Proton Collaborative Group

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4320 Winfield Road, Ste 200, Warrenville, IL 60555

LUN005-12
A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer

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PROTOCOL SIGNATURE PAGE

LUN005-12

A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer

Protocol Version: 28Feb2018

I certify that I have read the protocol. I agree to conduct the protocol according to ethical principles stated in the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations, whichever provides the greatest protection of the individual. I will accept the monitor's oversight of the study.

_____ _____

Signature of the Site Principal Investigator **Date**

_____

Principal Investigator's Printed Name

_____

Name of Facility

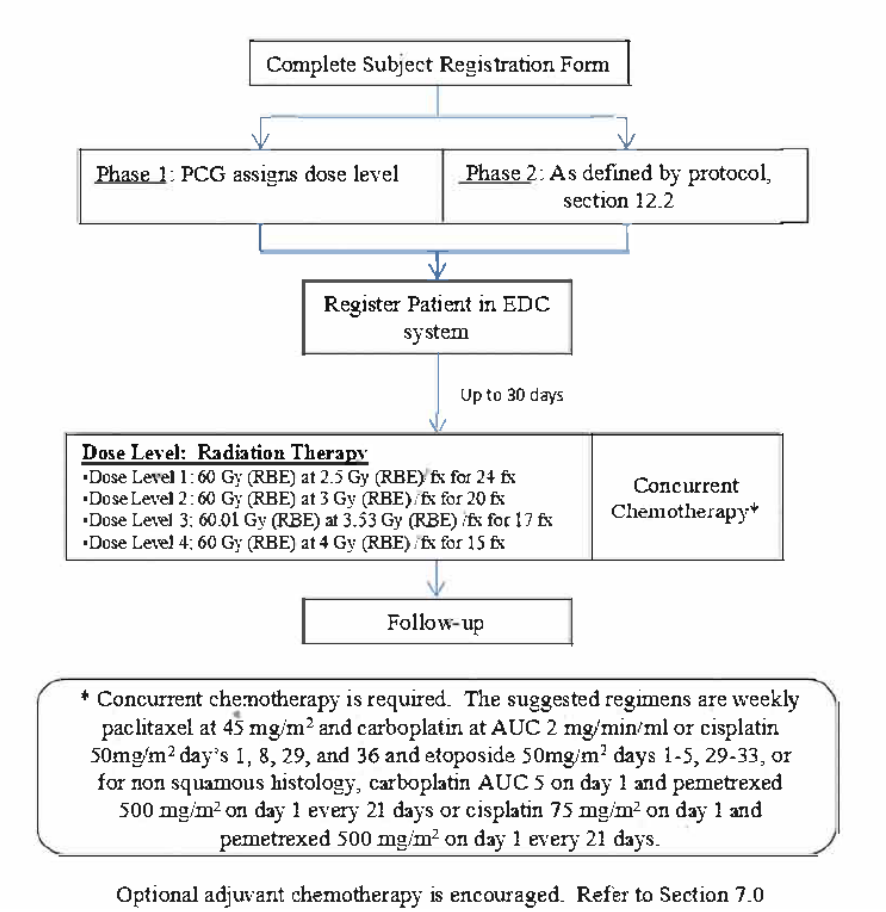
_____

Location of Facility (City, State)

PLEASE COMPLETE AND SEND TO THE PROTON COLLABORATIVE GROUP OFFICE VIA EMAIL: HQ@PCGRESEARCH.ORG

A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer

SCHEMA



Patient Population: Stage II-III non-small cell lung cancer

Eligibility Criteria: (see Section 3.0 for complete eligibility)

- Pathologically confirmed invasive non-small cell lung cancer within 12 weeks prior to study registration

OR

- Pathologically confirmed invasive non-small cell lung cancer within 6 months prior to study registration if the patient received induction chemotherapy.
- AJCC (American Joint Committee on Cancer) 7th or 8th Ed. clinical stage II-III.
- ECOG Performance status 0-1 within 8 weeks prior to study registration.
- Study-specific informed consent on an IRB-approved consent.
- Lab results per the following within 4 weeks prior to study registration:
    - Absolute neutrophil count (ANC) >1,800 cells/mm^3.
    - Platelets ≥ 100,000 cells/mm^3.
    - Hemoglobin ≥10 g/dl. The use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable.
    - AST/SGOT and ALT/SGPT < 2.5 x the institutional upper limit of normal (IULN).
- PFT (pulmonary function test) with a FEV1 > 0.75 liters/second within 16 weeks prior to study registration.
- No evidence of distant metastasis (M1) involvement.
- No prior radiotherapy to thoracic area.
- No unintentional weight loss >10% within 4 weeks prior to study registration.

Required Sample Size: Phase I- 2 to 28 patients; Phase II- 70 patients (including 7-28 pts from Phase I)

1.0 INTRODUCTION/BACKGROUND

Conventional fractionated photon-based radiotherapy to 60-63 Gy at 1.8-2 Gy/fraction with concurrent chemotherapy remains the standard treatment practice in patients with stage III non-small cell lung carcinoma (NSCLC) with local control rates of approximately 50% and a median overall survival of just 18 months[1, 2]. Unfortunately, even the standard treatment has significant toxicity with approximately 40% of patients developing grade 3 or higher acute toxicities in the RTOG 9410 study[1]. These outcomes are poor and more effective treatment regimens are needed.

Higher doses of radiation have been hypothesized to improve local control in patients with stage III NSCLC. This is expected to translate into better overall survival. In a study by Machtay et al, seven RTOG trials were retrospectively evaluated to better understand the impact of receiving a higher biologic effective dose (BED) on overall survival (OS) and local control. The study demonstrated an improvement in both local control and OS with the use of a treatment regimen with a BED $\geq$ 75Gy. However, a recent interim analysis from RTOG 0617, which randomized patients to 60 Gy (BED=72 Gy) or 74 Gy (BED=89 Gy) with concurrent chemotherapy, led to the closing of the high dose arm of 74 Gy because of an inability to demonstrate a statistically significant improvement in overall survival with the dose escalation[3].

Although conventionally fractionated high dose photon radiotherapy did not improve outcomes, MD Anderson has demonstrated on a phase II study for patients with stage III NSCLC, excellent local control rates of 91% with a median overall survival of 29 months[4]. Similarly, University of Florida Proton Therapy Institute (UFPTI) has reported outcomes in patients with stage III NSCLC and demonstrated excellent local control rates of 95%, although, distant metastases remained a problem with a rate > 50%[5]. In the UFPTI study, however, only 1 patient developed a grade 3 or higher acute toxicity out of 19 consecutive patients who were treated. In both studies, grade 3+ side effects were much lower than the 57% rate of grade 3+ non-hematological toxicity reported in RTOG 0117, a phase II study of 74 Gy of x-ray radiation with concurrent chemotherapy[6]. However, given the recent data from RTOG 0617 demonstrating no improvement with 74 Gy of x-ray radiation, there is less enthusiasm to continue with dose escalation in patients with stage III NSCLC.

Hypofractionated radiotherapy has had a tremendous impact in local control and survival outcomes in patients with early stage NSCLC. Local control for stage I NSCLC has improved from 50% with conventional fractionation to 90% using short courses of high dose radiotherapy. Unfortunately, extreme hypofractionation has been associated with increased risk of toxicity, especially for centrally located tumors. In fact, Timmerman et al., reported a 20% grade 3-5 toxicity rate among 70 patients treated with extreme hypofractionation delivered over just 3 days[7].

At UFPTI, we demonstrated significant reductions in normal tissue dose with the use of proton-based compared with photon-based SBRT,[8] which should translate into lower risks of toxicity. Loma Linda University Medical Center as well as several groups in Japan have corroborated this data clinically,[9, 10] demonstrating the effectiveness and safety of hypofractionation with proton therapy. At UFPTI, we have been treating with hypofractionated proton therapy for patients with Stage I NSCLC on an IRB approved protocol (UFJ-2009-029 LU03). Peripheral lesions receive 48 CGE in 4 fractions, while centrally located lesions receive 60 CGE in 10 fractions. UFPTI plans on continuing accrual on this hypofractionated protocol.

Given the significant improvements in outcome in patients receiving hypofractionation for stage I NSCLC, perhaps similar gains could be achieved if hypofractionated radiotherapy

could be safely delivered to stage II-III NSCLC with concurrent chemotherapy. Hypofractionated radiotherapy may offer improvement in local control compared with conventional fractionation that may translate into improved overall survival. Furthermore, hypofractionation will shorten the time interval during which patients are receiving less aggressive chemotherapy.

Several groups have already investigated various ways of delivering hypofractionated radiotherapy using photons. Although promising, they have been plagued by increased risks of grade 3 toxicities[11]. Given the close proximity of the esophagus, spine, heart, major blood vessels, trachea and contralateral lung, even the most conformal photon based radiation treatment approaches, such as intensity- modulated radiation therapy (IMRT), Cyberknife, and tomotherapy, result in high doses of radiation to these specified critical organs. This is likely part of the reason that centrally located stage I NSCLC has been associated with increased risk of grade 3 toxicity following SBRT[7]. Proton therapy, on the other hand, is a highly conformal radiotherapy technique that takes advantage of the proton's characteristic Bragg Peak, resulting in significant reductions in the exit dose of the treatment beam. Thus, proton therapy can substantially reduce the dose to critical structures even compared with IMRT. UFPTI has demonstrated a reduction to the esophagus and lung with the use of proton therapy compared with three-dimensional conformal radiation therapy (3DCRT) and IMRT[12]. Given this improvement in dosimetry with proton therapy and the great results already demonstrated with conventionally fractionated high dose proton therapy, a logical next step is to evaluate hypofractionated proton therapy in stage II-III NSCLC. Given the lack of data of using hypofractionated proton therapy in stage II-III NSCLC, we would propose a phase I/II study of hypofractionated proton therapy with BED doses ≥ 75 CGE.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 Phase I: Establish the maximum tolerated dose of radiotherapy in terms of Gy (RBE)/fraction using hypofractionated proton therapy concurrently with chemotherapy.

2.1.2 Phase II: Determine the percentage of patients that survive at least 12 months.

2.2 Secondary Objectives

2.2.1 To assess acute and late adverse events of concurrent chemotherapy with hypofractionated proton therapy.

2.2.2 To analyze for progression free survival and overall survival.

2.3 Exploratory Objectives

2.3.1 To assess cost-effectiveness of this hypofractionated treatment course.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Pathologically confirmed invasive non-small cell lung cancer within 12 weeks prior to study registration
OR
Pathologically confirmed invasive non-small cell lung cancer within 6 months prior to study registration if the patient received induction chemotherapy.

3.1.2 AJCC (American Joint Committee on Cancer) 7th or 8th Ed. clinical stage II-III.

3.1.3 ECOG Performance status 0-1 within 8 weeks prior to study registration.

3.1.4 Patient must give study-specific informed consent on an IRB-approved consent prior to any research-related procedures or study treatment.

3.1.5 Patient must be at least 18 years old at the time of consent.

3.1.6 Patient must complete all required tests in section 4.

3.1.7 Lab results per the following within 4 weeks prior to study registration:

- Absolute neutrophil count (ANC) >1,800 cells/mm^3.
- Platelets ≥100,000 cells/mm^3.
- Hemoglobin ≥10 g/dl. The use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable.
- AST/SGOT and ALT/SGPT < 2.5 x the institutional upper limit of normal (IULN).

3.1.8 Post exploratory thoracotomy must be done > 3 weeks prior to study registration if a patient had post exploratory thoracotomy.

3.1.9 PFT (pulmonary function test) with a FEV1 > 0.75 liters/second within 16 weeks prior to study registration.

3.1.10 Patients must be evaluated by a thoracic surgeon, pulmonologist or medical oncologist and deemed medically or surgically unacceptable for resection.

3.2 Ineligibility Criteria

3.2.1 Evidence of distant metastatic (M1) involvement.

3.2.2 Prior radiotherapy to thoracic area.

3.2.3 Unintentional weight loss >10% within 4 weeks prior to study registration.

3.2.4 Pregnant and/or breast-feeding women, or patients (men and women) of child-producing potential not willing to use medically acceptable forms of contraception while on study treatment and for at least 12 months after study treatment. Pregnancy testing is not necessary for women who have had a hysterectomy or have not had a menstrual period for at least 24 consecutive months. Please document as such.

3.3 Inclusion of International Subjects

Patients from outside of the United States may participate in the study. Enrollment and treatment must be completed at an approved PCG member institution in the United States.

4.0 PATIENT ASSESSMENTS

Assessments	Pre-registration	Pre-Treatment	Weekly During Chemo-RT	During Adjuvant Chemo (if applicable)	Follow-Up (From RT Start Date)				At Failure
					90 Days (+14 days)	Yr 1-2 Q3Mo (+/- 30 days)	Yr 3-4 Q6Mo (+/- 60 days)	Yr 5+ Annually (+/- 90 days)	
History/Physical Exam (RadOnc prior to and during treatment)	X within 8 wks		X			X	X	X	X
ECOG Performance Status	X within 8 wks		X		X	X	X	X	X
Weight	X		X			X	X	X	X
Height		X							
O_2 Saturation -resting (required) and walking (highly recommended)		X				X	X	X	X
Physical exam (Med Onc)	X within 8 wks		X[a]	X[a]		X[a]	X[a]	X[a]	
Adverse Event evaluation (CTCAE)		X Baseline	X		X	X	X	X	X
Biopsy of tumor	X								
Physician clinical stage documentation (using AJCC 7th or 8th Ed. Staging Manual)	X								
Planning 4DCT without IV contrast		X	X						
MRI or CT of the brain (with contrast unless contraindicated) (MRI preferred)	X within 12 wks								X
PET-CT scan (Tri-dimensional measurements preferred)–Follow-up exams can be CT or PET-CT	X within 16 wks				X[c]	X[c] (Q3Mo for Yr1 then Q6Mo for Yr2)	X[c]	X[c]	X[c]
PFT with FEV1 and DLCO	X within 16 wks					At 6 mo & 1 yr after RT[c]			
CBC with diff	X within 4 wks		X[a]	X[a]					
CMP	X within 4 wks		X[a]	X[a]					
Pregnancy test, serum or urine (prn)	X within 14 days								
Physics consultation[b]		X							

a. At the discretion of medical oncology

b. For patients with a pacemaker or internal defibrillator: The guidelines of the American College of Radiology (ACR) and American Association of Physicists in Medicine (AAAPM) will be strictly followed including that of specific recommendations of the device manufacturer. A special physics consultation will be requested and all guidelines strictly followed if needed.

c. Highly recommended, not required

4.1 Follow-Up Visits

Follow-up visits are based on the time from the start date of radiation treatment. It is highly recommended that patients will be seen in person by the treating investigator for all follow-up visits. If subjects refuse to return to the clinic for follow-up visits they must be contacted by phone to obtain information needed for data collection, or information from their visits with other physicians can be used to collect the necessary follow-up information. Collaborating medical records must be obtained if information from visits with other treating physicians is being used to fulfill the follow-up visit requirement. Follow-up assessments performed with the patient over the phone will be sufficient to fulfill the follow-up visits requirements related to obtaining adverse event information and performance status. Any failure to contact subjects for follow-up must be clearly documented in the source record.

4.2 Criteria for Removal from *Protocol Treatment* (reason must be clearly documented)

4.2.1 Progression of disease during study treatment.

4.2.2 Serious adverse events or life threatening events as assessed by the investigator and/or DSMB (data safety monitoring board).

4.2.3 Intercurrent, non-cancer-related illness that prevents continuation of therapy.

4.2.4 Changes in a patient's condition that renders the patient unacceptable for further treatment in the judgment of the investigator.

4.2.5 The patient may withdraw from the treatment at any time for any reason.

4.3 Criteria for Removal from *Protocol* (reason must be clearly documented)

4.3.1 Major protocol violation or discovery of information that, if previously known, would have rendered the patient ineligible for study.

4.3.2 The patient may withdraw from the study at any time for any reason.

4.4 Objective Tumor Response Criteria

4.4.1 A treatment failure will be defined as, after two consecutive CT scans, a tumor increase of at least 20% since baseline (if local/regional disease, should be confirmed by biopsy).

4.4.2 The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

4.4.3 Evaluation of Target Lesions (per treating physician):

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesion.
- 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.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.

5.0 REGISTRATION PROCEDURES

5.1 PCG headquarters must have documentation of each institution's IRB approval of the protocol on file prior to registering patients.

5.2 Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

5.3 Verify the patient meets the eligibility criteria prior to registering the patient. The protocol-specific eligibility checklist provided on the PCG website

(http://pcgresearch.org, PCG Member Portal) must be used to document eligibility (included treating physician's signature), placed in the participant's medical/research record and uploaded to the EDC. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.

5.4 Due to the complex nature of the dose escalation in this trial, PCG will monitor enrollment and subject toxicities closely for radiation related dose-limiting toxicities (DLTs) and appropriate dose escalation. Upon identification of a new patient to enroll on the study, sites must complete and submit the PCG Subject Registration Form for approval. The Subject Registration Form is available on the PCG website (http://pcgresearch.org, PCG Member Portal). Once approved by PCG, patients will be registered through the PCG Electronic Data Capture (EDC) system. Patients can be registered only after eligibility criteria are met.

5.5 Treatment plans for the initial 3 cases from the institution will be centrally reviewed prior to the start of treatment. Please refer to the Study Procedures Manual (SPM) for details.

5.6 Protocol treatment must begin within 30 days of study registration.

6.0 RADIATION THERAPY

6.1 Dose Specification

6.1.1 One hundred (100) % of the prescription dose must encompass 99% of the internal target volume (ITV) defined below (ITV D99%=100%). Ninety-five (95) % of the planning target volume (PTV) defined below should receive the prescription dose (PTV D95%=100%) and 100% of the PTV should receive 95% of the dose (PTV V95%=100%). No more than 2cc inside the PTV should receive > 140% of the dose.

Minor Deviation: If these dose constraints can't be met, a minor deviation is allowable as follows: One hundred (100) % of the prescription dose must encompass 95% of ITV (ITV D95%=100%). Ninety-five (95) % of the PTV must receive ≥ 95% of the prescription dose (PTV D95%≥95%).

6.1.2 The daily prescription dose will be determined by the dose level of the protocol that is currently open to accrual.

6.1.3 The prescription to the ITV shall be according to the dose escalation schema and no elective nodal irradiation will be given:

Dose Level 1: 60 Gy (RBE) at 2.5 Gy (RBE)/fraction x 24 fractions (BED=75 Gy (RBE))

Dose Level 2: 60 Gy (RBE) at 3 Gy (RBE)/fraction x 20 fractions (BED=78 Gy (RBE))

Dose Level 3: 60.01 Gy (RBE) at 3.53 Gy (RBE)/fraction x 17 fractions (BED=81.18 Gy (RBE))

Dose Level 4: 60 Gy (RBE) at 4 Gy (RBE)/fraction x 15 fractions (BED=84 Gy (RBE))

6.2 Target Volume Contouring

6.2.1 Gross tumor volume (GTV) will include all PET avid or malignant appearing lymph nodes on CT scan (GTVn) and all suspicious disease on the PET/CT scan for the primary lung tumor (GTVt).

6.2.2 Internal gross target volume (iGTVt and iGTVn) will include the GTV on all phases of the respiratory cycle correlated images or as defined on the Maximum Intensity Projection (MIP).

6.2.3 ITVt will include the iGTVt + 6 mm margin for microextension of the tumor within the lung parenchyma, ITVn = iGTVn. ITVn and ITVt will be combined to make ITV.

6.2.4 Planning Target Volume (PTV) is the ITV + 5-7 mm margin to account for variations in treatment delivery, including variations in setup between treatments. If 7 mm accuracy is not achievable, the PTV margin should be increased.

6.2.5 In the case of no target motion because of target location or motion mitigation techniques (e.g. breath-hold), a gross tumor volume (GTV) and clinical target volume (CTV) can replace iGTV and ITV, respectively.

6.3 Simulation and Immobilization

6.3.1 Patients will be immobilized for treatment according to institutional standards for treating lung cancer, but recommendations are for a supine position using a vacuum lock bag attached to a wing board with both arms raised above the head. The bag will be positioned superiorly of the shoulders. Another vacuum lock bag would be used to immobilize the patient's hips and legs. Try not to have any device between the treatment table and the patient on and around the treatment area. If one is used, it must be accounted for in the treatment plan.

6.3.2 CT scanning will extend from the hyoid to the diaphragm and include the entire lungs.

6.3.3 4D CT scans without IV contrast will be acquired for all patients for internal target volume segmentation. Contrast-enhanced CT scans may be acquired if necessary for correlation to PET/CT identified nodal target volumes. Additional motion mitigation measures, including breath holding and compression techniques, may be used to reduce target motion. The effectiveness of such additional measures should be confirmed through repeat scans using appropriate CT imaging techniques on the day of simulation or before treatment begins. If breathing motion is > 1 cm, breath hold technique should be considered.

6.4 Normal Tissue Constraints (NTC) that CANNOT be exceeded (unless otherwise noted)

Structure	2.5 GY (RBE)/fx	3 GY (RBE)/fx	3.53 GY (RBE)/fx	4 Gy (RBE)/fx
Lung-ITV mean	<18 Gy (RBE)	<18 Gy (RBE)	<18 Gy (RBE)	<18 Gy (RBE)
Lung-ITV V20	<30%	<30%	<30%	<30%
Lung-ITV V10	<40%	<40%	<40%	<40%
Esophagus mean	<30 Gy (RBE)	<30 Gy (RBE)	<30 Gy (RBE)	<30 Gy (RBE)
Esophagus V60	<15%**	<15%	<15%	<15%
Esophagus V50	<25%**	<25%	<25%	<25%
Brachial plexus D0.1cc	≤60 Gy (RBE)	<55 Gy (RBE)	<50 Gy (RBE)	<45 Gy (RBE)
Spinal cord (defined as spinal canal) D0.1cc*	44 Gy (RBE)	40 Gy (RBE)	37 Gy (RBE)	35 Gy (RBE)
Heart D15cc**	<60 Gy (RBE)	<47 Gy (RBE)	<44 Gy (RBE)	<40 Gy (RBE)
*If the spinal cord is not blocked out by a physical aperture for > 30% of the prescription dose, then the plan must be reviewed by a physics study chair.				

**Suggested, not required

6.5 Target Contouring/Treatment Technique

6.5.1 Proton treatment planning:

- Proton treatment planning should be performed according to institutional guidelines. Proton dose uncertainties due to organ motion and density variations, calculations of proton range in tissue, beam delivery and interplay effect (pencil beam scanning) should be considered and accounted for during plan optimization.
- Each plan should attempt to use 3 or more treatment fields and treat at least 2 fields a day, with special considerations for robustness of the treatment plan under all sources of uncertainties. A two treatment field plan will be considered under special circumstances by the Study Chair. Attempts should be made to block the cord out of 1 of the treatment fields.
- Motion assessment is mandatory for this protocol. As a first step, it is important to evaluate target motion. If the end-to-end target motion is more than 10mm (+/- 5mm relative to the mean position), the use of other active motion management techniques, such as breathing control, abdominal compression, free-breathing gating or gated breath hold may be used. Investigators should validate their residual uncertainties, for example via multiple sessions of CT/4DCT imaging as applicable, so that the use of these active motion management techniques matches with the expected uncertainties for patient treatments. If the end-to-end target motion is less than 10mm, the ITV approach is recommended. For pencil beam deliveries, interplay mitigation techniques should be considered for motion larger than 5mm.
- For passive scatter deliveries, the derived 4DCT time average should be used for dose calculation, range compensator design, and plan optimization. Organs at risk (OAR) doses should always be reported using the average 4D data set without any over rides. Target coverage throughout the entire breathing cycle should be ensured. Target HU overrides are recommended. iGTVt in the average CT dataset should be overridden by a value that is determined to be a representative value of the GTV prior to compensator and dose calculations. Voxel HU on the planning CT should never be overridden by lower values. Robustly optimized plans based on multiple breathing phases are an alternative to overrides.
- Intensity modulated proton therapy (IMPT) will be permitted for this protocol. It is strongly recommended that IMPT be delivered with a single-field-optimization (SFO) approach. Multi-field-optimization (MFO) should be avoided, when possible, for IMPT planning because it is difficult to maintain simultaneous anatomy consistency from multiple beam angles.
- Treatment plan robustness evaluation is recommended for all plans. That should include evaluating dose distributions recalculated on inhale and exhale phases of 4DCT and dose recalculation for a realistic set of scenarios of range and set up errors.

6.6 Quality Assurance

6.6.1 Institutional QA

The initial 3 cases from the institution will be centrally reviewed prior to the start of treatment. Please refer to the Study Procedures Manual (SPM) for details.

6.6.2 Assessments during radiation treatment

- Weekly verification 4D CT scans or other CT scan techniques appropriate for motion mitigation measures used for patient treatment will be performed during radiotherapy, and verification plans created to evaluate target coverage as well as critical organ doses due to patient anatomy reproducibility through the course of treatment, and effects of tumor regression or progression. The first weekly verification scan should be performed before or within day 1 or 2 of treatment. A verification plan on the verification CT scan images should be completed within 24 hours of each scan. In case of gross anatomy difference with the planning CT, treatment should be postponed until a more accurate patient setup or treatment plan is achieved. If consecutive verification plans show violation of constraints, replanning should be considered. On each subsequent verification plan, the iGTVt should be evaluated and should be recontoured if it is > 3mm outside of the original structure. ITV and PTV coverage should then be assessed and confirmed to meet at the minimum PTV D95%>95%. If coverage of the ITV and PTV has been compromised or if normal tissue constraints are exceeded, a new treatment plan should be developed.
- Cumulative target and critical organ doses should be calculated from summation of initial and verification plans using deformable registration methods if available when replanning is required. Daily imaging should be used for set-up of proton treatments. Breath-holding and/or compression techniques may be used for treatment in accordance with patient simulation and planning techniques.
- Weekly clinical assessment including weight, performance status, and toxicity assessment will be performed per radiation oncology to evaluate for evidence of toxicity or progression during the entire radiation treatment course. Acute and late toxicities related to radiation and chemotherapy will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

6.7 Dose Modifications

Dose modifications (including delays or early discontinuation of treatment) >3 consecutive days are not allowed. Photons are allowed for up to 3 days as a minor deviation.

PCG HQ must be notified within 72 hours of any dose modifications. See SPM for reporting instructions. Dose modifications and reason why must also be documented in the medical record and will be collected in the case report forms.

7.0 DRUG THERAPY

Concurrent chemotherapy is required and will be administered at the discretion of medical oncology per the treatment schedule guidelines suggested below.

Adjuvant chemotherapy is optional, but encouraged, and may be administered at the discretion of medical oncology. If given, adjuvant chemotherapy can be given prior to radiotherapy or after completion of concomitant chemoradiotherapy. Because of the abbreviated treatment course (as short as just 3 weeks for the radiotherapy), recommendations are for the patient to receive in total 4-5 cycles between the concurrent and adjuvant chemotherapy.

Adjuvant immunotherapy with durvalumab, pembrolizumab or nivolumab is allowed and may be administered at the discretion of medical oncology. Please record treatment information on the Follow-up eCRF.

7.1 Treatment Schedule (Chemotherapy)

Concurrent: **Options are:** paclitaxel at a dose of 45 mg/m^2 and carboplatin at a dose of AUC 2 mg/min/ml given as IV infusion (a total of 3-5 weekly doses) concurrent with radiation where 3 weekly doses constitute 1 cycle **or** cisplatin 50mg/m^2 days 1, 8, 29, and 36 and etoposide 50mg/m^2 days 1-5, 29-33 **or** for non-squamous histology, carboplatin AUC 5 on day 1 and pemetrexed 500 mg/m^2 on day 1 every 21 days or cisplatin 75 mg/m^2 on day 1 and pemetrexed 500 mg/m^2 on day 1 every 21 days. For the last week of proton treatment, concurrent last week chemotherapy may be held at the discretion of the treating physicians if proton treatment is less than 3 fractions.

Adjuvant: Adjuvant chemotherapy is optional but encouraged for 2 to 4 cycles. It will be given only at the discretion of the medical oncologist. If given, the following is suggested: paclitaxel at a dose of 175mg/m^2 followed by carboplatin at a dose of AUC 5 mg/min/ml as IV infusion; approximately every 3 weeks. Or cisplatin 50 mg/m^2 and etoposide 50 mg/m^2 approximately every 3 weeks for 2-4 cycles. Or carboplatin AUC 5 on day 1 and pemetrexed 500 mg/m^2 on day 1 every 21 days or cisplatin 75 mg/m^2 on day 1 and pemetrexed 500 mg/m^2 on day 1 every 21 days. **If given, adjuvant chemotherapy can be given prior to registration and, therefore, prior to concurrent chemotherapy and proton therapy or preferably to begin ≥ 4 weeks after completion of concomitant chemoradiotherapy.**

7.2 Supply (Chemotherapy)

Paraplatin (carboplatin), Taxol (paclitaxel), Platinol (cisplatin), and Vepesid (etoposide) are commercially available. Please see prescribing information/package insert for:

- Description
- Storage and Stability
- Administration
- Formulation and Preparation
- Toxicity

7.3 Supportive Medications

Patients will receive standard antiemetics at the discretion of the medical oncologist. Patients may receive the following suggested pre-medications prior to receiving paclitaxel:

- Dexamethasone 10-20 mg PO 12 and 6 hours before paclitaxel or per standard IV dosing
- Diphenhydramine 25-50 mg PO 30-60 minutes before paclitaxel or per standard IV dosing
- Cimetidine 300 mg IV or ranitidine 50 mg IV 30 to 60 minutes before paclitaxel

7.4 Dose Modifications

Dose modifications are at physician discretion. Dose modifications and reason(s) for modifications must also be documented in the medical record and will be collected in the case report forms.

7.5 Assessments

Assessments are at the discretion of the medical oncologist and are highly recommended. To include:

- Weight
- Toxicity assessment
- Performance status
- CBC with differential, CMP

8.0 SURGERY

If exploratory thoracotomy done, must be at least 3 weeks prior to study registration.

9.0 OTHER THERAPY

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

10.0 PATHOLOGY

Local review of pathology is highly recommended for all subjects enrolled into this trial.

11.0 DATA COLLECTION

Patients must be registered through the PCG Electronic Data Capture (EDC) system. All required study information will be entered and verified in the EDC system. Detailed guidelines for patient registration and electronic case report form (eCRF) completion can be found in the SPM and EDC Instructional Manual. Timelines for data submission must be followed closely in order to assure human subject safety.

The PI must make study data accessible to the Clinical Research Associate (CRA), to other authorized representatives of the Study Chair, and to the appropriate regulatory authority inspectors. The data in the EDC will be checked against source documents by the CRA.

The below are items expected to be present in the medical record for subjects enrolled in this protocol:

11.1 Pre-Treatment Data

- Consultation exam including weight, performance status and O_2 saturation.
- AJCC 7^{th} or 8^{th} Edition clinical stage
- Pathology report(s)
- Relevant lab work
- Relevant radiology scans/reports
- PFT results

11.2 On Treatment Data

- Acute toxicity (with scoring per CTCAE)
- Chemotherapy orders and infusion records

11.3 Dosimetric Data

- Radiation dose calculations
- Radiation treatment record
- Radiation isodose distribution
- Radiation localization imaging
- Planning CT scans

- Dose volume histograms
- Tumor location and measurements
- Verification Scan and Re-planning

11.4 Follow-up Data

- Exams including weight, performance status and O_2 saturation per follow-up schedule in patient assessment table
- Acute and late toxicity (with scoring per CTCAE)
- Disease status/Tumor measurements
- Radiological scans
- PFT results, if available

11.5 Failure Data

- Clinical exam including performance status, weight, and toxicity evaluation
- Type of failure: in-field, out-of-field, marginal miss or a combination
- Radiological scans
- Biopsy pathology results

11.6 Death certificate or autopsy report will be sought if applicable

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Endpoints

12.1.1 Primary Endpoints

- Phase I: Establish the maximum tolerated dose of radiotherapy in terms of Gy (RBE)/fraction using hypofractionated proton therapy concurrently with chemotherapy.
- Phase II: Determine the percentage of patients that survive at least 12 months.

12.1.2 Secondary Endpoints

- Assess acute and late adverse events of concurrent chemotherapy with hypofractionated proton therapy.
- Analyze for disease control and overall survival.

12.1.3 Exploratory Endpoints

- Evaluate the cost-effectiveness of the maximum tolerated dose (MTD).

12.2 Sample Size Derivation

For the phase I section of this trial, we will implement a 5+2 design as proposed by Ivanova (2006). The purpose of this phase is to determine the MTD that doesn't produce a radiation related dose-limiting toxicity (DLT) (acute grade 3 or higher esophageal or pulmonary toxicity possibly, probably or definitely related to radiation). This phase will have a minimum of 2 treated patients and we anticipate that the MTD will be located before a maximum of 28 patients are treated. The trial begins by treating up to 5 patients at 2.5 Gy (RBE)/fraction to a dose of 60 Gy (RBE). After up to 5 patients are treated, there are 3 possible scenarios in the next and successive steps:

Scenario 1) None of the initial 5 patients have a DLT. Escalate to the next higher dose and treat 5 more patients (3 Gy (RBE)/fraction then 3.53 Gy (RBE)/fraction then 4 Gy (RBE)/fraction).

Scenario 2) One of these 5 patients has a DLT. Treat 2 more patients at current dose. If a total of 1 of 7 patients experiences a DLT, then escalate to the next higher dose. If 2 or more of these 7 have a DLT, then this dose will be labeled as the

MTD. Treat a total of 7 at the lower dose. The ultimate goal is to find a dose where no more than 1 of 7 patients has a DLT.

Scenario 3) Two or more patients have a DLT. Halt dose escalation and treat 7 patients at the next lower dose. If no lower dose exists, the study will be stopped. Treat a total of 7 at the lower dose. The ultimate goal is to find a dose where no more than 1 of 7 patients has a DLT.

These three scenarios represent the first step. This step is repeated until the MTD is determined. Before escalating to a higher dose, the fifth patient should be 90 days post Day 1of RT.

This design gives at least 90% confidence that the true acute DLT rate at a given dose level is between 14% and 21% and for any given dose level, the probability of not escalating when the true toxicity rate is 40% or higher is at least 83%.

Phase II Sample Size

The phase II portion of the study can start enrolling patients once dose level 1 of the phase I portion of the study has successfully been completed. Patients will be offered treatment on the phase II portion of the study with any of the successfully completed dose levels from the phase I portion. Patients are eligible for phase II enrollment:

1) if phase I study is completed;
2) if phase I is closed while assessing 90 days of toxicity for dose levels 2, 3, or;
3) if dose constraints prevent enrollment on a higher dose level, but are acceptable for a lower dose level that has already safely completed assessment on the phase I study.

The historical control for this study is RTOG 9410, dose level 2, with 0.6233 proportions of patients surviving at least 12 months. Using a one-sided exact test for binomial proportion with $\alpha = 0.05$, a sample size of 58 gives 80% power to detect a 25% or greater relative increase, or an absolute increase of at least 0.1558, in the proportion of patients surviving at least 12 months (0.6233 versus 0.7791). Including all the patients enrolled on the phase I portion of this study means that an additional 27 to 58 will need to be accrued to the phase II portion. Allowing for 20% of the patients accrued to be ineligible or inevaluable, 70 patients total will need to be accrued to the phase II portion.

12.3 Patient Accrual and Study Duration

On average, between multiple participating sites, 3-6 patients a month are seen with stage II-III NSCLC. Allowing 6 months for RAC and IRB review and approval, accrual should be completed in approximately 39 months. We anticipate the trial will be open for 5 years after the 39 months of enrollment. However, we may extend the length of the study depending on the rate of enrollment.

12.4 Analysis Plan

Interim reports will be prepared for the PCG DSMB at least annually until the last subject has completed protocol treatment. In general, they will contain information about:

- Patient accrual rate with projected completion date of the trial.
- Status of compliance rate of required study treatment per protocol.
- Frequency/severity of G3-5 toxicities, rate of failures, and deaths.

12.5 Inclusion of Minorities and Women

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and/or gender with treatments. We project that 30% of patients in the study will be non-white and 30% will be women.

13.0 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

13.1 Adverse Events

An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation whether or not it is considered to be therapy related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the initiation of study treatment.

13.2 Grading of Adverse Events

The Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to grade the severity of adverse events. CTCAE version 4.0 will be utilized until June 30, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning July 1, 2018.

13.3 Documentation

All applicable data must be reviewed and confirmed by the PI or their designee for any G3-5 adverse events with the attribution of definite, possible, or probable relation to protocol therapy (radiation and/or chemotherapy).

13.4 Reporting Adverse Events

For the LUN005-12 protocol, only possibly, probably or definitely related (to either radiation and/or chemotherapy) adverse events will be collected. Refer to the SPM for additional information regarding collection and reporting of adverse events**.**

Please pay particular attention towards the following potential side effects:

- Radiation dermatitis
- Dysphagia, esophagitis, esophageal stenosis, nausea, vomiting, weight loss
- Cough, dyspnea, pain, pneumonitis, pulmonary fibrosis, bronchial stricture
- Secondary malignancy

13.5 Serious Adverse Events

Serious Adverse Events (SAE): An adverse event is considered serious if it results in any of the following:

- Death
- A life-threatening adverse experience
- A persistent or significant disability, incapacity, or is a congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization

The definition of serious adverse event also includes ‘important medical event’. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

13.6 Reporting Serious Adverse Events

13.6.1 SAE reporting is safety related, separate from and in addition to data management toxicity reporting requirements on the case report form. For the LUN005-12 study, investigators and other site personnel must report all SAEs within 1 business day of discovery of the event.

SAEs should be reported on an SAE Form via email to safety@pcgresearch.org. The SAE Form is available on the PCG website (http://pcgresearch.org, PCG Member Portal). If email is unavailable, a phone call to PCG Headquarters should be made to alert that an SAE Form will be forthcoming.

It is expected that all information may not be available at the time the initial SAE report is submitted. A follow-up report with complete information is expected within 10 business days of the initial report. As new information related to the SAE is made known to the investigator, the SAE report should be updated and resubmitted to PCG Headquarters. All de-identified supporting source documentation, if requested, must be emailed to the CRA at PCG Headquarters as soon as available. SAEs will also be recorded in the PCG Electronic Data Capture system. In addition to notifying PCG, the Investigator is responsible for reporting SAEs to the IRB per their requirements.

Additional information regarding adverse event collection is available in the SPM.

13.6.2 Adverse events must also be reported to the IRB as required per their policies. Copies of these reports will also be filed in the regulatory files for the study.

13.7 Early Stopping of Study Due to Adverse Events

It is expected that at most 20% of patients will experience grade 3 or higher radiation related adverse events. The study will not be continued if 40% or greater of patients experience a grade 3 or higher radiation related adverse event prior to any recurrence within 12 months of the start of treatment. Patients developing a grade 3 or higher radiation related adverse event following recurrence will be collected but will not count towards the early stopping of the study. The null hypothesis (H_0) is that the regimen is not safe versus the alternative hypothesis (H_A) that the regimen is safe. Let p denote the proportion of patients who have not experienced a adverse event by the end of year 1 among all analyzable patients. The hypotheses are therefore:

$$H_0: p \leq 0.40 \text{ vs. } H_A: p \geq 0.80$$

Based on the above hypotheses, the sample size was initially calculated with Fleming's One Sample Multiple Testing Procedure for Phase II Clinical Trials (1981), at a significance level of 0.05 and 80% statistical power. Using these criteria, a sample size of 9 would be needed to adequately assess adverse events. The sample size of 9 was adjusted for attrition or unanalyzable cases by 10%, and an additional case was added; a sample size of 10 patients would be required for adequate assessment of adverse events as it relates to stopping of the trial. Patient assessment for adverse events will be performed weekly during RT and at every follow-up visit. If a patient has indications of a adverse event as indicated in Section 13.5, the adverse event will be reported according to the criteria set forth in Section 13.6. Although a patient may have more than one reported adverse event during treatment, the patient will be counted only once as having the adverse event measurement of adverse event as it relates to early stopping of the study. The study will be discontinued if a total of 8 out of the first 10 patients recruited into the trial present with adverse events. By the same calculations, less than 32

patients out of the total of 61 patients included in the trial should present with adverse events during treatment.

14.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

This study will be conducted in full compliance with the Institutional Review Board regulations in 21 CFR 56. This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. Only staff members who have completed human subject protection training will obtain informed consent from the study participants.

Written informed consent and authorization of use and disclosure of PHI (as applicable in the U.S.) must be obtained from each patient before performing any Screening/Baseline evaluations that are specifically study related (outside the scope of routine care). One copy of the signed informed consent document and authorization will be given to the patient, and the investigative site will retain the original or a verified copy of the original. The consent document must contain the 20 elements of informed consent described in ICH E6 4.8. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations.

14.1 Study Data Storage and Confidentiality

If paper documents are collected, they should be stored in locked cabinets at all times when not in use. If electronic forms are used, they must be password protected. Electronic data will be in compliance with FDA CFR Title 21 Part 11.

No study documents will be destroyed or moved to a new location without prior written approval from the sponsor. If the site investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator or the institution where the study was conducted.

All information regarding the nature of the proposed investigation provided by the study chair to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating patients must be maintained. Patients will be identified by their initials and assigned patient numbers in CRFs (case report forms) and other documents submitted to the CRA. Documents that will not be submitted to the CRA and that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the CRA, or sponsor representatives.

14.2 Risk Benefit Assessment

By definition, this study is determined as greater than minimal risk. Patients treated in the protocol will have the potential benefit of treatment with state of the art technologies and medicines and thorough treatment quality assurance that is not available in common clinical practice. Furthermore, potentially the patient will benefit from treatment in two dose levels as the trial design is for equipoise. Thus, patients may benefit if the treatment is delivered regardless of the dose level. However, a data safety monitoring board will review the potential harmful effects of the treatment and stopping rules are in place in the protocol.

APPENDIX I

Performance Status

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100*).*

1 Restricted in physically strenuous activity but ambulatory and able to carry out 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 any self-care. Totally confined to bed or chair (Karnofsky 10-20).

5 Dead.

APPENDIX II

Staging System
AJCC, 7th Edition

LUNG STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Tis Carcinoma *in situ*	☐ Tis
☐ T1	Tumor ≤3 cm 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)*	☐ T1
☐ T1a	Tumor ≤2 cm in greatest dimension	☐ T1a
☐ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension	☐ T1b
☐ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	☐ T2
☐ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension	☐ T2a
☐ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension	☐ T2b
☐ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	☐ T3
☐ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe	☐ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	☐ N1
☐ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	☐ N2
☐ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	☐ N3
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1
☐ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**	☐ M1a
☐ M1b	Distant metastasis	☐ M1b
	**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where	

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LUNG STAGING FORM

these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
☐ Occult	TX	N0	M0	☐ Occult	TX	N0	M0
☐ 0	Tis	N0	M0	☐ 0	Tis	N0	M0
☐ IA	T1a	N0	M0	☐ IA	T1a	N0	M0
	T1b	N0	M0		T1b	N0	M0
☐ IB	T2a	N0	M0	☐ IB	T2a	N0	M0
☐ IIA	T2b	N0	M0	☐ IIA	T2b	N0	M0
	T1a	N1	M0		T1a	N1	M0
	T1b	N1	M0		T1b	N1	M0
	T2a	N1	M0		T2a	N1	M0
☐ IIB	T2b	N1	M0	☐ IIB	T2b	N1	M0
	T3	N0	M0		T3	N0	M0
☐ IIIA	T1a	N2	M0	☐ IIIA	T1a	N2	M0
	T1b	N2	M0		T1b	N2	M0
	T2a	N2	M0		T2a	N2	M0
	T2b	N2	M0		T2b	N2	M0
	T3	N1	M0		T3	N1	M0
	T3	N2	M0		T3	N2	M0
	T4	N0	M0		T4	N0	M0
	T4	N1	M0		T4	N1	M0
☐ IIIB	T1a	N3	M0	☐ IIIB	T1a	N3	M0
	T1b	N3	M0		T1b	N3	M0
	T2a	N3	M0		T2a	N3	M0
	T2b	N3	M0		T2b	N3	M0
	T3	N3	M0		T3	N3	M0
	T4	N2	M0		T4	N2	M0
	T4	N3	M0		T4	N3	M0
☐ IV	Any T	Any N	M1a	☐ IV	Any T	Any N	M1a
	Any T	Any N	M1b		Any T	Any N	M1b
☐ Stage unknown				☐ Stage unknown			

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Pleural/Elastic Layer Invasion (based on H&E and elastic stains)_____

Separate Tumor Nodules _____

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

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LUNG STAGING FORM

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
☐ 2 grade system	☐ Grade I or 1
☐ 3 grade system	☐ Grade II or 2
☐ 4 grade system	☐ Grade III or 3
☐ No 2, 3, or 4 grade system is available	☐ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ☐ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ☐ Lymph-Vascular Invasion Present/Identified
- ☐ Not Applicable
- ☐ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ☐ RX Presence of residual tumor cannot be assessed
- ☐ R0 No residual tumor
- ☐ R1 Microscopic residual tumor
- ☐ R2 Macroscopic residual tumor

General Notes (continued):

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

☐ Clinical stage was used in treatment planning (describe): _____

☐ National guidelines were used in treatment planning ☐ NCCN ☐ Other (describe): _____

_____

_____

Physician signature Date/Time

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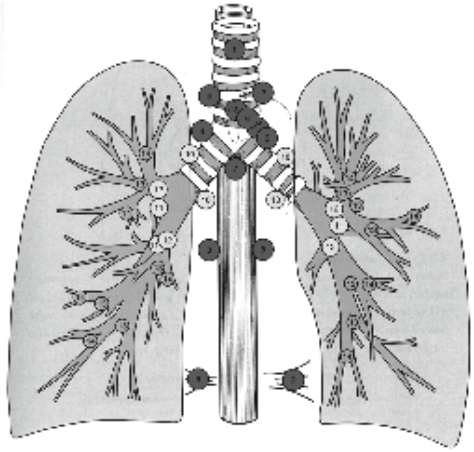
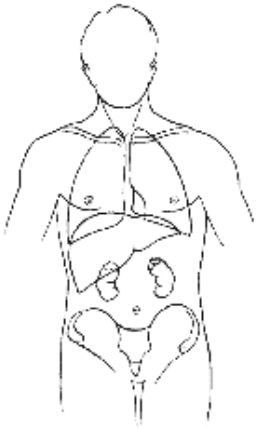
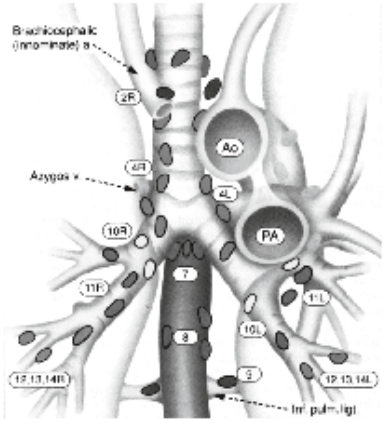
LUNG STAGING FORM

Illustration

(Top left) Indicate on diagram primary tumor and regional nodes involved. (From The Japan Lung Cancer Society. Classification of Lung Cancer. First English Edition. Tokyo: Kanehara & Co., 2000, used with permission.) (Top right) Indicate metastatic sites. (Bottom) See Chapter 25 of the *AJCC Cancer Staging Manual* for a description of the lymph node map of the lung. (From Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111: 1718–1723 used with permission.)







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AJCC, 8th Edition

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T)

T Category	T Criteria
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* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm 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)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension

T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

AJCC PROGNOSTIC STAGE GROUPS

When T is....	And N is...	And M is...	Then the Stage Group is...
Tx	N0	M0	Occult Carcinoma
Tis	N0	M0	0
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1a	N1	M0	IIB
T1a	N2	M0	IIIA
T1a	N3	M0	IIIB
T1b	N0	M0	IA2
T1b	N1	M0	IIB
T1b	N2	M0	IIIA
T1b	N3	M0	IIIB
T1c	N0	M0	IA3
T1c	N1	M0	IIB
T1c	N2	M0	IIIA
T1c	N3	M0	IIIB
T2a	N0	M0	IB
T2a	N1	M0	IIB
T2a	N2	M0	IIIA
T2a	N3	M0	IIIB
T2b	N0	M0	IIA
T2b	N1	M0	IIB
T2b	N2	M0	IIIA
T2b	N3	M0	IIIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T3	N2	M0	IIIB
T3	N3	M0	IIIC
T4	N0	M0	IIIA
T4	N1	M0	IIIA
T4	N2	M0	IIIB
T4	N3	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVA
Any T	Any N	M1c	IVB

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