A Single Arm Phase II Study of Hypofractionated Radiotherapy Alone in Locally Advanced NSCLC Patients who Decline or are Ineligible for Surgery or Chemotherapy

Wake Forest Baptist Comprehensive Cancer Center

WFBCCC # 62220

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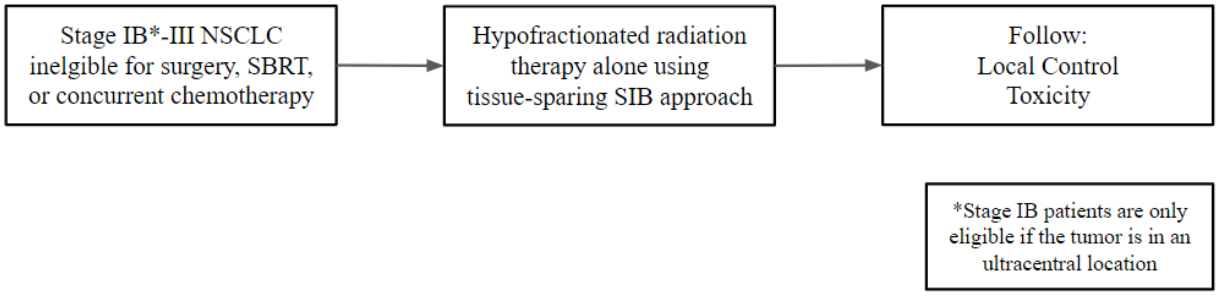
Table of Contents

STUDY SCHEMA



1.0 Introduction and Background

Synopsis

The selection of treatment modality for patients with non-small cell lung cancer is based on the stage, size, and distribution of disease. Patients with stage II-III NSCLC are routinely managed with surgery followed by adjuvant therapies or definitive chemoradiotherapy and consolidation immunotherapy. However, some patients may decline or be ineligible for surgery or systemic therapy due to surgically unresectable disease or medical comorbidity. In patients with early stage NSCLC who are not operative candidates, stereotactic body radiotherapy (SBRT) is the standard of care. However, there is a subset of patients with tumors in unfavorable locations who have a very high rate of high grade toxicity with SBRT. In these patients, fractionated radiotherapy alone is often the only therapeutic option available. No clear standard exists for the appropriate dose and fractionation of radiotherapy alone in this cohort. However, local intrathoracic failure rates of up to 50% are a major source of morbidity and mortality in this population. Published regimens have poor local control likely due to the lack of synergistic systemic therapy and inadequate biologically effective dose (BED) of radiation. In the past, dose escalation in the mediastinum has been severely limited due to inability to adequately spare normal tissues. With dramatic improvements in radiotherapy delivery and image guidance, it is now possible to achieve higher doses to tumor while simultaneously achieving reasonable normal tissue constraints.

We recently published a series on dose escalated hypofractionated radiation in patients with stage I - IIB NSCLC including patients with ultracentral tumors and N1 disease. Our 2 year local control approximated 70% and the regimen was well tolerated, with no grade 3+ acute esophagitis or grade 4-5 toxicities. We propose here a single-arm phase 2 study to investigate the efficacy and safety of an established hypofractionated radiotherapy regimen for varying stages of NSCLC.[13,21] We plan to improve on our prior delivery methods through utilization of a planning technique known as simultaneous integrated boost (SIB) with daily image guidance. This approach allows daily confirmation of target localization and simultaneous delivery of lower dose per fraction to low risk areas while maintaining a high dose per fraction to the highest risk areas. In our previous series all tissue was treated at the same high dose per fraction, including surrounding normal tissues. This current planning approach will further facilitate sparing normal tissues while allowing for slightly higher doses to the tumor.

Biologic Effective Dose and the Rationale for Hypofractionated Radiotherapy

Current guidelines recommend concurrent chemoradiotherapy followed by consolidative immunotherapy for patients with stage II-III NSCLC who are not surgical candidates. The rationale for the delivery of concurrent

chemoradiotherapy is based on a meta-analysis showing improved overall survival when compared to sequential chemoradiotherapy, primarily due to an increase in loco-regional control.[2] However, various comorbidities, medical contraindications or patient preference sometimes preclude the delivery of concurrent chemotherapy. In these cases, radiotherapy alone is often utilized. Local control with standard radiotherapy alone is poor. This has led to the investigation of multiple different fractionation regimens.

Multiple studies have employed various altered fractionation regimens in the management of NSCLC patients with radiotherapy alone and a benefit to survival outcomes has been suggested with the use of modified fractionation, typically accelerated hyperfractionation, compared to conventional fractionation. However, the total doses in these studies were still limited, and local control remained poor, with 2 year rates in the 45-50% range.[24] A pooled analysis of multiple RTOG studies, most of which included concurrent chemotherapy reported a loco-regional failure rate of 46%.[22] These regimens are often evaluated using biologic effective dose (BED), which converts different physical radiation doses to a standard model. BED is a function of the dose per fraction (df) of radiation, the total number of fractions (nf) and the α/β ratio, which measures the radiosensitivity of a given tissue, and is generally assumed to be 10 for tumors and 3 for normal tissues (conventionally written as BED_{10} and BED_3), and is calculated using the equation $\boldsymbol{BED = d(n)(1 + d/(\alpha/\beta))}$ (see Appendix E).[12,22] An important assumption of BED is that the radiation is given over the same total time period. This is important as many tumors, including NSCLC, exhibit rapid repopulation during radiotherapy, and prolonged treatment courses or treatment breaks may allow for greater tumor repopulation, in effect decreasing the BED delivered.[11] This has led to interest in hypofractionated radiotherapy (HRT) which would allow radiation to be completed prior to the onset of rapid repopulation.

Efficacy and Toxicity of HRT in Prior Studies

In patients with early stage NSCLC who are not operable candidates, SBRT is the current standard of care. Early experiences with SBRT identified a group of patients with centrally located lesions, defined as within 2 cm of the trachea, left and right mainstem bronchi and lobar bronchi, who were at an elevated risk of fatal toxicity. Slightly more fractionated regimens of SBRT, typically 5 to 8 fractions, have been reported as being well tolerated in these patients while maintaining local control rates over 90%.[3] However, more recently, a further subgroup of patients with ultra-central lesions has been identified as being at even greater risk for fatal toxicity. The definition of an ultra-central lesion is heterogenous, but generally includes patients with lesions within 1 cm of the proximal bronchial tree or esophagus, or with the planning target volume overlapping the proximal bronchial tree or the esophagus.[19,20]

The recently reported Nordic HILUS study defined ultra-central as tumors within 1 cm of the proximal bronchial tree, with the notable exclusion of patients with tumor invading the bronchus. Patients with these tumors were treated with dose de-escalated SBRT to 56 Gy in 8 fractions. However, the radiation was prescribed to approximately the 67% isodose line, leading to maximal doses in the radiation plan of around 150% of the prescription dose (84 Gy physical dose). The study found that even with dose de-escalated SBRT, rates of severe toxicity remained high, with 22 of 65 patients (33.8%) experiencing Grade 3-5 toxicity, including 10 with Grade 5 toxicity (15.4%), mostly bronchopulmonary hemorrhage. Notably, local control was also lower than with higher dose SBRT regimens, with 2 year local control of 83%. Due to the high rates of severe and fatal toxicity, the authors felt that 56 Gy in 8 fractions could not be recommended for ultracentral lesions closely abutting the trachea and mainstem bronchi, and could only be recommended caution in other ultracentral lesions.[19]

A treatment planning study reported that using 50 Gy in 5 fractions or 60 Gy in 8 fractions (both common dose-fractionation schemes for centrally located lung tumors) prioritized to maximize target coverage and tumor control yielded estimated tumor control rates over 90%, but with a predicted Grade 4 or higher toxicity rates of 44-68%. When the same tumors were planned to minimize toxicity, tumor control decreased to approximately 60%. This, combined with the results of the HILUS study, indicate that SBRT for ultracentral lung lesions may not be feasible without significantly compromising tumor control.[25]

In patients with stage II-III NSCLC who are medically inoperable and not candidates for chemotherapy, 45 Gy delivered in 15 fractions (BED10 = 58.5) is a commonly utilized HRT schedule with a favorable toxicity profile. Unfortunately, locoregional control rates ranged between approximately 40-60%, similar to that of conventionally-fractionated RT alone.[1] A randomized study of elderly NSCLC patients treated with conventionally fractionated radiotherapy (60 Gy in 30 fractions, BED_{10} = 72) with or without concurrent carboplatin observed recurrence or progression in the treated volume in 60% of patients in both arms. Another study which retrospectively assessed outcomes after moderate HRT alone (66 Gy in 30 fractions, BED10 = 80.52) found a 2 year local control rate of 57% This study also reported a significant difference in cause-specific survival in patients with local control, with a 2 year CSS of 56% in those with local control and only 32% in those who had local failure.[15] By comparison, locoregional failure in an observational study from this institution using 70.2 Gy in 26 fractions (a HRT regimen) was 32% at 3 years and treatment was very well tolerated.[13] Institutional review of a small number of patients treated with this regimen for Stage III NSCLC without concurrent chemotherapy showed excellent results and no high grade toxicity (unpublished data).

A Phase I dose escalation trial conducted by Westover and colleagues investigated the outcomes of 15 fraction hypofractionated radiation alone for patients with Stage II-IV NSCLC who were not candidates for other therapies. They found that the maximum tolerated dose was 60 Gy in 15 fractions (BED_{10} = 84 Gy). However, they were unable to provide estimates of local control due to poor OS (median 6 months), likely due at least in part to the inclusion of patients with metastatic disease (28% of patients).[31]

The Alliance CALGB 31102 protocol was a phase 1 study of concurrent chemotherapy with a HRT, escalating dose by progressive hypofractionation (60 Gy delivered in 27, 24, 22, and 20 fractions, respectively). HRT was given with concurrent carboplatin/paclitaxel. Twenty-six percent of patients had Grade 3 or greater toxicity and 3 cases of Grade 5 toxicity were observed. As a result, the maximum tolerated dose was set at 60 Gy in 24 fractions (BED_{10} = 75 Gy). Local progression occurred in only 24% of patients using this treatment paradigm suggesting an improvement in tumor control from RT alone as described previously. However, this regimen utilized concurrent chemotherapy, which was thought to have contributed to the significant toxicity rates. Additionally, the trial allowed patients with endobronchial tumors, tumors invading major cardiovascular structures, and did not constrain the doses delivered to the tracheobronchial tree.[30] As a result, many radiation oncologists today extrapolate the results of this study to patients not eligible for concurrent chemotherapy and treat patients with HRT alone using this regimen. At this point, there is no prospective evidence to support this treatment regimen for radiation therapy alone in this specific cohort.

Cannon and colleagues reported a Phase I trial that dose escalated radiotherapy for locally advanced NSCLC treated with 25 fractions of radiation without concurrent chemotherapy. Dose escalation was done using a Bayesian dose-escalation scheme based on the predicted risk of pneumonitis. They reported a MTD dose of 63.25 Gy, but were unable to determine the safety of doses between this and 75 Gy in 25 fractions, as there were only 3 patients treated between these dose levels. The reported Grade 4-5 toxicities were mostly (67%) related to damage to the tracheobronchial tree. Doses delivered to small volumes of the tracheobronchial tree were noted to be predictive of high grade toxicity, with EQD2 doses of 75 Gy to $3cm^3$ and 83 Gy maximal dose reported as correlating to a 5% toxicity rate at 2 years.[6] Of note, patients with endobronchial disease and disease with invasion of major cardiovascular structures were eligible for the trial, and there were no reported attempts to minimize dose to bronchial structures reported, which may have contributed to severe bronchial toxicity seen.

The SOCCAR trial was a Randomized Phase II trial investigating 55 Gy in 20 fractions of radiotherapy prescribed to the reference with concurrent or sequential cisplatin and vinorelbine (BED_{10} = 70.13 Gy, $EQD2_{10}$ = 58.44 Gy). Treatment was tolerated as expected, however, local control was only 45% at 2 years in the sequential arm. However, as regular follow up scans were not mandated, this must be interpreted with caution.[23]

A recent retrospective study reported a 5 year local relapse free survival of 55% and a 5 year overall survival of 40% in patients with Stage III NSCLC treated with hypofractionated radiation therapy of 66 Gy in 24 fractions (BED_{10} = 84.15 Gy) with low dose daily concurrent cisplatin. This treatment regimen was overall well tolerated, with 11% of patients with Grade 3-5 gastrointestinal toxicity, the majority of which was Grade 3 radiation

esophagitis, and a Grade 3-5 respiratory, thoracic, and mediastinal toxicity rate of 8.4%. Grade 5 toxicity in this series was acceptable at 2.6%, with one Grade 5 esophageal ulcer, one respiratory failure, one heart failure, and only one mediastinal hemorrhage.[9]

Simultaneous Integrated Boost for NSCLC

Simultaneous integrated boost (SIB), also known as dose painting, is an advanced radiotherapy technique that uses inverse planning to deliver different dose levels to different areas during the same fraction. This technique is commonly used is standard practice for many disease sites such as anal canal and head and neck malignancies.[16,18] The ability to use dose painting to deliver higher doses of radiation to selected volumes holds promise in NSCLC as it may allow dose escalation to gross disease while delivering lower doses to areas at risk for subclinical disease or in too close proximity to critical structures for ideal doses. However, prospective evidence with this technique is limited in the setting of NSCLC.

One of the first prospective experiences reporting a concomitant or integrated boost for locally advanced non-small cell lung cancer (LA-NSCLC) was a Phase II study conducted by the Korean Radiation Oncology Group. This study delivered 45 Gy in 25 fractions (BED_{10} = 53.1 Gy) to the planning target volume (PTV) with a boost to the gross tumor volume (GTV) to a total dose of 60 Gy in 25 fractions (BED_{10} = 74 Gy) with concurrent carboplatin and paclitaxel using 3D plans. Treatment was well tolerated considering the limitations of the treatment techniques available at the time, with two cases (4.1%) of Grade 5 hemoptysis, both in patients with T4 disease involving the heart or main pulmonary artery, and 3 total cases of Grade 4 toxicity (2 pharynx/esophagus and 1 lung). Unfortunately, the local control was suboptimal, with a 2 year local progression free survival of 53%, and a crude local failure rate of 39%.[7]

A more recent simultaneous integrated boost approach for Stage III NSCLC was reported in a Phase I study investigating 30 fraction radiotherapy with concurrent chemotherapy. The investigators delivered 60 Gy in 30 fractions to standard volumes with an escalating SIB to the iGTV plus a 5mm margin. The MTD for the SIB was determined to be 72 Gy in 30 fractions, with dose limiting toxicity seen in acute esophagitis. As these were preliminary results, late toxicity was not reported. The local control of this regimen was very promising, with a loco-regional recurrence rate of 7% (1 of 15 patients).[14]

Selection of HRT Dose

Various hypofractionated radiotherapy (HRT) regimens have been reported for the management of patients with early-stage NSCLC not amenable to surgery or SBRT, HRT is commonly implemented, but the optimal dose schedule has not been established. Selection of HRT dose has been informed by studies of HRT/stereotactic body radiotherapy (SBRT) which have established a direct correlation between BED and tumor control.[17,26] Generally speaking, RT doses with $BED_{10} > 100$ results in significantly improved disease control when compared to doses with $BED_{10} < 100$. For this reason, efforts to deliver various regimens of HRT that reach or approach a BED_{10} of 100 Gy are of interest. A study conducted by the Cancer and Leukemia Group B (CALGB) 39904 protocol[4] evaluated various HRT regimens to a total dose of 70 Gy in 17-29 fractions without concurrent chemotherapy for early stage T1-T2N0 NSCLC. In this Phase I study, disease control was favorable and no dose-limiting toxicity was observed.

For patients with NSCLC not amenable to SBRT, surgery or concurrent chemoradiotherapy, a commonly utilized HRT fractionation at our institution is 70.2 Gy in 26 fractions. This regimen has a BED_{10} of 89.15 Gy. Recent data from our institution show that this fractionation results in favorable disease control and toxicity profiles.[13] In our cohort, which included stage II patients and those with hilar (N1) nodal involvement, 96% were treated with 70.2 Gy in 26 fractions. The 3 year cumulative incidence of locoregional failure (including in untreated regional lymph nodes) was 32%, and only 2 (4%) of patients developed CTCAE version 4.0 Grade 3 radiation pneumonitis after treatment. No instances of Grade 3+ esophagitis occurred. Based on these data, a similar dose fractionation scheme of 70 Gy in 25 fractions (BED_{10} = 89.6 Gy) is likely to have a 2 year local control rate of approximately 70%. In cases where PBT dose constraints cannot be met, the dose to the PTV within 1 cm of the

PBT will be reduced slightly to 67.5 Gy in 25 fractions (BED_{10} = 85.73 Gy, BED_3 = 128.25 Gy) to reduce the risk of serious toxicity. A similar dose (66 Gy in 24 fractions, BED_{10} = 84.15 Gy, BED_3 = 126.5 Gy) has been previously reported to be well tolerated with concurrent low dose daily cisplatin.[9]

Selection of Dose Constraints for the Proximal Bronchial Tree, Esophagus, and Heart

Proximal Bronchial Tree

Based on reports of severe bronchial toxicity with SBRT of centrally located NSCLC, determining proper dose constraints for high dose radiotherapy to mediastinal structures has been of increasing interest.[29] The recently reported multi-institutional RTOG 0813 trial of SBRT for centrally located NSCLC found an MTD of 60 Gy in 5 fractions while limiting the proximal bronchial tree and esophagus adjacent to the target to 105% of the prescription dose and avoiding circumferential irradiation of these structures. Local control was also excellent, with in field control rates exceeding 90%.[3]

Attempts to use hypofractionation for more advanced disease have been less successful, with one series reporting 38% Grade 3 or higher toxicity, including 21% Grade 5 toxicity, in patients with mostly Stage IIB-IIIA NSCLC treated with 60 Gy in 12 fractions. However, this series made no attempt to constrain the proximal bronchial tree, and over 50% of patients had endobronchial tumors, and the BED_3 of this regimen is 160 Gy.[28]

Two Phase I studies, one with concurrent chemotherapy and one without, arrived at similar MTDs of 60 Gy in 24 fractions (with concurrent chemotherapy) and 63.25 Gy in 25 fractions (without concurrent chemotherapy).[6,30] The dose limiting toxicity seen in these trials was also largely driven by complications related to vascular and bronchial injury. As with other experiences, patients with endobronchial disease and pulmonary vascular invasion were included and no attempt was made to constrain the bronchial tree. Cannon and colleagues attempted to develop a normal tissue complication probability model for the tracheobronchial tree based their Phase I study.[6] They reported a 5% late Grade 5 toxicity risk with a bronchial dose of EQD2 of 75 Gy to $3cm^3$ of the tracheobronchial tree, assuming an α/β ratio of 3. For 25 fractions, this is approximately 66.25 Gy ($EQD2_3$ = 74.86 Gy, see Appendix E for BED and EQD2 calculations). However, this model is limited by the number of patients enrolled on dose levels between the reported MTD and dose levels where toxicity was reported (total of 3 patients). Similarly, the Nordic HILUS study estimated that patients with ultracentral lesions could likely be treated safely with a bronchial dose constraint of 70-80 Gy EQD2. However, this is limited by small numbers of patients and is particularly uncertain in patients with lesions abutting the trachea and mainstem bronchi.[19]

We plan to decrease bronchial toxicity risk in multiple ways. First, we will reduce the high dose level for the target area in close proximity to the PBT when dose constraints cannot be met.For these patients, a high dose level of 67.5 Gy in 25 fractions will be prescribed, which is nearly biologically equivalent to 66 Gy in 24 fractions, which has been reported to be safe when used in patients with Stage III NSCLC with daily cisplatin.[9] Second, during construction of the RT plan, any overlapping proximal bronchial tree plus a 5mm uniform expansion (planning organ at risk volume or PRV) will be excluded from the high dose PTV. Second, we will provide dose constraints to bronchial structures (mandatory for maximal dose, and ideal for volumetric constraints) in a similar fashion to RTOG 0813. Finally, we will limit the maximum dose in the entire plan to no more than 115%, unlike the Nordic HILUS study, further reducing the risk of very high doses of radiation being delivered to the proximal bronchial tree due to intrafractional motion.

Esophagus

As with the proximal bronchial tree, late esophageal toxicity is of concern in high dose radiotherapy to the mediastinum and centrally located lung tumors. In RTOG 0813, esophagus adjacent to the target was limited to 105% of the prescription dose. They noted minimal late esophageal toxicity with doses up to 60 Gy in 5 fractions[3] Additionally, in Alliance/CALGB 31102, the esophagus was limited to a maximal dose of 105% of the prescription, and a V55 Gy of under 30%, with no reported late Grade 3 or higher toxicity.[30] Furthermore, a recent normal tissue complication model of the esophagus developed based on patients treated with hypofractionated radiotherapy reported a 5% late high grade esophageal complication rate with a maximal $EQD2_3$ dose of 113.3 Gy.[10] Based on these data, we will plan for mandatory esophagus constraints of 73.5 Gy (105% of prescription, $EQD2_3$ = 87.3 Gy)

and a V55 Gy under 30%. As with the bronchial tree, the esophagus plus a 5mm uniform expansion will be excluded from the high dose target volume.

Heart

Dose constraints to the heart have become increasingly important in radiotherapy for NSCLC. RTOG 0617 has reported decreased overall survival for low doses of radiation to the heart.[5] This may have accounted for the poorer overall survival seen in the high dose arm of the trial. A recent analysis of this trial reported the heart V50 Gy as a significant stratification point, with a 1 year overall survival of 70.2% for patients with a heart V50 Gy under 25%, compared with 46.8% for those with a heart V50 Gy over 25%.[27] An additional secondary analysis of the trial revealed decreased heart dose with the use of IMRT compared with 3D, despite larger target volumes in the intensity modulated radiation therapy (IMRT) patients.[8] The same analysis reported that the heart V40Gy was significantly associated with overall survival on multivariable analysis. We will plan to use more strict dose constraints on this protocol, as well as anticipated near universal use of IMRT, in order to minimize the risk of late cardiac toxicity.

Clinical Summary

The therapeutic options for patients with Stage II-III NSCLC and ultracentral early stage NSCLC who are not eligible for surgery or definitive chemoradiotherapy are controversial. Fractionated radiation therapy alone is often the only option for these patients. Radiation therapy alone can be given in several manners, using conventional fractionation or hypofractionated radiotherapy. Conventional radiotherapy alone (without concurrent chemotherapy) results in inadequate disease control and survival. Multiple retrospective studies have evaluated the efficacy of HRT regimens with widely variable results. Prospective data on the use of HRT using modern radiotherapy techniques is lacking, and the available evidence is limited by the potentially poor patient selection and inadequate dose constraints to the tracheobronchial tree. In this proposed phase 2 study, we aim to assess prospectively, a regimen that our institution has shown to have efficacy and safety in patients with up to Stage IIB disease using an SIB technique to stay within the threshold of critical normal tissue tolerance, including major airway structures, the heart, and the esophagus.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 To determine the in-field control of hypofractionated radiotherapy consisting of 70 Gy in 25 fractions without concurrent chemotherapy measured at two years after the first post-radiotherapy scan.

2.2 Secondary Objective(s)

2.2.1 To determine the toxicity profile of thoracic HRT consisting of 70 Gy in 25 fractions as graded by CTCAE version 5.0

2.2.2 To determine proportion with local, regional, and distant progression at 1 and 2 years after the first post-radiotherapy scan, and compute progression-free and overall survival (PFS and OS, respectively).

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Histological confirmation of non-small cell lung cancer by either biopsy or cytology
3.1.2 AJCC 8th Edition Stage II-III or ultracentral Stage IB disease as determined by PET/CT and MRI Brain
  3.1.2.1 Ultracentral disease will be defined as edge of gross visible tumor within 1cm of the proximal bronchial tree
3.1.3 ECOG Performance Status of 0-3
3.1.4 Patient is not eligible for or has declined surgical resection or SBRT as determined by the treating physician
3.1.5 Patient is not eligible for or has declined concurrent chemotherapy as determined by the treating physician
  3.1.5.1 While we expect it to be an uncommon event, sequential use of systemic therapy after completion of RT is permissible if the patient's status improves such that they become eligible for such therapies, per the discretion of a multidisciplinary tumor board.
3.1.6 Negative serum or urine pregnancy test within 2 weeks of the date of enrollment for women of child-bearing potential
3.1.7 Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative).

3.2 Exclusion Criteria

3.2.1 History of previous thoracic radiotherapy with the exception of prior radiotherapy for breast cancer without overlap of the fields with the cancer to be treated
3.2.2 Prior systemic therapy or surgery for the study cancer
3.2.3 Prior malignancy within the past two years except for non-melanoma skin cancer, prostate cancer, or any in-situ malignancy
3.2.4 Receipt of anti-angiogenic therapy, such as bevacizumab, within 6 months of enrollment
3.2.5 Pregnant women are excluded from this study because radiation therapy has known potential for teratogenic or abortifacient effects.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study. The study consent form will also be provided in Spanish for Spanish-speaking participants.

Based on WFBCCC population estimates, we may expect approximately 44% of participants to be women. Translating this to our sample size estimate of **43**, we may enroll approximately **19** women. We may enroll approximately 10-13% Black or African American. Based on our catchment area and hospital demographics we do not expect accruals of individuals of Hispanic/ Latino, American Indian/Alaska Native or Asian ancestry; however, no individual will be excluded from the study if they satisfy the above inclusion/exclusion criteria. Should we not meet or exceed these estimates, the PI will engage the Office of the Center for Health Equity to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

Contact Information:
Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)
*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.
You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.
4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents. Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- Assign a patient study number
- Register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome measure will be presence/absence of any in-field progression by 2 years. In-field progression is defined as growth of the targeted lesions beyond the treated volume. The treated volume will be defined as the 28.75 Gy isodose line (50% of 57.5 Gy). Pathologic confirmation of tumor progression is preferred, but can be determined radiographically by Multidisciplinary Thoracic Oncology Program consensus if biopsy of the lesion in question is not feasible or safe.

5.2 Secondary Outcomes

5.2.1 Toxicities will be evaluated per CTCAE Version 5.0 one month following completion of therapy and then every 3 months thereafter until 25 months from completion of radiation therapy.

5.2.2 Patterns of progression will be defined as follows: Local progression will be defined as in field progression (see Section 5.1.1); regional progression will be defined as any new regional lymphadenopathy in the hilum or mediastinum that was not included in the gross tumor volume (GTV); distant progression will be defined as any radiographic or pathologic evidence of disease outside the primary tumor and regional lymph nodes, including subsequent pulmonary parenchymal lesions. Progression-free survival will be evaluated by considering the time from registration to progression of disease or death; those who do not experience either outcome will be censored at date of last visit. Overall survival will be evaluated by considering the time from registration to death from any cause; those who do not die will be censored at date of last visit. Progression will be assessed through CT scans administered immediately following treatment and then every 3 months after that, out to 25 months.

6.0 Treatment Plan

6.1 Study-Related Activities

Activity	Pre-Study[a]	Prior to First Fraction of RT	At Each Weekly Treatment Visit on RT	1 month after RT completion	Every 3 months after 1 month post-RT scan until 25 months after RT[l]
Informed consent	X				
Demographics	X				
Medical history	X			X	X
Concurrent meds	X				
Physical exam	X			X	X
Vital signs[g]	X			X	X
Height[d], Weight,[g]	X			X	X
Performance Status[g]	X		X	X	X
Tumor measurements[e]	X			X	X
B-HCG[b]	X				
FDG PET/CT Skull Base to Mid Thigh[j]	X				
MRI Brain with contrast[i]	X				
CT Chest/Abdomen[c]				X	X
Adverse event evaluation[f]	X		X	X	X
Mandatory target coverage/dose constraint compliance[k]		X			

[a] Pre-study requirements listed in table must be completed **within** 12 weeks prior to registration.
[b] Serum or urine pregnancy test (women of childbearing potential). This must be completed within one week prior to initiation of radiotherapy for women of childbearing potential. For our purposes postmenopausal women are defined as women over the age of 45 years old with at least 12 months from their date of last menstruation.
[c] CT Chest/Abdomen will be with contrast unless the patient has a documented contraindication to IV CT contrast (ie inadequate renal function or anaphylaxis). The scan must include the entire bilateral lungs, liver, and bilateral adrenal glands. CT Chest/Abdomen/Pelvis is also acceptable.
[d] Height measured at pre-study only
[e] See Appendix Q
[f] See Appendices F and G
[g] See Appendix L
[h] See Appendix C
[i] If MRI is contraindicated, CT Head with contrast is also acceptable.
[j] National guidelines indicates a PET scan is good for 3 months (12 weeks).
[k] See Appendix N
[l] For all follow-up imaging and clinic follow-up time points above, a flexibility window of +/- 8 weeks is allowed.

6.1.1 Radiation Therapy

Hypofractionated radiation therapy will be delivered to all patients. The prescribed dose will be **70 Gy in 25 fractions**

1. Technical Factors and Radiation Planning
   a. Radiation Dose Selection
      i. The radiation dose for the high dose PTV was selected based on previous clinical experience with 70.2 Gy in 26 fractions, and decreasing the treatment course by one fraction, leading to a **high dose of 70 Gy in 25 fractions.** As this dose is likely not necessary for control of microscopic disease treated in the clinical target volume (CTV), **a lower dose CTV will be treated to 57.5 Gy in 25 fractions**. This lower dose was selected based on BED and EQ2D calculations, which can be used to compare doses using non-standard (ie non 1.8-2 Gy) fraction sizes (see Table 1).
      ii.

Table 1. COMPARISON BED and EQD2 for Dose Fractionation Schemes

Dose / Fractions	BED_{10} Gy (Tumor)	BED_3 Gy (Normal Tissue)	$EQD2_{10}$ Gy (Tumor)	$EQD2_3$ Gy 2 (Normal Tissue)
60 Gy / 30 fx (SoC)	72	100	60	60
66 Gy / 30 fx	80.52	114.4	67.1	68.84
70.2 Gy / 26 fx	89.15	133.38	74.3	80.03
58.5 Gy / 26 fx	71.66	102.38	59.72	61.43
66 Gy / 24 fx	84.15	126.5	70.13	75.9
70 Gy / 25 fx	89.6	135.33	74.67	81.2
67.5 Gy / 25 fx	85.73	128.25	71.44	76.95
57.5 Gy / 25 fx	70.72	101.58	58.94	60.95

   b. CT Simulation
      i. All patients will undergo CT simulation of the chest. The use of intravenous contrast with the CT simulation is not mandatory.
      ii. 4D-CT will be obtained for motion management. The use of abdominal compression or respiratory gating is encouraged.
      iii. Immobilization will be done with a customized vacuum sealed bag.

   c. Target Volume Definitions:

i. GTV = gross tumor (both primary and lymph nodes) on CT simulation. Lymph nodes > 1 cm in short axis diameter or with an SUV > 3 are considered to be involved unless proven negative by biopsy.
ii. iGTV = GTV accounting for tumor motion on all phases of 4D CT
iii. CTV_7000 = iGTV with no expansion
iv. CTV_5750 = iGTV uniformly expanded by 5mm
    1. CTV_5750 can be excluded from normal structures without radiographic evidence of invasion (for example≤ vertebral bodies, chest wall, or ribs)
    2. CTV_5750 should not be excluded from the trachea, esophagus, proximal bronchial tree, or intrathoracic cardiovascular structures
v. PTV_7000 = CTV_7000 uniformly expanded 5mm minus Esophagus_PRV, PBT_PRV, and Brachial_Plexus_PRV (if applicable)
vi. PTV_5750 = CTV_5750 uniformly expanded by 5mm
vii. PTV_6750 = PTV_7000 minus PBT_1cm
    1. PTV_6750 will only be delineated in cases where dose constraints for the PBT cannot be met

d. Organs at Risk to be contoured
    i. *For all patients*
        1. Bilateral lungs
        2. Spinal cord (5 cm above and below the PTV)
        3. Aorta (5 cm above and below the PTV)
        4. Esophagus (entire length)
        5. Esophagus_PRV = Esophagus plus 5mm uniform expansion
        6. Heart (including the pericardial sac)
        7. Trachea/proximal bronchial tree
            a. 5 cm superior to the PTV to the end of all main lobar bronchi
        8. PBT_PRV = trachea and proximal bronchial tree plus 5mm uniform expansion
    ii. *For patients with the PTV within 2 cm of the organ at risk**
        1. Brachial plexus
            a. Only the major trunks of the brachial plexus need to be contoured
            b. Left and right brachial plexuses should be contoured separately with generation of separate Brachial_Plexus_PRVs if the PTV is within 2 cm of both brachial plexuses
        2. Brachial_Plexus_PRV = Brachial plexus plus 5mm uniform expansion
        3. Chest wall (3 cm superior and inferior to the PTV)
        4. Ribs
        5. Stomach
        6. Liver

        ** if non-coplanar beams or arcs are used then all organs at risk must be contoured*
    iii. *For patients who cannot meet PBT dose constraints*
        1. PBT_1cm = trachea and proximal bronchial tree plus 1 cm uniform expansion
    iv.

e. Target Coverage Requirements
    i. *Mandatory*
        1. 95% of PTV_5750 to at least 95% of prescription (54.63 Gy)
        2. 99% of PTV_5750 to at least 90% of prescription (51.75 Gy)
    ii. *Ideal*
        1. 95% of PTV_7000/6750 to at least 95% of prescription (66.5 Gy/64.13 Gy)
        2. 100% of PTV_7000/6750 to at least 95% of prescription (66.5 Gy/64.13 Gy)
        3. 95% of PTV_7000/6750 to at least 100% of prescription (70 Gy/67.5 Gy)
        4. 99% of PTV_7000/6750 to at least 90% of prescription (63 Gy/60/75 Gy)
        5. 100% of PTV_5750 to at least 95% of prescription (54.63 Gy)

f. Organ at Risk Constraints
   i. Mandatory
      1. Spinal Cord: D0.03 cm^3 < 45 Gy
      2. Esophagus: D0.03 cm^3 < 73.5 Gy;
      3. Lungs-GTV: V20 Gy ≤ 35%;
      4. Proximal Bronchial Tree: D0.03 cm^3 < 73.5 Gy; D3 cm^3 < 66.25
      5. Heart D100% < 30 Gy
      6. Stomach: D0.03cm^3 < 60 Gy
      7. Liver: Mean dose < 30 Gy; at least 700 cm^3 of normal liver to < 15 Gy
      8. Maximum physical dose < 115% of high dose prescription
         a. PTV_7000: maximum physical dose < 80.50 Gy
         b. PTV_6750: maximum physical dose < 77.63 Gy
   ii. Ideal
      1. Lungs-GTV: V40 Gy < 10%; V30 Gy < 15%; V20 Gy < 30%; V10 Gy < 60%; mean dose < 20 Gy
      2. Proximal bronchial tree: Gy; D15% < 60 Gy
      3. Esophagus: Mean dose < 34 Gy; D10 cm^3 < 60 Gy; D30% < 55 Gy
      4. Aorta: D0.03 cm^3 < 76 Gy; D10 cm^3 < 60 Gy
      5. Heart: Mean dose < 30 Gy; D25% < 50Gy; V45Gy < 30%;D0.03cm^3 <73.5Gy
      6. Brachial plexus: D0.03cm^3 < 60 Gy
      7. Stomach: D0.03cm^3 < 58 Gy; V50 Gy < 5 cm^3; V45Gy < 75 cm^3
      8. Liver: Mean dose < 28 Gy
      9. Chest Wall: V30 Gy < 70 cm^3
      10. Ribs: D0.03 cm^3 < 57 Gy
      11. Maximum dose < 108% of high dose prescription
         a. PTV_7000: maximum physical dose < 75.6 Gy
         b. PTV_6750: maximum physical dose < 72.9 Gy

g. Radiation Therapy prescription and planning
   i. Radiation prescription
      1. A simultaneous integrated boost will be used to treat all PTVs
      2. PTV_7000 = 70.00 Gy in 25 fractions (2.80 Gy per fraction)
         a. PTV_6750 = 67.5 Gy in 25 fractions (2.70 Gy per fraction)
      3. PTV_5750 = 57.50 Gy in 25 fractions (2.30 Gy per fraction)
   ii. 3D-CRT, static IMRT, or VMAT plans are acceptable
      1. IMRT or VMAT are strongly preferred
   iii. Heterogeneity corrections will be used for all dose calculations
   iv. At least 95% of PTV_5750 must be covered by at least 95% of the prescription dose for that PTV. If mandatory dose constraints to organs at risk are unable to be met, ideal target coverage requirements may be compromised at the discretion of the treating physician.
   v. Ideally no more than 1cm^3 of normal tissue outside the PTV_5750 may receive > 62.1Gy
   vi. Circumferential high dose irradiation (70 Gy or higher) of the trachea, bronchus, and esophagus should be avoided

h. Radiation Therapy Delivery
   i. Radiation therapy will be delivered once daily, 5 days per week, Monday-Friday.
      1. In cases where Radiation Oncology clinic is closed, the patient may receive only 4 fractions per week at the discretion of the treating radiation oncologist.
      2. Treatment breaks are allowable per the discretion of the treating radiation oncologist.
   ii. Daily image guidance with cone beam CT is recommended.

6.2 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.3 Duration of Therapy/Study Follow-up

Treatment may continue until the completion of radiotherapy or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment or ability to present for follow-up visits (i.e. hospitalized)
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or further follow-up on study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator

- If patients have disease progression or require further radiation treatment outside the protocol, they will be treated at the discretion of their treating physician. They will be followed for local control and survival for 25 months after they have completed their initial radiation.

6.4 Duration of Follow Up

Patients will be followed for a minimum of 30 days after the last radiation therapy fraction is administered for adverse events monitoring, unless otherwise specified in this section of the protocol. A different time frame may be longer but not shorter than 30 days unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. Follow-up for serious adverse events and mortality after the last study dose is administered will take place during the routine clinic visits that the patient will have during the 30 day follow-up window (Also referenced in Appendix D). If no visit occurs during this window, a phone call confirmation should be made to the patient to determine vital status and whether any adverse events and in particular, Grade 4 unexpected adverse events occurred during that window of time and recorded on Appendix F.

Patients will be followed 25 months or until death after the last study radiation treatment for monitoring survival study endpoints.

6.5 Criteria for Removal from Study

Patients may be removed from study when any of the criteria listed in section 6.3 applies.

7.0 Dosing Delays/Dose Modifications

7.1 Any Grade 3 or higher acute toxicity with the exception of hematologic and laboratory toxicity may result in a treatment break at the discretion of the treating investigator until it resolves to Grade 2 or less. Duration of treatment break is at the discretion of the treating radiation oncologist. All labs will

be assessed by the treating physician to determine whether they are considered clinically significant or not clinically significant and treatment will be held at their discretion.

8.0 Measurement of Effect

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.[1] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1.1 Survival Outcomes

Progression-Free Survival is defined as the duration of time from the start of treatment to the time of progression, death, or date of last contact; those lost to follow-up will be censored.

Overall Survival is defined as the duration of time from the start of treatment to date of death or date of last contact; those lost to follow-up will be censored.

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse Event List for Hypofractionated Thoracic Radiotherapy

9.1.1 Cardiac and Pericardial Injury

9.1.1.1
Although acute cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with larger doses per fraction of this study, a number of possible side-effects can be seen.

9.1.1.2
Dose to the heart has been shown to impact long term overall survival. All attempts to minimize dose to the heart will be made in accordance with the dose constraints in Section 6.2.1

9.1.2 Gastrointestinal/Esophageal Injury

9.1.2.1
The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases. The stomach and small bowel are also susceptible to radiation injury that manifests as nausea, anorexia, and vomiting (acute) or stenosis, ulceration, or rarely perforation (late). The liver is exquisitely sensitive to radiation therapy. Acute manifestation of liver toxicity is usually reflected by increasing hepatic enzymes (AST and ALT), as well as nausea. Late radiation hepatotoxicity is extraordinarily rare when treating intrathoracic malignancies, as large amounts of the liver can be irradiated to high doses as long as an adequate volume of liver is spared and the mean dose is kept below 30 Gy (see Section 6.2.1).

9.1.3 ***Central Airway/Bronchial Injury***

9.1.3.1

Severe injury to the proximal tracheobronchial tree, resulting in fistula formation or hemoptysis, which may be fatal, is possible but rare (<5%). This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0;

9.1.4 ***Lung Injury***

9.1.4.1

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. It is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined. Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

9.1.5 ***Spinal Cord or Brachial Plexus Injury***

9.1.5.1

Radiation myelitis and brachial plexopathy are rare late effects of radiation therapy (<1%). In the extremely rare cases where radiation myelitis occurs, common symptoms include neuropathic pain, progressive weakness, and sensory changes. Radiation-induced brachial plexopathy presents in a similar fashion to radiation myelitis, with symptoms being limited to areas innervated by the affected brachial plexus.

9.1.6 ***Chest wall pain/rib fractures***

9.1.6.1

Chest wall pain and/or pathologic rib fractures are uncommon complications of radical radiotherapy that are most frequently seen in the setting of SBRT to very peripheral lung lesions. The most common symptom of the syndrome is pain in an area of the chest wall in very close proximity to high dose areas which typically responds to NSAIDs.

9.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of

the CTCAE version 5.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

9.3 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Data Management

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Pre-Toxicity	WISER/OnCore
Off study, Off treatment, Withdrawal	WISER/OnCore
Vitals Form	REDCap
Con-med PRN Form	WISER/OnCore
Follow up Post Washout	REDCap
Treatment Response Evaluation	REDCap
Pattern of Progression	REDCap
Adverse Events Log	WISER/OnCore
Mandatory Target Coverage/Dose Constraint Compliance Confirmation	REDCap

This project will utilize REDCap Clinical Data Interoperability Services. This is a special feature for importing data into REDCap from WakeOne. It provides an adjudication process whereby REDCap users can approve all incoming data from WakeOne before it is officially saved in their REDCap project. REDCap Clinical Data Interoperability Services can only be enabled by a REDCap administrator who serves as an honest broker to PHI. REDCap's Clinical Data Interoperability Services can only be accessed by users with valid WakeOne credentials. Using the Clinical Data Interoperability Service requires using the Medical Record Number (MRN) as a key to automatically gather demographics and laboratory data and reduces data entry errors.

11.0 Statistical Considerations

With the exception of our primary aim, which is comparative and hypothesis-testing (relative to a historical control), the rest of our analysis plan is largely descriptive in nature.

11.1 Analysis of Primary Objective

11.1.1 We will compare the proportion of the sample with any in-field progression at 2 years to the historical control proportion of 0.5, using a one-sample z-test. We expect that a proportion

(around 10-15%) of our initial baseline sample will be missing data on this primary outcome at 2 years, and therefore we have correspondingly increased our target recruitment by this percentage (see section 11.3 below).

11.2 Analysis of Secondary Objective

11.2.1 We will compute the proportion of the sample developing any toxicity of grade 2 or higher over the 25 months, and construct a corresponding 95% confidence interval.

11.2.2 We will compute proportions of patients who have experienced local progression by 13 months (1 year following first post-radiotherapy scan) and by 25 months (2 years following first post-radiotherapy scan), and will also compute the same two proportions considering regional progression, distant progression, and any (of the 3 categories) progression. We will construct 95% confidence intervals around these proportions. Those patients for whom we are unable to determine progression status at 1 and 2 years (e.g., because they do not return for the necessary scans, or because they die without evidence of progression) will be left out of these analyses. We will evaluate PFS and OS first using the Kaplan-Meier lifetable method, and will estimate median survival and corresponding 95% CIs; we will also explore simple Cox proportional hazards models of each of these survival outcomes, to examine the predictive influence of variables such as age, gender, ECOG performance status, stage at diagnosis, PTV 7000+6750 volume, and PTV 5750 volume. Patients who are lost to follow-up will be censored at that time in these analyses.

11.3 Power and Sample Size

11.3.1 Prior studies suggest an average proportion of 0.50 of patients who are free from in-field progression at 2 years following standard radiotherapy alone.[4,9] Based on prior reports of dose escalated hypofractionated radiotherapy and our institutional experience using a similar dose fractionation scheme, we hypothesize that HRT will improve 2 year freedom from in-field progression from this 50% to 75%.[1,2,22] With a sample size of n=25, we will have 80% power to detect this increase, assuming a one-tailed α of 0.05. We anticipate that approximately 10% -15% of patients recruited will not provide data on our primary outcome at 2 years, so we anticipate recruiting n=30 patients total to allow us to have a total n of 25 for our primary analysis.

11.4 Estimated Accrual Rate

11.4.1 Based on review of recent case volume at WFBMC, we estimate one accrual per month across all sites, or 12 patients per year.

11.5 Estimated Study Length

11.5.1 Based on the estimated accrual rate, we anticipate a 2.5 year (29-31 months) duration of accrual.

11.6 Interim Analysis Plan

No formal interim analysis is planned; however, if 5 patients develop Grade 4 or 5 bronchial fistula, bronchopulmonary hemorrhage, esophageal fistula, hemorrhage or perforation as defined by CTCAE version 5.0, the study will be halted. Patients who have known in-field progression of disease or new or

progressive disease involving the structure that develops the Grade 4 or 5 toxicity prior to toxicity development will not be counted.

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Appendix A – Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No.62220**		
Study Title: ***A Single Arm Phase II Study of Hypofractionated Radiotherapy Alone in Locally Advanced NSCLC Patients who Decline or are Ineligible for Surgery or Chemotherapy***			
Principal Investigator Dr. Farris			
Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Histological confirmation of non-small cell lung cancer by either biopsy or cytology	□	□	
AJCC 8th Edition Stage II-III or ultracentral Stage IB NSCLC as determined by PET/CT and MRI Brain	□	□	
ECOG Performance Status of 0-3	□	□	
Patient is not eligible for or has declined surgical resection or SBRT as determined by the treating physician	□	□	
Patient is not eligible for or has declined concurrent chemotherapy as determined by the treating physician	□	□	
While we expect it to be an uncommon event, sequential use of systemic therapy after completion of RT is permissible if the patient's status improves such that they become eligible for such therapies, per the discretion of a multidisciplinary tumor board.	□	□	
Negative serum or urine pregnancy test within 2 weeks of the date of enrollment for women of child-bearing potential	□	□	
Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative)	□	□	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
History of previous thoracic radiotherapy with the exception of prior radiotherapy for breast cancer without overlap of the fields with the cancer to be treated	□	□	
Prior systemic therapy or surgery for the study cancer	□	□	
Prior malignancy within the past two years except for non-melanoma skin cancer, prostate cancer, or any in-situ malignancy	□	□	
Receipt of anti-angiogenic therapy within 6 months of enrollment	□	□	
Pregnant women are excluded from this study because radiation therapy has known potential for teratogenic or abortifacient effects	□	□	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN

☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** **No** ☐ ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D Safety and Toxicity Review Committee (STRC) Serious Adverse Event (SAE) Notification SOP

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites. There are three types of trials that are included in this category:
    a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is

any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)

11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology
Mercedes Porosnicu, MD-- Hematology Oncology
Ryan Hughes, MD – Radiation Oncology
Michael Goodman, MD -- Hematology Oncology
Daniel Reed, MD -- Hematology Oncology
Mary Beth Seegars, MD -- Hematology Oncology

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone

call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

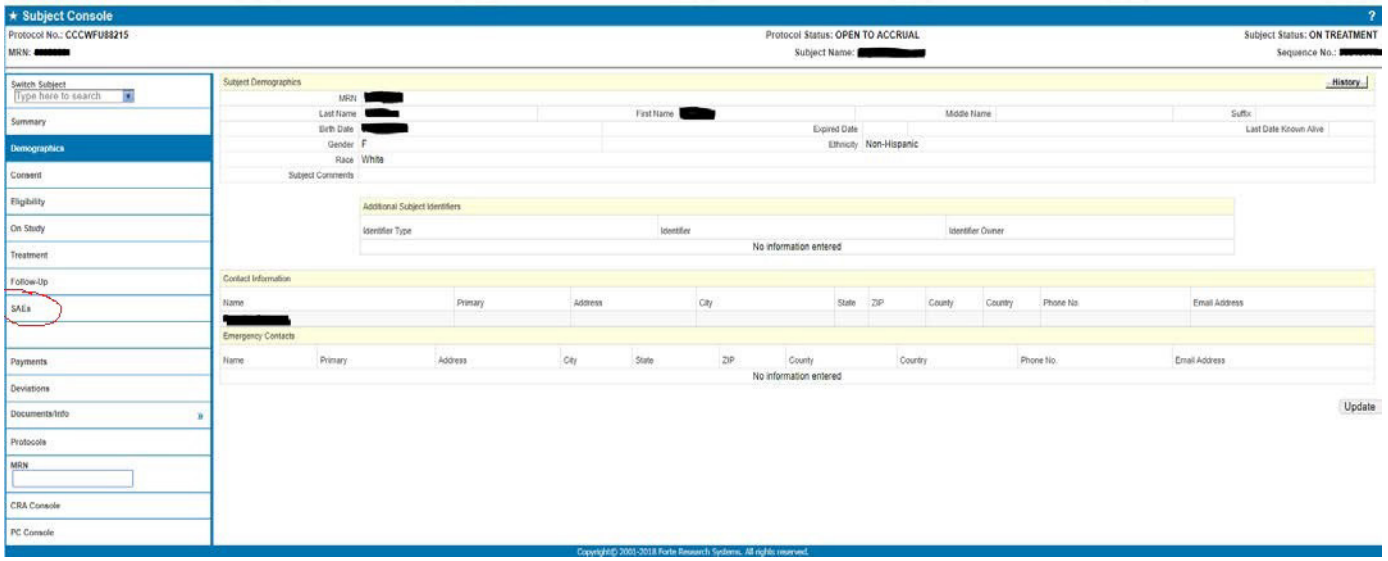
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

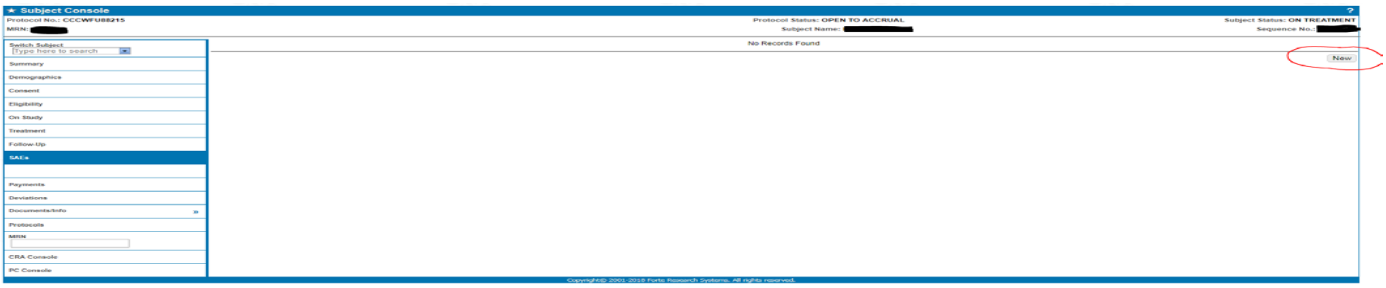
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

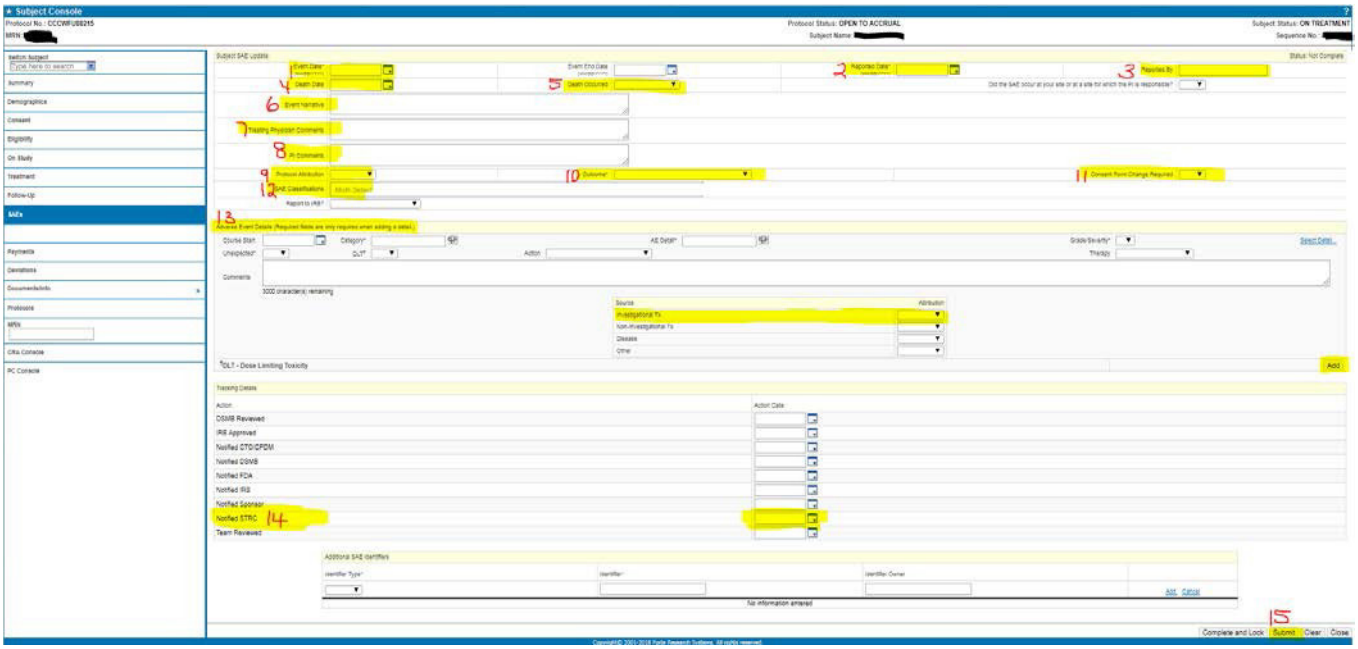
Screen Shot 1:



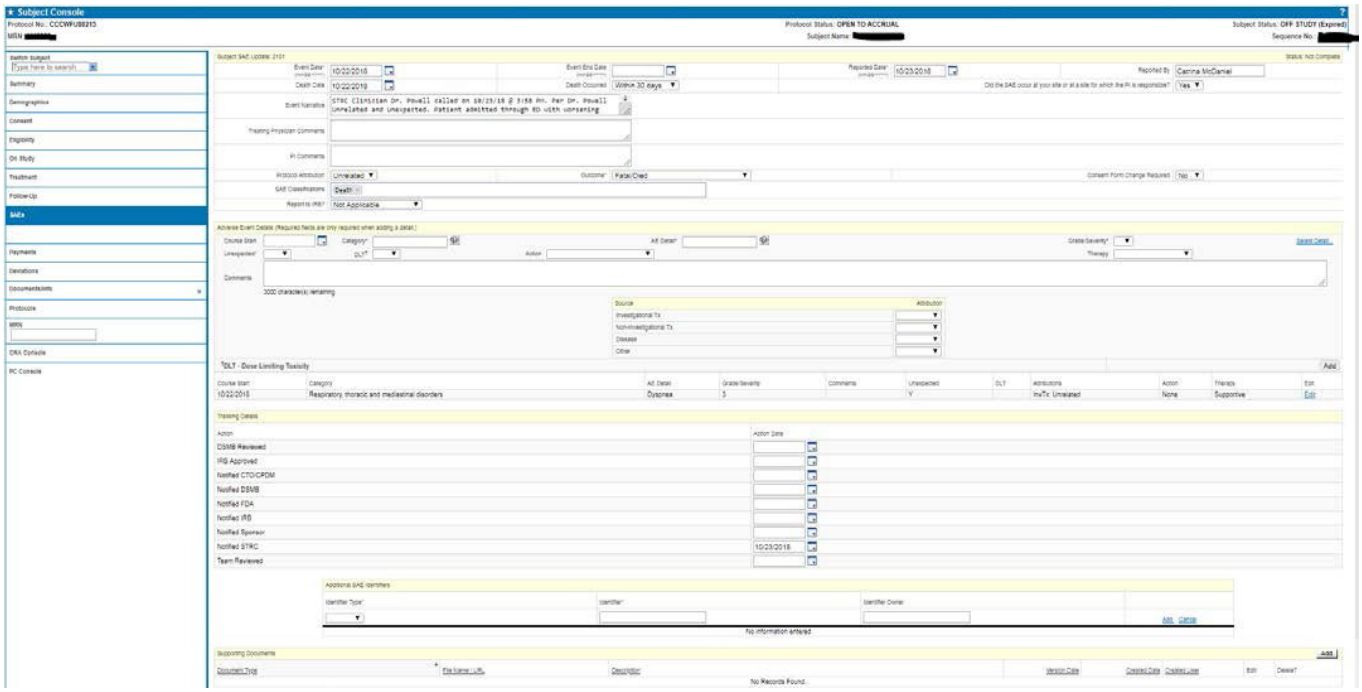
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix E: BED Calculations for Dose Levels and Constraints

$$\boldsymbol{BED = d(n)(1 + d/(\alpha/\beta)}$$

- Where:
  - BED = Biologic Effective Dose at a given alpha/beta ratio
  - *d* = dose per fraction
  - *n* = number of fractions
  - α/β= alpha/beta ratio

$$\boldsymbol{EQD2 = BED/(1 + (2/\alpha/\beta))}$$

- Where:
  - EQD2 = Equivalent dose in 2 Gy fractions

BED and EQD2 Calculations							
Parameter	**Total Dose (Gy)**	**Dose per fraction (Gy)**	**Number of Fractions**	**BED_{10} (tumor)**	**BED_3 (normal tissue)**	**$EQD2_{10}$ (tumor)**	**$EQD2_3$ (normal tissue)**
Standard Therapy	60	2	30	72	100	60	60
Prior Institutional HRT	70.2	2.7	26	89.15	133.38	74.3	80.03
Prior HRT with Low Dose Cisplatin	66	2.75	66	84.15	126.5	70.13	75.9
High Dose PTV	70	2.8	25	89.6	135.33	74.67	81.2
High Dose PTV (bronchial invasion)	67.5	2.7	25	85.73	128.25	71.44	76.95
Low Dose PTV	57.5	2.3	25	70.72	101.58	58.94	60.95
Volumetric PBT Constraint	66.25	2.65	25	83.81	124.77	69.84	74.86
*Brachial Plexus Constraint**	60	2.4	25	74.4	132	62	66
* α/β of 2 used for normal tissue calculations for nervous system							

Appendix F – Adverse Event Log

WFBCCC Adverse Event (AE) Log														
PI: Farris_ Subject PID: _____									**MRN: _____**					
Cycle #: _____ **Cycle Start Date: _____** **Cycle Start Time: _____** **Cycle End Date: _____** **Cycle End Time: _____**														
Adverse Event CTCAE Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxicity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP=Supportive VSUP=Vigorous supportive	**Reportable** IRB-STRC-FDA Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R=Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials /Date**
Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.														
CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf														
STRC- Safety and Toxicity Review Committee											Version 1/10/18			

Appendix G – Follow-up Form

_

Study Number: 62220 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Michael Farris M.D. Date: ___ ___/___ ___/___ ___

Instructions: Complete this form to follow-up with patients for adverse events.

Name of Person Competing form_____

Did the subject have any adverse events in the last 30 days? Yes ☐ No ☐
If yes, please describe nature and grade of AE (Note*: If an SAE occurs in this period, report the event as required in Appendix D):

_____
_____
_____
_____
_____
_____

Was the subject removed from the study by the PI? Yes ☐ No ☐

Did the subject withdraw from the study? Yes ☐ No ☐

Did the subject complete the full course of SBRT and take the study drug? Yes ☐ No ☐

Appendix H – Off-Study Form

Study Number: 62220 PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator:, Michael Farris M.D. Date: __ __/__ __/__ __

Off Study:

Off Study Date: __/__/____

Off Study Reason:

- ☐ Adverse Event/Side Effects/Complications
- ☐ Death (if death fill out Survival Form)
- ☐ Enrolling Physician Decision
- ☐ Patient lost to follow-up;
  Date of last contact (mm/dd/yy): __ __/__ __/__ __
- ☐ Patient refused follow-up
- ☐ Protocol-defined follow-up completed
- ☐ Other

Explain:
_____
_____
_____

Appendix I – Treatment Response Evaluation

Study Number: 62220 PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator: Michael Farris, M.D. Date: __ __/__ __/__ __

Study Visit:

☐ After First Progression
☐ Follow-Up
☐ Other visit: (please specify) _____

Date of Scan: ___ ___ /___ ___ /___ ___

Imaging Modality: ☐ CT ☐ PET/CT ☐ MRI ☐ Other_____

Overall Response this Visit

☐ Complete Response (CR)
☐ Partial Response (PR)
☐ Progressive Disease (PD): Date of progression ___ ___ /___ ___ /___ ___
☐ Stable Disease
☐ NE

Treating Physician Signature: _____ Date: ___ ___ /___ ___ /___ ___

PI Signature: _____ Date: ___ ___ /___ ___ /___ ___

Appendix J Off Treatment Form

Study Number: 62220 **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Michael Farris, MD **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Instructions:

Off Treatment:

Off Treatment Date: __/__/____

Off Treatment Reason:

- ☐ Adverse Event/Side Effects/Complications
- ☐ Alternative Therapy
- ☐ Cytogenetic resistance
- ☐ Death on Study
- ☐ Disease progression before active treatment
- ☐ Disease progression, relapse before active treatment
- ☐ Enrolling Physician Decision
- ☐ Lost to followup
- ☐ No treatment, per protocol criteria
- ☐ Patient off treatment for other complicating disease
- ☐ Patient withdrawal or refusal after beginning protocol therapy
- ☐ Patient withdrawal or refusal prior to beginning protocol therapy
- ☐ Treatment completed per protocol criteria
- ☐ Other

Explain:
_____
_____
_____
_____

Appendix K-Withdrawal of consent for the intervention and medical record use

Study Number: 62220 **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Michael Farris, MD **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Instructions:

☐ I withdraw consent for further study intervention/treatment. ☐Yes ☐No Initials: _____

☐ I withdraw from further research activities (surveys, questionnaires, research assessments and other non-invasive research activities). ☐Yes ☐No Initials: _____

☐ I withdraw my consent to allow the further collection of research-related information from my medical record to be used in this research project. ☐Yes ☐No Initials: _____

Specimen collection/use withdrawal (no research specimen collection, skip section)

I withdraw my consent for any use of my specimen for this current research.

☐Yes ☐ No Initials: _____

I withdraw my consent for any use of my specimen for future research.

☐Yes ☐No Initials: _____

I acknowledge that any data or deidentified materials that have already been created from my specimen may still be used for research. Initials: _____

Patient signature: _____ Date (mm/dd/yy): ___ ___/___ ___/___ ___

Investigator signature: _____ Date(mm/dd/yy): ___ ___/___ ___/___ ___

Comments:
_____
_____
_____
_____
_____
_____

Appendix L-Vitals Form

Only at pre treatment and at each follow-up, not during treatment

Study Number: 62220 **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Michael Farris, MD **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Instructions: Fill this form out at the baseline/pre-study visit, each cycle and

Study Visit

- ☐ Baseline
- ☐ Visit ____
- ☐ Other visit: (please specify) _____

1. **Height (inches):** ___ ___
2. **Weight (lbs):** ___ ___ ___
3. **BSA:** (Calculated using Mosteller's equation)
4. **BMI:** (Calculated)
5. **Temperature (°F):** ___ ___ ___.___
   a. Route: _____
6. **Blood Pressure**
   a. Systolic (mmHg): ___ ___ ___
   b. Diastolic (mmHg): ___ ___ ___
7. **Heart Rate (beats per minute):** ___ ___ ___
8. **ECOG Status:**

☐ 0: Fully active, able to carry on all pre-disease performance without restriction.

☐ 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

☐ 2: 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: Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.

☐ 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

☐ 5: Dead

9. **Respiration Rate**_____

Appendix M-Con-med PRN Form

Only prior to treatment

Study Number: 62220 **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Michael Farris **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Instructions: Fill this form out to capture Medications

1. Concurrent medications

a. List all prescription and over-the-counter medications. For PRN, circle "yes" or "no."

Medication Name	Is it PRN?	Medication Name	Is it PRN?
1.	yes no	11.	yes no
2.	yes no	12.	yes no
3.	yes no	13.	yes no
4.	yes no	14.	yes no
5.	yes no	15.	yes no
6.	yes no	16.	yes no
7.	yes no	17.	yes no
8.	yes no	18.	yes no
9.	yes no	19.	yes no
10.	yes no	20.	yes no

Appendix N: Mandatory Target Coverage/Dose Constraint Compliance Confirmation.

Study Number: 62220 **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Michael Farris, MD **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Structure	Protocol Coverage/Constraint	Coverage/Constraint Met (yes/no)	Plan value
PTV_5750	95% receives at least 54.63 Gy		
PTV_5750	99% of PTV_5750 receives at least 51.75 Gy		
Spinal Cord	D0.03 cm^3 < 45 Gy		
Esophagus	D0.03 cm^3 < 73.5 Gy		
Lungs-GTV	V20 Gy ≤ 35%		
Proximal Bronchial Tree	D0.03 cm^3 < 73.5 Gy		
Heart	D100% < 30 Gy		
Stomach	D0.03cm^3 < 60 Gy		
Liver	Mean dose < 30 Gy		
Liver	at least 700 cm^3 of normal liver to < 15 Gy		
Maximum dose PTV_7000	< 80.50 Gy		
Maximum dose PTV_6750	< 77.63 Gy		

Treating Radiation Oncologist Signature: _____

Date: _____

Appendix O: Pre-Toxicity

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __
PI:, Michael Farris, MD. **Study Number:** 62220

Evaluation Date	**Onset Date**	**Toxicity Code**	**Grade** (1-5) per CTC	**Lab value**	**UOM**	**Lower Limit Normal**	**Upper Limit Normal**	**Related to Disease** N=No Y=Yes	**Symptom Description**	**Comments**
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
_ _/_ _/_ _	_ _/_ _/_ _									
	CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf									
	Version 1/10/18									

Appendix P: Pattern of Progression Collection

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

	Yes	No
Local Progression		
Regional Progression		
Distant Progression		

Pattern of Failure:

☐ Isolated local Progression: (Local Progression = Y; Regional Progression = N; Distant Progression = N)
☐ Isolated Regional Progression: (Local Progression = N; Regional Progression = Y; Distant Progression = N)
☐ Isolated Distant Progression: (Local Progression = N; Regional Progression = N; Distant Progression = Y)
☐ Locoregional Progression: (Local Progression = Y; Regional Progression = Y; Distant Progression = N)
☐ Local and Distant Response: (Local Progression = Y; Regional Progression = N; Distant Progression = Y)
☐ Regional and Distant Progression: (Local Progression = N; Regional Progression = Y; Distant Progression = Y)
☐ Local, Regional, and Distant Progression: (Local Progression = Y; Regional Progression = Y; Distant Progression = Y)

Treating Radiation Oncologist Signature: _____

Date: _____

Appendix Q: RECIST

TUMOR RESPONSE WORKSHEET (RECIST v1.1) **WFBCCC #** _____

Patient Name: _____ **Patient MRN:** _____

Has patient had localized RT @ baseline? □ No □ Yes If yes, which lesions? : _____

Target Lesions

	Lesion	Site	Imaging *(ie,CT, MRI)*	Baseline Date: *(Se, Im)*	Cycle_____ Date: *(Se, Im)*	Cycle_____ Date: *(Se, Im)*	Cycle_____ Date: *(Se, Im)*	Cycle_____ Date: *(Se, Im)*
TARGET Lesions	01			mm	mm	mm	mm	mm
	02			mm	mm	mm	mm	mm
	03			mm	mm	mm	mm	mm
	04			mm	mm	mm	mm	mm
	05			mm	mm	mm	mm	mm
	Sum of Diameters			mm	mm	mm	mm	mm
	% Change (% Δ) from Baseline or Nadir* & absolute value (AbV)			NA / NA	% Δ / AbV			
	Target Lesion Response			**N/A**				

Non-Target Lesions

	Lesion	Site	Imaging	Baseline	Cycle_____	Cycle_____	Cycle_____	Cycle_____
NON-TARGET Lesions	01							
	02							
	03							
	04							
	05							
	Non-Target Lesion Response			**N/A**				

New Lesions

New	1			**N/A**				
	2			**N/A**				
	3			**N/A**				

Overall Tumor Response		Cycle_____	Cycle_____	Cycle_____	Cycle_____
Radiologist Signature/Date:					
Treating Physician Signature/Date:					
PI Signature:					

***Terms & Calculations**

Baseline: *The set of data collected prior to randomization*

$$\frac{\text{Current SLD} - \text{Baseline or Nadir SLD}}{\text{Baseline or Nadir SLD}} \times 100\%$$