microliter within 30 days prior to Step 1 registration.
  - **Note:** HIV testing is not required for eligibility for this protocol.

**3.3.8** Pregnant or lactating women or 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.