Official Title: Phase III Randomized Study of Standard versus Accelerated Hypofractionated Image-Guided Therapy (IGRT) in the Definitive Setting for Patients with Stage II-III or Recurrent Non-Small Cell Lung Cancer and Poor Performance Status

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Phase III Randomized Study of Standard versus Accelerated Hypofractionated Image-Guided Radiation Therapy (IGRT) in the Definitive Setting for Patients with Stage II-III or Recurrent Non-Small Cell Lung Cancer and Poor Performance Status

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Dallas, Texas 75390-9179

Signature Page-version 9

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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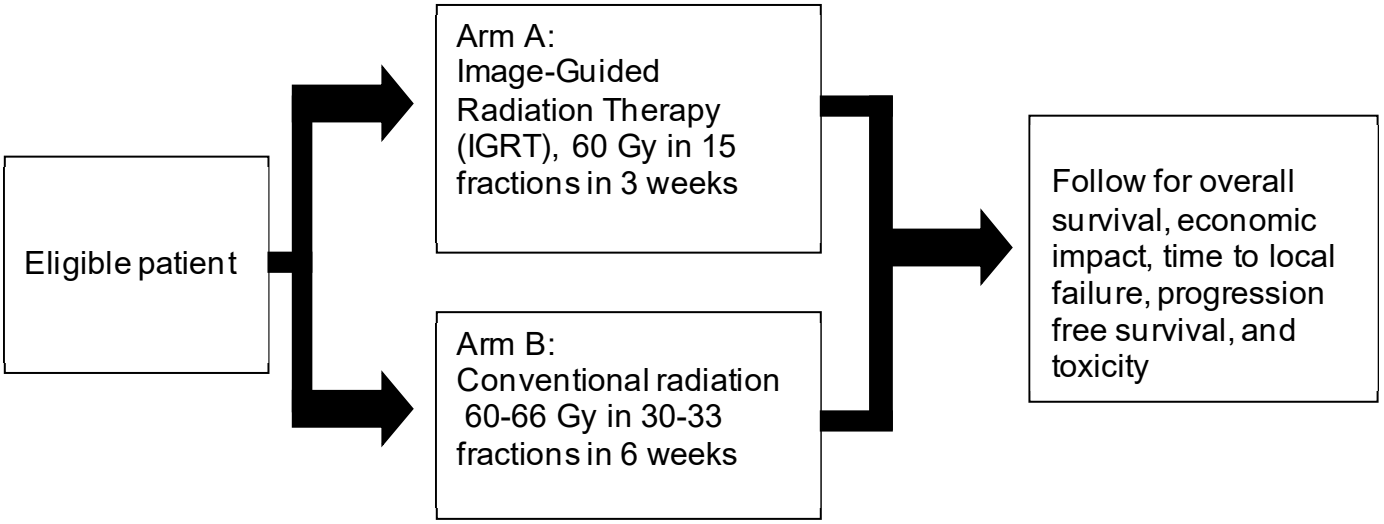
Schema

Number of patients = 226 (113) per arm)



ELIGIBILITY (see section 3.0 for full criteria)
- Stage II-III or Recurrent (after surgical resection) non-small cell lung cancer (NSCLC) that would benefit from local radiation therapy.
- Zubrod performance status of 2 or greater
  OR Zubrod performance status 0-1 and weight loss > 10% over the last 6 months prior to enrollment
  OR medically unable to tolerate or refusing standard combined modality therapy
-Total (aggregate) gross tumor volume ≤ 500 cm^3 (500 cc's or 0.5 Liters
- 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 enrollment except concurrent chemotherapy may be given at the investigator's discretion to patients randomized to the standard arm (arm B, 30-33 fractions)
- Study-specific consent form signed

Eligibility Checklist

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

_____ (Y) 1. Does the patient have histologically or cytologically documented NSCLC within 9 months of study enrollment?

_____ (Y) 2. Is TNM Stage II or III or does the patient have recurrent disease after surgical resection?

_____ What is the patient's TNM stage?

_____ (N) 3. Has the patient had prior radiotherapy to the chest or neck that would result in overlap of radiation therapy fields?

_____ (Y) 4. Is the Zubrod performance status 2 or greater?

_____ What is the patient's performance status (see Appendix III)?

_____ (Y) If not, does the patient have weight loss > 10% over the last 6 months?

_____ (Y) If not, is the patient medically unable to tolerate or refusing standard combined modality therapy?

_____ (Y) 5. Is the total (aggregate) gross tumor volume ≤ 500 cm^3 (500 cc's or 0.5 Liters)

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

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

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

_____ (Y) 9. Were all the required pre-registration/study enrollment evaluations administered as specified in Section 4, including CT with contrast of lung and upper abdomen within 12 weeks of registration/study enrollment?

_____ (Y/NA) 10. Has the patient agreed to use an effective method of contraception?
Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

10a. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the

following criteria:
* Has not undergone a hysterectomy or bilateral oophorectomy; or
* Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

_____ (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[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 and 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.

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-III NSCLC who are not candidates for surgical resection or stereotactic body radiation therapy as definitive treatment.

The study is designed to determine whether an accelerated course of hypofractionated radiation therapy with daily image guidance and motion assessment/control will allow more effective treatment of poor performance status patients with stage II-III NSCLC, who would benefit from local therapy compared to standard radiation therapy (60 Gy in 2 Gy per fraction). 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 thus no prospective study has evaluated the efficacy of other radiotherapy dose fractionations in these patients. 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 year overall survival was just 44% in these patients.

1.2 Rationale for Radiation Therapy Dose

A dose of 45 Gy in 15 fractions (3 Gy per fraction) 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 10th 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].

Standard radiation to the chest for unresectable stage III NSCLC is 60-66 Gy at 2 Gy per fraction. Radiobiologic calculations indicate that the accelerated therapy regimen of 3 Gy/fraction to 45 Gy is similar to 2 Gy per fraction to 60 Gy, with regrowth delay time (time to progression) of 92% and late complication biologically effective dose (BED) of 90% of that calculated for standard radiation. Additionally, 45 Gy at 3 Gy per fraction has been shown to have similar clinical outcomes and toxicity. This has been shown in a retrospective review at MD Anderson of 2 cohorts of node positive patients with inoperable LA-NSCLC treated with radiation alone [22]. One cohort (26 patients) had borderline prognostic factors (KPS < 70 but > 50 and/or weight loss of more than 5%) and was treated to 45 Gy over 3 weeks at 3 Gy/fraction. The second cohort (29 patients) had significantly better prognostic factors and was treated to 60-66 Gy over 6 to 6.5 weeks at 2 Gy per fraction during the same period. Despite having worse prognostic factors, the cohort treated to 45 Gy at 3 Gy per fraction over 3 weeks had response rates, locoregional control, and overall survival comparable to those in the cohort treated to a total dose of 60-66 Gy at 2 Gy per fraction over 6 weeks without difference in acute or late toxicity. Radiation dose intensification in locally advanced NSCLC has been studied in prospective trials. 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.[23] A group from Poland found similar toxicity profiles in patients treated with 21 fractions of radiation using 2.7, 2.8 and 2.9 Gy fractions. Of those patients, 7% had grade III acute esophageal toxicity and 6% had grade III or greater late pulmonary toxicity [24]. An Italian group reported a 30 patient trial wherein 60 Gy in 20 fractions was given to patients with locally advanced NSCLC. Grade 3 hematological toxicity occurred in 1 patient, grade 3 esophagitis in 1 patient and grade 3 pneumonitis in 2 patients [25]. Subsequently , the MD Anderson group reported a phase I trial evaluating 45, 52.5 and 60 Gy delivered in 15 fractions using proton beam and found similar, acceptable levels of toxicity in all arms[26]. Collectively, this information support both our trial concept and the dose intensity utilized.

Specifically, the experimental arm dose for this trial is based on a dose escalation trial at University of Texas Southwestern evaluating the maximum tolerated dose of hypofractionated IGRT in this patient population. Doses were escalated from 3 Gy per fraction (total dose 45 Gy) to 4.0 Gy per fraction (total dose 60 Gy) and evaluation for treatment related toxicity was being performed. 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 [27]. The trial design called for treating many patients per dose level, akin to a phase II trial, so as to collect outcome data on enough patients to simultaneously appreciate toxicity and efficacy in order to optimize dosing. The maximum tolerated dose (MTD) was never reached on this protocol up to 60 Gy in 15 fractions for effectively the same population treated on this protocol. 50 Gy, 55 Gy or 60 Gy in 15 fractions was delivered using image guided radiation therapy. Patents with tumor volumes larger than 500 cc were excluded. 18, 23 and 21 individuals were enrolled at each dose level respectively. The median follow-up is 195 days (range 26-927 days). Median follow-up is 452 days if patient deaths are censored in a population that succumbs commonly to non-cancer or treatment related causes. Of

the 52 patients enrolled, only 4 patients experienced grade 3 or higher treatment-related toxicity spread indiscriminantly among the tested dose levels. Long term tumor control from this trial is still being collected. Since previous trials described above show improving control and survival with radiation dose intensification and since the MTD was not reached, we have chosen the 60 arm to be the experimental arm of this protocol.

1.3 Comparative Economic Analysis

In the United States, total national health expenditures (NHE) increased from $7.14 billion in 1990 to $2.23 trillion in 2007, which represents an average annual growth rate of 7.0%. In contrast, over the same period, U.S. gross domestic product (GDP) increased from $5.8 trillion in 1990 to $13.8 billion, or average 5.2% annual growth rate. Given that national health expenditures have grown faster than GDP, the share of GDP devoted to health expenditures has increased from 12.3% in 1990 to 16.2% in 2007[28]. Moreover, national health expenditure growth is expected to continue to outpace income growth, with total NHE reaching $4.35 trillion by 2018, accounting for 20.3% of GDP (CMS 2009). There is growing concern that these trends in health expenditures are not sustainable. For the Medicare program, current estimates of the present value of total unfunded liabilities through the year 2083 (the present value of the difference between projected future Medicare expenditures and Medicare revenues over the next 75 years under current Medicare policy) total $89 trillion, with Medicare's Hospital Insurance ("Part A") trust fund projected to be depleted by 2017[29].

Prior studies have estimated that about half of the recent growth in health expenditures is attributable to advances in various forms of health technology, including new pharmaceutical products, surgical procedures, imaging modalities, and new biomarkers[29]. While almost all of these new technologies offer some potential to improve clinical outcomes, they also more often than not add to health expenditures. Within the context of unsustainable trends in health expenditures, a key policy question relates to whether the extent of improvement in outcomes associated with the use of a new technology is attained at a "reasonable" additional cost, compared to existing technology. Indeed, the value offered by new technologies is being subjected to increasing scrutiny by reimbursement authorities in many health systems worldwide. For example, in the United Kingdom, the National Health Service bases payment policy decisions for new technologies on recommendations from the National Institute for Health and Clinical Excellence (NICE), which in turn are substantially influenced by cost-effectiveness analysis yielding an estimated additional "cost per quality-adjusted life-year (QALY) gained" via use of the new technology. Currently, NICE usually considers technologies offering improved outcomes at a cost less than £20,000 to £30,000 per QALY gained (about $33,000 - $50,000) acceptable, though exceptions are common[30].

Therefore, we propose to collect cost information in both arms in this Phase III trial, and assess patients' health related quality of life, in order to evaluate the economical consequence of using the new technology proposed in this study and its impact on quality of life. We hypothesize that the new technology may be cost saving (cost less than the current standard of care) over the patient's entire treatment course, making it very attractive for adoption in treatment for lung cancer patients. Alternatively, we hypothesize that the new technology will increase quality-adjusted life-years for lung cancer patients (compared to the current standard of care) at a reasonable incremental cost, as defined by generally accepted cost-effectiveness thresholds.

1.4 Chemotherapy in Poor Performing Patients Enrolled On-study

Randomized trials that showed survival benefit for adding chemotherapy to radiotherapy generally excluded poor performing patients and often patients with significant weight loss. At trial initiation, our trial prohibited the use of specifically concurrent chemotherapy given with radiation based on the assumption that such therapy was not standard. Adjuvant chemotherapy, either prior to radiotherapy or afterwards, has been allowed since opening in either of the randomized arms.

However, with accrual, we have learned that medical oncologists use concurrent chemotherapy on a case by case basis such that the true population outcome is likely related to a more variable treatment with many getting radiotherapy alone, some getting adjuvant chemotherapy and some getting even concurrent chemotherapy. In a site query, it was learned that the prohibition of allowing concurrent chemotherapy led both to lower accrual and some potential sites refusing to open the protocol. In response, we have amended the protocol to allow concurrent chemotherapy with radiotherapy using the popular and less toxic Carboplating/paclitaxel regimen in standard concurrent dosing specifically in the standard arm only (30 fractions). Our hypothesis testing regarding the higher potency of hypofractionated radiation in the experimental arm (15 fractions) would be disrupted if concurrent, radiosensitizing chemotherapy were given; hence, concurrent chemotherapy will not be allowed on the experimental arm in any circumstance. Survival estimates related to the power and sample size determination of the study in all likelihood will not be affected given that concurrent therapy has never been shown to be superior to radiation alone in poor performing patients. Nonetheless, we will perform a statistical sensitivity analysis at the time of the interim analysis (50% patient enrollment) to determine is a change in the assumption and sample size determination need adjustment.

2.0 Objectives

2.1 Primary Objective

To compare the efficacy by overall survival of standard radiation versus accelerated, hypofractionated, image-guided conformal radiotherapy in treatment of stage II-III or recurrent NSCLC in patients with poor performance status.

2.2 Secondary Objectives

2.2.1 To compare toxicity, time to local progression, disease-free survival, quality of life, cost effectiveness, and quality adjusted life of two radiotherapy treatment regimens in patients with stage II-III or recurrent NSCLC and poor performance status.

3.0 Patient Selection

3.1 Conditions for patient eligibility

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

3.1.2 Patients must have appropriate staging studies identifying them as AJCC stage II or III 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 within 9 months of study enrollment.

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

3.1.4 The patient's Zubrod performance status must be 2 or greater, OR patients with Zubrod performance status 0-1 and weight loss >10% over the last 6 months prior to enrollment,

OR patients determined to be medically unfit or refusing combined modality therapy are considered eligible.

3.1.5 Age ≥ 18.

3.1.6 Patients must have measurable or evaluable disease by RECIST 9.3 criteria.

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

Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
* Has not undergone a hysterectomy or bilateral oophorectomy; or
* Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.8 Patients must sign study specific informed consent prior to study enrollment.

3.1.9 While patients randomized to the standard arm (Arm B, 30-33 fractions) may receive concurrent chemotherapy with carboplatin/taxol at their treating physician's discretion, patients enrolled to the experimental arm (Arm A, 15 fractions) cannot be treated with concurrent chemoradiation and must not have plans for concurrent chemoradiation therapy. Sequential chemotherapy (prior to or after radiotherapy) is allowed for either arm.

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

3.2 Conditions for patient ineligibility

3.2.1 Total (aggregate) gross tumor volume > 500 cm^3 (500 cc's or 0.5 Liters)

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

3.2.3 Chemotherapy given within one week of study registration/enrollment except concurrent chemotherapy may to be given at the investigator's discretion to patients randomized to the standard arm (arm B, 30-33 fractions).

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

4.0 Pretreatment Evaluations and Management

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining

informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 90 days prior to registration unless otherwise stated. The screening procedures include:

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 12 weeks prior to study 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 Pulmonary function tests including spirometry for forced expiratory volume in 1 second (FEV-1), and diffusing capacity (DLCO).

4.1.1.4 Complete Blood Count (CBC) with differential

4.1.2 The following test must be done within14 days prior to registration/study enrollment: Urine or serum pregnancy test in females of child-bearing capacity.

4.1.3 The following test must be done within 9 months prior to enrollment on the study: Tissue biopsy or cytology confirming non-small cell lung cancer.

4.2 Recommended Evaluations and Management

FDG-PET evaluations are not required for study enrollment, 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/study enrollment, 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 #: 214-645-8913. 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. 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 for Radiation Therapy for Arm A

Protocol treatment must begin within 4 weeks after patient registration/study enrollment to the trial. Simulation can take place before registration/study enrollment, but treatment must begin within 3 weeks of completion of simulation.

6.1.1 Image-guidance, adaptive radiation therapy, and motion control

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. 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.

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. If daily imaging is not feasible at a given center, axial reimaging (CT, etc) should be performed immediately before or after day 10 of treatment to assess whether adaptation is warranted.

Tumor Motion Control: 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 such that the unaccounted tumor motion during treatment is less than 1 cm. 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%).

6.1.2 Dose Fractionation for Arm A

Patients on Arm A will receive 15 fractions of radiation. Patients will receive 4.0 Gy per fraction for 15 fractions (total dose = 60 Gy). All fields must be treated daily. Plan adaptation for treatment response is allowed and encouraged. (see Section 6.1.1)

6.1.3 Normalization and Prescribing Dose for Arm A

Normalization of the treatment plan will be to the center of mass of the conjugate PTV. The prescription dose will cover 95% of the PTV (dose covering 95% of the PTV, D-95). In addition, 90% of the prescription dose should cover 99% of the PTV (D99). 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.

6.1.4 Target Volumes for Arm A

Definition of the GTV and CTV

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 Gross Tumor Volume (GTV). The GTV, strictly defined, does not include motion and hence is identified on a "motionless" image set (e.g., a fast spiral CT or a specific respiratory phase from a 4-D CT). 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) to account for microscopic infiltration by adding a minimum of 5 mm and a maximum of 10 mm in any direction (at the discretion of the treating physician) with careful attention to trim expansions into normal structures and bone. **Elective treatment of nodal areas is not allowed.**

Definition of the ITV:

The ITV 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 10mm. Thus, expansions will range from 0-10 mm. If it is observed that the tumor has no motion, then the ITV would be identical to the CTV.

Definition of the PTV

The PTV is defined as the ITV with additional margin for setup uncertainties. Daily imaging is used to reposition the patient to minimize setup errors (see Section 6.1.1). The ITV will be expanded by 5 mm in all directions to create the PTV.

6.1.5 Critical Structures and Constraints for Arm A

The following table lists maximum dose limits to a point or volume within several critical organs. Planning priorities are listed in Section 6.7.

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.

Dose constraints for the maximum dose allowed for several central chest structures are being modified because the tumor frequently abuts these structures, compliance testing in the initially treated patients showed that the original constraints could not be met, exceeding the constraints was not associated with toxicity in either the original phase I study patients or the patients initially treated on this protocol, and the proposed modified constraints still limit the dose to the prescription (i.e., avoids "hot spots"). The study committee agreed these changes are more reasonable and still maintain safety.

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	60 Gy	pericarditis
Great Vessels	<10 cc	48.9 Gy	60 Gy	aneurysm
Trachea and Large Bronchus	<5 cc	39.5 Gy	60 Gy	stenosis/fistula
Rib	<5 cc	48.9 Gy	60 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.

6.2 Dose Specifications for Radiation Therapy for Arm B

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

6.2.1 Image-guidance, adaptive radiation therapy, and motion control

IGRT, adaptive methods, and motion control are not required on this arm (see definitions above in 6.1.1); however, they are allowed per the treating physician's discretion.

6.2.2 Dose Fractionation for Arm B

Patients on Arm B will receive 30-33 fractions of radiation at 2 Gy per fraction (total dose 60-66 Gy). There will be no field reductions, and all fields must be treated daily including the entire PTV treated daily.

6.2.3 Normalization and Prescribing Dose for Arm B

Normalization of the treatment plan will be to the center of mass of the conjugate PTV. The prescription dose will cover 95% of the PTV (dose covering 95% of the PTV, D-95). In addition, 90% of the prescription dose should cover 99% of the PTV (D99). 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.

6.2.4 Target Volumes for Arm B

Note: The following definitions are written for Arm B with the assumption that image guidance, adaptive replanning, and motion assessment and control are not utilized as per standard lung radiotherapy practice. However, at the discretion of the treating physician, such methods may be utilized on Arm B as absolutely required for patients randomized for Arm A. If these technologies and techniques are utilized, the Target Volumes should be as described in Section 6.1.4 rather than 6.2.4.

Definition of the GTV and CTV

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 Gross Tumor Volume (GTV). The GTV, strictly defined, does not include motion and hence is identified on a "motionless" image set (e.g., a fast spiral CT or a specific respiratory phase from a 4-D CT). 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) to account for microscopic infiltration by adding a minimum of 5 mm and a maximum of 10 mm in any direction (at the discretion of the treating physician) with careful attention to trim expansions into normal structures and bone. **Elective treatment of nodal areas is not allowed.**

Definition of the ITV:

The ITV includes the envelope that encompasses the tumor motion for a complete respiratory cycle. A minimum of 1 cm in the axial direction and 2 cm in the superior-inferior direction will be added to the CTV to define the ITV. **If the motion quantified from the 4-D scan or real time fluoroscopy is greater, additional margin should be added accordingly**.

Definition of the PTV

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 added to the ITV to create the PTV.

6.2.5 Critical Structures and Constraints for Arm B

The following table lists maximum dose limits to a point or volume within several critical organs. Planning priorities are listed in Section 6.7.

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.

Dose volume limits for 30 fraction XRT

Serial Tissue	**Volume (cc)**	**Volume Max (Gy)**	**Max Point Dose (Gy)***	**Endpoint (≥Grade 3)**
Spinal cord	<5 cc	44 Gy	50 Gy	myelitis
Esophagus	<5 cc	55 Gy	60 Gy	stenosis/fistula
Brachial Plexus	<3 cc	54 Gy	66 Gy	neuropathy
Heart/Pericardium	<15cc	44 Gy	60 Gy	pericarditis
Great Vessels	<10 cc	60 Gy	70 Gy	aneurysm
Trachea and Large Bronchus	<5 cc	44 Gy	60 Gy	stenosis/fistula
Rib	<5 cc	60 Gy	66 Gy	pain or fracture
Skin	<10 cc	60 Gy	72 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	14 Gy 15 Gy	Mean dose <20 Gy, V-20<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.

6.3 Technical Factors (both Arms A and B)

6.3.1 Physical Factors
Photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 6-21 MV will be allowed. Proton beams will also be allowed, but Cobalt-60 and other charged particle beams (including electrons and heavier ions) are not allowed.

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

6.4 Localization, Simulation, and Immobilization (both Arms A and B)

6.4.1 Patient Positioning
Patients on both arms 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%).

6.4.2 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 for both arms). 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.

6.4.3 Intravenous (i.v.) contrast during the planning CT is strongly encouraged but 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.

6.4.4 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.

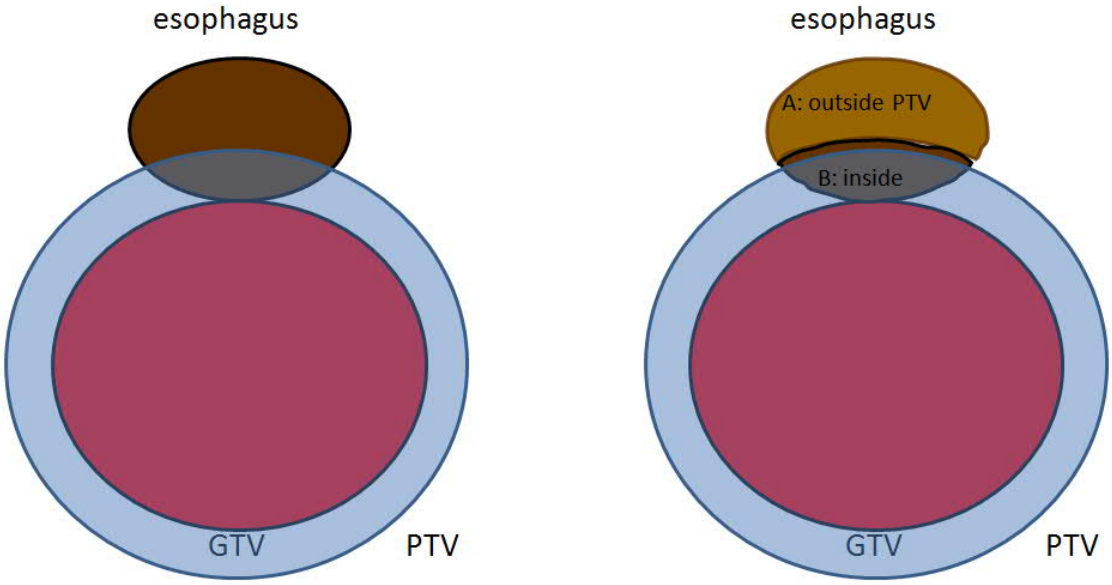
6.4.5 Tumors very near or abutting serially functioning normal structures (e.g., esophagus, great vessels) make it difficult to meet normal tissue constraints while giving compliant target dose coverage. PTV expansions may cross into adjacent normal tissues confounding the ability to respect the constraint. Priorities for planning are listed in section 6.7. These priorities must be respected. In cases where a higher priority takes precedence over a normal tissue constraint, attempts should non-the-less be made to spare as much high and intermediate dose to the normal tissue as possible. Specifically, since the prescription dose of 60 Gy in each arms is only required to cover 95% of the target volume, the 5% not fully covered by the prescription dose can be purposefully manipulate to anatomically occur in the vicinity of a critical normal structure or in the portion of a PTV/normal tissue overlap. While 90% of the prescription dose (i.e., 54Gy) must still cover the target, this allows the planner to at least lower the maximum dose to the adjacent structure to around 54 Gy with corresponding lowering of dose fall-off as well. This strategy potentially used for non-spinal cord serial tissues is depicted in the following figure (note: respecting the spinal cord constraints takes precedence over all priorities).

For the purposes of the esophagus, two approaches may be utilized to reduce the risk of acute toxicity to this linear structure. Even independent of the following options, we recommend that when planning to cover disease near the esophagus, an attempt should be made to prevent significant dose (i.e. prescription) to the entire circumference of the organ. The approaches to achieve this and in general limit toxicity include: 1) To remove the PTV out of the esophageal OAR structure and 2) To accept a lower PTV coverage of disease near the esophagus as a means of avoiding excessive spillage into the esophageal volume. The paragraph above highlights a means of reducing dose to adjacent normal structure while still following the guidelines for PTV coverage.

Abutting Targets/Serial Structures

Subvolume A: Try to strictly meet organ limits (e.g., using IMRT)

Subvolume B: Max dose no more than 90% of script dose



*** Does NOT apply to spinal cord!**

6.5. Contouring of normal tissue structures

6.5.1 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 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).

6.5.3 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.

6.5.4 Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. For the purposes of this protocol, only the major trunks of the brachial plexus will be contoured. The brachial plexus will be contoured starting proximally at the neuroforamina, following along the route of the subclavian vein ending after it crosses the second rib.

6.5.5 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.

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

6.5.7 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.

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

6.5.9 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 (both Arms A and B)

Planning Priorities:

1) Critical normal structure constraints (see sections 6.1.5 and 6.2.5): The spinal cord, brachial plexus, heart, and lung are considered critical normal structures and constraints on these structures will be prioritized. No plan will be accepted that exceeds the stated dosimetric goals for the spinal cord. If there is a need to drive dose to other normal structures, including lung, heart, etc., in order to not exceed spinal cord dose, this is acceptable as long as these changes in dose to other normal structures fulfills the protocol rules. Exceeding these limits for the brachial plexus, heart, or lung 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 (see figure below, section 6.4.7)). 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

The Principal Investigator, Robert Timmerman, MD, and Co-Chairs will perform a rapid review of the treatment plan for the first enrolled case from each institution **prior to the institution delivering any protocol treatment**. Institutions should allow 3 business days for each case to be received, processed, and reviewed. If the plan must be resubmitted, it will be given a rapid review (within 3 business days). Treatment plans for subsequent patients enrolled at a site will not be reviewed prior to delivery of treatment, but one may be requested by a site for helping with compliance. All de-identified plans, including the rapid review case, will be submitted electronically to the QA review co-PI, Dr. Lawrence Court, at MD Anderson Cancer Center. The electronic submission process involves (1) the treatment plan (CT images, contours and dose distribution) which is deidentified; (2) the electronic data is sent to MD Anderson using an encrypted transmission (e.g. sFTP). The details of the software used for deidentification and transmission are determined based on the software/network of each institution. As part of image guidance used in the study, many sites will generate frequent cone-beam CT scans on the treatment unit. Although not mandatory, it is encouraged to send these de-identified images to Dr. Court for secondary analysis of set up errors, etc.

The study PI and co-PIs will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received. They will perform the next review after complete data for the next and subsequent 50 cases enrolled has been received. 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 4.0 (CTCAE version 4.0) 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.

Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through *30* days post treatment will be considered acute adverse events.

Late Adverse Events (*as applicable*)

Adverse events occurring in the time period from the end of acute monitoring, to *2* years post treatment, will be defined as late adverse events. Only Radiation Oncology visits will be reviewed for adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

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.4.0

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; urgent operative intervention indicated
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.

A suggested course of prednisone for both severe and moderate pneumonitis is shown below.

Prednisone comes in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg strength

RADIATION PNEUMONITIS - PREDNISONE SCHEDULE			
SEVERE PNEUMONITIS		**MODERATE PNEUMONITIS**	
dose (mg)	days	dose (mg)	days
20 - 20 - 20	2	20 - 20 - 20	1
20 - 15 - 20	2	15 - 15 - 15	1
20 - 15 - 15	2	10 - 10 - 10	1
15 - 15 - 15	2	10 - 5 - 10	2
15 - 10 - 15	2	10 - 5 - 5	2
15 - 10 - 10	2	5 - 5 - 5	2
10 -10 - 10	2	5 - 2.5 - 5	3
10 - 5 - 10	2	5 - 2.5 - 2.5	3
10 - 5 - 5	2	2.5 - 2.5 - 2.5	3
5 - 5 - 5	2	2.5 - 2.5	4
5 - 2.5 - 5	3	2.5	4
5 - 2.5 - 2.5	3	2.5 qod	8
2.5 - 2.5 - 2.5	3	STOP	TOTAL = 34 days
2.5 - 2.5	4		
2.5	4		
2.5 qod	8		
STOP	TOTAL = 51 days		

For mild pneumonitis, consider non-steroidal treatment (e.g. 600-800 mg/day Ibuprofen in divided doses) with or without an inhaled steroid (e.g. Vanceril or Azmacort 2 puffs qid).

Use H-2 blocker, H+ pump blocker, or Sucralfate for gastric prophylaxis.

Consider Bactrim (if not allergic) in severely immunocompromised patients to avoid opportunistic infection. Consider other appropriate antibiotics if cough is productive of greenish sputum or if clinical suspicion indicates bacterial supra-infection within the areas of pneumonitis.

If patient has return of pneumonitis symptoms during weaning of steroids, go back to dose level where patient was last comfortable and resume wean at that level. It may be necessary to lengthen interval at each dose (e.g. double from 3 to 6 days at a particular level) in order to successfully wean the patient. Be patient with steroid taper as patients may experience rebound pneumonitis if weaning proceeds too quickly.

Periodically check blood sugars, especially in obese patients or those with overt or borderline diabetes.

Properly performed incentive spirometry appears to help re-expand collapsed alveoli.

Excessive coughing should be treated with antitussives (e.g. Tessalon Perles 100 tid PRN).

Consider inhaled bronchodilator in patients who have signs of bronchospasm or reactive airways (e.g. Albuterol inhaler 2 puffs qid).

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. When symptomatic pneumonitis resolves to grade 0, CTCAE, v. 4.0, the treating physician will contact Dr. Timmerman for a decision to continue or terminate protocol therapy.

6.9.4 Changes in Pulmonary Function Tests

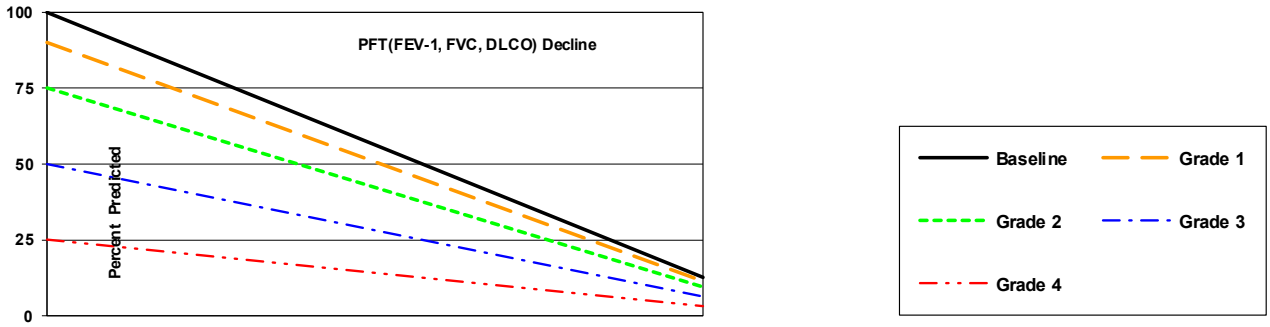
Patients enrolled to this study are allowed to have some degree of impaired pulmonary function as measured by pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV1), and Diffusing Capacity for Carbon Monoxide (DLCO). The Common Toxicity Criteria (CTCAE), v. 4.0 includes 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 4 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 4 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 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy.
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events to the end of the acute adverse events reporting period as defined in section 6.9.1. Any event that occurs during the late adverse event period as defined in section 6.9.1 and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

6.11 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. (See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited

reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to: UTSW Clinical Research Manager Email: sarmistha.sen@utsouthwestern.edu UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see

https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.0 Drug Therapy

At the treating physician's discretion, chemotherapy may be administered concurrently ONLY to patients enrolled on the standard arm (30 fractions) using a combination of carboplatin and paclitaxel (Taxol) with standard dosing for concurrent chemo-radiotherapy in lung cancer. Patients treated on this arm, however, may not receive any other chemotherapy regimens, targeted therapy, or drugs known to act as radiosensitizers. Patients on the experimental arm (15 fractions) may NOT receive any concurrent chemotherapy, targeted therapy or drugs known to act as radiosensisitizers. Patients on either arm of the study may go on to receive adjuvant chemotherapy if determined appropriate by their medical oncologist one week after completing radiation therapy.

8.0 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 Antiemetics
8.2 Anticoagulants
8.3 Antidiarrheals
8.4 Analgesics
8.5 Hematopoietic Growth Factors
8.6 Herbal products
8.7 Nutritional supplementation

9.0 Patient Assessments

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

9.2 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 4.0. A copy of the CTCAE v4.0 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.

9.3 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.

9.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

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. There can be no unequivocal new lesions.

9.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target *lesions*

9.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD

Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

9.3.4 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

9.4 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.

9.5 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.

Subjects will be removed from therapy when any of the criteria listed in Section 9.5 apply. Notify the Principal Investigator, and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

9.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

9.5.2 Subject withdraws consent (termination of treatment and follow-up);

9.5.3 Subject is unable to comply with protocol requirements;

9.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

9.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

9.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

9.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

9.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

9.5.9 Lost to follow-up.

9.5.10 Unacceptable toxicity.
9.5.11 A greater than two week delay in protocol treatment, as specified in Sections 6.0.
9.5.12 Development of intercurrent, non–cancer-related illnesses that prevent either continuation of therapy or regular follow-up.

9.6 Other response parameters

9.6.1 Time to Local Progression: The time to progression will be measured from the date of study enrollment to the date of documented local progression as determined by clinical exam and imaging studies.

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

9.6.3 Progression Free Survival: Progression free survival will be measured from the date of study enrollment to the date occurrence of local or regional progression, distant metastases, or death from any cause.

9.7 Comorbidity Data and Rating

The Charlson Comorbidity index will be used to assess pretreatment comorbidity status (see Appendix V).

9.8 Cost-Effectiveness

Health care utilization data needed to assess costs will be obtained at the baseline visit (for the prior one year period) and at each follow-up visit (see Appendix II). Questions will be asked for the utilization of all the health care services (see Appendix VI). The health utilization data will be collected at each study site. They will be transferred to the data management center located at the Department of Epidemiology and Biostatistics, Texas A&M Health Science Center (TAMHSC). At TAMHSC, a designated staff member will be responsible for calling each health service provider and obtain the bills that are associated with each service reported in the CRF, with costs calculated using methods outlined below and stored in a designated computer for analysis purpose. Patients will be given a diary at the beginning of the study to aid in recording all health related visits and expenditures. Additionally, in order to assess the treatment related indirect costs and patient out of pocket costs, a form will be administered during the last week of treatment or at the first available follow up visit after completion of radiation treatment (see Appendix VII).

Hospitalizations: Inpatient admissions (hospitalizations for any reason) with dates of admission and discharge and name of hospital. Patient bills (UB-04s) also will be obtained for each hospitalization. Inpatient facility costs will be estimated by total billed charges adjusted by a facility-specific cost-to-charge ration from Medicare Cost Reports. We also will attempt to obtain billing records for inpatient physician services. For hospitalizations with physician billing records, impatient physician costs will be estimated by applying Medicare payment rates under the RBRVS-based Medicare Fee Schedule to billed procedures in the physician billing records. For hospitalizations where physician billing records are not available, inpatient physician costs will be estimated using a multivariate regression model from data that combines Medicare inpatient and physician bills. This is to

be accomplished by merging the Medicare Provider Analysis and Review (MEDPAR) data set (a file that contains a record for each discharge of a Medicare beneficiary) and the 5 percent sample file of Medicare claims for physician services in the Medicare Beneficiary Survey. We will calculate the ratio between hospital costs and physician-allowable charges. Separate regression models will be estimated for all lung-related admissions (e.g., DRG 082) and for all other admissions. These regression models will be used to predict the ratio of inpatient physician costs to hospital costs for each admission. This predicted ratio multiplied by the hospital costs will be the estimated physician costs for the admission, but only for admissions without inpatient billing information.
Treatment Cost: Direct costs of radiation treatment including consultation, simulation, treatment planning, and treatment delivery. Patient bills related to treatment will be obtained and estimated by total billed charges adjusted by facility-specific cost-to-charge ration from Medicare cost reports as described above.

Emergency Room visits: The date of ER visit and name of the facility, and whether the ER visit resulted in a hospital admission. ER costs will be estimated using Medicare average payment rates for facility and physician charges, using the merged MEDPAR and MBS data as described above.

Physician and Clinic Visits: The date of the visit, the name of the physician or physician clinic, and the service provided (physician exam, lab test, physical therapy, etc.). Costs for physician and clinic visits will be calculated based on billing records obtained for such visits, using Medicare payment rates for procedures indicated in the clinic billing records.

Prescription Medications: Prescription drugs used, including dosage strength and frequency of administration. Information about name, dose, and frequency of all prescription medications will be recorded. The medications used by the study patients will be assigned an NDC drug code. Unit costs for these drugs will be estimated as the "AWP" price published in the Red Book less 15%. Outpatient drug costs will be calculated by multiplying unit cost by the number of pills used per day times the length of time the patient received the medication. The length of time a patient took a medication will be estimated by assuming that if a medication is not listed on the CRF for a follow-up visit, use was discontinued at the mid-point of the interval since the prior CRF assessment. Note that costs of drugs administered through a clinic (e.g., reimbursed under Medicare Part B) are included under "clinic visit costs" and impatient drug costs are included under "inpatient facility costs."

Home Health Care: The number of home health care visits will be recorded. Costs for home care visits will be calculated based on Medicare payment rates for home health care.

9.9 Health-Related Quality of Life (HRQOL) Analysis

The study design is to prospectively analyze the QOL among patients with stage III NSCLC randomized between standard radiotherapy (60 Gy) versus hypofractionated IGRT radiation therapy. While hypofractionation is hypothesized to yield greater tumor cell kill, it may also increase the normal tissue toxicity, in which case there may be a decrease in HRQOL. The primary normal tissue toxicities in patients receiving radiation for lung cancer are esophagitis and pneumonitis. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL.

In this randomized trial, we plan to assess the FACT-TOI in all arms at 4 specific

time points to minimize patient burden: baseline (pretreatment), at the end of treatment (last day of treatment), and at the 6 and 12 month follow ups (See Appendix II). In order to analyze the difference in QOL between all arms, we plan to use a brief, validated instrument that is user friendly and has clinical relevance (the Lung Cancer Subscale of the FACT-TOI). FACT-TOI is a measure that sums the functional well being (FWB), physical well being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy - Lung (FACT-L) QOL instrument, which has been extensively used for measuring QOL in patients with lung cancer.[31] In a review of the literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status, treatment response.[32] FACT has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx. The full FACT-L questionnaire can be completed in less than 10 minutes. This instrument has not only been shown to be prognostic for survival, but also sensitive to changes in QOL on serial evaluations throughout treatment. Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer.[33] The lung cancer sub-scale (LCS) consists of 9 items, involving lung cancer specific symptoms. All items are rated on a 5 item (point) Likert Scale, from 0 (not at all) to 4 (very much). It has been determined that a 3-point difference on the FACT-G subscales is associated with a meaningful difference in clinical and subjective indicators. Thus, a difference of 3 LCS points will be considered clinically significant. As the LCS focuses on lung cancer symptoms, this will be used for the primary endpoint; however, the more general subscales of physical and functional well-being (on the brief FACT-TOI) will also be collected. See Appendix VIII for the appropriate forms.

In addition, the EQ-5D health related quality of life questionnaire will be used as well. EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. . The US version of the EQ-5D will be used, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population. These utility scores are needed for cost-utility analysis (estimates of costs per "quality adjusted" life-year gained). See Appendix IX for the appropriate forms.

10.0 Data Collection

Patient, treatment, HRQOL, and patient perspective costs data (Appendix VII) should be submitted to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Sarmistha Sen, Project Manager
5641 Southwestern Medical Ave.
Dallas, TX 75235-8808
FAX #: 214-645-8913

Economic data (patient bills, and other cost documents) will be collected by:

Department of Epidemiology and Biostatistics
School of Rural Public Health
Texas A&M Health Science Center, TAMU 1266

Attn: Hongwei Zhao
224 SRPH Admin Building
College Station, Texas 77843-1266

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. Identifiable information will be released to Drs. Robert L. Ohsfeldt and Hongwei Zhao at Department of Epidemiology and Biostatistics, Texas A&M Health Science Center (TAMHSC) for obtaining the bills that are associated with each service reported in the case report forms.

Item	Due
Demographics	Within 2 weeks of study enrollment
Eligibility and Entry Characteristics, including baseline H&P and Zubrod PS	Within 2 weeks of study enrollment
Pathology Report	Within 2 weeks of study enrollment
Follow-up H&P data	At post XRT follow-up at 1, 3, 6, 9, and 12 months, then q 4 months year 2, then q6 months years 3-5; then annually
Tumor response evaluation	At post XRT follow-up at 3, 6, 9, and 12 months, then q 4 months year 2, then q6 months years 3-5; then annually
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, then q6 months years 3-5; then annually
Healthcare Utilization/Cost Worksheet (Appendix VI),	Within 2 weeks of study enrollment, at the end of treatment, and at post treatment follow up at 1, 3, 6, 9, and 12 months, then q 4 months year 2, then q6 months years 3-5; then annually until death
FACT-L (Appendix VIII), EQ-5D (Appendix IX)	Within 2 weeks of study enrollment, at the end of treatment, and at post treatment follow up at 6 and 12 months,
Patient Perspective Cost Assessment (Appendix VII)	Upon radiation completion or first possible post treatment follow up (1 month). To be administered just once.

Data collection for QA

11.0 Statistical Considerations

11.1 Study Endpoints

11.1.1 Primary Endpoint: Overall survival (Failure: death from any cause)

11.1.2 Secondary endpoints:

11.1.2.1 Quality of Life (QOL) as measured by the Functional Assessment of Cancer Therapy Lung subscale (FACT-L)

11.1.2.2 Cost effectiveness analysis

11.1.2.3 Progression-free survival (Failure: occurrence of local or regional progression, distant metastases, or death from any cause)

11.1.2.4 Toxicity: Grade 3-5 adverse events as graded by CTCAE v 4.0

11.2 Sample Size Determination

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 2-sided significance level of 0.05 and 80% statistical power using a 2-sample log rank test. 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 is that the there are no difference in 1-year survival rates between two arms. We assume that the patients will be accrued for 2 years with a 1-year follow-up. We hypothesize that the patients randomly assigned to the control arm and experimental arm have a 1-year survival rate of 45% (hazard rate [λc]) of 0.799) and 60% (hazard rate [λe]) of 0.511), respectively, which is translated to the hazard ratio of λe/λc = 0.640. One interim analysis and a final analysis are planned for early stopping for efficacy. The efficacy testing is based on the Lan-DeMets spending function, which resembles the O'Brien-Fleming boundary. The total sample size of 226 patients (113 in the control arm and 113 in the experimental arm) will be accrued to achieve the desired 80% statistical power and 2-sided significance level of 0.05. Guarding against ineligibility or lack-of-data rate of up to 5%, the final targeted accrual for this study will be 238 patients (119 per arm). Sample size was estimated using the sample size software EaST version 5.

11.3 Patient Accrual

Patient accrual is projected to be 4 patients per month. This trial should complete the accrual phase in 60 months. If the monthly accrual is less than 2 cases per month, the study will be reevaluated with respect to feasibility.

11.4 Randomization Scheme

Patients will be allocated to the treatment using a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables are Zubrod performance status (2 vs. > 2) and stage (II vs. III).

11.5 Analysis Plans

All eligible patients who are randomized to the study will be included in the comparison of treatment arms, regardless of treatment compliance (intent-to-treat analysis).

11.5.1 Overall Survival

Overall survival time will be estimated using the Kaplan-Meier approach. The stratified log-rank test will be used to test for a statistically significant difference in survival distributions. The null and alternative hypotheses are H_0: $S_1(t) < S_2(t)$ vs. H_A: $S_1(t) \geq S_2(t)$, where $S_i(t)$ is the distribution of overall survival times for patients in arm *i*.

The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in overall survival. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

11.5.2 Quality of Life (Functional Assessment of Cancer Therapy-L)*:*

Patient-reported functional status will be assessed with the lung cancer subscales of the Functional Assessment of Cancer Therapy-Lung (FACT-L). The FACT-L is a 36-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 =somewhat; 3 = quite a bit; 4 = very much). It will take less than 10 minutes to complete the questionnaire. The Trial Outcome Indices (TOI) also will be utilized to measure the summed functional well-being, physical well-being, and the additional concerns (lung symptom module) subscales of the FACT-L. A 5-point deterioration in the FACT-L TOI between pre-treatment and at year 1 will be considered clinically significant. The patient-reported endpoint will be a difference in the deterioration from the pre-induction FACT-L TOI score to the score at 6-month post-treatment. This score measures functional status and a difference of 5 FACT-L TOI points will be considered clinically significant.[33]

The first analysis of change in QOL from baseline to 6 months will only be performed on patients who are still alive at 6 months. Changes in QOL will be also analyzed using all available data at baseline, 6, and 12 months with generalized estimating equations (GEE). We will also compare the percentage of patients in each arm with an effect size for the change in FACT-L TOI scores between pre-induction and 6 months of < .2; this will allow us to compare the percentage of patients in each arm whose functional status remains more similar to baseline levels.

11.5.3 Cost Effectiveness Analysis

For the primary analysis, we will estimate cost accumulated within 2 years. A larger limit is possible if we have a reasonable number of people surviving at that time.

Since patients are enrolled into the study over time and some patients are still alive at the end of the study, so their survival time and costs are censored. Due to the presence censoring, we cannot use a simple average of the patients' total costs, a simple average of the patients' costs for those with complete cost information, or a Kaplan-Meier estimator on censored costs, since these all produce biased estimators of the mean costs[34]. Instead, we will use the inverse-probability weighting method to calculate average costs for each treatment group.[35, 36] The assumption used in this method is that censoring is independent of the survival time, or cost collection process, which is often satisfied in well-conducted clinical trials. If the new treatment can both extend patients' survival time (or quality-adjusted survival time), and save costs at the same time, the new treatment will be preferred to the current standard treatment under any willingness to pay threshold. However, if the new treatment extends survival time but costs more, cost-effectiveness analysis provides an estimate of the incremental cost of greater incremental effectiveness. For traditional cost-effectiveness analysis, treatment effectiveness is measured simply as survival time. The incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of survival. For cost-utility analysis, treatment effectiveness is measured as quality-adjusted survival time (which accounts for the impact of treatment on both mortality and morbidity, including any differences in adverse affects of treatment affecting HR-QoL). For cost-utility analysis, the incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of quality adjusted survival.

11.5.4 Quality-Adjusted Survival Time

The quality-adjusted survival time estimates need to account for the presence of censoring. Due to the induced informative censoring problem, the ordinary survival method (e.g.,

Kaplan-Meier estimator) cannot be applied in this case.[35-37] Accordingly, we will use the inverse-probability weighted method of Zhao and Tsiatis to carry out the survival time analysis.[35, 36] To estimate quality adjusted survival time, data from EQ-5D will first be translated into utility measures. These measures are obtained at discrete time points, so they will be interpolated into the time intervals between the visits. The quality-adjusted survival time is just an integration of the utility measures over a patient's survival time, or until the time limit similar as the cost calculation, whichever occurs earlier.

11.5.5 Projection Model and Sensitivity Analysis

If the new treatment is implemented in usual practice, some of its potential benefits to patients may extend beyond the time horizon of the clinical trial. We will explore the potential to use results from the clinical trial based cost-effectiveness analysis, augmented with information from secondary sources, to develop a model to project costs and effectiveness beyond the time horizon included in the clinical trial. Any such model projections would be subjected to probabilistic sensitivity analysis, to assess the impact of parameter uncertainty on estimated cost effectiveness results.

11.5.6 Progression-Free Survival (PFS) and Time to Local Progression

The time to disease progression and time to local regression will be estimated using the Kaplan-Meier approach. The stratified log-rank test will be used to test for a statistically significant difference in PFS and time to local progression distributions. The null and alternative hypotheses are H_0: $S_1(t) < S_2(t)$ vs. H_A: $S_1(t) \geq S_2(t)$, where $S_i(t)$ is the distribution of survival times for patients in arm *i*. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in progression-free survival and time to local progression. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

11.5.7 Toxicity

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Appendix II). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of all Grade 3-5 adverse events, and death during or within 30 days of discontinuation of protocol treatment will be tested for equality using a two-sided chi-square test with a 0.05 significance level.

11.5.8 Interim Reports to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared once a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints.

11.5.9 Interim Analysis of Study Endpoints

There will be one interim analyses of the primary study endpoint (overall survival). The interim analysis will be conducted using Lan-DeMets alpha spending function when half of patients are followed-up for 1-year. The significance level will be calculated to ensure an overall significance level of 0.05 (type I error). In addition, a conditional power analysis will be performed at an interim efficacy analysis.[38] If the 95% confidence interval of the conditional power is less than 25%, then a recommendation for study discontinuation will be made to the Data and Safety Monitoring Committee (DSMC). The results of the interim analyses only will be reported, in a blinded fashion, to the DSMC. This analysis will also track the outcomes of the first 44 patients (enrolled when concurrent chemotherapy was not allowed) to subsequent patients performing sensitivity assessment regarding the need for a change in survival assumptions or a change in sample size.

12.0 Study Management

12.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

12.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

12.3 Registration/Randomization Procedure

All subjects must be registered with the Radiation Oncology before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Radiation Oncology Study Coordinator. To register a subject, call 214-6458525 Monday through Friday, 9:00AM-5:00PM

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

12.4 Data Management and Monitoring/Auditing

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

Toxicity and dose escalation reviews will be performed annually. These reviews will be documented by written reports that will be distributed to the distributed to the stud team.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

12.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

  ➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others
  - **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
  - **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)
  - **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12. 7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The

Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix I: Sample Treatment Consent Form

Study Title: **Phase III Study of Standard versus Accelerated Hypofractionated Image-Guided Radiation Therapy (IGRT) in) in the Definitive Setting Patients with Stage II-III or Recurrent 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: 238 patients.

PURPOSE: The purpose of this study is to compare a new method of treating lung cancer with radiation with a more standard method. 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?
You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group. If you are in Group 1 (often called "Arm A"), you will receive 15 radiation treatments. If you are in Group 2 (often called “Arm B”), you will receive 30-33 radiation treatments.

Economic costs related to your treatment– you will be asked to provide information about the cost of your treatment and health care following the 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.

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

- At Texas A & M Health Science Center, a designated staff member will be responsible for calling each health service provider and obtain the bills that are associated with each service reported in the Case Report Form (CRF), with costs calculated using methods stored in a designated computer for analysis purpose. The following bills will be collected for:
- Hospitalizations, treatment cost, emergency room visits, physician and clinic visits, prescription medications and Home Health Care bills.
- The records also may include identifying information about you, such as your name, and address.

How long will I be in the study?
You will receive radiation therapy for 3-6 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 (tiredness), 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, anti-inflammatory 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
- Drs. Robert L. Ohsfeldt and Hongwei Zhao at Department of Epidemiology and Biostatistics, Texas A&M Health Science Center (TAMHSC) for obtaining the bills that are associated with each service reported in the case report forms.

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.

.

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 (214) 648-2171.

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 5 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

				During XRT	Follow-Up (months after therapy)					
		Within 12 weeks prior to registration/ study enrollment	prior to XRT	Weekly	1 month	3 months	6 months	9 months	12 months	Q 4 months during year 2, then q 6 months years 3-5, then annually
History / Physical		X		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[3]									
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[5]								
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
FACT-L and EQ-5D			X	X[6]			X		X	
Healthcare Utilization/ Cost Worksheet			X	X[6]	X	X	X	X	X	X
Patient Perspective Cost Assessment				X[4] (last week only)	X[4]					

[1]Preferably with IV contrast unless medically contraindicated
[2]CT if MRI medically contraindicated
[3] Within 9 months of study enrollment
[4]Upon completion or first follow up
[5] within 14 days of registration/study enrollment

[6]At end of treatment

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):

APPENDIX VI
Healthcare Utilization/Cost Worksheet

1. Have you been hospitalized since your last study visit/contact [since last form completed]?
   Yes ____ No ____
   IF "YES": How many times were you hospitalized? ____
   a. Please provide the following information for each hospitalization.

	Name of hospital	Date of hospitalization	# days of hospitalized
1			
2			
3			

2. Did you have any visits to an emergency room since your last study visit/contact?
   Yes ____ No ____
   IF "YES": How many ER visits did you have? ____
   a. Please provide the following information for each hospitalization.

	Name of hospital ER	Date of ER visit	Admitted to hospital?
1			
2			
3			

3. Did you visit a physician or receive services from a physician clinic at any time since your last study visit/contact?
   Yes ____ No ____
   IF "YES": How many times did you visit physician clinics? ____
   a. Please provide the following information for each clinic visit.

	Name of physician/clinic	Date of service	Type of service (MD visit, lab test, etc.)
1			
2			
3			

4. Have you started any new or changed your prescription drugs since your last study visit/contact (including oxygen)? (if "NONE" enter none):

	Name of drug	Dosage	Administration (once/twice daily, etc.)
1			

2			
3			
4			

5. Did you have any home health, respiratory therapy, or physical therapy visits since your last study visit/contact?
   Yes ____ No ____ IF "YES": How many home health visits? ____

APPENDIX VII
Patient Perspective Cost Assessment

We would like to ask you about your health coverage and the "out-of-pocket" costs you have had related to your cancer treatment.

1. Do you have any coverage that helps pay for your **medicines**, when you are **NOT** in the hospital: (Check **ALL** that apply)
   - ❑ Yes by Government (e.g. ,Medicare Part D,Tricare, etc.)
   - ❑ Yes by private or employer-paid health insurance (supplemental)
   - ❑ No coverage
   - ❑ Don't Know

2. Do you have any coverage that helps pay for **home health or therapy**, when you are **NOT** in the hospital (i.e. nursing, physiotherapy, respiratory therapy etc.): (Check **ALL** that apply)
   - ❑ Yes by Government (Medicare, Medicaid, Tricare)
   - ❑ Yes by private or employer-paid health insurance
   - ❑ No coverage
   - ❑ Don't Know

If you do NOT have private or employer paid health insurance ☞ Go to Question 4

3. If you have Private/Employer-paid health insurance, please describe your coverage for each type of service: (For each service, check the box that best describes your level of coverage.)

TYPE OF SERVICE	✓*Don't Know*	✓*Not Covered*	✓*Partial Coverage*	✓*Full Coverage*
Hospital supplemental charges (e.g. Private room, etc.)				
Prescription drugs (e.g. Antibiotics, pain medication, etc.)				
In home healthcare (e.g. home health nursing, physical therapist, respiratory therapy, etc.)				

Homemaking services (e.g. cleaning, cooking, etc.)				
Alternate Therapy (e.g. Homeopathy, Chinese medicine, over the counter drugs, etc.)				
Other (Specify) _____				

☞ **Proceed to Question 4**

4. Please supply the following details regarding your "out-of-pocket" costs for trips to and from your radiation treatments and doctor visits **related to your cancer *during the radiation treatment.***

Type of Visit	**Number of trips during radiation treatment**	**Distance <u>ONE WAY</u> OR** origin and destination points	**Method of transport (car, taxi, bus, train etc.)**	**Parking or Fare or Valet**	**Paid for by Insurance/ Government (circle one)**
Cancer Clinic/ Radiation Facility		Miles		$	❑ None ❑ Partial ❑ Full
Hospital		Miles		$	❑ None ❑ Partial ❑ Full
Family Doctor		Miles		$	❑ None ❑ Partial ❑ Full
Other (Specify, i.e. 2nd Hospital or 2nd Doctor, ER) _____ _____		Miles		$	❑ None ❑ Partial ❑ Full

5. For questions listed below indicate if you had cancer related costs, paid by yourself, private insurance or Medicare/Medicaid/Tricare ***during the radiation treatment.*** If you do not know the exact amount make your **best estimate,** rounded to the nearest dollar.

a) **Copays (during the radiation treatment)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known):		
$ _____	N/A	N/A

b) **Prescription Drugs (new during the radiation treatment)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known):		
$ _____	$ _____	$ _____

c) **In home healthcare (home health, physical therapy, respiratory therapy, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known):		
$ _____	$ _____	$ _____

d) **Complementary and Alternative Therapy (homeopathy, massage, acupuncture, counseling, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known):		
$ _____	$ _____	$ _____

e) **Vitamins and Supplements including special diets**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known): $ _____	$ _____	$ _____

f) **Family Care (child or elder)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known): $ _____	$ _____	$ _____

g) **Accommodation/Meals (hotel, motel, gas, car rental, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known): $ _____	$ _____	$ _____

h) **Devices or Equipment (<u>home oxygen</u>, wheelchair, walker, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known): $ _____	$ _____	$ _____

i) **Other (telephone costs, long distance, cell phone usage, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself	❑ paid by private insurance	❑ paid by government
Amount (if known): $ _____	$ _____	$ _____

6. Would you say this last month your "out-of-pocket" expenses related to your cancer were:

❑ More than other months ❑ Typical ❑ Less than other months
❑ Don't Know

We would like to ask you some questions about your healthcare visits related to this cancer as well as the impact these visits have had on your work.

7. Since you finished radiation, have you had: (Check all that apply)
NOTE: We will ask you specific questions about these in a separate form.

❑ Doctor visits
❑ Emergency room visits
❑ Overnight hospitalization – indicate duration ❑ one or _____ nights.
❑ Home nursing services
❑ Respiratory/ Physical/ Occupational Therapy services
❑ Medication changes
❑ Started oxygen treatment

8. How much time during radiation treatment did you take off work to receive treatment related to your cancer

❑ Unemployed ❑ No time off work ❑ _____ days
❑ Don't Know ❑ Retired

9. Was this time away from work: (Check ALL that apply)

❑ Not Applicable (not working) ❑ Vacation ❑ Time off **with** pay
❑ Time off **without** pay

10. Did friends or family take time away from work in the *last 30 days* related to your treatment

❑ No time off work **OR** ❑ _____ days

We would now like to ask you a little bit about you, your work and your education:

11. Year of Birth _____

12. Sex: ❑ Male ❑ Female

13. Marital Status:

❑ Married ❑ Common Law ❑ Single (never married)
❑ Widowed ❑ Separated ❑ Divorced

14. How many other people do you share your home with (do not include people who are only visiting):

❑ Live alone (**Go to Question 16**)
❑ Myself and one other
❑ 2 others
❑ 3 others
❑ More than 3 others

15. Are these people you share your home with:

❑ Family ❑ Friends ❑ Both Family and Friends

16. City or Town where you live _____Zip code_____

17. How would you rate your current health?

❑ Excellent ❑ Very good ❑ Good ❑ Fair

❑ Poor

18. What do you do for a living:

❑ *Full time work : Specify* _____ ❑*Part time work: Specify* _____

❑ *Retired* ❑ *Homemaker* ❑ *Unemployed* ❑ *Student*

19. What is the highest level of schooling you have completed?

- ❑ No schooling, some elementary school, or completed elementary school
- ❑ Some high school
- ❑ Completed high school
- ❑ Some university or community college
- ❑ Completed university or community college
- ❑ Post Graduate (MSc/MBA/PhD) or professional training (MD/LLB/DDS)

20. What was your total family income before taxes in the last year.
(include wages, salaries and self-employment earnings)

- ❑Less than $5,000
- ❑$5,000- $9,999
- ❑$10,000- $14,999
- ❑$15,000- $19,999
- ❑$20,000-$29,999
- ❑$30,000-$39,999
- ❑$40,000-$49,999
- ❑$50,000-$59,999
- ❑$60,000-$79,999
- ❑More than $80,000
- ❑Don't Know

21. How much of a financial burden are these out-of-pocket expenses listed in Q 4 & 5:

- ❑Not a burden at all
- ❑Only a slight burden
- ❑Somewhat of a burden
- ❑Significant burden, but manageable
- ❑Unmanageable burden

22. What treatments or services that are **not** currently available would you like to see paid for through government or private insurance:

_____

_____

23. Was this questionnaire completed by:

- ❑ The patient
- ❑ A caregiver
- ❑ Both the patient and a caregiver

We would like to learn more about your personal reactions to the treatment and the impact it had on your typical activities:

24. To what extent has your treatment **disrupted** your normal **daily activities**?

0	1	2	3	4	5	6	7	8	9	10

25. To what extent has your treatment **disrupted** your normal **recreation activities**?

0	1	2	3	4	5	6	7	8	9	10

26. To what extent has your treatment **disrupted** your normal activities with your **family and friends**?

0	1	2	3	4	5	6	7	8	9	10

27. To what extent has your treatment **disrupted** your **sleep pattern**?

0	1	2	3	4	5	6	7	8	9	10

28. To what extent has your treatment **disrupted** your **enjoyment of life**?

0	1	2	3	4	5	6	7	8	9	10

29. How **satisfied** are you with the **length of time** your treatment has taken to this point of time?

0	1	2	3	4	5	6	7	8	9	10

30. How **disruptive** has your treatment been to the other **important people in your life (example: family, spouse, close friends, coworkers)?**

0	1	2	3	4	5	6	7	8	9	10

Additional Comments

_____
_____
_____
_____
_____

Thank you *for helping us with our survey. If you have completed all sections please place the survey in the envelope, seal it, and return it to the attending clinic staff. You may ask for a copy of the survey for your records.*

APPENDIX VIII
FACT-L Worksheet

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this boxand go to the next section.*	☐				
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4

GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

ADDITIONAL CONCERNS

		Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

APPENDIX IX
EQ-5D Worksheet

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

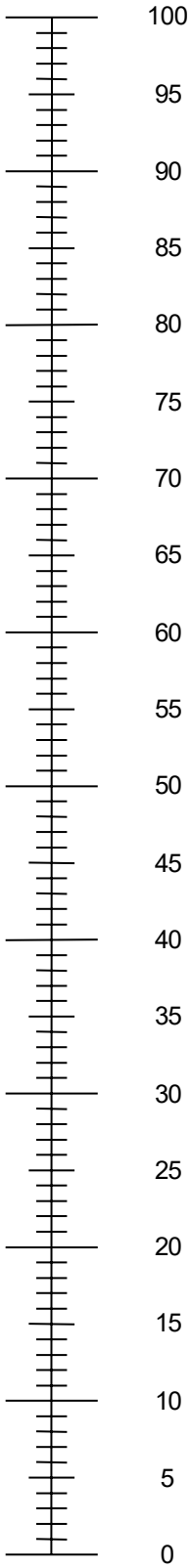
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is

The best health you can imagine



The worst health you can imagine

TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]