RADIATION THERAPY ONCOLOGY GROUP

RTOG 0214

A PHASE III COMPARISON OF PROPHYLACTIC CRANIAL IRRADIATION VERSUS OBSERVATION IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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***All Cooperative Group members who are not affiliated with RTOG will enroll patients to this study and submit data via the Cancer Trials Support Unit (CTSU).**

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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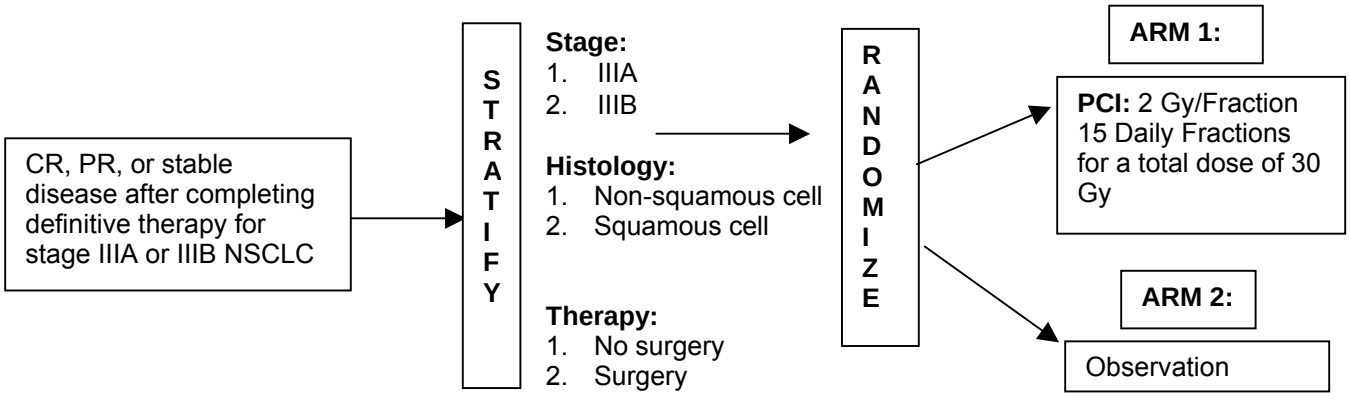
RTOG 0214

A PHASE III COMPARISON OF PROPHYLACTIC CRANIAL IRRADIATION VERSUS OBSERVATION IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

SCHEMA



ELIGIBILITY (See Section 3.0 for details) **[12/9/03]**

- Patients with newly diagnosed Stage IIIA or IIIB non-small cell lung cancer having completed definitive locoregional therapy (with surgery and/or radiation therapy, with or without chemotherapy) [chemotherapy alone does not constitute definitive therapy], with complete response, partial response, or stable disease after therapy;
- Patients must be ≥ 18 years of age;
- Patients will be restaged and enrolled within 16 weeks of completing previous therapy; any acute/subacute ≥ grade 3 toxicities from previous therapy must be resolved to ≤ grade 2 at the time of study entry;
- No evidence of progressive disease at the time of study entry;
- MRI or CT of the head showing no suspicion for CNS metastases within 6 weeks of study entry;
- No evidence of extracranial distant metastatic disease;
- No prior cranial irradiation;
- Patients may not be entered on other phase III studies;
- Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus
- Patients must sign a study-specific informed consent prior to study entry.

Required Sample Size: 1058

RTOG Institution # ____

RTOG 0214 **ELIGIBILITY CHECKLIST (12/9/03)**

Case # _____ **(page 1 of 2)**

_____(Y) 1. Newly diagnosed Stage IIIA or IIIB non-small cell lung cancer AND completion of all definitive locoregional therapy with surgery and/or radiation therapy, with or without chemotherapy, with complete response, partial response, or stable disease after therapy?

_____(N) 2. Did prior therapy include chemotherapy alone?

_____(Y) 3. Complete response, partial response, or stable disease at time of study entry?

_____(Y) 4. At least 18 years of age?

_____(Y) 5. Re-staging performed and patient entered on study within 16 weeks of completing all definitive therapy?

_____(Y) 6. Negative MRI (with and without gadolinium) OR CT scan (with and without contrast) of the head within 4-6 weeks of study entry?

_____(Y) 7. Have all ≥ grade 3 toxicities from prior therapy resolved to at least grade 2?

_____(N) 8. Is there evidence of progression or extracranial distant metastasis at the time of study entry?

_____(N) 9. Prior cranial irradiation?

_____(N) 10. Is the patient enrolled on another phase III trial?

_____(N) 11. Is there synchronous primary or prior malignancy, other than non-melanomatous skin cancer, within the 3 years prior to study entry?

_____(Y) 12. Will the patient of childbearing potential practice appropriate method of contraception?

_____(N) 13. If female, is the patient pregnant?

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?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

(continued on next page)

RTOG Institution # _____

RTOG 0214 **ELIGIBILITY CHECKLIST (12/9/03)**

Case # _____ **(page 2 of 2)**

_____ 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

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Treatment Start Date

_____ 17. Specify stage (IIIA or IIIB)

_____ 18. Specify histology (non-squamous or squamous)

_____ 19. Specify prior therapy (no surgery or surgery)

_____ 20. 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 BACKGROUND AND RATIONALE

1.1 Rationale

Fifty percent of patients with locally advanced non-small cell lung cancer (LA-NSCLC) will develop central nervous system (CNS) metastases at some time during the course of their disease. Prevention of CNS metastases, even for patients with other sites of failure, will improve quality of life and, for patients controlled extracranially, will improve survival.

Review of RTOG data has shown that longer survival for patients with LA-NSCLC treated with radiation alone or radiation and chemotherapy is associated with an increased incidence of CNS metastases.[1-2] Although studies have shown that the addition of chemotherapy to radiation therapy reduces extracranial distant metastases[1] and improves survival,[3-4] it does not alter brain relapse rates.[1] This emphasizes the need for treatment directed at CNS micrometastases.

Recently, several studies have reported excellent median and two-year survival rates of 15-25 months and 37-66% with tri-modality therapy (chemotherapy, radiation, and surgery) for LA-NSCLC. [5-8] These studies also have reported the brain to be one of the most frequent sites of initial failure. Overall CNS failure rates are 21-54%, and CNS as first site of relapse is 15-30% (Table 1).[5,7-10] These studies emphasize the significance of CNS failures with prolonged survival in patients treated aggressively for LA-NSCLC. This has prompted the inclusion of PCI into some clinical studies.[7,10,11]

TABLE 1

		CNS Metastases		MEDIAN SURVIVAL (MONTHS)
STUDY	STAGE	OVERALL	1ST FAILURE SITE	
Choi[5]	$T_{1-3}pN_2$	NA	30%	25
Stuschke[10]	$T_{1-4}pN_2$	54%	30%	20
SWOG[7]	pN_{2-3} or T_4	21%	15%	15
Andre[9]	cN_2	22%	15%	NA
Law[8]	IIIa-b or IV	31% (53% complete resection)	16.3% (28% complete resection)	20

PCI toxicity data is derived mainly from small cell lung cancer (SCLC). The highest rates of toxicity have been reported when PCI is given concurrently with chemotherapy or when given at high dose per fraction.[12] After low dose concurrent chemotherapy and PCI, 44% of patients with SCLC had abnormal neuropsychologic tests after a median follow-up of 6.2 years.[12] Unexpected neurocognitive deficits have been detected in patients with SCLC after combination chemotherapy, with no significant change in those deficits after PCI.[13] The authors suggest that neuropsychologic abnormalities associated with SCLC may be secondary to the disease itself (paraneoplasia) and systemic therapy. A definite conclusion about tolerance to PCI for NSCLC can be drawn only from prospective studies with serial longitudinal neuropsychologic testing of patients with NSCLC treated with and without PCI.

Late cognitive deficits with the use of PCI for patients with NSCLC have not been detected, partially due to lack of intensive neuropsychologic testing and limited survival. Stuschke et al. studied neuropsychologic function and brain MRI in patients with LA-NSCLC after PCI. T2-weighted magnetic resonance imaging revealed white matter abnormalities of higher grade in patients who received PCI than in those who did not.[10] Two of the nine patients treated with PCI and 0/4 patients not treated with PCI had grade 4/4 white matter abnormalities. There was a trend toward impaired neuropsychologic functioning in patients with higher-degree white matter

abnormalities. Impairments in attention and visual memory in long-term survivors was seen in both PCI and non-PCI patient groups after multimodality therapy.

PCI is used to decrease CNS failures in patients with small cell lung cancer (SCLC). It took several decades for PCI for SCLC to be accepted as a safe and effective method of managing CNS micrometastases. It has been shown to favorably impact QOL,[14] decrease the incidence of CNS metastases, and improve survival.[15,16] Despite routine use, there is still controversy over the use of PCI for patients with SCLC.[12,13,17-19] PCI is currently being used in studies as an optional or mandatory part of multimodality therapy for NSCLC.[7,10,11] A prospective randomized study evaluating the survival benefit of PCI for NSCLC needs to be conducted *now*, before strong biases prevent accrual to such a study.

1.2 Supporting Preliminary Data

1.2.1 *Randomized Studies*

Three randomized trials of prophylactic cranial irradiation (PCI) in patients with locally advanced non-small cell lung cancer (LA-NSCLC) have been published.[20,21,22] These studies show that PCI decreases or delays the incidence of brain metastases in patients with LA-NSCLC (Table 2).

In the early 1980's, RTOG conducted a prospective randomized study comparing PCI (30 Gy in 10 fractions) and chest irradiation to chest irradiation alone for patients with inoperable or unresectable T1-4N1-3M0 and resected T1-3N2-3M0 non-squamous NSCLC.[21] Development of symptomatic brain metastases was delayed. Overall incidence of CNS metastases was not significantly decreased. In a small subgroup of patients with prior complete surgical resection, PCI decreased the incidence of brain metastases from 25% to 0% (p=.06). Many of these patients did not live long enough to develop CNS failure. Also, ineffectiveness of locoregional therapy and lack of systemic therapy resulted in a high incidence of locoregional and distant failures which likely were sources of secondary seeding of the CNS after PCI was delivered. Median survival in this study was only 8 months due to ineffective therapy and relatively poor prognostic factors. Median survival in studies reporting a significant rate of CNS failures is 12-25 months.

The Veterans Administration Lung Group treated patients who were not candidates for curative resection and who had no evidence of distant metastases.[20] Patients were randomized to receive whole-brain irradiation (20 Gy in two weeks) or no brain treatment and to receive one of two regimes of thoracic irradiation. PCI decreased the incidence of brain metastases from 13% to 6% (p=0.038) in all non-small cell histologies and from 29% to 0% in adenocarcinoma (p=0.04). There was no difference in median survival.

Umsawasdi et al. treated patients with LA-NSCLC with combined chemoradiotherapy and randomized them to PCI (30 Gy in two weeks) or no PCI.[22] PCI significantly decreased the incidence of CNS metastases from 27% to 4% (p=0.002). PCI also increased the CNS metastasis-free interval.

1.2.2 *Non-Randomized Studies*

Five non-randomized multimodality studies for patients with LA-NSCLC have demonstrated the potential benefits of PCI (Table 2).[7,10-11,23,24] In the most notable of these studies, 75 patients with stage IIIA/IIIB NSCLC were treated with induction chemotherapy, preoperative radiochemotherapy, and surgery. PCI was introduced after the first half of the study because of a high incidence of brain relapses. Patients treated during the second half of the study were offered PCI (30 Gy in 15 fractions). PCI reduced the rate of brain metastases as the first site of relapse from 30% to 8% at 4 years (p=.005) and the rate of overall brain relapse from 54% to 13% (p<.0001).[10]

Skarin et al. treated 41 patients with stage III NSCLC with chemotherapy and radiation followed by surgery. Fourteen percent of patients treated with PCI developed CNS metastases compared to 27% of patients not treated with PCI.[24] SWOG performed a phase II study with neutron chest radiotherapy sandwiched between four cycles of chemotherapy.[7] PCI was administered concurrently with chest irradiation (30 Gy in 10 fractions or 36 Gy in 18 fractions). No patient who completed PCI had clinical or radiologic brain metastases. In another phase II SWOG study, patients with stage IIIA NSCLC were treated with chemoradiotherapy and

optional PCI (36 Gy in 18 fractions) followed by surgery.[23] Two of 18 (11%) treated with PCI and 24 of 108 (22%) not treated with PCI developed brain metastases. CALGB delivered 30 Gy in 15 fractions to patients with large cell or adenocarcinoma in a phase II trial of neoadjuvant chemoradiation and resection for LA-NSCLC. No brain relapse was observed among the 13 patients who received PCI.[11]

1.2.3 *Radiation Schedule*

Radiation regimens for PCI that have influenced patterns of CNS failures have included total doses of 30-36 Gy and fraction sizes of 2-3 Gy.[7,10,11,21] A smaller fraction size of 2 Gy and a total dose of 30 Gy is chosen for this study to minimize late tissue toxicity. This regimen has been shown to decrease CNS metastases from 54% to 13% with no difference in neuropsychologic testing in PCI versus non-PCI patients at 4 years.[10]

TABLE 2

			CNS Failures		Overall Survival	Median Survival (Months)
STUDY	DOSE OF PCI	PRIMARY TX	NO PCI	PCI		
VALG[20]	20 Gy (2Gyx10)	RT only (all NSCLC)	13% (16/145)	6% (7/136)	NA	NA
RTOG [21]	30 Gy (3Gyx10)	RT only (non-squam)	19% (18/94)	9% (8/93)	13% (2 years)	8
Albain[7]	36 Gy (2Gyx18)	Trimodality (all NSCLC)	16% (16/100)	8% (2/26)	37% (2 yrs) 27% (3 yrs)	15
Strauss[11]	30 Gy (2Gyx15)	Trimodality (non-squam)	12% (5/41)	0 (0/13)	58% (1 year)	15.5
Umsawasdi[22]	30 Gy (3 Gyx10)	ChT/RT or ChT/RT/S (all NSCLC)	27% (14/51)	4% (2/46)	NA	NA
Stuschke[10]	30 Gy (2Gyx15)	Trimodality (all NSCLC)	54% (15/28)	13% (6/47) ($p < 0.0001$)	31% (3 years)	20
Skarin[24]		Trimodality (all NSCLC)	26% (7/27)	14% (1/7)	31% (3-5 years)	32
Rusch[23]	30 Gy (3Gyx10) 36 Gy (2 Gy x18)	ChT/RT	0/0	(0/75)	NA	NA

1.2.4 *Neuropsychological Testing* **(6/24/03)**

Neuropsychologic testing will be performed to assess the neuropsychologic impact of the development of CNS metastases and the use of PCI. Mini-Mental Status Examination (MMSE), Hopkins Verbal Learning Test (HVLT)[25], and Activity of Daily Living Scale (ADLS)[26] will be used. Data will be collected at study entry and at 3, 6, 12, 18, 24, 30, 36, and 48 months.

MMSE is a rapidly and easily-administered tool used to detect mild dementia.[27] The HVLT is a well-validated and reliable assessment of memory, including encoding, retrieval, and retention of new information over time.[28-29] It has six alternate forms to minimize practice effects and takes only 5 minutes to administer. The HVLT has better sensitivity than the MMSE in detecting patients with mild dementia, whereas the MMSE has better specificity.[29]

ADLS is used as a complement to MMSE and HVLT as it provides vital information on day-to-day quality of life, which is not covered by MMSE, HVLT, or physical examination. ADLS and MMSE are independent in assessing minor dementia.[30]

Formal neuropsychometric evaluation remains the most comprehensive tool to assess cognitive and psychosocial function; however, this evaluation is relatively expensive and administration is lengthy. In addition, some participating institutions may not have the facilities for full-scale neuropsychometric testing, excluding them from participation. The proposed assessments are cost effective. RTOG 91-14 demonstrated the feasibility of performing MMSE and ADLS and collecting the data within RTOG.[31]

The feasibility of using the HVLT in multi-national trials of cancer agents has been established. These trials include the recently completed Phase III trial of Motexafin Gadolinium sponsored by Pharmacyclics, which accrued 400 patients tested multiple times in 88 sites in Europe and North America.[32-35] This instrument has also been successfully used in clinical trials of agents for primary brain tumors,[36] Phase I trials for solid tumors,[37] and in trials recently completed but not yet published in bone marrow transplantation, TAS-106 for solid tumors, and TNP-470 for solid tumors. It is also being used in a number of intervention trials against neurocognitive impairment, including methylphenidate for neurobehavioral slowing in brain tumor patients.[38]

1.2.5 *Quality of Life* **(6/24/03)**

There is limited information regarding the impact of prophylactic cranial irradiation (PCI) on quality of life and cognitive functioning. Two randomized controlled trials of PCI in patients with small cell lung cancer (SCLC) [39-40] have examined cognitive functioning as an outcome, one of which also examined quality of life.[40] Arriagada, et al.[39] 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 2-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.[40] 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, Complex Figure Test and Auditory Verbal Learning Tests were administered at randomization, 6 months and 12 months. At these time points, quality of life (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.[40] 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 quality of life follow up is not available such that there is insufficient evidence to comment on the long-term effects of PCI on quality of life. In the current study, quality of life will be assessed at baseline, 6 months, one year, and then yearly to year three.

Even for patients with SCLC, in which a recent meta-analysis has demonstrated a small survival benefit with prophylactic cranial irradiation,[41] much controversy remains regarding its potential for neurotoxicity which may negatively impact on quality of life. In a national survey of oncologists in the United States, Cmelak, et al.[42] found that while 38% of responding medical oncologists felt that PCI improved survival for limited stage SCLC patients, but 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.[43] 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 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[44] 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.

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).[45] 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 and 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).

Both the EORTC QLQ-C30 and the BCM20 have previously been shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas.[46-47] The QLQ-C30 is a 30-item, self report questionnaire.[48] Prior studies have demonstrated this questionnaire to have adequate reliability in patients with lung, breast, ovarian and head & neck cancer,[48-51] as well as other cancer diagnoses.[52-53] Compliance rates in multicenter, randomized clinical trials have been high for this questionnaire.[54-55] The BCM20 is a supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer.[47] 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 BCM version (BCM20) was devised, containing 4 multi-item scales. The QLQ-C30 will be scored according to methods described in the ERTC QLQ-C30 scoring manual.[56] The BCM20 will be scored in a manner analogous to the QLQ-C30.[47]

1.2.6 *Conclusion*

A large-scale phase III study is necessary to prove that PCI improves survival by safely decreasing the incidence of CNS metastases in patients who have had effective treatment for locally advanced non-small cell lung cancer. The benefit in preventing or delaying symptomatic CNS metastases in these patients, whether or not they are otherwise cured of their disease, cannot be overlooked. The successful prevention of CNS metastases will improve quality of life and, for patients controlled extracranially, will improve survival.

2.0 OBJECTIVES

2.1 Primary Objective

Determine whether prophylactic cranial irradiation (PCI) improves survival after effective locoregional/systemic therapy for patients with locally advanced non-small cell lung cancer (LA-NSCLC).

2.2 Secondary Objectives

2.2.1 Determine the neuropsychologic impact of PCI

2.2.2 Determine the impact of PCI on QOL

2.2.3 Determine the impact of PCI on the incidence of CNS metastases

3.0 PATIENT SELECTION

3.1 Eligibility (12/9/03)

3.1.1 Patients with newly diagnosed Stage IIIA or IIIB non-small cell lung cancer having completed definitive locoregional therapy (with surgery and and/or radiation therapy, with or without chemotherapy) [chemotherapy alone does not constitute definitive therapy], with complete response, partial response, or stable disease after therapy;

3.1.2 Patients must be ≥ 18 years of age;

3.1.3 Patients will be restaged and enrolled within 16 weeks of completing previous therapy; any acute/subacute ≥ grade 3 toxicities from previous therapy must be resolved to ≤ grade 2 at the time of study entry;

3.1.4 MRI or CT of the head showing no suspicion for CNS metastases within 6 weeks of study entry;

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

3.2 Conditions for Patient Ineligibility

3.2.1 Evidence of progressive disease at the time of study entry;

3.2.2 Evidence of extracranial distant metastatic disease;

3.2.3 Prior cranial irradiation;

3.2.4 Patients may not be entered on other phase III studies;

3.2.5 Patients with synchronous or prior malignancy, other than non-melanomatous skin cancer unless disease free greater than 3 years;

3.2.6 Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus; patients with childbearing potential must practice appropriate contraception.

4.0 PRETREATMENT EVALUATIONS (6/24/03)

4.1 Complete, detailed medical history & physical examination;

4.2 CT scan of chest, liver, adrenal glands; MRI of the brain with and without gadolinium; although brain MRI is preferred, CT of the brain with and without contrast is acceptable. It is recommended that studies be completed within 4 weeks prior to study entry, but up to 6 weeks will be permitted;

4.3 Laboratory studies: CBC, basic chemistry, including serum calcium; liver function tests, including alkaline phosphatase; Studies should be completed within 2 weeks prior to study entry.

4.4 Bone scan is required for patients with elevated serum calcium or alkaline phosphatase;

4.5 Completion of MMSE, HVLT, ADLS, (See Appendix VI and forms packet) and EORTC QLQ-C30 and BCM20 (See forms packet).

5.0 REGISTRATION PROCEDURES

5.1 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.

6.0 RADIATION THERAPY

6.1 Radiation Dose

6.1.1 Patients randomized to Arm I will receive PCI at 2 Gy per fraction, 5 days per week, for 3 weeks to a total dose of 30 Gy.

6.1.2 Treatment will be delivered with right and left lateral equally weighted fields with the dose calculated on the central ray at mid-separation of the beams.

6.1.3 Efforts should be made to avoid interruptions in therapy. Reasons for treatment interruptions should be documented in the patients chart.

6.1.3.1 Major protocol violation includes treatment interruptions of 10 or more business days.

6.1.3.2 Minor protocol violations include treatment interruptions of 5-10 business days.

6.2 Simulation and Target Volumes

6.2.1 Simulation must be done prior to the start of PCI.

6.2.2 Patients will be supine with radio-opaque markers placed at the lateral orbital canthi to assist in blocking the lenses.

6.2.3 The target volume is the entire intracranial contents.

6.2.4 There should at least 1 cm margin around the bony skull superiorly, inferiorly, anteriorly and posteriorly. The inferior border at the cervical vertebral bodies should be at the C1-C2 interspace. The radio-opaque markers at the lateral bony canthi should be used to assist in blocking the lenses from the therapy portal.

6.2.5 Individual shaped ports with tailor-made blocks or multileaf collimator must define the irradiation target volume.

6.3 Technical Factors

6.3.1 *Beam Energy*: Patients will be treated on a megavoltage linear accelerator with 4-6 MV photons.

6.3.2 *Treatment Distance:* Minimal treatment distance to skin should be 100 cm for SSD technique, and minimum isocenter distance should be 100 cm for SAD techniques.

6.3.3 *Blocking:* Blocking will be required for shaping of the ports to exclude volume of tissues that are not to be irradiated (see Section 6.2).

6.4 Anticipated Side Effects or Toxicity

6.4.1 *Acute toxicity monitoring*: Acute (< 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 version 2.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).

6.4.2 *Acute Reactions*: Reversible alopecia, erythema and/or hyperpigmentation of scalp, pharyngitis, and mild xerostomia are expected acute reactions to radiation. Other possible but less likely acute reactions include pruritis of external auditory canals, nausea, vomitting, and headache.

6.4.3 *Late toxicity monitoring*: Late (> 90 days from RT start) side effects will be evaluated and graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix IV).

6.4.4 *Late Reactions*: Lethargy, somnolence, and/or cognitive dysfunction; radiation necrosis, accelerated atherosclerosis, and radiation-induced neoplasm are unlikely but possible late effects of brain irradiation.

6.4.5 Toxicity requiring breaks in therapy are not anticipated.

6.4.6 All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management, and to the Study Chairman within 24 hours of discovery.

6.4.7 All life-threatening (grade 4) toxicity from protocol treatment must be reported by telephone to Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.

6.4.8 Appropriate data forms, and if requested, a written report must be submitted to headquarters within 10 working days of the telephone report.

7.0 DRUG THERAPY

Concurrent cytotoxic chemotherapy or biologic therapy for treatment of cancer is not allowed.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY (12/9/03)

Patients must have completed locoregional therapy prior to study entry. While the specifics of this therapy are not set by this study, the data relating to these prior therapies will be collected by RTOG on the Initial Evaluation Form **(I1)** [See Section 12.1].

After the patient has received PCI (Arm 1) or after the study entry of patients on Arm 2, additional therapy is at the discretion of the treating oncologist. All additional treatment should be documented. No chemotherapy or maintenance therapy should be given during PCI (Arm 1).

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/24/03)

			Month							
Assessments	**Pre-Study**	**Weekly During Therapy**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**48**
History/Physical[a]	X	X	X	X	X	X	X	X	X	X[g]
Performance Status	X		X	X	X	X	X	X	X	X[g]
Laboratory studies[b]	X									
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X[g]
Pregnancy test[c]	X									
CT of chest, liver and adrenal glands[d]	X									
Bone scan[e]	X									
Brain MRI or CT[f]	X			X	X		X		X	X[g]
MMSE, HVLT, ADLS	X		X	X	X	X	X	X	X	X
EORTC QLQ-C30, BCM20	X			X	X		X		X	X

a. Should include demographics and concurrent medication(s) and should be completed within 2 weeks of study entry
b. CBC; basic chemistry including serum calcium; liver function tests including alkaline phosphatase should be completed within 2 weeks prior to study entry
c. Serum or urine pregnancy test in women of child bearing potential
d. CT of chest, liver and adrenal glands documenting stable disease, partial response, or complete response to primary therapy is required within 6 weeks prior to study entry.
e. Bone scan is required for patients with elevated serum calcium or alkaline phosphatase.
f. MRI with and without gadolinium is preferred; CT scan with or without contrast is acceptable; MRI or CT is required within 6 weeks prior to study entry. Patients evaluated with pre-treatment MRI must be followed with brain MRI; patients evaluated with pre-treatment CT must be followed with CT.
g. Annually thereafter

11.2 Evaluation During Study (6/24/03)

11.2.1 Patients randomized to Arm 1 will be evaluated weekly for acute reactions while receiving PCI. Any changes from baseline physical examination and all acute radiation reactions must be documented.

11.2.2 Patients evaluated prior to study entry with MRI of the brain will have an MRI of the brain with and without gadolinium at 6 and 12 months after study entry, then annually. Patients evaluated prior to therapy with CT of the brain will have a CT of the brain, with and without contrast, 6 and 12 months after study entry, then annually.

11.2.3 MMSE, ADLS, and HVLT will be used to assess neuropsychological status at 3, 6, 12, 18, 24, 30, 36, and 48 months after study entry (See Appendix VI and forms packet); EORTC QLQ-C30 and BCM20 will be used to assess quality of life at 6, 12, 24, 36, and 48 months after study entry (See forms packet)

11.2.4 Evaluation of the status of locoregional disease is at the discretion of the treating oncologist, although CT scan of the chest or CXR is recommended at a minimum of every 6 months.

11.3 Quality of Life Assessments (6/24/03)

11.3.1 *EORTC QLQ-C30*

The EORTC QLQ-C30 is 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.[48]

11.3.2 *BCM20*

The 20-item BCM20 contains 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 *Scoring*

All scores for both the QLQ-C30 and BCM20 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/items, higher scores indicate more of the symptom with difficulty.

11.4 Criteria for Removal from Protocol Treatment

11.4.1 The patient may elect to withdraw from study at any time for any reason.

11.4.2 Development of intercurrent, non-cancer related illnesses that prevent regular follow-up.

11.4.3 All patients will be followed until death.

12.0 DATA COLLECTION (12/9/03)

Data should be submitted to:

RTOG Headquarters
1101 Market Street, 14th Floor
Philadelphia, PA 19107

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

12.1 Summary of Data Submission

Data	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pretreatment Mini-Mental Status Exam **(MS)** Pretreatment Neurocognitive Evaluation Summary Form **(CS)** Pretreatment Activities of Daily Living Scale **(PQ)** Pretreatment QLQ-C30 & BCM20 **(QL)**	Within two weeks of study entry
Radiotherapy Form **(T1)***	Within one week of RT end
Initial Follow Up **(FS)** Mini-Mental Status Exam **(MS)** Neurocognitive Evaluation Summary Form **(CS)** Activities of Daily Living Scale **(PQ)**	Week 13 (Day 90 from start of radiation therapy)
Follow Up **(F1)**	At 6 months from start of RT; every 6 months for 2 years; then annually
Mini-Mental Status Exam **(MS)** Neurocognitive Evaluation Summary Form **(CS)** Activities of Daily Living Scale **(PQ)**	At 6, 12, 18, 24, 30, 36, and 48 months after study entry
QLQ-C30 & BCM20 **(QL)**	At 6, 12, 24, 36, and 48 months after study entry
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.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint: overall survival

13.1.2 Secondary endpoints:

13.1.2.1 Neuropsychologic impact of PCI

13.1.2.2 Impact of PCI on QOL

13.1.2.3 Impact of PCI on the incidence of CNS metastases

13.2 Sample Size (6/24/03)

13.2.1 Since there will be both operable and inoperable patients in this study, the hazard ratios of the patients in Arm 2 (no PCI) are calculated based on different combinations of these two groups of patients. According to the analysis of the RTOG database, the median survival times are 38 and 17 months for operable and inoperable patients, respectively. The hazard rate of the combined patients is calculated as $\lambda_c = x_o * \lambda_o + x_i * \lambda_i$, where x_o and x_i are the proportions of operable and inoperable patients, respectively. With 1007 evaluable patients, the table below shows statistical powers based on a 20% relative improvement in hazard rate and its associated median survival time (MST) from no PCI to PCI arms.

Proportions of (operable, inoperable) patients	λ_c	MST_c (in months)	20% Relative Improvement (in months)	Power
(25%, 75%)	0.0351	19.7	24.6	80%
(50%, 50%)	0.0295	23.5	29.4	80%
(75%, 25%)	0.0239	29.0	36.2	80%

The power calculation is based on the log-rank test with a one-sided significance level of 0.025 (type I error). Under the alternative hypothesis then, 527 total deaths will be required. Assuming 5% of the patients are either retrospectively ineligible or inevaluable due to never starting any therapy, then a total of 529 patients per arm or **1058 randomized patients will be required.**

From four previous RTOG NSCLC studies (RTOG 88-08, 90-15, 91-06, and 92-04), it was found that 23.4% of patients developed brain metastases at four years after radiotherapy treatment. Umsawasdi et al.[22] have shown that PCI significantly decreased the incidence of CNS metastases from 27% to 4% in a randomized trial. In the study of stage III NSCLC by Stuschke et al.[10], 13% of patients treated with PCI developed CNS metastases compared to 54% patients not treated with PCI.

The sample size calculation is based on two-sample binomial sampling involving two incidences of CNS metastases, with and without PCI. It is hypothesized that the incidence rates of CNS metastasis after effective locoregional/system therapy are 23.4% and 15%, without PCI and with PCI, respectively, for patients who have either partial response or complete response. Therefore, the required sample size for 91% statistical power and a one-sided 0.025 type I error, is 500 patients per arm. This sample size assumes using a Fisher's exact test.[57]

The Mini-Mental Status Examination (MMSE) is affected by age and years of education. An age- and education-adjusted cutoff level will be used to define patients with possible cognitive dysfunction.[58-59] Patients with MMSE above the cutoff will be considered not to have severe cognitive impairment. Patients at or below the cutoff will be considered cognitive failures (see table below).

MMSE Cutoff Scores				
	Education (years)			
Age	≤ 8	9-11	12	13+
< 65	26	27	27	28
65-69	25	26	27	27
70-74	24	25	26	27
75-79	23	24	25	26
80+	23	23	24	24

The cutoff points have been shown to have a sensitivity of 82% and specificity of 98% for identifying cognitive dysfunction by MMSE. The above sample size is sufficient to detect an odds ratio of 0.643 in the reduction of the proportion of patients with cognitive failures between the two arms. The sample size will ensure 90% statistical power with a two-sided significance level of 0.05.

The QLQ-C30 and QLQ-BN20 will be used in this study to test the following hypotheses:

> Ho: The proportion of patients with a clinically meaningful decline in QOL at one year is higher in patients who received PCI than in patients who did not received PCI.
>
> Ha: The proportion of patients with a clinically meaningful decline in QOL at one year is the same in patients who received PCI as in patients who did not receive PCI.

This is an equivalency test, and the corresponding statistical hypotheses are:

Ho: $p_{PCI} - p_{OBS} \geq 0.10$

Ha: $p_{PCI} - p_{OBS} < 0.10$,

where p_{PCI} is the proportion of patients on the PCI arm who have a decline in QOL at one year, and p_{OBS} is the same proportion for the observation arm. The primary QOL endpoints will be measured on three different QLQ-C30 scales: global health status/QOL, cognitive functioning, and fatigue. Secondary QOL endpoints will be measured on two QLQ-BN20 scales: future uncertainty and communications deficit. Raw scores for each of these scales will be transformed to a 100-point scale using the methods in the EORTC QLQ-C30 Scoring Manual[68]. Fatigue scores from the QLQ-C30 and the future uncertainly and communications deficit scores from the QLQ-BN2 will be subtracted from 100 so that higher scores are favorable scores for all scales. A decline for an individual patient will be calculated as a decrease in more than 10 points in the scale score from the baseline measurement to the one-year measurement.
Starting from the required sample size of 1058 and using the hazard rates $\lambda_{PCI} = 0.02818$ and $\lambda_{OBS} = 0.03510$ from above, a total of 332 deaths are expected by one year in both arms combined. Assuming that 80% of the 726 patients expected to be alive at one year participate in the QOL measurement, 581 patients are expected to have both baseline and one-year QOL measurements. Using the methods of Blackwelder[69], the following table shows the highest possible statistical power to determine that the difference $p_{PCI} - p_{OBS}$ is less than 10%, i.e., p_{PCI} is equivalent to p_{OBS}, for a sample size of no more than 581 for a range of values for p_{PCI} and p_{OBS} using a Type I error probability of 0.05.

p_{PCI} and p_{OBS}	Statistical Power	n
.1	.99	568
.2	.91	572
.3	.83	568
.4	.79	578
.5	.77	570
.6	.79	578
.7	.83	568
.8	.91	572
.9	.99	568

13.3 Patient Accrual

Patient accrual is projected to be 29 patients per month. This trial should complete the accrual phase in 36 months. If the monthly accrual is less than 15 cases per month, the study will be re-evaluated with respect to feasibility.

13.4 Randomization Scheme

The treatment allocation will be one using a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables are disease stage IIIa vs. IIIb, non-squamous cell tumors vs. squamous cell tumors, and locoregional therapy without surgery vs. with surgery.

13.5 Analysis Plans

13.5.1 *Interim Analyses of Accrual and Toxicity Data*

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- the patient accrual rate with projected completion date for the accrual phase;
- distribution of patients with respect to pretreatment characteristics;
- compliance rate of treatment delivery with respect to protocol prescription;
- the frequency and severity of the toxicities, not split by treatment.

13.5.2 *Interim Analysis of Study Endpoints*

There will be two interim analyses of the primary study endpoint (survival). The interim analyses will proceed according to the following table:

Total Number of Deaths	Significance Level
222	0.0021
444	0.0100

If a significance level is smaller than the value listed above, then the null hypothesis will be rejected. The significance level was calculated to ensure an overall significance level of 0.025 (type I error). In addition, a conditional power analysis[60] will be performed at each interim efficacy analysis. If the 95% confidence interval of the conditional power is less than 25%, then a recommendation for study discontinuation will be made to the RTOG Data Monitoring Committee. The results of these interim analyses only will be reported, in a blinded fashion, to the RTOG Data Monitoring Committee as privileged communications. A report with recommendations will be given to the study chair. Any problems or recommendations identified by the Data Monitoring Committee, not results, will be reported to the lung committee, which is responsible for this study and, if necessary, the RTOG executive committee, so that corrective action can be taken.

13.5.3 *Analysis and Reporting of Initial Treatment Results* **(6/24/03)**

This major analysis will be undertaken after all patients have been potentially followed for a minimum of 12 months or 527 deaths have occurred. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.

Overall and disease-free survival will be plotted using the Kaplan-Meier method[61] and will be analyzed using the stratified log-rank statistic with a 0.025 one-sided significance level. In addition, survival will be analyzed using a Cox proportional hazards regression model.[62] The model will include effects for treatment, age, Zubrod performance scale, and some other prognostic variables.

The incidence of CNS metastases after effective locoregional/systemic therapy will be analyzed to compare the difference between the two groups. Analysis will also be performed by means of logistic regression so that categorical response (brain metastases – yes versus no) can be appropriately associated with important prognostic variables by controlling the treatment group. The relative risk for each variable will also be determined. The distributions of times to onset of brain metastasis will be estimated for each group using Kaplan-Meier estimates and will be analyzed using the log-rank test. A Cox proportional hazards regression model, including effects for treatment, age, disease stage, locoregional therapy, and Zubrod performance score, will also be performed. Tests for interactions with treatment will be conducted. The 95% confidence interval for the median time will be calculated using the method of Simon & Lee.[63]

Analysis of the percent of patients with cognitive failure at one year will be performed using a Chi-squared test. Secondary analyses of time to cognitive failure will be performed using a cumulative incidence, comparing the treatment arms using Gray's statistic.[64] The Hopkins Verbal Learning Test (HVLT) will be analyzed in conjunction with the MMSE to aide in a secondary definition of neurologic deterioration. Time to neurologic deterioration will be performed using the cumulative incidence model.

ADLS will be scored as independent versus dependent. Independence is defined as responding "independent" to all six categories on the ADLS. Patients who require assistance in any one of the six categories will be defined as dependent.[65] The cumulative incidence method will be used to determine the time-adjusted rates of dependence.

The percentages of patients on each arm with a deterioration of QOL at one year compared to baseline in each of the three QLQ-C30 scales (global health status/QOL, cognitive functioning, and fatigue) and the QLQ-BN20 scales (future uncertainty and communications deficit) will be tested using a chi-squared test with α = 0.05, and a corresponding p-value for each test calculated. Hommel's[70] stagewise rejective multiple test procedure then will be used to determine if each individual test should be rejected. The primary and secondary QOL endpoints will be tested separately using Hommel's stagewise rejective multiple test procedure on three and two tests, respectively. Each QOL scale will also be summarized using the AUC method adjusted for mortality[71]. The AUC analysis will use the baseline, 6-month, and 12-month scores. QOL assessments within ± 14 days of the scheduled 6- and 12-month assessments will be included. Patients with no QOL assessments in the first year, or who have only one QOL assessment and who did not die in the first year will be excluded from the AUC analysis. QOL between the two arms will be compared by a t-test of the mean QOL score for each scale, using Hommel's[70] stagewise rejective multiple test procedure. The primary and secondary QOL endpoints will be tested separately in groups of three and two tests, respectively.

13.6 Gender and Minorities

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer; however, the RTOG did not show this to be the case. Furthermore, an analysis of race did not indicate an association with outcome.[66-67] In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities 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 the interim analyses described above. The projected gender and minority accruals are shown below:

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	40	58	98
Not Hispanic or Latino	360	600	960
Ethnic Category: Total*			**1058***
Racial Category			
American Indian or Alaskan Native	5	10	15
Asian	10	15	25
Black or African American	75	106	181
Native Hawaiian or other Pacific Islander	2	2	4
White	308	525	833
Racial Category: Total*			**1058***

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APPENDIX I

RTOG 0214

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE III COMPARISON OF PROPHYLACTIC CRANIAL IRRADIATION VERSUS OBSERVATION IN PATIENTS WITH LOCALLY ADVANCED NON-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 non-small cell lung cancer.

WHY IS THIS STUDY BEING DONE?

In fifty percent of patients with locally advanced non-small cell lung cancer, the cancer will spread to the central nervous system at some time during the course of their disease. The usual treatment for patients who have had effective treatment for locally advanced non-small cell lung cancer is observation or monitoring of your health.

The purpose of this study is to compare the effects (good and bad) of brain irradiation with the standard treatment of observation to see if brain irradiation results in patients living longer. The study will also evaluate whether there is a lower risk of tumor in the brain with the use of radiation. In addition, the study will evaluate the effects of brain irradiation on the thinking skills and quality of life of those patients who receive it.

This research is being done because we do not know whether or not brain irradiation helps patients with non-small cell lung cancer live longer. We also do not know if brain irradiation is safe or if it prevents growth of small tumor deposits which already may be in the brain of patients with non-small lung cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 1058 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (6/24/03)

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 into which group you are placed. Neither you nor the researcher will choose what group you will be in. You will have approximately an equal chance of being placed in one of the two groups below:

Group 1
If you are randomized to this group, you will receive radiation therapy to the brain once a day, Monday through Friday, for three weeks.

Group 2
If you are randomized to this group, you will not receive radiation therapy to the brain. Your health and progress will be monitored.

If you take part in this study, you will have the following tests and procedures:

- A physical exam prior to study entry, and at 3, 6, 12, 18, 24, 30, 36, and 48 months; If you are randomized to Group 1, you also will have a physical exam weekly during radiation therapy.
- Blood tests prior to study entry
- A bone scan, only if indicated by your blood test results
- An MRI or CT scan of your head, with and without contrast material, prior to study entry, at 6 and 12 months after study entry, then annually
- A CT scan of your chest, liver, and adrenal glands prior to study entry
- For women who are able to have children, a test prior to study entry to see if you are pregnant
- Written and verbal tests to evaluate your memory and thinking skills prior to study entry and at 3, 6, 12, 18, 24, 30, 36 and 48 months. In addition, self-report questionnaires asking about you and your health prior to study entry and at 6, 12, 24, 36, and 48 months. These tests will take about 30 minutes to complete each time you take them.

HOW LONG WILL I BE IN THE STUDY?

If you are randomized to Group 1, you will receive brain irradiation for three weeks; follow-up for both Group 1 and 2 will continue for ten years after the end of treatment.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest or if your condition worsens. You may also be taken off this study if new information becomes available about how to better prevent growth of small tumor deposits already in the brain of patients with non-small lung cancer.

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
- Memory loss, behavioral change, and/or increased sleepiness (occurring 4-10 weeks after radiation therapy is complete and often lasting for several days up to a few weeks)

Less Likely, But Serious

- Drainage from the ears or plugging of the ears with decreased hearing
- Cataracts and eye damage with the possibility of blindness
- Severe local damage to normal brain tissue, which may require surgery
- In very rare cases, growth of abnormal tissue, which may be cancerous, and/or death may result

When possible, additional medications will be offered to you, such as medications to control nausea and to minimize the side effects associated with radiation therapy.

This study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study.

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. Brain irradiation may prevent growth of small tumor deposits already in the brain, but this is not certain or guaranteed. We hope the information learned from this study will benefit other patients with non-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) monitoring of your health and progress outside of this study.

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

WHAT ABOUT CONFIDENTIALITY? (6/24/03)

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 groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, the Cancer Trials Support Unit (CTSU), and other groups or organizations that have a role in this study. The CTSU is a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

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. Medicare should be considered a health insurance provider.
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 may leave the study at any time. 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, will 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

You also may call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-549-0715 (from the continental U.S. only) or 800-937-8281, ext. 4445 (from sites outside the continental U.S.).

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 at **http://cancertrials.nci.nih.gov** or for accurate cancer information including PDQ (Physician Data Query) visit **http://cancernet.nci.nih.gov.**

Cancer Fax: Includes NCI information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, dial 301-402-5874 or 800-624-2511 from a fax machine handset and follow the recorded instructions.

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

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 *(Karnofsky 90-100)*.

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 *(Karnofsky 70-80)*.

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 *(Karnofsky 50-60)*.

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40)*.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*.

APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 5th Edition)

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, 5th Edition)

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

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

APPENDIX V

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:

Definite:	The adverse event is *clearly related* to the treatment/procedure.
Probable:	The adverse event is *likely related* to the treatment/procedure.
Possible:	The adverse event *may be related* to the treatment/procedure.
Unlikely:	The adverse event is *doubtfully related* to the treatment/procedure.
Unrelated:	The adverse event is *clearly NOT related* 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 (≥ 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. <u>Adverse Event Reporting Related to Radiation Therapy</u>

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

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

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[1,2] within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting **NOT** required.	Report by phone to IDB[1,2] 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 **NOT** required.	Report by phone to IDB[1,2] 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 **NOT** required.	Report by phone to IDB[1,2] within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting **NOT** 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).

APPENDIX VI

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 that 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.

Trial 5 — HVLT Delayed Recall

Record the time on the scoring sheet.
Note: At least 15-20 minutes should have elapsed between the time Trial 4 was completed and Trial 5 begins.

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 (9/30/04)

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

CTSU ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments :**	**To mail study forms or data:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-888-823-5923 Fax – 215-569-0206	CTSU Data Operations Center Phone – 1-888-462-3009 Fax – 1-888-691-8039 [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062

For patient eligibility or treatment-related questions, contact the Study PI or RTOG Headquarters (215-574-3214).

All other questions (including forms-specific questions) should be communicated by phone or e-mail to the CTSU Help Desk at:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at http://members.ctsu.org

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:00 a.m. and 5:00 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU before they can enroll patients. All forms and documents associated with this study can be downloaded from the RTOG-0214 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for RTOG-0214 **site registration:**

- CTSU IRB certification
- IRB/Regulatory Approval Transmittal Form
- Radiation Therapy Facility Inventory Form (NOTE: Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.)

Requirements for **patient enrollment** on RTOG-0214:

- Patient meets all eligibility criteria.
- Patient signed and dated informed consent.
- All baseline laboratory tests and prestudy evaluations performed.
- Patient completed baseline MMSE, HVLT, and ADLS neuropsychological / quality of life forms.
- CTSU registrars will confirm investigator eligibility and review enrollment documents for completeness, but cannot confirm patient eligibility.

Patients must have completed definitive locoregional therapy (with surgery and/or radiation therapy, with or without chemotherapy) [chemotherapy alone does not constitute definitive therapy] with complete response, partial response or stable disease after therapy.Patients will be restaged and enrolled within 16 weeks of completing previous therapy.

CTSU Procedures for Patient Enrollment

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0214 Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 p.m., Mon-Fri, Eastern time. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU registrar will contact the RTOG to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site by phone followed by a confirmation of registration e-mail or fax.

DATA SUBMISSION

All forms and documents associated with this study can be downloaded from the RTOG-0214 Web page located on the CTSU registered member Web site (http://members.ctsu.org). CTSU investigators should use the protocol-specific RTOG forms and adhere to the RTOG schedule for data submission (Section 12.0 of protocol). Forms and reports should be submitted to the CTSU in the following manner:

- Patient entry forms should be faxed to the CTSU according to instructions in the CTSU patient registration procedures section of the protocol.
- All other original and amended forms, reports, and responses to query and delinquency letters must be mailed directly to the CTSU accompanied by a completed CTSU Data Transmittal Form; the CTSU will then forward all information to the RTOG.
- Copies of reports that are submitted to the CTSU must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.

All CTSU report forms and data must be sent to:

Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062
Phone: 1-888-823-5923
Fax: 1-888-691-8039

A CTSU Data Transmittal Form must accompany all data submissions. Data submitted with an improperly completed CTSU Data Transmittal Form or without a CTSU Data Transmittal Form will be returned to the site for corrective action without being processed. **An RTOG study/case label should be affixed to all case report forms and source documentation.**

SPECIAL MATERIALS OR SUBSTUDIES

Neuropsychological Testing / Quality of Life (QOL): Secondary endpoints of this study are to evaluate the neuropsychological impact of PCI and the impact of PCI on patient QOL. Evaluation tools are the Mini-Mental Status Examination (MMSE), Hopkins Verbal Learning Test (HVLT), and Activities of Daily Living (ADLS). Patients are to be evaluated within the intervals outlined in section 11.0 of the protocol. Forms must be completed in accordance with the schedule in section 12.0 of the protocol and submitted to the CTSU accompanied by a CTSU Data Transmittal form.

ADVERSE EVENT (AE) REPORTING

This study will utilize the CTC version 2.0 and the RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria for AE assessment. Links to the CTC guidelines and the RTOG/EORTC criteria are available on the RTOG-0214 protocol page on the CTSU registered member Web site. CTSU investigators should employ

definitions of adverse events as described in Sections 6.4 and Appendix V (subsection ‘D’) of the protocol and all reporting should be conducted within the manner and time frames specified.

CTSU sites must comply with the expectations of their local Investigational Review Board (IRB) regarding submission of documentation of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.