

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0212

### A PHASE II/III RANDOMIZED TRIAL OF TWO DOSES (PHASE III-STANDARD VS. HIGH) AND TWO HIGH DOSE SCHEDULES (PHASE II-ONCE VS. TWICE DAILY) FOR DELIVERING PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH LIMITED DISEASE SMALL CELL LUNG CANCER

(Companion study to the International Cranial Irradiation Trial, PCI 01-EULINT1)

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RTOG Headquarters/Statistical Unit  
215-574-3189

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.

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 0212

#### A PHASE II/III RANDOMIZED TRIAL OF TWO DOSES (PHASE III-STANDARD VS. HIGH) AND TWO HIGH DOSE SCHEDULES (PHASE II-ONCE VS. TWICE DAILY) FOR DELIVERING PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH LIMITED DISEASE SMALL CELL LUNG CANCER

#### SCHEMA (4/3/03)

<b>S T R A T I F Y</b>	<b>Age</b>	<b>R A N D O M I Z E</b>	<b>Prophylactic Cranial Irradiation (PCI)</b>
	1. $\leq 60$		<b>Arm 1:</b> 2.5 Gy once daily, M-F, in 10 fractions for a total of 25 Gy (50% of patients)
	2. $> 60$		<b>Arm 2:</b> 2.0 Gy once daily, M-F, in 18 fractions For a total of 36 Gy (25% of patients)
	<b>Interval from induction therapy to randomization</b>		<b>Arm 3:</b> 1.5 Gy twice daily, M-F, in 24 fractions for a total dose of 36 Gy (25% of patients)
	1. $\leq 90$ days		
	2. 91-180 days		
	3. 181-240 days		

#### **Eligibility:** (See Section 3.0 for details) [4/3/03]

- Histologic proof or unequivocal cytologic proof of SCLC
- Limited disease SCLC, clinical stages I-IIIB (AJCC, 1997), whatever the induction treatment
- Patients must have completed all prescribed chemotherapy  $\geq 1$  week prior to study entry before beginning PCI
- Patients must have achieved a complete response to induction chemotherapy (+/- thoracic radiation therapy) according to local habits (at least on a chest x-ray) at the time of study entry.
- Patients may have started consolidative chest irradiation by the time of study entry.
- Zubrod performance status  $\leq 1$
- Patients must have a normal brain CT scan or MRI  $< 1$  month prior to study entry.
- Neurological function class 1 or 2 (Appendix II)
- Absolute granulocyte count  $\geq 1,500 \mu\text{l}$ , HGB  $\geq 10.0 \text{ gm}/100\text{ml}$ , and platelet count of  $\geq 75,000 \mu\text{l}$  are required;
- Patients of childbearing potential must practice adequate contraception.
- A "certified" test administrator (Section 11.4) is required for administration of the neuropsychological tests.
- No radiographic evidence of brain metastases
- No minimal pleural effusion or lung metastases evident on CXR; minimal pleural effusion visible on chest CT is allowed.
- No prior external beam irradiation to the head or neck
- No current or past malignancy within the past five years other than non-melanomatous skin cancer or carcinoma *in situ* of cervix
- 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.
- Patients must sign a study-specific consent form prior to study entry.

**Required Sample Size: 264**

RTOG Institution # \_\_\_\_\_

RTOG 0212

**ELIGIBILITY CHECKLIST (8/6/03)**

Case # \_\_\_\_\_

(page 1 of 2)

- \_\_\_\_\_(Y) 1. Is there histologic or unequivocal cytologic proof of SCLC?
- \_\_\_\_\_(Y) 2. Does the patient have limited disease SCLC Stage I-IIIb based on clinical staging?
- \_\_\_\_\_(Y) 3. If Stage IIIb, is disease confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion and N3 disease based on contralateral hilar or contralateral supraclavicular involvement?
- \_\_\_\_\_(Y) 4. Was prior chemotherapy completed at least 1 week prior to study entry?
- \_\_\_\_\_(Y) 5. Has patient attained a complete response to induction chemotherapy (+/- thoracic radiotherapy) at the time of study entry?
- \_\_\_\_\_(≤1) 6. Zubrod Performance Status?
- \_\_\_\_\_(Y) 7. Did the patient have a normal brain CT scan or MRI < 1 month prior to study entry?
- \_\_\_\_\_(I or II) 8. Neurologic Function Status?
- \_\_\_\_\_(Y) 9. Are hemoglobin, ANC, and platelet values within the parameters stated in Section 3.1.9?
- \_\_\_\_\_(N) 10. Has the patient received any prior external beam radiotherapy to the head or neck, or prior stereotactic radiotherapy?
- \_\_\_\_\_(N) 11. Is there evidence of brain metastases and/or ipsilateral lung metastases/malignant pleural effusion on radiograph?
- \_\_\_\_\_(N) 12. Is there concurrent malignancy or malignancy within the last five years other than non-melanomatous skin cancer or carcinoma *in situ* of cervix?
- \_\_\_\_\_(N) 13. Is there evidence of pleural effusion or lung metastases on CXR?
- \_\_\_\_\_(Y) 14. If patient is of childbearing potential, has he/she agreed to use an adequate form of contraception?
- \_\_\_\_\_(N) 15. Does patient have a serious medical or psychiatric illness that would prevent informed consent or completion of protocol treatment and or follow-up visits?

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_(Y) 3. Is the patient eligible for this study?

**(Continued on next page)**

RTOG Institution # \_\_\_\_\_

RTOG 0212

**ELIGIBILITY CHECKLIST (12/9/03)**

Case # \_\_\_\_\_

(page 2 of 2)

- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- \_\_\_\_\_ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Specify the patient's age ( $\leq 60$  or  $> 60$ )
- \_\_\_\_\_ 17. Specify the interval from start of induction therapy to randomization ( $\leq 90$  days, 91-180 days, 181-240 days)
- \_\_\_\_\_ 18. Treatment Start Date
- \_\_\_\_\_ 19. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 \_\_\_\_\_

## **1.0 INTRODUCTION**

Small cell lung cancer (SCLC) accounts for approximately 20% of all patients with lung cancer. Approximately 35% of these patients are staged as having limited disease (LD). There has been reported improvement in overall survival (23% at five years) for this latter group of patients with concurrent chemotherapy and consolidative chest radiotherapy.<sup>1</sup> However, it has also been shown that long-term survivors have at least a 50% brain metastatic rate.<sup>2</sup> A recently reported meta-analysis of seven prospectively randomized trials demonstrated both an overall and disease-free survival advantage concerning patients with limited disease small cell lung cancer who received prophylactic cranial irradiation (PCI) versus those not undergoing PCI.<sup>3</sup> In this meta-analysis, the dose fractionation schedule of PCI was not uniform. However, there was a statistical trend in the reduction of brain metastases in the group of PCI patients who received a total radiation dose of at least 36 Gy at a daily fraction size of 2 Gy. A major weakness of the meta-analysis centers upon the lack of any assessment for the incidence of chronic neurotoxicity.

It is the concern for potential late effects on the brain following PCI that has steered some clinicians away from recommending its routine delivery.<sup>4</sup> Two major factors that have been implicated in the development of chronic neurotoxicity include the use of concurrent chemotherapy with PCI<sup>5</sup> and the presence of a para-neoplastic syndrome.<sup>6</sup> However, one report observed no significant neurological abnormalities in thirteen long-term survivors with SCLC who received PCI, with the exception of mild cerebral atrophy being detected.<sup>7</sup>

The use of altered fractionated radiotherapy has been evaluated in several types of tumors as a means of reducing the incidence of late normal tissue effects.<sup>8</sup> Since 1992, a single institution has been evaluating, within the confines of a phase II trial, the use of twice-daily PCI (1.5 Gy per fraction) for patients with LD SCLC who had previously achieved a complete response to combination chemotherapy and thoracic irradiation.<sup>9</sup> In this non-randomized study, 15 patients received PCI, while 12 deferred cranial irradiation of their own volition. With a median follow-up of 20 months, disease-free survival at 2 years was 54% versus 0% for the irradiated and non-irradiated cohorts, respectively ( $P = 0.013$ ). Overall, two-year survival was 62% with twice-daily PCI versus 23% without PCI ( $P = 0.032$ ). Moreover, no significant neurological deterioration was found in the PCI group. The small sample size of this single institutional study precluded a statistical analysis; however, there were 0 out of 7 patients (0%) who had brain relapses with a total dose of 36 Gy versus 2 out of 8 (25%) brain metastases in those receiving only 30 Gy. The selection of the 1.5 Gy fraction size was empirically derived.

If one assumes no tumor proliferation and uses an alpha/beta ratio of 2 for CNS tissue and 10 for tumor cells, then a fractionation regimen of 24 fractions at 1.5 Gy per fraction gives a CNS BED (biologically equivalent dose) of 63.0 and a tumor BED of 41.4. This may be compared to a once-daily fractionated regimen of 18 fractions at 2.0 Gy per fraction that yields a 57.6 CNS BED and a 40.3 tumor BED. Thus, the ratio of tumor BED/CNS BED for the twice-daily PCI schedule (36.0 Gy total radiation dose) versus the once-daily PCI schedule (36.0 Gy total radiation dose) is 0.66 and 0.70, respectively. Both of these high dose (HD) PCI regimens also may be compared to the standard dose (SD) PCI schedule of the Radiation Therapy Oncology Group (RTOG) of 10 fractions at 2.5 Gy per fraction (25 Gy total radiation dose) that results in a CNS BED of 56.3, a tumor BED of 31.3, and a tumor BED/CNS BED of 0.56. In other words, HD PCI (twice-daily) should be 18% and HD PCI (once-daily) should be 25% "better" than the standard dose PCI employed by RTOG in its SCLC trials without any significant increase in overall treatment time (Personal Communication, Jack Fowler). Therefore, a randomized trial is appropriate to determine whether HD PCI is in fact "better" than SD PCI for improving the outcome of patients with LD SCLC who are complete responders. Moreover, if HD PCI should be found to have a positive effect on this group of patients, then it is appropriate to determine if the fractionation schedule of HD PCI has further impact on the advantage of increased total dose without compromising brain functioning.

It must be pointed out that there is an ongoing study (The International Prophylactic Cranial Irradiation Trial – PCI 01 EULINT1) that is currently being coordinated by the Institut Gustave-Roussy (IGR), which is a phase III trial to evaluate "high" versus "standard" dose PCI in limited small cell lung cancer complete responders. The SD of PCI in this trial is 25 Gy in 10 daily fractions over 12 days. The HD arm can be (at institutional choice) either 36 Gy in 18 daily fractions over 24 days or 36 Gy in 24 fractions using twice-daily fractionation over 16 total days. The selection of twice-daily PCI as one of the treatment options in the HD arm was not based on any direct institutional experience with this fractionation regimen of PCI in Europe. Instead, its inclusion in the study arm was derived only from the extrapolation of the data on

“altered fractionation in the cranial irradiation of primary brain tumors, brain metastases, and CNS lymphomas”.

Since the cumulative doses in the SD PCI and HD PCI arms in the International PCI trial were equivalent to those in the proposed RTOG PCI study, the Chair of the RTOG Lung Committee was directly invited in October 1999 by a representative of the IGR to participate in the international effort (Personal Communication, Roger Byhardt). After considerable deliberation among members of the RTOG Lung Committee, a decision was made at the January 2000 Semi-Annual Meeting of the RTOG to proceed with an independent RTOG study. The main reasons for this decision at that time were as follows: 1) All data for centers participating in the International PCI study would have to be analyzed by the Department of Biostatistics at the IGR without independent analysis by the statistical group of the RTOG; 2) There was actual experience in the United States supporting the use of twice-daily PCI<sup>9</sup> which obviated the need to include a choice for “high” dose PCI; and 3) The International PCI trial did not include formal neuropsychological testing to more accurately evaluate chronic neurotoxicity.

However, at the recommendation of the National Cancer Institute, the current Chair of the RTOG Lung Committee met in February 2002 with representatives of the IGR to re-explore the feasibility of collaboration between the developing RTOG PCI study and the International trial (Personal Communication, Hak Choy). The results of this meeting determined that such a joint venture should be undertaken as long as there was randomization in the RTOG study as follows: patients are assigned to SD PCI, once daily HD PCI, or twice daily HD PCI (See Section 13.2, “Overview”). The randomization of any patients entered in the United States will be carried out through RTOG Headquarters. The patient assignments then will be sent regularly to the International PCI trial data center. Since most of the primary and secondary endpoints of the U.S. and European studies are similar (except for RTOG’s evaluation of chronic neurotoxicity), whenever possible there will be standardization of eligibility requirements, patient assessments, data collection instruments, and treatment parameters.

## **1.2 Neurotoxicity/Neuropsychological Testing**

**1.2.1** The LENT-SOMA scale will be compared to the pre-PCI scale on a yearly basis in order to evaluate possible late CNS sequelae from radiation. After baseline studies have been completed prior to PCI, neurotoxicity in this RTOG study will be evaluated by means of a neuropsychological test battery to be administered pre-treatment, and at six and twelve months for the first year post-treatment, then annually thereafter. Selection of the measures used for evaluating cognition focused on brevity, ease of training and use, as well as usefulness as an outcome measure based on the existing literature. In addition, tests were selected because they have demonstrated sensitivity in cancer clinical trials. In brain tumor trials, these tests predict time to tumor progression 30% earlier than MRI evidence. They are widely used, standardized psychometric instruments with published normative data and the availability of alternate forms of the test procedure (to reduce practice effects). A summary and description of the proposed procedures is provided in Appendix VII.

## **1.3 Quality of Life (7/8/04)**

**1.3.1** While a recent meta-analysis has demonstrated a small survival benefit with prophylactic cranial irradiation (PCI)<sup>10</sup> in small cell lung cancer (SCLC), much controversy remains regarding its potential for neurotoxicity which may negatively impact on quality of life (QOL). In a national survey of oncologists in the United States, Cmelak et al.<sup>11</sup> found that while 38% of responding medical oncologists felt that PCI improved survival for limited stage SCLC patients, only 11% believed PCI actually improved quality of life. Among radiation oncologists, 48% felt that PCI improved survival, whereas 36% felt that it improved quality of life. Similarly, medical oncologists believed PCI causes late neurocognitive sequelae more often than the radiation oncologists (95% versus 84%,  $p < 0.05$ ), with impaired memory (37%) chronic fatigue (19%), and loss of motivation (13%) as the most commonly seen side effects. Differences of opinion remain regarding not only the use of PCI, but also the most appropriate radiation dose and fractionation scheme to employ.

In a retrospective review, Tai et al.<sup>12</sup> assessed quality-adjusted survival utilizing the QTWiST methodology (quality time without symptoms and toxicity) in 98 patients in complete remission from SCLC who did or did not receive PCI. They reported a significant difference in the mean QTWiST survival between the 2 groups, favoring the PCI patients ( $p < 0.01$ ). However, this study did not incorporate patient-derived quality of life information.

Patient-derived quality of life can be a critical endpoint when comparing treatment options that may have similar survival outcomes. For example, a randomized trial<sup>13</sup> found no difference in survival in patients with low grade gliomas who received high dose radiation (59.4 Gy) versus low dose radiation (45 Gy). However, patients who received high dose radiation reported lower levels of functioning and more symptom burden over time. The differences were statistically significant for insomnia and fatigue/malaise soon after treatment. Interestingly, impairment of leisure time and emotional functioning were most affected about one year after treatment. Despite similar survival results, the high dose radiation in this study appeared to adversely impact on patients' QOL compared to the low dose brain RT.

There is limited information regarding the impact of PCI on QOL and cognitive functioning. Two randomized controlled trials<sup>14-15</sup> have examined cognitive functioning as an outcome, one of which also examined quality of life.<sup>15</sup> Arriagada et al.<sup>14</sup> randomized 300 patients with SCLC in complete remission to PCI versus observation. Neurologic examinations were performed to assess cranial nerves, sensory functioning, tendon reflexes, cerebellar function, walking, mood, and higher functions. No statistically significant differences were noted between the PCI and observation groups in the relative risks of two-year cumulative incidence of neuropsychological changes. A second prospective study which examined quality of life in addition to cognitive functioning was reported by Gregor et al.<sup>15</sup> Of 314 patients in the study, 136 patients (84 PCI, 52 control) were included in the evaluation of quality of life and cognitive functioning. Psychometric assessment included auditory mental tracking, perceptual organization, visual memory, memory span, and verbal learning. The National Adult Reading Test was administered at the time of randomization and the Paced Auditory Serial Addition Task, Rey Osterrieth Complex Figure Test, and Auditory Verbal Learning Tests were administered at randomization, 6 months, and 12 months. At these time points, QOL (physical and psychological symptoms and activities of daily living), anxiety, and depression were also assessed using the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale.

Gregor et al. reported that new cognitive impairments were observed at 6 and 12 months but that there were no notable differences between the PCI and control groups.<sup>15</sup> However, statistical comparisons were not provided. Regarding quality of life, symptoms showing the greatest deterioration from baseline to 6 months included tiredness, lack of energy, irritability, decreased sexual interest, shortness of breath, and cough. Progression of these symptoms was greater in the control group. On the Rotterdam Symptom Checklist, 92% of patients reported normal or near normal activities of daily living at baseline, 6 and 12 months. There was no difference in the Hospital Anxiety and Depression Scale between the PCI and control groups, although no significant values were provided. Longer QOL follow up is not available such that there is insufficient evidence to comment on the long-term effects of PCI on QOL. In the current study, QOL will be assessed at baseline, 6 months, one year, and then yearly to year 3.

Both the EORTC Core Quality of Life Questionnaire (QLQ-C30) and the Brain Cancer Module (BN20) have previously been shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas.<sup>16-17</sup> Prior studies have demonstrated the EORTC QLQ-C30 to have adequate reliability in patients with lung, breast, ovarian and head & neck cancer,<sup>18-21</sup> as well as other cancer diagnoses.<sup>22-23</sup> Compliance rates in multicenter, randomized clinical trials have been high for this questionnaire.<sup>24-25</sup> The BN20 is a supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer.<sup>17</sup>

In a study of patients with high-grade gliomas, Osoba et al. found the QLQ-C30 to have acceptable reliability (in terms of consistency and test-reliability).<sup>26</sup> Patients with dysphasia, mental confusion or motor deficit on neurologic examination reported significantly lower levels of physical, role, cognitive, emotional and social functioning level, and global quality of life than did patients who did not have these difficulties. In patients with deteriorating neurologic status, there was a marked decline in cognitive, physical, role, emotional and social functioning level, global quality of life and an increase in fatigue. Importantly, the health related quality of life

scores provided details not provided by either the Karnofsky Performance Scale or the Barthel Activities of Daily Living Index (BADLI).

## **2.0 OBJECTIVES (4/3/03)**

### **2.1 Primary** (Phase III component)

The primary objective is to participate in the International Prophylactic Cranial Irradiation Trial (PCI 01-EULINT1). The following study endpoints will be evaluated by this international study:

- 2.1.1 To determine the impact of an increase in the total PCI dose on the incidence of brain metastases at a minimum of 2 years of patient follow up; Thus, two PCI dose levels will be compared: 25 Gy (standard dose PCI) versus 36 Gy (high dose PCI) in limited disease small cell lung cancer (LD SCLC) patients in complete remission, whatever the initial treatment;
- 2.1.2 To determine the impact of PCI dose on overall and disease-free survival;
- 2.1.3 To determine the impact of PCI dose on quality of life and late treatment sequelae.

### **2.2 Secondary** (Phase II component)

In addition to the international study objectives, the following endpoints will be evaluated by the RTOG study:

- 2.2.1 To determine the impact of PCI dose *and schedule* on the incidence of chronic neurotoxicity;
- 2.2.2 To determine the impact of PCI dose *and schedule* on quality of life.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility (8/6/03)**

- 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 (See Appendix III): clinical TNM stages I-III B (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).
- 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 x-ray) 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 Zubrod performance status  $\leq 1$  (See Appendix II)
- 3.1.7 Normal brain CT scan or MRI  $< 1$  month prior to study entry
- 3.1.8 Neurological function class of 1 or 2 (See Appendix II)
- 3.1.9 HGB level of 10.0 gm/100 ml, an absolute granulocyte count of  $\geq 1,500/\mu\text{l}$ , and a platelet count of  $\geq 75,000/\mu\text{l}$  are required.
- 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 A "certified" test administrator (Section 11.4) is required for administration of the neuropsychological tests.
- 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.

### **3.2 Conditions for Patient Ineligibility**

- 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 Concomitant malignancy or malignancy within the past five years other than non-melanomatous skin cancer or carcinoma *in situ* of the cervix
- 3.2.4 Patients with minimal pleural effusion evident on CXR; minimal pleural effusion visible on chest CT is allowed.
- 3.2.5 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.

- 3.3 (7/8/04) SWOG, ECOG, and CALGB Institutions: All questions regarding eligibility should be directed to the RTOG Coordinating Center at (215) 574-3189.

#### **4.0 PRETREATMENT EVALUATIONS**

- 4.1 A complete history and physical examination, including assignment of Zubrod performance status and neurological function class (Appendix II)
- 4.2 Chest x-ray (PA and Lateral views) within one month prior to study entry
- 4.3 CT or MRI scans of the brain, with and without contrast, must be done within 1 month prior to study entry to document absence of metastatic disease.
- 4.4 Laboratory studies will include a CBC with differential and platelet count and will be done within 1 week prior to study entry.
- 4.5 Quality of Life Assessments to be done within 2 weeks prior to study entry
- 4.6 Baseline LENT-SOMA scale evaluation
- 4.7 Completion of neuropsychological test battery (Appendix VII) per Section 11.0 prior to initiation of PCI. A "certified" test administrator (Section 11.4) is required for administration of the neuropsychological tests.

**Forms packets for neuropsychological and QOL assessments are available from RTOG Headquarters (FAX 215-574-0300). Request a complete set before beginning to accrue patients.**

#### **5.0 REGISTRATION PROCEDURES (12/9/03)**

- 5.1 The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be certified by Dr. Meyers in order to participate in this protocol. Certification will be based on the criteria in Section 11.4.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.
- 5.3 **Southwest Oncology Group Institutions**  
The registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays. The SWOG Registration Form AND the current version of the RTOG Eligibility Checklist must be completed prior to placing the phone call to SWOG. The caller must have both of these completed documents available for reference during the call.

Exceptions to Southwest Oncology Group registration policies will not be permitted.

- a. Patients must meet all eligibility requirements.
- b. Institutions must be identified as approved for registration.
- c. Registrations may not be cancelled.
- d. Late registrations (after initiation of treatment) will not be accepted.

**NOTE:** Southwest Oncology Group institutions will follow normal procedures for documentation of IRB approval.

#### 5.4 **Randomization, ECOG Investigators**

NOTE: The healthcare professional (e.g. nurse, psychologist) who is responsible for test administration in this study must be certified by Dr. Meyers in order to participate in this protocol. Refer to Section 11.4 for certification criteria. If you have any questions regarding certification, please contact Dr. Meyers at 713-792-8296.

#### **Submitting Regulatory Documents**

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office  
Coalition of National Cancer Cooperative Groups  
1818 Market Street, Suite 1100  
Philadelphia, PA 19102  
FAX: (215) 569-0206

#### **Required Protocol Specific Regulatory Documents**

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.  
Note: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. A. CTSU IRB Certification Form.  
Or  
B. HHS 310 Form.  
Or  
C. IRB Approval Letter

#### **Note: The above submissions must include the following details:**

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB.
- Full protocol title and number.
- Version Date
- Type of review (full board vs. expedited).
- Date of review.
- Signature of IRB official.

The CTSU encourages you to link to the following RSS 2.0 web page so that more information on RSS 2.0 as well as the submission forms can be accessed:[http://www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp).

**If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail [CTSUContact@westat.com](mailto:CTSUContact@westat.com). Monday through Friday, 9:00 am- 6:00 pm.**

Patients must not start protocol treatment prior to registration. Patients can be registered only after pretreatment evaluations is completed (Section 4.0) and eligibility criteria are met (Section 3.0).

Prophylactic Cranial Irradiation (PCI) must begin **within 15 days after randomization.**

Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG web page using the Web-based Patient Registration Program (<http://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this

program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including

patient's initials, chart number, social security number and demographics (sex, birth date, race, nine-digit zip code and method of payment); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0 and pretreatment evaluations must be completed in Section 4.0. After completing the checklist on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the RTOG directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

## **5.5 CALGB Randomization (7/8/04)**

Note: The healthcare professional (e.g., nurse, psychologist) who is responsible for QOL test administration in this study must be certified by Dr. Meyers in order to participate in this protocol. Refer to Section 11.4 for certification criteria. If you have any questions regarding certification, please contact Dr. Meyers at 713-792-8296.

Confirm all eligibility criteria listed in Section 3.0. Registration will be accepted through CALGB Main Member/at-large institutions, selected affiliate institutions, and CCOPs. Registrations must occur prior to initiation of therapy. Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 AM-5 PM Eastern Time) with the following information:

- Study
- Name of group (CALGB)
- Name of institution where patient is being treated
- Name of treating physician
- Name of responsible CRA
- Name of radiation oncologist who gave approval to register patient
- CALGB patient ID #, if applicable
- Patient's first, last and middle initial
- Patient's Social Security #, date of birth, and hospital ID #
- Patient's gender
- Patient's race
- ECOG performance status
- Type of insurance (method of payment)
- Disease, type and stage, if applicable
- Patient's Postal Code, if applicable
- Treatment start date
- Date of signed consent
- Patient demographics
- Eligibility criteria met (no, yes)
- Stratification Factor: Stratum 1 vs. Stratum 2

The CALGB Registrar will then contact the RTOG Randomization Center to randomize the patient. Once the randomization is complete the CALGB registrar will then call the CALGB institution with the randomization assignment. Once the randomization is completed be sure to note the patient's treatment assignment in your records.

The Main Member Institution and registering institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Data Operations, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

## **6.0 RADIATION THERAPY**

### **6.1 Radiation Dose**

- 6.1.1 Patients must begin PCI within **15 days after randomization**.
- 6.1.2 Those patients randomized to Arm 1, standard dose (SD) PCI, will receive 2.5 Gy once daily, Monday through Friday, in 10 fractions for a total of 25 Gy.
- 6.1.3 Those patients randomized to Arm 2, high dose (HD) PCI, will receive once-daily HD PCI, 2.0 Gy, Monday through Friday, in 18 fractions for a total dose of 36 Gy. Those patients randomized to Arm 3 will receive twice-daily HD PCI, 1.5 Gy, Monday through Friday, in 24 fractions for a total dose of 36 Gy.
- 6.1.4 The time interval between fractions for the twice-daily HD PCI (Arm 3) will be 6-8 hours with two fractions being delivered daily. Treatment times (AM/PM) must be documented in the daily record.
- 6.1.5 The target dose shall be specified as follows:
  - 6.1.5.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
  - 6.1.5.2 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target volume.
- 6.1.6 Efforts should be made to avoid interruptions in therapy (Contact Study Chair to discuss any planned interruptions; routine holidays are understood.). Document the reason for treatment interruption in the patient's chart.
  - 6.1.6.1 Major protocol violations include interruptions of 10 or more business days; for patients randomized to b.i.d. radiation, more than 3 days in which the interfraction interval was less than 6 hours; or deviations of greater than 10% from protocol dose.
  - 6.1.6.2 Minor protocol violations include interruptions of 5-10 business days; for patients randomized to b.i.d. radiation, more than 1 or  $\leq$  3 days in which the interfraction interval was less than 6 hours; or 5-10% deviation from protocol dose.
- 6.1.7 **(7/8/04)** SWOG, ECOG, and CALGB Institutions: All questions regarding radiation treatment should be directed to the RTOG Radiation Oncology Study Chairs.

### **6.2 Equipment**

- 6.2.1 Patients will be treated on a megavoltage linear accelerator with 4-6 MV photons.
- 6.2.2 Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm; 100 cm is preferred. Patients should not be treated with cobalt 60.

### **6.3 Simulation/Target Volume/Beam Shaping**

- 6.3.1 Patients must have simulation done prior to start of cranial irradiation in the supine position.
  - 6.3.1.1 Patients may have CT simulation prior to fluoroscopic simulation of portals.
- 6.3.2 The treatment portals will consist of lateral opposed fields that cover the entire cranial contents. Treatment of C2-C3 is at the discretion of the treating physician.
  - 6.3.2.1 There should be a "fall-off" of at least 1 cm around the bony skull superiorly, inferiorly, anteriorly, and posteriorly.
  - 6.3.2.2 Radio-opaque markers to demarcate the bony canthi should be placed on the patient at the time of fluoroscopic simulation to ensure adequate blocking of the lens from the fields.
  - 6.3.2.3 There should be adequate immobilization of the patient's head during simulation to ensure a reproducible treatment technique.

### **6.4 Toxicity from Radiation Therapy**

- 6.4.1 Acute (< 90 days from treatment start)  
Hair loss, erythema of the scalp, headache, nausea and vomiting; Reactions in the ear canals and on the ear should be observed and treated symptomatically.
- 6.4.2 Early Delayed ( $\geq$  90 days from treatment start)  
Lethargy, transient worsening of existing neurological deficits
- 6.4.3 Late Delayed (See Appendix V)  
Radiation necrosis, cognitive dysfunction, accelerated atherosclerosis, radiation-induced neoplasms

### **6.5 Radiation Toxicity**

All grade 4 or grade 5 toxicities that are attributable to radiation therapy must be telephoned to RTOG Headquarters within 24 hours of discovery. An RTOG Research Associate will take an

SAE Phone Report of the event; a copy of the SAE Report then will be distributed to the RTOG Group Chair, RTOG Study Chairs, and faxed to the Institut Gustave-Roussy.

Please refer to Section D of the Adverse Event Reporting Guidelines (Appendix VI) for the appropriate reporting procedures for radiation therapy related toxicity.

**(12/9/03)** All Southwest Oncology Group institutions are responsible for reporting adverse events according to the guidelines located in Appendix VI, Section D.

- 6.5.1** Acute Radiation Toxicity Monitoring: Acute ( $\leq$  90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 2.0. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>).
- 6.5.2** Late Radiation Toxicity Monitoring: Late ( $>$  90 days from RT start) side effects will be documented using the RTOG Late Radiation Morbidity Scoring Scheme (Appendix V).
- 6.5.3** Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management Department within ten days of discovery.

## **7.0 DRUG THERAPY**

Patients should not be routinely placed on steroids prior to or during the cranial irradiation. Should the patient be deemed clinically in need of steroids during the radiation to the brain, then the daily dosage, route of administration, and duration of prescribed steroid use should be indicated.

Maintenance chemotherapy can be prescribed as long as it is not delivered concurrently to PCI. There must be an interval of one week without chemotherapy before and after PCI.

## **8.0 SURGERY**

Not applicable to this study.

## **9.0 OTHER THERAPY**

Thoracic irradiation can be administered concurrently with PCI. In case of extra-cranial progression, the patient will be treated according to each institutional policy. In case of isolated brain failure, patients may undergo further radiotherapy. However, the dose to the whole brain should be chosen so that the total dose (including that of the PCI) does not exceed the equivalent of 54 Gy in 30 fractions of 1.8 Gy.

## **10.0 PATHOLOGY**

Not applicable to this study.

## **11.0 PATIENT ASSESSMENTS**

### **11.1 Study Parameters**

<b>Assessments</b>	<b>Pre-entry</b>	<b>6 mos.</b>	<b>12 mos.</b>
Complete medical history and physical (including Zubrod and neurological function class)	X	X	X <sup>d</sup>
CXR +/- Chest CT Scans	X <sup>a</sup>	X	X
CT or MRI scans of brain, with and without contrast	X <sup>a</sup>	X	X <sup>d</sup>
CBC with differential and platelet count	X <sup>b</sup>		
QOL Assessments <sup>e</sup>	X <sup>c</sup>	X	X <sup>d</sup>
LENT-SOMA scale evaluation	X		X <sup>d</sup>
Neuropsychological Test Battery <sup>f</sup>	X	X	X <sup>d</sup>

a. within 1 month prior to study entry

b. within 1 week prior to study entry

c. within 2 weeks prior to study entry

d. then annually for 3 years

e. See Section 11.3

f. See Section 11.3 and Appendix VII

## 11.2 Post-treatment Evaluations

11.2.1 A complete medical history and physical examination to include Zubrod performance status and neurological function class; chest x-rays (or CT scans of chest); CT or MRI scans of the brain (with and without contrast); completion of the QOL assessments, and completion of the Neuropsychological Test Battery every 6 months for the first year post-treatment, then annually for 3 years; completion of the LENT-SOMA scale evaluation annually post-treatment for 3 years.

## 11.3 Neuropsychological/QOL Assessments

11.3.1 Five tests will be used to assess neurocognitive function and quality of life. These 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 Section 11.4 below), The following tests will be administered: (see Appendix VII for details of neuropsychological tests)

Cognitive Domain	Assessment	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test	5
Verbal Fluency	Controlled Oral Word Association	5
Visual-Motor Scanning Speed	Trail Making Test Part A	5
Executive Function	Trail Making Test Part B	5
Quality of Life	EORTC Quality of Life Questionnaire and Brain Cancer Module	20
	<b>Total Time</b>	<b>40 minutes</b>

### 11.3.2 Summary of Measures (See Appendix VII for more details)

- Hopkins Verbal Learning Test (HVLT): The patient learns 12 words read to them 3 times; immediate recall is tested after each learning trial. Following the third learning and recall trial, the patient completes a recognition test. Delayed recall (*savings or retention*) is evaluated after 15-20 minutes as the final assessment of the battery (*requires about 5 minutes to complete*) indexing learning and short-term memory.
- Controlled Word Association Test (COWAT): The patient produces as many words as possible in 1 min. (*each*) for a specific letter (*C, F, L or P, R, W*). Requires about 5 min to complete. Assesses language and executive/frontal skills
- Trailmaking Test (TMT): This is a measure of visuospatial scanning, attention, sequencing, and speed with two parts (*A & B*). Patients must 'connect the dots' either in a numbered sequence or alternating letters and numbers. Generally Part A requires less than 2 minutes to complete, and Part B requires less than 5 minutes.
- EORTC Core Quality of Life Questionnaire (QLQ-C30): A 30-item, self report questionnaire containing the following domains (scales): Physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), global quality of life (2 items), fatigue (2 items), pain (2 items), nausea and vomiting (2 items), and single items for dyspnea, insomnia, anorexia, constipation, diarrhea and financial impact.
- Brain Cancer Module (BN20): A supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer. Initially it contained 24 items, with 4 items dealing with "emotional distress" similar to the "emotional functioning" items in the QLQ-C30. Thus, a 20-item version was devised, containing 4 multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizure, drowsiness, hair loss, itching, weakness of both legs, and difficulties with bladder control).

### 11.3.3 (7/8/04) SWOG, ECOG, and CALGB Institutions

SWOG, ECOG, and CALGB institutions should follow the neuropsychological/QOL assessment instructions as outlined in Section 11.3.

#### **11.4 Certification for Test Administration (12/9/03)**

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study requires pre-certification by Dr. Meyers in order to participate in this protocol. (All examiners, including those previously certified for RTOG BR-0018, must be certified by Dr. Meyers to ensure current skill level.) Certification will be obtained as follows:

##### **11.4.1 RTOG Institutions**

A videotape of test administration and data collection methods will be provided by RTOG [upon request by FAX (215) 574-0300] for review and reference during the study. This videotape must be reviewed by all persons who will administer neuropsychological assessments.

##### **SWOG Institutions (1/27/04)**

For Southwest Oncology Group institutions, a videotape of test administration and data collection methods will be provided by the Southwest Oncology Group (upon request by FAX to (210) 677-0006; ATTN: Lisa Headlee) for review and reference during the study. This videotape must be reviewed by all persons who will administer neuropsychological assessments.

##### **ECOG Institutions**

For Eastern Cooperative Oncology Group institutions, a videotape of test administration and data collection methods will be provided by ECOG [upon request by FAX (617) 632-2990; see ECOG web site, <http://www.ecog.org/> for FAX Request Form] for review and reference during the study. This videotape must be reviewed by all persons who will administer neuropsychological assessments.

##### **CALGB Institutions (7/8/04)**

For Cancer and Leukemia Group B institutions, a videotape of test administration and data collection methods will be provided by CALGB (upon request by FAX (312) 345-0117) for review and reference during the study. This videotape must be reviewed by all persons who will administer neuropsychological assessments.

- 11.4.2** Test instructions and guidelines are provided in Appendix VII. The instructions must be reviewed and retained for reference. Data forms are available from RTOG (FAX (215) 574-0300).
- 11.4.3** Prior to the enrollment of any patient into the study, the healthcare professional who will be evaluating patients must complete a "practice" assessment, including completion of test forms/score sheets. Complete and sign the Certification Worksheet (Appendix VIII). Fax the signed Certification Worksheet to Dr. Meyers (FAX (713) 794-4999).
- 11.4.4** Once all of the above steps have been completed, call Dr. Meyers (Phone (713) 792-8296; Pager: (713) 404-2746 [call any time any day; voicemail is available]) or email: [cameyers@mdanderson.org](mailto:cameyers@mdanderson.org) to arrange a certification time. If Dr. Meyer's voicemail states she is out of the office, call (713) 792-0708 to arrange a certification time with alternative certifiers, Angela Saleeba or Lee Seabrooke.
- 11.4.5** Dr. Meyers (or the alternative certifier) will discuss the test administration and scoring issues over the phone with the healthcare professional (15-20 minutes). If the health professional is then certified, notification of certification will be sent to both the site and to RTOG Headquarters, and study enrollment may commence.
- 11.4.6** Dr. Meyers will review test forms and summary sheets for the **first two cases** from each site (see Section 12.2 for instructions). For quality control purposes, procedural deviations (*if any*) will be identified, and sites will be notified of the results of the review. If significant procedural variations are noted, re-training ('recertification') of the test administrator will be requested.
- 11.4.7** Completed test forms must be signed by the certified test administrator. Dr. Meyers will be available by telephone and e-mail (as listed in Section 11.4.4) if questions arise about the testing procedures.

#### **11.5 Criteria for Discontinuing Therapy**

- 11.5.1** The development of unacceptable toxicity, defined as unpredictable, irreversible, or Grade 4 (See Appendices IV and V)
- 11.5.2** Patient's noncompliance with protocol requirements
- 11.5.3** Patient refusal

### **11.6.1 Data and Protocol Management**

**11.6.1** All randomized patients will be considered evaluable. Follow-up data will be required for all randomized patients, including those who do not start protocol radiotherapy, those who start radiotherapy and discontinue early for any reason, and for patients who are deemed ineligible after study entry. There will be no exemptions.

**11.6.2** Except for the Quality of Life assessments, EORTC QLQ-C30 and BN20, results of all neuropsychological tests should be recorded on the Neuropsychological Assessment Summary Form (CS). Except for the QOL assessments, individual patient tests/forms will not be submitted to RTOG Headquarters (copies of test forms and summary sheets for the first two cases will be sent to Dr. Meyers per Sections 11.4.6 and 12.2) but will be kept on file at the institution as part of the patient's study file for submission upon request. The completed QOL forms) must be attached to and submitted with Neuropsychological Assessment Summary Form. Study/case specific labels must be applied to each page.

### **11.6.3 (12/9/03) ECOG institutions**

Except for the QOL assessments, copies of test forms and summary sheets for the first two cases will be sent to Dr. Meyers for quality control purposes. Please refer to Section 12.2 for instructions on submission of material for quality assurance. Study/case specific labels must be applied to each page. A hard copy of these forms must also be sent to the ECOG Coordinating Center per instructions in Section 12.4.

## **12.0 DATA COLLECTION (7/8/04)**

**\*Data should be submitted to:**

**RTOG Headquarters  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103**

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.

**\*ECOG institutions should follow the data submission instructions outlined in Section 12.4 below.**

### **12.1 Summary of Data Submission**

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form (A5) Randomization Form (I1) Treatment Planning Brain CT/MRI Report (ME) LENT/SOMA Evaluation Form (LE) Neuropsychological Assessment Summary Form (CS) EORTC QLQ-C30 & BN20 (QL)	Within 2 wks of study entry
<u>Final Dosimetry Information:</u> Treatment Form (T1)**	Within 1 week of RT end
Follow-up Form (F1) Post Treatment Brain CT/MRI Report (ME) Neuropsychological Assessment Summary Form (CS) EORTC Quality of Life Form, QLQ-C30 & BN20 (QL)	At six and twelvemonths the first year, then annually for 3 years. Also at progression/ relapse and at death.
LENT/SOMA Evaluation Form (LE)	Annually for 3 years
Autopsy Report (D3)	As applicable

**\*\*NOTE:** Copies of simulation and port films and the RT Daily Treatment Record for PCI will be submitted to RTOG Headquarters ONLY if specifically requested.

## **12.2 Neurocognitive Evaluation Submission Quality Assurance**

Copies of the HVL, COWAT, and TMT and Assessment Summary Form (CS) for each institution's **first two cases** should be faxed/emailed within 2 weeks of study entry to Dr. Meyers for review: FAX (713) 794-4999; cameyers@mdanderson.org

## **12.3 SWOG Institutions**

Southwest Oncology Group members, affiliate, and CCOP institutions must submit data directly to RTOG, as specified in Sections 12.0 and 12.1. With the exception of SAEs, data should not be submitted to SWOG. Include the RTOG protocol number and patient sequence number as well as the Southwest Oncology Group study number and patient number.

## **12.4 ECOG Institutions**

### **Forms Submission**

The required forms can be accessed on the RTOG web site, <http://www.rtog.org/members/forms/0212/main.html> (no password required). Additional forms packets will NOT be supplied when patients are registered. It will be the responsibility of the participating institutions to copy the attached forms and to maintain a supply of available forms for data submission.

**Originals of completed forms should be submitted at the required intervals to the ECOG Coordinating Center, Frontier Science (ATTN: DATA), 900 Commonwealth Avenue, Boston, MA 02215.** Include the RTOG and ECOG study number and patient ID number. The ECOG Coordinating Center will forward the forms to the RTOG Headquarters.

## **12.5 CALGB Institutions (7/8/04)**

CALGB members must submit data directly to RTOG, as specified in Sections 12.0 and 12.1. Data should not be submitted to the CALGB. Include the RTOG protocol number and patient sequence number as well as the CALGB study number and patient number.

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints (4/3/03)**

#### **13.1.1 Primary** (Phase III component)

The primary objective of this trial is to participate in the International Prophylactic Cranial Irradiation Trial, PCI 01-EULINT1. The investigators of that trial will analyze the following endpoints:

13.1.1.1 Incidence of brain metastases

13.1.1.2 Overall survival

13.1.1.3 Disease-free survival

13.1.1.4 Quality of life

13.1.1.5 LENT-SOMA

#### **13.1.2 Secondary** (Phase II component)

In addition, the following endpoints will be evaluated by the RTOG investigators; these endpoints will look at both dose *and schedule* (as opposed to only dose in the international study).

13.1.2.1 Incidence of chronic neurotoxicity

13.1.2.2 Quality of life

### **13.2 Overview (4/3/03)**

RTOG not only will participate in the International Prophylactic Cranial trial, PCI 01-EULINT1, but also simultaneously conduct a phase II trial using the same patient cohort. The international trial compares the incidence of brain metastases at 2 years between standard dose PCI and high dose PCI (both high dose schedules combined) using the log rank test adjusted on the stratification factors. The international trial will require 700 patients. All randomized patients will be included in this intent-to-treat analysis. The international investigators will also analyze overall and disease-free survival.

The international study randomizes patients to either standard PCI or high dose PCI. Each institution chooses one of two RT schedules for the high dose arm beforehand and will use it for all their patients assigned to that arm. The RTOG study cannot use this selection method because all estimates and comparisons between the two high dose schedules would be biased.

Therefore, in the RTOG study, patients will be randomized to either standard dose (Arm 1) or high dose (Arm 2 and 3); fifty percent of patients will be randomized to the standard dose arm, and 25% of patients will be randomized to each of the high dose arms. This randomization to each of the high dose arms, as opposed to institutional selection of high dose arms, is necessary to obtain unbiased estimates for the study endpoints. The randomized permuted block within strata design described by Zelen<sup>27</sup> will be used at randomization to balance risk factors other than treating institution. Patients will be stratified by age ( $\leq 60$  vs.  $> 60$ ) and by the interval from the start of induction therapy to randomization ( $\leq 90$  days vs. 91-180 days vs. 181-240 days).

### **13.3 Sample Size Determination**

**13.3.1** The study sample size for the international study is 700 patients with incidence of brain metastases as the primary endpoint. For this RTOG study, the sample size will be determined using incidence of neurotoxicity as the endpoint.

**13.3.2** Accordingly to Komaki et al.<sup>2</sup> the rate of brain recurrences in long term survivors can be as high as 50%. Fonesca et al.<sup>4</sup> reported 6 out of 35 patients (17%) receiving PCI had metastatic brain lesions. In a small study conducted by Wolfson et al.<sup>9</sup> there were 0 out of 7 patients (0%) who had brain relapses with a total dose of 36 Gy versus 2 out of 8 (25%) brain metastases in those receiving only 30 Gy. With regard to neurotoxicity, Fonesca's study also revealed that 5 out of 35 (14%) who underwent PCI developed leukoencephalopathy manifested primarily by memory alterations and motor ability deficits. The total dose of PCI delivered in Fonesca's study was 32 Gy at 2 Gy per fraction, and PCI was given concurrently with chemotherapy. In another study by Komaki et al.,<sup>6</sup> it was shown that prior cognitive impairment in a very high percentage of patients occurs before PCI is delivered. These changes involved memory and the frontal lobe; however, there was little change after PCI. Thus, it is important that analysis accounts for possible pre-PCI neurotoxic signs or symptoms. The incidence of chronic neurotoxicity between the three treatment arms also will be evaluated by means of employing a neuropsychological test battery (See Appendix VII).

**13.3.3** A neuropsychological test battery will be used to determine neurologic deterioration. Each patient will provide his/her own control to determine deterioration. The standard error of measurement (SEM)<sup>28</sup> will be computed for each neuropsychological test to determine the clinically meaningful deterioration for a particular test. The standard deviation of the baseline (pre-PCI) assessment for each test will be computed (SDx). The reliability of each test is known (rx). The SEM for a particular test is  $SEM = SD \times \sqrt{1-rx}$ . A clinically meaningful deterioration will be a drop of one SEM. The percent of patients deteriorating by one year will be estimated for all 3 treatment arms. Deterioration without development of brain metastases will be considered a chronic neurologic toxicity.

**13.3.4** With 50 evaluable patients on each of the high dose arms, the 90% confidence intervals around the proportion of patients with deterioration in each arm will extend at most  $\pm 11.7\%$ . With 200 total evaluable patients (100 standard, 50 each high dose), the 90% confidence intervals around the proportion of patients with deterioration in the high dose arm (both arms combined) and the standard dose arm will extend at most  $\pm 8.2\%$ . These widths are for proportions that maximize the estimated variability; for all other proportions, the width will be less. Turrisi et al.<sup>29</sup> showed median survival of 18 and 23 months for once-daily and twice-daily thoracic radiation, respectively, in limited small-cell lung cancer; this included all patients, not only complete responders. We anticipate that most patients entered onto the RTOG protocol will have been treated with twice-daily radiation. Given the results of this study, we are projecting a one-year death rate for complete responders of approximately 20%. Assuming 20% of patients will die prior to the neuropsychological test battery or otherwise fail to have the test completed, and if presumably 5% of the patients randomized are ineligible, then a **total of 264 patients will have to be entered on study to meet accrual goals** set by our statistical assumptions.

### **13.4 Patient Accrual**

The patient accrual is projected at 6 cases per month in order to reach the targeted total accrual in 3.5 years. The international study was originally projected to complete accrual within 3 years. As of January 1, 2002, the study had accrued 180 patients in 32 months. With the increased accrual provided by RTOG, the international study is projected to complete accrual within 4 to 5 years. The RTOG study will be monitored using the following guidelines: 1) if the RTOG accrual is very slow, patients will continue to be entered on the study in order to evaluate the endpoints of the international study; 2) if the international study meets its target accrual prior the RTOG study meeting its target accrual, the RTOG study will be reevaluated with respect to feasibility; 3) if the

RTOG study meets its accrual prior to the international study meeting its accrual, RTOG will reevaluate continuing participation in the international study; 4) if the international study is terminated early because of overwhelming evidence of superiority of the high dose, the RTOG Data Monitoring Committee will be asked to determine if randomization to the low dose should continue; and 5) if the international study is terminated early because of overwhelming evidence that the high dose is inferior or for futility, the RTOG Data Monitoring Committee will be asked to determine if the RTOG study should continue.

### **13.5 Analyses/Plans**

#### **13.5.1 Interim Analysis of Accrual and Toxicity Data**

Interim reports with statistical analyses will be prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information as follows: a) the patient accrual rate with projected completion date for the accrual phase; b) the distribution of patients with respect to pretreatment characteristics; c) compliance rate of treatment delivery with respect to protocol prescription; d) the frequency and severity of the toxicities (interim analyses of neurotoxicity will not be possible as the SEM only can be calculated once all patients have been accrued to the study); and e) accrual by gender in order to monitor the gender distribution of study admissions. The semi-annual reports will also contain information about the accrual of the international study with projected completion date and treatment morbidity data. The results of these interim analyses will be reported to the RTOG Lung Committee. Through examining the above items, the study chair and statistician can identify problems with the execution of the study. Any problems will also be reported to the Lung Committee, which has oversight for this trial. If necessary, the report will be made directly to the RTOG Executive Committee so that corrective action can be taken.

#### **13.5.2 Analyses of Study Endpoints and Reporting of Initial Treatment Results**

The major analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are as follows:

- a) tabulation of all cases entered and any excluded from this analysis with the reasons for such exclusions;
- b) institutional accrual;
- c) distribution of the important prognostic factors by assigned treatment; and
- d) observed results with respect to the study endpoints.

1. Analysis of incidence will be performed by Chi-Square test and logistic regression so that categorical response (neurotoxicity: yes versus no) can be appropriately associated with important prognostic variables. The relative risk for each variable will also be determined.

2. Time to onset of brain damage can be analyzed by a Cox<sup>30</sup> regression analysis associating treatment and prognostic variables to time to onset.

3. The standard deviation for the pre-PCI assessment of all the neuropsychological tests will be computed after all patients are accrued. The SEM for each test will be computed. Patients will be categorized as having neurologic deterioration if any test drops one SEM for that test. The proportion of patients with neurologic deterioration without brain metastases will be computed for each treatment arm. Ninety percent confidence intervals will be computed for these estimates.

4. Quality of Life

The QLQ-C30 will be scored according to methods described in the EORTC QLQ-C30 scoring manual. All scores will be converted to lie in a range between 0-100. For the functioning scales and global QOL scale, higher scores indicate better functioning, whereas for the symptom scales/item, higher scores indicate more of the symptom with difficulty. The BN20 will be scored in a manner analogous to the QLQ-C30. Higher scores will indicate more of the symptom with more difficulty.<sup>31</sup> An absolute difference of 10% on any question will indicate a clinically significant difference. The following domains will be evaluated: Role functioning, social functioning, global QOL, visual disorder, motor dysfunction, communication deficit, drowsiness, memory/concentration. We will also correlate the results of the neuropsychological test with quality of life.

### **13.6 Inclusion of Women and Minorities**

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer. However, RTOG did not show this to be the case in a recent study. Furthermore, an analysis of race did not indicate an association with outcome. In conformance with the National Institutes of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have also considered the possible interaction between gender/to race and treatments. The participation rates of men and women will be examined according to Section 13.5.1. The projected gender and minority accruals are shown below:

#### **Gender and Minority Accrual Estimates**

<b>Ethnic Category</b>	<b>Sex/Gender</b>			
	<b>Females</b>	<b>Males</b>	<b>Unknown</b>	<b>Total</b>
Hispanic or Latino	6	8	0	14
Not Hispanic or Latino	80	170	0	250
Unknown	0	0	0	0
<b>Ethnic Category: Total of all subjects</b>	<b>86</b>	<b>178</b>	<b>0</b>	<b>264</b>
<b>Racial Category</b>				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	10	21	0	31
Native Hawaiian or other Pacific Islander	0	0	0	0
White	76	157	0	233
More than one race	0	0	0	0
Unknown	0	0	0	0
<b>Racial Category: Total of all subjects</b>	<b>86</b>	<b>178</b>	<b>0</b>	<b>264</b>

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## **APPENDIX I**

**RTOG 0212**

### **SAMPLE CONSENT FOR RESEARCH STUDY**

#### **STUDY TITLE (4/3/03)**

**A PHASE II/III RANDOMIZED TRIAL OF TWO DOSES (PHASE III-STANDARD VS. HIGH) AND TWO HIGH DOSE SCHEDULES (PHASE II-ONCE VS. TWICE DAILY) FOR DELIVERING PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH LIMITED DISEASE SMALL CELL LUNG CANCER**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have small cell lung cancer, which may spread to the brain.

#### **WHY IS THIS STUDY BEING DONE?**

In fifty percent of patients with small cell lung cancer, the cancer will spread to the central nervous system at some time during the course of their disease. The purpose of this study is to compare the effectiveness of standard dose and high dose brain irradiation in preventing small cell lung cancer from spreading to the brain. In addition, the study will compare the effectiveness of two schedules of high dose brain irradiation in preventing lung cancer from spreading to the brain.

The study also will find out the effects (good and bad) of brain irradiation on you, including how your thinking skills and the quality of your life are affected.

#### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 264 people will take part in this study.

## **WHAT IS INVOLVED IN THE STUDY? 8/6/03**

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine the treatment into which you are placed. You will have an approximately one in two chance of receiving Treatment 1 below (standard dose) and a one in four chance of receiving either Treatment 2 or 3 below (high dose).

### **Treatment 1:**

If you are randomized to this treatment, you will receive standard dose brain irradiation once a day, Monday through Friday, for approximately 10 treatment days.

### **Treatment 2:**

If you are randomized to this treatment, you will receive high dose brain irradiation once a day, Monday through Friday, for approximately 18 treatment days.

### **Treatment 3:**

If you are randomized to this treatment, you will receive high dose brain irradiation twice a day, Monday through Friday, for approximately 12 treatment days. Each treatment day, you will need to return for your second treatment six to eight hours after your first treatment.

In addition you will have the following tests and procedures:

- A physical exam prior to treatment, every 6 months for the first year after treatment and then annually for 3 years
- Blood tests prior to study entry
- A chest x-ray and/or a chest CT scan prior to treatment and every 6 months for the first year after treatment
- A brain CT or MRI scan prior to study entry, every 6 months for the first year after treatment and then annually for 3 years
- Written and verbal tests to evaluate your memory and thinking skills, and 2 questionnaires about your quality of life prior to study entry, every 6 months for the first year after treatment, and then annually for 3 years. These tests will take a total of about 40 minutes each time you complete them.

## **HOW LONG WILL I BE IN THE STUDY?**

Depending on which schedule of treatment you receive, you will receive brain irradiation for either 2-3 or 3-4 weeks. Follow-up visits, including completion of tests to evaluate your memory and thinking abilities and 2 questionnaires about your quality of life, will continue for 3 years.

The researcher may decide to take you off this study if side effects become very severe, if you become too ill to continue, or if your doctor feels this treatment is no longer in your best interest.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

## **WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the brain irradiation is stopped, but in some cases side effects can be serious or long-lasting or permanent.

### **Brain Irradiation**

#### Very Likely

- Hair loss, which may be permanent
- Scalp reddening or tanning and irritation
- Dry mouth and/or change in taste
- Nausea and/or vomiting
- Headaches
- Tiredness

#### Less Likely, But Serious

- Drainage from the ears or plugging of the ears with decreased hearing
- Memory loss, behavioral change, and/or increased sleepiness (occurring 4-10 weeks after radiation therapy is complete and lasting for several days up to 2 weeks)
- Cataracts and eye damage with the possibility of blindness
- Severe local damage to normal brain tissue, which may require surgery
- In very rare cases, death may result from brain irradiation.

### **Blood Draws**

#### Very Likely

- Bleeding and/or bruising at the site
- Discomfort/anxiety about needles

#### Less Likely, But Serious

- Risk of infection at the site

**Reproductive risks**

Because radiation therapy and chemotherapy can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. The brain irradiation may prevent cancer from spreading to the brain, but this benefit is not guaranteed. We hope the information learned from this study will benefit other patients with small cell lung cancer in the future.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy outside this study or (2) no treatment except medications to make you feel better. With the latter choice, your tumor could continue to grow and your disease would spread.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY? (7/8/04)**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), and other

groups or organizations that have a role in this study, such as the Institute Gustave-Roussy, the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and Cancer and Leukemia Group B (CALGB).

### **WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

### **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*(This section must be completed)*

For information about your disease and research-related injury, you may contact:

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

For information about this study, you may contact:

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

For information about your rights as a research subject, you may contact:

*(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI’s Cancer Information Service at  
**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

Visit the NCI’s Web sites for comprehensive clinical trials information  
<http://cancertrials.nci.nih.gov> or for accurate cancer information  
including PDQ <http://cancernet.nci.nih.gov>.

**SIGNATURE**

**I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.**

**I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).**

\_\_\_\_\_  
Patient Signature (*or legal Representative*)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

## **APPENDIX II**

### **KARNOFSKY PERFORMANCE SCALE**

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

### **ZUBROD PERFORMANCE SCALE**

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

### **NEUROLOGICAL FUNCTION CLASS**

1	Able to work and perform normal activities. Neurological findings minor or absent.
2	Able to carryout 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 a coma.

## APPENDIX III

### **ANATOMICAL STAGING FOR LUNG CANCER (AJCC, 1997)**

#### **TNM CATEGORIES (Note Definitions)**

##### **Primary Tumor (T)**

- TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
- T0** No evidence of primary tumor.
- Tis** Carcinoma *in situ*.
- T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,\* (*i.e., not in the main bronchus*).
- T2** Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
- T3** Tumor of any size that directly invades any of the following: chest wall (*including superior sulcus tumors*), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
- T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.\*\*
- \*Note:** The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.
- \*\*Note:** Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathological examination of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3

##### **Regional Lymph Nodes (N)**

- NX** Regional lymph nodes cannot be assessed.
- N0** No regional lymph nodes metastasis.
- N1** Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.
- N2** Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).
- N3** Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

**APPENDIX III (cont'd)**

**ANATOMICAL STAGING FOR LUNG CANCER  
(AJCC, 1997)**

**Distant Metastasis (M)**

**MX** Distant metastasis cannot be assessed

**M0** No distant metastasis

**M1** Distant metastasis present

**Note:** M1 includes separate tumor nodule(s) in a different lobe (*ipsilateral or contralateral*)

**STAGE GROUPING**

<b>Occult Carcinoma</b>	TX	N0	M0
<b>Stage 0</b>	T <sub>is</sub>	N0	M0
<b>Stage IA</b>	T1	N0	M0
<b>Stage IB</b>	T2	N0	M0
<b>Stage IIA</b>	T1	N1	M0
<b>Stage IIB</b>	T2 T3	N1 N0	M0 M0
<b>Stage IIIA</b>	T1 T2 T3 T3	N2 N2 N1 N2	M0 M0 M0 M0
<b>Stage IIIB</b>	Any T T4	N3 Any N	M0 M0
<b>Stage IV</b>	Any T	Any N	M1

**APPENDIX IV**

**ACUTE TOXICITY : CTC CRITERIA – NCI BETHESDA**

**GASTROINTESTINAL**

<b>Toxicity</b>	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-
Vomiting	none	1 episode in 24h	2-5 episodes in 24h	6-10 episodes in 24h	> 10 episodes in 24h, parenteral support

**NEUROLOGIC**

<b>Toxicity</b>	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Cerebellar	none	slight incoordination, dysdiadochokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Constipation	none or no change	mild	moderate	severe	ileus >96 hrs
Cortical	none	mild somnolence	moderate somnolence	severe somnolence, confusion, disorientation, hallucinations	coma, seizures, toxic psychosis
Dizziness	none	mild	moderate	severe (includes fainting)	-
Headache	none	mild	moderate or severe but transient	unrelenting and severe	-
Altered hearing	none or no change	asymptomatic hearing loss on audiometry only	tinnitus, symptomatic hearing changes not req hearing aid or trt	hearing loss interfering with function but correctable with hearing aid or trt	hearing changes or deafness not correctable
Insomnia	none	mild	moderate	severe	-
Mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Motor	none or no change	subjective weakness, no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Vision	none or no change	blurred vision	-	symptomatic subtotal loss of vision	blindness
Other	none	mild	moderate	severe	life threatening

**APPENDIX IV (continued)**

**SKIN**

<b>Toxicity</b>	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Alopecia	no loss	mild hair loss	pronounced or total head hair loss	total body hair loss	-
Skin changes	none	localized pigmentation changes	generalized pigmentation changes or atrophy	subcut.fibrosis or localized shallow ulceration	generalized ulcerations or necrosis
Desquamation	none	dry desquamation	moist desquamation	confluent moist desquamation	-
Rash, itch	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoma	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Other	none	mild	moderate	severe	life threatening

## APPENDIX VI (12/9/03)

### ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

#### **A. Definitions and Terminology**

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

#### Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

<b>Definite:</b>	The adverse event is <i>clearly related</i> to the treatment/procedure.
<b>Probable:</b>	The adverse event is <i>likely related</i> to the treatment/procedure.
<b>Possible:</b>	The adverse event <i>may be related</i> to the treatment/procedure.
<b>Unlikely:</b>	The adverse event is <i>doubtfully related</i> to the treatment/procedure.
<b>Unrelated:</b>	The adverse event is <i>clearly NOT related</i> to the treatment/procedure.

#### **B. Grading of Adverse Events**

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

#### **C. General Guidelines**

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.

3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).

6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity ( $\geq$  grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

#### **D. Adverse Event Reporting Related to Radiation Therapy**

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.

3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

#### **E. Adverse Event Reporting Related to Systemic Anticancer Agents**

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	<b>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</b>	<b>Increased Incidence of an Expected AE<sup>1</sup></b>	<b>Hospitalization During Treatment<sup>2</sup></b>	<b>Secondary AML/MDS<sup>3</sup></b>
FDA Form 3500 <sup>4,5</sup> within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 10 days of diagnosis <sup>4,5</sup>				X
Call RTOG within 24 hrs of event <sup>7</sup>	X <sup>6</sup>			

- 1 Any increased incidence of a known AE.
- 2 Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
- 3 Reporting required during or subsequent to protocol treatment.
- 4 Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
- 5 Copy to RTOG Data Management labeled: Attention: Adverse Event Report.
- 6 All grade 5 known toxicity.
- 7 Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

**Attribution:** An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators' reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

**When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.**

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures. Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. Expedited Reporting for Phase 1 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Grade 2: Expedited report within 10 working days.  Grade 3: Report by phone to IDB <sup>1,2</sup> within 24 hrs. Expedited report to follow within 10 working days.  Grade 1: Adverse Event Expedited Reporting <b>NOT</b> required.	Report by phone to IDB <sup>1,2</sup> within 24 hrs. Expedited report to follow within 10 working days.  This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting <b>NOT</b> required.	Report by phone to IDB <sup>1,2</sup> within 24 hrs.  Expedited report to follow within 10 working days.  This includes deaths within 30 days of the last dose of treatment with an investigational agent.

- 1 Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
- 2 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days.  Grade 1: Adverse Event Expedited Reporting <b>NOT</b> required.	Report by phone to IDB <sup>1,2</sup> within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting <b>NOT</b> required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

- 1 Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
- 2 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

**Adverse Event Reporting for ECOG Investigators**

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the RTOG reporting guidelines in Sections A, B, C, and D of Appendix VI. This study utilizes NCI CTC version 2.0 to grade severity of adverse events. All adverse events must be reported directly to RTOG via phone within 24 hours of learning of the event. Based on the information given at the time of the phone call, RTOG will instruct the site on any further reporting requirements (including the need for any written reports). Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local IRB.

Reporting of AML/MDS

	NCI/CTEP Secondary AML/MDS Report Form <sup>1</sup>
AML/MDS	X

<sup>1</sup> To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and RTOG accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

**ECOG Telephone Number: (617) 632-3610**

**ECOG Fax Number: (617) 632-2990**

**ECOG Mailing Address:**

ECOG Coordinating Center

FSTRF

ATTN: Adverse Event

900 Commonwealth Avenue

Boston, MA 02215

**RTOG Mailing Address:**

**RTOG Data Management**

**Attn: Adverse Event Report**

1101 Market Street

Philadelphia, PA 19107

**Tele: 215/574-3214**

**Fax: 215/928-0153**

**APPENDIX VII**  
**Neuropsychological/QOL Assessments: Instructions and Procedures**

The following tests were selected because they have demonstrated sensitivity in cancer clinical trials. In brain tumor trials, these tests predict time to tumor progression 30% earlier than MRI evidence. They are widely used, standardized psychometric instruments with published normative data. The tests were also selected to minimize the effects of repeated administration. The memory test has six alternate forms. The other tests measure motor and information processing speed and are relatively resistant to the effects of practice.

<b>Cognitive Domain</b>	<b>Test</b>	<b>Time to Administer (minutes)</b>
Memory	Hopkins Verbal Learning Test <sup>1</sup>	5
Verbal fluency	Controlled Oral Word Association <sup>2</sup>	5
Visual-motor scanning speed	Trail Making Test Part A <sup>3</sup>	5
Executive Function	Trail Making Test Part B <sup>3</sup>	5
Quality of life	EORTC Quality of Life Questionnaire <sup>4</sup> and Brain Cancer Module <sup>5</sup>	20
	<b>Total Time</b>	<b>40 minutes</b>

**Statistical Considerations**

The difference between the pre-treatment baseline and follow-up assessments will be evaluated by the reliable change (RC) index.<sup>6</sup> This index is derived from the standard error of measurement (SEM) for each test in the battery. One advantage of this statistic is that the baseline level of performance of a given individual is not important. For example, a person can score high or low on a test at baseline, which may wash out differences when only group test means are analyzed.

The SEM is calculated from the test-retest reliability (*r*) and the standard deviation of test scores (*SD*):  $SEM = SD(1 - r)^{1/2}$ . The standard error of difference is then calculated:  $SEdiff = [2(SEM^2)]^{1/2}$ . A reliable change (RC) in test scores from baseline to follow-up is considered significant if it is within  $\pm (1.64)(SEdiff)$ , a 90% confidence interval. For each subject, the difference between the pre-treatment baseline and each follow-up assessment will be coded (according to the RC index) as 1 (deterioration), 2 (no change), and 3 (improved). Frequency tables will show the percentage of patients in each treatment protocol who show meaningful losses or gains in the various test domains over the course of the study. Treatment group differences can be compared using Cochran-Mantel-Haenzel chi-square analysis.

**References**

<sup>1</sup>Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test - Revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychologist*. 1998; 12:43-55.

<sup>2</sup>Benton AL, Hamsher KdeS. *Multilingual Aphasia Examination*. Iowa City, IA: AJA Associates, 1989.

<sup>3</sup>Lezak MD. *Neuropsychological Assessment*. 3<sup>rd</sup> ed. New York: Oxford University Press, 1995.

<sup>4</sup>Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 5: 139-50, 1996.

<sup>5</sup>Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 85: 365-76, 1993.

<sup>6</sup>Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991; 59:12-19.

## STEP 1 – ALTERNATE TEST FORMS/VERSIONS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. See the table below for the versions to be administered at pre-entry and subsequent sessions. **The forms packet will contain alternate versions of these neuropsychological tests.**

TEST	Pre-Entry	1 <sup>st</sup> visit	2 <sup>nd</sup> visit	3 <sup>rd</sup> visit	4 <sup>th</sup> visit	5 <sup>th</sup> visit	6 <sup>th</sup> visit
HVLT	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 1
COWAT	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'

### Additional comments:

1. Testing should be completed in one session.
2. **Request a sample forms packet** from RTOG Headquarters to have on hand before beginning to accrue patients.
3. Follow the **instructions on the Forms Packet Index** before submission of forms to RTOG.
3. Please keep all original test records. In the event of questions, contact Dr. Meyers (*see Section 11.4.4 for contact information*). Test results are not submitted to Dr. Meyers nor to RTOG Headquarters, except for copies of the test forms and summary sheets for the **first two cases** from each site to be reviewed by Dr. Meyers (*see Section 12.2*). Results remain on file at the institution as **source documentation** pending request for submission by RTOG or a Study Chair.
4. **Except for the QLQ-C30 and BN20, all test results are recorded on the Neuropsychological Assessment Summary Form (CS)**, which is found in the Forms Packet. The QLQ-C30 and BN20 must be submitted as **attachments** to the Neuropsychological Assessment Summary Form (CS). Study/case specific labels must be applied to all forms.
5. Patients should not be given copies of their tests to avoid learning the material between test administrations.
6. Before dismissing the patient, thank him/her for their cooperation. Remind the patient of their next appointment and that these tests will be repeated.
7. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.

## STEP 2 — Hopkins Verbal Learning Test (HVLT) - INSTRUCTIONS

**Trial 1:** *“Listen carefully while I read a list of 12 words. Try your very best to memorize as many of these words as you can. When I stop, you are to say back as many of the words as you can, in any order that you wish. Ready?”*

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

**Trial 2:** *“That was a good beginning. Now, I’m going to read the same list again. When I stop, I want you to tell me as many words as you can remember, including the words you said the first time. It does not matter in what order you say them. Just say as many words as you can remember whether or not you said them before. Ready?”*

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

**Trial 3:** *“Very good. I’m going to read the list again. Again, listen carefully and try to remember as many words as you can whether or not you said them before. Ready?”*

Continue to follow recording procedures from trials 1 & 2. Note that each learning and recall trial should last about 1 minute.

**Trial 4-Recognition:** *“Now I am going to read a list of 24 words to you. Some of these words are from the list that you learned and just tried to remember. Other words are new words, and I have not read them to you before. After each word, I want you to say ‘YES’ if you think the word was in the previous list and ‘NO’ if it was not.”*

- Record YES/NO answers by marking the Y/N boxes next to each word.
- Guessing is allowed.

Record the time (for example, 1 p.m.) on the scoring form when trial 4 is completed.

### **STEP 3 — Controlled Oral Word Association Test (COWAT) [Timed Test]**

Say: *“I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter”.*

*“You may say any words at all, except proper names such as the names of people or places. So you would not say ‘Rochester’ or ‘Robert’.”*

*“Also, do not use the same word again with a different ending, such as ‘Eat,’ ‘Eats,’ and ‘Eating.’”*

*“For example, if I say ‘s,’ you could say ‘sit,’ ‘shoe,’ or ‘show.’ Can you think of other words beginning with the letter ‘s’?”*

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

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

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

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

*“That is fine. Now I am going to give you another letter. Again, say all of the words beginning with that letter that you can think of.”*

*“Remember, no names of people or places, just ordinary words.”*

*“Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP.”*

*“You will have a minute for each letter.”*

*“The first letter is ‘\_\_\_’ (see scoring sheet).”*

#### Allow one minute.

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter.
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing for one minute each.

#### Recording and Scoring:

- The record sheet provides lines on which the patient’s responses can be entered (e.g., *write in the word that is said by the patient*). If his/her speed of word production is too fast to permit verbatim recording, a “+” should be entered to indicate a correct response.

- Incorrect responses either should not be recorded or, if recorded, should be struck through with a line.
- If the patient provides more responses than there are lines on the record sheet, keep writing the responses (or a "+") elsewhere on the record sheet.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form that is sent to the RTOG.

Comments on scoring:

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

**STEP 4 — Trail Making Test (Timed Test)**

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

Say: *"I want you to connect the dots in number order as fast as you can. Start here at number 1 and go from 1 to 2, then 2 to 3 and so on until you reach the end. You should connect the dots without lifting your pencil from the paper. Work as fast as you can. Ready?...go!"*

If the patient makes a mistake on Sample A, quickly point out the mistake and explain it. If the patient still cannot complete Sample A, take his/her hand and guide him/her through it, using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

After the practice trial, move on to Part A and say: *"I have some more of these. Start here at number 1 (point out start) and go from 1 to 2, then 2 to 3 and so on until you reach the end (point to end). Again, work as fast as you can. Ready?...go!"* Begin timing.

- Start timing as soon as the instruction to begin is given.
- Watch closely to catch any errors as soon as they are made.
- If an error is made, call it to the patient's attention and have him/her start again from the error point.
- Do not stop timing until the patient reaches the circle marked END.
- Record the time to completion on the test sheet in minutes and seconds, and say: *"That's fine. Now we'll try another one."*
- The test can be discontinued if the patient is extremely confused and is unable to perform the task. Write down the time you spent and how many dots the patient could connect. Be sure to indicate the test was not completed.

**Part B:** Show the patient the practice section for Part B and say: *"This time I want you to do something a little different. I want you to alternate numbers with letters of the alphabet. For example, you would go from 1 to A to 2 to B and so on. Do you understand? Again, I want you to work as fast as you can. Ready?...go!"*

Again, if the patient makes a mistake on Sample B, point out the error and explain it. If the patient still cannot complete Sample B, take his/her hand and guide him/her through it, using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

After the practice trial, move on to Part B and say: *"I have some more of these. Again, go from 1 to A to 2 to B and so on (point to circles) until you reach the end (point to end). Work as fast as you can. Ready?...go!"* Begin timing.

- Start timing as soon as the instruction to begin is given.
- Watch closely to catch any errors as soon as they are made.
- If an error is made, call it to the patient's attention and have him/her start again from the error point.
- Do not stop timing until the patient reaches the circle marked END.
- Record the time to completion on the test sheet in minutes and seconds.
- The test can be discontinued if the patient is extremely confused and is unable to perform the task. Write down the time you spent and how many dots the patient could connect. Be sure to indicate the test was not completed.

#### **STEP 5 — HVLТ Delayed Recall, Trial 5:**

Record the time on the scoring sheet.

Note: At least 15-20 minutes should have elapsed between the time HVLТ Trial 4 was completed and Step 5.

Say: *"I read you a list of words at the beginning of the session, and you practiced remembering the words. Now tell me as many words as you remember from the original list of words that you learned."* **Do not read the list again.**

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

APPENDIX VII (Continued)

Neuropsychological Test Forms

RTOG Case# \_\_\_\_\_

DATE: \_\_\_\_\_

Visit #: \_\_\_\_\_

Level of Consciousness: Alert \_\_\_\_\_

Lethargic \_\_\_\_\_

Fluctuating \_\_\_\_\_

Hopkins Verbal Learning Test (HVL-Form 1)

Words	Trial 1	Trial 2	Trial 3
Lion			
Emerald			
Horse			
Tent			
Sapphire			
Hotel			
Cave			
Opal			
Tiger			
Pearl			
Cow			
Hut			
Number Correct:			

**Neuropsychological Test Forms (continued)**

**Trial 4: HVLТ Recognition**

The score for this portion of the HVLТ is the number of list words correctly identified (*hits*) minus the number of non-list words incorrectly identified (*false alarms*). Therefore, the actual score can range from -12 (*no list words identified and all nonlist words identified*) to +12 (*all list words identified and no nonlist words identified*).

HORS	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			EMERALD	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			balloon	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			apartment	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N		
Y	N																						
Y	N																						
Y	N																						
Y	N																						
E																							
house		mountain		boat		COW																	
HUT		CAVE		dog		LION																	
TENT		TIGER		HOTEL		PEARL																	
ruby		SAPPHIRE		coffee		Penny																	
OPAL		Cat		scarf		diamond																	

HVLТ Recognition Score: \_\_\_\_\_

Clock time for completion of Trial 4: \_\_\_\_\_

**Trial 5: HVLТ Delayed Recall**

Clock time for start of verbal delayed recall: \_\_\_\_\_

Lion		Tent		Cave		Pearl	
Emerald		Sapphire		Opal		Cow	
Horse		Hotel		Tiger		Hut	

**TOTAL Delayed Verbal Recall:** \_\_\_\_\_ (12 max)

**Neuropsychological Test Forms (continued)**

**CONTROLLED ORAL WORD ASSOCIATION (COWAT) (use 'CFL' or 'PRW' -- circle letter used)**

Letter:	C or P	F or R	L or W
	1.	1.	1.
	2.	2.	2.
	3.	3.	3.
	4.	4.	4.
	5.	5.	5.
	6.	6.	6.
	7.	7.	7.
	8.	8.	8.
	9.	9.	9.
	10.	10.	10.
	11.	11.	11.
	12.	12.	12.
	13.	13.	13.
	14.	14.	14.
	15.	15.	15.
	16.	16.	16.
	17.	17.	17.
	18.	18.	18.
	19.	19.	19.
	20.	20.	20.
<b>TOTALS:</b>			

**COWAT TOTAL:** \_\_\_\_\_

**Neuropsychological Test Forms (continued)**

**TRAIL MAKING DATA SHEET**

**Instructions:** For each test (Part A and Part B), record the total time for the patient to perform the test. Record comments, as needed, to describe factors affecting performance or any other difficulties, encountered while testing. If the patient was NOT TESTED or testing was prematurely DISCONTINUED, complete section IV.

**I. Part A:**

TOTAL TIME (MIN:SEC): \_\_\_\_\_ : \_\_\_\_\_ \_\_\_\_\_

**II. Part B:**

TOTAL TIME (MIN:SEC): \_\_\_\_\_ : \_\_\_\_\_ \_\_\_\_\_

**III. COMMENTS:**

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**IV. TRAIL MAKING NOT COMPLETED AS PLANNED:** Complete ONLY if applicable. Place an "x" in NOT TESTED or DISCONTINUED and mark the reason for not completing the Sample Trail Making as planned:

**Part A:**

("x" one):  NOT TESTED **OR** REASON ("x" one):  DISABILITY **OR**  
 DISCONTINUED  OTHER (specify)\_\_\_\_\_

**Part B:**

("x" one):  NOT TESTED **OR** REASON ("x" one):  DISABILITY **OR**  
 DISCONTINUED  OTHER (specify)\_\_\_\_\_

**APPENDIX VIII ( 7/8/04)**

**Certification Worksheet for Test Administrator**

**RTOG 0212**

**A PHASE II/III RANDOMIZED TRIAL OF TWO DOSES (PHASE III-STANDARD VS. HIGH) AND TWO HIGH DOSE SCHEDULES (PHASE II-ONCE VS. TWICE DAILY) FOR DELIVERING PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH LIMITED DISEASE SMALL CELL LUNG CANCER**

This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Meyers prior to the registration of any patients to RTOG 0212. Refer to protocol Section 11.4 for details.

- \_\_\_\_\_ (Y) 1. Have you watched the Neuropsychological Assessment Administration video?
- \_\_\_\_\_ (Y) 2. Have you reviewed the Neuropsychological/QOL Assessments Instructions and Procedures in Appendix VII of the protocol?
- \_\_\_\_\_ (Y) 3. Have you completed a "practice" Neuropsychological Assessment (See Section 11.4.3)?

\_\_\_\_\_  
Signature of test administrator  
*(person who watched video and performed "practice" Neuropsychological Assessment)*

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed name of test administrator

\_\_\_\_\_  
RTOG, SWOG, ECOG, CALGB (**Circle one**)  
Institution number/Name

\_\_\_\_\_  
Telephone number of test administrator

\_\_\_\_\_  
Fax number of test administrator

If you have any questions regarding the certification, please contact Dr. Meyers. Once you have completed this form, please attach the Neuropsychological Assessment forms from the "practice" individual and submit to:

Christina Meyers, Ph.D.  
(713) 792-8296  
FAX (713) 794-4999  
*cameyers@mdanderson.org*

**For Dr. Meyer's Use Only** (to fax to 215-574-0300, RTOG HQ)

\_\_\_\_\_ (Y/N) The above individual has been certified for administering the neurocognitive assessments for this study.

Signature \_\_\_\_\_ Date \_\_\_\_\_

**APPENDIX IX**  
**Publication Policy**

If RTOG completes patient accrual prior to the international study, the data concerning the secondary objectives of the study will be analyzed by the RTOG statistical unit and eventually published by the study chair of RTOG 0212, Dr. Wolfson. This publication would concern only the secondary objectives: the impact of PCI dose and schedule on the incidence of chronic neurotoxicity and the impact of PCI dose and schedule on quality of life.

The final publication of this trial will be written by the study coordinator of International Cranial Irradiation Trial, PCI 01-EULINT1, based on the final analysis performed at the Institute Gustave Roussy statistical center. A draft manuscript will be submitted by the study coordinator to the co-chairs of the participating groups for review no later than six months after receiving the final statistical analysis. After revision of the manuscript based on feedback from all co-chairs, the study coordinator will submit the article to a major scientific journal.

The final publication will be made in the name of the PCI199-EULINT collaborative group; however, all of the participating groups will be clearly indicated. All active investigators in the international trial will be listed in alphabetical order, with their group affiliation, and the number of patients accrued by each participating group. Key members of data centers/statistical units also will be listed.