

## **Prospective Study of Intensity-Modulated Proton Therapy (IMPT) for Small Cell Lung Cancer**

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Drug Under Investigation: None

## **1. Objectives**

### **1.1 Primary Objective**

The primary objective of this prospective trial is to assess the safety of intensity-modulated proton therapy (IMPT) for small cell lung cancer (SCLC)

### **1.2 Secondary Objectives**

- To determine the optimal schedule for three-dimensional verification imaging and necessary re-planning of patients undergoing IMPT for a rapidly changing tumor (small cell lung cancer)
- To determine the rate of cardiac toxicities from IMPT in patients with small cell lung cancer compared with historical controls receiving photon-based treatment.
- To determine the rate of pneumonitis and esophagitis from IMPT and compare with historical controls receiving photon based treatment

## **2. Background**

### **2.1 Proton-beam Therapy for Small Cell Lung Cancer (SCLC)**

An estimated 234,030 new cases of lung cancer will be diagnosed in the United States in 2018. Small cell lung cancer (SCLC) represents approximately 15% of all lung cancers. Extensive stage SCLC (ES-SCLC) accounts for about 70% of all small cell lung cancers, with an estimated absolute number of 25,000 cases [1]. Historically, the prognosis of ES-SCLC is poor with a median survival of 12 months and 2-year overall survival (OS) of 5% [2]. Although distant failure is the predominant cause of mortality, local failure is also common (36%-52%) [3].

Several studies have shown that addition of thoracic radiotherapy for patients with ES-SCLC who responded to chemotherapy is associated with improved local control and overall survival [4-5]. Early thoracic radiotherapy with concurrent chemotherapy is the standard of care for limited-stage SCLC (LS-SCLC). However, SCLC usually arises submucosally in central airways, appearing as large hilar mass with bulky mediastinal adenopathy [6]. As a result, the tumor is often in close proximity to critical organs at risk (OARs) including normal lung parenchyma, heart, esophagus, spinal cord and bronchus. Proton-beam therapy (PBT) allows delivery of conformal high-dose radiation to the target while sparing surrounding normal tissues. Studies have shown PBT is associated with both dosimetric and clinical benefits for locally advanced non-small cell lung cancer (NSCLC) [7-12]. An ongoing phase III randomized trial is

investigating PBT versus photon radiation for locally advanced NSCLC (Radiation Therapy Oncology Group [RTOG] 1308) [13].

However, there is very limited evidence on the use of PBT for SCLC. Further study of PBT for SCLC is critical for advancing the treatment of SCLC. Colaco et al published a single-institution experience of 6 patients who underwent concurrent chemoradiation for limited-stage SCLC (LS-SCLC). PBT allowed better sparing of lung and esophagus without acute grade 3+ esophagitis or acute grade 2+ pneumonitis [14]. Rwigema et al recently published a prospective institutional study of PBT for LS-SCLC [15]. Thirty patients were enrolled in the study. The median dose was 63.9 cobalt gray equivalents delivered in 33 to 37 fractions daily (n = 18 [60.0%]) or twice daily (n = 12 [40.0%]). The concurrent chemotherapy was cisplatin/etoposide (n = 21 [70.0%]) or carboplatin/etoposide (n = 9 [30.0%]). In comparison with the backup intensity-modulated radiotherapy (IMRT) plans, PBT allowed statistically significant reductions in the spinal cord, heart, and lung mean doses and the volume receiving at least 5 Gy but not in the esophagus mean dose or the lung volume receiving at least 20 Gy. The median OS was 28.2 months. There was 1 case each (3.3%) of grade 3 or higher esophagitis, pneumonitis, anorexia, and pericardial effusion. Grade 2 pneumonitis and esophagitis were seen in 10.0% and 43.3% of patients, respectively. Notably, only 1 out of 30 patients received pencil-beam scanning IMPT. The remaining patients received passive-scattering PBT.

Currently, PBT can be delivered using two methods. The older method, referred to as passive-scattering PBT, uses a three-dimensional (3-D) conformal technique. It combines passively scattered proton beams of differing energies to form a “spread-out Bragg peak” (SOBP) that fully encompasses the target. The most common beam arrangement uses two opposed lateral beams, and customized apertures and compensators are fabricated to shape the field and alter the dose–depth profile to conform the SOBP to the actual tumor better. Recent technological advances enabled us to utilize pencil-beam scanning (PBS) PBT, which allows more conformal and complex “IMRT-like” distribution. This is known as intensity-modulated proton therapy (IMPT) with a greater ability to conform the dose to irregularly shaped target [16]. In our prospective study, all patients will be treated with IMPT.

Respiratory motion of lung tumors and changes in lung density during respiration poses unique challenges for the accuracy and planning of PBT. In addition, SCLC is known to be radiosensitive and the tumor volume can shrink significantly during the radiation course. Therefore, adaptive radiotherapy (ART) is crucial in PBT planning as it can adjust the treatment plan for geometrical uncertainties and tumor regression, allowing dose escalation to target and dose reduction to OARs [28]. There is very limited data on IMPT treatment for small cell lung cancer, thus a feasibility study utilizing this approach is necessary to advance the applications of PBT. Small cell lung cancer is a particular unique patient group given large tumors prone to respiratory motion as well as characteristically rapid response to radiation that creates a variable

target volume. Determining the best schedule of tumor monitoring during treatment and determining the rate at which adaptive re-planning is necessary with IMPT is crucial and necessary before this technology can have greater applicability within this small cell lung cancer population.

## **2.2 Cardiac Effects of Radiation Therapy in SCLC**

Radiation therapy (RT) is increasingly appreciated as a cause of cardiac morbidity following the management of lung cancer [18-27]. The non-small cell lung cancer (NSCLC) trial Radiation Therapy Oncology Group (RTOG) 0617 unexpectedly yielded lower overall survival (OS) for the high-dose (74 Gy) RT arm compared to the standard-dose (60 Gy) RT arm, and cardiac RT dose was subsequently posited as a potential contributor to this finding [17]. Heart V5 (volume of heart receiving 5 Gy) and heart V30 were associated with increased risk of death on multivariable analysis (MVA) [17]. A secondary dosimetric analysis of the trial was performed and demonstrated that heart V40 was an independent predictor of inferior OS [19]. Outside the randomized setting, a large single institutional analysis of 332 patients demonstrated a significant relationship on MVA between increasing heart volume and heart V50 with OS. A meta-analysis of 25 randomized NSCLC dose-escalation trials demonstrated association between higher RT doses and worse OS; again, dose-escalation here has been a presumed surrogate for increased cardiac dose [18].

Until recently, there were no correlate studies in small cell lung cancer (SCLC); and the differences between NSCLC and SCLC precludes direct extrapolation. A recently published analysis from our group utilized SEER-Medicare data to report on rates of cardiac events for patients receiving chemotherapy(CTX) and RT as compared to matched patients receiving CTX-only in a mixed population of limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) patients. This study demonstrated photon-based RT was associated with cardiac events ( $p= 0.008$ ), with cumulative incidence as follows for the CTX + RT and CTX-only groups: 36.4% (95% confidence interval [CI] 34.8%-37.9%) versus 35.4% (33.8%-36.9%) at 12 months and 44.1% (42.5%-45.7%) versus 39% (37.4%-40.6%) at 60 months, respectively [28].

## **3. Participating Institution**

Winship Cancer Institute of Emory University School of Medicine (Atlanta, GA) is the only participating institution. Study/trial information will be made available to the Georgia Center for Oncology Research and Education (CORE) at <https://www.georgiacancerinfo.org>. Detailed trial information, including the protocol and all supplemental information will be submitted to, and

made available to the Online Collaborative Research Environment (OnCore) at <https://oncore.emory.edu> in accordance with institutional regulations.

#### **4. Study Design and Methods**

This is the first prospective study to investigate the safety and efficacy of IMPT for the treatment of SCLC. We will utilize adaptive planning throughout the radiation course. In addition, we will study the dosimetric parameters of IMPT and their correlation with treatment-related toxicities, particularly cardiac events.

##### **4.1 Duration of Study**

We plan to enroll a total of 30 patients with small cell lung cancer, including limited stage and extensive stage. Our Department sees approximately 50 eligible small cell lung cancer patients per year. It is estimated that it will take about 1 year to accrue 15 patients to this study. Radiation will last 6 weeks, and the total proposed follow-up time for this study is 12 months. We therefore project that this study will require approximately 2.5-3 years to complete.

##### **4.2 Pre-treatment Evaluation**

All patients will receive pre-treatment consultation. A detailed history and physical exam will be performed in each patient. Pre-treatment whole-body PET-CT and Brain MRI are required for all enrolled patients.

#### **5. Patient Selection**

##### **5.1 Inclusion Criteria**

5.1.1 Pathologically confirmed small cell lung cancer, limited or extensive stage.

5.1.2 Patients who are offered thoracic radiotherapy with intensity-modulated proton therapy (IMPT) techniques delivering 30-66 Gy in 15-33 fractions at 2 Gy per fraction, at the recommendation of the treating radiation oncologist.

5.1.3 Age 18 or greater

##### **5.2 Exclusion Criteria**

5.2.1 Prior radiation therapy which would provide significant dose overlap with the planned target volume(s)

5.2.2 Pregnancy

### **5.3 INCLUSION OF WOMEN AND MINORITIES**

Both men and women and members of all ethnic groups are eligible for this trial. No special recruitment will be performed based on gender or minority status. No person shall, on the grounds of race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

### **5.4 SOURCES OR METHODS OF RECRUITMENT**

PATIENTS WILL BE RECRUITED FROM THOSE SEEN AT THE DEPARTMENT OF RADIATION ONCOLOGY AT WINSHIP CANCER INSTITUTE. AFTER ELIGIBILITY CRITERIA HAVE BEEN REVIEWED, ELIGIBLE PATIENTS WILL BE OFFERED THE OPPORTUNITY TO PARTICIPATE IN THE STUDY. A BRIEF DESCRIPTION OF THE STUDY WILL BE GIVEN VERBALLY TO THE PATIENTS, FOLLOWED BY WRITTEN INFORMED CONSENT, AND ANY RELEVANT SUPPLEMENTAL MATERIAL AS NEEDED. THE PATIENTS WILL BE GIVEN AMPLE TIME TO REVIEW THE CONSENT AND A TIME FOR QUESTIONS AND ANSWERS WILL BE PROVIDED. NO FINANCIAL INCENTIVES WILL BE PROVIDED TO THE PATIENTS.

### **5.5 STUDY ENROLLMENT PROCEDURES**

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the Online Collaborative Research Environment (OnCore, <https://oncore.emory.edu>) and available to the Emory University Office for Clinical Research) before any patients may enter. The Winship Cancer Center institution consent form must be reviewed and approved and all documents must be received (i.e., IRB approved documentation, IRB approved consent form, etc.).

## **6. Patient Registration**

All patients entering this study will be registered with the Clinical Trials Office (CTO) at the Winship Cancer Institute, Atlanta, GA. The CTO is open Monday through Friday from 8am-5pm (EST). OnCore will be used to record information for all registered patients including their assigned patient ID.

## **7. Study Plan**

### **7.1 Radiation Therapy**

Aspects of radiation therapy, i.e. simulation, treatment planning and delivery should follow standard of care practices, and are at the discretion of the treating radiation oncologist. A multi-disciplinary approach should be implemented when applicable. Guidelines for the delivery of radiation therapy are provided below.

### **7.1.1 Required Criteria/Technical Factors**

The goal of intensity-modulated proton therapy (IMPT) is to deliver radiation to the tumor while minimizing exposure to surrounding normal tissues. Commercially available linear accelerators with image guidance capabilities should be used.

### **7.3.2 Dose Prescription and Fractionation**

Patients will receive between 30- 66 Gray Equivalent (GyEq) in 15-33 fractions at 2 GyEq per fraction. Twice daily treatment is not allowed. Dose prescription will be at the discretion of the treating radiation oncologist. It should be in accordance with standards of care and acceptable to peer review. Dose constraints to organs at risk likewise should follow institutional standards and acceptable to peer review. Patients who do not have evidence of brain metastases on initial staging MRI will be offered prophylactic cranial irradiation.

### **7.3.3 Patient Positioning and Immobilization**

Patients should be immobilized in a position capable of accurately reproducing the target position from treatment to treatment. Positions that are uncomfortable should be avoided to reduce the risk of unexpected patient movements during treatments. Immobilization systems designed for lung IMPT setups should be used, examples include CIVCO with Vac-Lok™.

### **7.3.4 Simulation**

Patients should undergo CT-based treatment planning in custom-made immobilization devices. The CT scanning parameters should allow for the accurate target volume delineation of all treated lesions and relevant organs at risk. High-resolution 4D-CT scans should be obtained with uniform slice thickness of  $\leq 3$ mm throughout.

### **7.3.5 Isocenter Placement**

The isocenter is defined as the intersection of gantry, collimator, and couch rotational axes for linear accelerator based treatment systems. If multiple target lesions are planned to receive radiation therapy, multiple isocenters, each centered on a separate lesion, should be used. Localization is optimal if the isocenter is placed in the center of each target and image guidance is performed individually.

### **7.3.6 Management of Internal Organ Motion**

Special considerations should be made to account for the effects of respiratory motion on target positioning and reproducibility. Tumors with significant ( $\geq 1$ cm) of maximum displacement should be limited with motion management solutions, such as respiratory-gated treatment, abdominal compression, active-breath control or breath-holding techniques. Methods of limiting internal organ motion should be sufficiently reliable to ensure that the gross tumor volume does not deviated beyond the confines of the planning target volume with any significant probability. An ITV approach may be sufficient for tumors with minimal ( $< 1$ cm) tumor motion.

### **7.3.7 Localization and Imaging**

Image-guidance implementation is considered a standard component of IMPT treatment. kV localization images should be acquired prior to delivery of each IMPT fraction to ensure the proper alignment of the geometric center of the simulated fields. Cone-beam CTs will be acquired daily to verify the target volume and assess for shrinkage of the tumor that may necessitate adaptive re-planning.

### **7.3.8 Target Volume Determination**

The gross tumor volume (GTV) should compass all CT-defined visible disease, using the CT lung windows, aided by co-registered PET/CT. For tumors with significant displacement ( $\geq 1$ cm) due to respiratory motion, gated treatment will be utilized. GTV is contoured on the free breathing CT scan for patients who do not need gated treatment. For those who require gated treatment, GTV is contoured on the averaged CTs of the gated phases. Selection of the gated phases is at the discretion of the treating radiation oncologist. The CT-defined visible disease on a reconstructed maximum intensity projection (MIP) image is used to create the internal target volume (ITV). A uniform 5mm margin around ITV is added to create the clinical target volume (CTV). Planning target volume (PTV) will not be utilized in IMPT. The use of any additional diagnostic studies to aid planning is at the discretion of the treating physician.

## **7.4 Concomitant Therapies**

### **7.4.1 Systemic therapy**

The regimen, dosing and timing of concurrent chemotherapy will be decided by the treating medical oncologist. Most commonly used regimen at Emory University Hospital is 4 cycles of cisplatin and etoposide given every 3 weeks. Etoposide dosing will be 100 mg/m<sup>2</sup> intravenously on days 1-3, and cisplatin dosing will be 75 mg/m<sup>2</sup> intravenously on day 1. Immunotherapies can be given at the discretion of the treating medical oncologist.

### **7.4.2 Other Treatments**

Other treatments are allowed as long as they do not preclude the patient from either receiving radiation therapy or undergoing imaging studies as intended.

## **8. Patient Assessments**

Patients will be seen by radiation oncology for an on-treatment visit once per week during treatment. During these visits, adverse events (AEs) will be logged. Patients will be seen for a history and physical at 4 weeks post-treatment, then at 3 months, 6 months and 1 year. Thereafter, visits will be every 4-6 months. Follow-up imaging will include a CT of the chest every 6 months for 5 years. Initial imaging following treatment completion will occur at the discretion of the treating radiation oncologist and can consist of a chest CT or a PET/CT. Follow-up PET imaging will be obtained at the discretion of the treating physician. For calendar schedule of events, see Appendix A.

Case report forms (at end of radiation and every 6 months in follow up) will contain detailed questions regarding development of cardiac events including unstable angina, myocardial infarction, arrhythmia, pericarditis, myocarditis, congestive heart failure, or valvular dysfunction during and after treatment.

### **8.1.1 Adverse Events (AEs)**

Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). CTCAE version 4.0 will be used to assign AE term and grade. If specific grading is not available in the CTCAE for a particular AE's severity, the investigator will use general definitions of grade 1-5 using his/her best judgment (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening or disabling, Grade 5 = death). These events will be recorded for each subject during treatment at weekly on treatment visits with radiation oncology and at each follow up visit. All AEs will be entered into the OnCore database by research coordinators within 14 calendar days of data capture. AEs are subject to review by the investigators and data safety monitoring committee (DSMC). Dose limiting toxicities (DLTs) are considered to be any grade 3 or higher AEs that are possibly, probably, or definitely treatment related. Non-treatment related AEs, grade 3 or higher, will not be considered to be a DLT. Subsites must report DLTs within 48 hours. The following symptoms will be considered to be treatment related:

- Grade 3-5 Cardiac Disorders: acute heart disease, acute myocardial infarction, cardiomyopathy, dysrhythmia, heart failure, pericarditis, pericardial effusion
- Grade 3-5 Gastrointestinal Disorders: dysphagia, esophagitis, esophageal fistula, esophageal ulcer, esophageal hemorrhage, esophageal perforation, esophageal obstruction
- Grade 3-5 Central Nervous System Disorders: myelitis, brachial plexopathy
- Grade 3-5 Pulmonary Disorders: bronchial fistula, tracheal fistula, pneumonitis, pulmonary fibrosis, bronchopulmonary hemorrhage
- Any Grade 5 event attributed to treatment

### **8.1.2 Serious Adverse Events (SAEs)**

Any adverse event that results with any of the following outcomes:

- Death
- Life-threatening experience
- Inpatient Hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important events

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, 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. These events will also be recorded for each subject and is subject to review by the investigators and data safety monitoring committee (DSMC). In addition, these events will be reported to the responsible Institutional Review Board (IRB) and the study PI. All SAEs will be reported within 24 hours of discovery to Study Coordinator and the study PI, Dr. Kristin Higgins ([kristin.higgins@emory.edu](mailto:kristin.higgins@emory.edu), 404-778-0603). SAEs will be reported using the SAE form in Appendix B. SAE should be emailed to both the study coordinator and Dr. Higgins as well as inputted into OnCore.

## **9. Removal of Patient from Study**

Participation in the study should continue until one of the following criteria applies:

- 9.1** Intercurrent illness that prevents delivery of planned radiation therapy
- 9.2** Unacceptable treatment-related adverse event(s), including patient death
- 9.3** Withdrawal of informed consent (subject's decision to withdraw for any reason)

- 9.4 Noncompliance with treatment plan, including delays to treatment or acquisition of additional diagnostic imaging that significantly exceeds the proposed timeline of study events
- 9.5 General or specific changes in the patient's condition that render the patient unacceptable to receive further treatment in the judgment of the investigator

## **10. Data Collection and Records**

Data to be collected will include patient's name and medical record number, date of birth, basic disease characteristics, including staging information, location of and extent of involvement, relevant imaging characteristics of the tumor, prior cancer-directed therapies. Information will also be collected regarding radiation treatment parameters including dose and fractionation, dosimetric details, and regarding any concomitant therapies received, such as chemotherapy or immunotherapy. Information will also be collected regarding CTCAE-graded toxicities. Emory approved case report forms (CRFs) for data collection will be used and data entered into OnCore. For participating subsites, initial visit CRFs and eligibility checklist must be submitted within 14 days of patient registration.

## **11. Data and Safety Monitoring**

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will

include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

## **12. Multi-Institutional Guidelines**

This is a single-institution study at Winship Cancer Institute.

## **13. Statistical Considerations**

### **13.1 Study Endpoints**

- The primary objective of this prospective trial is to assess the safety of intensity-modulated proton therapy (IMPT) for small cell lung cancer. Primary endpoints will be the following:

Patients enrolled will experience <35% incidence of cardiac events at 1-year. Cardiac events included: acute heart disease, acute myocardial infarction, cardiomyopathy, dysrhythmia, heart failure, pericarditis, pericardial effusion

#### **13.1.2 Secondary Endpoints**

- Determination of the optimal frequency of conebeam CT during treatment and subsequent need for adaptive re-planning
- Local control
- Distant metastases
- Patterns of failure
- Radiation pneumonitis
- Radiation esophagitis
- Overall survival at 1, 2, and 5 years

### **13.2 Sample Size and Power Calculations**

This pilot study is designed to enroll 30 patients, and criteria for patient selection are outlined in sections 5. The power and sample size calculation is based on the primary objective of the study to study Cardiac events rate at 1 year. A sample size of 30 produces a two-sided 95% confidence interval with a width equal to 0.281 assuming the true cardiac events rate at 1 year is 0.15. Therefore, the sample of 30 patients in the study will

demonstrate a cardiac event rate  $< 35\%$  at the confidence level of 95%.

### 13.3 Study Analysis/Statistics

Statistical analysis will be conducted using SAS Version 9.4. The significance level was set at 0.05. Summary statistics will be first estimated for all variables collected. Continuous variables will be presented as means, standard deviation, and the range, while categorical variables will be summarized with frequencies and percentages.

For the primary objective in terms of safety, Cardiac events rate at 1 year will be estimated among all patients and the 95% confidence interval will be constructed assuming a binomial distribution. The association of Cardiac events with categorical covariates will be tested with Chi-square test. Logistics regression model will be employed to measure the association of Cardiac events with continuous covariates with and without adjusting for other factors.

A mixed model will be employed to determine the optimal frequency of conebeam CT during treatment and subsequent need for adaptive re-planning. The local control, distant metastases, patterns of failure will first be summarized as frequency and percentage. Chi-square test will be further used to test their relationships with other categorical variables. General linear model will be employed to measure their association with continuous covariates with and without adjusting for other factors.

The rates of cardiac toxicities, pneumonitis, and esophagitis from IMPT will be estimated among all patients and their 95% confidence interval will be constructed assuming binomial distribution, respectively. Exact binomial test will be employed to compare the rates of cardiac toxicities, pneumonitis and esophagitis from IMPT with historical controls receiving photon based treatment, respectively. Logistics regression model will be employed to estimate the associations of cardiac toxicities, pneumonitis, and esophagitis with other factors.

The overall survival curve of all patients will be generated with Kaplan-Meier method and overall survival rates at 1, 2, and 5 years will be also estimated along with 95%CI. Log-rank tests will be used to compare overall survival difference between different groups stratified by other factors. Cox proportional hazards models will be applied for multivariate analysis of the survival data in the study.

## 14. Human Subjects

## **14.1 Subject Population**

This study will enroll patients with small cell lung carcinoma with good response to chemotherapy who are candidates for thoracic radiotherapy with intensity-modulated proton therapy techniques delivering 30-66 GyEq in 10-33 fractions at 2 GyEq per fraction, at the recommendation of the treating radiation oncologist.

## **14.2 Potential Risks**

Risks of IMPT is specific to the treatment volume, location of disease site, and proximity to critical organs at risk. Patients will be provided the opportunity to provide written informed consent for treatment separately, per institutional and departmental standards.

Protected health information (PHI) will be collected for this study, and efforts will be made to keep PHI private. Results input into the main research database will be de-identified. Patient identifiers can only be accessed by key members of the study team. A file containing patient identifiers will be password protected; information transfer, if performed by means of memory storage devices, will also be password protected. Physical forms used for collecting information will contain a minimum of personal information, and will utilize study numbers for identification.

## **14.3 Consent Procedures**

Informed consent is to be obtained prior to commencing any research procedures. A study investigator shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

## **14.4 Potential Benefits**

Patients enrolled on this study will receive IMPT according to accepted standard of care per the treating physician as clinically indicated.

## **14.5 Gender and Minorities**

No person shall, on the grounds of race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

## **15. Economic/Financial Considerations**

The costs of the patient's primary treatment, including pre-treatment consultation and necessary evaluations, 4D- CT simulation, IMPT treatment course and pre-, during- and post-treatment imaging are expected to be covered by the patient's insurer/primary payor.

## **16. Publication of Research Findings**

The policies and procedures of Emory University School of Medicine, Winship Cancer Institute will govern publication of this pilot study. It is expected that the results of this study will be submitted for publication in a timely manner following its conclusion. The Winship Cancer Institute PI(s), and all other co-authors prior to submission or use, must review any abstract or manuscript.

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## APPENDIX A

<b>Study Procedures</b>	<b>Pre-treatment evaluation</b>	<b>CTX + RT Treatment</b>	<b>1 month</b>	<b>3 month</b>	<b>6 month</b>	<b>Year 1</b>	<b>Year 1.5</b>	<b>Year 2</b>	<b>Year 2.5</b>	<b>Year 3</b>	<b>Year 3.5</b>	<b>Year 4</b>	<b>Year 4.5</b>	<b>Year 5</b>
PET-CT	X													
MRI Brain	X													
Biopsy	X													
History	X		X	X	X	X	X	X	X	X	X	X	X	X
Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4D CT		X												
CT simulation		X												
Cone beam CT		With every RT fraction												
RT		X												
CTX		X												
CT-chest				X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X