NRG ONCOLOGY

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)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, and SWOG.

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NRG ONCOLOGY
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)

Participating Sites (1/30/14)
☐ US Only
☐ Canada Only
☒ US and Canada
☒ Approved International Member Sites

Document History

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NRG Oncology
1-800-227-5463, ext. 4189

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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)

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<td>CTSU Regulatory Office&lt;br&gt;1818 Market Street, Suite 1100&lt;br&gt;Philadelphia, PA 19103&lt;br&gt;Phone – 1-866-651-CTSU&lt;br&gt;Fax – 215-569-0206&lt;br&gt;Email: <a href="mailto:CTSUREgulatory@ctsu.coccg.org">CTSUREgulatory@ctsu.coccg.org</a> (for submitting regulatory documents only)</td>
<td>See Sections 5.0 and 5.5 for instructions for the Oncology Patient Enrollment Network (OPEN).&lt;br&gt;Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
<td>Submit study data to: NRG Oncology&lt;br&gt;1818 Market Street, Suite 1600&lt;br&gt;Philadelphia, PA 19103&lt;br&gt;Submit data electronically via the NRG Oncology/RTOG website, <a href="http://www.rtog.org">www.rtog.org</a>&lt;br&gt;Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
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For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

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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 (6/24/14)

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<tr>
<th>S</th>
<th>Response to Treatment</th>
<th>R</th>
<th>Arm 1: Prophylactic Cranial Irradiation</th>
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<tr>
<td>T</td>
<td>1. Complete Response (CR)</td>
<td>A</td>
<td>2.5 Gy per fraction for a total of 25 Gy</td>
</tr>
<tr>
<td>R</td>
<td>2. Partial Response (PR)</td>
<td>N</td>
<td></td>
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<tr>
<td>A</td>
<td>D</td>
<td>Arm 2: Prophylactic Cranial Irradiation</td>
<td></td>
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<tr>
<td>T</td>
<td>O</td>
<td>2.5 Gy per fraction for a total of 25 Gy</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Number of Metastatic Lesions</td>
<td>M</td>
<td>and</td>
</tr>
<tr>
<td>F</td>
<td>1.1</td>
<td>I</td>
<td>Consolidative Radiation to</td>
</tr>
<tr>
<td>Y</td>
<td>2. 2-4</td>
<td>Z</td>
<td>Locoregional and Residual Metastatic Disease</td>
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<tr>
<td>Age</td>
<td></td>
<td>E</td>
<td>45 Gy at 3 Gy per fraction*</td>
</tr>
<tr>
<td>1.</td>
<td>&lt;65</td>
<td></td>
<td>*Acceptable alternative regimens: 30-40 Gy in 10 fractions</td>
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<td>2.</td>
<td>≥65</td>
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**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
NRG Oncology Institution #
RTOG 0937
Case #

(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) 5. 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 ≥ 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) 10. 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 ≤ 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
NRG Oncology Institution #
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Case #

_____ (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. Institutional person randomizing case?

_________ (Y) 2. Has the Eligibility Checklist been completed?

_________ (Y) 3. In the opinion of the investigator, is the patient eligible?

_________ 4. Date Informed Consent Signed

_________ 5. Patient Initials

_________ 6. Verifying physician

_________ 7. Patient ID

_________ 8. Date of Birth

_________ 9. Race

_________ 10. Ethnicity

_________ 11. Gender

_________ 12. Country of Residence

_________ 13. Patient Zip Code

_________ 14. Method of Payment

_________ 15. Any care at VA or military hospital?

_________ 16. Calendar Base Date

_________ 17. Randomization date
NRG Oncology Institution #
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Case #

18. Specify response to treatment (Complete Response vs. Partial Response) (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 (One vs. Two to Four)

20. Did the patient receive prior thoracic radiation therapy?

21. If Arm 2, will the patient receive treatment to metastatic site(s)?

22. If yes, specify the most complex treatment approach (IMRT, 3D Conformal, or 2D).

23. Specify treatment approach for PCI (3D Conformal or 2D).

24. Specify use of IMRT.

25. Age (<65 or ≥65)

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/NRG Oncology audit.

Completed by ____________________________ Date ____________________________
1.0 INTRODUCTION (4/3/14)

1.1 Background

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 Natl 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)

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

### Disease-Free Survival (DFS)

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

*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).

**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 (4/3/14)

2.1 Primary Objective
To determine the 1-year overall 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 (4/3/14)
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

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:
- History/physical examination;
- 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.
- Measurements for all pre- and post-chemotherapy measurable disease must be submitted.

3.1.7 Zubrod Performance Status 0-2;
3.1.8 Age ≥ 18;
3.1.9 For patients who will be treated with radiation to the liver, adequate hepatic function, defined as follows:
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:
- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm³;
- Platelets ≥ 75,000 cells/mm³;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 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 ≤ 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:
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- 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 (6/24/14)

Access requirements for OPEN and TRIAD:
Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members’ web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

5.1 Pre-Registration Requirements for 3DCRT or IMRT Treatment Approaches (4/3/14)

5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information may enter patients onto this study using that treatment modality.
Additional requirements are provided for institutions intending to use an IMRT treatment approach.

5.1.2 The new or updated Facility Questionnaire (one per institution, available on the Imaging and Radiation Oncology Core (IROC) Houston (former Radiologic Physics Center [RPC]) web site at http://irochouston.mdanderson.org) is to be completed for review prior to entering any cases.

5.1.3 Credentialing Status Inquiry Form
Institutions will complete this form on the IROC Houston web site at http://irochouston.mdanderson.org to determine if the site has met all of the requirements. When the requirements are met, the site and NRG Oncology will be notified. NRG Oncology will then update the RSS database.

5.2 Additional Pre-Registration Requirements for Institutions Using IMRT Treatment Approach (4/3/14)
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 IROC Houston web site. Visit http://irochouston.mdanderson.org and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with IROC Houston 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 IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “NRG Oncology”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will update the RSS database when the IMRT credentialing requirement has been met.

5.3 Digital RT Data Submission to RTOG Using TRIAD (1/30/14)
TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:
- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics users must have been assigned the ‘TRIAD site user’ role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG web site Core lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.4 Regulatory Pre-Registration Requirements (4/3/14)
This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on CTEP Web site:
The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members’ web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Site registration forms may be downloaded from the RTOG 0937 protocol page located on the CTSU members’ web site. Go to https://www.ctsu.org and log in to the members’ area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG 0937
- Click on the Site Registration Documents link

Requirements for RTOG 0937 site registration:
- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form (if applicable)

**NOTE:** Per NCI policy, all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. If this form has been previously submitted to CTSU, it does not need to be resubmitted unless updates have occurred at the RT facility.

- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to NRG Oncology.
- IRB/REB assurance number renewal information, as appropriate
- See the additional pre-registration requirements in Sections 5.1 and 5.2.

Non-English Speaking Canadian and Non-North American Participating Sites
*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 optional but due to the prohibitive costs involved NRG Oncology 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.*
Submit completed forms along with a copy of your IRB Approval and Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Check the status of your site’s registration packets by querying the RSS site registration status page of the members’ section of the CTSU web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members’ area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.4.1 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from NRG Oncology prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/LinkClick.aspx?fileticket=0tMdct9KHSs%3d&tabid=117

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.

5.5 Registration (4/3/14)

5.5.1 OPEN Registration Instructions
Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:
- See Section 5.0 for obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the ‘Registrar’ role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of NRG Oncology, you must have an equivalent ‘Registrar’ role on the NRG Oncology roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members’ web site. This will allow them to assign staff the "Registrar" role.
The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (4/3/14)

Note: See Section 5.3 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

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 (6/24/14)

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

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.

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).

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 0.03 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

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 (6/24/14)

#### 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

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, intrathoracic, abdominal, or pelvic organs. In these cases, it must be possible to localize the skeletal lesions on simulation films.

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 is recommended for all treatment planning for proper calculation of cumulative doses to GTV, PTV, and normal tissues. More than one scan is acceptable if there is no overlap of treatment fields.

### 6.4 Treatment Planning/Target Volumes (6/24/14)

#### 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.

**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 NRG Oncology trials is available in Section 6.5.1 below.

**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.

**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.

**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. In order to calculate cumulative dose to the PTVs and organs at risk it is recommended plans for all treated sites be included on the same planning CT scan. More than one scan is acceptable if there is no overlap of treatment fields. 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.

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

### Critical Structures (6/24/14)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>V20 &lt; 30%</td>
</tr>
<tr>
<td></td>
<td>MLD &lt; 20Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>≥ 700 cc &lt; 18 Gy</td>
</tr>
<tr>
<td>Each Kidney</td>
<td>V18 &lt; 25%</td>
</tr>
<tr>
<td>Spinal cord/Brachial plexus</td>
<td>Maximum dose 36 Gy</td>
</tr>
<tr>
<td>Heart/Pericardium</td>
<td>Maximum dose 105% prescribed dose AND</td>
</tr>
<tr>
<td></td>
<td>V45 &lt; 30%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Maximum dose 105% of prescribed dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small Bowel</th>
<th>Dose (Gy)</th>
<th>3 Gy/Fx</th>
<th>Recommended Maximum Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td></td>
<td>150 cc</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td></td>
<td>100 cc</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td>50 cc</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td></td>
<td>1 cc</td>
</tr>
</tbody>
</table>
6.5.1 Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the DICOM standard name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD.

<table>
<thead>
<tr>
<th>DICOM Standard Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Gross Tumor Volume Required for lesions that have not had CR to chemotherapy</td>
</tr>
<tr>
<td>ITV</td>
<td>Internal Tumor Volume (&quot;if using ITV approach is used&quot;) Optional</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume Required</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume Required</td>
</tr>
<tr>
<td>Lungs</td>
<td>Right Lung + Left Lung minus GTV Required</td>
</tr>
<tr>
<td>BrachialPlexus</td>
<td>Brachial Plexus Required, if in path of beam</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart/Pericardium Required</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophagus Required</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Spinal Cord Required</td>
</tr>
<tr>
<td>nonPTV</td>
<td>External minus PTV Required</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>Right Kidney (&quot;if in path of beam) Optional</td>
</tr>
<tr>
<td>Kidney_L</td>
<td>Left Kidney (&quot;if in path of beam) Optional</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver (&quot;if in path of beam) Optional</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>Small Bowel (&quot;if in path of beam) Optional</td>
</tr>
</tbody>
</table>

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 (6/24/14)
6.7.1 Variations in Dose Prescription for Thoracic Irradiation and Metastatic Sites

Per Protocol: Dose delivered as per Section 6.1.2.

Variation Acceptable:
Variations of this magnitude are acceptable only when the geometrical arrangement of the target and critical structures is challenging. Minimum and maximum doses are defined using a
sampling volume of 0.03 cc as described above. The maximum dose within the PTV may exceed 120% of the prescribed dose provided it is no more than 125% of the prescription dose.

**Deviation Unacceptable:** Dose distributions falling in this category are not acceptable and plan modifications should be attempted to improve results. A Deviation Unacceptable occurs if any of the Variation Acceptable dose limits stated above are exceeded. Additionally, a Deviation Unacceptable is assigned if more than 1 cm³ of tissue outside the PTV receives ≥ 110% of the prescribed dose.

6.8 **R.T. Quality Assurance Reviews (6/24/14)**

The Radiation Oncology Principle Investigator, Elizabeth Gore, MD and Radiation Oncology Co-Chair, Alex Sun, MD will perform an RT Quality Assurance review after complete data for the first 20 cases enrolled have been received at IROC Philadelphia RT. Drs. Gore and Sun will perform the next review after complete data for the next 20 cases enrolled have been received at IROC Philadelphia RT. 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 IROC Philadelphia RT, 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**

**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.

**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**

**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.

**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 brachialpalexopathy are possible but unlikely side effects of radiation.

6.9.3 **Additional Adverse Events Associated with Abdominal/Pelvic Radiation**

**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.

**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**

**Acute Reactions:** Minor skin reactions are likely; moist desquamation is possible but unlikely.
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 (4/3/14)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribute of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

Routine adverse event reporting guidelines are on the NRG Oncology/RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx).

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.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table below will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below. Contact the CTEP-AERS Help Desk if assistance is required.

CTEP-AERS REPORTING REQUIREMENTS
All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, https://eapps.ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Office by phone, (1-800-227-5463, ext. 4189). An electronic report must be submitted immediately upon re-establishment of the Internet connection.
CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.

Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation the NRG Oncology dedicated SAE FAX, 215-717-0990.

A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS 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

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td></td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 CTEP-AERS 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.
Serious 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

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 CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

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

### 6.10.1 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) [1/30/14]
AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS within 30 days of AML/MDS diagnosis.

**Secondary Malignancy**
A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy**
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

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

11.3.7 Other Imaging
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:

NRG Oncology*
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 (4/3/14)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>2 weeks after registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>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.</td>
</tr>
<tr>
<td>Dosimetry Information for All Treated Sites</td>
<td>Within 1 week of end of RT</td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Digital RT data for all treated sites with 3DCRT and IMRT will be submitted via TRIAD.
12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD) (4/3/14)

For All Treated Sites with 3DCRT and IMRT

Due

Preliminary Dosimetry Information

Digital Data Submission – Treatment Plan submitted to via TRIAD exported from treatment planning system

Digital data submission includes the following, required in DICOM format:

- CT Planning File
- RT Plan Files
- RT Composite Dose Files
- RT Structure Files (see table in Section 6.5)

Digital Data Submission Information Form (DDSI) – Submitted online (Form located at http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx)

Final Dosimetry Information

Within 1 week of RT end

Radiotherapy Form (T1)

Daily Treatment Record (T5)

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 TRIAD (1/30/14)

See Section 5.3 for account access and installation instructions.

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 (6/24/14)

13.2.1 Stratification and Randomization

Patients will be stratified before randomization according to response to therapy (complete response [CR] vs. partial response [PR]), the number of metastatic lesions (1 vs. 2-3), and age (<65 vs. ≥65). 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 (H₀) is that the experimental treatment is not effective versus the alternative hypothesis (Hₐ) that the experimental treatment is effective. The hypotheses are:

H₀: S(t₂) ≤ S(t₁) vs. Hₐ: S(t₂) > S(t₁)
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 \( [\lambda_0] \) of 1.204) (Slotman, 2007) and those in Arm 2 will have a 1-year overall survival rate at least 45% (hazard rate \( [\lambda_t] \) of 0.799), which is translated to the hazard ratio of \( \lambda_t/\lambda_0 = 0.663 \). 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 ineligible 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 NRG Oncology Data Safety Monitoring Board (DSMB) will begin evaluating patient accrual semi-annually following the anticipated initial quiet period. The participation of non-NRG Oncology institutions and 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 (6/24/14)

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:

\[ H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_1: \lambda_1 > \lambda_2 \]

where \( \lambda_1 \) and \( \lambda_2 \) 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, the number of metastatic lesions and 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.

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 \( \lambda_1 \) and \( \lambda_2 \) 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.

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

*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 (6/24/14)

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, the number of metastatic lesions and age), and race (as appropriate) will be considered when it is adjusted in the analysis.

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.

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, the number of metastatic lesions and 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.

**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 (6/24/14)

We will closely monitor the rate of grade 3 or higher adverse events definitely, probably, or possibly related to treatment for the following adverse events that occur within 1 year from randomization:

- **Blood and lymphatic system disorders**
  - Anemia
  - Febrile neutropenia
- **Gastrointestinal**
  - Diarrhea
  - Gastritis
  - Esophagitis
  - Nausea
- **Musculoskeletal and connective tissue disorders**
  - Avascular necrosis
- **Renal and urinary disorders**
  - Acute kidney injury
- **Respiratory, thoracic and mediastinal disorders**
  - Pneumonitis
  - Pulmonary fibrosis
- **Any grade 5 adverse events attributed to treatment**

Interim analysis of the protocol-specified adverse events is planned after 25 and 40 analyzable patients (eligible patients who received any protocol treatment) have been accrued in each arm, and have a minimum of 1-year potential follow up time or have died within 1 year. 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.

The Kaplan-Meier method will be used to estimate the 1-year rate of protocol-specified adverse events. The event of interest is the protocol-specified adverse event, and deaths without protocol-specified AE are treated as censoring. If the 1-year rate exceeds 33%, then the study chairs, NRG Oncology Lung Cancer Committee Chair, and statistician will review the AE data and make appropriate recommendations to the NRG Oncology 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, NRG Oncology’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 NRG Oncology Data Monitoring Committee (DMC) will officially review this study twice per year in conjunction with the NRG Oncology 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.

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>60</td>
<td>77</td>
<td>137</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>66</td>
<td>88</td>
<td>154</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Black or African American</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>56</td>
<td>71</td>
<td>127</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>66</td>
<td>88</td>
<td>154</td>
</tr>
</tbody>
</table>
REFERENCES


REFERENCES (Continued)


**APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (4/3/14)**

*See Section 11.2 for details and exceptions*

<table>
<thead>
<tr>
<th>Assessments</th>
<th>After Chemotherapy</th>
<th>Within 1 Week of Study Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, including weight and performance status</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CT of the chest/abdomen with contrast or PET/CT</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Bone scan or PET</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>MRI of the brain (or CT with contrast)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, Platelets</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>LFTs (AST, ALT, Serum Bilirubin)</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>Recommended but not required</td>
<td></td>
</tr>
<tr>
<td>Whole body PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition eval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor response evaluation (documentation of measurable disease)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (4/3/14)

*See Section 11.2 for details and exceptions

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Weekly During Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, including weight and performance status</td>
<td>X</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, Platelets</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event evaluation (CTCAE, v. 4)</td>
<td>X</td>
</tr>
</tbody>
</table>
## APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (4/3/14)

*See Section 11.2 for details and exceptions

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 weeks after completion of therapy</td>
</tr>
<tr>
<td>History/physical, including weight and performance status</td>
<td>X</td>
</tr>
<tr>
<td>CT of the chest/abdomen with contrast or PET/CT</td>
<td></td>
</tr>
<tr>
<td>Bone scan or PET</td>
<td></td>
</tr>
<tr>
<td>MRI of the brain (or CT with contrast)</td>
<td>X*</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, Platelets</td>
<td>X</td>
</tr>
<tr>
<td>LFTs (AST, ALT, Serum Bilirubin)</td>
<td>X*</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>X*</td>
</tr>
<tr>
<td>Tumor response evaluation (documentation of measurable disease)</td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation (CTCAE, v. 4)</td>
<td>X</td>
</tr>
</tbody>
</table>
APPENDIX II: ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX III: AJCC STAGING SYSTEM


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 in situ
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
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 III (Continued)

<table>
<thead>
<tr>
<th>STAGE GROUPING</th>
<th>T, N, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
<td>TX, N0, M0</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a-b, N0, M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a, N0, M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b, N0, M0</td>
</tr>
<tr>
<td></td>
<td>T1a-b, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T2a, N1, M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1a-b, N2, M0</td>
</tr>
<tr>
<td></td>
<td>T2a-b, N2, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N1-2, M0</td>
</tr>
<tr>
<td></td>
<td>T4, N0-1, M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1a-b, N3, M0</td>
</tr>
<tr>
<td></td>
<td>T2a-b, N3, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N3, M0</td>
</tr>
<tr>
<td></td>
<td>T4, N2-3, M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, Any N, M1a-b</td>
</tr>
</tbody>
</table>