Title: Patient-Reported Outcomes following Chemoradiotherapy for Locally Advanced Non-small Cell Lung Cancer

NCT03481114
IRB#: 2017-8065

IRB Approval Date: 11/22/2019

Patient-Reported Outcomes following Chemoradiotherapy for Locally Advanced Non-small Cell Lung Cancer: A Randomized Trial Comparing Two Radiotherapy Schedules

CONFIDENTIAL

The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Principal Investigator
Nitin Ohri, MD
Albert Einstein College of Medicine
Department of Radiation Oncology
1300 Morris Park Avenue, Mazer 610
Bronx, NY 10461
Phone: 718-920-7750
Fax: 718-430-8618
Email: nohri@montefiore.org

Co-Investigators (Radiation Oncology)
Madhur Garg, MD
Montefiore Medical Center
Department of Radiation Oncology
111 East 210th Street
Bronx, NY 10467
Phone: 718-920-4361
Fax: 718-882-6914

William Bodner, MD
Montefiore Medical Center
Department of Radiation Oncology
111 East 210th Street
Bronx, NY 10467
Phone: 718-920-4361

Fax: 718-882-6914

Rafi Kabarriti, MD
Montefiore Medical Center
Department of Radiation Oncology
111 East 210th Street
Bronx, NY 10467
Phone: 718-920-4361
Fax: 718-882-6914

Jana Fox, MD
Montefiore Medical Center
Department of Radiation Oncology
111 East 210th Street
Bronx, NY 10467
Phone: 718-920-4361
Fax: 718-882-6914

Keyur Mehta, MD
Montefiore Medical Center
Department of Radiation Oncology
111 East 210th Street
Bronx, NY 10467
Phone: 718-920-4361
Fax: 718-882-6914

Co-Investigators (Medical Oncology)
Balazs Halmos, MD
Montefiore Medical Park at Eastchester
1695 Eastchester Road
Bronx, NY 10461
Phone: 718-405-8404
Fax: 718-405-8433
Email: bahalmos@montefiore.org

Haiying Cheng, MD, PhD
Montefiore Medical Center
Montefiore Medical Park at Eastchester
1695 Eastchester Road
Bronx, NY 10461
Phone: 718-405-8505
Fax: 718-405-8501
Email: hcheng@montefiore.org

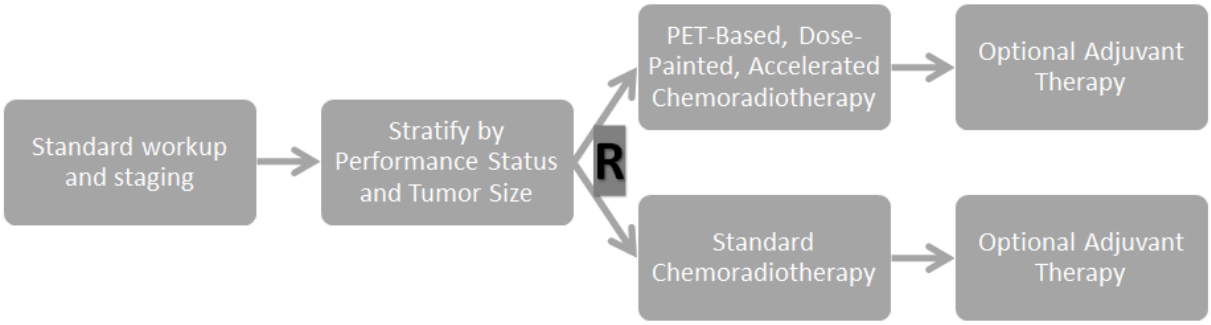
Roman Perez-Soler, MD
Montefiore Medical Center
Department of Oncology, Hofheimer 100
111 East 210th Street
Bronx, NY 10467-2490
Phone: 718-920-4826
Fax: 718-798-7474
Email: rperezso@montefiore.org

Rasim Gucalp, MD
Montefiore Medical Center-Moses Division
Department of Oncology, Hofheimer 100
111 East 210th Street
Bronx, NY 10467-2490
Phone: 718-920-4826
Fax: 718-798-7474
Email: rgucalp@montefiore.org

Co-Investigators (Nuclear Medicine)
Tony Abraham, DO
Montefiore Medical Park
1695A Eastchester Road
Bronx, NY 10461
Tel: 718-405-8461
Fax: 718-824-0830
Email : toabraha@montefiore.org

Co-Investigators (Statistics)
Shankar Viswanathan, DrPH, MSc
Albert Einstein College of Medicine
1300 Morris Park Avenue, Belfer 1312D
Bronx, New York 10461
Phone: 718-430-3762
Fax: 718-430-8780
Email: shankar.viswanathan@einstein.yu.edu

SCHEMA



50 subjects will be stratified by performance status (2 v. 0-1) and primary tumor size (>4 cm v. ≤ 4 cm) and then will be randomized 1:1 between the two study arms.

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
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
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
ULN	Upper limit of normal
VMAT	Volumetric modulated arc therapy

Contents

1.0 OBJECTIVES

1.1 Primary Objective

- To characterize patient-reported outcomes during and after concurrent chemoradiotherapy for locally-advanced non-small cell lung cancer.

1.2 Secondary Objectives

- To compare patient-reported outcomes observed during and after treatment with PET-based, dose-painted, accelerated chemoradiotherapy against patient-reported outcomes observed during and after treatment with standard chemoradiotherapy for locally-advanced non-small cell lung cancer.
- To compare physician-reported adverse event rates during and after treatment with PET-based, dose-painted, accelerated chemoradiotherapy against physician-reported adverse event rates during and after treatment with standard chemoradiotherapy for locally-advanced non-small cell lung cancer.
- To compare clinical outcomes (local disease control, progression-free survival, and overall survival) following dose-painted, accelerated chemoradiotherapy against clinical outcomes after treatment with standard chemoradiotherapy for locally-advanced non-small cell lung cancer.
- To explore associations between radiotherapy doses delivered to normal structures and declines in patient-reported outcomes.

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 to a dose of approximately 60-66 Gy with concurrent, platinum-based chemotherapy. This treatment approach, however, yields median survival times of only 16-30 months. Randomized trials have tested changes or additions to systemic therapy[3-7], radiotherapy dose escalation[6], and the addition of surgical resection[8] but have failed to improve outcomes for this patient population.

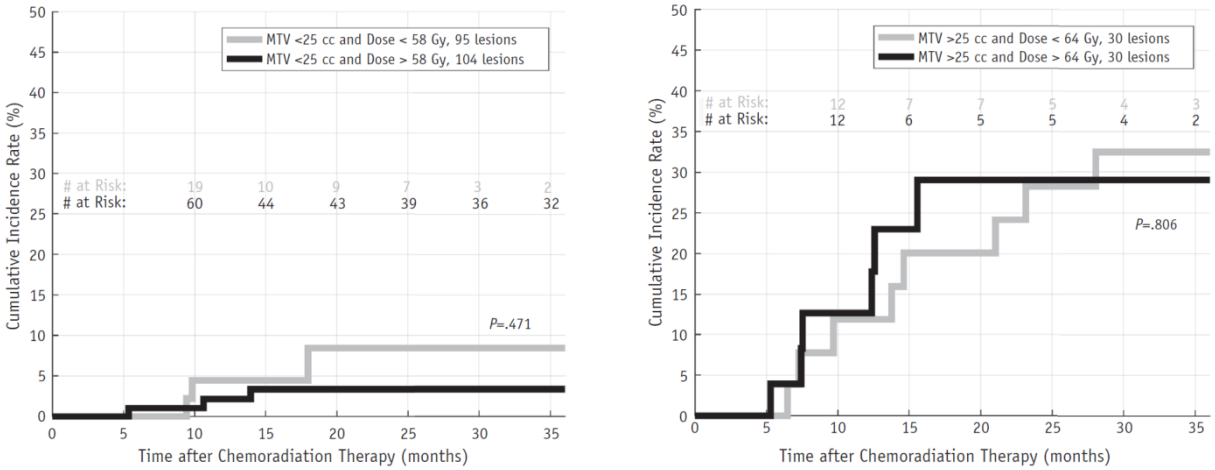
Toxicities of thoracic chemoradiotherapy include acute esophagitis, radiation pneumonitis, and increased risk of cardiac events. The risk and severity of these complications is directly related to the extent of normal tissue irradiation[9-12]. Acute esophagitis can dramatically impair patients' quality of life and lead to hospitalizations and treatment interruptions that reduce treatment efficacy[13,14]. Recent high-profile analyses demonstrate that, even when modern radiotherapy planning techniques are utilized, incidental cardiac irradiation significantly increases the risk of death following

treatment of LA-NSCLC with chemoradiotherapy[6,15,16]. Strategies to reduce irradiation of normal tissues during the treatment of LA-NSCLC can therefore be expected to improve patients' quality of life and prolong survival.

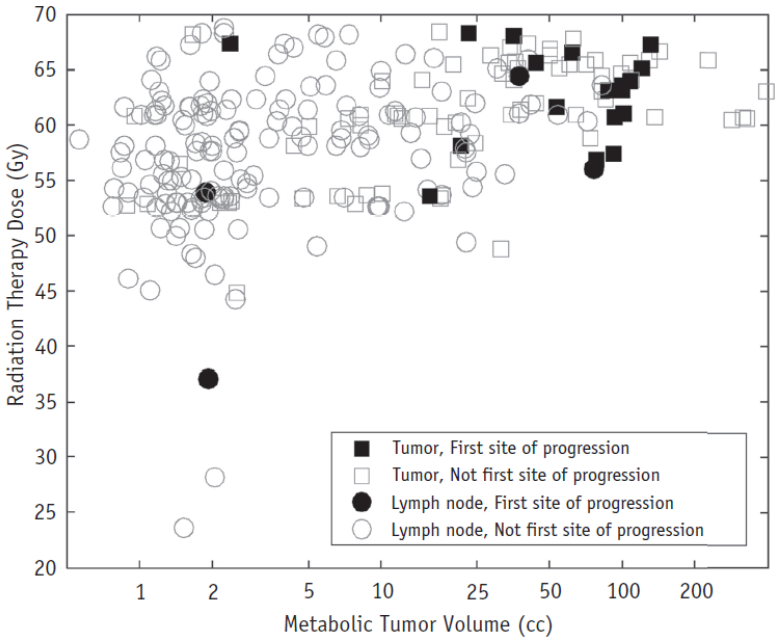
2.2 PET Imaging for LA-NSCLC

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[17-19]. Implementation of PET imaging may somehow alter the management of NSCLC patients in up to 40% of cases[18,20,21].

Beyond its use as a staging tool, PET may provide meaningful prognostic information for LA-NSCLC patients treated with chemoradiotherapy. In a multi-institutional trial (ACRIN 6668 / RTOG 0235), post-treatment PET findings (maximum or peak SUV) were found to predict locoregional disease progression and overall survival[22]. In a secondary analysis of that study, we found that pre-treatment disease burden, measured as total metabolic tumor volume (MTV), was also a powerful predictor of clinical outcomes[23]. Additionally, we found that individual tumors or lymph nodes with high MTV before treatment were most likely to retain high levels of activity after chemoradiotherapy. Using data from Montefiore/Einstein, we found that MTV may be used to identify specific tumors or lymph nodes at risk for progression following chemoradiotherapy[24]. We then validated these findings in a separate patient cohort[25]. Of note, we found no evidence that the use of relatively high radiotherapy doses would improve local control rates for large lesions and no evidence that the use of relatively low doses would reduce local control rates for small lesions.



Cumulative incidence rates of local disease progression in lesions with low MTV (left) and high MTV (right) in 89 LA-NSCLC subjects treated with concurrent chemoradiotherapy at Montefiore/Einstein.



Scatterplot of radiation therapy dose (PTV D90, or minimum dose that encompassed at least 90% of target volume) versus MTV. MTV is plotted on a logarithmic scale. Squares represent primary tumors, and circles denote lymph nodes. Lesions that were the first site of disease progression are shaded in black

.

Based on our findings that in-field disease progression nearly always occurs in lesions with high MTV, we performed a prospective study entitled "The PET-Adjusted IMRT for NSCLC Trial (PAINT, NCT02073968)". Patients with inoperable stage IIB-III NSCLC and ECOG performance status 0-2 who underwent staging PET were eligible for this single-arm study. All patients were treated with a 25-fraction course of dose-painted IMRT over 5 weeks. Tumors or lymph nodes with MTV exceeding 25 cc were deemed "high risk" and received 65 Gy. Lesions smaller than 25 cc were considered "low risk" and treated with 57 Gy until November 2014, when the study was amended to reduce the prescription dose for such lesions to 52.5 Gy. All patients received concurrent weekly carboplatin (AUC 2) and paclitaxel (45-50 mg/m^2) during radiotherapy, and adjuvant chemotherapy with the same agents was optional. Patients underwent post-treatment PET 12-16 weeks after completion of IMRT. The primary study endpoint was the absence of high residual metabolic activity (maximum SUV > 6) in the lungs and regional lymph nodes on post-treatment PET. Thirty-five enrolled subjects with 116 hypermetabolic tumors and lymph nodes were eligible for analysis. The primary endpoint was met for 24/30 patients (80%) who underwent post-treatment PET, satisfying our pre-specified efficacy objective. Median overall survival duration for all subjects was 22.5 months, and median survival for subjects with performance status 0-1 has not yet been reached. Treating progression in other sites and death without disease progression as competing risks, the two-year cumulative incidence rate of local disease progression in the 25 high-risk lesions was 9%. The two-year cumulative incidence rate of local disease progression in the 91 low-risk lesions that were treated with a low radiotherapy dose was only 3%. These results will be reported in an oral presentation at the ASTRO 2017 Annual Meeting.

In this study, we will shorten the radiotherapy course for patients receiving dose-painted IMRT to 20 fractions over 4weeks. A 20 fraction radiotherapy course is standard in some countries[26]. This shortened course will be more convenient for our patients and

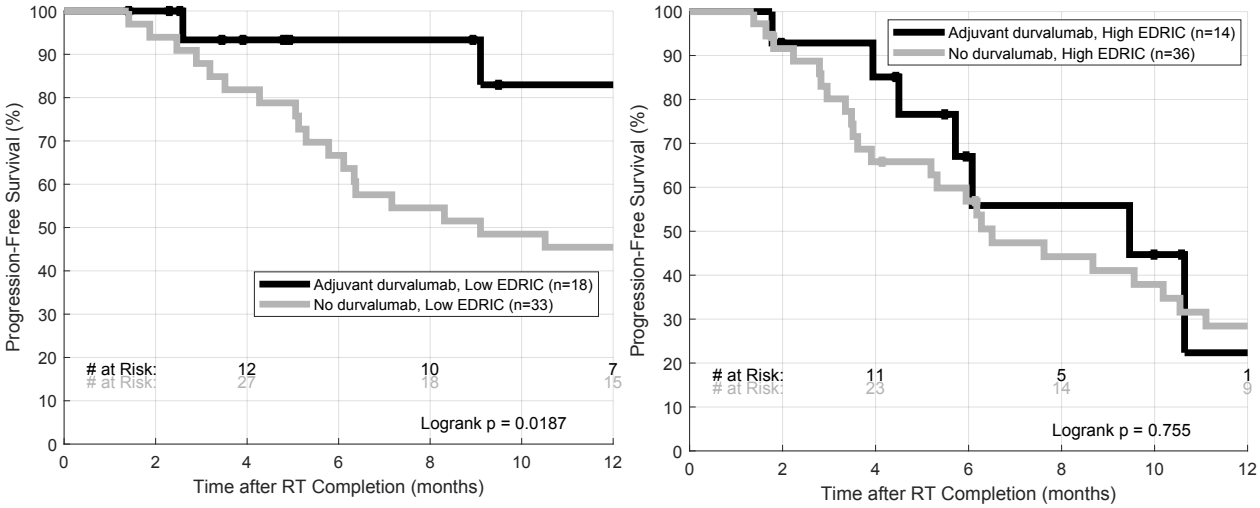
can be expected to improve treatment compliance[14,27]. Accelerated radiotherapy may also be ideal for future studies incorporating radiotherapy and immunotherapy, as long radiotherapy courses are expected to suppress antitumor immune responses[28]. We will define high v. low-risk lesions using a slightly more conservative MTV cutoff (20 cc) than we previously used, based on tumor control probability modeling results[25] and the fact that we have observed local progression in 2/14 lesions with MTV between 20 and 25 cc (unpublished data from our 93 patient LA-NSCLC database).

Rationale for 2019 Amendment Lowering the Radiotherapy Dose for Low-Risk Lesions

Based on promising interim study results as well as emerging literature supporting selective radiotherapy de-intensification for LA-NSCLC, we are amending this protocol to reduce the dose delivered to low-risk tumors and lymph nodes from 48 Gy to 44 Gy.

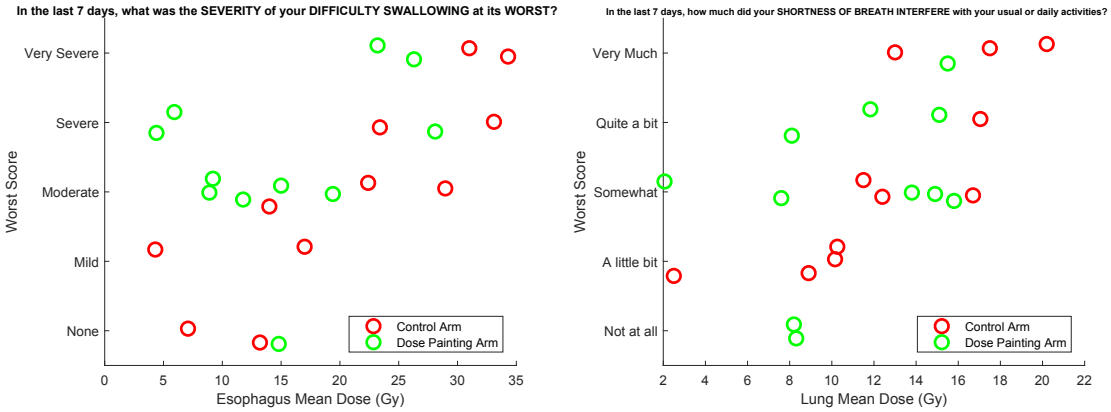
As of July 2019, 24 study subjects have completed radiotherapy. Ten of those subjects were randomized to receive dose-painted IMRT. Three of those subjects have experienced disease recurrence. One subject developed small bilateral lung metastases seven months after completing radiotherapy, one subject was found to have brain metastases ten months after completing radiotherapy, and one developed rib metastases two months after completing radiotherapy. Local disease progression in a tumor or lymph node targeted with dose-painted radiotherapy has not occurred. Only one subject on the dose-painted IMRT arm has died. He experienced a fatal stroke 20 months after completing radiotherapy and had no evidence of recurrent lung cancer at that time. The 12-month actuarial progression-free survival rate for the dose-painted IMRT arm is 55%, which compares favorably to the 25% 12-month progression-free survival rate that was seen in our PAINT trial[29].

The excellent disease control rates observed so far in the present study are likely related to the recent introduction of adjuvant immunotherapy (durvalumab) after chemoradiotherapy. In a landmark randomized trial, durvalumab was shown to significantly improve rates of distant metastasis, local disease recurrence, overall disease progression, and death[30,31]. This development strengthens the argument for selective radiotherapy de-intensification in the modern era. In fact, recent data from our institution demonstrates that durvalumab may be particularly beneficial for subjects who receive conservative doses of radiotherapy, which has known immunosuppressive effects[32-34]:



Montefiore-Einstein data suggesting that adjuvant durvalumab may be particularly beneficial for patients who receive a low Estimated Dose of Radiation to Immune Cells (EDRIC). EDRIC is a function of radiotherapy course duration and the dose delivered to the heart, lungs, and whole body[35].

As expected, we are observing that reducing the radiotherapy dose delivered to thoracic organs is associated with improved patient-reported outcomes (examples below). These gains should be enhanced by reducing the dose-painted radiotherapy dose for low-risk lesions to 44 Gy.



Regimen	Description	EQD2 – Tumor	EQD2 - Normal Tissues
RTOG 0617: Control Arm	2.0 Gy x 30 = 60 Gy (6 weeks)	55.5 Gy	60.0 Gy
PAINT: Low-risk lesions (MTV<25 cc)	2.1 Gy x 25 = 52.5 Gy (5 weeks)	49.9 Gy	53.6 Gy
PAINT: High-risk lesions (MTV>25 cc)	2.6 Gy x 25 = 65 Gy (5 weeks)	68.3 Gy	72.8 Gy
Present Trial: Low-risk lesions (MTV<20 cc) BEFORE 2019 AMENDMENT	2.4 Gy x 20 = 48 Gy (4 weeks)	48.8 Gy	51.8 Gy
Present Trial: Low-risk lesions (MTV<20 cc) AFTER 2019 AMENDMENT	2.2 Gy x 20 = 44 Gy (4 weeks)	43.0 Gy	45.8 Gy
Present Trial: High-risk lesions (MTV>20 cc)	2.75 Gy x 20 = 55 Gy (4 weeks)	59.4 Gy	63.3 Gy

Proposed dosing schedules for high- and low-risk lesions, defined by MTV on pre-treatment PET/CT imaging. EQD2 refers to biologically equivalent dose, calculated using the Linear Quadratic Model[36,37] (α/β=10 Gy and potential doubling time=5.6 days for tumor, α/β=3 Gy for normal tissues)

2.3 Patient-Reported Outcomes

Patient-reported outcomes are becoming the standard tool for evaluating health-related quality of life, treatment preferences, and treatment quality assessment[38]. They may be particularly important in studies involving radiotherapy for NSCLC. This is exemplified by the results of RTOG 0617, which was a multi-institutional randomized trial testing uniform radiotherapy dose escalation (including all tumors and regional lymph nodes) with concurrent chemotherapy for LA-NSCLC. Dose escalation from 60 Gy to 74 Gy was unexpectedly found to increase the risk of mortality, with median overall survival durations of 29 months with the standard dose of 60 Gy and only 20 months for subjects treated with 74 Gy[6]. Investigators found no statistically significant differences in serious (grade ≥ 3) adverse events between radiotherapy dose groups, demonstrating the disconnect between physician-scored toxicity and important clinical outcomes. Impairments in patient-reported quality of life, on the other hand, occurred more frequently in the high dose radiotherapy arm[39]. Additionally, baseline quality of life score was found to be a powerful predictor of overall survival.

The National Cancer Institute recently developed the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[40]. The PRO-CTCAE item library is comprised of 78 symptomatic adverse events, each of which is elicited using between one and three questions (representing frequency, severity, and/or interference), for a total of 124 individual questions. For any given clinical trial, relevant PRO-CTCAE items can be selected from the online library to create a concise patient questionnaire that has been validated in several languages. This promising tool has not yet been utilized extensively in chemoradiotherapy trials for NSCLC. One recent study demonstrated the extent to which CTCAE and PRO-CTCAE findings may differ in this setting[41]. As an example, clinicians using CTCAE reported that high-level anxiety occurred in 0/130 subjects. PRO-CTCAE demonstrated that 28/120 subjects had high-level anxiety. Large differences between CTCAE and PRO-CTCAE were observed for several other adverse events, including anorexia, cough, dysphagia, fatigue, and pain.

We have developed a concise PRO-CTCAE tool that includes the elements that are likely most relevant to LA-NSCLC patients who are treated with chemoradiotherapy (Appendix). Patient-reported outcomes for each of these elements might be improved with the use of dose-painted radiotherapy compared to standard radiotherapy in this setting.

3.0 PATIENT ELIGIBILITY

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):
    - Stage IIIA or IIIB
    - Stage II NSCLC with contraindication to curative surgical resection
    - Stage IV disease with solitary brain metastasis that has been treated radically (eg: with surgical resection and/or stereotactic radiosurgery) and thoracic disease that would be classified as stage II-III
- Appropriate diagnostic/staging workup, including:
    - Complete history and physical examination
    - PET/CT within 42 days prior to study entry demonstrating hypermetabolic pulmonary lesion(s) and/or thoracic lymph node(s). If PET/CT was obtained more than 42 days prior to study entry and is not repeated, chest CT within 28 days prior to study entry demonstrating stable disease is required.
    - MRI of the brain or head CT 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 recommended but not required.
- No prior chemotherapy or thoracic radiotherapy for lung cancer
- ECOG Performance Status 0-2 (Appendix)
- Age $\geq$ 18
- Able to read and write in one of the following languages, in which the PRO-CTCAE tool is available: English, Danish, German, Italian, Japanese, Korean, Spanish
- 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 $\geq$ 100,000 cells/µl
    - Hemoglobin $\geq$ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb $\geq$ 9.0 g/dl is acceptable.)
    - Total bilirubin < 3.0 times the institutional Upper Limit of Normal (ULN)
    - AST and ALT $\leq$ 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 thoracentesis 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

Subjects will undergo standard evaluations, detailed in the Study Calendar, prior to enrollment, during treatment, and after treatment. Additionally, patient-reported outcomes will be assessed periodically using the PRO-CTCAE tool.

Upon study enrollment, subjects will be randomized to receive PET-based, dose-painted, accelerated chemoradiotherapy versus standard chemoradiotherapy. Patients receiving standard radiotherapy will receive a total dose of 60 Gy in 30 fractions over 6 weeks, delivered to all involved lesions (tumors and lymph nodes). For patients

receiving PET-based, dose-painted, accelerated chemoradiotherapy, lesions with MTV exceeding 20 cc will be treated with 55 Gy in 20 fractions over 4 weeks, while lesions with MTV below 20 cc will receive 44 Gy in 20 fractions over the same 4 weeks.

All subjects will receive standard weekly doses of carboplatin (AUC 2) and paclitaxel (50 mg/m^2) during radiotherapy. This may be followed by adjuvant systemic therapy, at the discretion of the treating physicians. The recommended adjuvant chemotherapy regimen is 3 cycles of full dose adjuvant carboplatin (AUC 6) and paclitaxel (200mg/m^2) every 3 weeks, but another regimen may be selected by the treating physicians.

4.2 Study Calendar

	Eval	chemoRT	chemoRT	chemoRT	chemoRT	chemoRT	chemoRT	chemo	chemo	chemo	Eval	Eval	Eval
	Pre-rx	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 9*	Wk 12*	Wk 15*	Wk 19*	Wk 32*	Wk 45*
History, Physical, Toxicity Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO-CTCAE Assessment	X		X		X		X	X			X	X	X
MRI Brain	X												
PET/CT	X										X	X^	X^
Chemotherapy		X	X	X	X	X**	X**	X^^	X^^	X^^			
Radiotherapy		XXXXX	XXXXX	XXXXX	XXXXX	XXXXX**	XXXXX**						

* - Approximate
** - Only for subjects receiving standard radiotherapy
^ - May be replaced by CT
^^ - Optional

For subjects receiving adjuvant immunotherapy after radiotherapy completion or salvage therapy for disease recurrence, the type and timing of restaging imaging studies will be left to the discretion of the treating physicians and may deviate from the Study Calendar.

4.3 Primary Endpoint

- PRO-CTCAE adverse events with score ≥ 3, observed 6 weeks after initiation of chemoradiotherapy

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
- Grade 3-5 adverse events, scored using CTCAE v. 4
- PRO-CTCAE adverse events with score ≥ 3 at any time
- PRO-CTCAE adverse events with any score

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. 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 will 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 ensure 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. Axial acquisitions with gantry 0 degrees and spacing ≤ 3.0 mm between scans in the region of the tumor are required Images will be transferred to the treatment planning system for radiotherapy planning.

Isocenter or reference point port localization images (anterior/posterior and lateral) should be obtained immediately before each treatment to ensure proper alignment of the geometric center (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. If 4D CT simulation is used, gross tumor volumes (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).

For patients treated with dose-painted radiotherapy, the low-risk GTV (GTV_4400) 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_5500), will also be defined and will include only lesions with MTV > 20 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[42]. GTV_5500 will be contained within GTV_4400.

Each GTV (or ITV) will be expanded by 7-10 mm to form a CTV (CTV_4400 and CTV_5500). CTVs may be trimmed to exclude anatomic boundaries to microscopic tumor spread. CTV_5500 will contained within CTV_4400.

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 approximately 10 mm in the superior and inferior directions. PTV_5500 will be a subset of PTV_4400.

For subjects treated with standard radiotherapy, a single set of target volumes (GTV_6000, CTV_6000, and PTV_6000) will be created following the same procedures utilized to generate the low-risk volumes described above.

Adaptive radiotherapy (adjustment of target volumes during the course of radiotherapy) 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) should be used for dose-painting in this protocol. If these treatment techniques are not available for some reason (eg: a subject's insurance company refuses to authorize IMRT), treatment will be delivered using a sequential boost technique (2.75 Gy x 16 to the low-risk PTV followed by 2.75 Gy x 4 to the high-risk PTV). All treatment planning will be performed using tissue heterogeneity corrections.

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 (to 0.3 cm^3) 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 contoured based on atlases published on the RTOG web site. Dosimetric constraints for organs at risk are listed below. These have been adopted from recent RTOG LA-NSCLC protocols.

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	Mean Dose	≤34 Gy	≤35 Gy	>35 Gy
Spinal Cord	Max Dose (30 fractions) Max Dose (20 fractions)	≤50 Gy ≤44 Gy	≤52 Gy ≤46 Gy	>52 Gy >46 Gy
Brachial Plexus	Max Dose	≤63 Gy	≤65 Gy	>65 Gy

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 occur when the pericardium and spinal cord receive doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung may occur, typically within lung volumes receiving≥ 20 Gy and within the first six months after treatment. It is important to spare as much normal lung as possible 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 using CTCAE v.4.0. If high grade esophagitis occurs, and a treatment interruption is being considered, every effort should be made to minimize the treatment break duration. Acute esophageal toxicity, which typically manifests as dysphagia, odynophagia, and reflux symptoms, should be pharmacologically managed with the following approach:

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 (50 mg/m^2, IV) will be started on week 1 of thoracic radiotherapy and will be continued weekly during the course of radiotherapy. 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 50 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 Therapy

5.3.1 Adjuvant Chemotherapy Dosing

Adjuvant systemic therapy may start approximately 4-6 weeks after the completion of all radiotherapy. The recommended regimen is carboplatin and paclitaxel (detailed below). However, another standard regimen may be selected, at the discretion of the treating physicians.

Adjuvant carboplatin and paclitaxel may be started 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/m^2, 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 study procedures and will be managed at the discretion of their treating physicians. These patients will continue to be followed as specified in the protocol. Tissue confirmation to confirm

progressive disease is recommended in cases where this might affect patient management.

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. 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 non-hematologic toxicity 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 Chemotherapy Modifications

The use of adjuvant systemic therapy is allowed but not required by the protocol. The decision to administer adjuvant therapy for a particular subject will be left to the discretion of the treating physicians. The recommended regimen is carboplatin and paclitaxel (detailed below). However, another standard regimen may be selected, at the discretion of the treating physicians.

Patients receiving adjuvant carboplatin/paclitaxel 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 adjuvant 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 adjuvant cycles. When a chemotherapy dose reduction is required during the adjuvant 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 adjuvant 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 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: carboplatin/nab-paclitaxel) that will be administered using a standard dosing schedule. Radiotherapy and other protocol-specified procedures will proceed as planned. These patients will be followed for primary and secondary endpoints, in keeping with the "intent to treat" principle.

6.0 RESPONSE ASSESSMENT

Secondary endpoints of this study include locoregional progression-free survival and progression-free survival. Evaluation for progressive disease will follow RECIST criteria[43]:

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

At the time of study registration, subjects will be stratified by performance status (2 v. 0-1) and primary tumor size (>4 cm v. ≤ 4 cm) and then will be randomized 1:1 between the two study arms with the aid of the study statistician, using a modified permuted block treatment allocation scheme[44]. We are using tumor size to stratify patients because it can be determined easily at the time of study registration and is

highly correlated with total disease burden, which is a prognostic factor for both disease control and treatment-related toxicity.

The primary objective of this study is to explore patient-reported outcomes using the PRO-CTCAE tool in LA-NSCLC patients who are treated at our institution with standard or dose-painted thoracic chemoradiotherapy. The primary endpoint is the occurrence of patient-reported adverse event(s) with score ≥ 3, observed 6 weeks after initiation of chemoradiotherapy. For each study arm, we will report the distribution of PRO-CTCAE scores at each time point data is collected. As this is an exploratory study, no formal power calculation is performed. We plan to accrue 25 subjects to each arm. The following table describes the precision with which we will be able to characterize true event rates based on the frequency of observed events.

# of Events (%)	90% CI for Event Rate	95% CI for Event Rate
5/25 (20)	8-38%	7-41%
6/25 (24)	11-42%	9-45%
7/25 (28)	14-46%	13-49%
8/25 (32)	17-50%	15-54%
9/25 (36)	20-54%	18-57%
10/25 (40)	24-58%	21-61%
11/25 (44)	27-62%	24-65%
12/25 (48)	31-66%	28-69%
13/25 (52)	34-69%	31-72%

Toxicity outcomes and patterns of failures will be summarized and tabulated along with Clopper-Pearson exact confidence intervals.

Exploratory comparisons of continuous variables will be performed using Student t-tests. If data are not normally distributed, appropriate non-parametric tests (Wilcoxon rank-sum test or van Elteren test) will be used. Categorical variables will be presented using frequencies and percentages, and comparisons may be performed using the chi-square test or Fisher's exact test. Time-to-event outcomes will be analyzed using the Kaplan-Meier method. Exploratory comparisons may be made using logrank tests.

As patient-reported outcomes will be assessed repeatedly over the follow-up period, exploratory analyses of differences between groups will be analyzed using generalized linear mixed effects modeling.

7.4 Subject Accrual

In the Einstein/Montefiore Department of Radiation Oncology, approximately five patients are treated with definitive chemoradiotherapy 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 25 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 bimonthly basis. During its bimonthly 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). 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.

12.0 REFERENCES

1. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA: A Cancer Journal for Clinicians 61:69-90, 2011
2. Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours. Journal of Thoracic Oncology 2:706-714 10.1097/JTO.0b013e31812f3c1a, 2007
3. Vokes EE, Herndon JE, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B. Journal of clinical oncology 25:1698, 2007
4. Hanna N, Neubauer M, Yiannoutsos C, et al: Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 26:5755-60, 2008
5. Kelly K, Chansky K, Gaspar LE, et al: Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 26:2450-6, 2008
6. Bradley JD, Paulus R, Komaki R, et al: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. The Lancet Oncology 16:187-199, 2015
7. Senan S, Brade A, Wang L-h, et al: PROCLAIM: Randomized phase III Trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non–small-cell lung cancer. Journal of Clinical Oncology 34:953-962, 2016
8. Albain KS, Swann RS, Rusch VW, et al: Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 374:379-86, 2009
9. Palma DA, Senan S, Oberije C, et al: Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. International Journal of Radiation Oncology* Biology* Physics 87:690-696, 2013
10. Marks LB, Bentzen SM, Deasy JO, et al: Radiation dose–volume effects in the lung. International Journal of Radiation Oncology* Biology* Physics 76:S70-S76, 2010
11. Gagliardi G, Constine LS, Moiseenko V, et al: Radiation dose–volume effects in the heart. International Journal of Radiation Oncology* Biology* Physics 76:S77-S85, 2010
12. Werner-Wasik M, Yorke E, Deasy J, et al: Radiation dose-volume effects in the esophagus. International Journal of Radiation Oncology* Biology* Physics 76:S86-S93, 2010
13. Bar-Ad V, Ohri N, Werner-Wasik M: Esophagitis, treatment-related toxicity in non-small cell lung cancer. Reviews on recent clinical trials 7:31-35, 2012
14. Ohri N, Rapkin BD, Guha C, et al: Radiation Therapy Noncompliance and Clinical Outcomes in an Urban Academic Cancer Center. International Journal of Radiation Oncology* Biology* Physics 95:563-570, 2016
15. Chun SG, Hu C, Choy H, et al: Impact of intensity-modulated radiation therapy technique for locally advanced non–small-cell lung cancer: A secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. Journal of Clinical Oncology:JCO691378, 2016
16. Wang K, Eblan MJ, Deal AM, et al: Cardiac Toxicity After Radiotherapy for Stage III Non–Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. Journal of Clinical Oncology:JCO. 2016.70. 0229, 2017

17. Maziak DE, Darling GE, Inculet RI, et al: Positron emission tomography in staging early lung cancer: a randomized trial. Ann Intern Med 151:221-8, W-48, 2009
18. Fischer B, Lassen U, Mortensen J, et al: Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 361:32-9, 2009
19. Weder W, Schmid RA, Bruchhaus H, et al: Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 66:886-92; discussion 892-3, 1998
20. Fischer BM, Mortensen J, Hojgaard L: Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. Lancet Oncol 2:659-66, 2001
21. Subedi N, Scarsbrook A, Darby M, et al: The clinical impact of integrated FDG PET-CT on management decisions in patients with lung cancer. Lung Cancer 64:301-7, 2009
22. Machtay M, Duan F, Siegel BA, et al: Prediction of Survival by [18F]Fluorodeoxyglucose Positron Emission Tomography in Patients With Locally Advanced Non-Small-Cell Lung Cancer Undergoing Definitive Chemoradiation Therapy: Results of the ACRIN 6668/RTOG 0235 Trial. J Clin Oncol 31:3823-30, 2013
23. Ohri N, Duan F, Machtay M, et al: Pretreatment FDG-PET Metrics in Stage III Non–Small Cell Lung Cancer: ACRIN 6668/RTOG 0235. Journal of the National Cancer Institute 107:djv004, 2015
24. Ohri N, Piperdi B, Garg MK, et al: Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer. Lung Cancer 87:23-27, 2015
25. Ohri N, Bodner WR, Halmos B, et al: 18 F-Fluorodeoxyglucose/Positron Emission Tomography Predicts Patterns of Failure After Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. International Journal of Radiation Oncology* Biology* Physics 97:372-380, 2017
26. Prewett S, Aslam S, Williams M, et al: The management of lung cancer: a UK survey of oncologists. Clinical Oncology 24:402-409, 2012
27. Ohri N, Rapkin BD, Guha D, et al: Predictors of radiation therapy noncompliance in an urban academic cancer center. International Journal of Radiation Oncology* Biology* Physics 91:232-238, 2015
28. Formenti SC, Demaria S: Combining radiotherapy and cancer immunotherapy: a paradigm shift. Journal of the National Cancer Institute:djs629, 2013
29. Ohri N, Bodner WR, Kabarriti R, et al: Positron Emission Tomography–Adjusted Intensity Modulated Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. International Journal of Radiation Oncology* Biology* Physics, 2017
30. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. New England Journal of Medicine 377:1919-1929, 2017
31. Antonia SJ, Villegas A, Daniel D, et al: Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. New England Journal of Medicine, 2018
32. Tang C, Liao Z, Gomez D, et al: Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. International Journal of Radiation Oncology* Biology* Physics 89:1084-1091, 2014
33. Crocenzi T, Cottam B, Newell P, et al: A hypofractionated radiation regimen avoids the lymphopenia associated with neoadjuvant chemoradiation therapy of borderline resectable and locally advanced pancreatic adenocarcinoma. Journal for immunotherapy of cancer 4:45, 2016
34. Shiraishi Y, Fang P, Xu C, et al: Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy. Radiotherapy and Oncology 128:154-160, 2018

35. Ladbury C, Rusthoven C, Camidge DR, et al: Impact of Radiation Dose to the Host Immune System on Tumor Control and Survival for Stage III Non-Small Cell Lung Cancer Treated with Definitive Radiotherapy. International Journal of Radiation Oncology• Biology• Physics, 2019

36. Fowler JF: The linear-quadratic formula and progress in fractionated radiotherapy. The British journal of radiology 62:679-694, 1989

37. Machtay M, Bae K, Movsas B, et al: Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 82:425-34, 2012

38. Gotay CC, Kawamoto CT, Bottomley A, et al: The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials. J Clin Oncol 26:1355-1363, 2008

39. Movsas B, Hu C, Sloan J, et al: Quality of life (QOL) analysis of the randomized radiation (RT) dose-escalation NSCLC trial (RTOG 0617): the rest of the story. Int J Radiat Oncol Biol Phys 87:S1-S2, 2013

40. Basch E, Reeve BB, Mitchell SA, et al: Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Journal of the National Cancer Institute 106:dju244, 2014

41. Fogh S, Deshmukh S, Berk LB, et al: A Randomized Phase II Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis During the Treatment of Lung Cancer: Results of Trial. International Journal of Radiation Oncology* Biology* Physics, 2016

42. Werner-Wasik M, Nelson AD, Choi W, et al: What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. International Journal of Radiation Oncology* Biology* Physics 82:1164-1171, 2012

43. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

44. Zelen M: The randomization and stratification of patients to clinical trials. Journal of chronic diseases 27:365-375, 1974

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
   - 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.

13.5 Appendix E – PRO-CTCAE Assessment Tool

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
5.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

6.	In the last 7 days, what was the SEVERITY of your WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

8.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

11.	In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe