The University of Texas
M. D. Anderson Cancer Center

A Bayesian randomized trial of Image-Guided Adaptive Conformal Photon vs Proton Therapy, with Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence

Note: This protocol is intended for multi-institutional enrollment at Masachusetts General Hospital and MD Anderson Cancer Center as a part of and NCI-funded P01 Program Project entitled "Optimizing Proton Therapy." The **Overall PI** of the P01 is Dr. Thomas Delaney of MGH and the **Overall PI** of the sub-contract at MD Anderson Cancer Center is Dr. Radhe Mohan. The leading institution for this protocol is MD Anderson Cancer Center.

1.0 Background

1.1 Background

Lung cancer is the second most common form of cancer in most western countries and the leading cause of cancer death worldwide. For locally advanced (stage II-IIIB) non-small cell lung cancer (NSCLC), the current treatment of choice is concurrent chemotherapy and conformal photon radiotherapy (XRT) (1). However, the effectiveness of concurrent chemoradiation remains modest because of treatment-related pneumonitis (TRP), an acute, dose-limiting toxic effect of chemoradiation for NSCLC that limits the delivery of tumoricidal doses and thus can result in high rates of local and distant failure.

TRP is mediated by the induction of proinflammatory cytokines in response to radiation damage of lung tissue (2). Most such cytokines, including tumor necrosis fac-tor alpha (TNF-α), the interleukin (IL)-1 family, and IL-6, are pro-duced within the treatment field and can evoke autocrine, paracrine, or endocrine responses (3).

The diagnosis of TRP, which typically becomes apparent 3-9 months after Radiotherapy (RT), is established by a history of RT, radiographic evidence (areas of ground-glass opacity and/or consolidation in the irradiated lungs that conform to the shape and size of the treatment portals (4)) and clinical presentation (most often dry cough, low-grade fever, chest pain, and shortness of breath) as well as ipsilateral pleural effusion and consolidation of the lung. Untreated TRP eventually advances to lung fibrosis, leading to loss of lung volume and poor pulmonary function, which negatively affect quality of life (5). Treatment for TRP is largely empirical and nonspecific, consisting of oral or intravenous steroids, oxygen, and sometimes assisted ventilation. Currently, the most effective way to reduce TRP is by avoidance and prevention through the use of biophysical risk assessment and reduction.

TRP is directly linked with radiation dose and the volume of the irradiated tissue. In clinical practice, the total radiation dose that can be tolerated depends on the volume of tissue irradiated. Indeed, preclinical and clinical studies have shown that morbidity from TRP depends on the volume (6-7) and region of the normal lung irradiated (8-10). Dosimetric factors such as mean lung dose (MLD) (11) and percentage of lung volume receiving more than a threshold dose (Vdose) (11-13) are also well-known predictive factors for TRP. We recently demonstrated in a retrospective analysis that the actuarial incidence of grade $\geq$3 TRP in patients with locally advanced NSCLC receiving 3-dimensional conformal radiotherapy (3D-CRT) and concurrent chemotherapy was 22% at 6 months and 32% at 1 year. In univariate analyses, the MLD, relative V5 (rV5), and V25-V55 were significantly associated with grade $\geq$ 3 TRP. In multivariate analyses, rV5 was highly predictive of grade $\geq$ 3 TRP, with 1-year actuarial rates of 3% for those with rV5 $\leq$ 42% and 38% for those with rV5 > 42% (P = 0.001) (10).

1.1.1 Intensity-modulated radiation therapy

Techniques that reduce radiation dose and volume to the normal lung can reduce the incidence of TRP. One such technique, intensity-modulated RT (IMRT), can increase conformality and provide greater sparing of normal tissues that traditional 3D-CRT (14). Murshed et al. (15) reported that using IMRT led to median absolute reductions in V10 of 7% and V20 of 10%. This corresponded to a decrease of > 2 Gy in the total MLD and 10% in the risk of TRP. Using the parameters described by Murshed in predictive models (16-17), we estimated that the median risk of TRP would decrease from 13%-36% with the 3D-CRT plans to 7%-9% with the IMRT plans, a statistically significant reduction.

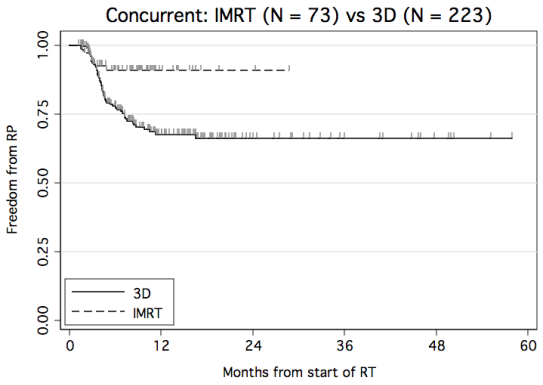


Figure 1. Incidence of treatment-related pneumonitis in patients with NSCLC treated with 3D-CRT or IMRT and concurrent chemotherapy.

In our own use of IMRT with concurrent chemotherapy for the definitive treatment of advanced NSCLC (15,18),

we found significant reductions in the rates of grade ≥ 3 TRP (8% for IMRT vs 29% for 3D-CRT); at 1 year, the corresponding rates were 9% vs 33% (*P*=0.028) (Fig 1). These reductions were due to significant reductions in irradiated volumes of and doses to normal tissue (mean dose to normal lung was 16.6 Gy [range, 2.5–28.5] for IMRT and 22.1 Gy [range, 1.0–38.9] for 3D-CRT). IMRT also led to significant decreases in median irradiated volumes at several dose levels, including V15–V65 (*P* < 0.0001). However, V5, V10, and V70 were no different between the two techniques, suggesting that IMRT is of limited benefit in terms of minimizing lung exposure to low-dose radiation (19).

1.1.2 Concerns about low-dose exposure with IMRT

As noted above, efforts to use IMRT for lung cancer have been limited by serious concerns about potential increases in the volume of lung irradiated to low doses, especially V5 (15) or rV5 (10). Analyses of a subgroup of patients with an rV5 > 70% suggested that higher rV5 levels are associated with increased risk of severe pulmonary toxicity, confirming our 3D-CRT experience that rV5, in addition to other higher-dose factors, is a parameter that needs to be controlled (10).

Other clinical studies also support the concept that low-dose radiation to large volumes of lung can increase the risk of toxicity. Loss of the diffusing capacity for carbon monoxide was observed in lungs exposed to as little as 13 Gy (20), and the risk of complications in another study rose steeply above an MLD of 10 Gy (21). For patients already at risk of pulmonary complications because of large tumor volumes requiring extensive coverage or medical conditions that compromise respiratory function, irradiating a large volume of lung poses a concern that cannot be addressed with the use of photon irradiation.

1.1.3 Proton-beam therapy

Findings from simulation and planning studies suggest that use of proton beams (rather than photon beams) can reduce the radiation dose to and volume of normal tissue, including low-dose volumes. This is of particular interest in the treatment of lung cancer, as proton therapy would reduce the volume of lung irradiated to a low dose, whereas IMRT involves a greater volume of the lung in low-dose regions if more than five beam angles are used.

In our planning study comparing IMRT and proton therapy (22,23), we found that proton therapy spared 15%–17% of total lung and 19%–23% of contralateral lung from receiving 5 Gy compared with IMRT, a difference that could greatly reduce lung toxicity. Photon therapy at a prescribed dose of 63 Gy led to a mean total lung dose of 20.1 Gy, with V5, V10, and V20 values of 58.5%, 45.3%, and 34.5%; the corresponding values for proton therapy at a prescribed dose of 63 cobalt Gray equivalent (CGE) were 17.5 Gy, 43.1%, 37%, and 30.8% (*P* = 0.002), and those for proton therapy with dose escalation to 74 CGE were 21.2 Gy, 44%, 39.3%, and 33.2%. Low-dose exposure (i.e., V5) in the contralateral lung from photon therapy was 45.5% at 63 Gy and 49.7% at 74 Gy; with proton therapy, those values were reduced to 26.6% at 63 CGE and 27.1% at 74 CGEProton therapy also led to reductions in mean whole-body nontarget integral dose: with photon therapy, the doses were 6.8 Gy at 63 Gy and 8.1 Gy at 74 Gy, but with photon therapy they were only 4.5 Gy at 63 Gy and 5.4 Gy at 74 Gy, a 33% absolute improvement. Even in patients with contralateral hilar disease, proton therapy significantly reduced low-dose exposures of contralateral lung (V5 25%) relative to IMRT (V5 45%). Doses to heart V40, spinal cord, and esophagus V55 were also reduced. These findings indicate that even in extreme cases that pose challenges for proton planning, proton therapy still achieved a better dose-volume histogram than did IMRT (22,23).

Preliminary findings from a clinical study of 25 consecutive patients with NSCCL who underwent proton-beam radiation and concurrent chemotherapy showed that even with a higher median radiation dose (74 CGE vs 63 Gy with XT), proton-beam therapy permitted higher total doses (17%+) to be given with concurrent chemotherapy yet were associated with reduced esophageal reactions compared with 3D-CRT (24). Moreover, no increase in the incidence of TRP has been noted.

1.2 Rationale and Hypothesis for the Proposed Trial

On the basis of the evidence reviewed here, we believe that the incidence of TRP can be minimized by using proton-beam therapy. Indeed, no randomized clinical trials have compared standard photon and proton radiation in terms of the development of TRP.

We hypothesize that proton therapy will expose significantly smaller lung volumes to damaging dose levels and spare larger volumes of normal tissue than does photon therapy without compromising local regional tumor control.

Specifically, we propose that image-guided adaptive proton therapy (IGAPT) will lead to lower rates of TRP and equivalent tumor control compared with image-guided adaptive photon therapy (IGAXT) for patients with stage II-IIIB NSCLC who are receiving concurrent chemotherapy. The primary objectives of this Bayesian adaptive randomization trial are to compare time to the appearance of (1) grade 3 pneumonitis (according to the NCI Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) and (2) locoregional recurrence among patients given 74 Gy in 37 fractions (2 Gy each) of protons vs. photons.

This clinical trial will be the first Bayesian randomization trial to compare IGAXT and IGAPT in patients with locally advanced, surgically unresectable NSCLC. Patients who are candidates for concurrent chemoradiation will be randomly assigned to undergo either standard IGAXT or IGAPT to 74 Gy in 37 fractions of 2 Gy each. Adaptive randomization will be used so that more patients can be offered the treatment that is found to be more effective.

We will also collect positron emission tomography (PET) images and blood samples and document comorbidity and symptoms by using validated test instruments for correlative and translation research. Inflammatory cytokines and genomic DNA will be extracted from the serum and lymphcytes to analyze tha correlations of these biomarker and TRP after the completion of the study.

2.0 Objectives

2.1 Primary Objective

2.1.1 Assess and compare the incidence and time to development of CTCAE v3.0 grade $\geq$ 3 TRP or local failure, whichever comes first, among patients with locally advanced (stage II-IIIb and selected stage IV) non-small cell lung cancer (NSCLC) treated with image-guided adaptive photon therapy (IGAXT, Group 1) or proton therapy (IGAPT, Group 2) using Bayesian randomization.

2.2 Secondary Objectives

2.2.1 Assess and compare the incidence and time to development of CTCAE v3.0 grade $\geq$ 3 radiation esophagitis in treatment Groups 1 and 2.

2.2.2 Investigate the association of inflammatory cytokines with the incidence and time to development of TRP and outcomes in treatment Groups 1 and 2.

2.2.3 Investigate the association of relevant pharmacogenetic markers, biomarkers, and gene polymorphisms with the time to development of TRP and treatment outcomes in treatment Groups 1 and 2. Serum of the blood samples will be transferred to collaborating laboratories at The Methodist Research Institute for analysis of specific biomarkers. All material transfer will follow institutional policy and all transferred material will be de-identified.

2.2.3.1 For the proposed research, we will use a rapid and high-throughput nanopore-based array to enrich low molecular weight (LMW) proteins to identify circulating LMW peptide markers in blood samples from patients with or without NSCLC. By optimizing the nanotexture of silica films through the engineering of the physicochemical properties (e.g., pore size, pore structure, surface affinity) on the nanoporous silica chip, we can selectively enrich low-abundance, LMW

peptides from serum samples. We will process the samples on nanoporous silica chips for LMW protein fractionation, and analyze the isolated fractions by MALDI-TOF mass spectrometry and principal component analysis. LMW peptide signatures associated with lung cancer will be identified by LC-MS/MS.

2.2.4 Evaluate IGAXT using weekly computed tomography (CT) in the assessment of tumor response and impact on treatment planning and delivery.

2.2.5 Compare overall survival, progression-free survival, and median survival time in treatment Groups 1 and 2.

2.2.6 Evaluate the role of functional imaging with FDG-PET in assessing and predicting the time to the development of TRP and tumor response.

2.2.7 Document and compare symptom burden weekly during treatment, monthly up to 6 month after the treatment, and at each follow-up visit by using the M. D. Anderson Symptom Inventory for Lung (MDASI-Lung) in treatment Groups 1 and 2.

2.2.8 For Group 3 and Group 4 patients who are treated with protons or photons depending on higher dose achievable, compare the local control, overall survival, progression-free survival, median survival and toxicities of protons vs. photons (see Section 7.5).

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Pathologically proven, unresected, locoregionally advanced NSCLC without evidence of hematogenous metastases (stage II-IIIB disease according to the 7th edition of the AJCC Staging Manual) with exception as defined by inclusion #2.

3.1.2 Patients with solitary brain metastasis without sign of progression in the brain at the time of registration will be eligible for this trial if there is clinical indication for concurrent chemoradiation to the primary disease in the lung.

3.1.3 Suitability for concurrent chemoradiation therapy per treating radiation oncologist or treating medical oncologist's assessment:

3.1.3.1 Karnofsky performance score of $\geq$ 70, or ECOG 0-1

3.1.3.2 Unintentional weight loss $\leq$ 10% during the 3 months before study entry.

3.1.4 Receipt of induction chemotherapy followed by referral for concurrent chemoradiation is allowed for this protocol.

3.1.5 Measurable disease on chest x-ray, contrast-enhanced CT, or PET scan.

3.1.6 Locoregional recurrence after surgical resection, if suitable for definitive concurrent chemoradiation, is allowed for this protocol.

3.1.7 Forced expiratory volume in the first second (FEV1) ≥ 1 liters.

3.1.8 Fluorodeoxyglucose (FDG) -PET scan within 3 months before registration.
The pretreatment (diagnostic) PET/CT should, whenever possible, be performed together with the 4-D CT simulation. PET images acquired either at the time of simulation or acquired separately should be registered with the planning CT to assist in tumor delineation.

3.1.9 Standard pretreatment evaluations (as decided by treating radiation oncologist, medical oncologist, surgeons or pulmonalogist), to include MRI or CT scan of the brain, Whole-body PET/CT, contrast CT scan of the thorax and upper abdomen, pulmonary function tests, lung and cardiac single proton emission computed tomography (SPECT), liver function tests (LFT), blood chemistry, renal function tests, and complete blood count.

3.1.10 Age≥18 years but ≤ 85 years.

3.1.11 A signed specific informed consent form before study entry.

3.2 Exclusion Criteria

3.2.1 Small cell histology.

3.2.2 Prior thoracic radiotherapy to regions that would result in overlap of radiation therapy fields.

3.2.3 Pregnancy (female patients of childbearing potential must practice appropriate contraception).

3.2.4 Enrollment in a clinical trial that specifically excludes IGAPT treatment.

3.2.5 Body weight exceeds the weight limit of the treatment couch.

3.2.6 Oxygen dependent due to preexistent lung disease (COPD, emphysema, lung fibrosis).

4.0 Pretreatment Evaluations

4.1 Complete History and Physical Examination, including documentation of history of smoking, COPD, cardiac disease, performance status, weight loss

4.2 Laboratory and Radiographic Tests

4.2.1 Laboratory Studies and routine blood test (to be obtained within 8 weeks before study entry, at the direction of the treating medical oncologist or radiation oncologist):

4.2.1.1 CBC, diff, platelets, and ACE (angiotensin converting enzyme).

4.2.1.2 SMA-12 (serum creatinine, electrolytes, aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, inorganic phosphorous, calcium, blood urea nitrogen [BUN], magnesium) within +/-50% of the normal reference ranges as specified by each participating institution.

4.2.1.3 Calculated creatinine clearance according to participating institutions' standard (optional)

4.2.2 Imaging Studies (to be obtained within 8 weeks except for the whole body PET which may be completed within 3 months before registration).

4.2.2.1 Required Images:

4.2.2.1.1 Whole-body PET/CT

4.2.2.1.2 Brain scan (MRI is preferred, but CT is acceptable)

4.2.2.2 Optional Images:

4.2.2.2.1 CT scans of the chest and abdomen, with or without contrast (MRIs are acceptable)

4.2.2.2.2 Cardiac SPECT for patients with lower lung tumor

4.2.2.2.3 Lung SPECT if FEV1≤1.4 liters

4.2.2.2.4 Chest X-ray
4.2.2.2.5 Bone scan is optional if PET scan is done

4.2.3 Pulmonary function tests including DLCO

4.2.4 Pregnancy blood test for female patients at risk of pregnancy

4.2.5 Documentation of T and N stages according to AJCC staging manual 7th Edtion.

5.0 Evaluation During Study/Post Treatment

5.1 Weekly blood (about 1 teaspoon) will be drawn for routine tests, ACE (angiotensin converting enzyme) will be drawn once during concurrent chemoradiation and at the first follow-up visit after treatment.

5.2 Weekly CT scan as clinically indicated

5.3 Patients will be clinically evaluated by a treating physician (a radiation oncologist or medical oncologist) at least once a week during the chemoradiation; toxicity will be evaluated and MDASI-Lung scores will be obtained as part of those evaluations.

5.4 Patients will be seen by a radiation or medical oncologist for the first follow-up visit at 4–8 weeks after completion of the treatment, then every 3–4 months for 3 years, then every 6 months for to the next 2 years, and then annually thereafter.

5.5 PET/CT scanning will be performed at week 4-5 during the treatment, and 4- to 8-week follow-up visit as medically indicated for disease restaging after completion of the chemoradiation treatment.

5.6 Repeat cardiac and lung SPECT will be obtained at first follow-up and at 6 months after completion of chemoradiation as medically indicated.

5.7 Repeat pulmonary function tests will be obtained at each follow-up visit as medically indicated.

5.8 Additional Optional Tests

5.8.1 Blood samples, obtained periodically (baseline, week 1 or 2 of treatment, week 3 or 4 of treatment, week 6 or 7 of treatment, and 1st follow up after treatment) , for translational research (see appendix E for details).

5.8.2 M. D. Anderson Symptom Inventory (MDASI)-Lung

6.0 Schema

6.1 Study Schedule

Procedure	Before CRT	Week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9-35	1-2 months post-TX	Follow-ups 3- 6 months
Physical Exams	x	x	x	x	x	x	x	x	x		x	x
Staging & re staging work up	x										x	x
Routine blood work	x	x	x	x	x	x	x	x			x	x
PET/CT	x				x[f]						x[f]	x[f]
Brain scan (MRI is preferred, but CT is acceptable)	x											
PFTs	x										x	x[c]
Bone Scan	X[c]											
Chest x-ray	X[c]											
SPECT[c]	x[c]										x[c]	x[c]
Informed consent	x											
4-D CT simulation	x											
[a]3-D/IMRT CRT plan	x											
[b] Radiation therapy		xxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xx			
Chemotherapy		x	x	x	x	x	x	x				
[c] Weekly CT		x	x	x	x	x	x	x				
[d] Toxicity evaluation		x	x	x	x	x	x	x	x	x	x	x
[e] MDASI-Lung	x	x	x	x	x	x	x	x	x	x	x	x
[g]GQL	x								x		x	
[h]Optional blood draw	x	x	x	x	x		x	x			x	x

a. Modification of the treatment plan will be performed if repeat 4D CT simulation shows significant change of the target volume or patient anatomy.
b. Radiation dose prescription will be according to the strategy specified in Section 7.5 and delivered in 2 CGE per fraction
c. Clinically indicated.
d. The patient will be contacted monthly +/- 2 weeks to report their symptoms of treatment related toxicity. The methods of contacting patients include but not limited to clinic visit, phone calls, Emails, or letters. If deemed necessary, patient will come to the clinic to be evaluated in addition to their regular follow-up.
e. MDASI-Lung Chemoradiation will be administered before, weekly during chemoradiation and after chemoradiation until 16 weeks, and then every other week until 6 months
f. PET/CT could be done during 4th or 5th week during treatment, and 1st and/or 2nd follow-up after treatment according to treating physician's judgment.
g. GQL will be administered at baseline, at the end of chemoradiation treatment, and at the first follow-up clinic visit.
h. Five times throughout the whole protocol process: baseline, week 1 or 2 of treatment, week 3 or 4 of treatment, week 6 or 7 of treatment, and at a follow up after treatment.

7.0 Radiotherapy

(Note: All procedures specified in this section will be performed by or under the direction of the treating radiation oncologist)

7.1 Definition of Target Volumes

GTV Gross tumor volume is all known gross disease as demonstrated on the planning CT, and modified as deemed necessary based on PET and other clinical studies.

iGTV GTV plus margin for tumor motion. A structure will be created equal to the union of the GTV on all respiratory correlated images this will be referred to as the iGTV. This may be created by auto propagation of the GTV from a reference phase to other phases or by directly contouring on a maximum intensity projection (MIP) dataset. The delineated iGTV will be compared with the actual position of the GTV on each of the respiratory correlated CTs and modified, if necessary, to encompass the extent of motion of the GTV (hence iGTV). The iGTV may also be modified as deemed necessary based on PET and other clinical studies that may better distinguish the true GTV from other near unit density tissues.

CTV Clinical target volume is the subclinical involvement around the GTV. The CTV is the GTV plus an 8-mm margin for microextensions of the tumor (CTV=GTV+8 mm).

ITV Internal target volume is the envelope of the CTV during the time of irradiation, thus accounting for intrafractional motion. In this study, the ITV will be created by expanding the iGTV by 8 mm to include subclinical microscopic disease; this volume will be reviewed and edited if necessary based on clinical experience, as is our current clinical practice standard.

PTV Planning target volume is ITV plus a margin to ensure that the prescribed dose is actually delivered to the ITV. This margin accounts for variations in treatment delivery, including variations in setup between treatments. The ITV is expanded by 5 mm to generate the PTV in accordance with our current clinical practice. The PTV is relevant to photon planning.

7.2 Radiation Doses

7.2.1 The total radiation dose for the tumor target will be according to the specification in section 7.5 and delivered at 2 CGE per fraction, once a day, 5 fractions per week. 100% of the ITV will be covered by the prescribed dose. Greater than or equal to 95% of the prescribed dose to the ITV will be acceptable if 100% cannot be reached.

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. For passively scattered proton therapy (PSPT), the PTV is assumed to be beam-specific PTV (see section 7.4.2.4).

7.2.3 Deviations from dose prescription for target volumes:

7.2.3.1 No deviation: ≥ 99% of the PTV receives ≥ 95% of the prescribed dose, and a contiguous volume of no more than 2 cc inside PTV exceeds 120% 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 140% of the prescribed dose at the discretion of the attending physician.

7.2.3.3 Treatment interruptions: Interruption of radiation therapy up to 5 consecutive fractions for any reason will be considered as minor deviation.

7.2.4 Tolerance Limits for Critical Structures **(See Table 3b**)
Note: if any portion of a critical structure is part of the planning target volume (PTV), the treating physician should make the decision based on medical necessity on the maximal radiation dose to that portion of the critical structure to ensure adequate tumor dose.

7.2.4.1 Normal lung (right lung + left lung - GTV): V20 ≤ 37%; and mean lung dose (MLD) ≤ 20CGE. MLD of ≤ 22 CGE or V20 up to 40% will be acceptable as minor deviations.

7.2.4.2 Esophagus: 33% volume must be ≤ 65 CGE, 66% ≤ 55 CGE and whole volume mean dose ≤ 45 CGE.

7.2.4.3 Brachial Plexus: V66≤3.0 cc, V70≤ 2.0 cc, V74≤ 1.0 cc, V75≤ 0.5 cc. For superior sulcus tumor or upper lobe tumors where the brachial plexus is part of the target volume, the involved segment should be excluded from the contour of the normal brachial plexus.

7.2.4.4 Spinal cord: Maximum dose to 2cc highest dose volume ≤ 50 CGE.

7.2.4.5 Heart: The mean dose to the whole heart should be ≤33CGE. V70 ≤ 45% and V45≤ 70**%.** Dose constraints to atria and ventrical of the heart is specified in table 3b.

7.2.4.6 Liver: V50 ≤ 35% and the whole liver must be ≤ 25 CGE.

7.2.5 Major deviation: Doses outside the limits of the minor deviation for target volumes and exceeding normal tissue tolerance limits or greater than the limit of minor deviation (where indicated) will be considered major deviations and not acceptable.

Interruption of radiation therapy more than 5 consecutive fractions for any reason will be considered as major deviation.

7.2.6 Dose reporting: The digital dose distribution data to be reported includes the complete treatment plan. Its components include patient images, 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. In addition summary data shown in Table 3 will be reported for the purposes assessing compliance with protocol and for searching the data base.

Note: Vx is defined as the total lung volume receiving a dose of 2x CGE or more

- For superior sulcus tumor or upper lobe tumors where the brachial plexus is part of the target volume, the involved segment should be excluded from the volume of the normal brachial plexus AOR.
- if any portion of a critical structure is part of the planning target volume (PTV), the treating physician should make the decision on the maximal radiation dose to that portion of the critical structure to ensure adequate tumor dose.

Table 3a. Target Dose Specifications and Dosimetric Data to be Reported

All volumes will be reported in units of cubic centimeters. All doses will be reported in units of CGE. All DVH data will be reported in increments of 0.2 CGE. Generally, the expectation is that the cumulative DVH will be used for analysis. The "actual" columns will be populated by automatically extracting data from plans.

Target

	Specification						Actual			
	Prescription (CGE)	Fraction size	No Deviation		Minor Deviation		Dose received by the specified volume			
							95%	99%	110	120%
PTV (Note 1)	74/66 CGE (see Sec. 7.5)	2 CGE	≥ 99% volume receives ≥ 95% of prescription	No more than 2 cc receives ≥ 110% of prescription	≥ 95% volume receives ≥ 95% of prescription	No more than 2 cc receives ≥ 120% of prescription				
							Tumor motion data (see note 2)			

Notes
1. For protons, this represents beam-specific PTV.
2. GTV motion in cm as assessed from 4D CT: dX, dY, dZ, vector magnitude; Respiratory gating used: (Y/N); Breath-hold used: (Y/N).

Table 3b. Critical Structure Dose Specifications and Dosimetric Data to be Reported

All volumes will be reported in units of cubic centimeters. All doses will be reported in units of CGE. All DVH data will be reported in increments of 0.2 CGE. Generally, the expectation is that the cumulative DVH will be used for analysis. The "actual" columns will be populated by automatically extracting data from plans.

	Constraints	Minor Deviation	End Point	Actual
Normal lung (right lung + left lung - GTV)	V20 ≤ 37%; MLD ≤ 20CGE Total Lung Volume = total lung - GTV	V20 ≤ 40 % or MLD ≤ 22 CGE	Clinical pneumonitis	V5; V10; V25; V50; MLD
Esophagus	V45≤ 100% V55≤ 66% V65≤ 33% V70≤ 10% V75≤ 5% V78≤ 1.0 cc	Not Permitted	Clinical stricture and perforation	Minimum dose to 1/3, 2/3 and whole volume
Brachial Plexus*	V66 ≤ 3.0 cc V70 ≤ 2.0 cc V74 ≤ 1.0 cc V75 ≤ 0.5 cc	Not Permitted	Clinically manifested nerve damage	Maximum dose
Spinal cord	V 50 ≤ 2cc.	Not Permitted	Myelitis	Maximum dose
Heart	MHD ≤ 30 Gy V33 ≤ 100% V45 ≤ 70% V60 ≤ 35% Atria Ventricle V30 ≤100% ≤ 70% V40 ≤70% ≤ 40% V50 ≤ 50% ≤20% V60 ≤ 30% ≤ 5% V65 ≤15% ≤ 3% V74 <2% 0%	Not Permitted	Clinical pericarditis	Minimum dose to 1/3, 2/3 and whole volume
Liver	V25≤ 100% V35≤ 50%	Not Permitted	Clinical Hepatitis	Minimum dose to 1/2 and whole volume

1

Note: Vx is defined as the total lung volume receiving a dose of 2x CGE or more

- For superior sulcus tumor or upper lobe tumors where the brachial plexus is part of the target volume, the involved segment should be excluded from the volume of the normal brachial plexus AOR.
- if any portion of a critical structure is part of the planning target volume (PTV), the treating physician should make the decision on the maximal radiation dose to that portion of the critical structure to ensure adequate tumor dose.

7.3 Simulation, Immobilization, Image-Guided Radiation

7.3.1 Simulation: All simulations will be done on CT scanners capable of acquiring 4D CT image data sets.

7.3.1.1 For proton planning, only CTs which have been calibrated for protons should be used.

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

7.3.1.3 The imaging session will consist of acquisition of CT image data sets. These may include 4D CT, free breathing CT, and/or breath hold CTs.

7.3.1.4 The pretreatment diagnostic PET/CT should be performed together with 4-D CT simulation if at all possible.

7.3.2 Localization image studies with the patient in the treatment position will be obtained at the time of treatment.

7.3.3 Image-guided adaptation

7.3.3.1 Patients will be treated only on units with image guided capabilities. Such units include ones with on-board imaging, CT-on-rails, or other dedicated patient positioning image systems, e.g. those associated with the proton delivery system.

7.3.3.2 In addition to the CT data sets obtained for planning of treatments, CT scans will be obtained at least in weeks 2, 3, 4 and 7 from the start of the treatments. Optionally, additional CTs may be acquired in weeks 1, 5 and 6.

7.3.3.3 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 or their designee. 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. Target and normal tissue dose constraints and the limits of minor deviations are given in Table 3.

7.3.3.4 Composite dose distribution received by the patient over the course of radiotherapy will be computed. Such computations are necessary mainly to correlate dose distributions with response. They need to be performed only at the time of outcomes analyses. They involve, for each patient, computation for

dose distributions for each of ten phases of the respiratory cycle. These will be deformed to a reference phase (typically the end-exhale phase) and averaged. Such calculations will be performed for each of the CT scans acquired over the course of RT. All these dose distributions will be deformed to the reference phase of the initial 4D CT and averaged.

7.3.3.5 Patients randomized to be in proton therapy arm may receive up to five fractions with photons in the event the proton machine is not available.

7.4 Treatment Planning

7.4.1 Critical structures

7.4.1.1 The normal tissues including the right lung, the left lung, the esophagus, the heart, liver, brachial plexus, and the spinal cord need to be contoured in their entire region included in the simulation images.

7.4.1.2 The lungs are expected to be the primary dose-limiting structure and basis for randomization. Every effort should be made to keep the total lung dose (defined as the volume of both lungs minus the GTV in the appropriate respiratory correlated CT image, the mid-ventilation phase of 4-D CT for ITV based treatments or the mid position of gated planning CTs for gated treatments) to a minimum.

7.4.1.3 The tolerance doses to various organs shown in Table 3b above are to be used as guidelines. The treating radiation oncologist/dosimetrists should make every effort not to exceed these tolerance levels. (All tolerance doses are assumed to be delivered at 2 CGE/fx.)

7.4.2 IGAXT and IGAPT planning

7.4.2.1 All patients on this protocol will have one or more treatment plan(s) created for treatment with photons and one or more plan(s) created for treatment with protons to assess eligibility for randomization.

7.4.2.2 This protocol does not mandate any specific field arrangement to be used. In photon planning, the PTV is to be treated with any combination of coplanar or noncoplanar 3D conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D or inverse IMRT planning to produce the optimal conformal plan in accordance with volume definitions.

7.4.2.3 Tumor Motion Management: If the centroid of the GTV is determined to move more than +/-0.5 cm, additional motion assessment tests will be performed either in the same simulation session or additional simulaiton sessions when the treatment plan is evaluated to determine if the limits of deviations for target coverage specified in Table 3 are exceeded. The final decision on the use of any particular motion management strategies, such as gating, breath-hold, or the ITV approach, will depend on patient's physical condition, level of irregular breathing, ability/inability to hold breath, and/or the availability of respiratory gating at the treatment unit etc., at the discretion of treating radiation oncologist.

7.4.2.4 Definition of B-PTV (beam specific PTV) and treatment planning for IGAPT: For proton planning, each beam has an individual and unique PTV expansion from the ITV. In the plane perpendicular to the proton

beam axis, the PTV expansion from the ITV is consistent with the method used for photons. However, along the direction parallel with the proton beam axis, the PTV expansion from the ITV distal margin and proximal margins, which are computed using established algorithms based on range uncertainty of the beam.

7.4.2.5 Treatment planning parameters including distal and proximal margins, block margin and smearing radius will be calculated based on published formulae, modified locally and adopted as standard of practice.

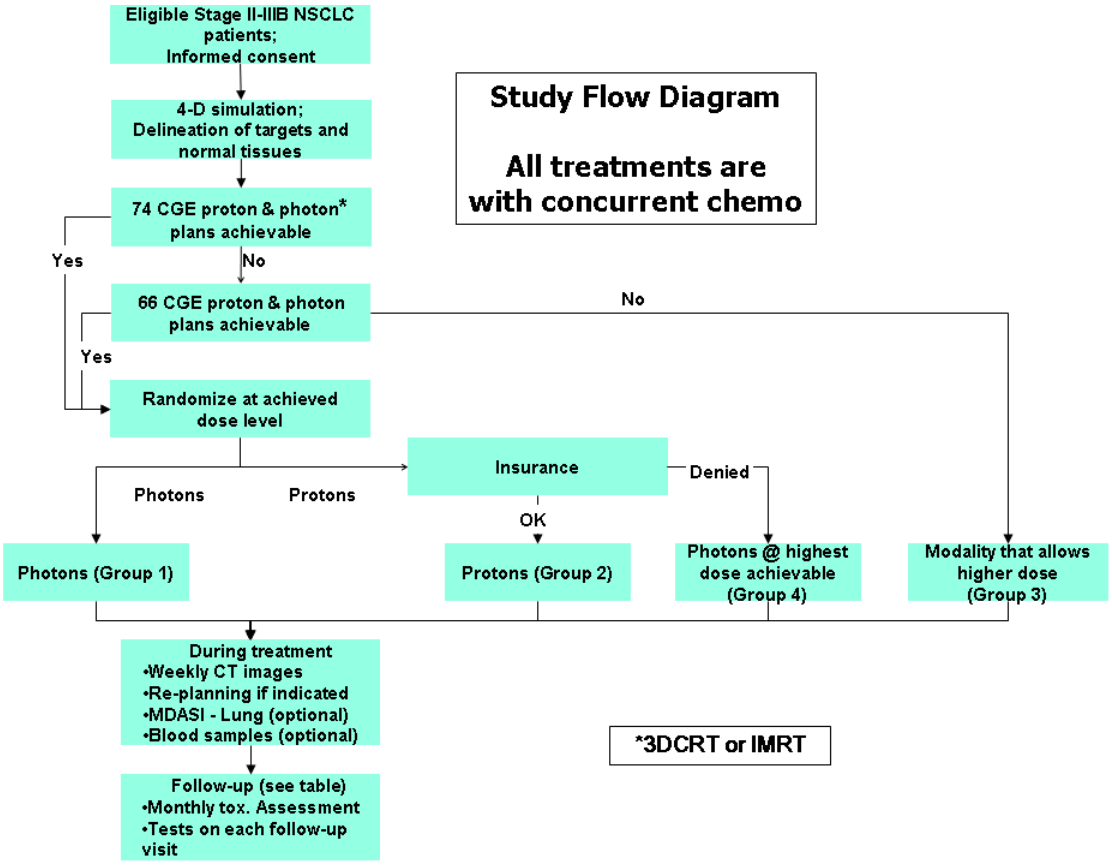
7.4.3 Dose calculation

7.4.3.1 Doses are to be calculated with 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.

7.5 Randomization

Radiation therapy component of the study is shown in the flow chart below:



7.5.1 The proton (PT) and photon (IMRT or 3DCRT) plans will be designed and evaluated by the treating radiation oncologist for acceptability according to current clinical practice, meaning that the dose constraints for normal tissue toxicity specified on Table 3b have been met.

Radiation dose will be prescribed at 1 of 2 dose levels: 74 Gy (CGE), 66 Gy (CGE). If either proton or photon plan at 74 Gy (CGE) is not acceptable, prescribed tumor dose will be reduced to 66 Gy (CGE) and another pair of proton and photon plans will be designed. If the plans at one of prescribed dose levels of 66 or 74 Gy (CGE) are achievable, the patient will be randomized between photons (Group 1) and protons (Group 2) at the highest achieved dose level. Patients not randomizable will be treated in Group 3 as described in section 7.6.

7.5.1.1 Patients randomized to Group 1 or 2 will be treated with the approved IGAXT or IGAPT plan.

7.5.1.2 Patients randomized to Protons (Group 2) and subsequently denied insurance reimbursement may elect to forego treatment with Protons and be treated with Photons. Such patients will be removed from the randomized part of the study and moved to Group 4 and treated with photons at the highest practical dose (74 CGE, 66 CGE).

7.5.2 Patients will be randomized to either IGAXT or IGAPT using the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/boutiquetrials) which is housed on a secure server at MDCC and maintained by the MDACC Department of Biostatitics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to personnel at MDACC and MGH responsible for enrolling patients and updating, reviewing, and analyzing patient data.

Training on the use of the Clinical Trial Conduct website to randomize and enroll patients on the study will be provided by Mark Munsell for the study personnel at MDACC and via WebEx for the study personnel at MGH. The imporance of timely updating the follow-up times and occurrence of events, if any, will be emphasized.

Patients described in section 7.5.1.2 will be removed from the randomization website.

7.6 Patients with target volumes too large for a clinically acceptable photon or proton plan at the lowest stratification dose level of 66 Gy (CGE) will be treated without randomization (Group 3) . They will be treated with the modality (protons or photons) that allows the higher dose at the limits of normal tissue tolerances. We hypothesized that the toxicity for protons and photons will be similar and the modality allowing higher dose to the target will lead to improved outcomes. The data of such patients will be used to compare local control, overall survival, progression-free survival, median survival and toxicities of protons vs. photons.

7.7 Radiation Therapy Quality Assurances

Radiation treatment plans will be reviewed by all the participating insitutions to ensure a common understanding of the procedures listed on 7.2 through 7.6 by each participating institution. This will be done during the trial periodically as needed.

7.7.1 All treatment plans will be reviewed for quality assurance according to the standard of peer review at each participating institution.

7.7.2 All plans will also be reviewed by the responsible physicst or his/her designee at each participating institution for compliance with the protocol and stardard of practice at each institution.

7.7.3 Plan review for the patients from one institution by the staff of the other institution, when performed, will utilize the resources of Image-Guided Therapy QA Center (ITC) at Washington University, St. Louis, webex, and/or other feasible resources that comply with HIPPA.

8.0 Chemotherapy

(Note: All procedures specified in this section will be performed by or under the direction of the treating medical oncologist)

8.1 Concurrent Chemotherapy with Radiation Treatment

8.1.1 All patients on this trial will receive concurrent weekly carboplatin and paclitaxol chemotherapy with radiation therapy as part of the standard treatment. Pemetrexad is allowed for adenocarcinoma.

Paclitaxel; 50mg/m^2 in NS 250 ml over 1 hour IV using non-PVC bags and connections.
Carboplatin: AUC = 2 in D5W 150ml -250ml over 30 minutes IV.

8.1.2 Carboplatin Dosing Standards:

1) A correction factor should NOT be used to calculate creatinine clearance

- IDMS-measured creatinine (the serum creatinine valued reported in ClinicStation) should be used to in calculations that estimate GFR.

2) The maximum value of GFR calculated by the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min .
   - For an AUC of 6, this would mean a maximum dose to be administered would be 900 mg
   - For an AUC of 2 the maximum dose to be administered would be 300 mg

3) Consider adjusting the creatinine to a higher value (i.e. 1 mg/dL) in:
   - elderly patients (those over the age of 70)
   - those with cachexia
   - patients that weigh less than 50 kg

4) When concerned about safety in a specific patient, measure the GFR (using 24-hour urine collection).

The chemotherapy will be given once a week for seven weeks. Each treatment will last 3-4 hours.

8.1.3 Etoposide and cisplatin (EP 50/50) is allowed as an alternative non-taxane based chemotherapy regimen.

EP 50/50 dose schedule is as follows:
Etoposide (50 mg/m2/day IV, days 1-5) and cisplatin 50 mg/m2 IV days 1 and 8) every 3-4 weeks

8.2 Induction Chemotherapy

Additioinally, platinum and taxane-based induction chemotherapy as part of the standard treatment will be allowed. Pemetrexad is allowed for adenocarcinoma.

8.3 Consolidation Chemotherapy

8.3.1 Consolidation chemotherapy is allowed; it should be started at least 3 –8 weeks after the protocol treatment.

8.3.2 Regimen and doses will be decided by the treating medical oncologist according to the institutional standard of care.

8.4 Delivery will be according to the institutional standard of care.

8.5 Patients who develop disease progression can be started on appropriate therapy any time as medically indicated.

8.6 Patients on other carboplatin and paclitaxel chemotherapy or targeted therapy protocols are eligible as long as IGAPT is allowed on those protocols.

9.0 Assessments of Primary Endpoints

(Note: All procedures specified in this section will be performed by a research nurse under the direction of the treating radiation oncologist)

9.1 Assessment of Treatment-Related Pneumonitis

9.1.1 TRP will be diagnosed clinically by the treating investigator. TRP events will be graded per the CTCAE v3.0. Any questions regarding the diagnosis or grade of TRP will be resolved by the Protocol PI or by his/her designee(s).

9.1.2 The patient will be contacted monthly +/- 2 weeks to report their symptoms of treatment related toxicity until 6 months after chemoradiation. The methods of contacting patients include but not limited to clinic visit, phone calls, Emails, or letters. If deemed necessary, patient will come to the clinic to be evaluated in addition to their regular follow-up.

9.1.3 Since TRP typically occurs 1-6 months after the completion of radiation therapy, and criteria used in CTCAE v3.0 are subjective, it is critical to use MDASI-lung tool to perform weekly symptom assessment until 6 months from the baseline. The response of the patients will be assessed and if clinically indicated, patient will be instructed to obtain medical attention and necessary radiographic imaging studies.

9.2 Tumor Response Assessment

Tumor response and local failure will be assessed according to RECIST criteria (see appendix). Images suspicious for local failure will be scheduled for review monthly by the protocol PI or his/her designee(s).

*Complete Response (CR):	Disappearance of all target lesions
*Partial Response (PR):	At least a 30% decrease in the sum of the LD
*Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, takig as reference the smallest sum LD records since the treatment started or the appearance of one or more new lesions
*Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.0 Reasons for Removal from Study

10.1 Unacceptable adverse event (at the discretion of the treating physician)

10.2 Patient choice (patients can withdraw from the study at any time, for any reason)

11.0 Adverse Event Reporting

All serious adverse experiences will be reported to the institutional review board (IRB) of The University of Texas M. D. Anderson Cancer Center according to institutional reporting guidelines and using institutional reporting forms (see Appendix A).

Reports of serious adverse events will be delivered to Clinical Research Compliance and will be submitted to the U.S. Food and Drug Administration by the safety coordinator according to 21CFR 312.32.

All AEs at the participting institutions must be reported to the Protocol PI and the Overall PIs.

11.1 Grading Criteria

The Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0; available at http://ctep.info.nih.gov) will be used to grade all treatment-related adverse events. All appropriate treatment areas should have access to a copy of these criteria.

11.2 Adverse Events to be Reported

The following AEs experienced by patients accrued to this protocol and attributable to the protocol treatment (definitely, probably, or possibly related) should be reported (from the start of protocol treatment to 30 days after protocol treatment):

11.2.1 Death on study

11.2.2 Hospitalization or prolongation of hospitalization on study

11.2.3 Life-threatening event

11.2.4 Persistent or significant disability or incapacity

11.2.5 Congenital anomaly/birth /defect for which intervention is required to prevent permanent impairment/damage

11.3 Procedures for Reporting Adverse Events

The following steps must be taken to report serious adverse events that occur while the patient is on this trial.

11.3.1 Within 24 hours of discovery of the adverse event, the PI must be called and a written notification will be sent to the IRB .

11.3.2 Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment must be reported by telephone to the PI and the IRB within 24 hours of discovery. Any late death (more than 30 days after last treatment) attributable to the protocol treatment (possible, probable, or definite) should also be reported to the PI and the IRB.

11.3.3 Known/expected adverse events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, the drug insert, or the Investigator's Brochure.

11.3.4 Unknown/unexpected adverse events are those thought to have resulted from the protocol treatment.

12.0 Multi-Institutional Trial and Registration

12.1 This trial will be a multi-institutional study. All patients will be enrolled by M. D. Anderson Cancer Center and Massachusettes General Hospital.

12.2 All patients will be registered in the CORE system at MDACC.

12.3 Protected health information will be appropriately annonymized before being transmitted to be shared with non-MDACC groups, e.g. MGH or ITC.

12.4 Patients will be notified of these requirements through the informed consent document.

13.0 Statistical Considerations

13.1 Study Endpoints

13.1.1 Primary Endpoint

Time to development of CTC v3.0 grade ≥ 3 TRP or local failure, whichever occurs first, in both treatment groups

13.1.1.1 An outcomes review committee has been formed to discuss every patient who develops symptons suggesting clinical symptomatic TRP, local failure, or regional failure to ensure consistent and unbiased grading of study outcomes. The Charter of this committee is the following:

Outcomes Review Committee

The primary outcome for trial 2008-0133 is time to local failure or grade 3 treatment related pneumonitis (TRP), according to CTCAE v3. Local failure after radiation could be confused with lung fibrosis or infection. CTCAE v3 is a subjective grading system, and grading of TRP could vary between physicians and research nurses.

Committee will be chaired by the Protocol PI. Its membership will include MDACC thoracic radiation oncologists, MGH CO-PI, MDACC radiation physicists, dosimetrists, research nurses, data coordinator, and statistician participating in the conduct of this trial. The treating physician (or his or her designee) and at least one other radiation oncologists, one physicist, one research nurse, statisrician and the data coordinator would comprise the quorum. Meeting will be open to others provided no HIPPA regulations are violated.

The committee will meet as needed to review all patients who are suspected of achieving either study outcome (local failure, TRP). All relevant medical, dosimetric, and treatment related information will be reviewed. The committee will reach a consensus as to whether the outcome has been achieved. For local failure the committee will reach consensus on the type of local failure (see section 13.1.1 of the protocol) and the date of local failure. For TRP the committee will reach consensus on the CTCAE v3 grade (see section 9.9 of the protocol) and attribution (i.e., relationship to treatment). Outcomes for a patient will not be recorded in the randomization website until the committee has reached consensus on the patient.

The committee will also review patients who were decided to have outcomes before the formation of the committee. However, the outcomes and dates of outcomes for these past cases will not be changed in the randomization website. The committee's review of each past case will be noted for inclusion in sensitivity analyses and for discussion in the final study report. Meeting minutes will be recorded to document the discussion and final decision of the committee for all cases brought before it.

13.1.1.2 TRP is defined and graded according to CTCAE v3.0. Since the CTCAE grading criteria for TRP is quite subjective, the grading of TRP could vary among individual treating physicians. The outcomes review committee will meet to discuss each and every patient reported to have developed symptomatic TRP. The final grading of TRP will be decided by the outcomes review committee.

13.1.1.3 **Procedure in diagnosing and grading radiation pneumonitis for 2008-0133 (CTCAE v. 3)**

1) The following factors must exist to diagnose radiation pneumonitis (RP):
   a. Patient must have had radiation treatment that included certain volume of the normal lung
   b. There must be radiographic changes suggesting inflammation consistent with radiation dose distribution
   c. Time of scoring: 1 – 12 months after starting of chemoradiation
   d. Symptoms attributable to RP

2) The following steps are used in grading radiation pneumonits:
   a. Grade 1: a + b + c + d only
   b. Grade 2: (1), a + b + c + d, plus (2), or (3), or plus (2)+(3). (2) Symptomatic with one or more related symptoms (e. g. persistent dry cough, shortness of breath, reduced exercise tolerance, short term ER visit, oral steroids, cough medicine, etc) and/or (3) affect activities of daily living (ADL) related to work
   c. Grade 3: (1), a+b+c+d plus (2), or (3), or (4), or plus any combination of (2) or (3) or (4). (2) Symptomatic (severe) requires hospitalization, (3) O2 indicated, (4) bed ridden or unable to care for self due to RP
   d. Notes: The following toxicity should be scored as independent category
      i. Pleural effusion will be diagnosed and scored under pleural effusion
      ii. Hypoxia without a+b+c+d will be scored under the category of hypoxia
      iii. ARDS will be scored under the category of ARDS
      The differential between RP and ARDS is best made as follows: A CT scan of the chest should be obtained. If the inflammatory changes correspond to the radiation therapy dose distribution as seen on the axial slices, one can assume it is RP. On the other hand, if the symptoms are acute and the CT reveals generalized interstitial infiltrates outside the radiation treatment volume, e.g. infiltrates in the lower lobes when only an upper lobe tumor was treated, the diagnosis is ARDS or other type of inflammation such as aspiration or pneumonia.
      iv. Fibrosis is scored under the category of fibrosis
      v. Pulmonary edema is scored under the category of pulmonary edema
      vi. Pulmonary embolism is scored under the category of pulmonary embolism
      vii. Hemoptysis is scored under the category of Hemoptysis
      viii. Pneumonia is scored under the category of Pneumonia

13.1.1.4 Local failure is defined as any of the following that occurs inside the PTVp and/or PTVn, or ≤ 1cm outside the margin of the PTVp and/or PTVn:

a) Tumor recurrence after achieving complete response,
b) Residual tumor enlargement of 20% or more on CT according to RECIST criteria,
c) Recurrence of PET FDG Avidity after achieving complete metabolic response,
d) Increase in FDG avidity in residual tumor,
e) Pathologically proven recurrence.

Regional failure is defined as disease occurrence on the same side of the thorax that is > 1 cm outside the PTVp and/or PTVn boundary.

The PET or CT images that reported local failure will be fused with the radiation dose distribution to allow accurate assessment of the location of the local failure. Biopsy to allow difnitive documentation of local failure is highly recommended whenever possible, but not required. When in question, the case will be discussed by the outcomes review committee to make final decision.

13.1.2 Secondary endpoints

13.1.2.1 Assess and compare the incidence and time to development of CTCAE v3.0 grade ≥ 3 radiation esophagitis in treatment groups 1 and 2.

13.1.2.2 Investigate the association of inflammatory cytokines with the incidence and time to development of TRP and outcomes in treatment groups 1 and 2.

13.1.2.3 Investigate the association of relevant pharmacogenetic markers, biomarkers, and gene polymorphisms with the time to development of TRP and treatment outcomes in treatment groups 1 and 2.

13.1.2.4 Evaluate IGAXT using weekly computed tomography (CT) on-rail or cone beam CT in the assessment of tumor response and impact on treatment planning and delivery.

13.1.2.5 Compare overall survival, progression-free survival, and median survival time in treatment groups 1 and 2. Disease progression is defined as: 1) local failure as defined above, 2) regional failure as defined above, 3) distant metastases (any disease that occurs outside of the thorax and/or disease that occurs in the contralateral lung).

13.1.2.6 Evaluate the role of functional imaging with FDG-PET in assessing and predicting the time to the development of TRP and tumor response.

13.1.2.7 Document and compare symptom burden weekly during treatment, monthly up to 6 month after the treatment, and at each follow-up visit by using the M. D. Anderson Symptom Inventory for Lung (MDASI-Lung) in treatment groups 1 and 2.

13.1.2.8 For Group 3 and Group 4 patients who are treated with protons or photons depending on higher dose achievable, compare the local control, overall survival, progression-free survival, median survival and toxicities of protons vs. photons.

13.2 Sample Size Calculation and Data Analysis Plan

13.2.1 Hypothesis

The primary endpoint of the study is time to treatment failure, defined as the interval from the time of randomization to the development of treatment-related pneumonitis (TRP) or local failure, whichever occurs first. We are interested in studying whether IGAPT can reduce the TRP rate compared with IGAXT. Although local disease control rates are thought to be similar for IGAPT and IGAXT, this assumption needs to be prospectively tested, and hence we chose a combined endpoint of TRP and local failure as the primary endpoint.

Our primary outcome is time to treatment failure. Treatment failure is defined as TRP or local failure. These 2 types of failure are equally important. Based on the preliminary data, it is assumed that the time to treatment failure follows a log-normal distribution, with 6-month and 12-month treatment failure rates for the IGAXT arm of 30% and 40%, respectively (27). We also assume that under the null hypothesis (H0), failure in the IGAPT arm is the same as failure in the IGAXT arm, and under the alternative hypothesis (H1), IGAPT can reduce the corresponding failure rates to 20% and 25%, respectively.

Eligible patients will be assigned to receive either IGAXT or IGAPT based on the Bayesian adaptive randomization method. Adaptive randomization will allocate more patients to the treatment that yields more favorable outcomes based on the interim observed data. This design is appealing ethically because if a difference is found in treatment efficacy, more patients in the trial can be treated with the more effective treatment. If no difference is found in treatment efficacy, patients will be assigned with equal probability to either treatment, as is the case in the conventional randomized trials with equal allocation ratio. With a maximum of 150 eligible patients, we will have 81% power to detect this difference with a one-sided type I error rate of 10% or less (see subsequent sections and Table 4 [Operating Characteristics] for details). Under H1, there is a 48% chance of early stopping with about

58% of the patients randomized into the IGAPT group in a median sample size of 128. The sample size calculation assumes an accrual rate of 7 patients per month with 32 months of accrual plus an additional 24 months of follow-up. The total sample size is up to 250 patients, to account for patients being ineligible or lost to follow-up.

Patients randomized to IGAPT may be denied insurance reimbursement for this treatment, and therefore, they may elect not to be treated with IGAPT. These patients will be transferred to Group 4, as described in section 7.5, and they will be treated with the highest dose of IGAXT possible (74 CGE, 66 CGE).

13.2.2 Model specification for Bayesian adaptive randomization design using time-to-treatment-failure as the endpoint.

The time to treatment failure is assumed to follow a log-normal distribution. A Bayesian lognormal regression model with adaptive randomization will be used. Let *ti* be the time to development of CTCAE v3.0 grade ≥ 3 treatment-related TRP or local failure for individual *i;* then the distribution of *ti* will be

$$\log(t_i) \sim N(\beta_{IGAXT}, \sigma_{IGAXT}^2) \text{ if } t_i \text{ is in IGAXT group,}$$
$$\log(t_i) \sim N(\beta_{IGAPT}, \sigma_{IGAPT}^2), \text{ if } t_i \text{ is in IGAPT group.}$$

We assume conjugated prior, i.e., the prior distributions are normal distribution (1, 100) distributions for β's and gamma (0.0001, 0.0001) distributions for the inverses of the σ's. We are particularly interested in treatment failure rates for each treatment group, which give us an insight about the treatment effect (IGAXT vs. IGAPT).

The probability for treatment assignment in the adaptive randomization is chosen to be proportional to the posterior 1-year treatment failure rate. Two steps are followed to complete the assignment of treatments for the next patient given current data.

(1) Determine the parameters, β's and σ's, based on their posterior estimates.

$$\hat{\beta} = median(\beta \mid data_i),$$
$$\hat{\sigma} = median(\sigma \mid data_i),$$

where $data_i$ contains the information of previous *i* subjects.

(2) Estimate the 1-year treatment failure rates (TF), TF_{IGAXT} and TF_{IGAPT} based on the $\hat{\beta}$ s.

$$TF = \Pr(t < 12 month \mid \log(t) \sim N(\hat{\beta}, \hat{\sigma}^2))$$

Then, the chance that the next patient is assigned to the IGAPT group will be

$$1 - TF_{IGAPT} / (TF_{IGAXT} + TF_{IGAPT}).$$

13.2.3 Decision rule for comparing treatment efficacy

IGAPT is considered better than IGAXT (i.e., with lower failure rates than IGAXT) if

$$\Pr(t_{IGAPT} > t_{IGAXT} \mid t_{IGAXT} < 24 \text{ OR } t_{IGAPT} < 24, data) > P_L.$$

On the other hand, IGAXT is considered better if

$$\Pr(t_{IGAXT} > t_{IGAPT} \mid t_{IGAXT} < 24 \text{ OR } t_{IGAPT} < 24, \textit{data}) > P_L.$$

Specifically, we will conclude that IGAPT is better if, given the current data, the probability of time to treatment failure for IGAPT being longer than for IGAXT is greater than P_L. The proposed design allows continuous monitoring. The trial can be stopped early should the interim results indicate a high probability of one treatment being better than the other. Specifically, we set $P_L = 0.70$ for interim monitoring. If the trial continues to the end without being stopped early, we set $P_L = 0.59$ in the final analysis. The probability calculation is confined to within the 24-month period, which corresponds to the clinical implication of the relevance and importance of recurrence or TRP during this period.

Patients will be randomized to the achievable radiation dose [74, 66] as described in section 7.5. We assume that approximately 1/3 of patients will be randomized to each dose level. However, we do not expect any differences between doses with respect to the treatment effects on TRP or local failure. The calculations of randomization probabilities and decision rules described above will include all data across dose levels.

13.2.4 Operating characteristics

The operating characteristics from 1,000 simulation runs are summarized in Tables 4a, 4b and 4c. According to the specifications given in the above two sections, a total of 150 eligible patients are uniformly enrolled during the 24-month accrual period. An event of either grade $\geq$ 3 TRP or local failure is defined as a treatment failure. The first 20 patients are equally randomized into one of the two groups. After enrolling the first 20 patients and after one event is observed in each group, patients are adaptively randomized based on the posterior 1-year failure rate estimates of the two groups. Failure or losses to follow-up for randomized patients are updated as they occur, i.e., the observed failure or loss to follow-up is updated as it happens. In addition, when new patients enter the study, the censoring time is updated for all patients who are still on study but have not yet developed an events. The early stopping rule applies after a total of 20 events is observed in the entire sample. The decision rules for declaring that one treatment is better than the other are given in the previous section.

Under H**0** (Scenario 0 in Table 4a), where IGAPT is assumed to produce the same 1-year treatment failure rate (40%) as IGAXT, there is a 4.9% chance of early stopping because IGAPT is better than IGAXT and a 5.3% chance of early stopping because IGAXT is better. The 2.5th, 50th, and 97.5th percentiles for the proportion of patients randomized into the IGAPT group are 37%, 50%, and 65%, respectively. The median sample sizes are 75 and 74 for the IGAPT and IGAXT groups, respectively. There is an 8.7% chance to claim IGAPT as being better and an 8.1% chance to claim IGAXT as being better at the end of the study. The average trial length is 3.70 years.

Under H**1 (**Scenario 1 in Table 4a), where IGAPT is assumed to produce lower 1-year treatment failure rates than IGAXT (25% versus 40%), there is a 48% chance of early stopping because IGAPT is better than IGAXT, but there is virtually no chance of early stopping because IGAXT is better. The 2.5th, 50th, and 97.5th percentiles for the proportion of patients randomized into the IGAPT group are 44%, 58%, and 73%, respectively. The median sample sizes are 74 for the IGAPT group and 54 for the IGAXT group. There is an 81% chance to claim IGAPT as being better and virtually no chance to claim IGAXT as being better at the end of the study. The average trial length is 2.70 years.

Additional simulations summarized in Table 4a show that we have more than a 90% chance to claim IGAPT as being better and virtually no chance to claim IGAXT as being better at the end of the study for a situation where the treatment failure rate decreases with dose for both

IGAXT and IGAPT (Scenario 2). We also have more than an 80% chance to claim IGAPT as being better and virtually no chance to claim IGAXT as being better at the end of the study for a situation where the difference in treatment failure rates between IGAXT and IGAPT decreases with dose (Scenario 3).

Simulations summarized in Table 4b show that with 10% of patients randomized to IGAPT and then denied insurance coverage for their treatment, we still have at least 80% power for Scenarios 1-3 and about a 10% significance level under Scenario 0. With 10% of patients randomized to IGAPT and then denied insurance coverage for their treatment the trial will need to enroll a few more patients on average, it will last a little longer, and the proportion of patients treated on IGAPT will be a 2%-3% less than if there was no insurance denial.

Simulations summarized in Table 4c show that with 25% of patients randomized to IGAPT and then denied insurance coverage for their treatment, we still have at least 80% power for Scenarios 1 and 2, about 80% power for Scenario 3, and about a 10% significance level under Scenario 0. With 25% of patients randomized to IGAPT and then denied insurance coverage for their treatment the trial will need to enroll a few more patients on average, it will last a little longer, and the proportion of patients treated on IGAPT will be a 7%-8% less than if there was no insurance denial.

In both cases of 10% or 25% insurance denial, the trial will have only modest (<10%) increases in the total sample size and study duration.

Table 4. Operating characteristics (n=150 eligible patients). Assumes 90% of patients at 74 CGE and 10% of patients at 66 CGE. Also assumes 10% of patients assigned to IGAPT dropped due to insurance denial.

		Scenario 0 (H_0)		
True 1-Year Treatment Failure Rates for Doses 74, 66 CGE:		IGAXT 0.40, 0.40	IGAPT 0.40, 0.40	Total Sample Size (including insurance denial)
	Percentile			
Distribution of number of patients after adaptive randomization	2.5%	33	27	74
	50.0%	77	70	156
	97.5%	96	90	163
Distribution of the proportion of patients randomized to IGAPT	2.5%		0.33	
	50.0%		0.47	
	97.5%		0.63	
Probability of early stopping		0.050	0.059	
Probability of final selection		0.084	0.104	
Average trial length (years)		3.77		
		Scenario 1 (H_1)		
True 1-Year Treatment Failure Rates for Doses 74, 66 CGE:		IGAXT 0.40, 0.40	IGAPT 0.25, 0.25	Total Sample Size (including insurance denial)
	Percentile			
Distribution of number of patients after adaptive randomization	2.5%	26	38	76
	50.0%	58	71	153
	97.5%	86	95	163
Distribution of the proportion of patients randomized to IGAPT	2.5%		0.41	
	50.0%		0.56	
	97.5%		0.71	
Probability of early stopping		0.0	0.473	
Probability of final selection		0.0	0.811	
Average trial length (years)		2.80		
		Scenario 2		
True 1-Year Treatment Failure Rates for Doses 74, 66 CGE:		IGAXT 0.40, 0.30	IGAPT 0.25, 0.15	Total Sample Size (including insurance denial)
	Percentile			
Distribution of number of patients after adaptive randomization	2.5%	27	41	81
	50.0%	58	69	153
	97.5%	90	94	163
Distribution of the proportion of patients randomized to IGAPT	2.5%		0.39	
	50.0%		0.55	
	97.5%		0.71	
Probability of early stopping		0.0	0.493	
Probability of final selection		0.0	0.815	
Average trial length (years)		2.76		
		Scenario 3		
True 1-Year Treatment Failure Rates for Doses 74, 66,CGE:		IGAXT 0.40, 0.40	IGAPT 0.20, 0.25	Total Sample Size (including insurance denial)
	Percentile			
Distribution of number of patients after adaptive randomization	2.5%	26	40	81
	50.0%	46	68	117
	97.5%	82	96	162
Distribution of the proportion of patients randomized to IGAPT	2.5%		0.43	
	50.0%		0.58	
	97.5%		0.73	
Probability of early stopping		0.0	0.692	
Probability of final selection		0.0	0.952	
Average trial length (years)		2.26		

13.2.5. Statistical analyses and additional statistical considerations

Standard statistical methods including descriptive statistics and exploratory data analysis will be applied for checking data quality; identifying outliers, patterns, or associations; and providing summaries of the data distribution. Patients' medical-demographic information at baseline will be tabulated by treatment group to assess comparability between the IGAXT and IGAPT groups. Student's *t* tests or Wilcoxon rank sum tests will be used to compare continuous variables between the two different groups. Chi-square tests or Fisher's exact tests will be applied to assess the association between two categorical variables. Time-to-event outcomes, including overall survival, progression-free survival, time to radiation esophagitis, time to treatment-related pneumonitis (TRP), time to local failure, as well as time to treatment failure, will be estimated by using the Kaplan-Meier method. Log-rank tests will be used to test the difference in time-to-event distributions between treatment groups. Cox proportional hazards models will be used for multi-covariate time-to-event analysis to test the treatment effect adjusted by other important covariates such as dose and inflammatory cytokines. In addition, the association of relevant pharmacogenetic endpoints and gene polymorphisms with the time to the development of TRP or local failure will also be analyzed by the Cox model and other exploratory tools. Toxicity data will be summarized using frequency tables. Associations between the types and severity of toxicity and treatment will be evaluated as well. We will also perform subset analyses by dose level. Patients who are not randomized (Group 3 and Group 4) will be analyzed using descriptive statistics separately from those who are randomized. Patients in Group 3 and Group 4 will be analyzed separately. Exploratory analyses may also be performed by combining Group 3 and Group 4.

14.0 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interactions between sex and treatments and race and treatments. Participation rates of men and women will be examined in the interim analyses.

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