

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0937

RANDOMIZED PHASE II STUDY COMPARING PROPHYLACTIC CRANIAL IRRADIATION ALONE TO PROPHYLACTIC CRANIAL IRRADIATION AND CONSOLIDATIVE EXTRA-CRANIAL IRRADIATION FOR EXTENSIVE DISEASE SMALL CELL LUNG CANCER (ED-SCLC)

Study Team (8/9/12)

Co-Principal Investigator/Radiation Oncology

Elizabeth Gore, MD
Medical College of Wisconsin
9200 W. Wisconsin Ave
Milwaukee, WI 53226
414-805-4465/FAX 414-805-4354
egore@mcw.edu

Medical Physics Co-Chair

Daniel F. Grimm, MS
Medical College of Wisconsin at Zablocki VA
5000 W. National Avenue
Milwaukee, WI 53295
414-384-2000, X46941/FAX 414-382-5380
dgrimm@va.gov

Co-Principal Investigator/Radiation Oncology

Alexander Sun, MD
Princess Margaret Hospital/Univ. of Toronto
610 University Avenue
Toronto, Ontario Canada M5G2M9
416-946-2126/FAX 416-946-6561
Alex.Sun@rmp.uhn.org

Senior Statistician

Chen Hu, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-940-48423174/FAX 215-928-0153
chu@acr.org

Medical Oncology Co-Chair

Suresh S. Ramalingam, MD
Emory University/ Winship Cancer Institute
1365 Clifton Road NE, Room C-3090
Atlanta, GA 30322
404-778-5378/FAX 404-778-5520
suresh.ramalingam@emory.edu

Document History

	Version/Update Date	Broadcast Date
Update	August 9, 2012	August 9, 2012
Amendment 2	October 21, 2011	October 27, 2011
Amendment 1	February 16, 2011	March 4, 2011
Activation	March 18, 2010	March 18, 2010

**RTOG Headquarters/Department of Statistics
1-800-227-5463, ext. 4189**

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.

INDEX

Schema

Eligibility Checklist

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations/Management
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Tissue/Specimen Submission
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Study Parameters
- Appendix III - Performance Status Scoring
- Appendix IV - Staging System

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0937

Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extra-Cranial Irradiation for Extensive Disease Small Cell Lung Cancer (ED-SCLC)

SCHEMA (10/21/11)

S	Response to Treatment	R	Arm 1: Prophylactic Cranial Irradiation
T	1. Complete Response (CR)	A	2.5 Gy per fraction for a total of 25 Gy
R	2. Partial Response (PR)	N	
A		D	Arm 2: Prophylactic Cranial Irradiation
T		O	2.5 Gy per fraction for a total of 25 Gy
I	Number of Metastatic Lesions	M	and
F	1. 1	I	Consolidative Radiation to
Y	2. 2-4	Z	Locoregional and Residual Metastatic Disease
		E	45 Gy at 3 Gy per fraction*
			*Acceptable alternative regimens: 30-40 Gy in 10 fractions

Patient Population: (See Section 3.0 for Eligibility) [2/16/11]

Patients with extensive disease small cell lung cancer, excluding CNS metastases; patients must have had radiographic evidence of 1-4 extra-cranial metastatic lesions **prior** to platinum-based chemotherapy AND have had radiographic partial or complete response to chemotherapy in a minimum of one site of disease and no progression in any site.

Required Sample Size: 154

- _____(Y) 1. Does the patient have a proven (histologically or cytologically) diagnosis of extensive disease small cell lung cancer?
- _____(Y) 2. Has the patient completed 4-6 cycles of platinum-based chemotherapy within 8 weeks of registration?
- _____(Y) 3. Prior to chemotherapy, did the patient have extensive stage disease defined as disease beyond the ipsilateral hemithorax with 1-4 metastatic lesions excluding brain metastases, with extent of disease based on the minimum diagnostic workup specified in Section 3.1.4?
- _____(Y) 4. After chemotherapy and within 8 weeks prior to registration, was the patient restaged?
- _____(Y) If yes, does the patient have:
- no CNS metastases;
 - radiographic partial or complete response to chemotherapy in a minimum of one site of disease using the RECIST criteria;
 - no progression in any site?
- _____(Y) 5. Have the pre-chemotherapy and post-chemotherapy measurements for all measurable disease been submitted?
- _____(Y) 6. Is the patient's Zubrod Performance Status 0-2?
- _____(Y) 7. Is the patient \geq 18 years of age?
- _____(Y) 8. Were all pre-registration labs done within 1 week prior to registration and are values for hepatic, renal, and bone marrow function within the parameters of eligibility specified in Section 3.1?
- _____(Y) 9. For women of childbearing potential, was a serum pregnancy test completed within 1 week of registration?
- _____(Y) If yes, was the serum pregnancy test negative?
- _____(Y/NA) 10. If a male participant who is sexually active or a woman of child bearing potential, did the patient agree to use medically acceptable forms of contraception?
- _____(Y) 11. Have all toxicities related to chemotherapy resolved to \leq grade 1 prior to initiation of study therapy (with the exception of neuropathy and alopecia)?
- _____(Y) 12. Did the patient provide study specific informed consent prior to study entry?
- _____(N) 13. Did the patient have prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields? (see Section 3.1.6 for exception)
- _____(N) 14. Did the patient have a diagnosis of limited stage disease?

Continued on next page

_____(N) 15. Does the patient have central nervous metastases?

_____(N) 16. Does the patient have any severe co-morbidities as defined in section 3.2?

The following questions will be asked at Study Registration:

3D-CRT (and if used, IMRT) CREDENTIALING IS REQUIRED BEFORE 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 patient provided study-specific consent prior to study entry
- _____ 5. Patient's Initials (First Middle Last)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.

RTOG Institution #
RTOG 0937
Case #

ELIGIBILITY CHECKLIST (8/9/12)
(page 3 of 3)

- _____ 18. Specify response to treatment (Complete Response [CR] vs. Partial Response [PR])
Note: For the purposes of stratification, a response to treatment is only considered a CR if the patient has had a complete response in all sites of measurable disease.
- _____ 19. Specify the number of metastatic lesions (1 vs. 2-4)
- _____ 20. Did the patient receive thoracic radiation therapy?
_____ If no and the patient is randomized to Arm 2 (PCI and consolidative radiation), specify the treatment approach (3DCRT or IMRT).
- _____ 21. If the patient is randomized to Arm 2 (PCI and consolidative radiation), will the patient receive treatment to metastatic site(s)?
_____ If yes, specify the most complex treatment approach (IMRT, 3DCRT, or 2D).
- _____ 22. Specify treatment approach for PCI (3DCRT or 2D).

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

- 1.1** Approximately 35,000 Americans are diagnosed with small cell lung cancer annually. The incidence of extensive disease (ED) or stage IV disease is 60-70%. This percentage of patients with ED has increased over the last 20 years, and this is at least partially due to stage migration secondary to routine use of CT scans, brain MRIs, and PET. PET alone upstages 8% of patients diagnosed with limited disease (LD) based on conventional staging (Bradley 2004; Niho 2007). Standard therapy for limited disease small cell lung cancer (LD-SCLC) is chemotherapy with concurrent thoracic irradiation followed by prophylactic cranial irradiation for patients who achieve a complete response to chemotherapy and radiation therapy. Standard therapy for ED small cell lung cancer (ED-SCLC) is chemotherapy +/- radiation therapy for symptomatic disease.

In the 1960s, multi-agent chemotherapy became the primary therapy for all stages of disease. Due to high locoregional failure rates after chemotherapy alone, thoracic radiation in combination with chemotherapy was investigated for patients with limited stage disease. Several randomized studies compared chemotherapy alone to chemotherapy and radiation (Bunn 1987; Perry 1987). Two meta-analyses confirmed locoregional control advantage with thoracic irradiation and demonstrated a 5.4% improvement in survival (Warde 1992; Pignon 1992). Other studies evaluated timing of thoracic irradiation. The current standard of care is concurrent chemotherapy and radiation, with radiation being delivered early in the course of chemotherapy (Murray 1993; Fried 2004). Locoregional control and survival is better with concurrent rather than sequential therapy but at the cost of increased toxicity. Sequential therapy is acceptable for patients who may not tolerate the added toxicity of concurrent therapy or have large tumor volumes and/or poor pulmonary function. Volume reduction with chemotherapy may allow for sparing of normal tissue and better therapy tolerance.

The current standard of care for ED-SCLC is platinum-based combination chemotherapy. Overall response rate to multi-agent chemotherapy is 40-70% (Hanna 2006), and complete response rate is estimated at 10-20%. Recurrence of disease is the rule, even following an excellent response to initial chemotherapy. Unfortunately, there are no effective treatment options for patients with recurrent disease. Therefore, efforts to improve the outcomes with initial therapy of ED-SCLC have the best chance of improving survival. Several lines of evidence suggest that the use of radiation therapy to treat patients with oligometastatic disease after systemic chemotherapy may in fact be associated with prolonged patient survival. However, this issue has not been studied adequately in well-designed prospective studies.

1.2 The Role of Thoracic Radiation Therapy in ED-SCLC

The use of radiation therapy in ED-SCLC is reserved for patients with bulky symptomatic disease, brain metastases, or other sites of symptomatic metastases. Despite this standard for ED-SCLC, which is supported by the NCCN guidelines, clinicians will frequently treat asymptomatic patients with thoracic radiation therapy and/or prophylactic cranial irradiation (PCI), if they have had a complete response (CR) or near CR to chemotherapy. This approach is supported by the fact that many patients in early studies that established the role of thoracic radiation therapy in LD-SCLC actually harbored low volume ED. At the time of the studies, technology for staging and staging requirements were limited (Bunn 1987; Warde 1992).

The treatment paradigm for LD-SCLC is based on the assumption that chemotherapy, in responding patients, eradicates sites of microscopic disease both distantly and in the regional lymphatics and that radiation is needed to maximize control of macroscopic disease. We hypothesize that the application of this concept to ED patients with favorable prognostic factors will decrease tumor volume and may improve survival and quality of life.

This approach is supported by results of a phase III trial published by Jeremic, et al. (1999). Patients with ED-SCLC were treated initially with 3 cycles of cisplatin and etoposide (CE). Those who achieved a CR or partial response (PR) locally and a CR at distant sites were treated with 2 cycles of carboplatin and etoposide +/- concurrent hyperfractionated radiation therapy to the thorax. Both groups received PCI. Median survival (17 months versus 11 months, $p=0.041$), 5-year survival (9.1% versus 3.7%, $p=0.041$), and median time to local recurrence (30 versus 22 months, $p=0.062$) were all improved in the radiation therapy group. Distant metastatic rate remained high in both groups. The majority of patients had 1-2 sites of metastatic disease at diagnosis. The pattern of failure relative to initial pattern of distant disease was not described.

Bonner, et al. (1995) evaluated the use chemotherapy and systemic radiation (sequential upper and lower hemibody radiation) in patients with ED-SCLC without brain metastases. Treatment also included thoracic radiation and PCI. Patients received 7 cycles of chemotherapy. Radiation to the brain to 17 Gy in 5 fractions was delivered during cycles 2 and 3 (34 Gy total). Radiation to the chest to 20 Gy in 5 fractions was delivered during fractions 5 and 6 (40 Gy total). Hemibody irradiation was delivered 5 weeks after completion of 6 cycles of chemotherapy. The upper body received 6 Gy in one fraction and 6 weeks later the lower body received 8 Gy in one fraction. The median survival time was 11.5 months. Five-year progression-free and overall survival was 27% and 16%. Three patients lived longer than 5 years, and 4 patients died without evidence of disease. Two patients that survived longer than 5 years received all therapy, and one received all therapy except lower hemibody irradiation. Sites of disease at diagnosis in the long-term survivors included lung, liver, retroperitoneal soft tissue, and bone.

1.3 Prophylactic cranial irradiation (PCI) [2/16/11]

The incidence of brain metastases at some point during the course of disease in patients with small cell lung cancer is nearly 80% (Nugent 1979). Even when treated, outcome is poor with significant impact on physical and psychological functioning (Fellitti 1985). Prophylactic cranial irradiation (PCI) is a component of standard management for patients with LD-SCLC (J Nat'l Comprehensive Cancer Network 2008). PCI improves survival in patients with LD-SCLC who have had a complete or near complete response to chemotherapy and radiation (Auperin 1999) and favorably alters failure patterns (Gregor 1997; Arriagada 1995).

Studies that have evaluated PCI have included all patients with complete response to chemotherapy including ED-SCLC. In the meta-analysis by Auperin, et al. (1999) approximately 15% of patients had ED-SCLC; additionally, initial staging was limited and restaging in some cases only required a chest x-ray (CXR) to document CR. Interestingly the outcomes of these studies, including patients with ED-SCLC and limited assessment to determine CR, have resulted in application of PCI to a narrowly defined patient population with LD-SCLC with extensive restaging assessments to determine CR. PCI is considered standard therapy for LD patients who, in the current era, are defined by CT scans of the chest, MRI of the brain, bone scan, and frequently, PET. Additionally, clinicians are inclined to define CR with CT rather than CXR and frequently with PET. Arguably, this restricted patient population is the most likely group to benefit from PCI. Some but not all clinicians recommend PCI in carefully selected ED patients or LD patients with PR. Further study is needed to define the benefits of PCI in a carefully defined patient population with ED.

The EORTC completed a randomized phase III trial that specifically addressed the issue of PCI for patients with ED who had responded to chemotherapy with no clinical evidence of brain metastases (Slotman 2007). Not only did they show a decrease in CNS metastases but also an improvement of overall survival at 1 year (27% versus 13%). The cumulative risk of brain metastases at 1 year was 40.4% in the observation arm and 14.6% in the therapy arm. Patients in this study did not have routine CNS imaging. Brain CT or MRI was done only if patients had symptoms of metastases. This study provides further support to the use of PCI in patients with ED-SCLC. Further study is needed to confirm the results with current staging standards in the United States.

Overall Survival (OS)

Study	Treatment	N	1yr	2 yr	5yr	Median Survival
Schiller 2001	Standard ChT Only (measured from start of primary therapy)	402	35%	5%	---	9.6 mos.
Schiller 2001	Standard ChT + Topotecan/observation (measured after completion of primary therapy)	112	25%*	8%*	---	9.3* mos.
Hanna 2006	ChT Only	331	35%	8%	0-5%	9 mos.
Jeremic 1999	ChT/RT/PCI	55	65%	38%	9.1%	17 mos.
	ChT/PCI	55	46%	28%	3.7%	11 mos.
Bonner 1995	ChT/Hemibody RT/PCI	20	50%	25%	16%	11.5 mos.
Slotman 2007	ChT/PCI	143	27%**	5%**	---	6.7 mos.**
	ChT	143	13%**	5%**	---	5.4 mos.**

Disease-Free Survival (DFS)

Study	Treatment	6 mos.	1yr	Median Survival
Schiller 2001 (measured from after completion of primary therapy)	Standard ChT Only	7%*	2%*	2.3*mos.
	Standard ChT + Topotecan	22%*	2%*	3.7* mos.
Jeremic 1999	ChT/RT/PCI	NA	58%	14 mos.
	ChT/PCI	NA	55%	16 mos.
Bonner 1995	ChT/Hemibody RT/PCI	NA	50%	NA
Slotman 2007	ChT/PCI	23.4%**	2%**	3.7 mos.**
	ChT	15.5%**	2%**	3 mos.**

*Outcomes measured from start of maintenance chemotherapy

**Outcomes measured from the time of study entry rather than from diagnosis. Median time to study entry from diagnosis was 4.2 months

1.4 Rationale for Current Study (10/21/11)

We hypothesize that consolidative thoracic radiation and radiation therapy to residual oligometastatic disease in patients with ED-SCLC who achieve a complete or partial response with platinum-based systemic chemotherapy will result in improved overall outcome. To test this hypothesis, we will conduct a randomized phase II study evaluating PCI versus PCI and consolidative radiation therapy to the primary intrathoracic disease and residual extracranial metastatic lesions patients with ED-SCLC with 1-4 extracranial metastases who achieve a CR/PR following platinum-based chemotherapy.

Radiation and chemotherapy will be given sequentially to minimize acute toxicity. It is recommended that the radiation therapy regimens are limited to 3 weeks to minimize the burden of therapy. Maximum dose allowances to normal tissues are provided and must be adhered to. In addition, all efforts should be made to design therapy that minimizes toxicity.

PCI will be delivered at 2.5 Gy per fraction to 25 Gy to all patients. Patients on Arm 2 will be treated with radiation to the mediastinum and residual metastatic lesions with 3D-CRT at 3 Gy per fraction to 45 Gy. Alternative biologically similar regimens of 30-40 Gy in 10 fractions are acceptable (see Section 6.1.2.3).

NOTE: IMRT is discouraged but permitted if it is required to comply with normal tissue dose restrictions. See Section 5.0 for pre-registration credentialing requirements.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the 1-year overall median survival rate in patients with ED-SCLC with the administration of PCI alone versus PCI with consolidation extracranial RT following platinum-based chemotherapy

2.2 Secondary Objectives

- 2.2.1 To compare treatment-related adverse events;
- 2.2.2 To evaluate patterns of failure;
- 2.2.3 To compare the time to first failure;
- 2.2.4 To evaluate the percentage of the planned radiation dose given to each site.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (8/9/12)

- 3.1.1 Pathologically (histologically or cytologically) proven diagnosis of extensive disease small cell lung cancer without brain metastases and with 1-4 metastatic lesions; **Note:** This does NOT include patients initially diagnosed with LD-SCLC who have progressed.
- 3.1.2 Patients must have completed 4-6 cycles of platinum-based chemotherapy.
- 3.1.3 Patients must be registered on study within 8 weeks of completing chemotherapy.
- 3.1.4 **Prior to chemotherapy** (at diagnosis), patients must have extensive stage disease with 1-4 extracranial metastatic lesions (no brain metastases). For example, the patient could have 2 lesions in the liver and 2 in the contralateral lung; or 1 in the bone, 1 in the contralateral lung, and 2 in the liver; or 3 liver lesions and 1 in the bone, etc. Lesion is not defined as “organ”.

The patient should have no clinical signs or symptoms of CNS metastases. Brain imaging is not required prior to chemotherapy if the patient is asymptomatic; however, brain imaging is required and must be negative for metastases prior to study entry. Extent of disease will be based on the following minimum diagnostic workup:

- 3.1.4.1 History/physical examination;
- 3.1.4.2 CT of the chest and abdomen with contrast or PET/CT. ;
- 3.1.5 **After chemotherapy**, patients will be **restaged** using the following diagnostic work up :
 - History/physical examination;
 - CT of the chest and abdomen with contrast (does not have to be done if the patient has had a PET/CT scan within 8 weeks prior to registration);
 - Bone scan (does not have to be done if the patient has had a PET scan within 8 weeks prior to registration);
 - MRI of the brain or CT with contrast of the brain, if MRI is contraindicated.

Patients must have:

- no CNS metastases;
- radiographic partial or complete response to chemotherapy in a minimum of 1 site of disease using RECIST criteria (**see Section 11.4**); **Note:** if radiation has been delivered to primary disease with chemotherapy, there must be complete or partial response in at least 1 of the sites that has not been treated with radiation.
- no progression in any site;
- for the purposes of stratification, a response to treatment is only considered a “CR” if the patient has had a complete response in all sites of measurable disease.
- 3.1.6 Patients who have had thoracic radiation concurrently or prior to chemotherapy for the current diagnosis and meet all other eligibility criteria are eligible for the study but will not receive mediastinal radiation per protocol.
 - 3.1.6.1 Measurements for all pre- and post-chemotherapy measurable disease must be submitted.
- 3.1.7 Zubrod Performance Status 0-2;
- 3.1.8 Age \geq 18;
- 3.1.9 For patients who will be treated with radiation to the liver, adequate hepatic function, defined as follows:
 - 3.1.9.1 Serum ALT and AST within 2.5 X ULN within 1 week prior to registration;
 - 3.1.9.2 Serum bilirubin $<$ 1.5 X ULN within 1 week prior to registration.

- 3.1.10 For patients who will be treated with radiation to the kidneys, adequate renal function defined as a serum creatinine < 1.5 X ULN within 1 week of registration;
- 3.1.11 CBC/differential obtained within 1 week prior to registration, with adequate bone marrow function defined as follows:
 - 3.1.11.1 Absolute neutrophil count (ANC) \geq 1,000 cells/mm³;
 - 3.1.11.2 Platelets \geq 75,000 cells/mm³;
 - 3.1.11.3 Hemoglobin \geq 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dl is acceptable.).
- 3.1.12 For women of childbearing potential, a negative serum pregnancy test within 1 week of registration;
- 3.1.13 All toxicities related to chemotherapy must be resolved to \leq grade 1 prior to initiation of study therapy (with the exception of neuropathy and alopecia, which may take a longer period to recover). Laboratory abnormalities, with the exception of those specified in Sections 3.1.9, 3.1.10, and 3.1.11, are allowed if they are not deemed clinically significant.
- 3.1.14 Patients must provide study-specific informed consent prior to study entry.
- 3.2 Conditions for Patient Ineligibility**
 - 3.2.1 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields (see Section 3.1.6 for exception);
 - 3.2.2 Limited stage disease at diagnosis;
 - 3.2.3 Central nervous metastases;
 - 3.2.4 Severe, active co-morbidity, defined as follows:
 - 3.2.4.1 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - 3.2.4.2 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration.
 - 3.2.5 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

See Appendix II; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.2 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended prior to treatment as part of good clinical care of patients on this trial but are not required.

- 4.2.1 Pulmonary function tests;
- 4.2.2 Whole body PET scan;
- 4.2.3 Formal consultation by a nutritionist.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for 3DCRT or IMRT Treatment Approaches

- 5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3DCRT Quality Assurance Guidelines may enter patients onto this study using that treatment modality. Additional guidelines are provided for institutions intending to use an IMRT treatment approach.
- 5.1.2 The Facility Questionnaire (one per institution, available on the ATC web site at <http://atc.wustl.edu>) is to be sent to RTOG for review prior to entering any cases. Institutions intending to use IMRT should indicate this on the questionnaire by entering both 3D-DRT and IMRT in Part I of this questionnaire. Institutions are encouraged to complete information relating to IGRT if they will use this technology (IGRT is not required for this protocol). **The questionnaire must be updated for each new protocol opened by the institution.** Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this

requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.2 Additional Pre-Registration Requirements for Institutions Using IMRT Treatment Approach

5.2.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit <http://rpc.mdanderson.org/rpc> and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at <http://rpc.mdanderson.org/rpc/>; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.3 Regulatory Pre-Registration Requirements (8/9/12)

5.3.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/readfile.aspx?fname=public/CTSU-IRBcertif_Final.PDF

The study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.cocccg.org. This must be done prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
***Note:** Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.3.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.3.2 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.3.2.1 For institutions that do not have an approved LOI for this protocol:

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See <http://www.rtog.org/LinkClick.aspx?fileticket=0tMdct9KHSs%3d&tabid=117>

5.3.2.2 For institutions that have an approved LOI for this protocol:

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.4 Registration (10/21/11)

5.4.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://phrp.nihtraining.com/users/login.php>).
- A representative from the institution must complete the Password Authorization Form (<http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219>), and fax it to 215-923-1737. RTOG Headquarters

requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrrs.org

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

NOTE: INTENSITY MODULATED RT (IMRT) IS DISCOURAGED BUT PERMITTED IF IT IS NECESSARY TO COMPLY WITH NORMAL TISSUE DOSE RESTRICTIONS. See Section 5.0 for pre-registration credentialing requirements.

Questions regarding radiation therapy should be directed to the Principal Investigator, Dr Gore.

Patients must be registered on study within 8 weeks of completing chemotherapy.

6.1 Dose Specifications (10/21/11)

6.1.1 Prophylactic Cranial Irradiation (PCI)

All patients will receive PCI in 10 daily fractions of 2.5 Gy, 5 days per week, to a total dose of 25 Gy. 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.

6.1.2 Thoracic Radiation and Radiation to Metastatic Disease

6.1.2.1 Thoracic Radiation

Patients on Arm 2, with the exception of those that received thoracic radiation therapy prior to or concurrent with chemotherapy, will receive thoracic radiation to the site of original primary disease and involved regional lymphatics.

6.1.2.2 Radiation to Metastatic Disease

Patients on Arm 2 will be treated to radiographic residual disease that has not completely responded to chemotherapy and/or is symptomatic (up to 4 sites excluding the primary disease and regional lymphatics).

6.1.2.3 Radiation Dose

The recommended maximum total dose to all sites is 45 Gy given in 15 daily fractions of 3 Gy. Alternatively, 30-40 Gy in 10 fractions is acceptable. The maximum dose for any

contiguous volume of no more than 2 cc inside the PTV must not exceed 120% of the prescribed dose. Safe delivery of treatment with limited acute toxicity is a priority. It is appropriate to adjust the total prescribed dose to meet normal tissue dose constraints. The treatment plans for the chest and the metastatic lesions will be normalized such that the plan should cover 95% of the PTV with the prescription dose. The minimum PTV dose must not fall below 95% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections. Superposition/convolution dose calculation algorithms must be used for this protocol. Institutions using alternative algorithms (i.e., Clarkson or pencil beam) will not be allowed to register patients for this protocol.

- 6.1.3** All protocol therapy should be completed over a time period of 2-5 weeks. PCI should be started on day 1 of radiation therapy. Other sites should be treated concurrently with PCI if possible. Sequencing of protocol therapy will be left to the discretion of the treating physician and will depend on anticipated tolerance to therapy with regards to acute reactions and practical arrangements of daily therapy.

6.2 Technical Factors

- 6.2.1** Beam Energy: 4-6MV beam energy is to be used for PCI and 6MV is recommended for mediastinal and lung irradiation. Beam energy and type will be left to the discretion of the treating radiation oncologist in order to obtain the best dose distribution for the site being treated. In general, megavoltage photon beams will be used. Electrons may be used if this provides the best dose distribution.

- 6.2.2** Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.

6.3 Localization, Simulation, and Immobilization (10/21/11)

6.3.1 PCI

Simulation must be done prior to the start of PCI. Patients will be supine with radio-opaque markers placed at the lateral orbital canthi to assist in blocking the lenses. Aquaplast or similar immobilization per institution standard must be used.

6.3.2 Mediastinum/Lung and Metastatic Disease

- 6.3.2.1** A volumetric treatment planning CT study will be required for treatment of primary disease and regional lymphatics. Volumetric planning is recommended for the metastatic sites. An exception is treatment of peripheral skeletal lesions that does not involve treatment of esophagus, intra-thoracic, abdominal, or pelvic organs. In these cases, it must be possible to localize the skeletal lesions on simulation films.

- 6.3.2.2** Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices will be obtained through the regions harboring gross disease and the entirety of all organs in the treatment field. This is necessary for proper volumetric studies. At a minimum, scans are obtained from the level of the cricoid cartilage and inferiorly through the entire liver for treatment of the primary disease and regional lymphatics. If infra-diaphragmatic disease is to be treated, the scan will extend through the entire pelvis. One scan will be used for all treatment planning for proper calculation of cumulative doses to GTV, PTV, and normal tissues.

6.4 Treatment Planning/Target Volumes

6.4.1 PCI

The target volume is the entire intracranial contents. There should be at least a 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. Individual shaped ports with tailor-made blocks or multileaf collimator must define the irradiation target volume.

6.4.2 Mediastinum/Lung and Metastatic Disease

The definitions of volumes will be in accordance with the 1993 ICRU Reports #62.

- 6.4.2.1** Definition of GTV: Gross tumor volume (GTV) will include known disease as determined by physical examination and post-chemotherapy imaging studies. Regional thoracic lymph nodes > 1 cm short axis diameter on diagnostic or planning CT or positive on PET will be included in the thoracic GTV and labeled GTVn. If multiple nodes are contoured, they will be distinguished numerically (GTVn1, GTVn2, etc.) Separate GTVs will be defined for each extra-cranial treatment site. Each GTV should be uniquely identified either by number or treatment site and designated as GTVm. Each GTVm will be uniquely identified by number

(GTVm1, GTVm2, etc.). The Uniform Tissue Naming scheme for RTOG trials is available at http://atc.wustl.edu/resources/RTOG-ATIC/ATIC-ATC_Uniform_Tissue_Names.pdf.

6.4.2.2 Definition of CTV: Recommended clinical target volume (CTV) is GTV + 0.5 cm to account for microscopic extension of tumor. CTV=GTV plus 0-1.0 cm is allowed. It is acceptable to have CTV=GTV to protect critical structures. Alternatively for tumors with indistinct margins, CTV=GTV+1.0 cm may be preferred. For patients that have had a complete response to chemotherapy at the primary site and regional lymphatics, the CTV will be defined as the region of origin of clinically evident disease at diagnosis. This is not the same as pretreatment volume. For example, if the patient had a 10 cm mediastinal mass that involved the paratracheal and subcarinal lymph nodes and had a complete response to chemotherapy, the CTV would not necessarily be a 10 cm volume but rather a carefully defined volume including the subcarinal and paratracheal tissues. CTVs will be labeled to correspond to the appropriate GTV. In general, each GTV will have a CTV. In some situations, the CTVs may overlap and can be combined into one CTV.

6.4.2.3 Definition of PTV: The planning target volume (PTV) is the CTV plus a margin to account for treatment set-up uncertainty and motion. In most cases CTV + 1.5 cm=PTV. For all treatment sites, a 0.5 cm margin should be added to the CTV for set-up uncertainty. A 1 cm margin should be added to the CTV for internal motion if free breathing CTs are used for planning. This may be reduced to 0.5 cm for breath hold or gating techniques or if ITV approach is used to define the GTV through the use of 4DCT. PTVs will be labeled to correspond to appropriate CTV. In general, each CTV will have a PTV. In some situations the PTVs may overlap and can be combined into one PTV.

6.4.2.4 3DCRT Treatment Planning: The PTVs are to be treated with any combination of coplanar or non-coplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to normal tissues. Field arrangements will be determined by the 3D planning to produce the optimal conformal plan in accordance with volume definitions. Plans for all treated sites will be included on the same planning CT scan in order to calculate cumulative dose to the PTVs and organs at risk. The treatment plan used for each patient will be based on an analysis of volumetric dose including DVH analysis of the cumulative dose to each PTV and all critical normal structures.

6.4.2.5 IMRT Treatment Planning: IMRT is allowed as long as the participating institution is credentialed by the RTOG for intra-thoracic IMRT treatments (see Sections 5.1-5.2).

6.5 Critical Structures

Organ	Dose Constraint		
Lung	V20 < 30% MLD < 20Gy		
Liver	> 700 cc < 18 Gy		
Each Kidney	V18 < 25 %		
Spinal cord/Brachial plexus	Maximum dose 40 Gy (≤ 2.5 Gy per fraction) Maximum dose 36 Gy (> 2.5 - ≤ 3 Gy per fraction) Maximum dose 30 Gy (> 3 Gy per fraction)		
Heart/Pericardium	Maximum dose 105% prescribed dose AND V45 < 30%		
Esophagus	Maximum dose 105% of prescribed dose		
Small Bowel	Dose (Gy)	3 Gy/Fx	4 Gy/Fx
		Recommended Maximum Volume	
	30	150 cc	100 cc
	35	100 cc	50 cc
	40	50 cc	1 cc
	45	1 cc	0
50	0	0	

6.6 Documentation Requirements

- 6.6.1 Portal images of each field must be obtained on or before the first day of therapy but will not be submitted.
- 6.6.2 Verification films of each site will be done weekly, but not submitted.
- 6.6.3 Cone beam or other in-room imaging for set-up and field verification are allowed.
- 6.6.4 Isodose plans for 3-D radiotherapy and DVHs of GTV, PTV, and critical structures are required for all sites requiring 3-D planning and will be submitted. Although 3-D planning is not required for brain and peripheral skeletal sites, it is recommended.
- 6.6.5 Images and dosimetry information for treatment fields treated with 2D planning are not required to be submitted (see Section 12.0 for details of data submission).

6.7 Compliance Criteria

6.7.1 Variations in Dose Prescription for Thoracic Irradiation and Metastatic Sites

- 6.7.1.1 Per Protocol: Dose delivered as per Section 6.1.2.
- 6.7.1.2 Variation Acceptable: Deviations of this magnitude are not desirable but are acceptable. The minimum dose within the PTV falls below 95% of the prescribed dose, but is not less than 93% of this dose. The dose to any contiguous volume of more than 2 cc inside the PTV exceeds 20% of the prescribed dose but does not exceed 25%.
- 6.7.1.3 Deviation Unacceptable: These dose within the PTV falls outside of the minimum and maximum limits stated in Section 6.4.2.3. More than 1 cm³ of tissue outside the PTV receives \geq 120% of the prescribed dose, or 93% of the prescribed dose.

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Principle Investigator, Elizabeth Gore, MD, will perform an RT Quality Assurance review after complete data for the first 20 cases enrolled have been received at ITC and/or RTOG Headquarters. Dr. Gore will perform the next review after complete data for the next 20 cases enrolled have been received at ITC and/or RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at ITC and/or RTOG HQ, whichever occurs first.

6.9 Radiation Therapy Adverse Events (2/16/11)

Toxicity will be assessed using version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

Alopecia, skin hyperpigmentation, and erythema are likely in all treatment fields. It is likely that all patients treated on study will develop some level of fatigue. Side effects of treatment will vary depending on the location of disease and volume of normal tissues in the radiation therapy portals. All attempts should be made to minimize side effects by limiting the normal tissue in the radiation therapy portals and adhering to the normal tissue dose constraints of this study.

6.9.1 Additional Adverse Events Associated with PCI

- 6.9.1.1 Acute Reactions: Pharyngitis, and mild xerostomia are expected acute reactions to radiation. Other possible but less likely acute reactions include pruritus of external auditory canals, nausea, vomiting, and headache.
- 6.9.1.2 Late Reactions: Lethargy, somnolence, and/or minor cognitive dysfunction and cataracts are possible late effects. Other possible but rare late effects include damage to the eye with the possibility of blindness, accelerated atherosclerosis, severe neuropsychological dysfunction, and radiation-induced neoplasm.

6.9.2 Additional Adverse Events Associated with Lung/Mediastinal Radiation

- 6.9.2.1 Acute Reactions: Cough and esophagitis (if the esophagus is included in the radiation therapy portal) are likely. Severe esophagitis requiring IV hydration, therapy interruption, or feeding tube, severe cough, shortness of breath, and hemoptysis are possible but less likely.
- 6.9.2.2 Late Reactions: Asymptomatic fibrotic changes in the lung seen on chest imaging are likely. Severe fibrosis of lung resulting in severe respiratory compromise, symptomatic esophageal stricture, radiation pericarditis, and myocardial injury, spinal cord injury, and brachioplexopathy are possible but unlikely side effects of radiation.

6.9.3 Additional Adverse Events Associated with Abdominal/Pelvic Radiation

- 6.9.3.1 Acute Reactions: Anorexia, diarrhea, nausea, and vomiting are likely but dependent on the volume of stomach and bowel in the treatment fields. Urinary urgency and dysuria are likely if the bladder is in the radiation therapy fields. Severe nausea, vomiting, and/or diarrhea that requires therapy interruption or IV fluid replacement, abnormal liver function or renal function tests, and low blood counts are less likely but possible.

- 6.9.3.2 Late Reactions: Radiation myelitis, hepatitis, nephritis, bowel obstruction or perforation, radiation cystitis, or proctitis are possible but unlikely.
- 6.9.4 Additional Adverse Events Associated with Radiation to the Soft Tissues or Bones in the Extremities
- 6.9.4.1 Acute Reactions: Minor skin reactions are likely; moist desquamation is possible but unlikely.
- 6.9.4.2 Late Reactions: Swelling of the treated region is possible. Pathologic fracture of the bone, severe debilitating swelling, weakness, and radiation-induced neoplasm are possible but unlikely.
- 6.9.5 Treatment of Adverse Events:
All attempts should be made to limit the symptoms and the overall impact of acute and late effects of radiation. Gastrointestinal side effects including esophagitis, nausea, vomiting, and diarrhea can result in dehydration and associated complications. Anti-emetics should be used for abdominal treatment. Diarrhea should be managed with diet modification and Imodium® or Lomotil®. Esophagitis should be treated empirically for candidiasis with fluconazole or nystatin, and managed with topical anesthetic, H2 blocker or proton pump inhibitor, NSAID or narcotic pain medications, if necessary.

6.10 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements (8/9/12)

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

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

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

AdEERS REPORTING REQUIREMENTS (2/16/11)

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. Version 4 of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)). Use the patient’s case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS **must also be reported to RTOG on the AE case report form (see Section 12.1)**. In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of the Intervention^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days		

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the intervention was last administered. Footnote “1” above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials: Not applicable to this study.

RTOG REPORTING REQUIREMENTS (2/16/11)

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the descriptions and grading scales found in version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. Version 4 of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of CTCAE v. 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

6.10.1 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [2/16/11]

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE v. 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.0 DRUG THERAPY

Concurrent chemotherapy is not allowed during study therapy.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of assessments and time frames.

11.2 Details of Pre-Treatment Evaluations (2/16/11)

11.2.1 For restaging after chemotherapy, the CT of the chest and abdomen with contrast does not have to be done if the patient has had a PET/CT scan within 8 weeks prior to registration.

11.2.2 For restaging after chemotherapy, the bone scan does not have to be done if the patient has had a PET scan within 8 weeks prior to registration.

11.2.3 Evaluation of liver function only is required if the liver will be included in the therapy fields, and serum creatinine only is required if one or both kidneys will be included in the therapy fields (see Sections 3.1.9 and 3.1.10).

11.3 Details of Evaluations During Follow Up (8/9/12)

11.3.1 Patients will be seen at 2 weeks, 1 and 2 months after completion of therapy (2 months after completion of therapy is the same as 3 months from the start of treatment), at 6, 9, and 12 months from the start of treatment; every 6 months for years 2 & 3; then annually.

11.3.2 At Every Visit

11.3.2.1 History and physical (including documentation of performance status) toxicity assessment (using CTCAE, v. 4), CBC, liver function tests (AST, ALT, serum bilirubin) **NOTE:** Evaluation of liver function only is required if the liver was included in the therapy fields, and serum creatinine only is required if one or both kidneys were included in the therapy fields.

11.3.3 Two Months After Completion of Therapy

11.3.3.1 History and physical (including documentation of performance status) toxicity assessment, CT scan of the chest and abdomen or PET/CT scan, MRI or CT of the brain, imaging of all previously involved sites, CBC, liver function tests (AST, ALT, serum bilirubin) if the liver was included in the therapy fields, and serum creatinine if one or both kidneys were included in the therapy fields. Measurements of all treated measurable lesions is required, and response must be reported using RECIST criteria.

11.3.4 Thoracic Imaging (CT of the chest with contrast or PET/CT)

11.3.4.1 Thoracic imaging will be done at 2 months following the completion of therapy and at every subsequent visit.

11.3.5 Brain Imaging (MRI of the Brain or CT with contrast, if MRI is contraindicated)

11.3.5.1 Brain imaging will be done at 2 months following the completion of therapy. Brain imaging is recommended for all patients at subsequent visits and is required if patients have symptoms of CNS disease, including the following:

- Signs of increased intracranial pressure;
- Headache;
- Nausea/vomiting;
- Cognitive or affective disturbances;
- Seizures;
- Focal neurologic symptoms.

11.3.6 Bone Scan

11.3.6.1 A bone scan is required at follow-up visits if PET has not been done.

11.3.7 Other Imaging

11.3.7.1 Imaging of all sites that have been treated will be imaged at 2 months and at all subsequent visits to evaluate new or progressive symptoms.

11.4 Response Assessment (8/9/12)

11.4.1 Measurement of Response Prior to Study Entry

The revised RECIST guideline, v. 1.1 [*European Journal of Cancer*. 45: 228-247, 2009] will be used as a guideline to determine study eligibility. See http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

11.4.2 Response Criteria: Evaluation of Target Lesions

- | | |
|---------------------------|--|
| Complete Response (CR): | Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD): | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). |
| Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study |

11.4.3 Assessment of Failure Patterns

Disease failure is defined as:

- Progressive disease (section 11.3.2) in areas treated with radiation;
- Development of measurable disease at sites that had achieved a CR either with chemotherapy prior to study entry or following radiation;
- Development of new disease characteristic of SCLC dissemination as determined by imaging and physical examination.

12.0 DATA COLLECTION

Data should be submitted to:

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

***If a data form is available for web entry, it must be submitted electronically.**

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 (10/21/11)

Item	Due
Demographic Form (A5)	2 weeks after registration
Initial Evaluation Form (I1)	
Follow-up Form (F1)	At 2 weeks and at 1 month after completion of therapy; every 3 months from the start of treatment for the first year; every 6 months for years 2-3; then annually.
Dosimetry Information for All Treated Sites	Within 1 week of end of RT
Daily Treatment Record (T5) [Copy sent to HQ and ITC]	
Radiotherapy Form (T1) [Copy sent to HQ and ITC]	

Note: Dosimetry information for all treated sites with 3DCRT and IMRT will be submitted to ITC.

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

For All Treated Sites with 3DCRT and IMRT	Due
Preliminary Dosimetry Information (DD)	
†Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
<ul style="list-style-type: none"> • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV) 	
Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)	
Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)	
NOTE: Sites must notify ITC via e-mail	

(itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form (T1) [copy to HQ and ITC]	
Daily Treatment Record (T5) [copy to HQ and ITC]	
Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	
†Available on the ATC web site, http://atc.wustl.edu/	

NOTE: ALL PORTAL FILMS AND SIMULATION FILMS FOR PCI AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Overall survival (death due to any cause)

13.1.2 Secondary Endpoints

- Comparison of treatment-related adverse events;
- Patterns of failure (see Section 11.4.2 and 11.4.3);
- Comparison of time to first failure;
- Evaluation of the percentage of the planned radiation dose to each site.

13.2 Sample Size

13.2.1 Stratification and Randomization

Patients will be stratified before randomization according to response to therapy (complete response [CR] vs. partial response [PR]), and the number of metastatic lesions (1 vs. 2-3). Patients will be randomized to 1 of 2 treatment arms until the accrual of each arm is met in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.2.2 Sample Size Derivation

The sample size calculation is based on the primary endpoint, overall survival at 1 year, and the assumption that patients are randomized until the end of accrual. The sample size is calculated with the 1-sided significance level of 0.1 (the probability of false positive) and 80% statistical power (the probability of a false-negative result is 0.2) using a 1-sided, 2-sample log rank test (Mantel 1966; Kim 1990). We assume that the overall survival function follows an exponential distribution for each arm. Accrual to the study is assumed to be uniformly distributed. The null hypothesis (H_0) is that the experimental treatment is not effective versus the alternative hypothesis (H_A) that the experimental treatment is effective. The hypotheses are:

$$H_0: S(t_2) \leq S(t_1) \text{ vs. } H_A: S(t_2) > S(t_1)$$

where, $S(t_1)$ denotes the overall survival function in Arm 1 and $S(t_2)$ denotes the overall survival function in Arm 2.

We hypothesize that the patients randomly assigned to the Arm 1 have a 1-year overall survival rate similar to 30% (hazard rate $[\lambda_c]$ of 1.204) (Slotman, 2007) and those in Arm 2 will have a 1-year overall survival rate at least 45% (hazard rate $[\lambda_i]$ of 0.799), which is translated to the hazard ratio of $\lambda_i/\lambda_c = 0.663$. Two interim analyses and a final analysis are planned for early stopping for efficacy and futility. The efficacy testing is based on the power family of test (Pampallona 1994) with $\Delta=0$ and the futility testing is based on the Freidlin and Korn (2005) method at a nominal significance level of 0.005. The number of events required is 112, so a sample size of 146 patients will be accrued to achieve the desired 80% statistical power and 1-sided significance level of 0.1. Guarding against an ineligibility or lack-of-data rate of up to 5%, **the final targeted accrual for this study will be 154 patients.**

13.2.3 Patient Accrual

Based on patient accrual in previous RTOG studies, the initial 6-month accrual will be negligible while institutions are obtaining IRB approval. In a previous RTOG study of SCLC, RTOG 0212, 4.4 patients were accrued per month. Assuming these conditions, we expect to accrue 6 patients per month for this study. We project to complete accrual in 3.7 years with a 3.2-year accrual period considering the first 6 months a starting period and a uniform accrual rate of 4 patients per month. The final analysis is projected to be done in 5 (4.7) years, when each patient has been followed for at least 1 year.

The RTOG Data Safety Monitoring Board (DSMB) will begin evaluating patient accrual semi-annually following the anticipated initial quiet period. The participation of non-RTOG institutions and cooperative groups through CTSU is expected to follow a similar pattern as seen in prior RTOG trials.

13.3 Analysis Plan

Only patients that meet the eligibility requirements of this protocol and start protocol treatment will be included. Analyzable patients are defined as eligible patients who received any protocol treatment.

The result from this phase II trial does not give definitive results. However, we will consider the results from this trial as convincing if the level of evidence favoring a beneficial effect for one arm. A phase III study should be pursued in order to reliably define the treatment's contribution to the therapy.

13.3.1 Analysis of the Primary Endpoint

The analysis for reporting the initial results of treatment will be undertaken when each analyzable patient has been potentially followed for a minimum of 12 months.

The failure event of the primary endpoint, overall survival, is a death due to any cause. Time to failure event is defined as time to death from randomization date. The Kaplan-Meier method (1958) will be used to estimate overall survival at 1 year. This hypothesis will be tested using a log-rank test statistic (Mantel 1966; Kim 1990) at a significance level $\alpha = 0.1$. The hypotheses are:

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

where λ_1 and λ_2 are the hazard rate for Arm 1 and Arm 2, respectively.

Cox proportional hazards regression (1972) will be used to model the association of covariates with the time to overall survival. Both unadjusted and adjusted hazard ratios and the respective 80% confidence interval will be computed. Appropriate covariates, such as the treatment arm, the stratification variables (response to therapy and the number of metastatic lesions), age, and race (as appropriate) will be adjusted for in this analysis. The distribution of bone marrow metastasis between the 2 arms will be monitored and any imbalance will be adjusted in the analysis if needed.

The following will be reported at the time of primary endpoint analysis:

- Tabulation of all cases entered and any patients excluded from the analysis with reasons for exclusion;
- Patient accrual rate;

- Institutional accrual;
- Distribution of important prognostic baseline and other pretreatment variables;
- Frequency and severity of adverse events;
- Compliance rates of treatment delivery with respect to the protocol prescription.

13.3.1.1 Group Sequential Testing for Early Termination and Reporting of Efficacy and Futility

A group sequential test with two planned interim analyses and a final analysis will be performed. The interim analysis will be carried out when the cumulative deaths are met. At each planned interim analysis, the p-value from the log-rank test statistic assessing treatment efficacy and futility with respect to the primary endpoint, OS, will be compared to the nominal significance level. The efficacy testing is based on the power family of test (Pampallona 1994) with $\Delta=0$ (see Table below for nominal significance level for efficacy testing) and for the futility testing boundary we will use a less aggressive boundary, Rule C (at a nominal significance level of 0.005) in Freidlin and Korn (2005). The following hypotheses are tested:

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

where λ_1 and λ_2 are the hazard rate for Arm 1 and Arm 2, respectively. If the H_0 is rejected, then we conclude that the OS rate of Arm 2 will be better than Arm 1 and stop accrual if applicable.

Schedule for the Planned Interim Analysis

Information Time	Estimated Analysis Time*	Cumulative Number of Deaths in the Two Arms	Nominal Significance Level for Efficacy (Z-value)
0.33	1.1 years	37	0.008 (2.39)
0.67	1.8 years	75	0.049 (1.69)
1.00	2.4 years	112	0.1 (1.38)

*Time to the interim analysis from the first patient entry without considering ineligibility or lack-of-data rate and under the null hypothesis

For futility testing, the alternative hypotheses, $H_A (\lambda_1 = \lambda_2 + 0.405)$ will be tested at 0.005 level (the futility nominal significance level). If the computed p-value is less than 0.005, then we will **consider stopping the trial in favor of the H_0 and will conclude that the overall survival rate of Arm 1 will be better than Arm 2. Otherwise, we will continue the trial.**

13.3.2 Analysis of the Secondary Endpoints (2/16/11)

13.3.2.1 Comparison of Incidence of Treatment-Related Adverse Events

The rate of treatment-related adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE, v. 4) will be reported with the frequency and severity by arm. The analysis will be performed at the time of primary endpoint analysis. Logistic regression (Agresti 1990) will be used to model the distribution of adverse events with and without adjusted for covariates. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed and tested using a one-sided Chi-Square test statistic with the significance level of 0.025. At least the treatment arm, the stratification variables (response to therapy and the number of metastatic lesions), age, and race (as appropriate) will be considered when it is adjusted in the analysis.

13.3.2.2 Patterns of Failure

The analysis will be performed at the time of primary endpoint analysis. The frequency table by site(s) of first failure will be tabulated by treatment arm. Disease failure is defined as:

- Progressive disease in areas treated with radiation;
- Development of measurable disease at sites that had achieved a CR either with chemotherapy prior to study entry or following radiation;
- Development of new disease characteristic of SCLC dissemination as determined by imaging and physical examination.

13.3.2.3 Comparison of Time to First-Failure

The analysis of the first failure endpoint will be performed at the time of primary endpoint analysis when all analyzable patients have at least a minimum of 12 months follow-up. Disease failure event is defined in Section 13.4.2.2. Time to first-failure is measured from the date of randomization to the earliest event or to the date of most recent follow-up if no event

occurred. The treatment effect on disease failure events may impact the observable measures of outcomes and other competing risks may dilute the sensitivity. We will use the cause-specific hazard rate (Kalbfleisch 1980; Gaynor 1993) [the instantaneous rate of disease failure events in the presence of competing failure types as a function of time] approach to consider the competing event, specifically, death without a disease failure event. Freidlin and Korn (Freidlin 2005) showed that the cause-specific hazard rate approach is better than other approaches in most cases, such as, for example, the cumulative incidence method (Gray 1988). The log-rank test on the times to first failure, which considers the presence of death without a disease failure event (competing event), will be used to test whether the failure rates in Arm 1 are higher than that of Arm 2 at a significance level of 0.1 (one-sided test). In addition, Fine and Gray's regression (Fine 1999) will be used. Both unadjusted and adjusted hazard ratios and the respective 80% confidence interval will be computed. Appropriate covariates, such as the treatment arm, the stratification variables (response to therapy and the number of metastatic lesions), age, and race (as appropriate) will be adjusted for in this analysis. Further subgroup analyses will be undertaken if the sample sizes involved in each subgroup are adequate to support such analyses

13.3.2.4 Evaluation of the Percentage of the Planned Radiation Dose Given to Each Site

This analysis will be done at the first protocol specified interim analysis. The distribution of the percentage of the planned RT dose by site in each arm will be calculated.

13.3.3 Interim Analysis for Unacceptable Adverse Events (2/16/11)

Two interim analyses of adverse events (AEs) are planned after 15 and 30 analyzable patients have been accrued in each arm and have at least a minimum of 12 months follow up. The interim analysis will include all of the treatment-related AEs reported at the time of the interim analysis. All AEs regardless of treatment also will be tabulated.

A rate of treatment-related grade 3 and 4 (CTCAE, v. 4) AEs of 33% or any grade 5 will be considered too excessive. If this occurs, the study chairs, RTOG Lung Cancer Committee Chair, and the statistician will review the AE data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study.

13.3.4 Interim Reports

Interim reports with descriptive statistics will be prepared twice per year 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 a projected completion date for the accrual phase, compliance rate of treatment delivery with the distributions of important prognostic baseline variables, and the frequencies and severity of the adverse event by treatment arm. The interim reports will not contain the results of the treatment comparisons with respect to the primary endpoint and secondary endpoints.

13.3.5 Deaths Due to Treatment (2/16/11)

All deaths reported as related to treatment will be reviewed by an independent reviewer, Dr. Hak Choy, RTOG's Vice-Chair of Disease Sites. In addition, deaths reported as not related to treatment occurring while a patient is on protocol treatment or within 30 days after stopping protocol treatment will be reviewed by Dr. Choy.

13.3.6 CDUS Reports

This study will be monitored by the Clinical Data Update System (CDUS), v. 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.3.7 Data Monitoring Committee (2/16/11)

To monitor the safety of this study, the RTOG Data Monitoring Committee (DMC) will officially review this study twice per year in conjunction with the RTOG semi-annual meeting and on an "as needed" basis in between meetings.

13.4 Inclusion of Women and Minorities

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

Ciampi, et al. (1989) performed a recursive partitioning analysis on small cell lung cancer dataset and found that gender does influence overall survival in limited stage patients. This has not been shown to be consistent by all authors. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 regarding inclusion of women and minorities in clinical research, we have considered the possible interaction between gender and treatments and race and

treatments. The participation rates of men and women will be examined according to the table below. The projected gender and minority accruals, which are based upon previous similar RTOG studies, are: 0241, 0239, 0212, 97-12, and 96-09.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	6	11	17
Not Hispanic or Latino	60	77	137
Ethnic Category: Total of all subjects	66	88	154
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	3	3
Asian	3	3	6
Black or African American	7	11	18
Native Hawaiian or other Pacific Islander	0	0	0
White	56	71	127
Racial Category: Total of all subjects	66	88	154

REFERENCES

- Arriagada R, LeChevalier T, Bori F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst.* 87:183-90, 1995.
- Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *NEJM.* 342:476-484, 1999.
- Bonner JA, Eagan RT, Liengswangwong V, et al. Long term results of a phase I/II study of aggressive chemotherapy and sequential upper and lower hemibody radiation for patients with extensive stage small cell lung cancer. *Cancer.* 76:406-12, 1995.
- Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: A prospective study. *J Clin Oncol.* 22(16):3248-54, 2004.
- Bunn PA, Lichter AS, Makuch RW, Cohen MH, Veach SR, et al. Chemotherapy alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer. *Ann Internal Med.* 106: 655-662, 1987.
- Ciampi A, Thiffault J, Sagman U. RECPAM: A computer program for recursive partition amalgamation for censored survival data and other situations frequently occurring in biostatistics. II. Application to data on small cell carcinoma of the lung (SCCL). *Comp Meth Prog Biomed.* 30:283-296, 1989.
- Dixon WJ, Massey FJ. 4th Ed. *Introduction to Statistical Analysis.* McGraw-Hill; 1983.
- Dixon DO, Simon, R. Sample size considerations for studies comparing survival curves using historical controls. *J. Clin. Epidemiol.* 41:1209-1213, 1988.
- Fellitti R, Souhami RL, Spiro SG, et al. Social consequences of brain or liver relapse in small cell carcinoma of the bronchus. *Radiother Oncol.* 4:335-9, 1985.
- Fine J, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 94:496-509, 1999
- Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol.* 22(23): 4837-45, 2004.
- Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med.* 24:1703-1712, 2005.
- Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. *JASA.* 88:400-403, 1993.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annual Statistics.* 16:1141-1143, 1988.
- Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: Results of a multicentre randomised trial. *Eur J Cancer.* 33:1752-8, 1997.
- Hanna N, Bunn PA, Langer C, Einhorn L, et al. Randomized phase III trial comparing Irinotecan/Cisplatin with Etoposide/Cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol.* 24: 2038-43, 2006.
- Jeremic B, Shibamota Y, Nikolic N, Milicic B, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol.* 17:2092-99, 1999.

REFERENCES (Continued)

- J Natl Comprehensive Cancer Network*. Small cell lung cancer. 6(3): 296-306, 2008.
- Kalbfleisch JD, Ross LP. *The statistical analysis of failure time data*. New York: John Wiley & Sons; 1980.
- Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 53:457-81, 1958.
- Murray N, Coy P, Pater JL, et al. The importance of timing of thoracic irradiation in the combined-modality treatment of limited-stage small cell lung cancer. *J Clin Oncol*. 11: 336-44, 1993.
- Niho S, Fujii H, Murakami K, et al. Detection of unsuspected distant metastases and/or regional nodes by FDG-PET in LD-SCLC scan in apparent limited-disease small-cell lung cancer. *Lung Cancer*. 57(3): 328-33, 2007.
- Nugent JL, Bunn PA Jr, Matthews MJ, et al. CNS metastases in small cell bronchogenic carcinoma: Increasing frequency and changing pattern with lengthening survival. *Cancer*. 44: 1885-93, 1979.
- Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *NEJM*. 316: 912-918, 1987.
- Pignon JP, Arriagada R, Ihde D. Meta-analysis of small-cell lung cancer. *NEJM*. 327:1618-24, 1992.
- Schiller J, Adak S, Cella D, DeVore R, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593 — A phase III trial of the Eastern Cooperative Oncology Group. *J Clin. Oncol*. 19(8): 2114-2122, 2001.
- Slotman B, Faivre-Finn C, Kramer G, Rankin E, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *NEJM*. 357:664-72, 2007.
- Warde P, Payne D: Does thoracic irradiation improve survival and local control in limited-stage small-cell lung cancer? A meta-analysis. *J Clin Oncol*. 10: 890-95, 1992.
- Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 27:365-375, 1974.

APPENDIX I

RTOG 0937

Informed Consent Template for Cancer Treatment Trials **(English Language)**

Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extra-Cranial Irradiation for Extensive Disease Small Cell Lung Cancer (ED-SCLC)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have extensive disease small cell lung cancer.

Why is this study being done? (10/21/11)

The standard treatment for extensive disease small cell lung cancer is chemotherapy. In many patients, even those who respond well to chemotherapy, the cancer can grow back in the chest or grow in the brain or other places after chemotherapy.

One study found that radiation to the brain improves survival in patients with extensive disease small cell lung cancer. Based on that study and due to the high risk of cancer growth in the brain, radiation to the brain is often recommended. It is not known if radiation therapy to the chest or other sites of disease that do not completely respond to chemotherapy improves survival.

The purpose of this study is to treat patients who have small cell lung cancer that did not completely respond to chemotherapy. The study will compare the effects, good and/or bad, of radiation given to the brain versus radiation to the brain, chest and up to 4 other sites to find out which is better.

How many people will take part in the study?

About 154 people will take part in this study.

What will happen if I take part in this research study?

All patients will have completed chemotherapy before they participate in this study.

Patients will be "randomized" into one of the 2 study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in one of the 2 groups

If you are in group 1 (often called "Arm 1"), you will receive radiation to the brain daily, Monday-Friday, for 2 weeks.

If you are in group 2 (often called "Arm 2"), you will receive radiation to the brain daily, Monday-Friday, for 2 weeks and radiation to the chest and other sites of cancer that did not completely respond to the chemotherapy. You and your doctor will discuss whether you will have radiation to the chest and other sites on the same days as the brain radiation or if you will receive radiation to the chest and other sites after the brain radiation is finished. If you receive radiation to the chest and other sites after brain radiation is finished, you will have treatment daily, Monday-Friday, for an additional 2-3 weeks.

Radiation therapy for all patients will take no longer than 5 weeks.

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical examination
- You will be weighed and asked about your ability to carry out your daily activities
- A CT scan with contrast of your chest and abdomen, unless a PET/CT scan has been done
 - CT (Computed Tomography) scan: A study using x-rays to look at one part of your body;
 - Contrast: Certain imaging requires a special dye, called contrast, given before the image is made to highlight specific areas inside the body and create a clearer image);
 - PET (Positron Emission Tomography) scan: A computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body).
- A bone scan (a type of x-ray to find out if cancer has spread to your bones), unless a PET scan has been done
- An MRI of your brain (Magnetic Resonance Imaging: Imaging using a strong magnetic field to look at one part of your body) or, if your doctor recommends, a CT scan of your brain with contrast
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- For women who are able to have children, a pregnancy test
- And if your study doctor recommends:
 - Tests of your lung function
 - A PET scan of your entire body
 - An evaluation of your diet and ability to chew and swallow

Weekly during radiation therapy:

- A physical examination
- You will be weighed and asked about your ability to carry out your daily activities
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having

When radiation therapy is finished: (2/16/11)

At 2 weeks and 1 month after treatment:

- A physical examination, including your weight
- You will be asked about your ability to carry out your daily activities
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having

At 2 months after treatment:

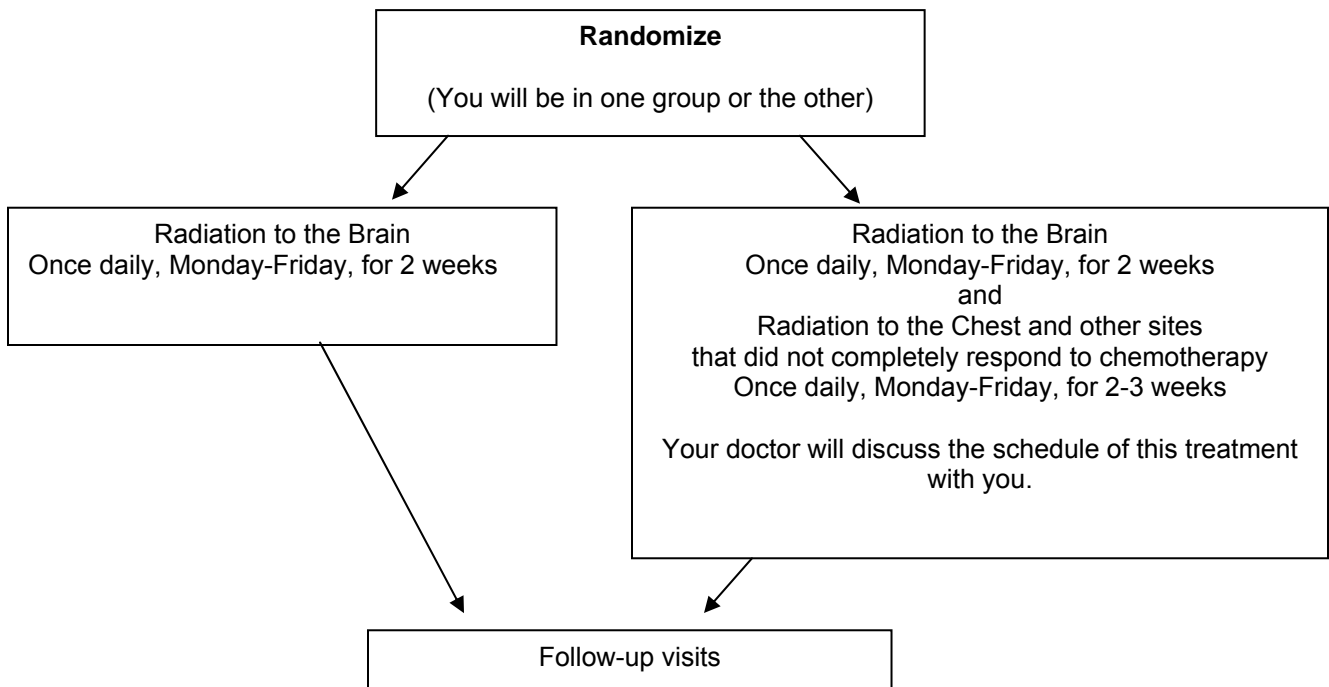
- A physical examination, including your weight
- You will be asked about your ability to carry out your daily activities
- A CT scan or a PET/CT scan of your chest and upper abdomen
- An MRI or CT scan with contrast of your brain
- Imaging of places other than the brain and chest that were treated with radiation
- A bone scan, if your study doctor recommends it
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having

At 6, 9, and 12 months from the start of treatment; every 6 months for the next 2 years; then yearly for your lifetime:

- A physical examination, including your weight
- You will be asked about your ability to carry out your daily activities
- A CT scan or a PET/CT scan of your chest and upper abdomen
- An MRI or CT scan with contrast of your brain, if your doctor recommends it
- Imaging of places other than the chest that were treated with radiation in which cancer has grown
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

You will receive radiation to the brain OR radiation to the brain, chest, and other sites of cancer that did not completely respond to the chemotherapy in 2-5 weeks. You will be seen in follow-up visits at 2 weeks, 1 month, and 2 months after treatment; at 6, 9, and 12 months from the start of treatment; every 6 months for the next 2 years; and then yearly for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving radiation treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks Associated with Radiation to the Brain

Likely

- Hair loss, which may be permanent
- Scalp reddening or tanning and irritation
- Dry mouth and/or change in taste
- Sore throat
- Tiredness
- Increased sleepiness (occurring 4-10 weeks after radiation therapy is complete and often lasting for several days up to a few weeks)
- Temporary plugging of the ears with decreased hearing
- Itching in the ear canal

Less Likely

- Nausea and/or vomiting
- Headache
- Cataracts (clouding of the lens in the eye)
- Memory loss and behavioral change, which may be permanent

Rare, but Serious

- Eye damage, resulting in worsening of vision or possible blindness
- Progressive thickening and hardening of the walls of medium-sized and large arteries
- Impairment of your thinking
- Cancer caused by the radiation
- Death

Risks Associated with Radiation to the Chest

Very Likely

- Skin in treatment area may become reddened and/or dry, and chest hair may not grow back
- Cough
- Difficulty, pain, or burning sensation when swallowing
- Fatigue (tiredness) for no apparent reason
- Permanent scarring in the normal lung that does not cause symptoms

Less Likely

- Shortness of breath
- Difficulty and pain with swallowing that results in weight loss and the need for fluids given through your vein; in rare cases, a feeding tube for nutrition is needed.
- Bleeding with a cough

Rare, but Serious

- Inflammation or scarring of the lung, which can lead to shortness of breath, fever, and pain. In rare cases, this is severe, requiring intensive medical treatment and can be life threatening.
- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular or rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Irritation and/or damage to the nerves of the arm, if the upper part of the chest is being treated; this can cause numbness and weakness in the arm, and rarely, loss of function.
- Narrowing of the esophagus (tube to the stomach)

If you have radiation therapy to parts of your body other than the brain and chest, your doctor will discuss those risks and side effects with you.

Reproductive risks: You should not become pregnant or father a baby while on this study because the radiation treatment in this study can affect an unborn baby. Women who are able to have children are required to have a pregnancy test before participating in this study. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. The radiation treatment used in the study may make you unable to have children in the future.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope that radiation to the brain and chest after chemotherapy may decrease the regrowth and spreading of your cancer, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the effects of radiation treatment to the brain and chest. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting the standard treatment of chemotherapy without radiation after chemotherapy
- Taking part in another study
- Getting no treatment

- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study? (2/16/11)

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Where can I get more information? (8/9/12)

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE (2/16/11)
 (*See Section 11.2 For Details)

Assessments	Pre-Treatment		Weekly During Radiation	Follow Up			Long-Term Follow Up At 6, 9, and 12 months from start of treatment; then every 6 months for years 2-3; then annually
	After chemotherapy	Within 1 week of study entry		2 weeks after completion of therapy	1 month after completion of therapy	2 months after completion of therapy (same as 3 mos. from start of tx)	
History/physical, including weight and performance status	X		X	X	X	X	X
CT of the chest/abdomen with contrast or PET/CT	X*					X	X
Bone scan or PET	X*					X*	
MRI of the brain (or CT with contrast)	X					X	X*
CBC w/ diff & ANC, Platelets		X	X	X	X	X	X
LFTs (AST, ALT, Serum Bilirubin)		X*		X*	X*	X*	X*
Serum Creatinine		X*		X*	X*	X	X*
Serum pregnancy test (if applicable)		X					
Pulmonary function tests	Recommended but not required						
Whole body PET							
Nutrition eval							
Tumor response evaluation (documentation of measurable disease)	X					X	Document progression in any treated sites or elsewhere if it occurs.
Adverse event evaluation (CTCAE, v. 4)			X	X	X	X	X

APPENDIX III

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 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**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed**
- 5 Death**

APPENDIX IV

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

LUNG

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 <i>in situ</i>
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)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, 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 or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

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
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody 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 classified as M0.

APPENDIX IV (Continued)

STAGE GROUPING	
Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T1a-b, N1, M0
	T2a, N1, M0
Stage IIB	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T1a-b, N2, M0
	T2a-b, N2, M0
	T3, N1-2, M0
	T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0
	T2a-b, N3, M0
	T3, N3, M0
	T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b