Study Title:

Phase I Study of Accelerated Hypofractionated Image-Guided Radiation Therapy (IGRT) in Patients with Stage II-IV Non-Small Cell Lung Cancer and Poor Performance Status

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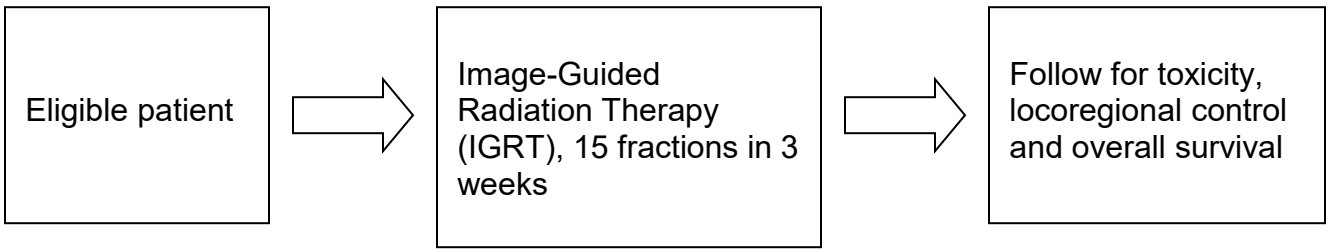


Number of patients = between 7-45 (depending on tolerance)

Patients in each dose cohort will all be treated as a single group for dose escalation. The starting dose will be 3.33 Gy per fraction for 15 fractions (total dose = 50 Gy). Subsequent cohorts of patients will receive a higher dose per fraction as follows:

No. Fractions	Dose per fraction (Gy)	Total Dose (Gy)	No. Patients
15	3.33	50	7-15
15	3.67	55	7-15
15	4.00	60	7-15

Minimum waiting periods will be assigned between each dose cohort to observe toxicity.

ELIGIBILITY *(See Section 3.0 for details)*

- Stages II (not eligible for definitive surgical resection or stereotactic body radiation therapy,), III or IV non-small cell lung cancer that would benefit from local radiation therapy
- Recurrent non-small cell lung cancer that would benefit from local radiation therapy
- Zubrod performance status of 2 or greater, age > 18
- No prior radiotherapy to the chest or neck that would result in overlap of radiation therapy fields
- No chemotherapy within one week prior to study registration
- Study-specific consent form signed

Eligibility Checklist

_____(Y) 1. Does the patient have histologically or cytologically documented NSCLC?

_____(Y) 2. Is TNM Stage II, III or IV or does the patient have recurrent disease?

_____(N) 3. Is the patient eligible for definitive surgical resection or stereotactic body radiation therapy?

_____(N) 4. Has the patient had prior radiotherapy to the chest or neck that would result in overlap of radiation therapy fields?

_____(Y) 5. Is the Zubrod performance status 2 or greater? **Or**
Has patient lost >10% of body weight in the past 6 months? **Or**
Patient is not eligible for concurrent chemoradiation as determined by a Medical Oncologist and Radiation Oncologist

_____(Y) 6. Is patient ≥ 18 years of age?

_____(N) 7. Has the patient had any chemotherapy within a week prior to study registration?

___(Y/Quit/Never) 8. Does the patient smoke?

_____(Y) 9. Were all the required pre-registration evaluations administered as specified in Section 3, including CT with contrast of lung and upper abdomen within 8 weeks of registration?

_____(Y/NA) 10. Has the patient agreed to use an effective method of contraception?

_____(N) 11. If female, is the patient pregnant or lactating?

_____(Y) 12. Has the patient signed the protocol consent?

1.0 Introduction

1.1 Locally Advanced NSCLC and Radiation Therapy

Lung cancer is the leading cause of cancer-related mortality in the United States each year with an estimated 215,000 new cases and over 160,000 deaths, [1]. The majority of these, approximately 80%, are non-small cell lung cancers (NSCLC). Only 15-20% of these cases present with early or localized disease and the rest are more advanced, with large tumors, regionally involved lymph nodes, or distant metastatic disease [2].

Surgical resection is the mainstay of treatment for stage I and II NSCLC, often followed by adjuvant chemotherapy. For stage III NSCLC, selected cases can be treated surgically, while for many patients, combined chemotherapy and radiation therapy is the best curative option. If a NSCLC patient has co-morbid conditions or poor performance status, the treatment options are more limited. Surgery may not be possible for curative treatment of early stage disease, and concurrent chemoradiation may not be tolerable as treatment of more advanced disease. Conventionally fractionated radiation therapy alone as definitive treatment for locally advanced NSCLC has poor survival rates, with a median survival of only 10 months in an RTOG trial that established 60 Gy as the standard dose for a time [3]. Since then, there have been many efforts to increase the efficacy of radiation therapy for locally advanced lung cancer. Clinical trials have suggested a benefit from dose escalation. For example, A University of Michigan phase I study that included mainly stage III NSCLC, showed a 5 year overall survival improvement from 4% to 28% when dose was increased from 63-69 Gy to 92-103 Gy [4]. Also, a median survival of 24.7 months was achieved in 112 patients treated on four University of North Carolina phase I/II trials of high dose (60-90 Gy) radiation therapy in unresectable stage III NSCLC [5]. However, local failure remains a significant problem even with high dose radiation therapy, with local failure rates of 22-50% in multiple studies [5, 6].

The best method found to date for improving the efficacy of radiation therapy for locally advanced NSCLC is to combine it with chemotherapy. One of the early phase III trials showing a benefit to chemotherapy followed by radiation therapy was the CALGB 8433 trial, which showed a median survival increase from 9.6 to 13.7 months with the addition of chemotherapy [7]. Since then, multiple trials of locally advanced NSCLC in good performance status patients have shown even better outcomes with concurrent chemotherapy and radiation therapy, rather than sequential [8-12]. A recent randomized phase III trial even achieved a median survival time of 21.7 months in inoperable stage III NSCLC [13].

However, the better local control and survival achievable by adding chemotherapy to radiation therapy comes at the expense of increased toxicity. Some of the most commonly used chemotherapy combinations in locally advanced NSCLC are cisplatin/etoposide and carboplatin/paclitaxel. All of these agents are associated with myelosuppression, nausea, and vomiting and several are associated with neuropathy and nephrotoxicity. When given with radiation therapy, these toxic effects can be worsened; also, the adverse effects commonly seen with radiation therapy to the chest, such as esophagitis, can be intensified. The CALGB 8433 trial reported higher rates of serious adverse effects including neutropenic infections, vomiting, and severe weight loss in the group of patients receiving chemotherapy and radiation therapy [14]. Toxicity with concurrent chemoradiation therapy can be even greater than with sequential. RTOG 94-10 reported higher rates of acute grade 3-4 non-hematologic toxicity, including esophagitis, with concurrent compared to sequential chemoradiation

therapy [9]. In a phase III trial by the CALGB and ECOG, patients receiving carboplatin with radiation therapy suffered more neutropenia, thrombopenia, and anemia than did patients receiving radiation therapy alone [15]. These adverse effects can decrease quality of life for patients and cause administration of combined modality therapy to be impractical in poor performance status patients. This protocol will attempt to provide effective local control of NSCLC in the chest, while avoiding the toxicity and potentially decreased quality of life caused by adding concurrent chemotherapy.

Progress in technology has changed the delivery of radiation therapy to allow more precise targeting of tumor and avoidance of normal structures. 3D conformal radiotherapy (3-DCRT) and intensity modulated radiation therapy (IMRT), based on computed tomography (CT) planning, are possible due to modern computer and software advances. These treatment techniques have allowed reduction of treatment volumes and dose escalation of fractionated radiotherapy. RTOG 9311 showed the feasibility of delivering up to 83.8 Gy at 2.15 Gy per fraction for stage I-III NSCLC [6]. Recently, there has been increasing use of image-guided radiation therapy (IGRT), which involves frequent imaging to account for interfraction and sometimes intrafraction motion of the target and thus improves the accuracy of dose delivery. IGRT involves modalities such as daily ultrasound, kilvoltage (kV) imaging such as x-rays or kV cone beam CT, or megavoltage (MV) imaging such as helical MV CT or MV cone beam CT. Adaptive radiotherapy is the concept of using frequent imaging to alter treatment based on changes in the tumor or normal tissue during the course of treatment. This can be important in treatment of NSCLC since tumors can shrink considerably during treatment, allowing greater avoidance of normal structures when the treatment plan is modified. Kupelian et.al. reported an average decrease in the tumor volume of 1.2% per day in a study of 10 NSCLC patients [16]. Imaging can also be used to account for organ motion with respiration, which is crucial in treatment of lung tumors. One method to manage respiratory motion is by limiting tumor motion, using techniques such as abdominal compression or breath holding. The other method to account for respiratory motion is to allow free tumor motion but keep the target constantly in the beam's eye view when the beam is on, using techniques such as beam tracking, couch-based motion compensation, or respiratory gating.

All of these advances in treatment planning and delivery have allowed the development of stereotactic body radiation therapy (SBRT) as a promising treatment for early stage NSCLC. This treatment method combines the previously mentioned techniques with stereotactic targeting to allow a dramatic reduction in treatment volumes, enabling delivery of hypofractionated, ablative doses of radiation therapy. SBRT can be safely used in patients with co-morbid conditions or poor performance status and can achieve local control rates as high as 95% at 2 years [17]. The technological advances making possible SBRT in early stage NSCLC could be transferred to treatment of locally advanced NSCLC as well, to allow a shorter overall treatment time without increasing toxicity. Notably, the reported dose escalation trials for locally advanced NSCLC utilize 3-D conformal radiation therapy but do not include daily image guidance or methods for compensating for tumor motion with respiration. With these technological advances, it should be possible to further limit dose to normal tissue and thus treat lung tumors to a higher dose in fewer fractions of radiation therapy. This protocol will address the management of stage II-IV NSCLC who are not candidates for surgical resection or stereotactic body radiation therapy as definitive treatment.

The study is designed to determine whether daily image guidance and motion assessment/control will allow treatment of poor performance status patients with stage II-IV NSCLC, who would benefit from local therapy, with an accelerated course of hypofractionated radiation therapy. Poor performance status patients can be a heterogeneous group, with tumor-related factors, other co-morbidities, or advanced age placing patients in the category. These patients have traditionally been underrepresented in clinical trials, and no treatment method is standard. One phase III trial of "poor-risk" locally advanced NSCLC (RTOG 93-04) included just over 40% Karnofsky performance status 60-70 patients and showed median survival times of 9.5 and 10.3 months with 60 Gy of conventional radiation therapy alone or with recombinant β-interferon [18].

1.2 Rationale for Radiation Therapy Dose

A dose of 45 Gy in 15 fractions (3 Gy per fraction), often with a one week break, has been commonly employed in the past to treat poor performance status NSCLC patients. A pilot study of accelerated radiation therapy with concurrent carboplatin/paclitaxel for stage III NSCLC was closed after enrollment of only 5 patients due to excessive toxicity. The radiation therapy dose used was 60 Gy in 4 weeks of daily treatment, using a concomitant boost [19]. Our protocol is different in that it will not permit concurrent chemotherapy, it will not allow treatment of elective nodal regions as was done in that trial, and it will use daily image guidance so that treatment volumes will be significantly smaller. In a small study of 14 patients, Tsoutsou et.al. showed the feasibility of treating with 3.5 Gy daily for 15 fractions (52.5 Gy total) with a one week break after the 10^{th} fraction, along with concurrent chemotherapy, in locally advanced non-small cell lung cancer PS 0-2 patients [20]. Slotman et.al. treated 301 stage III NSCLC patients with three different hypofractionated radiation therapy regimens of 40 Gy in 8-10 fractions with a one week break, 30-32 Gy in 6 fractions or 24 Gy in 3 fractions. These regimens were all well tolerated [21].

The starting dose for this trial will be 3.33 Gy for 15 fractions to a total dose of 50 Gy which is higher than the commonly employed 3.0 Gy for 15 fractions yet predicted to be tolerated given the smaller volumes of irradiation with image guidance. If tolerated, the dose will be escalated while keeping the fraction number at 15. Doses of 3.67 Gy per fraction for a total of 55 Gy and then 4 Gy per fraction for a total dose of 60 Gy will be tested. Critical structure dose constraints will be expressed as organ dose-volume limits, with limits formulated with the approval of the study investigators using known tolerance data, radiobiological conversion models, and norms used in current practice at academic centers [22].

2.0 Objectives

2.1 Primary Objective

2.1.1 To escalate the dose of accelerated, hypofractionated, image-guided conformal radiotherapy to a potent tumorcidal dose without exceeding the maximum tolerated dose in treatment of stage II-IV NSCLC in patients with poor performance status. The maximum tolerated dose will be defined using the following criteria:

- For determination of appropriate dose escalation, the protocol is designed to capture rates of treatment-related (definitely and probably, but not possibly related to treatment*) grade 3 adverse events (per CTCAE, v.3.0, with the exception of pulmonary function tests as noted in Section 6.9.4) related to the following specific symptoms, including:

    - Gastrointestinal: dysphagia, esophagitis, esophageal stricture/stenosis, esophageal ulceration;
    - Cardiac: pericarditis, pericardial effusion, restrictive cardiomyopathy, ventricular dysfunction (left ventricular diastolic dysfunction, left ventricular systolic dysfunction, right ventricular dysfunction);
    - Neurologic: myelitis, neuropathy (cranial and motor);
    - Hemorrhage: pulmonary or upper respiratory;
    - Pulmonary: decline in pulmonary function as measured by pulmonary function tests (DL_{CO},and FEV_1,) using the modified criteria in relation to baseline (see section 6.9.4), pneumonitis, pulmonary fibrosis, hypoxia, pleural effusion, cough, and dyspnea
    - Any grade 4 or 5 adverse event attributed to the therapy (definitely and probably, but not possibly related to treatment)

  *Patients enrolled on this study are highly likely to have associated tobacco related cardiopulmonary co-morbidities that would result in adverse events (e.g., hospitalizations) irrespective of any cancer treatment. In published trials referenced in the introduction, adverse event analysis was confounded by problems distinguishing whether adverse events were treatment related versus part of the natural history of co-existing co-morbidities. As such, in this protocol only adverse events deemed probably and definitely related to treatment are considered for formal adverse event assessment. Adverse events deemed possibly related will be collected and reviewed but not used in adverse event analysis (e.g., for defining the maximum tolerated dose).

2.2 Secondary Objectives

2.2.1 To evaluate local regional tumor control and overall survival in patients with stage II-IV NSCLC and poor performance status treated with accelerated, hypofractionated, image-guided conformal radiotherapy.

3.0 Patient Selection

3.1 Conditions for patient eligibility

3.1.1 All patients must be willing and capable to provide informed consent to participate in the protocol.

3.1.2 Patients must have appropriate staging studies identifying them as AJCC stage II, III or IV non small cell lung cancer, [according to AJCC Staging, 6th edition; see appendix III], or recurrent non small cell lung cancer. Histologic confirmation of cancer will be required by biopsy or cytology.

3.1.3 Patients must have the potential for benefit from local therapy (at the discretion of the investigator).

3.1.4 Patient must have a Zubrod performance status of 2 or greater

Or

Patient must have had >10% weight loss in the past 6 months

Or

Patient is not eligible for concurrent chemoradiation as determined by a Medical Oncologist and Radiation Oncologist

3.1.5 Age ≥ 18.

3.1.6 The tumor must be ineligible for definitive surgical resection.

3.1.7 The tumor must be ineligible for stereotactic body radiation therapy.

3.1.8 Patients must have measurable or evaluable disease.

3.1.9 Women of childbearing potential and male participants must agree to use an effective method of contraception.

3.1.10 Patients must sign study specific informed consent prior to study entry.

3.1.11 Patients must complete all required pretreatment evaluations (section 4.0)

3.2 Conditions for patient ineligibility

3.2.1 Evidence of small cell histology.

3.2.2 Tumor eligible for definitive surgical resection.

3.2.3 Tumor eligible for definitive stereotactic body radiation therapy.

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.

3.2.5 Chemotherapy given within one week of study registration.

3.2.6 Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus.

4.0 Pretreatment Evaluations and Management

4.1 Required Evaluation and Management

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

4.1.1 The following tests must be done within 8 weeks of enrollment:

4.1.1.1 Computed tomographic (CT) with contrast of the lung and upper abdomen. A CT done in conjunction with a Positron Emission Tomography (PET) scan is satisfactory as long as the images are of adequate quality to be interpreted by a radiologist.

4.1.1.2 An MRI of the brain with contrast (or CT if MRI is medically contraindicated).

4.1.1.3 Complete Blood Count (CBC) with differential

4.1.2 Pulmonary function tests including spirometry for forced expiratory volume in 1 second (FEV-1), diffusing capacity (DLCO), and arterial blood gas (PaO-2) should be performed within 12 weeks of enrollment.

4.1.3 The following test must be done within 3 days prior to radiotherapy:
Urine or serum pregnancy test in females of child-bearing capacity.

4.1.4 The following test must be done prior to enrollment on the study:
Tissue biopsy or cytology confirming non-small cell lung cancer.

4.1.5 Charleston Comorbidity Index must be completed within 8 weeks of enrollment

4.2 Recommended Evaluations and Management

FDG-PET evaluations are not required for study entry, but are generally recommended for staging purposes.

5.0 Registration Procedures

5.1 Pre-Registration

5.1.1 Preregistration Requirements for diagnostic pathology review:
There are no requirements for central review of pathology used for initial diagnosis.

5.1.2 Pre-Registration Requirements for IGRT Treatment Approach:
In order to utilize IGRT in this protocol, the institution must have met technology requirements and have provided a description of techniques, methods, training, and experience showing competency to the study PIs.

5.2 Registration

Prior to registration, participating investigators and institutions should review the eligibility checklist and confirm eligibility. Patients can be registered only after eligibility criteria are met. To register a patient, the site should fax the Enrollment Form to the Project Manager (fax #: 214-648-5923). A unique, participant ID number will then be assigned.

5.3 Accreditation

Institutional Processes:

Prior to treating patients on protocol, the institution's specific methods for targeting, dose construction, daily imaging for verification of accuracy, ongoing assessment of accuracy and Quality Assurance policies must be described to and approved by the study PI and other approved institutional PIs. The primary purpose of accreditation will be to insure that dose is delivered to the targets and avoiding normal tissues according to protocol criteria. This accreditation may be assessed by written documentation, conference calls, or direct observation via site visits. Additional data may be required of institutions to verify that techniques are performing as intended.

6.0 Radiation Therapy

6.1 Dose Specifications

Protocol treatment must begin within 4 weeks after patient registration to the trial.

6.1.1 Image Guided Radiation Therapy

Image-guided radiation therapy (IGRT) is a process of using various imaging technologies to locate a tumor target prior to each treatment with radiation therapy. The purpose of this process is to improve the treatment accuracy and eliminate the need for large target margins which have traditionally been used to compensate for errors in localization. As a result, the amount of healthy tissue exposed to radiation can be reduced, minimizing the incidence of side effects. An example of three-dimensional (3D) IGRT is localization of a cone-beam computed tomography (CBCT) dataset with the planning computed tomography (CT) dataset from planning. Example of two-dimensional (2D) IGRT includes matching planar kilovoltage (kV) radiographs or fluoroscopy with digital reconstructed radiographs (DRRs) from the planning CT.

6.1.2 Adaptive Radiation Therapy

With daily imaging, the change in tumor size during the course of treatment can be easily monitored. At physician discretion, the treatment plan can be modified if enough response is attained to meaningfully reduce dose to normal tissue. All patients should have GTV, lung, esophagus and heart contoured on a scan at day 10 of treatment for assessment of possible normal tissue sparing with plan revision.

6.1.3 Dose Fractionation

Patients will receive 15 fractions of radiation. Total dose will depend on the dose cohort of the study (see schema). The starting dose level will be 3.33 Gy per fraction for 15 fractions (total dose = 50 Gy).

6.1.4 Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose must not fall below 90% of the prescription dose. All radiation doses will be calculated with tissue density (heterogeneity) corrections that take into account the density differences within the irradiated volume (i.e., air in the lung and bone). The following heterogeneity correction algorithms are not allowed because of known deficiencies: pencil beam and Clarkson's method.

6.1.5 Variations of dose prescription**:**

6.1.5.1 No deviation: 95% of the PTV receives the prescribed dose, ≥ 99% of the PTV receives ≥ 90% of the prescribed dose, and a contiguous volume of no

more than 2 cc anywhere within the patient receives ≥ 110% of the prescribed dose.

6.1.5.2 Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. 95% of the PTV receives < 100% but ≥ 97% of the prescribed dose, ≥ 99% of the PTV receives < 90% but ≥ 87% of the prescribed dose, or a contiguous volume of no more than 2cc anywhere within the patient receives between 110-115% of the prescribed dose.

6.1.5.3 Major deviation: Doses in this region are not acceptable. 95% of the PTV receives < 97% of the prescribed dose, ≥ 99% of the PTV receives < 87% of the prescribed dose, or a contiguous volume of > 2cc anywhere within the patient receives ≥ 115% of the prescribed dose.

6.2 Technical Factors

6.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 6-21 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.

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

6.3.1 Patient Positioning

Patients will be positioned supine in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.2 A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV), and planning target volume (PTV) (see definitions below). Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having 3 mm or less thickness through the regions harboring gross tumor and grossly enlarged lymph nodes, and 8-10 mm or less thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire lung volume. The GTV, PTV and normal organs will be outlined on all appropriate CT slices.

6.3.3 Inhibition of Effects of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques.

All systems used to account for internal organ motion must be validated and accredited by the Study Committee (Principal Investigator and Co-Chairs) before enrolling or treating patients on this trial. Internal organ inhibition maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.4 Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT if the patient can tolerate it.

6.3.5 A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

6.3.6 Localization

Isocenter or reference point port localization films should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study using the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification CT scans and portal films may be taken but are not required for protocol participation.

6.4 Treatment Planning/Target Volumes

6.4.1 Definition of the GTV/CTV/ITV

The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. The GTV should be expanded into a Clinical Target Volume (CTV) by adding a minimum of 5 mm and a maximum of 10 mm in any direction (at the discretion of the treating physician). **Elective treatment of nodal areas is not allowed.** The ITV (if a 4D CT scan is done for planning) includes the envelope that encompasses the tumor motion for a complete respiratory cycle. The motion quantified from the 4-D scan or real time fluoroscopy will be added to the CTV to constitute the ITV. If the motion is greater than 10-15 mm in any direction, special maneuvers such as abdominal compression, gating, chasing or regimented breath hold should be used to reduce the final motion below 10-15 mm. If it is observed that the tumor has no motion, then the CTV would be identical to the ITV.

6.4.2 Definition of the PTV:

Internal organ inhibition maneuvers, such as breath-hold, gating or abdominal compression, must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%). The PTV is defined as the ITV with additional margin for setup uncertainties and may be individualized but should not be less than 0.5 cm or greater than 1.0. Daily imaging is used to reposition the patient to minimize setup errors.

6.5 Critical Structures

6.5.1 Critical Organ Dose-Volume Limits

The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a protocol violation (See Section 6.7). The dose is listed as for a total of 15 fractions.

Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow in section 6.5.2.

Dose volume limits for 15 fraction XRT:

Serial Tissue	**Volume (cc)**	**Volume Max (Gy)**	**Max Point Dose (Gy)***	**Endpoint (≥Grade 3)**
Spinal cord	<5 cc	39 Gy	42.3 Gy	myelitis
Esophagus	<5 cc	51.3 Gy	55.3 Gy	stenosis/fistula
Brachial Plexus	<3 cc	44.5 Gy	50.6 Gy	neuropathy
Heart/Pericardium	<15cc	39.5 Gy	48.9 Gy	pericarditis
Great Vessels	<10 cc	48.9 Gy	54.3 Gy	aneurysm
Trachea and Large Bronchus	<5 cc	39.5 Gy	45.6 Gy	stenosis/fistula
Rib	<5 cc	48.9 Gy	52.2 Gy	pain or fracture
Skin	<10 cc	49 Gy	55.4 Gy	ulceration
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	**Other Constraints**	**Endpoint (≥Grade 3)**
Lung (Right and Left minus GTV)	1500 cc 1000 cc	15.5 Gy 16.3 Gy	Mean dose <18 Gy, V-18 <37%	Basic Lung Function Pneumonitis

* A maximum point dose is defined as the highest dose to 0.035 cc of tissue within the critical structure.

6.5.2 Contouring of normal tissue structures

6.5.2.1 Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal, starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.5.2.2 Lung (Right & Left) minus GTV

Contour right and left lung as one structure including all parenchymal lung tissue but excluding the GTV and major airways (trachea and main/lobar bronchi).

6.5.2.3 Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

6.5.2.4 Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.

6.5.2.5 Heart/Pericardium

The heart, along with the pericardial sac, should be contoured from its base to apex, beginning superiorly at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extending inferiorly to the apex of the heart.

6.5.2.6 Great Vessels

Contour the wall and lumen of the named vessel at least 10 cm superior and inferior to PTV.

6.5.2.7 Trachea and Large Bronchus

Contour the trachea and cartilage rings starting 10 cm superior to the PTV extending inferiorly to the bronchi ending at the first bifurcation of the named lobar bronchus.

6.5.2.8 Rib

Contour each rib separately within 5 cm of the PTV in any direction.

6.5.2.9 Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head.

6.6 Documentation Requirements

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 Compliance Criteria

Planning Priorities:

1) Critical normal structure constraints (see sections 6.5): The spinal cord, brachial plexus, heart, and lung are considered critical normal structures and constraints on

these structures will be prioritized. Exceeding these limits for these structures by more than 5% in any circumstance constitutes a minor protocol violation. Exceeding these limits by more than 10% constitutes a major protocol violation. It is understood that other normal structures dose limits would be exceeded in some patients because of their corresponding tumor distribution and meeting target coverage requirements. In general, when targets are within 1 cm of normal structures, attempts must be made to avoid exceeding constraints on these structures especially sparing of the contralateral wall to avoid circumferential radiation. Normal structures > 1 cm away from the target are subject to the above protocol violation description.

2) Variations of dose prescription**:**

No deviation: 95% of the PTV receives the prescribed dose, ≥ 99% of the PTV receives ≥ 90% of the prescribed dose, and a contiguous volume of no more than 2 cc anywhere within the patient receives ≥ 110% of the prescribed dose.

Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. 95% of the PTV receives < 100% but ≥ 97% of the prescribed dose, ≥ 99% of the PTV receives < 90% but ≥ 87% of the prescribed dose, or a contiguous volume of no more than 2cc anywhere within the patient receives between 110-115% of the prescribed dose.

Major deviation: Doses in this region are not acceptable. 95% of the PTV receives < 97% of the prescribed dose, ≥ 99% of the PTV receives < 87% of the prescribed dose, or a contiguous volume of > 2cc anywhere within the patient receives ≥ 115% of the prescribed dose.

6.8 Radiation Quality Assurance Reviews

Dr. Timmerman, along with a medical physicist, will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at the University of Texas Southwestern. They will perform the next review after complete data for the next and subsequent 20 cases enrolled has been received at the University of Texas Southwestern. 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 has been received, whichever occurs first.

6.9 Radiation Adverse Events

Adverse Events will be categorized and graded based primarily on the Common Toxicity Criteria for adverse events Version 3.0 (CTCAE version 3.0) with the exception of changes in pulmonary function tests (see section 6.9.4 below).

Radiotherapy should be interrupted for Grade 4 in-field toxicity and resumed when that toxicity has decreased to Grade ≤ 2 as detailed below. If treatment is interrupted for > two weeks, the patient should be removed from study treatment.

6.9.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥20 Gy, usually within the first six months after

initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.9.2 Esophagitis

Esophageal complaints are common with thoracic radiation therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 3 or 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Timmerman.

Esophagitis should be graded according to the CTCAE v.3.0

Table 4. Esophagitis grading system

Grade	Clinical Scenario
1	Asymptomatic pathologic, radiographic, or endoscopic findings only
2	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements), IV fluids indicated <24 hrs
3	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake), IV fluids, tube feedings, or TPN indicated >24 hrs
4	Life-threatening consequences
5	Death

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are as follows:

1) Ketoconazole 200 mg PO q day OR Fluconazole 100 mg PO q day until the completion of radiation.
2) Mixture of: 2% viscous lidocaine: 60 cc, Mylanta: 30 cc, sucralfate (1 gm/cc): 10 cc; Take 15-30 cc PO q3-4 hrs prn. (Contraindications: pts on Dilantin, Cipro, Digoxin)
3) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation
4) Grade 4 esophagitis: hold XRT until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.

6.9.3 Pneumonitis

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Note: It is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture

may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve. At that point, a clinical decision whether to finish therapy will be made in conjunction with the treating physician in conjunction with Dr. Timmerman, study Principal Investigator. When symptomatic pneumonitis resolves to grade 0, CTCAE, v. 3.0, the treating physician will contact Dr. Timmerman for a decision to continue or terminate protocol therapy.

6.9.4 Changes in Pulmonary Function Tests

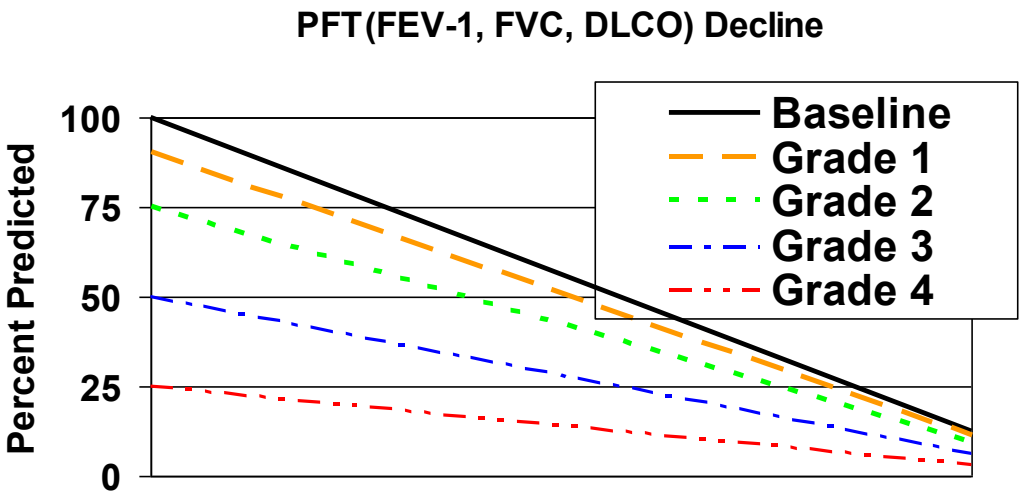
Patients enrolled to this study are allowed to have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV1), and Diffusing Capacity for Carbon Monoxide (DLCO). The Common Toxicity Criteria (CTCAE), v. 3.0 includes specified criteria for grading adverse events related to these PFT parameters under the category of pulmonary/upper respiratory. The grading criteria for these PFT changes use the "percent predicted" values from 0-100% which are recorded on the patient's PFT report. A percent predicted of 90% conveys that the patient is able to perform the PFT test to a result that is 90% of what would be expected for the normal general population of the same height, age, and sex. The CTCAE version 3 specified grading criteria for PFTs assumes that all patients have normal baseline pulmonary function. This assumption is not appropriate for this protocol enrolling patients with abnormal baseline function.

As a remedy to monitor treatment effects on PFTs, we will define a protocol specific toxicity classification for PFTs that adjusts for baseline abnormalities. Changes that occur after therapy will be referenced to the baseline for a given patient, which will be abnormal for most patients. We have defined a proportional decline from the baseline. Grade 1 toxicity will be a decline from baseline to a level 0.90 times the baseline, grade 2 will be a decline to a level 0.75 of baseline, grade 3 will be a decline to a level 0.5 of baseline, grade 4 will be a decline to a level 0.25 of baseline, and grade 5 will be death. This scheme is depicted in the table below and graphically represented in the following figure .

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 3 event in the original CTCAE version 3 criteria; however, under this modified PFT toxicity classification for patients with abnormal

baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.

The SBRT Pulmonary Toxicity Scale					
	Grade				
Adverse Event	1	2	3	4	5
FEV-1 Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
Forced Vital Capacity Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
DLCO Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death



6.10 Serious Adverse Event Reporting

Electronic Research Grant Organizer (ERGO) constitutes a mechanism for reporting serious adverse events to the UTSW IRB for reporting purposes.

Any adverse event equivalent to CTCAE V.3 grade 3, 4, or 5 or which precipitates hospitalization or prolongs an existing hospitalization must be reported regardless of designation (expected or unexpected) along with the attribution. This includes all deaths that occur within 30 days after the patient was discontinued from the study regardless of attribution AND any events that occur beyond 30 days and are considered probably related to treatment.

Participating sub-sites must file an SAE report (the CRF plus information describing the event, the grade, and the attribution) within 48 hours of the investigator's awareness of the occurrence of the event.

Attribution of an event can be categorized as:

- Not Related
- Possibly Related
- Probably Related
- Definitely Related

Adverse events (below grade 3) do not need to be submitted immediately. Rather, they should be documented in the Adverse Events CRF along with a brief description of the event, grade, and attribution).

All SAE reports should be made via FAX transmission to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
FAX #: 214-648-5923

7.0 Drug Therapy

Not applicable to this trial.

8.0 Other Therapy

Patients must not receive other concomitant antineoplastic therapy (including standard fractionated radiotherapy to the chest, chemotherapy, biological therapy, vaccine therapy, and surgery) within a week prior to, during, or within one week after completing hypofractionated image-guided radiation therapy on protocol.

8.1 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.

8.1.1 Antiemetics
8.1.2 Anticoagulants
8.1.3 Antidiarrheals
8.1.4 Analgesics
8.1.5 Hematopoietic Growth Factors
8.1.6 Herbal products
8.1.7 Nutritional supplementation

9.0 Companion Protocol Enrollment

Not applicable to this study.

10.0 Patient Assessments

10.1 Study Parameters: Please see Appendix II for the patient assessment schedule. Patients will be followed until death.

10.2 Criteria for Toxicity

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.

10.3 Response Assessment (RECIST Criteria)

Response will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. See http://ctep.cancer.gov/protocolDevelopment/docs/therasserecistjnci.pdf for further details.

Response Criteria: Evaluation of target lesions

*Complete Response (CR):	Disappearance of all target lesions
*Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD

*Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

*Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.4 Target lesion assessment guidelines

The longest diameter (LD) for the target lesion (or lesions) will be calculated from the treatment planning CT scan using pulmonary and/or mediastinal windowing and reported as the baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor.

10.4 Criteria for Removal from Protocol Treatment

All reasons for discontinuation of treatment must be documented. All patients will be followed until death or 5 years post treatment (whichever time point comes first). If protocol treatment is discontinued for any reason other death, follow up and data collection will continue as specified in the protocol.

10.4.1 Unacceptable toxicity.

10.4.2 A greater than two week delay in protocol treatment, as specified in Sections 6.0.

10.4.3 Development of intercurrent, non–cancer-related illnesses that prevent either continuation of therapy or regular follow-up.

10.5 Other response parameters

10.5.1 Time to Local Progression: The time to progression will be measured from the date of study entry to the date of documented local progression as determined by clinical exam.

10.5.2 Overall Survival: The survival time will be measured from the date of accession to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

10.5.3 Disease-Specific Survival : Disease-specific survival will be measured from the date of study entry to the date of death due to lung cancer. The following will be considered as failure events in assessing disease specific survival:

Death certified as due to lung cancer.

Death from other causes with active malignancy (clinical progression).

Death due to complications of treatment, irrespective of the status of malignancy.

Death from other causes with previously documented relapse but inactive at the time of death will not be considered in disease-specific survival, but will be analyzed separately.

10.6 Comorbidity Data and Rating

The Charlson Comorbidity index will be used to assess pretreatment comorbidity status per Appendix V.

11.0 Data Collection

Data should be submitted to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
5801 Forest Park Road
Dallas, Texas 75390-9183
FAX #: 214-648-5923

Patients will be identified only by initials (first middle last) and a unique study ID number assigned to each study participant; 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. Participating sub-sites must remove or black-out identifiers from source documentation that is sent to UTSW.

Item	Due
Demographics	Within 2 weeks of study entry
Eligibility and Entry Characteristics, including baseline H&P and Zubrod PS	Within 2 weeks of study entry
Pathology Report	Within 2 weeks of study entry
Follow-up H&P data	At post XRT follow-up at 1, 3, 6, 9, and 12 months, then q 4 months year 2, after 2 years at the discretion of the investigator/institution
Tumor response evaluation	At post XRT follow-up at 3, 6, 9, and 12 months, then q 4 months year 2, after 2 years at the discretion of the investigator/institution
Adverse Event assessment	After each weekly treatment visit, then post XRT follow-up at 1, 3, 6, 9, and 12 months, then q 4 months year 2, after 2 years at the discretion of the investigator/institution

12.0 Statistical Considerations

12.1 Study Endpoints

12.1.1 Primary endpoint

The primary endpoint of the study is to either reach the maximum tolerated dose (MTD) or a dose of 60 Gy total (whichever comes first) by escalating the dose of hypofractionated IGRT toward the total dose of 60 Gy. Patients will be treated in cohorts of seven to fifteen.

A dose limiting toxicity (DLT) is defined as treatment-related (definitely and probably, but not possibly related to treatment*) grade 3 adverse events (per CTCAE, v.3.0, with the exception of pulmonary function tests as noted in Section 6.9.4) related to the following specific symptoms, including:

- Gastrointestinal: dysphagia, esophagitis, esophageal stricture/stenosis, esophageal ulceration;
- Cardiac: pericarditis, pericardial effusion, restrictive cardiomyopathy, ventricular dysfunction (left ventricular diastolic dysfunction, left ventricular systolic dysfunction, right ventricular dysfunction);
- Neurologic: myelitis, neuropathy (cranial and motor);
- Hemorrhage: pulmonary or upper respiratory;
- Pulmonary: decline in pulmonary function as measured by pulmonary function tests (DL_{CO},and FEV_1,) using the modified criteria in relation to baseline (see section 6.9.4), pneumonitis, pulmonary fibrosis, hypoxia, pleural effusion, cough, and dyspnea

In addition, a DLT will include any grade 4 or 5 adverse event attributed to the therapy (definitely and probably, but not possibly related to treatment).

*Patients enrolled on this study are highly likely to have associated tobacco related cardiopulmonary co-morbidities that would result in adverse events (e.g., hospitalizations) irrespective of any cancer treatment. In published trials referenced in the introduction, adverse event analysis was confounded by problems distinguishing whether adverse events were treatment related versus part of the natural history of co-existing co-morbidities. As such, in this protocol only adverse events deemed probably and definitely related to treatment are considered for formal adverse event assessment. Adverse events deemed possibly related will be collected and reviewed but not used in adverse event analysis (e.g., for defining the maximum tolerated dose).

All reported DLTs will be verified by study chair and data monitoring committee, before final determination that a DLT has in fact occurred. Doses will be escalated an additional 0.33 Gy per treatment for 15 treatments (total 5 Gy per increment). The study will be completed when either of the following events occur: 1) the MTD for a cohort is reached or 2) when the highest dose level allowed by the protocol is treated and tolerated (4 Gy per fraction, total 60 Gy).

12.1.2 Dose escalation

This study is designed to end if the rate of DLTs within 90 days from the start of treatment is 33% or higher. For each dose level cohorts, a total of seven to fifteen patients will be enrolled. If zero out of the first seven with 90 day follow-up, two or fewer out of the first nine with 90 day follow-up, three or fewer out of the first twelve with 90 day follow-up, or four or fewer out of the first fifteen of patients with 90 day follow-up experience a DLT as defined above, then the dose will escalate to the next dose level. If three or more of the first nine patients, four or more of the first twelve, or five or more of the first fifteen patients experience a DLT, then the MTD will be considered to have been exceeded. The MTD will be defined as the immediately previous lower dose level tolerated.

12.1.3 Waiting period

Dose escalation on this study should not occur until a sufficient waiting period has occurred after patients have been treated. A period of 90 days must pass in order to assess toxicity. If 90 days have transpired without DLT in each of the first seven (7) patients enrolled to a specific dose level, then dose escalation to the next level may proceed. Patients will continue to be enrolled to each dose level (up to a maximum of 15 patients) with ongoing assessment of those reaching 90 day follow-up so long as either criteria for defining the MTD (section 12.1.2) or criteria for further dose escalation is not reached. If fifteen patients are enrolled to a given dose level yet criteria for adequate follow-up are not reached in a representative sample of patients (section 12.1.2), further enrollment to the protocol will be suspended until adequate follow-up is reached.

12.1.4 Other endpoints

A secondary endpoint is to evaluate local regional tumor control and overall survival by actuarial analysis.

12.2 Analysis Plan

Interim Reports: Interim reports will be prepared every six months until the results of the study are published or the study is closed. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

12.2.1 Estimation of Secondary Endpoints Related to the Efficacy: Cumulative incidence approach [23] will be used to estimate the failure rate for local-regional and distant failures. Kaplan-Meier method [24] will used to estimate the overall survival rate.

13.0 Data Safety and Monitoring Plan

13.1 Data Safety Monitoring Committee and Institutional IRB reporting

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. The data safety monitoring committee will review and verify all reported DLTs. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to basic patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment at regular defined intervals defined in the statistics section of this protocol. Unexpected toxicities occurring between defined interim analyses points will be reported to the treating center's IRB and also to the University of Texas Southwestern IRB. Simmons Cancer Center Data Safety Monitoring Committee (DSMC) will review reported serious adverse events and contact Radiation Oncology DSMC for any discrepancies.

References

1. Jemal A, e.a., *Cancer Statistics 2008.* CA: a cancer journal for clinicians, 2008. **58**: p. 71–96.
2. Shields, T.W., *Surgical therapy for carcinoma of the lung.* Clin Chest Med, 1993. **14**(1): p. 121-47.
3. Perez, C.A., et al., *A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group.* Cancer, 1980. **45**(11): p. 2744-53.
4. Kong, F.M., et al., *High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study.* Int J Radiat Oncol Biol Phys, 2005. **63**(2): p. 324-33.
5. Lee, C.B., et al., *Late complications of high-dose (>/=66 Gy) thoracic conformal radiation therapy in combined modality trials in unresectable stage III non-small cell lung cancer.* J Thorac Oncol, 2009. **4**(1): p. 74-9.
6. Bradley, J., et al., *Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma.* Int J Radiat Oncol Biol Phys, 2005. **61**(2): p. 318-28.
7. Dillman, R.O., et al., *Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial.* J Natl Cancer Inst, 1996. **88**(17): p. 1210-5.
8. Belani, C.P., et al., *Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol.* J Clin Oncol, 2005. **23**(25): p. 5883-91.
9. Curran, W., et al., *Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresectable NSCLC: RTOG 9410.* Proceedings of ASCO, 2003. **22**: p. 621a.
10. Le Chevalier, T., et al., *Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients.* J Natl Cancer Inst, 1991. **83**(6): p. 417-23.
11. Sause, W.T., et al., *Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer.* J Natl Cancer Inst, 1995. **87**(3): p. 198-205.
12. Schaake-Koning, C., et al., *Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer.* N Engl J Med, 1992. **326**(8): p. 524-30.
13. Hanna, N., et al., *Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology.* J Clin Oncol, 2008. **26**(35): p. 5755-60.
14. Dillman, R.O., et al., *A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer.* N Engl J Med, 1990. **323**(14): p. 940-5.
15. Clamon, G., et al., *Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia*

Group B and the Eastern Cooperative Oncology Group. J Clin Oncol, 1999. **17**(1): p. 4-11.
16. Kupelian, P.A., et al., *Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment.* Int J Radiat Oncol Biol Phys, 2005. **63**(4): p. 1024-8.
17. Timmerman, R., et al., *Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer.* J Clin Oncol, 2006. **24**(30): p. 4833-9.
18. Bradley, J.D., et al., *A phase III comparison of radiation therapy with or without recombinant beta-interferon for poor-risk patients with locally advanced non-small-cell lung cancer (RTOG 93-04).* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1173-9.
19. Machtay, M., C. Washam, and P. Devine, *Pilot study of accelerated radiotherapy with concurrent chemotherapy for stage III non-small cell lung cancer.* Semin Oncol, 2005. **32**(2 Suppl 3): p. S9-12.
20. Tsoutsou, P.G., et al., *Hypofractionated/accelerated radiotherapy with cytoprotection (HypoARC) combined with vinorelbine and liposomal doxorubicin for locally advanced non-small cell lung cancer (NSCLC).* Anticancer Res, 2008. **28**(2B): p. 1349-54.
21. Slotman, B.J., et.al., *Hypofractionated Radiation Therapy in Unresectable Stage III Non-Small Cell Lung Cancer.* Cancer, 1993. **72**(6): p. 1885-1893.
22. Park, C., et al., *Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy.* Int J Radiat Oncol Biol Phys, 2008. **70**(3): p. 847-52.
23. Gray, R., *A class of K-sample tests for comparing the cumulative incidence of a competing risk.* Ann Stat, 1988. **16**: p. 1141-1154.
24. Kaplan, E., Meier, P, *Nonparameteric estimation from incomplete observations.* J. Amer. Statist. Assoc., 1958. **53**: p. 457-481.

Appendix I: Sample Treatment Consent Form

Study Title:

Phase I Study of Accelerated Hypofractionated Image-Guided Radiation Therapy (IGRT) in Patients with Stage II-IV Non-Small Cell Lung Cancer and Poor Performance Status

INVITATION: You are invited to participate in this research because you have lung cancer.

NUMBER OF PARTICIPANTS: Up to 45 patients (depending on how the treatment is tolerated).

PURPOSE: The purpose of this study is to find the highest reasonably safe daily dose of radiation therapy that can be delivered to treat lung cancer. Modern technology uses frequent imaging and other techniques that allow precise delivery of a large radiation dose to a tumor while avoiding normal tissue. The higher dose technique may work better to kill cancer cells.

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

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

1. History and physical examination
2. A biopsy of your tumor proving you have cancer
3. CT scan of the chest and upper abdomen or a PET/CT
4. MRI scan of the brain (or CT if the MRI cannot be performed for medical reasons)
5. Pulmonary function studies
6. Routine blood tests

During the study …
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

1. Physical exam – following completion of radiation therapy at 1 month, 3 months, 6 months, 9 months, 12 months, and every 4 months for the second year, every 6 months for years 3-5, and then yearly.
2. CT imaging to follow the cancer – following completion of radiation therapy at 3 months, 6 months, 9 months, 12 months, and every 4 months for the second year, every 6 months for years 3-5, and then yearly.
3. Pulmonary function testing at 6 and 12 months after completing therapy.

How long will I be in the study?

You will receive radiation therapy for 3 weeks. Follow up visits and exams will continue for the rest of your life according to the schedule given above, in order to monitor the status of your cancer.

Can I stop being in the study?
Yes. You can decide to stop at any time. It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
While on the study, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There may be other side effects that we cannot predict. Many side effects go away soon after you stop being treated with radiation therapy. But in some cases, side effects can be serious, long lasting, or may never go away. Drugs may be given to make side effects less serious and uncomfortable. It is also possible that your cancer may not respond to radiation therapy.

Risks and side effects related to radiation therapy to the chest include those which are:
Likely (>10%):

- Difficulty, pain, or a burning sensation when swallowing, which is temporary
- Fatigue, which is temporary
- Tanning, redness of the skin, and hair loss within the treatment area, which is temporary
- Skin in the treatment area may remain permanently dry, and chest hair may not grow back
- Cough and some difficulty in breathing due to lung damage

Less Likely:

- Decrease in blood counts while undergoing treatment that may result in bleeding, and bruising easily
- Fever
- Chest wall discomfort or pain
- Rib fracture, which may cause pain
- Narrowing of the esophagus causing difficulty swallowing meals (requiring internal dilation or a feeding tube)

Rare, but serious:

- Pericarditis – irritation of the heart sac causing a rapid heart rate, chest discomfort, or chest pain
- Myocarditis – irritation of the heart muscle causing shortness of breath, chest pain, or permanent heart muscle damage
- Transverse myelitis – irritation of the spinal cord causing weakness or paralysis
- Bleeding from the airway
- Narrowing of the airway causing shortness of breath
- Death

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as chest pain, shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. Treatment for this lung damage involves pain medicines, antiinflammatory medicines (corticosteroids), and rarely, oxygen therapy, which may be permanent. You should tell your doctors immediately if you have any of these symptoms.

Risks from radiation exposure from diagnostic tests:
There is no additional risk of harm from radiation as a result of your participation in this study except as standard care for your medical condition.

Risks from blood samples:
You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint. On a rare occasion, an infection could develop at the site where the blood was collected.

Risks from Loss of Confidentiality:
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep information confidential; however, this cannot be guaranteed.

Reproductive Risks:
You should not become pregnant or father a baby while on this study because the radiation therapy in this study can affect an unborn baby. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

How you can help reduce some of the risks:
During your participation in this research, your study doctor will watch closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the study doctor’s instructions.
- Let your study doctor know if your telephone number changes.
- Tell your study doctor before you take any new medication even if it is prescribed by another doctor for a different medical problem.
- Tell your regular doctor about your participation in this research.
- Talk to a family member or friend about your participation in this research.

What to do if you have problems:
If you have any problems such as unusual symptoms or pain at any time during your participation in the research, your study doctor can recommend treatment. Please report the problem to your study doctor promptly. Telephone numbers where your study doctor may be reached are listed on the first page of this consent form.

If you suddenly have a serious problem (such as difficulty breathing) or severe pain, go to the nearest hospital emergency room, or call 911 (or the appropriate emergency telephone number in your area). Tell emergency personnel about your participation in this research. Ask them to telephone your study doctor immediately.

Are there benefits to taking part in the study?
Benefit to you: Taking part in this study may or may not make your health better. While doctors hope accelerated hypofractionated, image-guided radiation therapy will be more useful against your lung cancer compared to the usual treatment, there is no proof of this yet.

Benefit to other people with lung cancer: In the future, other people with lung cancer could benefit from the results of this research. Information gained from this research could lead to improved medical care for them. However, your study doctor will not know whether there are benefits to other people with lung cancer until all of the information obtained from this research has been collected and analyzed.

What other choices do I have if I do not take part in this study?
Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

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

What are the costs of taking part in this study?
Expenses related to standard medical care for lung cancer are your responsibility (or the responsibility of your insurance provider or government program).

All tests and procedures performed during your treatment and follow up visits will be billed as standard of care.

There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

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

What happens if I am injured because I took part in this study?
Compensation for an injury resulting from your participation in this research is not available from The University of Texas Southwestern Medical Center.
You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to discontinue participation in the research at any time. You retain your legal rights during your participation in this research.

Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you receive at this center.

NEW INFORMATION: Any new information which becomes available during your participation in the research and may affect your health, safety, or willingness to continue in the research will be given to you.

Will my medical information be kept private?
Information about you that is collected for this research study will remain confidential unless you give your permission to share it with others, or as described below. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified personnel at The UT Southwestern Medical Center

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

To help us further protect the information, the investigators will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). This Certificate adds special protections for research information that identifies you and will help researchers protect your privacy.

With this Certificate of Confidentiality, the researchers cannot be forced to disclose information that may identify you in any judicial, administrative, legislative, or other proceeding, whether at the federal, state, or local level. There are situations, however, where we will voluntarily disclose information consistent with state or other laws, such as:

- to DHHS for audit or program evaluation purposes;
- information regarding test results for certain communicable diseases to the Texas Department of State Health Services, including, but not limited to HIV, Hepatitis, Anthrax, and Smallpox;
- if you pose imminent physical harm to yourself or others;
- if you pose immediate mental or emotional injury to yourself;
- if the researchers learn that a child has been, or may be, abused or neglected; or
- if the researchers learn that an elderly or disabled person has been, or is being, abused, neglected or exploited.

The researchers will not, in any case, disclose information about you or your participation in this study unless it is included in the Authorization for Use and Disclosure of Protected Health Information for Research Purposes as stated above.

The Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your involvement in this research study. In addition, the researchers may not use the Certificate to withhold information about your participation in this research study if you have provided written consent to anyone allowing the researchers to release such information (including your employer or an insurance company). This means that you or your family must also actively protect your privacy. A Certificate of Confidentiality does not represent an endorsement of this research project by the Department of Health & Human Services or any other Federal government agency.

YOUR QUESTIONS: Your study doctor is available to answer your questions about this research at 214-645-8525. The Chairman of the IRB is available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research. You may telephone the Chairman of the IRB during regular office hours at [enter IRB contact number].

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

Signature:

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

Participant _____

Date _____

Interpreter Statement:

I have interpreted this consent form into a language understandable to the subject and the subject has agreed to participate as indicated by their signature above.

Name of Interpreter (printed) _____

Signature of Interpreter _____

Date _____

Appendix II: Study Parameter Table

	Pre-Registration						During XRT		Follow-Up (months after therapy)		
		Within 8 weeks	Within 12 weeks	Within 3 days prior to XRT	Weekly	1 month	3 months	6 months	9 months	12 months	Q 4 months during year 2, after 2 years at the discretion of the investigator/institution
History / Physical		X				X	X	X	X	X	X
Zubrod PS		X			X	X	X	X	X	X	X
Weight		X			X	X	X	X	X	X	X
Biopsy / cytology	X										
CT of Chest[1]		X					X	X	X	X	X
MRI Brain[2]		X									
PFT's (including DLCO and FEV1)			X					X		X	
CBC w/ diff		X									
Serum or urine pregnancy test (if applicable)				X							
Informed consent	X										
Comorbidity index (Appendix V)		X									
Adverse event evaluation					X	X	X	X	X	X	X
Tumor response evaluation							X	X	X	X	X

[1]preferably with IV contrast unless medically contraindicated

[2]CT if MRI medically contraindicated

APPENDIX III

ZUBROD PERFORMANCE SCALE

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

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX IV

AJCC STAGING SYSTEM
AJCC Staging, Lung, 6th Edition, 2002

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0 No evidence of primary tumor.
Tis Carcinoma *in situ*
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)
T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

***Note:** The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

****Note:** Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

Regional Lymph Nodes (N)

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

APPENDIX IV (continued)

AJCC STAGING SYSTEM
AJCC Staging
Lung, 6th Edition, 2002

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

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

STAGE GROUPING

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

Appendix V: Comorbidity Scoring

Instructions for completing the CHARLSON COMORBIDITY INDEX (CCI):

1. Complete all patient information.
2. Follow the “Rules for Completing The Charlson Comorbidity Index” in this appendix.
3. Complete The Charlson Comorbidity Index” by noting “yes” or “no” for each disease.

Instructions for completing THE COMORBIDITY RECORDING SHEET:

1. Complete all patient information.
2. Extract all comorbidity elements you can identify and note them on the Recording Sheet. Place the elements in the most appropriate category. Be comprehensive.
3. Include past surgeries, diseases, smoking history, and functional problems, such as incontinence or constipation.
4. For each condition include:
   - When (e.g., 6 months ago, 5 years ago, etc.);
   - Current symptoms;
   - Related treatment (e.g., surgery, stent placement, hearing aides, glasses, etc.);
   - Related laboratory values (e.g., CR, bilirubin);
   - Medications (scheduled/prn).
5. If a functional problem appears to be related to tumor or treatment, place **TR** after the diagnosis.
6. Specify as much as possible the dose/frequency of medications; the rater may use this information to rate the severity of a disease.
7. Leave the scoring column blank.

Appendix V

Rules for Completing the Charlson Comorbidity Index (CCI)

(Charlson et al. *J Chron Dis*. 40:373-383, 1987) Adaptation: Do not count non-melanotic skin cancers or in situ cervical carcinoma.

Myocardial infarct	Hx of medically documented myocardial infarction
Congestive heart failure	Symptomatic CHF w/ response to specific treatment
Peripheral vascular disease	Intermittent claudication, periph. arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (>=6cm)
Cerebrovascular disease (except hemiplegia)	Hx of TIA, or CVA with no or minor sequelae
Dementia	chronic cognitive deficit
Chronic pulmonary disease	symptomatic dyspnea due to chronic respiratory conditions (including asthma)
Connective tissue disease	SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA
Ulcer disease	Patients who have required treatment for PUD
Mild liver disease	cirrhosis without PHT, chronic hepatitis
Diabetes (without complications)	diabetes with medication
Diabetes with end organ damage	retinopathy, neuropathy, nephropathy
Hemiplegia (or paraplegia)	hemiplegia or paraplegia
Moderate or severe renal disease	Creatinine >3mg% (265 umol/l), dialysis, transplantation, uremic syndrome
2nd Solid tumor (non metastatic)	Initially treated in the last 5 years exclude non-melanomatous skin cancers and in situ cervical carcinoma
Leukemia	CML, CLL, AML, ALL, PV
Lymphoma, MM...	NHL, Hodgkin's, Waldenström, multiple myeloma
Moderate or severe liver disease	cirrhosis with PHT +/- variceal bleeding
2nd Metastatic solid tumor	self-explaining
AIDS	AIDS and AIDS-related complex Suggested: as defined in latest definition

APPENDIX V (Continued)
CHARLSON COMORBIDITY INDEX (CCI)
Scoring Sheet

Name/Number:_____
Patient Initials (First Middle Last):_____ Number:_____
Name of Person Completing Sheet:_____
Phone Number:_____
Date Completed:__-___-_____

Comorbidity	**Present (Y or N)**	Points
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd Solid tumor (nonmetastatic)		2
Leukemia		2
Lymphoma, MM...		2
Moderate or severe liver disease		3
2nd Metastatic solid tumor		6
AIDS		6

APPENDIX V (Continued)

Completing the Comorbidity Recording Sheet

Examples of conditions in each category are listed below. The list is not all-inclusive. Please list other conditions that are present. All conditions, including abnormal values, are **before** the start of therapy.

Heart: MI, Arrhythmia, CHF, Angina, Pericardial disease, Valvular disease
Vascular/Hematopoietic: Hypertension, Peripheral vascular disease, Aneurysms, Blood abnormalities (anemia, leukopenia, etc.)
Respiratory: Bronchitis, Asthma, COPD, Tobacco history (pack/year)
HEENT: Vision impairment, Sinusitis, Hearing loss, Vertigo
Upper GI (esophagus, stomach, duodenum): Reflux, PUD
Lower GI (intestines, hernia): Constipation/Diarrhea, Hemorrhoids, Diverticulitises
Liver/Pancreas/GB: Cholelithiasis/Cholecystectomy, Hepatitis/pancreatitis
Renal: Creatinine, Stones
GU (ureters, bladder, urethra, prostate, genitals, uterus, ovaries): Incontinence, UTI, BPH, Hysterectomy, Abnormal PAP smear, Bleeding
Musculoskeletal/Skin: Arthritis, Osteoporosis, Skin cancer, Psoriasis
Neurological: Headaches, TIAs/Stroke, Vertigo, Parkinson's Disease/MS/ALS
Endocrine (record height and weight): Diabetes, Hypo/hyperthyroid, Obesity
Psychiatric: Dementia, Depression

APPENDIX V (Continued)
COMORBIDITY RECORDING SHEET

Name/Number:_____
Patient Initials (First Middle Last):_____ Number:_____
Name of Person Completing Sheet: _____Phone Number:_____
Date Completed:__-___-_____

Comorbidities (Add **TR** if related to tumor or its treatment)	**Score**
Heart	
Vascular (Hemoglobin:_____)	
Respiratory (include tobacco history)	
Eyes and ENT	
Upper GI	
Lower GI	
Liver and Pancreas	
Renal (Creatinine: _____)	
GU	
Musculoskeletal/Integument	
Neurological	
Endocrine/Metabolic and Breast (Weight:_____Height:_____)	
Psychiatric	

Medications (prn or scheduled):
