

Cover page

Protocol Title: Phase II escalated/accelerated proton radiotherapy for inoperable stage

I (T1-T2, N0, M0) Non-Small Cell Lung Cancer (NSCLC)

Approval Date: 04/19/2010

CT.gov number: NCT00495040

Other Study ID Number: 2004-0977

Phase II Escalated/Accelerated Proton Radiotherapy for Inoperable Stage I (T1-T2, N0, M0) and Selected Stage II (T3N0M0) Non-Small Cell Lung Cancer (NSCLC)
2004-0977

Core Protocol Information

Short Title	Phase II escalated/accelerated proton radiotherapy for inoperable stage I (T1-T2, N0, M0) Non-Small Cell Lung Cancer (NSCLC)
Study Chair:	Joe Y. Chang
Additional Contact:	Beth DeGracia Donna M. Walker Toni Williams
Department:	Radiation Oncology
Phone:	713-563-2300
Unit:	97
Full Title:	Phase II Escalated/Accelerated Proton Radiotherapy for Inoperable Stage I (T1-T2, N0, M0) and Selected Stage II (T3N0M0) Non-Small Cell Lung Cancer (NSCLC)
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 02/15/2012
Version:	15
Submitted by:	Toni Williams--8/6/2010 4:34:01 PM
OPR Action:	Accepted by: Leola M. Griffin -- 8/19/2010 12:10:20 PM

Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

To assess the therapeutic efficacy and toxicities of proton radiotherapy with escalated/accelerated dose for patients with inoperable centrally/superiorly located stage Ia (T1, N0, M0), any stage Ib (T2, N0M0) and selected stage II (T3N0M0) non-small cell lung cancer (NSCLC).

Primary goals:

1. Improve the 2 year local control rate at the primary site over historical results
2. Reduce acute and chronic toxicity (according to the NCI Common Terminology Criteria for Adverse Events version 3.0 [CTCAE v3.0])

Secondary goals:

1. Improve the disease specific survival rate at 2 years over historical results.
2. Study the potential of pre- and post treatment PET/CT in predicting clinical outcome.
3. Study the role of biomarkers in predicting therapeutic response and toxicities.

2.0 Rationale

1. Uncontrolled local-regional tumor is a major source for continuous seeding to distant organs and causes eventual treatment failure in medical inoperable stage I NSCLC. With conventional photon radiotherapy, the 2 years progression free survival is 30-50% for stage I NSCLC (Kaskowitz et al), which is significantly less compared with surgical resection (70-80%). The eradication of the local-regional tumor is an essential step for cure.
2. Current literature indicates that there is a dose-response relationship for both local tumor control and survival in stage I NSCLC (Dosoretz et al). However, toxicities related to the high dose of photon treatments limit the potential for dose escalation. For a given level of normal tissue toxicity, the Maximum Tolerable Dose (MTD) of proton radiotherapy (RT) is likely higher than that of conventional photon RT because of the physical characteristics of proton RT (e.g., the Bragg peak, finite range and lower entrance dose). Therefore, proton RT may have an advantage over conventional photon RT in achieving local tumor control and improving survival with reduced toxicities.
3. Our preliminary data showed that high levels of FDG avidity in pre-treatment PET scans correlate with poor survival in NSCLC (Komaki et al). Comparison of pre- and post-treatment PET/CT scans may predict both local control and survival in patients with stage I NSCLC treated with proton radiotherapy.
4. The response of NSCLC to radiation is heterogeneous with a subset of tumors being resistant to radiotherapy. Clinical radiation sensitivity likely differs from patient to patient in terms of tumor response and treatment-related toxicities. Novel biomarkers may help us to identify patients with different radiation sensitivities and individualize each patient's treatment in the future.

Data that support dose escalation and potential associated toxicities for stage I NSCLC:

1. Conventional radiation dose schedules of 60-66 Gy resulted in a 5-year cause-specific survival rate of 13-31% in medically inoperable stage I (T1-2N0M0) NSCLC (Kaskowitz et al, Krol et al). However, this level of radiation dose was still associated with a local regional failure rate of >75% at 5 years. The distant failure rate was also noted to be between 30-40%.
2. A dose-response relationship for disease-free survival in stage I NSCLC has been reported. Dosoretz et al showed that actuarial disease-free survival at 2-years was 50%, 33%, 22%, and < 20% with 70 Gy (n=4), 60-69 Gy (n=116), 50-59 Gy (n=26), and < 50 Gy (n=6), respectively. The actuarial risk for local failure at 3 years was 33%, 60% and 58% for > 70 Gy (n=4), 60-69 Gy (n=91) and 50-59 Gy (n= 19), respectively.
3. The preliminary data from the RTOG 9311 (Bradley et al) phase I dose escalation study showed that acute toxicity rates were acceptable for dose up to 90.3 Gy (less than 15% grade ≥ 3 pneumonitis and no esophagitis). However, late toxicities were more pronounced. Late grade ≥ 3 radiation pneumonitis occurred at a rate of 15% for patients with a V20<25% for patients treated to dose levels of 77.4 Gy or above with fraction size of 2.15 Gy. For patients with a V20 of 25-37%, late grade ≥ 3 pneumonitis occurred at the rate of 15% for the doses of 70.9 Gy or above. Late grade ≥ 3 esophagitis occurred in less than 7% of patients. The rate of late esophagitis was not directly correlated with dose, but it may be related to the volume of the esophagus treated.

Data in support of proton therapy in early stage NSCLC:

1. Shioyama reported the clinical outcome of 28 patients with stage I NSCLC treated with proton radiotherapy to the median fraction of 3 Cobalt Gray Equivalent (CGE) (range 2-6 CGE) and to a median total dose of 76 CGE (range 49-93 CGE). The 5-year overall survival rate was 70% with local control of 89% for stage IA. However, for stage IB, the local control was 39% and the 5-year overall survival was 15%. Only one case of grade 3 acute toxicity and little late toxicity was observed. In this study, the clinical outcome for stage IA patients was comparable to surgical resection. However, for stage IB patients, the result was much worse than surgical resection and 21% patients recurred in the mediastinum. Since PET scanning was not used for clinical staging, it is possible that the group of patients with stage IB was understaged and significant tumor volume was missed.
2. Bush reported his experience in 27 patients with stage I NSCLC treated with proton and photon radiotherapy. The total dose was 73.8 Gy with 45 Gy delivered with photons (1.8 Gy/fraction) and 28.8 CGE delivered with protons (1.8 CGE/fraction). Proton treatments and the last 16 fractions of photon treatments were given as BID. The local control was 87% and the 2-year disease free survival was 86%. Only two patients developed pneumonitis which resolved after oral steroid treatment.
3. Japan National Cancer Center Hospital East reported their result of 36 patients with stage I NSCLC treated with proton radiotherapy to a total dose of 70-94 CGE delivered in 20 fractions. The 2-year local control was 92.6% and the overall survival was 81%. No grade 2 or above acute toxicities were observed. Late grade 3 toxicities were observed in 3 patients. Among 19 patients with stage IB disease, two had local progression and eight developed regional lymph node and/or distant metastasis. Again, understaging without PET could be a concern here.

4. MD Anderson Cancer Center analyzed our preliminary data of phase I/II study in early stage NSCLC treated with dose escalated/accelerated proton therapy (IASLC 2009 presentation). Fifteen patients with medical inoperable T1N0M0 (central location) or T2-3N0M0 (any location) NSCLC were treated on our phase I/II study using dose-escalated proton therapy to 87.5 cobalt-Gray equivalents (CGE) at 2.5 CGE/fraction without adjuvant chemotherapy. At a median follow-up time of 16.5 months (range, 5-24.1 months), no patient had experienced grade 4 or 5 toxicity. The most common adverse effect was dermatitis (grade 2, 11 patients [73%], grade 3, 2 patients [13%]), followed by grade 2 fatigue (5 patients [33%]), grade 2 pneumonitis (1 patient [7%]), grade 2 esophagitis (1 patient), and grade 2 chest wall pain (1 patient). Rates of local control were 93% (14/15), regional lymph node failure 7% (1/15), and distant metastasis 20% (3/15). Twelve patients (80%) were still alive at last follow-up; 2 had died of metastatic disease and 1 of preexisting cardiac disease. In conclusion, proton therapy escalated to ablative doses is well tolerated and produces promising local control rates for medically inoperable early-stage NSCLC. Distant metastasis remains the most common pattern of failure. Longer follow up is needed.

In summary, the standard radiotherapy dose for early stage NSCLC is about 66 Gy with 2 Gy/fraction. However, more than 50% of cancers recur locally. Based on RTOG 9311, which used photon radiotherapy, 90.3 Gy at 2.15 Gy/fraction in patients with lung V20 <25% (mostly early stage lung cancer) was not considered acceptable due to toxicity: Fifteen percent of the patients experienced grade ≥ 3 pneumonitis and there was one case of grade 5 esophagitis. Preliminary data from proton therapy revealed a much lower toxicity profile and promising local control comparable to surgical resection in stage IA patients. However, the reported total doses and fraction sizes of proton radiotherapy varied significantly. The doses used ranged from 70 Gy to 94 Gy and the fraction sizes ranged from 2 Gy to 6 Gy. In many centers, the dose and fraction size were chosen based on the access to the proton facility. Although hypofractionated radiotherapy showed promising results in the literature mentioned above, more clinical studies with long term follow up are needed since hypofractionated radiotherapy is considered to have possible higher long term toxicities, particularly for centrally located lesions.

Our virtual clinical trial (Chang et al. 2006) showed that even dose escalation to 87.5 CGE using proton in stage I lung cancer reduced normal tissue doses compared with photon therapy using the standard dose 66 Gy. In this proposed study, we will use proton radiotherapy to treat inoperable centrally/superiorly located stage Ia (T1, N0, M0), any stage Ib (T2, N0M0) and selected stage II (T3N0M0) NSCLC to a total dose of 87.5 CGE at 2.5 CGE/fraction, which is equivalent to a schedule of 90.3 Gy given in 42 fractions with 2.15 Gy each (for a tumor α/β of 10 Gy), corresponding to a BED_{10} of 109.4 Gy. While 90.3 Gy in 42 fractions was the highest dose considered for the RTOG 9311 dose escalation photon therapy trial, 83.8 Gy in 39 fractions was considered acceptable dose and 90.3 Gy in 42 fractions was considered to be too toxic (Bradley et al. 2005). However, we anticipate that the proposed proton regimen will achieve improved local control with decreased long-term toxicities compared with the highest safe photon dose regimen of RTOG 9311. This expectation is based on significantly higher BED, a potentially reduced impact of accelerated tumor cell repopulation due to the reduced overall treatment time, and reduced dose to critical normal tissue structures due to the superior dose distribution of protons. In addition, preliminary results from the M.D. Anderson phase I/II study show excellent local control and acceptable toxicity with 87.5 Gy. Treatment planning will be based on PET/CT and 4D CT. Local control at the primary site, disease-specific survival, and toxicities will be analyzed and compared with the historical data of photon radiotherapy.

3.0 Patient Eligibility

3.1 Inclusion Criteria:

- 3.1.1. Histologically or cytologically documented NSCLC.
- 3.1.2. Patients with inoperable centrally/superiorly located tumors, defined as those (with any tumor edge measured within 30 days by the CT image using lung window level including simulation CT or MRI or PET/CT) located within 2 cm of the bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi), major vessels (aorta, pulmonary artery trunk, left/right pulmonary artery/vein main branches, superior/inferior vena cava, brachiocephalic artery trunk or left/right brachiocephalic vein, left/right subclavian artery/vein), esophagus, heart, tracheal, pericardium, mediastinal pleural and brachial plexus and vertebral body, but no direct invasion, T1N0M0 (stage IA), or any location of T2N0M0 (stage IB) and T3N0M0 (selected stage II with chest wall involvement) NSCLC.
- 3.1.3. Performance score KPS 60-100.
- 3.1.4. Negative pregnancy test for women of child bearing potential.

3.2 Exclusion criteria:

- 3.2.1. Prior radiotherapy to the chest.
- 3.2.2. Previous or concomitant malignancy other than (a) curatively treated carcinoma in situ of cervix, (b) basal cell carcinoma of the skin, (c) curatively treated superficial transitional cell carcinoma of the urinary bladder, and (d) early stage tumor treated more than 2 years for cure with life expectancy more than 5 years .
- 3.2.3. Pregnancy. (Patients, both men and women, of child bearing potential should use an effective method of birth control throughout their participation in this study.)

4.0 Pre-treatment evaluation

- 4.1 Complete History and Physical: A complete history and physical to include performance status, recent weight loss, and concurrent non-malignant disease and its therapy will be recorded within 30 days before registered. (Table 1)
- 4.2 Laboratory and Radiographic Tests
 - 4.2.1 Laboratory studies will include a CBC with differential, platelet count, electrolytes, BUN, creatinine within 30 days. LFTs will be optional. 10 ml of additional peripheral blood will be collected optionally at the time of pre-registration blood work up. The blood sample will be frozen using -80 degree centigrade refrigerator for future biomarker studies. In the future, a separate protocol will be developed for the biomarker studies. (Table 1)
 - 4.2.2 Chest X-ray, MRI or CT scans of the brain, CT of chest or PET scan should be done within 3 months prior to radiotherapy. PET/CT scan is preferred whenever possible. Radionuclide bone scan is optional.
 - 4.2.3 PFTs including FEV1, DLCO, TVC, FEV should be obtained within 3 months prior to radiotherapy. EKG is required within 3 months as a baseline test. Cardiac SPECT is recommended if lesion is close to heart and cardiac toxicity

is of concern and/or when EKG is abnormal.

5.0 Evaluation Criteria

5.1 Treatment evaluation:

Acute radiation reactions including esophagitis, pneumonitis and other adverse events will be evaluated weekly during the course of treatment. The adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE 3.0). Laboratory studies will include a CBC with differential, platelet count every three weeks during the radiotherapy.

5.2 Post-treatment evaluation:

Patient follow-up is recommended 6 weeks after RT and then required every 3 months (± 1 month) for two years, then every 6 months (± 1 month) for three years and then annually for the rest of the patient's life, which is the standard of care. For the purpose of this protocol, we are going to follow the patients for a minimum of two years. Afterwards, patients will be continuously followed according to the standard of care. Follow-up will be conducted at the treating institution or other clinical facilities. If the follow-up is performed at other facilities, the information about medical history, physical examination, PFT, image data and radiologist's report must to be sent to the treating institution to be reviewed and documented. Follow-up at the treating institution is strongly recommended.

Two Pulmonary function tests will be performed within first one year ± 5 month after the completion of RT, then annually for two years. It is preferred that PFT is performed in the second and fourth follow up visit after completion of concurrent radiotherapy and chemotherapy, and then annually for two years. If no 6 week follow-up, then PFT is preferred to be performed in the first and third visit. EKG will be conducted in the third or fourth f/u visit and then annually for two years. If cardiac toxicity is of concern based on treatment plan and/or when EKG is abnormal, cardiac SPECT should be performed in the third or fourth f/u visit and then as clinically indicated. Physical examination, medical history, and CXR will be performed in every follow up. A chest CT scan will be performed in the second follow up after radiotherapy and then every three months (± 1 month) for two years and then every 6 months (± 1 month) for 3 years; then annually. PET scan is required between 2-6 months after finishing treatment, including chemotherapy, When a PET scan is available for the follow up visit, a chest CT is not required for this visit. A PET/CT scan is preferred whenever possible.

All diagnostic exams and follow up are subjected to insurance approval or patients' affordability or patients' compliance. If there are metastatic tumors or tumor recurrences, all follow-ups and exams are still recommended.

Local control at the primary site will be evaluated by a series of CT scans of the chest with contrast (if possible) as stated above. If an abnormal lesion is suspicious for recurrent disease by CT image, PET or PET/CT scan is required to evaluate for recurrence and biopsy is recommended to confirm the recurrence. For un-confirmed recurrent disease, continuing follow up images including CT or PET should be considered. Timing of recurrence will be scored at the time of first image (PET and/or CT) showing

abnormalities. Two-year progression free survival (PFS) rate will be calculated. PET information will be considered for calculation of PFS particularly for distant metastasis and/or additional lesions.

Progression free survival will be evaluated.

Grade \geq 3 acute and chronic toxicities by Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE 3.0) will be analyzed.

Response assessment: This protocol will use a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See <http://ctep.info.nih.gov/guidelines/recist.html> for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of the target lesion; ideally, this determination will be made based on CT image evaluation. Negative PET can be also considered to be a CR.

Partial Response (PR): At least a 30% decrease in the LD (The longest diameter for the target lesion will be calculated from the treatment planning CT scan using pulmonary windowing and reported as the baseline LD) of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.

Stable Disease (SD) Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started.

Local Enlargement (LE): At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; ideally, this determination will be made based on CT image evaluation.

Local Progression (LP): Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on PET imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.

For outcome analysis, Marginal Failures (MF; see below) will also be counted as LP; however, they should be distinguished specifically as MF, not LP,. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathologic for cancer recurrence vs. inflammation.⁴⁶

Local Control (LC) The absence of Local Progression.

Evaluation of Non-Target Lesions:

Marginal Failure (MF): Refers to the appearance after protocol therapy of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV and meeting the following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV should be avid on PET imaging with uptake of a similar intensity

as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.

Regional Failure (RF): Refers to the appearance after protocol therapy of measurable tumor within lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease only with dimension of at least 1.0 cm on imaging studies (preferably CT scans) within the lung, bronchial hilum, or the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma.

Metastatic Dissemination (MD): Refers to the appearance after protocol therapy of cancer deposits characteristic of metastatic dissemination from NSCLC. Appropriate evaluations for making this determination include physical examination and imaging studies. PET scan OR biopsy to confirm MD is encouraged but not required.

PFS at the primary site: Patient remains alive without **local** progression (**LP**) at the primary site.

Criteria for going off proton treatment:

1. Development of distant metastasis during the proton radiotherapy.
2. Development of unpredictable, irreversible, or persistent non-hematological grade 4 toxicity.
3. Patient refusal or non-compliance of treatment requirements.

6.0 Schema for Study

	Pre-Registration	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Follow-Up (f)	At Relapse
History & PE, KPS	x	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x	x
CBC, Differential, Platelets	x			x			x			x	x
SMA-12	x ^a										x
PET	x									x ^g	x
Chest X-Ray/Chest CT	x ^b									x ^g	x
Brain Scan (CT or MRI)	x ^b									x ^g	x
PFTs/EKG/Cardiac SPECT	x ^c									x ^c	
Toxicity Evaluation		x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	x ^e	
Pregnancy Test	x ^d										
Biomarker Study	x ^h										
4DCT		x ^k	x ^k	x ^j	x ^j	x ^k	x ^k	x			
Radiation Therapy ^f		x	x	x	x	x	x	x	x		

- SMA-12 = serum creatinine, cholesterol, SGOT, glucose, Alk Phos, total bilirubin, total protein, albumin, uric acid, phos, calcium, BUN. SMA-12 is optional. CBC with differential, platelet count, electrolytes, BUN, creatinine within 30 days is required.
- Chest X-ray (optional), MRI or CT scans of Brain, PET or CT of chest are required within 3 months prior to radiotherapy.
- PFTs (FEV-1, FVC, and DLCO) and EKG should be obtained within three months prior to the initiation of XRT. Cardiac SPECT is recommended if lesion is close to heart and cardiac toxicity is of concern and/or when EKG is abnormal.
 Two Pulmonary function tests will be performed within first one year \pm 5 month after the completion of RT, then annually for two years. It is preferred that PFT is performed in the second and fourth follow up visit after completion of concurrent radiotherapy and chemotherapy, and then annually for two years. If no 6 week follow-up, then PFT is preferred to be performed in the first and third visit. EKG will be conducted in the third or fourth f/u visit and then annually for two years. If cardica toxicity is of concern based on treatment plan and/or abnormal EKG, cardiac SPECT should be performed in the third or fourth f/u visit and then as clinically indicated.
- Serum pregnancy test pre-study entry as applicable.
- PE including weight, performance status, vital signs. Radiation induced acute reactions including esophagitis, pneumonitis should be evaluated weekly.
- Follow-up is at 6 weeks after completion of radiotherapy, then every 3 months (+/-1 month) x 2 year, then every 6 months (+/- 1 month) x 3 years, then yearly. CBC with differential, platelet count, electrolytes, BUN, creatinine is recommended during the follow-up. Long term toxicity for esophagus and lung will be evaluated.
- Obtain chest CT if symptoms. If no symptoms, obtain chest CT in the second follow up after completion of radiotherapy and then every 3 months (+/-1 month) during years 1 and 2, then every 6 months (+/- 1 month) for three years and then annually. Brain scan is indicated if patient develops neurological symptoms. PET scan is required between 2-6 months after finishing treatment including chemotherapy if it is given. When PET is available, chest CT is not required. PET scan is required to evaluate recurrent disease.

- h. 10 ml of additional peripheral blood will be collected at the time of pre-registration blood work up. The blood sample will be frozen using a -80 degree centigrade refrigerator for future biomarker study.
- i. Radiotherapy need not start on a Monday but shall not start on a Friday.
- j. 4D-CT scanning will be performed at least in weeks 3 or 4 and 7
- k. 4DCTs in weeks 1, 2,5,and 6 are optional.

7.0 Radiation Therapy

7.1 Definition of Target Volumes

- GTV** Gross tumor volume is all known gross disease as demonstrated on end ventilation data set (30% phase as determined by Varian RPM or equivalent respiratory monitoring system) of the planning 4DCT using a lung window, and modified as deemed necessary based on PET/CT, diagnostic CT and other clinical studies.
- iGTV** The envelope of motion of the GTV constructed by any means but verified across all phases of the 4DCT dataset and the PET scan.
- CTV** Clinical target volume is the subclinical involvement around the GTV on the end ventilation dataset (30% phase as determined by Varian RPM or equivalent respiratory monitoring system). The CTV is estimated by an 8-mm isotropic expansion of the GTV to encompass microextensions of the tumor (CTV=GTV+8 mm). This should be edited by the attending based on clinical experience of disease spread.
- iCTV** Internal Clinical target volume is the envelope of motion of the CTV during In this study, The iCTV is estimated by an 8-mm isotropic expansion of the iGTV to encompass microextensions of the tumor (iCTV = iGTV+8mm); This should be edited by the attending based on clinical experience of disease spread.
- PTV** Planning target volume is iCTV plus a margin to ensure that the prescribed dose is actually delivered to the iCTV. For the purpose of reporting the PTV for proton treatment shall only include lateral uncertainties for each beam and not include any depth uncatinties (ICRU 78). The PTV shall be the iCTV expanded isotropically by 5 mm. This reporting sturtuce should not replace a beam-by-beam analysis of coverage using beam-specific PTV (see below).
- B-PTV** Beam specific PTV. For proton planning, each beam has an individual and unique PTV expansion from the iCTV. In the plane perpendicular to the proton beam axis, the PTV expansion from the iCTV is a fixed distance of 5 mm for setup uncertainites. However, along the direction parallel with the proton beam axis, the PTV expansion (distal and proximal margins) from the iCTV is based on the range uncertainty of the beam.

Treatment planning parameters, including distal and proximal margins, will be calculated based on published formulae, modified locally and adopted as standard of practice (Moyers et al, 2001; Engelsman et al, 2006; Kang et al,

2007).

PRV: Planning organ at risk volume (OAR) is used *to ensure with a high probability that adequate sparing of the OAR will actually be achieved* (ICRU 78) for this study OARs require PRVs will be identified in the planning constraints table.

7.2 Radiation Doses

7.2.1 The total radiation dose for the tumor target will be 87.5 Cobalt Gray Equivalent (CGE) at 2.5 CGE per fraction, once a day, 5 fractions per week. 100% of the iCTV should be covered by the prescribed dose. For proton treatments this will be achieved by ensuring that each beam covers the iCTV plus the margins for not only lateral but also range uncertainties (ICRU 78). Caution should be used as beams should not be modified based on a static evaluation.

7.2.2 Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose must not fall below 95% of the prescription dose. The PTV is assumed to be the beam-specific PTV.

7.2.3 Deviations from dose prescription for target volumes:

7.2.3.1 No deviation: $\geq 99\%$ of the PTV receives $\geq 95\%$ of the prescribed dose, and a contiguous volume of no more than 2 cc inside PTV exceeds 110% of the prescribed dose.

7.2.3.2 Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage that is equal to 95% of the prescribed dose and falls between 99% and 95% of the PTV, or a contiguous volume of no more than 2 cc inside the PTV exceeds 120% of the prescribed dose. Similar considerations apply for each beam-specific PTV.

7.2.3.2 Major deviation: Coverage that is less than 95% of the prescribed dose and falls between 99% and 95% of the PTV, or a contiguous volume of greater than 2 cc inside the PTV exceeds 120% of the prescribed dose. Similar considerations apply for each beam-specific PTV.

7.2.4 Tolerance Limits for Critical Structures (2.5 CGE/Fraction)

Table 1: OAR Dose Limits

OAR	Label	Dose limit	Description
Normal Lung	Lung	20 CGE < 40% 10 CGE < 50% 5 CGE < 60% Mean Lung Dose (MLD) < 20 CGE	Normal lung - C contoured on ventilation dataset
Esophagus:	Esophagus	60 CGE < 50% 74 Gy < 10 cc Max Dose < 80 CGE	Esophagus contou on any dataset
Spinal Cord	Cord	Max Dose < 45 CGE	Spinal Canal
Spinal Cord PRV	Cord PRV (5 mm)	Max Dose < 60 CGE	Spinal Canal + 5 radial expansion
Brachial Plexus:	BP	Max Dose < 74 CGE 70 CGE < 10 cc	

Liver	Liver	30 CGE < 40%	
Kidney	Kidney	20 CGE < 50%	Both kidneys combined if both are functional
Functional Kidney	FunKidney	20 CGE < 25%	If only one kidney function, it should be contoured separately
Bronchial tree PRV	BroncPRV	87.5 CGE < 10 cc	Bronchial tree contoured down to tertiary bronchus on a lung window/level
Major vessels PRV	VesselPRV	87.5 CGE < 10 cc	See inclusion criteria
Heart-Atria	Atria	70 CGE < 10% 60 CGE < 15% 50 CGE < 20% 45 CGE < 30% 40 CGE < 40% 30 CGE < 50%	
Heart-Ventricles	Ventricles	70 CGE < 5% 60 CGE < 10% 50 CGE < 15% 45 CGE < 20% 40 CGE < 30% 30 CGE < 40%	

7.2.5 Major deviation: Doses outside the limits for OARs listed in table 1 will be considered major deviations and not acceptable.

7.2.6 Dose reporting: The digital dose distribution data to be reported includes the complete treatment plan. Its components include patient images on the mid ventilation dataset, contours of all structures, beam configurations and characteristics including beam shaping devices or scan patterns as appropriate, treatment couch parameters, dose distributions, dose volume histograms for target volumes and critical normal structures.

7.3 Simulation, Immobilization, Image-Guided Radiation Simulation

7.3.1. All simulations will be done on CT scanners capable of acquiring 4D CT image data sets. Only CT scanners and scanning protocols which have been calibrated specifically for proton calculations should be used.

7.3.2. Each patient will be positioned in an immobilization device in the treatment position on a flat table and imaged in treatment position.

7.3.3. The imaging session will consist of acquisition of a 4DCT covering the entire lungs as well as the entire treatment volume plus at least 5 cm. (Also see section 7.3.5.)

7.3.4. If the tumor is observed to move more than 1 cm on the 4DCT (edge to edge at motion extremes) or if critical normal tissue sparing is of concern, respiratory gated treatment, either free breathing or breathhold, should be considered.

7.3.5. An extended range free breathing scan may be acquired at the same time to serve as an anatomical reference and/or to look for distant metastasis.

7.3.6 Image-guided adaptation

- 7.3.6.1 All treatments must be done on treatment units with kilovoltage radiographic imaging.
- 7.3.6.2 In addition to the 4D CT simulation for planning of treatments, 4D-CT scanning will be performed at least in weeks 3 (or 4) and 7. Optionally, additional 4D CTs may be acquired in weeks 1, 2, 5 and 6.
- 7.3.6.3 The original CT will be fused with the weekly CT. The original contours will be transferred to the new CT and reviewed by the attending physician. If deemed necessary by him or her, new contours will be drawn and new dose distribution calculated using the original beam configuration. If the changes in DVHs derived from new dose distribution exceed the level of minor deviation of the target or normal tissue dose constraints, a new treatment plan will be designed for the remainder of the treatments.
- 7.3.6.4 Composite dose distribution received by each patient over the course of radiotherapy will be computed. Dose calculations will be performed for each of ten phases of the respiratory cycle for each of the CT scans acquired over the course of RT. They will be deformed to a reference phase (typically the end-exhale phase) and averaged. Such computations are necessary mainly to correlate dose distributions with response. They need to be performed only at the time of outcomes analyses.

7.4 Treatment Planning

7.4.1 Critical structures

- 7.4.1.1 All OARs listed in the section 4.0 and likely to receive more than 50% of their tolerance doses shall be contoured.
- 7.4.1.2 The tolerance doses to various organs are provided in Table 1.

7.4.2 Motion Management

- 7.4.2.1 All patients on this protocol will undergo a 4D CT for treatment planning. Tumors that are found to move more than 1 cm will be treated with appropriate motion management.
- 7.4.2.2 Planning shall be done in accordance with the P01 physics document.

7.4.3 Dose calculation

- 7.4.3.1 Doses are to be calculated with CT based heterogeneity correction, i.e., correction is to be made for density differences between air spaces, lung, water-density or bony tissue.
- 7.4.3.2 Treatment planning should be performed in accordance with the prescribed doses to each target, together with restrictions in dose to normal tissues
- 7.4.3.3 The average intensity projection (AveIP) derived from the 4DCT set should be used as a reference scan for dose calculation.

7.5 Patient Registration

- 7.5.1 Patients should be registered as required by either MGH or MDACC institutionally

mandated systems. At MGH, the Quality Assurance for Clinical Trials office defines the required registrations. At MDACC, CORE, the Clinical Oncology Research System is used.

- 7.5.2 Patient data will be entered onto TrialDB, independent of which institution the patient originates from. This registration must be disclosed as part of the informed consent.

The delivered treatment dose distribution, with structures and DVH, will be sent to the ITC at Washington University in St. Louis. This should be disclosed as part of the informed consent. The ITC will provide digital data integrity quality assurance (DDIQA), which will facilitate the review of delineation and dosimetry of GTV, CTV, PTV, and designated organs at risk (critical structures) on all cases. Detailed instructions for submitting digital data to the ITC may be found on the ATC web site <http://atc.wustl.edu/>

7.6 Radiation Therapy Quality Assurances

- 7.6.1. All contours and treatment plans will be peer reviewed, following the normal practice of the institution which enrolls the patient. Contours will be reviewed by the physician co-PI of the protocol or his/her designee

- 7.6.2 Plans will be reviewed by the physician co-PI and physics co-PI of the protocol or his/her designee for compliance with the protocol.

- 7.6.3 Plan review for the patients from one institution by the staff of the other institution will utilize the resources of the Image-Guided Therapy QA Center (ITC) at Washington University, St. Louis.

8.0 Chemotherapy

Adjuvant Chemotherapy 4 weeks after RT would be allowed at the discretion of the treating physicians.

9.0 Statistics

The local control rate at 2 years is 50% with historical photon data. We anticipate that proton therapy will increase the local control rate to 75%. With a sample of 40 patients we will have 93% power to detect an increase in the local control rate at 2 years from 50% to 75% with a 1-sided significance level of 5%. This calculation assumes that we will accrue 20 patients per year for 2 years and that we will follow all patients for 2 years. We will estimate the local control rate at 2 years with a 95% confidence interval using the Kaplan-Meier product-limit estimator.

With current photon therapy using similar relative biological effectiveness (RBE) the rate of grade 3 acute pneumonitis is less than 15%, and the chronic pneumonitis rate is 15%. With a sample of 40 patients we will have 81% power to detect a decrease in the rate of grade 3 acute pneumonitis from 15% to 3.75% with a 1-sided significance level of 5%. We will estimate the

grade 4 acute pneumonitis rate with an exact binomial 95% confidence interval.

We will enroll and evaluate a maximum of 40 patients at a rate of 20 patients per year. We will monitor the rate of grade 3+ pneumonitis, which is assessed within 3 months following completion of therapy. Our target grade 3+ pneumonitis rate is 10% or less, based on RTOG Study 9311. We assume a beta(0.2, 1.8) prior distribution for this toxicity rate. This prior distribution has a mean of 10% and a standard deviation of 17%.

We will stop the trial early if $P(\text{grade 3+ pneumonitis} > 10\% \mid \text{data from the trial}) > 0.925$. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than a 92.5% chance that the grade 3+ pneumonitis rate is more than 10% we will stop the trial. This decision rule gives the following stopping rule. Stop the trial if

$$\begin{aligned}
 & [\# \text{ of pts with grade 3+ pneumonitis} / \# \text{ of pts evaluated}] \\
 & \geq 4/15, 5/17, 6/24, 7/31, 8/38
 \end{aligned}$$

The operating characteristics of this monitoring rule are shown in Table 1.

Grade 3+ Pneumonitis Rate	Probability of Stopping Early	Sample Size		
		P ₂₅	P ₅₀	P ₇₅
0.050	0.012	40	40	40
0.075	0.053	40	40	40
0.100	0.131	40	40	40
0.150	0.413	21	40	40
0.200	0.709	15	22	40
0.250	0.895	15	15	25
0.300	0.970	15	15	16

Once we have completed the study we will estimate the grade 3+ pneumonitis rate with a 90% credible interval. If we have grade 3+ pneumonitis in 4 of the 40 patients (10%), then our 90% credible interval for the grade 3+ pneumonitis rate will be 3.7% to 18.5%. If we have grade 3+ pneumonitis in 2 of the 40 patients (5%), then our 90% credible interval for the grade 3+ pneumonitis rate will be 1.1% to 11.8%.

In addition, if there is any grade 4 or 5 toxicity directly caused by proton therapy, the trial will be re-evaluated and decision will be made about modification of treatment or stopping the trial.

10.0 References

Bradley JD, Graham MV, Winter KW, et al. Acute and late toxicity results of RTOG 9311: A

dose escalation study using 3D conformal radiation therapy in patients with inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;57:S137.

Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest* 1999; 1116:313-1319.

Chang JY, Zhang X, Kang Y, Mohan R, Komaki R, Cox JD. Significantly reduced normal tissue dose with proton radiotherapy compared with 3D-CRT or IMRT in stage I or stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65(4):1087-1096.

Dosoretz DE, Galmarini D, Rubenstein JH, et al. Local control in medically inoperable lung cancer: an analysis of its importance in outcome and factors determining the probability of tumor eradication. *Int J Radiat Oncol Biol Phys*. 1993;27:507-516.

Engelsman M, Rietzel E, and Kooy HM. Four-dimensional proton treatment planning. *Int J Radiat Oncol Biol Phys* 2006; 64:1589-1595.

Kang Y, Zhang X, Chang JY, Wang H, Wei X, Liao Z, Komaki R, Cox JD, Balter P, Liu H, Zhu RX, Mohan R, Dong L. 4D Proton treatment planning strategy for mobile lung tumors. *Int J Radiat Oncol Biol Phys* 2007; 67(3):906-914.

Kaskowitz L, Graham MV, Emami B, et al. Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 1993;27:517-23.

Krol AD, Aussems P, Noordijk EM, et al. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? *Int J Radiat Oncol Biol Phys*. 1996;34:297-302.

Moyers MF, Miller DW, Bush DA, et al. Methodologies and tools for proton beam design for lung tumors. *International Journal of Radiation Oncology Biology Physics* 2001;49:1429-1438.

Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;56:7-13.