PET-Adjusted IMRT for NSCLC Trial (PAINT)

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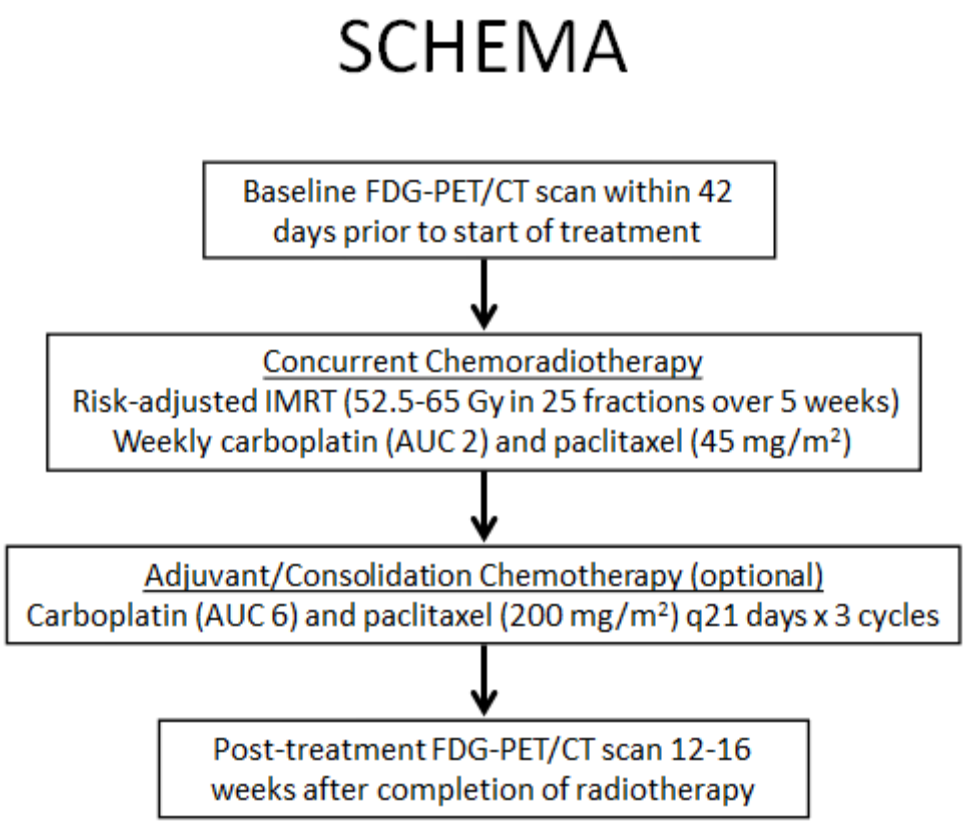
SCHEMA



Sample size: 39 patients

Abbreviations

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BSA	Body surface area
chemoRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTV	Clinical Target Volume
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EQD2	Equivalent dose in 2-Gy fractions
FEV1	Forced expiratory volume
Fx	Fractions
FDG	Fludeoxyglucose
GFR	Glomerular filtration rate
GTV	Gross tumor volume
Gy	Gray
IMRT	Intensity modulated radiotherapy
ITV	Internal target volume
IV	Intravenous
LA-NSCLC	Locally-advanced non-small cell lung cancer
LD	Longest diameter
LLN	Lower limit of normal

LRC	Locoregional control
MTV	Metabolic tumor volume
NSCLC	Non-small cell lung cancer
OS	Overall survival
PET	Positron emission tomography
PHI	Protected health information
PI	Principal investigator
PO	By mouth
PTV	Planning target volume
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
RTOG	Radiotherapy Oncology Group
Rx	Prescription
SAE	Serious adverse event
SUV	Standardized uptake value
TGA	Total glycolytic activity
ULN	Upper limit of normal
VMAT	Volumetric modulated arc therapy

Contents

1.0 OBJECTIVES

1.1 Primary Objective

To estimate the efficacy (based on post-treatment PET findings) of dose-painted intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy for locally-advanced non-small cell lung cancer (LA-NSCLC).

1.2 Secondary Objectives

To estimate the efficacy (based on clinical endpoints including locoregional control [LRC], disease-free survival [DFS], and overall survival [OS]) of dose-painted IMRT with concurrent chemotherapy for LA-NSCLC.

To evaluate the safety of dose-painted IMRT with concurrent chemotherapy for LA-NSCLC.

To evaluate the utility of post-treatment PET/CT imaging as a predictor of clinical outcomes following treatment with this novel approach.

To explore, in a preliminary manner, whether metabolomic markers in the blood and urine prior to and during the course of treatment are associated with treatment response, clinical endpoints, and treatment-related adverse events such as radiation pneumonitis.

To evaluate the rate of local disease progression in lesions deemed to be low-risk based on pre-treatment PET findings and treated with a conservative RT dose

2.0 BACKGROUND

2.1 Locally-advanced Non-small Cell Lung Cancer (LA-NSCLC)

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the United States and worldwide, causing nearly one million deaths each year.[1] Approximately one-third of NSCLC patients are diagnosed with locally-advanced disease, which may be defined as unresectable stage II disease or stage III disease.[2] For locally-advanced non-small cell lung cancer (LA-NSCLC), the standard treatment approach is conventionally-fractionated (1.8-2.0 Gy/day) radiotherapy (RT) to a dose of approximately 60-66 Gy with concurrent, platinum-based chemotherapy. This treatment approach, however, yields median survival times of only 16-23 months and local control rates of only 40-66%.[3-7]

Attempts to improve survival for LA-NSCLC patients through the extension of systemic therapy have yielded disappointing results in phase III trials. Administration of induction chemotherapy prior to chemoradiotherapy (ChemoRT) did not decrease the rate of distant relapse or improve overall survival (OS).[8] Similarly, addition of consolidation

docetaxel to conventional ChemoRT increased toxicity but did not improve survival.[9] Maintenance therapy with a targeted agent was found to decrease survival.[10]

The failure of intensified systemic therapy to improve survival in LA-NSCLC, in combination with the poor local control rates observed following conventional chemoRT, suggest that intensification of locoregional therapy may provide the best chance of improving outcomes for this patient population. This is supported by a meta-analysis of 6 randomized trials that compared concurrent chemoRT against sequential chemoRT.[11] Concurrent chemoRT was found to significantly improve OS and locoregional disease control (LRC), but it did not decrease the rate of distant progression. This is direct evidence that intensification of locoregional therapy can improve overall survival in LA-NSCLC.

Since concurrent chemoRT has been adopted as the standard of care for LA-NSCLC, several approaches to further improving locoregional therapy have been explored. Trimodality therapy, consisting of neoadjuvant ChemoRT followed by surgical resection, improved progression-free survival but not OS in a phase III study.[12] The value of RT dose escalation in the setting of definitive chemoRT was evaluated in RTOG 0617, a large, randomized trial in which patients were randomized to conventional dose (60 Gy in 30 fractions) versus high dose (74 Gy in 37 fractions) RT with concurrent weekly carboplatin and paclitaxel. Based on a second randomization, ½ of enrolled patients also received daily cetuximab. The 74 Gy arms of that trial were closed when it was determined that RT dose escalation was unlikely to yield a survival benefit.[13] Post-hoc analyses suggest that target coverage for many patients on the 74 Gy arm was suboptimal, possibly because treating physicians were concerned about treating large volumes to such a high dose. Additionally, the fact that the RT course of the high dose arm was approximately 10 days longer than that of the 60 Gy arm raises the possibility that accelerated repopulation may counteract the benefits of dose escalation using standard fractionation.

2.2 PET Imaging for LA-NSCLC

FDG-PET/CT imaging is recommended as part of the staging workup for most patients with suspected or newly-diagnosed NSCLC. Depending on the presumed stage based on clinical findings and anatomic imaging, PET leads to upstaging in 12-21% of patients.[14-16] Implementation of PET imaging may alter the management of NSCLC patients in up to 40% of cases.[15,17,18] Several reports indicate that for NSCLC patients, PET metrics such as maximum SUV (SUVmax), metabolic tumor volume (MTV), and total glycolytic activity (TGA) may be independent predictors of overall survival.[19-22].

The clinical significance of quantitative PET findings before and after conventionally-fractionated chemoradiotherapy for LA-NSCLC was the subject of the multi-institutional ACRIN 6668 / RTOG 0235 trial. In that Phase II study, PET imaging was collected before and 12-16 weeks after the completion of definitive, concurrent chemoRT for LA-NSCLC. Treatment details were not specified, but the protocol required a RT dose of at least 60 Gy and the use of one platinum-based

chemotherapeutic agent with a second non-platinum agent. In the primary analysis of that study, pre-treatment SUVmax and peak SUV (SUVpeak) values were not found to be prognostic with respect to LRC or OS. Post-treatment SUVmax and SUVpeak, on the other hand, correlated with both LRC and OS.[23] In exploratory analyses, an SUVpeak cutoff of 5.0 on post-treatment imaging effectively stratified patients into favorable and unfavorable groups. (Personal communication with ACRIN/RTOG investigators, **Figure 1**)

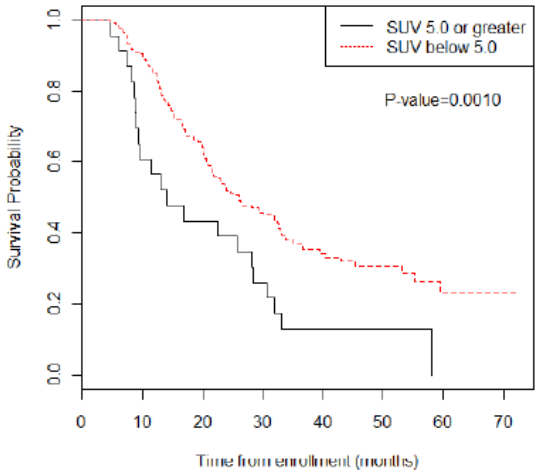


Figure 1 – Unpublished results from ACRIN 6668 / RTOG 0235. Kaplan-Meier curves were generated using data from 173 patients who underwent post-treatment PET imaging. Post-treatment SUVpeak predicts for OS. An SUVpeak value of 5.0 corresponds to an SUVmax value of approximately 6.0.

Our group has been working with the ACRIN 6668 / RTOG 0235 dataset to evaluate additional metrics derived from pre- and post-treatment PET imaging. We have found that pre-treatment MTV, defined as the composite volume of all hypermetabolic lesions delineated on PET imaging, is an independent predictor of both LRC and OS. (**Figures 2a and 2b**) We have also found that for individual tumors and hypermetabolic lymph nodes, pre-treatment MTV correlates with the risk of persistent hypermetabolic activity on post-treatment imaging. (**Figure 3**) Based on these results, ***we hypothesize that pre-treatment MTV identifies high-risk lesions for which RT intensification is likely to provide clinical benefit***.

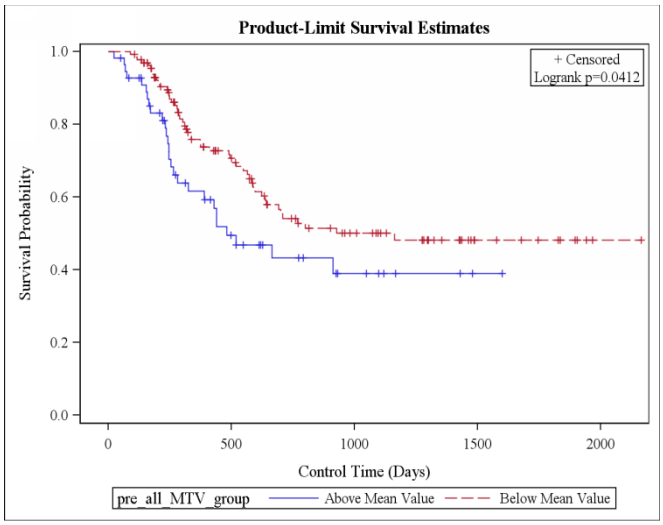


Figure 2a – Unpublished results from ACRIN 6668 / RTOG 0235. Kaplan-Meier curves for locoregional progression-free survival were generated after dividing patients into two groups based on pre-treatment MTV (above/below mean value of 92 cc).

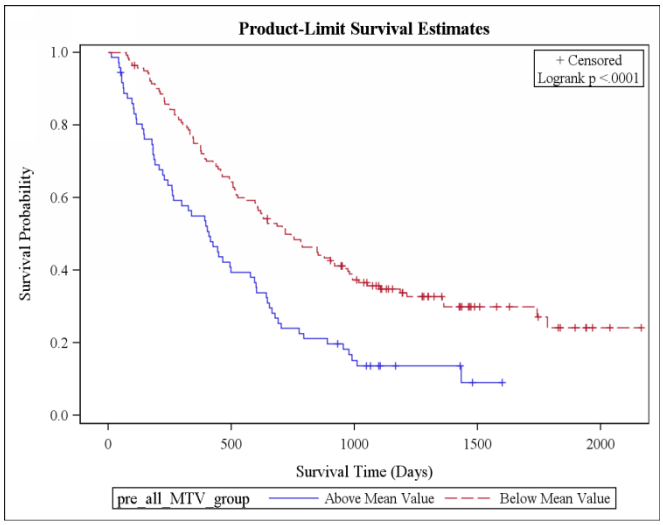


Figure 2b – Unpublished results from ACRIN 6668 / RTOG 0235. Kaplan-Meier curves for overall survival were generated after dividing patients into two groups based on pre-treatment MTV (above/below mean value of 92 cc).

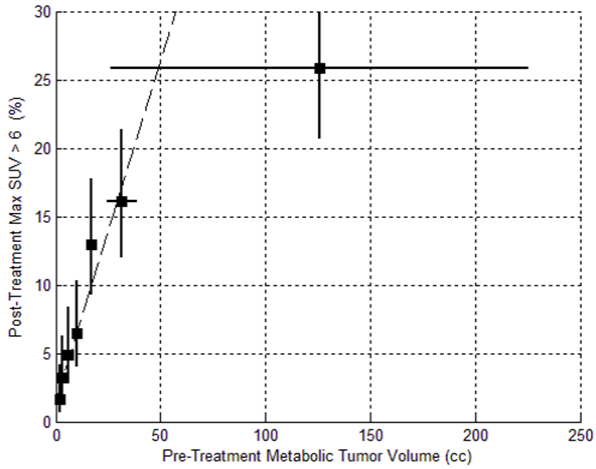


Figure 3 – Pre-treatment MTV correlates with the risk of significant (SUVmax>6) activity on post-treatment PET imaging. Data shown are for 434 lesions in 157 patients from ACRIN 6668 / RTOG 0235 who underwent both pre- and post-treatment imaging. Lesions were sorted into seven groups based on pre-treatment MTV. **Lesions with pre-treatment MTV above 25 cc have a >15% risk of significant post-treatment activity**.

2.3 Intensity-Modulated Radiotherapy (IMRT) for LA-NSCLC

In intensity-modulated radiotherapy (IMRT), multiple beam angles and dozens of beam segments are used to deliver highly conformal RT. Computerized inverse planning is used to identify the combination of beam segments that optimally covers the target volumes with the prescribed RT dose while limiting the dose to surrounding normal structures based on pre-specified constraints.[24] IMRT is commonly used for a number of malignancies, including LA-NSCLC. In a large single-institution experience, the adoption of IMRT for LA-NSCLC was associated with significant improvements in OS.[25] In the aforementioned RTOG 0617 trial, approximately 50% of patients were treated with IMRT.[13]

An additional benefit of IMRT compared to older treatment techniques is that IMRT can be used to perform "dose painting", also referred to as the "simultaneous integrated boost technique". This means that in a single session, various target volumes can be treated with different RT doses, which are generally based on historical failure patterns. This approach is commonly used for head and neck cancer[26] and anal cancer[27], where dose levels are based on lesion type (primary tumor v. lymph node) and size. This approach has not yet been adopted for the treatment of NSCLC, presumably because locoregional failure patterns have been difficult to establish using anatomic imaging, and distant failure remains common.

2.4 Safety of RT Intensification

We hypothesize that pre-treatment PET imaging can be used to identify high-risk lesions for which RT dose escalation is likely to provide clinical benefit. In this trial, we will utilize IMRT to selectively treat high-risk lesions with intensified RT dosing. The safety of chemoRT dose escalation to larger volumes has already been established, as has the safety of modest chemoRT hypofractionation (use of daily fraction sizes > 2.0 Gy). Therefore we are confident that our regimen will be well-tolerated.

In RTOG 0617, patients on the experimental arm were treated with high-dose concurrent chemoRT. They received an RT dose of 74 Gy in 37 fractions over 7 ½ weeks, along with weekly carboplatin (AUC=2) and paclitaxel (45 mg/m^2).[13] This RT schedule was based on previous phase I and II studies demonstrating the safety of chemoRT dose escalation up to 74 Gy.[28-30] Preliminary results from RTOG 0617 indicate that high-dose chemoRT was well-tolerated, and treatment-related toxicities did not account for the study's negative results.

Several single-institution reports indicate that gentle chemoRT hypofractionation is well-tolerated. In a Japanese study, 10 patients with stage III NSCLC were treated with daily RT fraction sizes of 2.5 Gy to a median dose of 65 Gy.[31] All patients received concurrent chemotherapy consisting of weekly carboplatin and paclitaxel. Treatment was extremely well-tolerated, with no reported acute or late grade ≥ 3 toxicities. In a second trial, 14 patients were treated with 52.5 Gy in 15 fractions (3.5 Gy/fraction) with concurrent liposomal doxorubicin and vinorelbine.[32] No grade ≥ 3 nonhematologic toxicities were observed. At the University of Michigan, over 50 LA-NSCLC patients have been treated with hypofractionated RT along with carboplatin and paclitaxel. Daily fraction sizes were based on predicted complication probabilities, and patients were treated to biologically equivalent doses of 80-100 Gy over 30 fractions. Based on encouraging toxicity and efficacy results from the Michigan group, the RTOG has opened a phase II study using a similar design. (RTOG 1106 protocol)

Table 1 describes our proposed RT dosing schema along with RT schedules used in other studies. Time-adjusted biologically equivalent doses are also provided, using the Linear Quadratic Model and published estimates for model parameters.[33,34] Based on the data summarized above, "high-risk" lesions shall be defined as tumors or lymph nodes with MTV greater than 25 cc on pre-treatment PET imaging.

Regimen	Description	EQD2 – Tumor	EQD2 - Normal Tissues
RTOG 0617: Control Arm	2.0 Gy x 30 fx = 60 Gy (6 weeks)	55.5 Gy	60.0 Gy
RTOG 0617: High-dose Arm	2.0 Gy x 37 fx = 74 Gy (7.5 weeks)	67.8 Gy	74.0 Gy
Current Trial: Low-risk lesions (MTV<25 cc)	2.28 Gy x 25 fx = 57 Gy (5 weeks)	56.4 Gy	60.2 Gy
Current Trial: High-risk lesions (MTV>25 cc)	2.6 Gy x 25 fx = 65 Gy (5 weeks)	68.3 Gy	72.8 Gy

Table 1 – Proposed dosing schedules for high- and low-risk lesions, defined by MTV on pre-treatment PET/CT imaging. fx=fractions. EQD2 refers to biologically equivalent dose, calculated using the Linear Quadratic Model (α/β=10 Gy and potential doubling time=5.6 days for tumor, α/β=3 Gy for normal tissues)

2.5 Biomarker Studies

Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind".[35] The metabolome represents the collection of all metabolites in a biological cell, tissue, organ or organism.[36] The tools most commonly used to quantify metabolite levels are nuclear magnetic resonance (NMR) spectroscopy and mass spectroscopy (MS). Metabolomics is an emerging discipline that may one day change medical practice in fields such as nutrition, toxicology, endocrinology, and oncology.[37-40]

A number of biomarkers are theorized to have implications in the detection, prognosis, and post-treatment evaluation of NSCLC patients.[41,42] Reported metabolite derangements in NSCLC include changes in plasma levels of Krebs cycle components and certain amino acids.[42] Urine markers for NSCLC have also been identified.[43] Metabolomics may also prove helpful for the early detection of radiation-induced lung injury.[44]

Our group is fortunate to collaborate closely with Dr. Irwin J. Kurland, who is an Associate Professor in the Department of Medicine and Director of the Stable Isotope and Metabolomics Core Facility of the Diabetes Research Center. Blood and urine samples collected as part of this protocol we be used to study of the metabolomics of lung cancer and how they evolve during chemoradiotherapy. These exploratory analyses will identify promising subjects for future prospective study.

2.6 Rationale for Treating Low-risk Lesions with a Conservative RT Dose

This protocol is being amended such that tumors or lymph nodes deemed to be low-risk (based on having pre-treatment MTV < 25 cc) will be treated with a total RT dose of 52.5 Gy (2.1 Gy per fraction). This is a modest decrease compared to the initial study design, where such lesions were treated with 57 Gy (2.28 Gy per fraction). This change is supported by a number of studies whose results have become available since the initial design of this trial as well as older studies that can now be viewed in a different context:

Updated results of RTOG 0617 have been presented.[45] In this randomized study testing high-dose RT (74 Gy) against a standard RT dose (60 Gy), dose

escalation unexpectedly led to a statistically and clinically significant decrease in overall survival. Median survival was 29 months in the control arm and only 20 months in the high-dose arm. Rates of Grade 5 treatment-related toxicity were 2% and 4% in the control and experimental arms, respectively. Although this difference does little to explain the large difference in outcomes between the two arms, multivariable analysis revealed that the occurrence of severe acute radiation esophagitis and the RT dose received by the heart were independently predictive of inferior overall survival.[46] This suggests that the additional RT delivered to thoracic organs in the high-dose arm may directly lead to decreased patient survival. Decreasing the dose delivered to these organs, conversely, may be expected to improve outcomes.

A large National Cancer Database analysis of over 30,000 locally-advanced NSCLC patients who underwent potentially-curative resection demonstrated that the use of postoperative RT with a dose above 54 Gy was associated with significantly lower 5-year survival than the use of a dose between 45 and 54 Gy (28% v. 38%).[47] The use of high RT doses remained statistically significantly associated with inferior overall survival on multivariable analysis.

A retrospective review performed at our institution has demonstrated that, although locoregional progression is common following definitive chemoradiotherapy for locally-advanced NSCLC, the specific site of tumor progression can be predicted based on pre-treatment PET.[48] We found that the 2-year cumulative incidence rate for progression in lesions larger than 25 cc was 45%, compared to only 5% for lesions under 25 cc ($p < 0.001$). Many of the lesions smaller than 25 cc were treated with doses below 55 Gy, and only one such lesion progressed following treatment (Figures 4 and 5).

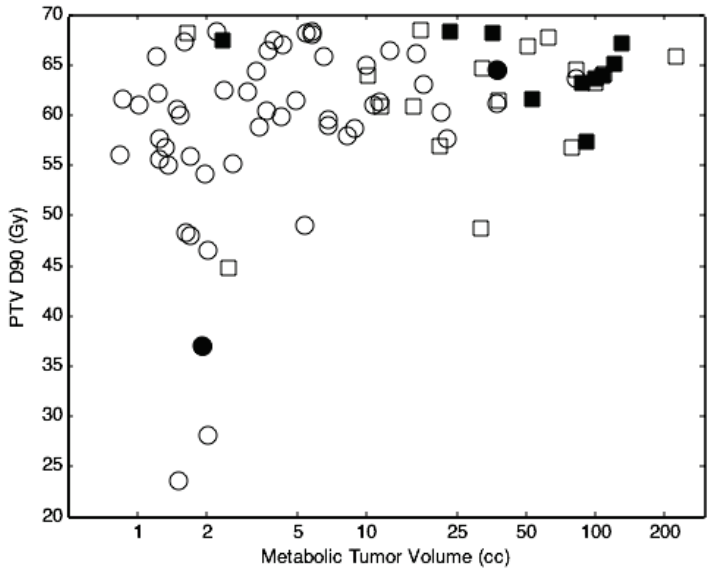


Figure 4 – Scatter plot of PTV D90 versus MTV for 82 lesions. MTV is plotted on a logarithmic scale. Squares represent primary tumors, while circles denote lymph nodes. Lesions that were the first site of disease progression are shaded in black.

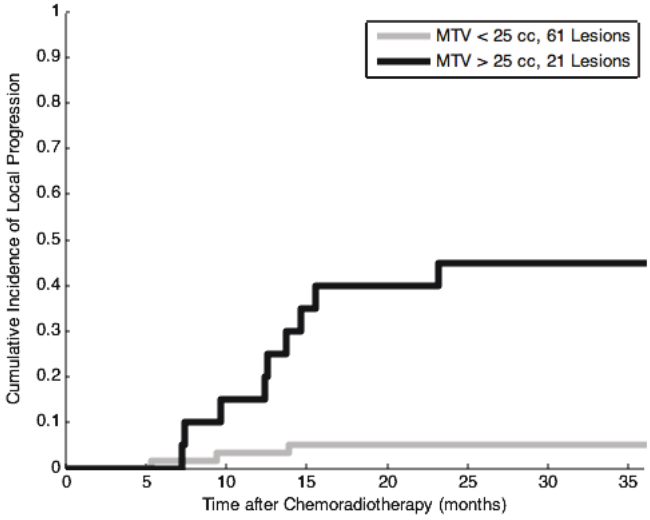


Figure 5 – Cumulative incidence of local disease progression in individual lesions after grouping by pre-treatment MTV. Death and progression at any other disease site were treated as competing risks. Gray's test p-value is less than 0.001.

RTOG 73-01 was a randomized trial testing four RT schedules for locally-advanced NSCLC.[49] Its results are often cited as the rationale for the "standard" dose of 60 Gy. Review of the results from that study, however, demonstrates that there was no difference in overall survival between patients who were treated with 50 Gy and those who received 60 Gy (Figure 6). In light of this, reducing the RT dose for lesions deemed to be at low risk for disease progression to 52.5 Gy is unlikely to detract from patients' outcomes.

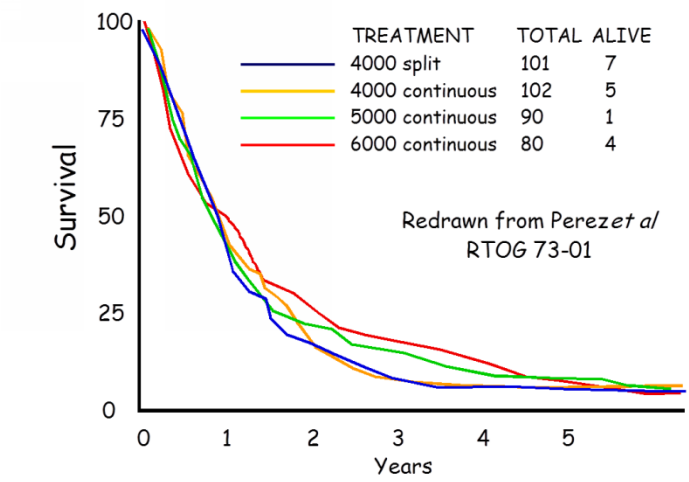


Figure 6 – Overall survival curves from RTOG 73-01, a randomized study that tested four radiotherapy schedules for patients with locally-advanced NSCLC

The data summarized above support reduction of the RT dose administered to low-risk tumors and lymph nodes. While de-escalation of therapy for a patient population where cure rates are limited seems counterintuitive, it is important to note that we are only scaling back therapy for lesions whose local control has been excellent (Figure 5). The new dose of 52.5 Gy for these lesions was chosen because it exceeds the 50 Gy dose studied in RTOG 73-01 but remains within the acceptable range of doses suggested by the National Cancer Database study.[47] If patients enrolled on this study develop disease progression in low-risk lesions treated with 52.5 Gy, we will revise this amendment.

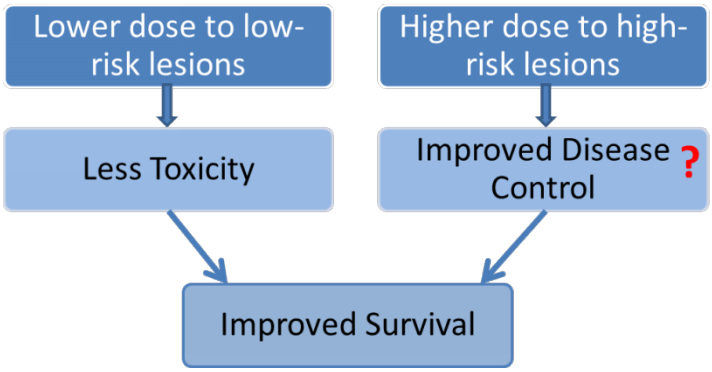


Figure 7 – Rationale for pursuing risk-adjusted dose painted RT for locally-advanced NSCLC

3.0 PATIENT ELIGIBILITY

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. This checklist must be photocopied, completed and maintained in each patient's chart.

3.1 Inclusion Criteria

Pathologically proven (either histologic or cytologic) diagnosis of NSCLC with any of the following stages (according to the AJCC Staging Manual, 7th edition, Appendix D):

- Stage IIIA or IIIB
- Stage II NSCLC with medical contraindication to curative surgical resection
- Stage IV disease with solitary brain metastasis that has been treated radically (eg: with surgical resection or stereotactic radiosurgery) and thoracic disease that would be classified as stage II-III

Appropriate diagnostic/staging workup, including:

- Complete history and physical examination
- Whole body PET/CT Scan within 42 days prior to study entry demonstrating hypermetabolic pulmonary lesion(s) and/or thoracic lymph node(s)**, with a maximum SUV > 6 for at least one lesion.** If PET/CT was obtained more than 42 days prior to study entry and is not repeated, CT scan of the chest within 28 days prior to study entry demonstrating stable disease is required.
- MRI of the brain or CT Scan of the head with contrast within 42 days prior to study entry
- Biopsy confirmation of suspected metastatic disease identified by PET/CT is recommended.
- PFTs within 6 weeks of study entry are highly recommended but not required.

No prior chemotherapy or thoracic radiotherapy for lung cancer

ECOG Performance Status 0-2 (Appendix C)

Age $\geq$ 18

Laboratory studies obtained within 28 days prior to study entry demonstrating adequate bone marrow and end organ function defined as:

- Absolute neutrophil count (ANC) $\geq$1,500 cells/µl

- Platelets ≥ 100,000 cells/µl
- Hemoglobin ≥ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.)
- Total bilirubin < 3.0 times the institutional Upper Limit of Normal (ULN)
- AST and ALT ≤ 3.0 x the ULN
- Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 ml/min (by Cockroft-Gault formula)

Women of childbearing potential must:

- Have a negative serum or urine pregnancy test within 72 hours prior to the start of study therapy
- Agree to utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study therapy is completed
- Be advised of the importance of avoiding pregnancy during trial participation and the potential risks of an unintentional pregnancy.

All patients must sign study specific informed consent prior to study entry.

3.2 Exclusion Criteria

Pleural or pericardial effusion

- A patient with pleural effusion may be enrolled the effusion is sampled by thoracentisis and cytology is negative or the effusion is seen on axial imaging but not on chest x-ray and deemed too small to tap under CT or ultrasound guidance.

Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness

Women who

- are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after cessation of study therapy
- have a positive pregnancy test at baseline
- are pregnant or breastfeeding

Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of

medications. Patients with diabetes will preferably be scheduled for PET/CT imaging in the morning, and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians

4.0 STUDY DESIGN

4.1 General Design

Treatment

This will be a single stage phase II study testing the efficacy and feasibility of hypofractionated, dose-painted IMRT (based on target lesion volumes on pre-treatment PET/CT imaging) with standard concurrent chemotherapy (low dose weekly carboplatin and paclitaxel) for the treatment of LA-NSCLC. Any lesions with pre-treatment MTV greater than 25 cc will be prescribed the higher dose (2.6 Gy per fraction), and lesions with MTV less than 25 cc will be treated with the lower dose (2.28 Gy per fraction). All patients will be treated with 25 daily fractions over 5 weeks.

All patients will receive standard weekly dosing of carboplatin (AUC 2) and paclitaxel (45 mg/m^2) chemotherapy weekly for five weeks during RT. This may be followed by 3 cycles of full dose adjuvant carboplatin (AUC 6) and/ paclitaxel (200mg/m^2) every 3 weeks, at the discretion of the treating physicians. Adjuvant chemotherapy should be started 4-6 weeks after completion of radiotherapy. Patient will have restaging PET/CT scan after completion of adjuvant chemotherapy or 12-16 weeks from completion of chemoradiation.

Follow-up

Patients will be evaluated with a history and physical examination at least once each week during the course of RT. Patients will be seen four weeks after completion of RT for toxicity evaluation. Patients may be seen more frequently to manage treatment-related toxicities if needed. Patients will be evaluated for response with post-treatment PET/CT imaging 12-16 weeks after completion of RT. Subsequent follow-up visits will occur every three months for the first two years and then every six months for a total of five years. Chest imaging with CT or PET/CT is recommended every three months over the first two years. Patients will be followed for survival and recurrence every 3 months for the first two years and every 6 months thereafter, and this data will be recorded on follow-up forms.

4.2 Study Calendar

		ChemoRT	ChemoRT	ChemoRT	ChemoRT	ChemoRT	Chemo	Chemo	Chemo	Response Evaluation	Follow-up[E]
	Pre-rx	Wk 1	Wk2	Wk 3	Wk 4	Wk 5	Wk 9	Wk 12	Wk 15	Approx Wk 19	
History	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Vital Signs & Weight	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential[A]	X	X	X	X	X	X	X	X	X	X	X
BMP, LFTs, Calcium[A]	X	X	X	X	X	X	X	X	X	X	X
Serum HCG[A]	X										
PFTs[B]	X										
PET/CT	X									X	
CT chest (including liver) or PET/CT	X									X	X
MRI Brain or CT Head with Contrast[C]	X										
Radiotherapy		XXXXX	XXXXX	XXXXX	XXXXX	XXXXX					
Carboplatin AUC 2		X	X	X	X	X					
Paclitaxel 45 mg/m^2		X	X	X	X	X					
Carboplatin AUC 6							X[D]	X[D]	X[D]		
Paclitaxel 200 mg/m^2							X[D]	X[D]	X[D]		
Blood/Urine for Correlative Studies	X			X			X			X	

A: Pre-enrollment laboratory tests should be performed within 28 days of study entry. HCG is required only for women with childbearing potential and must be done within 72 hours prior to start of study therapy.

B: PFTs within 6 weeks of study entry are highly recommended but not required.

C: Additional imaging of the brain may be obtained at any point if clinically indicated.

D: Adjuvant chemotherapy is optional, at the discretion of the treating physicians. Clinic visits and evaluations, including blood tests, can be skipped at weeks 12 and 15 for subjects who are not receiving adjuvant chemotherapy.

E: After Week 19 visit, patients will be seen every three months (+/- 2 weeks) for two years and then every six months (+/- 4 weeks) for a total of five years

4.3 Primary Endpoint

The primary endpoint of this study is the metabolic response of all pulmonary lesions and thoracic lymph nodes on post-treatment PET/CT imaging. For the purposes of this study, response will be defined as having maximum SUV less than 6.0 on post-treatment PET/CT, which will be obtained 12-16 weeks after completion of RT. Persistent metabolic activity above this threshold in a single lesion will qualify the subject as a nonresponder.

4.4 Secondary Endpoints

Locoregional progression-free survival: the interval from study registration to date of local or regional disease progression or death, censored at the date of data collection

Progression-free survival: the interval from study registration to date of disease progression or death, censored at the date of data collection

Overall survival: the interval from study registration to death, censored at the date of data collection

Lung cancer cause-specific survival: the interval from study registration to death directly from lung cancer, censored at the date of data collection (a patient will be considered to have died from lung cancer if he or she had evidence of disease progression at any site and no direct evidence of other cause of death)

Grade ≥ 2 radiation-induced lung toxicity, scored using CTCAE, v. 4

Any grade ≥ 3 treatment-related toxicity, scored using CTCAE, v. 4

5.0 STUDY THERAPY

5.1 Radiotherapy

5.1.1 Immobilization, Simulation, and Localization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, active breath-holding techniques, and use of 4D simulation CT to generate internal target volumes (ITVs). Internal organ inhibition maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans should be performed with IV contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between target lesions and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0

mm between scans in the region of the tumor. Images will be transferred to the treatment planning computers for treatment planning.

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

5.1.2 Target Volumes and Treatment Planning

Target lesions will be drawn on simulation CT imaging, using lung or mediastinal window levels as appropriate. PET imaging may be fused to simulation CT scans to aid with localization of hypermetabolic lesions. The low-risk gross tumor volume (**GTV_5250**) shall include the pulmonary tumor(s) as well as any suspicious lymph nodes (based on appearance, size ≥ 1cm in short axis, or pathologic data). A high-risk gross tumor volume (**GTV_6500**), will also be defined and will include only lesions with MTV > 25 cc on pre-treatment PET imaging. MTV calculations will be performed on PET imaging using a semiautomatic gradient-based contouring algorithm ("PET Edge", MIMvista Corp, Cleveland, OH) or using a thresholding tool to encompass all voxels with SUV > 40% of the SUVmax.[50] By definition, **GTV_6500 will be a subset of GTV_5250**.

If 4D CT simulation is used, GTVs should be generated on each CT phase that will be used for treatment (typically 4/10 phases if respiratory gating is employed, or 10/10 phases if the patient will be treated while breathing freely). GTVs will be combined to form internal target volumes (ITVs).

Each GTV (or ITV) will be expanded by 7-10 mm to form a CTV (**CTV_5250** and **CTV_6500**). CTVs may be trimmed to exclude anatomic boundaries to microscopic tumor spread. **CTV_6500 will be a subset of CTV_5250**.

Each CTV will be expanded to form a PTV. PTV expansions will be 5 mm in all directions if respiratory motion has been accounted for (eg: with beam gating, breath hold, or use of 4D-CT to form internal target volumes). Otherwise, PTV expansions will be 5 mm radially and 10 mm in the superior and inferior directions. **PTV_6500 will be a subset of PTV_5250.**

For high-risk lesions that are in close proximity to a dose-limiting structure (eg: large supraclavicular lymph node abutting brachial plexus), the prescription dose will be 2.4 Gy x 25 fractions = 60 Gy. A **GTV_6000**, **CTV_6000**, and **PTV_6000** shall be generated for those lesions as described above.

Adaptive RT (adjustment of target volumes during the course of RT) is not allowed in this protocol, unless difficulties with daily patient setup require repeating the CT simulation procedure.

Megavoltage equipment is required with effective photon energies of 6-18 MV. Use of IMRT or volumetric modulated arc therapy (VMAT) is required for this protocol. All fields must be individually shaped to minimize structures and lung not within the target volume. Divergent custom-made blocks or multi-leaf collimation will be used. All treatment planning will be performed using tissue heterogeneity corrections.

Treatment may alternatively be delivered using proton beam therapy. In that case, all of the dosimetric guidelines described herein must be followed after converting physical dose to gray-equivalent (GyE).

5.1.3 Target Coverage

The goal is to deliver conformal treatment that minimizes normal tissue irradiation. As a guideline, a conformity index (ratio of the volume of the prescription isodose surface to the PTV) of < 1.5 is desirable. The prescription isodose surface should encompass at least 95% of each PTV. The minimum PTV dose must not fall below 90% of the prescription dose. The maximum dose must not exceed a value that is 115% of the highest prescribed dose, and the hot spot must be located within the PTV.

5.1.4 Critical Structures

Lung, spinal cord, esophagus, brachial plexus, and heart/pericardium should be based on the published atlases available on the RTOG web site (http://www.rtog.org/CoreLab/ContouringAtlases.aspx). Dosimetric constraints for organs at risk are listed in **Table 2**. These have been adopted from the ongoing RTOG 1106 protocol for LA-NSCLC.

Structure	Metric	No Deviation	Deviation Acceptable	Deviation Unacceptable
Lungs-CTV	Max Dose Mean Dose Volume>20 Gy Volume>5 Gy	≤110% Rx Dose ≤20 Gy ≤35% ≤50%	≤113% Rx Dose ≤21 Gy ≤36% ≤55%	>113% Rx Dose >21 Gy >36% >55%
Heart & Pericardium	Max Dose Mean Dose Volume>40 Gy Volume>60 Gy	≤65 Gy ≤30 Gy ≤80% ≤30%	≤67 Gy ≤31 Gy ≤85% ≤33%	>67 Gy >31 Gy >85% >33%
Esophagus	Max Dose Mean Dose	≤72 Gy ≤34 Gy	≤74 Gy ≤35 Gy	>74 Gy >35 Gy

Spinal Cord	Max Dose	≤50 Gy	≤52 Gy	>52 Gy
Brachial Plexus	Max Dose	≤63 Gy	≤65 Gy	>65 Gy

Table 2 – Dosimetric Constraints

5.1.5 Radiotherapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely when the pericardium and spinal cord receive doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the first six months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy, provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required. It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. Esophagitis should be graded according to the CTCAE v.4.0. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit the treatment break to 3 days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify the principal investigator (PI).

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, and reflux symptoms, should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are listed in the table below. In cases where the treating physicians are concerned that inanition will occur due to disease burden and/or chemoradiotherapy (eg, based on the patient's RT plan), prophylactic feeding tube placement may be considered.

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

5.2 Concurrent Chemotherapy

5.2.1 Concurrent Chemotherapy Dosing

Chemotherapy will be administered weekly concurrent with radiation on the same day each week. Carboplatin (AUC 2, IV) and Paclitaxel (45 mg/m2, IV) will be started on week 1 of thoracic radiotherapy and will be continued weekly for 5 weeks. Patients may receive chemotherapy on any day of the week from Monday to Friday, but the day of administration should remain constant during the course of chemoradiotherapy. A 1-day shift in the day of weekly chemotherapy infusion will be allowed if necessary.

Paclitaxel 45 mg/m^2 IV will be given by one hour infusion. Paclitaxel is mixed in non-PVC containers per the usual guidelines of the pharmacy. Carboplatin will be given at AUC 2 (calculated using the Calvert formula) over 1/2 hour immediately after paclitaxel. GFR will be calculated using the Cockroft-Gault formula. A > 10% change in the serum creatinine will warrant a recalculation of the carboplatin and paclitaxel doses.

Calvert Formula

Calculated dose of carboplatin (mg) = target AUC x (glomerular filtration rate (GFR) + 25)

Cockroft-Gault Formula

GFR = (140 – Age) x Weight (in kg) x 0.85 (females only) ÷ (72 x Serum Creatinine (in mg/dL))

Prior to receiving carboplatin and paclitaxel, all patients should receive standard premedication. One standard that is recommended is:

Dexamethasone 20 mg orally 12 and 6 hours before paclitaxel or 20 mg IV just prior to paclitaxel

Diphenhydramine 25 or 50 mg IV (or equivalent) prior to paclitaxel

Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) prior to paclitaxel

Granisetron 1 mg orally (or equivalent) prior to chemotherapy

Dose modifications are outlined in section 5.4.2.

5.2.2 Chemotherapy Adverse Events

Adverse events caused by carboplatin may include:

Hematologic: Myelosuppression

Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia

Neurological: Peripheral neuropathy, ocular changes

Other: Ototoxicity, myalgia, fatigue, allergic reaction

Adverse events caused by paclitaxel may include:

Hematologic: Myelosuppression

Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (AST, ALT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis

Cardiac: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness

Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma

Allergic: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome flushing, rash, pruritus

Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

Required dose modifications for adverse events are detailed in sections 5.4.2 and 5.4.3.

5.3 Adjuvant/Consolidation Chemotherapy

5.3.1 Adjuvant/Consolidation Chemotherapy Dosing

Consolidation chemotherapy will start approximately 4-6 weeks after the completion of all radiotherapy when esophagitis and chemotherapy-induced neuropathy are grade 1 or less, ANC > 1500, and platelet count > 100,000. If the ANC and platelet

count are not at the required levels, chemotherapy should be delayed until the following week. Carboplatin (AUC 6, IV, over ½ hour) and Paclitaxel (200 mg/m2, IV, over 3 hours) will be given on day 1. This will be repeated every 21 days for a total of 3 cycles, on the same day of the week for each cycle. Patients should receive standard premedication as outlined above.

Dose modifications are outlined in section 5.4.3.

Potential complications of carboplatin and paclitaxel are detailed in section 5.2.2.

5.4 Treatment Modifications

If treatment is interrupted due to a non-dose-limiting adverse event or any reason other than toxicity, such as a holiday, bad weather, or a transportation problem, the duration of therapy will be extended accordingly. If a patient misses a day of radiation and chemotherapy, then the weekly chemotherapy should be delivered the next day and the missed radiation fraction will be given after the completion of planned treatments.

Patients who exhibit distant tumor progression will discontinue all study procedures and will be medically managed. These patients will continue to be followed as specified in the protocol. These patients may be treated with other agents. Patients who exhibit local-regional tumor progression will complete radiation as described in Section 6.0. Tissue confirmation is recommended to confirm the progressive disease in locoregional or metastatic sites.

5.4.1 RT Interruption

Recommended treatment modifications for in-field RT toxicities are detailed below. If treatment is interrupted for > 2 weeks, protocol treatment should be discontinued. Follow up and data collection will continue as specified in the protocol. RT should be held for all Grade 4 nonhematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2. Further treatment off protocol is at the discretion of the treating physician. If the patient experiences esophagitis so that IV fluid support is needed, insertion of a feeding tube should be considered. RT should be discontinued if Grade 4 pulmonary toxicity occurs.

Treatment Modification for In-field Non-Hematologic Toxicity				
In-field	**CTCAE, v. 4 Toxicity Grade**	**XRT**	**Paclitaxel**	**Carboplatin**
Esophagus/pharynx *(on day of XRT)*	4	Hold treatment until ≤ Grade 2; evaluate at least weekly	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	3	No change or hold ≤ 5 days (See Sections 7.6.12 and 7.6.13)	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	2	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	3	No change	No change	No change

5.4.2 Concurrent Chemotherapy Modifications

Recommended dose modifications for hematologic toxicity are detailed below. Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, chemotherapy doses will not be adjusted. Doses that are missed during weekly schedule concurrent with radiotherapy will not be made up but will be documented. If either chemotherapeutic agent is withheld for greater than two consecutive weeks, that drug will be held for the duration of concurrent therapy.

Toxicity CTCAE Grade (CTCAE, v. 4)	Paclitaxel Dose At Start of Subsequent Cycles of Therapy [a]	Carboplatin Dose at Start of Subsequent Cycles of Therapy [a]
Neutrophil count decreased (Neutropenia)		
1 <LLN - 1500/mm^3; <LLN - 1.5 x 10e9 /L	Maintain dose level	Maintain dose level
2 <1500 - 1000/mm^3; <1.5 - 1.0 x 10e9 /L	Maintain dose level	Maintain dose level
3 <1000 - 500/mm^3; <1.0 - 0.5 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
4 <500/mm^3; <0.5 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
Febrile neutropenia (Neutropenic fever)	Hold therapy[b]	Hold therapy[b]
Platelet count decreased (Thrombocytopenia)		
1 <LLN - 75,000/mm^3; <LLN - 75.0 x 10e9 /L	Maintain dose level	Maintain dose level
2 <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
3 <50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
4 <25,000/mm^3; <25.0 x 10e9 /L	Hold therapy[b]	Hold therapy[b]
Other Hematologic toxicities	There will be no dose modifications for changes in white blood cell counts (leukopenia) or lymphocyte count decreased (lymphopenia).	

Recommended dose modifications for <u>non-hematologic toxicity</u> are detailed below. For CTCAE Grade ≤ 2 non-hematologic toxicity, maintain dose levels. Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy,

paclitaxel and carboplatin doses will not be adjusted. Note that concurrent chemotherapy will also be held for certain in-field RT toxicities (see section 5.4.1).

Worst Toxicity CTCAE Grade (CTCAE, v. 4) [a, c]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b]
Neuropathy (peripheral sensory)		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities		
≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

5.4.3 Adjuvant/Consolidation Chemotherapy Modifications

Patients will be treated at the following chemotherapy dose levels:

Dose Levels of Paclitaxel and Carboplatin

	Starting Dose	Dose Level -1	Dose Level -2
Concurrent Therapy[a]			
Paclitaxel	45 mg/m^2	NA	NA
Carboplatin	AUC=2	NA	NA
Consolidation Therapy[b]			
Paclitaxel	200 mg/m^2	150 mg/m^2	NA
Carboplatin	AUC=6	AUC=4.5	NA

[a] For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[b] For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed.

Recommended dose modifications for hematologic toxicity are detailed below. Dose levels are relative to the levels in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed. Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles. When a chemotherapy dose reduction is required during the consolidation therapy, reescalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

Toxicity CTCAE Grade (CTCAE, v. 4)	Paclitaxel Dose At Start of Subsequent Cycles of Therapy [a, c]	Carboplatin Dose at Start of Subsequent Cycles of Therapy [a, c]
Neutrophil count decreased (Neutropenia)		
1 <LLN - 1500/mm^3; <LLN - 1.5 x 10e9 /L	Maintain dose level	Maintain dose level
2 <1500 - 1000/mm^3; <1.5 - 1.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
3 <1000 - 500/mm^3; <1.0 - 0.5 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
4 <500/mm^3; <0.5 x 10e9 /L	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Febrile neutropenia (Neutropenic fever)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Platelet count decreased (Thrombocytopenia)		
1 <LLN - 75,000/mm^3; <LLN - 75.0 x 10e9 /L	Maintain dose level	Maintain dose level
2 <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
3 <50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
4 <25,000/mm^3; <25.0 x 10e9 /L	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3
Other Hematologic toxicities	There will be no dose modifications for changes in white blood cell counts (leukopenia) or lymphocyte count decreased (lymphopenia).	

Recommended dose modifications for <u>non-hematologic toxicity</u> are detailed below. Dose levels are relative to the dose levels in the previous cycle. If paclitaxel doses must be withheld for greater than 2 consecutive weeks, the drug will be held permanently for the duration of consolidation therapy.

Worst Toxicity CTCAE Grade (CTCAE, v. 4) [a]	Paclitaxel Dose At Start of Subsequent Cycles of Therapy [b]	Carboplatin Dose At Start of Subsequent Cycles of Therapy [b]
Neuropathy (peripheral sensory) See Section 7.6.18 for further details		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities		
Worst Toxicity CTCAE Grade (CTCAE, v. 4) [a]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b]
Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

5.4.4 Allergic Reactions

If, at any point in the course of study therapy, a subject is deemed to develop an allergic reaction to carboplatin or paclitaxel, carboplatin/paclitaxel chemotherapy can be discontinued at the discretion of the treating physicians. This regimen can be replaced by another platinum doublet (eg: cisplatin/etoposide) that will be administered using a standard dosing schedule. Radiotherapy and other protocol-specified procedures, including the post-treatment PET/CT, will proceed as planned. These patients will be followed for primary and secondary endpoints, in keeping with the "intent to treat" principle.

5.5 Biospecimen Collection

Blood (less than 10 mL in an EDTA tube) and urine (less than 15 mL) samples will be collected from patients prior to therapy, and at week 3, at week 9, and at the time of response evaluation (at approximately week 19). These collections are included in the Study Calendar (section 4.2). Blood tests are routinely performed on a weekly basis for patients receiving chemotherapy, so only the week 19 collection will cause patient inconvenience outside of standard clinical care. Urine samples will also be collected at the same time points.

Instructions for the handling of blood and urine samples are described in detail on the Albert Einstein Stable Isotope & Metabolomics Core website. (http://www.einstein.yu.edu/uploadedFiles/Research/Shared-Facilities/stable-isotopes-metabolics/Sample%20preparation%20guideline.pdf) Samples will be directed to:

Einstein Metabolomics Core Facility

c/o Albert Einstein College of Medicine

1301 Morris Park Ave, Price Bldg 368

Bronx, NY 11743

Each specimen will be analyzed in the Stable Isotope & Metabolomics Core Facility of the Diabetes Research Center, which is directed by Dr. Irwin Kurland. We will test each sample for over 150 metabolites that are involved in pathways such as the urea cycle, fatty acid metabolism, and spermidine and spermine metabolism. Additional information about these tests is available at http://www.einstein.yu.edu/research/shared-facilities/stable-isotope-metabolomics-core/services/.

6.0 RESPONSE ASSESSMENT

6.1 Primary Endpoint – PET Response

The primary endpoint of this study is achieving metabolic response in the primary tumor and all thoracic lymph nodes on post-treatment PET/CT imaging, which will be obtained 12-16 weeks after completion of RT. For the purposes of this study, metabolic response will be defined as having maximum SUV less than 6.0 on post-treatment imaging. Persistent metabolic activity above this threshold in a single lesion will qualify the subject as a nonresponder.

This assessment will be performed by the PI and co-investigators from the Department of Nuclear Medicine. For each patient, every hypermetabolic thoracic lesion visible on post-treatment PET/CT imaging will be contoured using a semiautomatic gradient-based contouring algorithm ("PET Edge", MIMvista Corp, Cleveland, OH) or using a thresholding tool to encompass all voxels with SUV > 40% of the SUVmax. The maximum SUV for each lesion will be recorded, as will the maximum SUV for each study subject.

6.2 Secondary Endpoints – Progression-free Survival

Secondary endpoints of this study include locoregional progression-free survival and progression-free survival. Evaluation for progressive disease will follow RECIST criteria.[51]

Response Criteria: Evaluation of target lesions

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

7.0 STATISTICAL CONSIDERATIONS

7.1 Sample Size Calculation

Based on data we have generated from the ACRIN 6668 / RTOG 0235 dataset, approximately 35% of patients can be expected to have significant (SUVmax>6.0) residual hypermetabolic activity on post-treatment PET/CT after chemoRT for LA-NSCLC. We hypothesize that this rate will be less than or equal to 15% for patients treated on this protocol. Based on this assumption, 31 post-treatment PET/CT scans will be required to provide 80% power to detect an improvement in PET response rate at a target error rate of 5% and actual error rate of 0.046. If 7 or fewer out of 31 patients have significant residual activity, we will accept the hypothesis that the rate of residual activity is less than or equal to 15%. Adjusting for a 10% dropout rate, a total of 39 patients will be accrued to this study.

7.2 Primary Efficacy Analysis

Descriptive statistics of baseline demographic and clinical characteristics will be presented. The demographic and clinical characteristics will be compared between responders and non-responder's using chi-square statistics or Fishers exact test for categorical variable and t-test or Wilcoxon Mann-Whitney U test for continuous variables. The efficacy analysis of the primary endpoint, which is the metabolic response of all pulmonary lesions and thoracic lymph nodes on post-treatment PET/CT imaging, will be performed using single sample pre-post proportion test.

7.3 Secondary and Other Efficacy Analyses

Secondary endpoints of this study include locoregional progression-free survival, progression-free survival and overall survival. Kaplan-Meier survival plots will be produced for disease-free survival and overall survival. The survival probabilities will be presented. Log-rank testing will be used to compare the survival probabilities between categorical predictors. A Cox regression model will be used to estimate the hazard rates for progression free survival and overall survival among the predictor variables. In addition, for patients who are assessed as responders, time to objective response and objective response duration will be summarized. The safety parameters will be presented as frequency and percentages. The relationship of metabolic markers during the course of time with treatment response and clinical endpoints will be assessed using logistic regression and time-dependent Cox regression models.

7.4 Subject Accrual

In the Einstein/Montefiore Department of Radiation Oncology, approximately five patients are treated with definitive chemoRT for LA-NSCLC each month. We expect

that 40-50% of such patients will be enrolled on this study, for an average of 2 patients per month. Thus, we anticipate that enrollment will span over a period of approximately 18 months.

8.0 REGULATORY CONSIDERATIONS

8.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

8.2 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to the PI. The PI should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

The investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the PI.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

What protected health information (PHI) will be collected from subjects in this study

Who will have access to that information and why

Who will use or disclose that information

The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.0 DATA SAFETY AND MONITORING BOARDS

The Albert Einstein College of Medicine/Albert Einstein Cancer Center Data Safety Monitoring Committee (DSMC) has the responsibility for ensuring data and safety monitoring along with the PI who is ultimately responsible for the ongoing monitoring and safety of clinical protocols. The primary functions of the AECC DSMC are as follows:

1. To review and ensure protocol compliance with dose escalation in phase I trials

2. To review/assure protocol compliance for all trials that have two-stage phase II designs,
3. Reviewing all internal and external serious adverse reports, investigator alerts, action letters, and other safety reports for trials being performed at AECC-affiliated institutions and;
4. To implement and to determine the adequacy of DSM plans of all approved protocols.

The DSMC is an independent committee and meets on a monthly basis. During its monthly meeting, the DSMC will review serious (grade 3 or higher) adverse events from this study. In the event that the DSMC decides that a revision is warranted, the committee will immediately notify the principal investigator of this study. The DSMC has the authority to close trials to patient accrual should the risk to patients be excessive or outweigh the potential benefits of the study. All study suspensions and closures will be forwarded to the IRB/CCI and study sponsor from the DSMC.

11.0 ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of treatment. During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

AEs will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial intervention or medication. All AEs considered related to trial intervention or medication will be followed until resolution, even if this occurs post-trial.

11.1 Adverse Event Definitions

Adverse Event (AE): any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious Adverse Event (SAE): An AE occurring at any dose that results in any of the following outcomes (CFR 312.32)

Death

Life-threatening adverse experience

Inpatient hospitalization or prolongation of existing hospitalization excluding those for study therapy administration, transfusional support, disease staging/re-staging procedures, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events

Persistent or significant disability or incapacity

Congenital anomaly / birth defect.

The definition of SAE 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 or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of “related” is that there is a reasonable possibility that the drug or the study intervention caused the adverse experience.

Unexpected Adverse Event: An AE that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening: Any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

AEs will use the descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix B). A list of AEs that have occurred or might occur can be found in sections above.

11.2 Adverse Event Reporting

Study site personnel must notify the PI and the sponsor immediately of any SAE experienced by a patient. In general, SAEs assessed as clearly being due to disease progression, and not due to study drug(s), should be excluded from AE reporting. Study-specific clinical outcomes of death because of disease progression are exempt from SAE reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not an SAE.

The following steps will be taken to report promptly and document accurately any SAE, even if it may not appear to be related to the study treatment:

Report the SAE to the PI and the treating physician by email, telephone or fax within 24 hours of becoming aware that a patient has experienced an SAE.

Record the SAE accurately on the AE page of the patient's CRF.

Using the standard IRB-SAE report form, submit all known patient information within 24 hours of SAE occurrence to the clinical trial office to submit to IRB and DSMB. Date and sign each report before submission. Include the following information (or as much as possible to obtain and still report the event within 24 hours):

- Study protocol number and indication
- Study site and investigator's identification
- Patient's ID (patient number and initials), age or date of birth, and sex
- Date of enrollment
- Description of SAE, including date of onset and duration, severity, and outcome
- Date of first and most recent (last) dose administered
- Action taken regarding study treatment
- Relationship of SAE to study treatment
- Concomitant medications, including regimen and indication
- Intervention, including concomitant medications used to treat SAE
- Pertinent laboratory data/diagnostic tests conducted and date
- Pertinent medical history of patient

- Date of hospital admission/discharge
- Date of death (if applicable)

Within 10 days of initial IRB notification, the PI is required to submit a completed Adverse Event Report to the IRB. The treating physicians should perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to the PI, IRB, and DSMB.

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13.0 APPENDICES

13.1 Appendix A – Eligibility Checklist

Inclusion Criteria

Must be answered **YES** for eligibility

1. Does the patient have pathologically proven NSCLC?

   Yes / No

2. Is the patient's disease stage one of the following? (using AJCC 7th edition):
   - Stage IIIA or IIIB
   - Stage II with medical contraindication to curative surgical resection
   - Stage IV with solitary brain metastasis that has been treated radically (eg: with surgical resection or stereotactic radiosurgery) and thoracic disease that would be classified as stage II-III

   Yes / No

3. Has the patient had an appropriate staging workup, including:
   - Complete history and physical examination
   -Whole body PET/CT Scan within 42 days prior to study entry demonstrating hypermetabolic pulmonary lesion(s) and/or thoracic lymph node(s), with a maximum SUV > 6 for at least one lesion. If PET/CT was obtained more than 42 days prior to study entry and is not repeated, CT scan of the chest within 28 days prior to study entry demonstrating stable disease is required.
   - MRI of the brain or CT Scan of the head with contrast within 42 days prior to study entry

   Yes / No

4. Does the patient have ECOG Performance Status 0-2?

   Yes / No

5. Is the patient at least 18 years old?

   Yes / No

6. Does the patient have laboratory studies obtained within 28 days prior to study entry demonstrating adequate bone marrow and end organ function defined as:
   - Absolute neutrophil count (ANC) >1,500 cells/µl
   - Platelets > 100,000 cells/µl
   - Hemoglobin > 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb > 9.0 g/dl is acceptable.)
   - Total bilirubin < 3.0 times the institutional Upper Limit of Normal (ULN)
   - AST and ALT < 3.0 x the ULN
   - Serum creatinine < 1.5 x ULN or calculated creatinine clearance ≥ 50 ml/min (by Cockroft-Gault formula)

Yes / No

7. Is either of the following true?:
   - The patient is not a woman of childbearing potential.
   - The patient has undergone negative serum or urine pregnancy test within 72 hours prior to the start of study therapy, agrees to utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study therapy is completed, and has been advised of the importance of avoiding pregnancy during trial participation and the potential risks of an unintentional pregnancy.

   Yes / No

8. Has the patient signed study-specific informed consent?

   Yes / No

Exclusion Criteria

Must be answered **NO** for eligibility

1. Has the patient had prior chemotherapy or thoracic radiotherapy for lung cancer?

   Yes / No

2. Does the patient have a pleural or pericardial effusion that can be sampled using CT or ultrasound guidance but has not yet been sampled?

   Yes / No

3. Is the patient compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness?

   Yes / No

4. Is the patient pregnant or breastfeeding?

   Yes / No

5. Does the patient have poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of medications.

   Yes / No

If patient is eligible, fax eligibility checklist to Hilda Haynes, NP: 718-231-5064

13.2 Appendix B – Common Toxicity Criteria

NCI CTCAE Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.0

13.3 Appendix C – ECOG Performance Status

Performance Status	Definition
0	No symptoms; normal activity level
1	Symptomatic, but able to carry out normal daily activities
2	Symptomatic; in bed less than half of the day; needs some assistance with daily activities
3	Symptomatic; in bed more than half of the day
4	Bedridden

13.4 Appendix D – AJCC Lung Cancer Staging (7th Edition)

TNM staging system for lung cancer (7th edition)

Primary tumor (T)			
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus		
T1a	Tumor ≤2 cm in diameter		
T1b	Tumor >2 cm but ≤3 cm in diameter		
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:		
	Involves main bronchus, ≥2 cm distal to carina		
	Invades visceral pleura		
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T2a	Tumor >3 cm but ≤5 cm		
T2b	Tumor >5 cm but ≤7 cm		
T3	Tumor >7 cm or any of the following:		
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)		
	Atelectasis or obstructive pneumonitis of the entire lung		
	Separate tumor nodules in the same lobe		
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe		
Regional lymph nodes (N)			
N0	No regional lymph node metastases		
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)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

Adapted from: Goldstraw, P, Crowley, J, Chansky, K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groups in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2:706.

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