OSU PROTOCOL #: 14091
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TITLE: **A Phase II trial Combining Hypofractionated Radiation Boost with Conventionally- Fractionated Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer Not Suitable for Surgery**

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Commercially Available Agents: Cisplatin & Etoposide;
Carboplatin & Paclitaxel

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List of Abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BOLD	blood oxygenation level dependent
BP	blood pressure
CBCP	complete blood count with platelets
CDDP	cisplatin
CFR	Code of Federal Regulations
Cmax	maximum concentration of drug
CMP	comprehensive metabolic panel
CPK	serum creatine phosphokinase
CrCl	creatinine clearance
CRT	chemoradiation treatment
CT	computed tomography
CTV	clinical target volume
CTCAE	Common Terminology Criteria for Adverse Events
DCE/PWI	dynamic contrast enhanced/perfusion weighted imaging
DLCO	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicities
DSMC	Data Safety Monitoring Committee
DWI	diffusion weighted imaging
FDA	Food and Drug Administration
FDG PET	fluorodeoxyglucose positron emission tomography
FEV-1	forced expiratory volume at 1 second
g/dL	grams per deciliter
gLQ	generalized linear quadratic
GTV	gross tumor volume
Gy	Gray (unit of radiation)
HCT	hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996

IGRT	Image guided radiation therapy
IMRT	Intensity modulated radiation therapy
IRB	Investigational Review Board
ITV	internal target volume
IV	intravenous
L	liter
LDH	lactate dehydrogenase
LLN	lower limit of normal
LQ	linear quadratic
LVEF	left ventricular ejection fraction
mg/m^2	milligrams per square meter
mL/min	milliliter per minute
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	millisecond
MTD	maximum tolerated dose
MV	megavoltage photons
NCI	National Cancer Institute
ng/mL	nanograms per milliliter
NIH	National Institutes of Health
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PHI	protected health information
PI	primary investigator
PK	pharmacokinetic
PMN	polymorphonuclear cells
PT	prothrombin time
PTT	partial thromboplastin time
PTV	planning target volume
QD	once daily
RECIST	Response Evaluation Criteria In Solid Tumors

RT	radiation therapy
SAE	serious adverse event
SBP	systolic blood pressure
SBRT	stereotactic body radiation therapy
Tmax	maximum body temperature
TNM	tumor, (lymph) nodes, metastasis (cancer staging system)
UICC	International Union Against Cancer
ULN	upper limit of normal
VMAT	volumetric modulated arc therapy
VP16	etoposide
WOCBP	Women of child-bearing potential

Study Summary

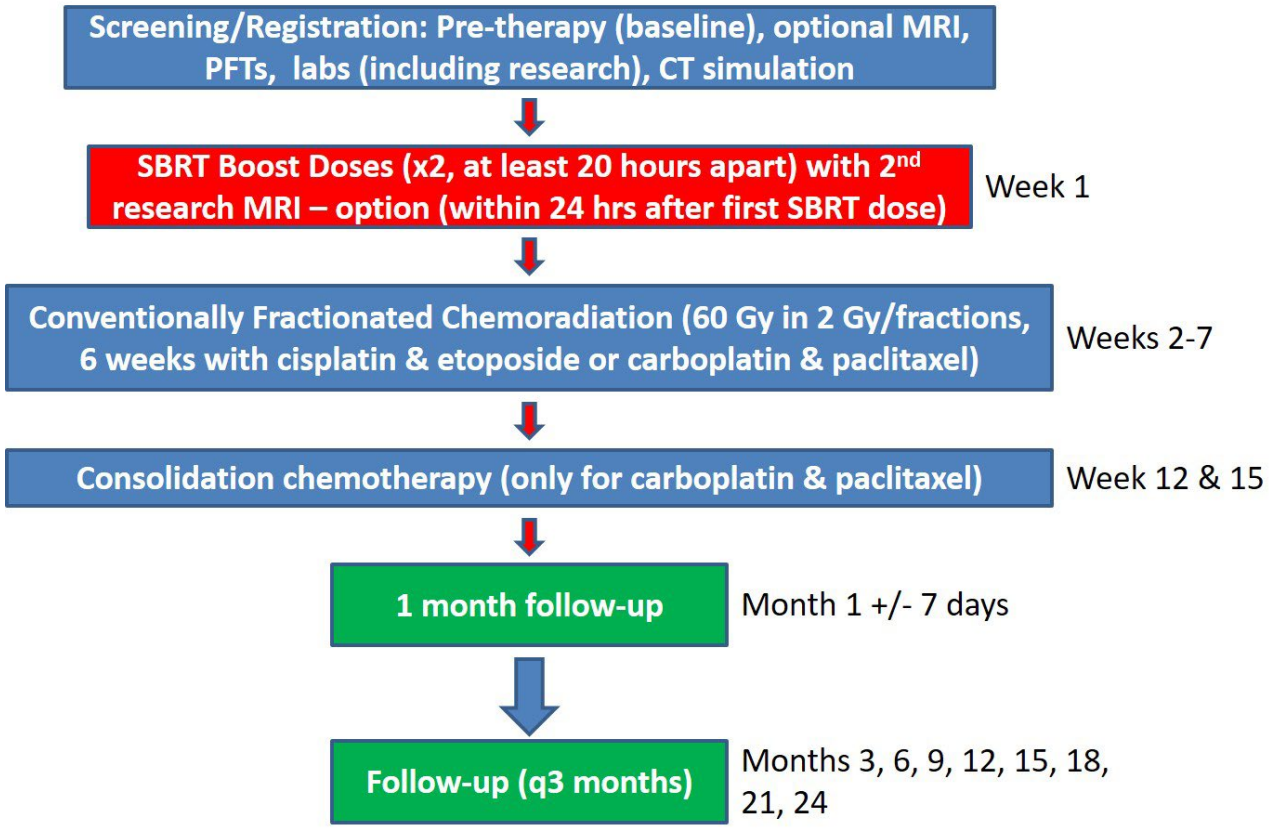
Title	A Phase II trial Combining Hypofractionated Radiation Boost with Conventionally-Fractionated Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer Not Suitable for Surgery
Short Title	Hypofractionation Boost with Chemoradiation for Locally Advanced Cancer
Protocol Number	OSU-14091 IRB #2014C0112
Phase	2
Methodology/Study Design	Open-label, single-arm, phase II study to evaluate the efficacy and safety of hypofractionated, stereotactic body radiation therapy (SBRT) boost doses in patients with Stage II-III unresectable (or medically-inoperable) locally-advanced non-small cell lung cancer. Our goal is to improve on local control of the primary tumor. We will deliver 2 boost doses of SBRT in Week 1 to the primary tumor prior to the start of conventional chemoradiation, which will begin Week 2.
Study Duration	36 months for accrual of all patients
Study Center(s)	Single center
Objectives	*Primary Objectives:* • To estimate the primary tumor control rate at 12 months. *Secondary Objectives:* • To further establish feasibility, safety and tolerability of this regimen. • To estimate the rates of objective response rates (ORR) and rates of regional, distant control as well as progression-free survival and overall survival. • To evaluate the response of tumors to stereotactic (high-dose) radiation using magnetic resonance tumor perfusion imaging modalities (MR-DCE/PWI, MR-diffusion, BOLD sequences). • To correlate circulating tumor DNA and miRNA biomarkers with response and toxicity.
Number of Subjects	34

Diagnosis and Main Inclusion Criteria	Male and female patients ≥ 18 years old with Stage II or III locally advanced non-small cell lung cancer, who are unresectable or medically inoperable. *Key Inclusion Criteria:* • Non-small cell lung cancer (NSCLC), histologically and/or cytologically proven. • Clinical AJCC stage IIA-IIIB NSCLC (T1-4N0-3M0), deemed unresectable or medically inoperable. • Patients must have primary tumor ≤ 10 cm as defined by CT largest axial dimension. • ECOG performance status of 0-1. • Estimated life expectancy ≥ 12 weeks. • Able to undergo two MRI scans, one before study treatment begins and one shortly after first dose of radiation (optional study)
Study Regimen	Patients will be registered on trial, followed by blood-work, and CT simulation. For ten patients who consent for correlative MRI studies, baseline MR imaging will be obtained during Weeks -2 to 0. During Week 1, the patient will receive 2 SBRT boost doses (with optional MR imaging performed within 24 hours after SBRT boost dose 1). Following this, patients will be treated with standard conventionally-fractionated chemoradiation during Weeks 2-7 (60 Gy in 30 fractions, with cisplatin & etoposide or carboplatin & paclitaxel chemotherapy).
Duration of Treatment	7 weeks (with 2 additional consolidation cycles of carboplatin & paclitaxel chemotherapy for those receiving carboplatin & paclitaxel concurrent with radiation at the discretion of the medical oncologist)
Reference therapy	Standard chemoradiation for 6 weeks (60 Gy in 2 Gy fractions) over 6 weeks with cisplatin & etoposide or carboplatin & paclitaxel.

Statistical Methodology	***Analytic plan for Primary Objective:*** Primary tumor control rate at 12 months, as well its 95% confidence interval, will be reported for all eligible subjects who received treatment. In addition, the local control failure over time will be plotted using Kaplan-Meier survival analysis. Rates of primary tumor control and local control at 1, 2 years and 3 years will also be summarized
	(a) Analytic plan for Secondary Objectives: Rates of all adverse agents, with special attention to grade 3-5 esophagitis, cardiac, and pneumonitis adverse events, and death during or within 30 days of discontinuation of protocol treatment will be calculated. Rates of tolerability will be determined at the end of study. Regional and distant failure, PFS, and OS will be measured from date of treatment initiation to the event of

	interest or otherwise censored at last follow-up. Kaplan-Meier (K-M) analysis will be used to estimate PFS and OS. PFS will include any failure (local, regional, or distant) or death from any cause. For MRI correlative studies, all 3 metrics (perfusion/diffusion/oxygenation measurements) will be tested by comparing mean values pre- and post-SBRT using a paired t-test. Should there be concern for outliers, we will determine the median for each metric and compare medians using a corresponding non-parametric procedure.

SCHEMA


Screening/Registration: Pre-therapy (baseline), optional MRI, PFTs, labs (including research), CT simulation
SBRT Boost Doses (x2, at least 20 hours apart) with 2nd research MRI – option (within 24 hrs after first SBRT dose)
Week 1
Conventionally Fractionated Chemoradiation (60 Gy in 2 Gy/fractions, 6 weeks with cisplatin & etoposide or carboplatin & paclitaxel)
Weeks 2-7
Consolidation chemotherapy (only for carboplatin & paclitaxel)
Week 12 & 15
1 month follow-up
Month 1 +/- 7 days
Follow-up (q3 months)
Months 3, 6, 9, 12, 15, 18, 21, 24

1.1 OBJECTIVES

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.2 PRIMARY OBJECTIVE

The primary objective of this work is:

- To estimate the primary tumor control rate at 12 months after a combined regimen of stereotactic body radiation therapy (SBRT) with conventionally-fractionated chemoradiation in unresectable or medically-inoperable non-small cell lung cancer (NSCLC).

1.3 SECONDARY OBJECTIVES

The secondary objectives of this work are:

- To further establish safety and tolerability of this regimen.
- To estimate the rates of regional, distant control as well as progression-free survival and overall survival.
- To evaluate the objective response rate (ORR) to this regimen.
- To evaluate the response of tumors to stereotactic (high-dose) radiation using magnetic resonance tumor perfusion imaging modalities (MR-DCE/PWI, MR-diffusion, BOLD sequences).

2.0 BACKGROUND AND RATIONALE

2.1 Local Control in Locally-advanced NSCLC

Concurrent chemoradiation (CRT) is the standard of care for ECOG PS 0-1 patients with unresectable tumors or medically-inoperable locally advanced NSCLC (see Table A, Appendix IV, for a summary of the major trials). In these trials, an average of 60-66 Gy of conventionally- fractionated radiation (1.8-2.0 Gy/day) was delivered to sites of clinically involved cancer, including the primary tumor, hilum, mediastinal, and supra-clavicular regions. Despite this, rates of local failure at the site of the primary tumor ranged from **25-40%.** *Local progression is well- established to be a major driving force of mortality in lung cancer patients(1-3).* These high rates of local failure argue for better control of the primary tumor, which could decrease morbidity and mortality due to local disease progression, as well as reduce survival of remaining clonogens and development of metastatic disease from any residual primary tumor.

While local failure remains high after standard CRT, regional nodal failures are low in both early stage and locally advanced NSCLC (4-6). In a large group of Stage I-III patients treated with involved field irradiation (IFI) at Memorial Sloan-Kettering Cancer Center, local failure occurred much more commonly than regional recurrence at 49% and 6%, respectively.(7) Classically, locally advanced NSCLC patients were treated with elective or prophylactic nodal irradiation (PNI). PNI treats uninvolved nodal basins (i.e. ipsilateral hilum, mediastinum, +/- supraclavicular region) in an attempt to eliminate subclinical microscopic disease. Modern practice has shifted towards omitting PNI to spare patients the added toxicities associated with comprehensive nodal radiation. Involved field irradiation (IFI) directs radiation only to areas involved with tumor on imaging, or confirmed via biopsy (mediastinal/endoscopic staging). Modern studies suggest that the rates of nodal failure are low when using IFI. Multiple studies have shown regional failure to be 10% or lower in patients treated with involved field radiation (i.e. no elective nodal RT) with standard doses. (2, 7, 8) It appears that local failure, not regional nodal recurrence, accounts for the majority of thoracic recurrences for both early stage and locally advanced stage NSCLC patients treated with standard CRT. *This argues*

that additional control should be focused on the primary tumor, not the regional lymphatics.

2.2 Potential Toxicity from Dose-Escalation

The results of RTOG 0617 were recently presented at the ASCO Annual Meeting 2013. This trial compared standard 60 Gy in 30 fractions concurrent with weekly carboplatin+paclitaxel chemotherapy to a dose-escalated schedule of 74 Gy in 37 fractions with the same chemotherapy, followed by consolidation carboplatin+paclitaxel chemotherapy. The results showed, disappointedly, that after a median follow-up of 18 months, higher dose was associated with inferior median survival of 19.5 months versus 28.7 months (HR 1.56, p<0.001). More deaths that considered to be treatment-related occurred in the high-dose arm (10 versus 2). In addition, local failure was unexpectedly higher in the high-dose arm at 34.3% (versus 25.1%). In multivariate analysis, higher radiation dose and higher cardiac radiation exposure were associated with inferior survival. Given that the high-dose arm included radiation not only to the primary tumor but also the involved nodes in the hilum and mediastinum, one possible explanation is that the high mediastinal/cardiac dose resulted in these excess deaths.

2.3 Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a novel technique that permits highly conformal radiation therapy which facilitates high doses of radiation to tumors, while minimizing dose to normal tissues. SBRT is a type of *hypofractionated radiation*, which is defined as radiation delivered in larger doses and less than once a day compared to conventional fractionation. SBRT has shown excellent control rates in treating tumors of the lungs, liver, and other sites. *With 3-year local control rates commonly 90-95% following SBRT in early-stage (T1-2N0M0) NSCLC (4, 5, 9), it is attractive to hypothesize that SBRT may be one potential way to improve on the high local failures rates in locally advanced NSCLC***.** As a single treatment modality, SBRT in early stage NSCLC is associated with minimal toxicity. Rates of pneumonitis are reported to be 11% or less from large series of patients treated with SBRT (10-12). Furthermore, long-term changes in pulmonary function appear to be sub-clinically evident, with only minimal reductions in pulmonary function such as FEV-1 and DLCO (12-15). Recently, investigators reported on the safety of a SBRT boost dose for Stage III NSCLC with residual disease (16). SBRT boost doses were given approximately several weeks after completion of conventional chemoradiation (~60 Gy in 30-33 fractions). With SBRT boost doses ranging from19.5-20 Gy in 2-3 fractions for both central and peripherally-located primary tumors, rates of radiation pneumonitis were low, with grade 3 and 4 rates of 8.6% and 2.9%, respectively. Local control appeared to be improved compared to historical controls, but was only 83%, which perhaps was due to several weeks of treatment break following completion of CRT, which could have allowed for repopulation of tumor clonogens. Importantly, they found that the addition of SBRT to standard chemoradiation was safe: their findings confirm the safety of this approach and obviate the need for another phase I trial based on the doses we propose in this trial (which are similar to theirs). Furthermore, a recent study published in 2015 by Woody et al., shows the relative safety and efficacy of treating larger tumors with radiation (Woody et al., *Int J Radiat Oncol Biol Phys*, volume 92(2), pp 325-31). In this study with primary tumors ranging from 5.1 cm to 10 cm in size, SBRT showed high local control rates with low rates of grade 3 or higher toxicity.

2.4 Radiobiologic High Dose Modeling

Mathematical models have been created to permit comparison of tumor control across various radiation schedules and fraction sizes. The most prevalent model applied to conventionally-fractionated radiation is the linear quadratic (LQ) equation, which allows for comparison across treatment schedules by converting dose and fractionation into a term referred to as the "biological effective dose (BED)". Different tissues are assigned "α/β ratios", which essentially is a reflection of a tissue's sensitivity to changes in fraction size. With regard to tumor cells, a high α/β ratio confers "high sensitivity" to radiation, while a lower α/β predicts "low sensitivity" to radiation. Based on both laboratory and clinical trial data, the LQ model only appears to predict BED accurately for fraction sizes less than 3.25 Gy.(17) SBRT doses, however, fall well outside of this range. The LQ model, therefore, may not accurately predict the BED for extremely hypofractionated radiotherapy.(17-20) Several models have attempted to more accurately predict the response of tumors to hypofractionated radiotherapy relative to the LQ model. The universal survival curve (USC) (21), modified linear quadratic model (formerly the MLQ model, now termed the LQL model) (20), and the generalized linear quadratic (gLQ) model(17) all have been shown to radiobiologically model high dose per fraction (HFRT) better than the LQ model, with varying success at retaining accuracy in the low dose per fraction (CFRT) region (17, 18, 20). The gLQ model (developed at the Ohio State University) has been shown to radiobiologically model high dose per fraction better than the LQ model, and can accurately model tumor cell survival both at the low and high dose fraction range (17).

In early stage NSCLC, commonly used SBRT treatment fractionations for peripherally located tumors include 54 Gy in 3 fractions and 48-50 Gy in 4 fractions. For more centrally-located lesions (those lying within 2 cm of the trachea, carina, main stem or lobar bronchi), excessive toxicity was associated with these standard regimens (22). Thus, standard dosing for centrally- located lesions is 50-60 Gy in 5-10 fractions.

Using the gLQ model, we have determined that the effective α/β ratio for lung cancer (from fitting the model to the published lung cancer cell survival data in the literature) is **~5.45 Gy**, using cell lines, or 4.3 Gy using our own clinical data of approximately 85 patients treated with SBRT for early-stage NSCLC at the Ohio State University. In this modeling, we have also accounted for a potential tumor doubling time of 7 days, and that the onset of time of accelerated repopulation starts at 14 days based on published data in NSCLC. Thus, we have calculated the SBRT boost doses which when added to 60 Gy in 2 Gy per fraction (conventional chemoradiation dose), will bring the total biological effective doses to that of 54 Gy in 3 fractions (for peripheral primary tumors) and 60 Gy in 5 fractions (for central primary tumors) for tumor control (Table B, Appendix IV) that would provide much more effective local control than traditional doses. The differences in dose between centrally-located and peripherally-located primary tumors is necessary due to previous findings from *Timmerman et al*.: centrally-located tumors need to receive a more protracted radiation schedule with lower radiation dose per day, due to toxicity observed with three fraction regimens (22). Using this modeling, we calculated that **17.3 Gy** (2 fractions) and **13.95 Gy** (2 fractions) is necessary for peripheral and central tumors respectively using a cell-line derived α/β ratio of 5.45 Gy (Table B). If we use the clinical data and an α/β ratio of 4.3 Gy, then the calculated doses are **13 Gy** (2 fractions) and **11.5 Gy** (2 fractions) for peripheral and central tumors respectively (Table B). In order to translate this clinically, and understanding that there are limitations related to radiobiologic modeling, we have integrated these data and have determined that the optimal SBRT boost doses to the primary tumor only, will consist of an additional 8 Gy for 2 fractions for peripherally-located tumors (**total 16 Gy**), and 6 Gy for 2 fractions (**total 12 Gy**) for centrally-located tumors. In terms of safety, 9-10 Gy x 2 fractions for a boost has been shown to be associated with acceptable acute and late toxicity (i.e. pneumonitis) as mentioned above in a trial exploring SBRT boost doses several weeks after completion of standard

conventionally fractionated chemoradiation(16).

2.5 Magnetic Resonance Imaging Biomarkers

Tumor oxygenation and microvasculature are well investigated components of the tumor microenvironment. Tumor hypoxia and impaired vascularity are associated with radiotherapy and chemotherapy resistance, high invasiveness, increased metastatic potential and poor prognosis (23). There is substantial literature that hypofractionated radiation or SBRT has dramatic effects on tumor vasculature in the acute post-radiation period. From a review of about 25 pre-clinical publications, moderately-high doses of radiation (i.e. 5-10 Gy), causes increases in tumor blood flow initially, which return to pre-irradiation levels 3 days later (24). In addition, in this same report, studies have shown that low or moderate radiation doses can increase tumor oxygenation and oxygen tension, therefore decreasing hypoxia, which could result in improved efficacy of chemotherapy and radiation, since hypoxia is known to promote therapeutic resistance. However, this effect has not been well-studied in human patients. Furthermore, this phenomenon has potential therapeutic implications. We propose that treating a primary lung tumor with a single dose of stereotactic radiation during the SBRT boost, will result in increased tumor blood flow to the tumor, which could allow better accessibility and efficacy of standard radiation and chemotherapy. Thus, we will incorporate functional MRI methods (DCE/PWI, BOLD, and DWI) immediately before and after the first dose of SBRT (i.e. within 1 week before and 24 hours after SBRT) to evaluate and quantitate the changes in the tumor microenvironment. MRI DCE/PWI (dynamic contrast enhanced, perfusion weighted imaging) provides information on tumor vascularity, vessel permeability and blood volume with time dependent delivery of IV contrast agent. DCE/PWI parameters also correlate with tumor oxygenation (25). MRI BOLD (blood oxygenation level dependent) is based on T2* contrast induced by deoxyhemoglobin which is paramagnetic, whereas oxyhemoglobin is not. Several studies have shown relationship between BOLD signal response and tumor oxygenation. BOLD will be performed during delivery of room air and oxygen via face mask (26). DWI (diffusion weighted imaging) is based on the random or Brownian motion of water molecules in relation to their thermal energy. Tumor cell death is supposed to lead to unrestricted extracellular water motion and increase in the apparent diffusion coefficient (ADC) derived from DWI (27). Such imaging correlative studies will be informative in documenting tumor perfusional changes after SBRT and may provide additional information on optimal dosing of chemotherapy. Functional MRI methods are also expected to provide prognostic information.

3.0 STUDY DESIGN

3.1 GENERAL DESIGN

Open-label, single-arm, Phase II study to evaluate the efficacy and safety of SBRT hypofractionated radiation boost doses in patients with Stage II-III unresectable (or medically- inoperable) locally-advanced non-small cell lung cancer. Given that a recently reported phase I trial has shown minimal toxicity using similar doses as a boost for residual disease after conventional chemoradiation for this group of patients, we believe a phase I trial is not necessary (16).

Patients will be registered on trial after meeting eligibility criteria, blood-work, baseline MRI imaging (optional study), and CT simulation during Weeks -2 to 0. During Week 1, the patient will receive 2 SBRT boost doses at least 20 hours apart (with MR imaging performed within 24 hours after SBRT boost dose 1, prior to SBRT boost dose 2 if patient elects to have MRI). Following this, patients will be treated with conventionally fractionated chemoradiation for Weeks 2-7 (60 Gy in 30 daily fractions, 5 days/week, with chemotherapy).

The decision to perform the SBRT boost before the start of conventional CRT instead of immediately after CRT was: 1) due to the ease of performing 1 simulation for SBRT and conventional CRT; 2) to be able to accurately calculate and meet dosimetric constraints by

simultaneous planning of SBRT and conventional radiation plans; 3) moderate doses of radiation may transiently increase tumor perfusion thereby reducing hypoxia and allowing for improved subsequent chemotherapy delivery and ultimately, chemoradiation response; 4) to minimize interaction with chemotherapy (since the normal tissue side effects of the addition of high-dose radiation concurrent with radiosensitizing chemo are largely unknown); and 5) allow for more objective analysis of the effects of SBRT on tumor perfusion for the correlative MRI studies.

3.2 PRIMARY STUDY ENDPOINTS

Primary tumor control (of the primary tumor) at 12 months after all chemo/RT. Local failure is the combination of the primary tumor and involved lobe failure, with local control being the absence of local failure. Local failure rate is measured from the time of treatment completion until the first documented date of local failure. Local failure will be assessed by CT chest imaging during follow-up as detailed in the Evaluation section. See assessment of primary tumor and local failure in Section 9.2. Confirmation of local failure will be required by one of the study P.I.s.

3.3 SECONDARY STUDY ENDPOINTS

-Safety is measured by the frequency of all adverse events, with special attention to grade 3-5 esophagitis, pneumonitis, and cardiac adverse events as defined by the NCI Common Terminology Criteria for Adverse Events CTCAE v5.0.

-Tolerability will be measured by the number of patients who discontinue treatment.

-Clinical endpoints such as regional control, distant control, progression-free survival, and overall survival will be determined by progression or failure (occurrence of local, regional, and distant progression) or death, as measured from the time of treatment completion, and calculated at 12 and 24 months of follow-up, with medians also estimated.

-Objective response rate as measured by RECIST criteria.

-Correlative MR imaging as measured by correlating pre-SBRT baseline perfusion, diffusion, hypoxia measurements with clinical endpoints, and measuring changes in tumor perfusion, diffusion, and hypoxia measurements after SBRT.

3.4 IMAGING CORRELATIVE ENDPOINTS

For imaging correlative endpoints, there will be multiple measurements made. For DCE-MRI, we will measure semi-quantitative (e.g. peak enhancement) and pharmacokinetic (e.g. washout rate constant kel) parameters derived from the analysis of the DCE (dynamic contrast enhancement) curve. For DWI, we will measure differences in mean apparent diffusion coefficient (ADC) between baseline and post-SABR images. Lastly, for BOLD-MRI, we will measure differences in BOLD (blood oxygenation level dependent) contrast between baseline and post-SABR images.

4.0 SUBJECT SELECTION AND WITHDRAWAL

Patients must have baseline evaluations performed prior to the first dose of SBRT and must meet all inclusion and exclusion criteria. Results of all baseline evaluations will be reviewed by the treating physician prior to enrollment, to verify that all inclusion and exclusion criteria have been satisfied. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 INCLUSION CRITERIA

All prior treatment-related toxicities must be CTCAE (Version 5.0) ≤ grade 1 (**except alopecia**) at the time of enrollment.

Adequate baseline organ function defined in the **Table** below**,** obtained within 30 days of study registration:

System	**Laboratory Values**
Hematologic	
Absolute neutrophil count	$\geq 1.5 \times 10^9$/L
Hemoglobin	≥9 g/dL
Platelets	$\geq 100 \times 10^9$/L
Hepatic	
Total bilirubin	≤1.5 x ULN
AST and ALT	≤2.5 x ULN
Renal	
Creatinine **or**	<1.5 mg/dL
Calculated creatinine clearance[a] **or**	≥ 50 mL/min
24-hour urine creatinine clearance	≥ 50 mL/min
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; LLN = lower limit of normal; a= Calculated by the Cockcroft-Gault formula.	

1. ≥ 18 years old
2. Non-small cell lung cancer (NSCLC), histologically and/or cytologically proven
3. Clinical AJCC stage IIA-IIIB NSCLC (T1-4N0-3M0).
4. Patients must be considered unresectable or medically-inoperable.
5. Patients must have primary tumor ≤ 10 cm as defined by CT largest axial dimension.
6. Within 60 days of registration: patients must have FDG-PET-CT scan (or CT chest/abdomen/pelvis with IV contrast), and MRI brain with IV contrast (preferred) or CT scan of the brain with contrast. Non-contrast MRI scans of the

chest/abdomen/pelvis or brain are permitted for workup if patient has allergy to CT contrast or renal insufficiency.

7. Within 30 days of registration: patients must have vital signs, history/physical examination, laboratory studies (CBCP with differential, chemistries including liver function tests, CrCl assessment; pregnancy test if needed within 14 days of registration).
8. If a pleural effusion is present and visible on both CT scan AND chest Xray, the investigator should exclude malignant disease by pleurocentesis to confirm cytologically-negative pleural fluid. If fluid is exudative or cytologically positive for tumor cells, patient is excluded.
    - Patients with effusions that are minimal (i.e. not visible on chest x-ray) and that are too small to safely tap are eligible.
9. Life expectancy of at least 12 weeks in the opinion of investigator.
10. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 within 30 days of registration.
11. Patients must have a measurable primary tumor (undetectable NSCLC primary tumor is ineligible).
12. Patients must be a minimum of 3 weeks from thoracotomy (if performed) and well-healed before starting treatment.
13. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed.
14. Women of child-bearing potential (WOCBP) must have a negative pregnancy test within 14 days of registration. Urine HCG is an acceptable pregnancy assessment.
15. Nursing women may participate only if nursing is discontinued, due to the possibility of harm to nursing infants from the treatment regimen.
16. Women/men of reproductive potential must be counselled on contraception/ abstinence while receiving the study treatment.
17. Patient is suitable to receive standard chemotherapy with radiation during Weeks 2-7 (e.g. cisplatin+ etoposide or carboplatin+paclitaxel).

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Patients with contralateral hilar involvement (greater than 1.5 cm on short axis or positive on PET scan, or biopsy-proven).
2. Documented or pathologically-proven metastatic disease.
3. Presence of nodules considered neoplastic in the same lobe or other ipsilateral lobe as the primary tumor (stage T3-4), unless the nodule can be encompassed in the stereotactic boost (GTVboost) without exceeding a total GTVboost size of 10 cm as defined by the sum of the largest CT axial dimensions of each nodule.
4. Presence of nodules considered neoplastic in contralateral lobes (M1a).
5. Patients with history of pneumonectomy.

6. Prior cytotoxic chemotherapy or molecularly-targeted agents (e.g. erlotinib, crizotinib) as anticancer therapy, unless > 2 years prior.

7. Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, or carcinoma in situ of the cervix. Patients with a previous malignancy without evidence of disease for ≥ 3 years will be allowed to enter the trial.

8. History of active connective tissue disease (scleroderma) or idiopathic pulmonary fibrosis.

9. History of previous radiation therapy which would result in overlapping radiation fields.

10. Uncontrolled neuropathy grade 2 or greater, regardless of cause.

11. Subjects who are breast-feeding and plan to continue breast-feeding during therapy, or have a positive pregnancy test will be excluded from the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

12. If patient elects to have two research MRIs, medical contraindication to MR imaging (e.g. pacemakers, metallic implants, aneurysm clips, known contrast allergy to Gadolinium contrast, pregnancy, nursing mothers, weight greater than 350 pounds) or severe anxiety/claustrophobia related to MR imaging despite medications to relieve anxiety/claustrophobia

13. Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator. This could include severe, active co-morbidities such as:

    - unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

    - transmural myocardial infarction within the last 6 months

    - Acquired immune deficiency syndrome (AIDS) based upon the current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive

    - Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration

    - Hepatic insufficiency resulting in jaundice and/or coagulation defects

4.3 GENDER/MINORITY/PEDIATRIC INCLUSION FOR RESEARCH

This study includes both genders and minority patients. Pediatric patients are excluded.

4.4 SUBJECT RECRUITMENT AND SCREENING

Patients who are 18 year of age or older with non-metastatic locally advanced non-small cell lung cancer are eligible for the study. Patients can be recruited from PI or co-investigators' clinical practices. Potential study subject should be notified to PI and study designated research nurse/research associate. Appropriate laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria will be ordered through the recruiting physician. The treating physician will screen and determine the final eligibility of the subject for enrollment.

4.5 EARLY WITHDRAWAL OF SUBJECTS

4.5.1When and How to Withdraw Subjects

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

1. Intercurrent illness
2. Occurrence of an unacceptable adverse event
3. A treatment delay in radiation therapy >1 weeks
4. Patient request
5. Protocol violations
6. Non-compliance
7. Administrative reasons
8. Failure to return for follow-up
9. General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
10. Progressive disease

The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

According to FDA regulations, when a subject withdraws from the study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. A subject who is withdrawing needs to state whether he/she wishes to provide continued follow-up and further data collection subsequent to withdrawal from the study. If a subject withdraws from the study, but agrees to continued follow-up of associated clinical outcome information, the subject will continue follow up visit and evaluation per the protocol.

If a subject withdraws from the study and does not consent to continued follow-up of associated clinical outcome information, study data related to the subject collected prior to the subject's withdrawal from the study will be included in the study analysis.

Patient with progressive disease will be followed for survival, non-protocol related treatment, and adverse events. AEs for patient with progressive disease should be recorded until patient starts a new treatment for progressive disease or hospice care (whichever comes first). The follow-up assessment may be done over the phone by the study nurse/CRC.

5.0 STUDY PROCEDURES

5.1 TREATMENT OVERVIEW

The study will consist of the following schedule:

- Patients will be registered and obtain baseline laboratory studies (CBCP, chemistries, liver function tests). If no pulmonary function tests (including FEV-1 and DLCO) within last 90 days, patient will be sent to obtain these. Within 3 weeks of planned start (Weeks-3 to 0), patients will undergo a CT simulation.

- Treatment will then proceed with two SBRT boost doses (directed at the primary tumor only) in Week 1 (Days 1-5). For peripheral tumors, 8 Gy x 2 fractions will be administered, while for central tumors, 6 Gy x 2 fractions will be administered. SBRT boost doses must be a minimum of 20 hours apart. If research MRIs are being performed, the 1st research MRI must occur prior to SBRT boost dose 1, and the 2nd research MRI must occur within 24 hrs of SBRT boost dose 1, and prior to SBRT boost dose 2. Ideally, these treatments would begin towards the end of Week 1 (Wednesday-Friday), if standard chemoradiation will be started the following week (Week 2).

- This will be followed by standard fractionated radiation with chemotherapy in Week 2. Chemoradiation will occur during Weeks 2-7, with 60 Gy in 30 fractions concurrent with cisplatin (50 mg/m2 IV, days 8, 15, 36, 43) and etoposide (50 mg/m2 IV, days 8-12, 36-40), or carboplatin (AUC=2 mg/min/mL IV weekly) and paclitaxel (50 mg/m2 IV weekly)

- If carboplatin and paclitaxel is administered concurrently with radiotherapy, 2 cycles of carboplatin (AUC=6 mg/min/mL IV on day 1, 22) and paclitaxel (200 mg/m^2 IV on day 1, 22) consolidation chemotherapy are required, to be administered starting 4-6 weeks after concurrent chemoradiation has ended. Each cycle is 21 days long. At the discretion of the medical oncologist, consolidation chemotherapy can be omitted if patient plans to receive durvalumab immunotherapy. If cisplatin and etoposide is administered concurrently with radiotherapy, consolidation chemotherapy is not allowed.

5.2 SCREENING

Within 7 days of starting treatment, patient will have the first research blood draw.

Within 14 days of registration, patient will have optional research MRI, and women of childbearing potential will have a pregnancy test.

Within 21 days of registration, patient will have CT simulation.

Within 30 days of starting treatment, patients will have CT chest with contrast unless there is an issue with insurance coverage, or patient has an allergy to CT contrast or renal insufficiency. Patient will also have baseline hematologic studies including complete blood count, blood chemistries, hepatic and renal function tests.

Within 60 days of registration, patients will have PET/CT scan (or CT chest/abdomen/pelvis with contrast), and MRI brain with intravenous contrast (or CT of the brain with IV contrast).

Within 90 days of registration, patient must have pulmonary function tests including FEV-1 and DLCO.

5.3 RADIATION THERAPY

Note: The experimental Week 1 treatments (hypofractionated boost) need to occur at the James Cancer Hospital. However, standard chemoradiation treatments (Weeks 2-7) and consolidation chemotherapy (for patients receiving carboplatin and paclitaxel) can be performed locally if performed by a James Cancer Network physician (e.g. Foster J. Boyd Regional Cancer Center, Wilmington, OH).

5.3.1 CT Simulation and Target Delineation

During CT simulation for the Week 1 treatment, patients will undergo a 4D-CT simulation with or without abdominal compression and stereotactic immobilization (e.g. Vac-Lock bag), along with a free-breathing or breath hold CT scan for treatment planning. If 4D-CT scan cannot be performed, a series of exhale and inhale scans can be performed to assess motion.

For the Week 2-7 treatments, a separate CT scan can be performed without abdominal compression on a standard wingboard/arm shuttle, which will be used for radiation planning for the conventional chemoradiation portion of the treatment. This scan can also be performed with a 4D-CT scan, or series of exhale & inhale scans to assess motion. Administration of IV contrast will be left to the discretion of the treating physician.

CT simulation images for the stereotactic planning should be 2.5 mm or less in slice thickness.

Alternatively, if all radiation treatments will be performed at the James, a single CT simulation can be performed for both the stereotactic boost treatment and conventionally fractionated treatments, but must include a 4D-CT (or exhale/inhale series) and a free-breathing scan at the minimum, and either abdominal compression or respiratory gating.

After CT simulation, images will be transferred to the treatment planning system for radiation planning. Radiation planning for both SBRT and conventional treatments will be performed concurrently, so that summation plans can be assessed for meeting normal tissue constraints as

delineated in the protocol. Therefore, for patients treated at James Cancer Network affiliate sites by a James radiation oncologist, the Weeks 2-7 radiation DICOM plan must be sent to the James Cancer Hospital, Department of Radiation Oncology, for evaluation.

Patients can be treated with or without respiratory-gating, including breath-hold technique. Contouring normal structures:

- Heart/pericardium: superior aspect is the inferior aspect of the aortic arch.
- Esophagus: contour from one slice below the inferior aspect of the cricoid cartilage to the gastroesophageal junction
- Spinal cord: contour at least 5 cm above and below superior and inferior extent of PTVs
- Brachial plexus: contour for cases with apical tumors or supraclavicular nodal disease as necessary depending on location of PTVs, using the RTOG brachial plexus contouring atlas from C5-T2.
- Whole Lung: not to include GTVs.
- Skin: outer 0.5 cm of the body surface.
- Ipsilateral proximal bronchial tree (for SBRT planning scan only): The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as "ipsilateral proximal bronchial tree GTV", not as part of the "ipsilateral proximal bronchial tree".
- Great vessels (for SBRT planning scan only): for right sided tumors, contour the vena cava. For left sided tumors, contour the aorta. Contour at least 5 cm above and below superior and inferior extent of PTVs.

Target Delineation for SBRT Plan

Using the treatment planning scan, the physician will designate the boost gross tumor volume [**GTVboost**] by delineating the primary tumor. The primary tumor will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical). Then, an internal target volume (ITV) boost [ITVboost] will be constructed to account for motion using the 4D-CT, unless the patient is being treated with breath-hold technique, in which case there will be no ITV. Finally, ITVboost will be expanded by a minimum of 0.5 axially and craniocaudally (at the discretion of the radiation oncologist) to make the final **PTVboost** for planning.

Target Delineation for Conventionally-Fractionated Radiation Plan

Please note: elective nodal irradiation is not permitted, except in the case of the ipsilateral hilum. The decision to include the ipsilateral hilum will be left to the discretion of the radiation oncologist.

Gross tumor volume (GTV) for all clinically involved disease will be designated by the treating physician on the CT planning dataset. Internal target volumes (ITVs) will be generated from the

GTVs to account for motion noted on the 4D-scans (or exhale/inhale scans).

Next, CTVs will be made from the ITVs (or GTVs if no ITVs) by expanding all ITVs/GTVs by 0.5-1.0 cm in both axial and craniocaudal dimension, as determined by the treating physician. CTVs will be edited by the physician to exclude uninvolved organs (bone, air, muscle, etc) as necessary.

Finally, CTVs will be expanded by a minimum of 0.5-1.0 cm axially and craniocaudally (at the discretion of the radiation oncologist) to make the final PTVs for planning. Each individual PTVs will be summed together to create a total PTV (PTV60).

5.3.2 Radiation Treatment Planning and Treatment Delivery

***NOTES:** SBRT boost and conventionally-fractionated radiation plans should be created at the same time in order to evaluate sum dose between the 2 radiation plans. It is recommended that the conventionally-fractionated plan (60 Gy in 30 fractions) be planned first using the objectives outlined below, followed by planning of the SBRT boost. It is REQUIRED to have both plans signed and evaluated by a study PI prior to having the patient start treatment.

Radiation Planning for SBRT

Density corrections will be employed for planning. 6-18 MV photons will be used for planning. The PET-CT can be used to help delineate the primary tumor but should not be used solely for defining the GTVboost.

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non- coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of *seven* non-opposing beams should typically be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized.

Field aperture size and shape should typically correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions. As such, prescription lines covering the PTV will typically be the **60-90% line (**rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue.

The isocenter in stereotactic coordinates will be determined directly from the tumor in the case of volumetric imaging and translated to the treatment record.

Intensity Modulated Radiation Therapy and Volumetric Modulated Arc Therapy
Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) technologies are allowed.

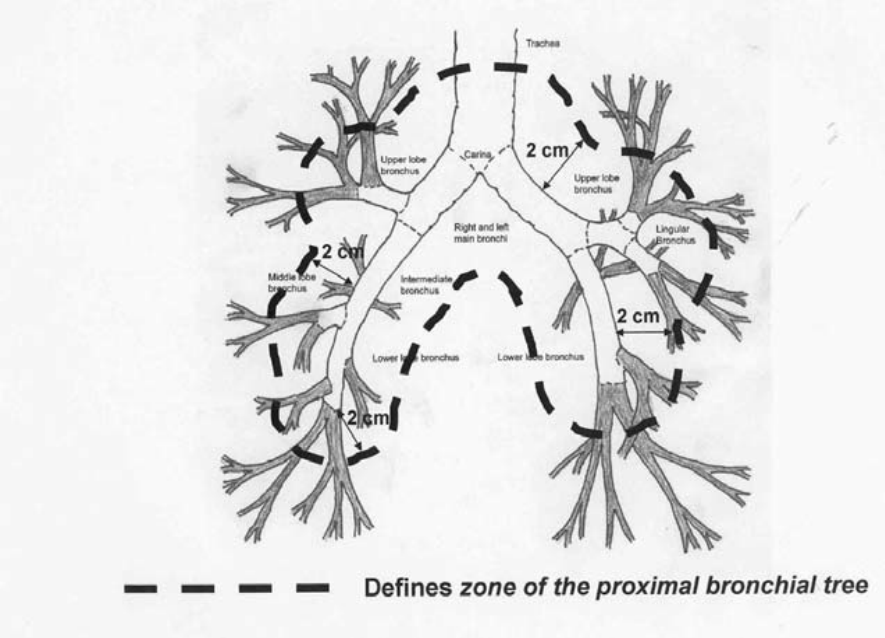
Prescription Isodose Surface Coverage: The dose per fraction is to be prescribed to the prescription line at the edge of the PTVboost. The prescription isodose surface will be chosen such that the goal will be to have 95% of the target volume (PTVboost) be conformally covered by the prescription isodose surface and 99% of the target volume (PTVboost) receiving a minimum of

90% of the prescription dose.

The dose for <u>peripheral</u> tumors will be <u>8 Gy x 2 fractions</u> (or a total of 16 Gy). The dose for <u>central</u> tumors will be <u>6 Gy x 2 fractions</u> (or a total of 12 Gy), delivered at least 20 hours apart.

Central tumors are defined as those tumors within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). *[See figure below from RTOG stereotactic radiation lung protocols]* Tumors that are immediately adjacent to mediastinal or pericardial pleura are also considered central tumors.

With central tumors, efforts should be made with beam angles to minimize dose to heart and mediastinum (e.g. esophagus).



<u>High Dose Spillage:</u>

a. *Location*: Any dose > 105% of the prescription dose should occur primarily within the PTVboost itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all normal tissue outside the PTVboost receiving a dose > 105% of prescription dose should ideally be no more than 15% of the PTVboost volume
b. *Volume*: Conformality of PTVboost coverage will be judged such that the ratio of the volume of the prescription isodose volume of the PTVboost is ideally < 1.2 (see Table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

<u>Low Dose Spillage:</u> The falloff gradient beyond the PTVboost extending into normal tissue structures must be rapid in all directions and should ideally meet the following criteria:

a. *Location*: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTVboost in any direction should be no greater than D2cm where D2cm is given by the table below.
b. *Volume*: The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV should be no greater than R50% where R50% is given. See Table below (*derived from RTOG 0813* protocol).

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)	
	Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0

Planning for Conventionally Fractionated Radiation

As for the SBRT planning, density corrections will be employed for planning. 6-18 MV photons will be used for planning. The PET-CT can be used to help delineate the primary tumor but should not be used solely for defining the GTVs.

A multi-field three-dimensional conformal or IMRT plan is recommended, and VMAT is allowed. Respiratory-gating techniques are also allowed.

All efforts will be made to ensure that with normalization of the treatment plan, 95% of the PTV60 will be covered with the prescription dose ideally. The maximum dose within the PTV60 should ideally not exceed a value that is 110% of the prescribed dose.

The final plan normalization is based upon the Plan Sum coverage of the PTV60 and PTVboost. Normalization values may need to be altered to maintain 95% PTV60 receiving ≥95% of the prescription dose (60 Gy), while respecting OAR (summed dose) constraints. Additional recommendations include keeping hot spots in the plan sum within the PTV boost.

5.3.3 Normal Tissue Constraints

For SBRT boost doses (6 Gy or 8 Gy per day x 2 fractions), the following objectives and their associated priorities for planning are listed:

Spinal cord (**PRIORITY 1**):
- 5.5 Gy max point dose per fraction (0.03 cc) REQUIRED
- <0.25 cc receives 4.5 Gy per fraction (ideal)
- <0.5 cc receives 2.5 Gy per fraction (ideal)

Ipsilateral Brachial Plexus (**PRIORITY 1**)
- 7.5 Gy max point dose per fraction (0.03 cc) REQUIRED
- <3 cc receives 5.5 Gy per fraction (ideal)

Esophagus (**PRIORITY 2**)
- Max 105% of PTVboost prescription (0.03 cc)
- <5 cc receives 5 Gy per fraction

Heart/Pericardium (**PRIORITY 2**)
- Max 105% of PTVboost prescription (0.03 cc)
- <15 cc receives 5 Gy per fraction

Trachea and ipsilateral bronchus (non-adjacent wall) (**PRIORITY 3**)
- Max 105% of PTVboost prescription (0.03 cc)
- <4 cc receives 3.5 Gy per fraction

Great vessels (non-adjacent wall) (**PRIORITY 4**)
- Max 105% of PTVboost prescription (0.03 cc)
- <10 cc receives 9 Gy per fraction

Skin (**PRIORITY 4**)
- Max 6 Gy per fraction (0.03 cc)
- <0.25 cc receives 4.5 Gy per fraction
- <0.5 cc receives 2.5 Gy per fraction

Chest Wall (2 cm rind) (**PRIORITY 4**)
- 30 cc < 6 Gy per fraction

Stomach (**PRIORITY 4**)
- Max 7 Gy per fraction (0.03 cc)

The spinal cord maximum dose is an absolute limit and treatment delivery that exceeds this limit will constitute a major protocol violation. However, some organs at risk (OAR) (e.g. esophagus, trachea, bronchi, and heart) may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumor that are immediately adjacent to that organ will not be able to be treated to any of the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning needs to be done so that there is no hot spot within that organ, even if that organ is part of the GTV/PTV (i.e., that no part of any OAR receives more than 105% of the prescribed dose). In addition, the volume of the OAR in question needs to be minimized both in length and in width (circumference), with efforts made to reduce the dose to the contralateral wall of the organ.

For non-spinal cord OAR with known sensitivity to high doses of radiation (including the esophagus,

trachea/bronchus, and stomach) included within a PTVboost or immediately adjacent to PTVboost, it is reasonable to underdose the PTVboost to achieve the goals of the sum plan. Additionally, every effort should be made to cover the GTV with the prescription dose while ensuring rapid falloff to the OAR. Coverage of a section of PTVboost including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation.

For Conventionally Fractionated Radiation Plans (2 Gy per day in 30 fractions, total 60 Gy), the following objectives and their associated priorities for planning are listed:

Spinal cord (**PRIORITY 1**):

- 45 Gy max point dose (0.03 cc)

Ipsilateral Brachial Plexus (**PRIORITY 1**)

- 65 Gy max point dose (0.03 cc)

Esophagus (**PRIORITY 2**)

- Mean dose ≤ 34 Gy
- V50 < 33%
- V60 < 17% (ideal, but strive for V60 <30%)

Heart (**PRIORITY 2**)

- Mean heart dose ≤ 35 Gy
- V30 ≤ 50%
- V45 ≤ 35%

Total Lung – all PTVs (**PRIORITY 2**)

- Mean lung dose ≤ 20 Gy
- No more than 25% is to exceed 30 Gy
- No more than 35% is to exceed 20 Gy
- No more than 50% is to exceed 10 Gy
- No more than 65% is to exceed 5 Gy

For Sum Plan between SBRT boost and conventionally fractionated radiation:

******NOTE THAT THESE ARE STRICT REQUIREMENTS AND ARE NOT TO BE EXCEEDED UNLESS DEEMED ACCEPTABLE BY ONE OF THE STUDY P.I.s (in which case a note needs to be made in the chart explaining that this was deemed acceptable by one of the study P.I.s)***

Spinal cord (**PRIORITY 1**):

- 45 Gy max point dose (0.03 cc)

Ipsilateral Brachial Plexus (**PRIORITY 1**)

- 65 Gy max point dose (0.03 cc)

Total Lungs – all PTVs (including PTVboost) (**PRIORITY 2)**

- Mean Lung Dose (MLD) should be ideally ≤18 Gy (max ≤ 20 Gy)
- V20 ≤ 30% ideally (max ≤ 35%)

Esophagus (**PRIORITY 2**)

- Mean dose ≤ 34 Gy
- Max dose ≤ 65 Gy (0.03 cc)

Heart (**PRIORITY 3**)

- Mean heart dose ≤ 35 Gy
- V30 ≤50% (ideal; acceptable ≤ 55%)
- V45 ≤35% (ideal; acceptable ≤ 40%)
- Maximum not to exceed 70 Gy

******* If any of these values are exceeded, please contact study P.I.s for recommendations. One option is to decrease coverage to the PTVboost in order to meet Sum Plan objectives as stated above (i.e. coverage of a section of PTVboost including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation). However, if the sum plan is deemed unacceptable by one of the study P.I.s, the patient will be removed from the clinical trial and treated with standard chemoradiation (with no SBRT boost).

*** All plans are required to be reviewed by one of the study P.I.s prior to initiation of treatment.

5.3.4 Treatment Delivery and IGRT

Patients will receive 2 fractions of SBRT radiation, with a minimum of 20 hours between treatments, and which must occur during Week 1.

SBRT may be delivered via VMAT, IMRT, conformal arc, or conventional stereotactic radiation, and may use Varian RPM gating if the patient will be treated with respiratory-gated or breath-hold methods.

Daily image-guided radiation therapy (IGRT) will include a daily cone-beam CT for each PTVboost fraction.

For the conventionally-fractionated treatment plan starting on Week 2, the daily prescribed dose is 2 Gy per day with treatment given five days per week. All radiation fields shall be treated once per day.

Recommended image-guided radiation therapy (IGRT) methods include orthogonal pair imaging, port film verification, and/or cone beam CT. The type and frequency of IGRT will be determined by the investigator but should include a minimum of one CBCT per week for matching. Portal verification of all fields should be performed prior to the delivery of the first fraction for patients treated with 3D conformal radiotherapy.

5.3.5 Treatment Modification/Interruption/Toxicity:

No treatment interruptions are planned. Treatment may be interrupted for acute toxicity. Chemotherapy will be held if RT is held. No modifications in total dose will be made for interruptions in therapy. Toxicities will be graded according to the NCI CTCE v.5.0. If grade 3 dysphagia or esophagitis occurs, it is at the discretion of treating physician whether to interrupt treatment. If interruption is warranted, every effort should be made to limit the treatment break to 3 days or less. If grade 4 dysphagia or esophagitis occurs, all treatments including chemotherapy and radiation therapy should be put on hold until patient is stable enough to continue with the treatment. If radiation is interrupted for grade 4 dysphagia or esophagitis, hold radiation until grade 2 or less and do not restart chemotherapy even if radiation is restarted. Radiotherapy also will be

held for grade 4 skin reaction until it is stable enough to continue. Chest Radiation Therapy may cause: 1) esophagitis, 2) fatigue (tiredness), 3) skin reaction within the radiation fields, 4) loss of chest hair, 5) decrease in white blood cells and platelets with increased risk of infection and/or bleeding, 6) lung fibrosis, 7) delayed wound healing or non-healing (fistulae), 8) chest pain, and 9) muscle spasm.

5.4. CHEMOTHERAPY

Note: The experimental Week 1 treatments (hypofractionated boost) need to occur at the James Cancer Hospital. However, standard chemoradiation treatments (Weeks 2-7) and consolidation chemotherapy (for patients receiving carboplatin and paclitaxel) can be performed locally if performed by a James Cancer Network physician (e.g. Foster J. Boyd Regional Cancer Center, Wilmington, OH).

5.4.1. Concurrent Chemotherapy Schedule:

Chemotherapy and radiation therapy will begin within 24 hours of each other with chemotherapy delivered first if possible/feasible. However, alternate scheduling is allowed. A single platinum-based doublet chemotherapy regimen is to be administered during radiotherapy. The choice of the chemotherapy regimen is at the discretion of the treating physician. One of the following recognized standard, protocol-allowed regimens must be given with radiation therapy:

- Paclitaxel (50 mg/m^2) intravenous over 1 hour followed by Carboplatin AUC = 2 mg/min/mL intravenous weekly (every 7 days) during radiotherapy. Standard premedications with steroids, famotidine, diphenhydramine, and antiemetics must be administered per individual institutional guidelines.

OR

- Etoposide (50 mg/m^2/d) intravenous on days 8-12 and days 36 to 40 and Cisplatin (50 mg/m^2/d) intravenous on days 8, 15, 36, and 43. Standard premedications with steroids and antiemetics must be administered per individual institutional guidelines. Standard intravenous hydration must be administered in conjunction with cisplatin.

Filgrastim and pegfilgrastim may not be used during concurrent chemoradiotherapy. Erythropoiesis-stimulating agents (epoetin alfa, darbepoietin alfa) may not be used during concurrent chemoradiotherapy.

Chemotherapy scheduling modifications of +/- 3 dyas are allowed due to weekends and holidays.

5.4.2 Consolidation Chemotherapy Schedule:

****Please note: At the discretion of the medical oncologist, consolidation chemotherapy can be omitted if patient is planned to receive durvalumab. See section 5.5.1 for detailed information.**

The treating physician will administer 2 cycles of consolidation chemotherapy 4-6 weeks after concurrent chemoradiotherapy has ended, only if patients receive concurrent carboplatin and paclitaxel with radiotherapy. Each cycle length is 21 days. The consolidation chemotherapy regimen is carboplatin and paclitaxel.

- Paclitaxel (200 mg/m^2) intravenous over 3 hours on day 1, and carboplatin at an area under the plasma concentration time curve (AUC) = 6 mg/min/mL intravenous on day 1. A second cycle of paclitaxel and carboplatin will be administered on day 22.

Standard premedications with steroids, famotidine, diphenhydramine, and antiemetics must be administered per individual institutional guidelines.

Patients who receive concurrent cisplatin and etoposide with radiotherapy are not allowed to receive consolidation chemotherapy.

Filgrastim, pegfilgrastim, or erythropoiesis-stimulating agents (epoetin alfa, darbepoietin alfa) may be used during consolidation chemotherapy (Rizzo 2010).

5.4.3 Cisplatin (CDDP) (Platinol®) (NSC-119875)

Refer to package insert for detailed pharmacologic and safety information.

Formulation

Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH. Cisplatin also is available in vials containing 50mL or 100mL of a 1mg/mL solution.

Storage and Stability

Reconstituted solution of cisplatin is stable for 20 hours when stored at 25°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

Adverse Events

Human toxicity includes nausea, vomiting, anaphylaxis, neuropathies, ocular disturbances, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected

Supply

Commercially available.
The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

5.4.4 Etoposide (VP-16) (Vepesid®) (NSC-141540)

Refer to package insert for detailed pharmacologic and safety information.

Storage and Stability

Store the unopened vials under refrigeration 2º to 8º C (36º-46º F). Retain in original package to protect from light.

Adverse Events
Hematologic: Myelosuppression is dose related and dose limiting with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20. Acute myeloid leukemia has been reported in rare instances.

Gastrointestinal: Nausea and vomiting are the major gastrointestinal toxicities. Nausea and vomiting can usually be controlled with standard antiemetic therapy.

Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension have been reported to occur in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the drug and to the administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. One fatal acute reaction associated with bronchospasm has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients. 44 RTOG 1308; version date 10/24/13

Other: The following adverse reactions have been infrequently reported: aftertaste, hypertension, rash, fever, pigmentation, pruritus, abdominal pain, constipation, dysphagia, transient cortical blindness, and a single report of radiation recall dermatitis.

Supply
Commercially available.
The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

5.4.5 Carboplatin (NSC-241240)
Refer to package insert for detailed pharmacologic and safety information.

Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Carboplatin also is available as a 10 mg/mL solution in 50, 150, and 450 mg vials.

Preparation
When available, prediluted vials of carboplatin should be utilized. Otherwise, the preparation of carboplatin should proceed as described below:

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP.

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin

Storage and Stability
Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30˚C or 59-86˚F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

Adverse Events
Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leucopenia, and anemia are common but typically resolve by day 28 when carboplatin is given as a single agent.

Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy. Desensitization per the allergy team is allowed.

Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common gastrointestinal events; both usually resolve within 24 hours and respond to antiemetics. Other gastrointestinal events include diarrhea, weight loss, constipation, and gastrointestinal pain.

Hepatic: Elevated alkaline phosphatase, total bilirubin, and SGOT have been reported.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

Supply
Commercially available.
The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

5.4.6 Paclitaxel (Taxol®) (NSC 125973)

Refer to package insert for detailed pharmacologic and safety information.

Preparation
Paclitaxel injection is a sterile solution concentrate, 6 mg/ml in 5, 16.7, and 50 ml vials (30, 100, and 300 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D5W, NS, or D5NS, in glass or polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the intravenous fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting

excessive particulate matter formation should not be used.

Storage and Stability
Paclitaxel vials should be stored between 20-25°C (68°-77°F). When prepared as suggested (0.3 – 1.2 mg/ml), the solution is stable for 27 hours.

Adverse Effects
Hematologic: Myelosuppression;

Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain;

Heart: Arrhythmias, heart block, hypertension;

Neurological: Sensory and peripheral neuropathy;
Allergy: Severe anaphylactic reactions;

Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), hypotension, irritation to the injection site, mucositis

5.4.7 Dose Modifications:

Note: Chemotherapy doses that are omitted due to the indicated toxicities below are not made up.

5.4.7.1 Dose Modifications During Concurrent Chemoradiotherapy With Weekly Carboplatin and Paclitaxel

Hematologic Toxicity
Absolute neutrophil count (ANC) and platelet count (plt) must be obtained within 72 hours prior to each dose of carboplatin and paclitaxel, except for on day 8.

If ANC < 1000 or plt < 75,000, omit weekly carboplatin and paclitaxel. Restart weekly carboplatin and paclitaxel at same dose if ANC > 1000 and plt > 75,000.

Dysphagia/Radiation Esophagitis
If radiation is interrupted for grade 3 or 4 dysphagia or radiation esophagitis, hold weekly carboplatin and paclitaxel. If radiation is interrupted for grade 3 dysphagia or radiation esophagitis and radiation is to be restarted, it is at the discretion of the treating physician whether or not to restart chemotherapy. If the decision is made to restart chemotherapy in this setting, consider reducing weekly carboplatin and paclitaxel dose by up to 50%. If radiation is interrupted for grade 4 dysphagia or radiation esophagitis, hold radiation until grade 2 or less and do not restart chemotherapy even if radiation is restarted.

Neurologic Toxicity
Paclitaxel doses will be modified for neurologic toxicity:

- If grade 1 neurologic toxicity, no dose modification
- If grade 2 neurologic toxicity, reduce dose to 75%.
- If grade > 2 neurologic toxicity, hold chemotherapy until neurologic toxicity improves to grade ≤ 2, then either reduce dose to 50% or discontinue chemotherapy, at the physician‘s

discretion.

Renal Toxicity
Carboplatin dose will be modified for renal toxicity. Serum creatinine must be obtained within 72 hours prior to each dose of weekly carboplatin, except for day 8. Serum creatinine is required within 10 days prior to day 8 carboplatin.

- If renal toxicity occurs, the AUC will be re-calculated with a new serum creatinine, to account for the necessary dose adjustment.

Neutropenic Fever [defined as temperature ≥ 38.3 C (101 F) and ANC < 500]

- If neutropenic fever occurs and the patient subsequently meets criteria for further chemotherapy, the doses are reduced to 75%

Other Toxicities Not Defined Above

- If toxicities ≤ grade 2, then manage symptomatically, if possible, and retreat without dose reduction.
- If toxicities ≥ grade 3 and attributed to the protocol treatment (possible, probably, or definite), drug should be withheld until patient is stable enough to continue with the treatment. When medically appropriate to restart, consider reducing dose up to 50%.

If carboplatin or paclitaxel doses are reduced, all future weekly doses are reduced.

5.4.7.2 Dose Modifications During Concurrent Chemoradiotherapy With Cisplatin and Etoposide
Hematologic Toxicity
ANC and plt must be obtained within 72 hours prior to day 36 chemotherapy.

For day 8 and day 36 cisplatin and etoposide:

- If ANC ≥ 1250 and plt ≥ 100,000, give full dose
- If ANC < 1250 or plt < 100,000, hold chemotherapy and recheck ANC and plt in 1 week.
- If after a 1 week delay ANC ≥ 1250 and plt ≥100,000, give full dose. If after a 1-week delay ANC < 1250 or plt < 100,000, hold chemotherapy and recheck ANC and plt in 1 more week (total of a 2-week delay). If after a 2-week delay ANC ≥ 1250 and plt ≥ 100,000, reduce dose of chemotherapy by 25%. If after a 2-week delay ANC < 1250 or plt < 100,000, omit chemotherapy.

For day 15 and day 43 cisplatin:
ANC and plt must be obtained within 72 hours prior to day 15 and 43 chemotherapy.

- If ANC ≥ 1000 and plt ≥ 75,000, give full dose
- If ANC < 1000 or plt < 75,000, hold chemotherapy and recheck ANC and plt in 1 week.
- If after a 1-week delay ANC ≥ 1000 and plt ≥ 75,000, give full-dose cisplatin. If after a 1-week delay ANC < 1000 or plt < 75,000, hold chemotherapy and recheck ANC and plt in 1 more week (total of a 2-week delay). If after a 2-week delay ANC ≥ 1000 and plt ≥ 75,000, reduce dose of cisplatin to 75%. If after a 2-week delay ANC < 1000 or plt < 75,000, omit the dose of cisplatin.

Dysphagia/Radiation Esophagitis
If radiation is interrupted for grade 3 or 4 dysphagia or radiation esophagitis, hold cisplatin and etoposide. If radiation is interrupted for grade 3 dysphagia or radiation esophagitis and radiation is to be restarted, it is at the discretion of treating physician whether or not to restart chemotherapy. If the decision is made to restart chemotherapy in this setting, consider reducing cisplatin and etoposide

doses up to 50%. If radiation is interrupted for grade 4 dysphagia or radiation esophagitis, hold radiation until grade 2 or less and do not restart chemotherapy even if radiation is restarted.

Neurologic Toxicity
Cisplatin dose will be modified for neurologic toxicity:

- If grade 1 neurologic toxicity, no dose modification
- If grade 2 neurologic toxicity, reduce dose to 75%.
- If grade > 2 neurologic toxicity, hold cisplatin until neurologic toxicity improves to grade ≤ 2, then either reduce dose to 50% or discontinue cisplatin, at the physician‘s discretion.

Renal Toxicity
Cisplatin dose will be modified for renal toxicity.
Serum creatinine must be obtained within 72 hours prior to each dose of cisplatin, except for day 8.
Serum creatinine is required within 10 days prior to day 8 cisplatin.

- If serum creatinine ≤ 1.5 mg/dL, give full cisplatin dose.
- If serum creatinine 1.5-2.0 mg/dL, calculate creatinine clearance. If calculated creatinine clearance is ≥ 50 ml/min give full cisplatin dose.
- If serum creatinine 1.5-2.0 mg/dL and calculated creatinine clearance is < 50 ml/min, omit cisplatin dose and recheck serum creatinine at next scheduled cisplatin dose. If creatinine is < 2.0 and creatinine clearance has improved to ≥ 50 mL/min, reduce cisplatin dose to 75%.
- If serum creatinine > 2.0 mg/dL, omit cisplatin dose, and recheck serum creatinine at next scheduled cisplatin dose. If creatinine is < 2.0 mg/dL and creatinine clearance ≥ 50 mL/min, reduce dose to 50%; otherwise continue to omit cisplatin dose, recheck serum creatinine again at next scheduled cisplatin dose, and follow the same guidelines.

Neutropenic Fever [defined as temperature ≥ 38.3 C (101 F) and ANC < 500]

- If neutropenic fever occurs and the patient subsequently meets criteria for further chemotherapy, the doses are reduced by 25%.

Other Toxicities Not Defined Above

- If toxicities ≤ grade 2, then manage symptomatically, if possible, and retreat without dose reduction.
- If toxicities ≥ grade 3 and attributed to the protocol treatment (possible, probable, or definite), drug should be withheld until patient is stable enough to continue with the treatment. When medically appropriate to restart, consider reducing dose up to 50%.

If cisplatin or etoposide doses are reduced, all future doses are reduced.

5.4.7.3 Dose Modifications for Consolidation Chemotherapy With a Carboplatin and Paclitaxel Regimen

Hematologic Toxicity
ANC and plt must be obtained within 72 hours prior to each dose of carboplatin and paclitaxel.

- If ANC ≥ 1500 and plt ≥100,000, give full dose
- If ANC < 1500 or plt < 100,000, hold chemotherapy and repeat ANC and plt in 1 week. If ANC ≥ 1500 and plt ≥100,000, give full dose. If ANC < 1500 or plt < 100,000, hold chemotherapy again and repeat ANC and plt in 1 week (total of a 2-week delay). If ANC ≥ 1500 and plt ≥ 100,000, give full dose; otherwise omit chemotherapy dose.

Neurologic Toxicity
Carboplatin and paclitaxel doses will be modified for neurologic toxicity:

- If grade 1 neurologic toxicity, no dose modification
- If grade 2 neurologic toxicity, reduce dose to 75%.
- If grade > 2 neurologic toxicity, hold chemotherapy until neurologic toxicity improves to grade ≤ 2, then either reduce dose to 50% or discontinue chemotherapy, at the physician's discretion.

Renal Toxicity
Carboplatin dose will be modified for renal toxicity.
Serum creatinine must be obtained within 72 hours prior to each dose of carboplatin.

- If renal toxicity occurs, the AUC will be re-calculated with a new serum creatinine, to account for the necessary dose adjustment.

Neutropenic Fever [defined as temperature ≥ 38.3 C (101 F) and ANC < 500]
If neutropenic fever occurs and the patient subsequently meets criteria for further chemotherapy, the doses are reduced to 75%.

Other Toxicities Not Defined Above

- If toxicities ≤ grade 2, then manage symptomatically, if possible, and retreat without dose reduction.
- If toxicities ≥ grade 3 and attributed to the protocol treatment (possible, probable, or definite), drug should be withheld until patient is stable enough to continue with the treatment. When medically appropriate to restart, consider reducing dose up to 50%.

If carboplatin or paclitaxel doses are reduced, all future doses are reduced.

5.5 PERMITTED THERAPIES

5.5.1 Immunotherapy:

At the discretion of the medical oncologist, durvalumab can be administered to patients after completion of chemoradiation, since it is now FDA-approved after completion of chemoradiation, based on the results of the PACIFIC trial, which showed improved progression-free survival for patients receiving durvalumab for up to 12 months for patients who have not progressed after completion of platinum-based chemoradiation [Antonia SJ, et. al, N Engl J Med, 2017. 377(20): p. 1919-1929].

At the discretion of the medical oncologist, consolidation chemotherapy can be omitted if patient is planned to receive durvalumab, since patients on the PACIFIC trial did not receive consolidation chemotherapy.

Durvalumab should ideally be started within 4 weeks of finishing chemoradiation or consolidation chemotherapy (if they receive consolidation chemotherapy). However, alternate scheduling is allowed.

5.6 ON TREATMENT EVALUATIONS

Patients will be examined every week by the treating physician during chemoradiotherapy to assess toxicity, with history and physical exam, vital signs, assessment of performance status. A complete blood count (CBCP) with differential will be obtained during chemoradiotherapy at the

discretion of the medical oncologist. Chemistries including liver function tests, sodium, potassium, chloride, blood urea nitrogen, creatinine, and glucose will be checked at the discretion of the medical oncologist.

6.0 MR IMAGING

For eligible patients, this trial includes correlative MRI studies to assess the effects of stereotactic body radiation therapy on tumor perfusion, diffusion, and oxygenation. There is literature that hypofractionated radiation or SBRT has significant effects on tumor vasculature in the acute post-radiation period. From a review of about 25 pre-clinical publications, moderately high doses of radiation (i.e. 5-10 Gy), causes increases in tumor blood flow initially, which return to pre-irradiation levels 3 days later (24). However, this effect has not been well-studied in human patients. Furthermore, this phenomenon has potential therapeutic implications, in particular when to dose chemotherapy. The goal of these correlative imaging studies is to determine what changes occur in the tumors after stereotactic body radiation therapy. If SBRT boost doses are found to reproducibly allow for increased tumor blood flow, this could inform when to dose chemotherapy in future trials. Thus, we will incorporate functional MRI methods (DCE/PWI, BOLD, and DWI) immediately before and after the first dose of SBRT (i.e. within 1 week before and within 24 hours after the first SBRT) to evaluate and quantitate the changes in the tumor microenvironment. MRI DCE/PWI (dynamic contrast enhanced, perfusion weighted imaging) provides information on tumor vascularity, vessel permeability and blood volume with time dependent delivery of IV contrast agent. DCE/PWI parameters also correlate with tumor oxygenation (25). BOLD-MRI (blood oxygenation level dependent) is based on T2* contrast induced by deoxyhemoglobin which is paramagnetic, whereas oxyhemoglobin is not. Several studies have shown relationship between BOLD signal response and tumor oxygenation. BOLD-MRI will be performed during delivery of room air and oxygen via face mask (26). DWI (diffusion weighted imaging) is based on the random or Brownian motion of water molecules in relation to their thermal energy. Tumor cell death is supposed to lead to unrestricted extracellular water motion and increase in the apparent diffusion coefficient (ADC) derived from DWI (27). Such imaging correlative studies will be informative in documenting tumor perfusional changes after SBRT and may provide additional information on optimal dosing of chemotherapy. Functional MRI methods are also expected to provide prognostic information.

For imaging correlative endpoints, there will be multiple measurements made. For DCE-MRI, we will measure semi-quantitative (e.g. peak enhancement) and pharmacokinetic (e.g. washout rate constant kel) parameters derived from the analysis of the DCE (dynamic contrast enhancement) curve. For DWI, we will measure differences in mean apparent diffusion coefficient (ADC) between baseline and post-SABR images. Lastly, for BOLD-MRI, we will measure differences in BOLD (blood oxygenation level dependent) contrast between baseline and post-SABR images.

MRI correlative imaging will be conducted at the Wright Center for Innovation in Biomedical Imaging.

For eligible patients, each patient will receive a total of 2 MRIs, one within 2 weeks before the first SABR dose and the second within 24 hours after the first SABR dose. The MRI testing is mandatory for the first 10 patients on the study who do not have contra-indications to MRI as defined in the Exclusion Criteria.

6.1 ANATOMICAL IMAGING

Tumor will be located on breath-hold fast spin echo and fast multi-planar gradient-recalled echo anatomical images. The anatomical imaging protocol will include axial T1- and T2-weighted images for optimal tumor localization and delineation.

6.2 DWI (diffusion weighted magnetic resonance imaging)

DWI will be acquired with an electrocardiographic (ECG) and respiratory-gated single-shot spine echo sequence using two b values (0 and 1000 sec/mm^2). ADC maps will be generated from DWI images by using these two b values.

6.3 BOLD-MRI (blood oxygenation level dependent magnetic resonance imaging)

Respiratory-gated multi-echo gradient-echo technique will be used for BOLD imaging. Patients will wear a face mask for delivery of oxygen. T2*-weighted BOLD images will be obtained for a single sagittal slice through the center of the tumor. Three to four dynamics will be obtained when patients breathed room air, followed by another six to eight dynamics while breathing 100% oxygen at 8 L/min via the face mask.

6.4 DCE-MRI (dynamic contrast enhanced magnetic resonance imaging)

T1-weighted 3D spoiled gradient echo (SPGR) sequence will be used for DCE-MRI acquisition with coverage of the entire tumor volume as determined on the anatomical images. The 3D SPGR sequence will be repeated for 10 minutes with a temporal resolution of 5-10 seconds/volume to allow a comprehensive analysis of contrast agent pharmacokinetics. Bolus injection of a commercially available low-molecular-weight MR contrast agent (0.1 mmol/kg) will be administered using an MR-compatible power injector with a flow rate of no faster than 5 ml/sec after the first 5-10 volumes are acquired.

6.5 SIDE EFFECTS AND RISKS OF MR IMAGING

While scheduling the patient, it will be ascertained that the patient does not have an implant or device that may be contraindicated or requires special attention for the MR procedure (e.g., pregnancy, renal failure, metallic foreign body, ferromagnetic aneurysm clip, pacemaker, neurostimulation system, etc.). Preliminary screening helps to prevent scheduling patients that may be inappropriate candidates for MR examinations. Risks of MR imaging are potential bruising or contest extravasation at the contrast injection site. Management of contrast extravasation will include application of warm compresses, notification of the treating physician and follow-up with the patient by phone within the next day. Allergies to the MRI contrast occur rarely. The common side effects of the contrast agent include mild to moderate temporary headache (4.8%), nausea (2.7%), skin tingling (2.3%), metallic taste (1.3%), and dizziness (1%). Gadolinium-based contrast agents have been linked to the development of nephrogenic systemic fibrosis (NSF) or nephrogenic fibrosing dermopathy (NFD). The disease has occurred in patients with moderate to end-stage renal disease after being given a gadolinium-based contrast agent to enhance MRI or MRA scans. NSF/NFD is a debilitating and sometimes fatal disease. To eliminate the risk of renal toxicity from to the MRI contrast effects, only patients with a GFR of >30 will be included in the MRI study.

7.0 RESEARCH BLOOD DRAWS

7.1 **Overview:** Each patient enrolled on the trial will undergo 6 research blood draws for correlative research for circulating tumor DNA and miRNA biomarkers.

7.2 **Collection of Specimens:** Blood draws will be collected in the Department of Radiation Oncology or Martha Morehouse. At each blood draw, venous whole blood (approximately 30 mL) will be drawn into three 10 mL lavender-top tubes containing EDTA (total of 3 tubes). Research blood draws will occur within 7 days prior to the first radiation treatment in Week 1, at the start of Weeks 2 and Week 5 (prior to chemotherapy administration on days 8 and 29), and at 1, 6, and 12 months after all treatment is completed (including chemoradiation and consolidation chemotherapy). **Note: If patients are being treated during Weeks 2-7 or are being seen in follow-up after treatment at a James Cancer Network affiliate site, these specimens are not required to be**

collected.

7.3 **Handling of Specimens:** The tubes will be filled completely, and mixed by gentle inversion 8-10 times. Tubes will be labeled with protocol number, de-identified subject number, date, time collected, and reference timepoint relative to protocol (e.g. Week 1 predose, Week 2 predose, Week 5 predose, 1 month, 6 month, etc). Samples will be stored at room temperature or 4 degrees Celsius until pickup by the Clinical Trials Processing Lab (CTPL). Blood should be centrifuged at 1,200g for 10 minutes at either room temperature or 4°C. Aliquot plasma into 8 equal cryovials and store at -70°C until pickup by the Williams laboratory until the end of November 2020, after which point all samples will be taken to the Clinical Trials Processing Lab (CTPL).

7.4 **Pickup and Storage of Specimens:** Plasma samples will be brought to the Williams Laboratory by a member of Dr. Williams' laboratory every 3 months or more frequently if requested by PI. Samples will go to the Williams lab until the end of November 2020, after which point all samples would then be housed with CTPL. Samples should be accompanied by a specimen inventory spreadsheet. Samples will be stored in a -70° C freezer until subsequent analysis. Analysis for miRNA in plasma and circulating tumor DNA will be conducted in collaboration with (BRT 486).

8.0 ADVERSE EVENTS, COMMON TOXICITY ASSESSMENT CRITERIA AND SUPPORTIVE CARE

8.1 Adverse Events

8.1.1 Adverse Events(AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse events will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTC version 5.0 for toxicity and Adverse Drug Experience reporting. A copy of the CTC version 5.0 can also be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

All adverse events should be treated appropriately. Once an adverse event is detected, it should be followed until its resolution or stabilization of the event (to ≤ grade 2), whichever comes first. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome

8.1.2 Serious Adverse Events (SAEs)

Definition of an SAE: Any adverse experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant disability/incapacity to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition,

Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported as a medically significant event.

Any serious event should be reported to the DSMC within 48 hours of becoming aware of the event.

Any unexpected late death (more than 30 days after the last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported within 24 hours of discovery.

8.1.3 SAE Reporting Requirements

The investigator is required to submit all unexpected and serious adverse events to the OSU IRB within the institutional required timeframe. All AE/SAEs will be reported to the Data and Safety Monitoring Committee (DSMC) at the quarterly DSMC review meetings; however, the investigator determines corrective action is necessary, and "ad hoc" DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported within 10 days of the Investigators first awareness of the event to the OSU IRB and the DSMC. Fatalities not related to the study must be reported within the institutional required timeframe.

The Ohio State University
Office of Responsible Research Practices
1960 Kenny Road
Columbus, Ohio 43210
Phone: 614-688-8457
Fax: 614-688-0366

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the treatment from other sources; including published literature, scientific meetings, to determine if the trial should be terminated before completion. Serious adverse events and responses will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

8.2 Interruption and discontinuation

Treatment delays are occasionally encountered during radiation therapy due to logistic problems (e.g. machine break downs, patient transportation issues) or public holidays. If this occurs radiation therapy shall be completed as soon as possible, but with no more than one fraction per day, 5 fractions per week.

For patients who are unable to tolerate the protocol-specified chemotherapy dosing schedule, dose adjustments are permitted in order to keep the patient on study chemotherapy. Toxicity will be assessed using CTCAEv4.0 as noted above. All interruption or changes to study chemotherapy administration must be recorded.

In the absence of treatment delays due to toxicity, treatment continues per protocol until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Patient develops progressive disease warranting change in treatment
- Unacceptable toxicity
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

8.3 Management of Toxicity and Supportive Care

8.3.1 Nausea/vomiting

Prophylaxis and secondary treatment: Anti-emetics should be initiated at the onset of symptoms and continued as directed by the treating physician until resolution of symptoms to grade 0-1. Additional supportive care measures, e.g. oral or intravenous rehydration, etc., should be instituted as required by the patient's clinical condition. Additional medical evaluation is recommended for those patients with continued nausea/vomiting > grade 2, lasting > 48 hours despite institution of optimal supportive care measures. Primary prophylaxis should be initiated once nausea or vomiting has occurred with the prior treatment. Admit to hospital and administer IV fluids and all supportive measures for symptoms unresponsive to medication and signs of dehydration.

8.3.2 Hematopoietic Growth Factors

WBC growth factors (G-CSF/GM-CSF) and erythropoietin will not be permitted during radiation.

8.3.3 Management of Pneumonitis and Other Respiratory Symptoms

Pneumonitis has been observed in subjects receiving chemoradiation. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, and evaluated with imaging and functional tests. For cough, dextromethorphan, benzonatate, or mild narcotic medications (e.g. codeine syrup) can be used.

8.3.4 Management of Esophagitis

Esophagitis can be managed by the preference of the treating physician and may commonly include medications such as Magic Mouthwash (e.g. custom mix of Benadryl, Maalox, lidocaine), proton pump inhibitors, or narcotics for pain.

8.4 Follow up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event (to ≤ grade 2), whichever comes first.

All patients will be followed for new adverse events and serious adverse events up to 30 days after the last study treatment. For toxicities that occur patients will be closely followed until resolution or stabilization of the event (to ≤ grade 2), whichever comes first. Any new adverse events or serious adverse events beyond 30 days after the study treatment that are possibly, probably, or definitely related to the study treatment should also be collected, and reported if necessary.

9.0 FOLLOW-UP AND OUTCOME ASSESSMENT

Outcome data will be collected during the study period, and beyond the study period for 5 years post-therapy. Subjects who discontinue study therapy for any reason other than death, lost to follow-up, or withdrawal of consent will be followed through the completion of the study period. Patients can be followed in Radiation Oncology, Medical Oncology, or Thoracic Surgery at OSU or Foster J. Boyd Regional Cancer Center (Wilmington, OH).

For patients who develop progression, data that will be collected will include survival, non-protocol related treatment, and adverse events (up to starting a new treatment for progressive disease or hospice care).

9.1. Visit Schedule

Follow-up will consist of regular clinic visits (including vital signs, history & physical examination, and/or laboratory studies including CBCP, comprehensive metabolic panel) at 1 month, every 3 months up to 2 years, and every 6 months up to 5 years after end of all treatment (including consolidation chemotherapy).

Laboratory studies including CBCP, comprehensive metabolic panel will be obtained at the discretion of the medical oncologist.

CT chest with IV contrast or chest x-rays will be obtained at every follow-up visits. MRI scans are allowed should the patients have contraindications to CT scan. Contrast is recommended unless allergies to contrast or renal insufficiency.

PET-CT will be performed if suspicion of tumor recurrence based on CT scan, as well as potential biopsy to document recurrence. Other imaging will occur at the discretion of the physician and if warranted for clinical symptoms.

9.2. Efficacy Assessments

Criteria for Evaluation and Endpoint Definitions

(a) Definition of primary outcome/endpoint: The primary efficacy analysis will be based upon investigator assessment of primary tumor control at 12 months and on the intent-to-treat

principle. Primary tumor control is defined as the absence of primary tumor failure. Primary tumor failure is based on meeting both criteria: (1) local enlargement defined as at least a 20% increase in the longest diameter of the gross tumor volume per CT scan and (2) evidence of tumor viability. Tumor viability could be affirmed by either demonstrating PET imaging with uptake of a similar intensity as the pretreatment staging PET, or by repeat biopsy-confirming carcinoma. Primary tumor failure includes marginal failures occurring within 1 cm of the planning target volume (1.5-2.0 cm from the gross tumor volume). Failure beyond the primary tumor but within the involved lobe is collected separately from disseminated failure within uninvolved lobes. Local failure is the combination of the primary tumor and involved lobe failure with local control being the absence of local failure. If sufficient evidence for radiologic progression is noted on serial imaging over 3-6 months despite a negative biopsy(s), then a failure can be declared by investigator. Please note: each primary tumor and/or local failure will be confirmed with one of the study P.I.s.

(a) Definition of secondary outcomes/endpoints: Data from all subjects who received the treatment will be included in the safety analyses. The severity of toxicities will be graded according to the NCI CTCAE version 4.0 whenever possible. For toxicities, unacceptable adverse events [occurring within ≤ 30 days after treatment completion defined as possibly, probably, or definitely related to treatment] will include development of **grade 3-5** toxicities for:

- cardiac (cardiac arrhythmia [supraventricular, ventricular], left or right ventricular dysfunction, pericardial effusion, pericarditis, restrictive cardiomyopathy)
- pulmonary/upper respiratory (atelectasis [grade 4-5 only], FEV-1 [provided grade
- is worse than baseline], fistula, hypoxia [provided grade 3 is worse than baseline], obstruction/stenosis of airway, pleural effusion, pneumonitis, pulmonary fibrosis, vital capacity [provided grade 3 is worse than baseline])
- hemorrhage (pulmonary/upper respiratory)
- neurologic (brachial plexopathy, laryngeal nerve dysfunction, myelitis, phrenic nerve dysfunction)
- Also **grade 4-5** gastrointestinal (dysphagia, esophagititis, and esophageal fistula/obstruction/perforation/stricture/stenosis/ulcer) and **any grade 5** adverse event attributable to therapy will be considered unacceptable adverse events.

Tolerability will be defined as the percent of patients who complete treatment without discontinuing treatment due to toxicity.

Regional failure will be defined as failure in the intra-parenchymal/hilar (N1, or stations 10-14) and mediastinal (N2, or stations 1-9) lymph nodes, or supraclavicular/scalene (N3) lymph nodes. Distant failure will be defined as failure in an uninvolved/contralateral lobe or extrathoracic sites.

Objective response rate (ORR) will be defined as the rate of complete response + partial response per RECIST 1.1 criteria (Appendix II), with complete response being disappearance of all target lesions, and partial response being at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

For imaging correlative endpoints, there will be multiple measurements made. For DCE-MRI, we will measure semi-quantitative (e.g. peak enhancement) and pharmacokinetic (e.g. washout rate constant kel) parameters derived from the analysis of the DCE (dynamic contrast enhancement) curve. For DWI, we will measure differences in mean apparent diffusion coefficient (ADC) between baseline and post-SABR images. Lastly, for BOLD-MRI, we will measure differences in BOLD (blood oxygenation level dependent) contrast between baseline and post-SABR images.

RECIST measurements to document primary tumor response in patients with regional and distant failure should be continued up until the point a patient starts a new treatment for progressive disease targeting the primary tumor, systemic therapy, or hospice.

10. DURATION OF STUDY

Patients are expected to be accrued over 36 months. Following the last accrual, 12 months will need to pass before reporting on 12 month primary tumor and local control can proceed. Follow-up will continue for all patients for at least 5 years, with evaluation of primary tumor and local control.

The duration of the MRI correlative imaging study will extend from the pre-therapy phase (pre-SBRT MRI) to after the first SBRT boost dose (within 24 hours after initial SBRT boost dose). The duration of the imaging study will be limited to the first eligible and consenting 10 patients in this study.

11. REGULATORY AND REPORTING REQUIREMENTS

This study will utilize the CTCAE version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). All appropriate treatment areas should have access to a copy of the CTC version 5.0.

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

This study is designed to preliminarily assess the efficacy of SBRT with conventionally-fractionated chemoradiation in patients with unresectable or medically-inoperable non-small cell lung cancer (NSCLC). Our primary endpoint is the primary tumor control rate at 12 months (from date of treatment initiation). Due to long follow-up time, we will use a single stage design. A primary tumor control rate at 12 months of 70% or less was considered unacceptable, and a primary tumor control rate of at least 90% is desirable. A sample size of 28 provides at least 80% power to detect a significant improvement of primary tumor control rate of 90% or greater based on a one-sided test at significance level of 5%. If, by the end of the study, we have equal or more than 24 patients with primary tumor control, then we will claim it is effective. Considering up to 15% attrition, such as ineligibility, or lost to follow-up, we will accrue a total of 34 patients.

12.2 Feasibility

We have an average of 4-6 patients per month with unresectable/medically inoperable locally advanced NSCLC per month at the Ohio State University. There are currently no competing investigator-initiated trials for this patient population. Assuming we accrue about 25% of these patients to this trial (1-2 patients per month), time for accrual is about 36 months.

12.3 Data Analysis Plan

12.3.1 ***Analytic plan for primary objective:***

Primary tumor control rate at 12 months, as well its 95% confidence interval, will be reported for all eligible subjects received treatment. In addition, the primary tumor and local control failure over time will be plotted using Kaplan-Meier survival analysis. Rate of primary tumor and local control at 2 years and 3 years will also be summarized.

12.3.2 ***Analytic plan for secondary objectives:***
Rates of all adverse agents, with special attention to grade 3-5 esophagitis, cardiac, and pneumonitis adverse events, and death during or within 30 days of discontinuation of protocol treatment will be calculated. Rates of tolerability will be determined at the end of study.

Regional and distant failure, PFS, and OS will be measured from date of treatment initiation to the event of interest or otherwise censored at last follow-up. Kaplan-Meier (K-M) analysis will be used to estimate PFS and OS. PFS will include any failure (local, regional, or distant) or death from any cause.

For MRI correlative studies, all 3 metrics (perfusion/diffusion/oxygenation measurements) will be tested by comparing mean values pre- and post-SBRT using a paired t-test. Should there be concern for outliers, we will determine the median for each metric and compare medians using a corresponding non-parametric procedure.

13.0 SUBJECT POPULATION(S) FOR ANALYSIS

All patients are 18 years of age or older who have non-small cell lung cancer, Stage II-III, that is medically inoperable or unresectable. Men and women are allowed on this study.

14.0 STUDY CALENDAR

See Appendix I.

15.1 STUDY FINANCES

15.2 Funding Source

We have multiple sources of support, including philanthropic and internal funding mechanisms (Radiation Oncology, James Cancer Center). MRI correlative imaging will be performed at and may also be funded through the Wright Center for Innovation in Biomedical Imaging, Ohio State University (Director, Michael Knopp, MD, PhD).

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17.1 ATTACHMENTS/APPENDICES

Appendix I: Study Schedule

	Pre-Treatment		During Treatment				Follow-up		
	≤ 30days of entry	≤ 14days of entry	Week 1	Week 2-7	Week 12	Week 15	Mo 1	Q3 mos for years 1-2	Q6 mos for years 3-5
Visit window (+/- days)			3	3	7	7	14	30	30
Informed consent	X								
History and physical exam	X		X	X	X	X	X	X	X
CBC w/diff & ANC, platelets[1]	X			X	X	X	X		
CMP including LFTs[1]	X			X	X	X	X		
CrCl assessment	X								
Serum pregnancy test (females of child-bearing potential)		X							
CT simulation		X (≤21 days)							
MRI or CT brain with contrast	X (≤60 days)								
PET-CT scan of body (or CT chest/abdomen/pelvis with contrast)	X (≤60 days)								
CT chest with IV contrast	X[2]								
Contrast-enhanced CT chest or MRI chest or PET-CT							X	X (Mos 6, 12, 18, 24)	X (Mos 36, 48, 60)
Chest X ray (PA and lateral) or CT chest with IV contrast								X (Mos 3, 9 15, 21)	X (Mos 30, 42, 54)
Pulmonary function tests (including FEV- 1, DLCO)	X (≤90 days)							X	

[1] A complete blood count (CBCP) with differential and CMP including LFTs during the treatment and follow-up will be obtained at the discretion of the medical oncologist.
[2] CT chest with contrast unless there is an issue with insurance coverage, or patient has allergy to CT contrast or renal insufficiency.

								(mos 6, 12, 24)	
	Pre-Treatment		**During Treatment**				**Follow-up**		
	≤ 30days of entry	≤ 14days of entry	Week 1	Week 2-7	Week 12	Week 15	Mo 1	Q3 mos for years 1-2	Q6 mos for years 3-5
Research MRI studies (DCE/PWI, DWI, BOLD) – optional study		X (pre-SBRT scan)	X (≤24hrs of 1st SBRT)						
Research blood draws			X (pre-dose)[3]	X (Day 8, 29)			X	X (Mos 6, 12)	
SBRT (2 doses)			X						
Radiation Therapy (30 doses, 5 days/week)[4]									
Concurrent chemotherapy[4]				X					
Consolidation chemotherapy (only for patients receiving concurrent carboplatin & paclitaxel)[5]					X	X			
AE assessment[6]			X	X	X	X	X	X[7]	X[7]

[3] Week 1 research blood should be collected within 7 days prior to the 1st SBRT treatment.
[4] Concurrent chemotherapy and radiation should be done as soon as after the SBRT treatment, within 7 days after the 1st SBRT treatment unless there are contraindications determined by treating doctors.
[5] Consolidation chemotherapy: 2 cycles, each 21 days long, beginning at 4-6 weeks after chemoradiation. At discretion of medical oncologist.
[6] AE assessment during the treatment will be performed weekly, and generally coordinated with chemotherapy schedule.
[7] AEs will be followed until resolution or stabilization of the event (to ≤ grade 2), whichever comes first.

Appendix II: RECIST 1.1 Criteria

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.

(LD= longest diameter)

Appendix III: ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.
5	Dead

Appendix IV: Supplementary Tables

Table A. Local control in phase III randomized trials of concurrent chemoradiation for locally advanced NSCLC.

Study	N	Med FU (mos)	RT DOSE (Gy/fxs)	BED Gy_{10}	LC (%)	MS (mos)	%OS (years)
RTOG 9410(6)	195	120	63/34	74.7	**70**	17	16 (5)
GLOT NPC 95-10(28)	100	57.6	66/33	79.2	**76**	16.3	61 (1) 39 (2) 25 (3) 21 (4)
WJLCG(29)	156	60	58/28*	67.2	**67**	16.5	64.1 (1) 34.6 (2) 22.3 (3) 16.9 (4) 15.8 (5)
CZECH(30)	52	39	60/30	72	**60**	16.6	-

Table B. Calculated SBRT boost doses necessary after conventional fractionation to bring total dose equivalency to that of SBRT regimens in early stage NSCLC. Comparisons between LQ and gLQ modeling.
LQ= linear quadratic; gLQ= generalized linear quadratic

Model Type	α/β ratio	BED (Gy) for 54 Gy in 3 fractions	BED (Gy) for 60 Gy in 5 fractions	BED for standard fractionation (60 Gy in 2 Gy per fraction)	SBRT Boost dose needed in 2 fractions for biological equivalency to 54 Gy in 3 fractions	SBRT Boost dose needed in 2 fractions for biological equivalency to 60 Gy in 5 fractions
LQ	10 Gy	151.2	132	72 Gy	31 Gy	26 Gy
gLQ (cell line)	5.45 Gy	89.37	83.89	60.51 Gy	**17.3 Gy**	**13.95 Gy**
gLQ (clinical)	*4.3* Gy	79.78	77.30	59.42 Gy	**12.94 Gy**	**11.52 Gy**

Appendix V: Covid-19 Precautions

Due to the emerging pandemic for *SARS*-CoV-2 virus, it has become necessary to enact social distancing and limit hospital and outpatient facility interactions and visits for vulnerable patient populations. Patients receiving active therapy to control their cancer are particularly vulnerable.

This study involves patients receiving a radiation boost alongside conventionally-fractionated chemoradiation, and though it is vital that these patients continue to receive these therapies, it is also important that we mitigate the risk of virus transmission for patients, providers, and family members. In the coming weeks and months, as governments continue to manage the *SARS*-CoV-2 virus pandemic, it is quite possible that travel between states and cities may be limited, or that cities may have curfews. This amendment seeks to mitigate risk and enable ongoing care as feasible.

This appendix proposes the following changes for this investigator-initiated trial:

- Convert whenever possible all outpatient office visits to tele-medicine (video and phone) as necessary to continue monitoring, care, and treatment. Patients with concerning symptoms or labs from tele-medicine visits may be escalated to in-person evaluations as needed in the appropriate setting. This will serve to triage patients based on needs versus risk.
- Patients will continue to have necessary blood work and scans to monitor for toxicities and disease status. Basic study procedures such as blood draws, radiographic scans, and MRIs, can be done by patients' local providers. These results will be reviewed by the Study Team centrally.
- Depending on circumstances, local healthcare providers in another city may be required to assess and evaluate patients, and the PI and/or the study team will communicate with these providers to facilitate care as it relates to study treatment.

Time Frame: These changes are being made to minimize risk of COVID infection during the pandemic, as it continues to be an urgent and serious world health emergency. As research activities have resumed at OSUCC, we will consider the Appendix V changes to be permanent until the lifting of COVID restrictions or a vaccine is developed, which is not expected until at least 2021. Therefore these changes are valid until the time at which Covid-19 related restrictions are no longer deemed necessary by the State and/or University.