07-RAD-01-UK/P4:
Stereotactic Body Radiation Therapy for Post-chemoradiation Residual Disease in Stage II/III Non-small Cell Lung Cancer

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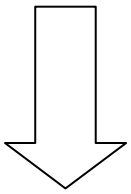
SCHEMA

Eligible patients with Stage II/III NSCLC[#]

Completed Definitive Chemoradiation to min 5940 cGy*

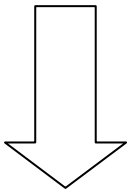


CT scan or PET/CT 21-30 days post chemo RT

SBRT boost

Peripheral Tumors: 1000cGy X 2 to residual primary mass

Medial Tumors: 650cGy x 3 to residual primary mass



Routine Followup with CT chest and/or chest x-ray at ~3 months

PET/CT if suspected recurrence/metastasis clinically indicated

Sample size: 42 patients

***choice of chemotherapy at the discretion of treating medical oncologist, standard RT to dose at discretion of treating radiation oncologist**

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1.0 Background

Lung cancer represents one of the most challenging malignancies to manage. Cure rates have only marginally improved in the last 20 years. It is the most commonly fatal cancer in both men and women with overall 5 year survivals of 15%. Lung cancer kills more Americans than the next three most common malignancies combined.

Most non small cell lung cancer (NSCLC) presents at advanced stages. Only approximately 25% present with stage I/II disease, 40% with stage III and 35% pts present with stage IV. (1) The optimal treatment of stage II/III NSCLC is complex. For those patients who are surgical candidates and a complete resection is technically feasible, radical surgery remains the standard of care. Traditionally, those patients with multiple N2 nodal levels or T4 disease are considered inoperable. Given that the average age of patients diagnosed with NSCLC is in their mid-60's and usually have long smoking histories, many patients are medically inoperable.

1.1 Current Radiation Therapy for NSCLC

In the early 1980's, the CALGB completed a protocol for the treatment of stage III NSCLC that employed chemotherapy first, which they called "proto-adjuvant." They based the treatment on two cycles of cis-platinum and 4 weekly doses of vinorelbine – no alkylating agents. This landmark, paradigm shifting trial widely known as the Dillman trial (2) altered the course of non-surgical therapy by demonstrating that treatment regimens including chemotherapy were significantly better than radiotherapy alone. The median survival was nearly 14 months with the chemotherapy and only in the range of 9 months with radiotherapy alone to 60 Gy (2). The study was replicated by an Intergroup effort (3). The theory and apparent fact was that these tactics reduced distant metastasis, but did not alter local control and failure in the chest remains a significant problem in the management of NSCLC(3).

1.2 Radiation Therapy – What dose to use.

The optimal doses of radiation therapy are undefined but the high local failure rates (vary between 20 and 50%) would suggest that higher doses of radiation therapy could potentially improve outcome in these patients. Local failure results in significant morbidity and theoretically could act as a nidus for metastasis. While various dose

escalation trials are beginning to suggest a benefit to increasing the RT dose to obtain better local control, thus far no prospective trials have shown benefit to escalation of the most common RT dose, 60Gy, established in the Dillman trial (2), probably due to the limitations of dose imposed by patient anatomy. Tolerance of organs such as esophagus, spinal cord and heart are important, but the lungs themselves are of primary importance with a dose limiting toxicity being pneumonitis. Pneumonitis has a dose volume relationship which is not clearly definable due to the variability in lung physiology (e.g. emphysematous bullae, upper vs. lower lobes) and attempts to develop predictive models for pneumonitis are fraught with difficulties. We often examine the so-called V_{20} value, basically the volume of lung encompassed by the 20Gy isodose line in patients receiving standard fractionation (180-200 cGy/fraction)(4).

Most studies of dose escalation have included patients with high stage disease. Due to the high risk of local recurrence, several studies have undertaken dose escalation using different strategies to maintain toxicity at acceptable levels. Most strategies try to equate dose/fractionation schemes by employing linear quadratic normalization (biological effective doses (BED)). This is somewhat difficult since it does not take into account the lengths of treatment time in hypofractionated schemes. Applying the linear quadratic equation ($BED=nd(1+d/\alpha/\beta)$ where n=the number of fractions, d=the dose/fraction and α/β ratio of 10 for acute reacting tissue and tumor cells), 70 Gy will only have a BED of approximately 84 Gy. Using a mathematical model, Martel et al. (5) predicted that for NSCLC patients, the dose to achieve significant probability of tumor control may be at least 84 Gy (100 Gy BED at 200 cGy/fraction) for longer (>30 months) local progression-free survival. RTOG 9311 was a multi-institutional trial in which a total of 179 patients were enrolled in a Phase I-II three-dimensional radiotherapy dose-escalation fashion (6). Patients were stratified at escalating radiation dose levels depending on the percentage of the total lung volume that received >20 Gy with the treatment plan (V(20)). Patients with a V(20) <25% (Group 1) received 70.9 Gy in 33 fractions, 77.4 Gy in 36 fractions, 83.8 Gy in 39 fractions, and 90.3 Gy in 42 fractions, successively. Patients with a V(20) of 25-36% (Group 2) received doses of 70.9 Gy and 77.4 Gy, successively. V(20) has been used as an indicator of risk for pneumonitis (see below). The radiation dose was safely escalated using three-dimensional conformal

techniques to 83.8 Gy for patients with V(20) values of <25% (Group 1) and to 77.4 Gy for patients with V(20) values between 25% and 36% (Group 2), using fraction sizes of 2.15 Gy. The 90.3-Gy dose level was too toxic, resulting in dose-related deaths in 2 patients. Elective nodal failure occurred in <10% of patients. This study showed that for patients receiving RT alone or radiation following induction chemotherapy, doses of 83.8 Gy using 3-dimensional conformal RT techniques were tolerable, with excess mortality observed at 90.3 Gy. On a theoretical basis when converted to BED, this represents a borderline dose of RT to gain a high probability of local control, especially considering that patients entered on these trials were highly selected.

Since the advent of concurrent chemotherapy and 3-dimensional conformal RT the maximum tolerated dose of radiation has been reduced, and current indications suggest that the maximum tolerated dose in this setting is in the range of 70 to 74 Gy (4,6). Nonetheless, it has not been prospectively demonstrated that dose escalation has produced superior outcomes and careful planning is needed to avoid toxicities. Willner et al. (7) retrospectively examined the influence of total dose and tumor volumes on local control and survival in primary radiotherapy of non-small cell lung cancer. They concluded that there is a dose effect on local control and survival with doses of at least 70 Gy (standard fractionation) and that tumors with volumes >/= 100cc may require higher doses.

It thus stands to reason that improved local control may result from higher local radiation doses and hypofractionated stereotactically delivered radiation therapy is proving effective at long term control of early stage NSCL (8-10). In an analysis of various hypofractionated stereotactic-delivered radiation schemes, Wulf et al. (11) reports that for an optimal control of a stage one lung cancer, a BED of >100Gy is required in agreement with the Martel analysis. Moreover as tumors get larger, with greater central hypoxia and numbers of cancer cells to kill, the amount of radiation needed to sterilize a given cancer should theoretically be higher.

1.3 Hypothesis

In light of the above information, it becomes apparent that local control for NSCLC remains a significant problem. Conventional radiation therapy techniques have limitations for the dose that can be delivered to a chest tumor mass due to the adjacent

dose limiting organs. Mounting evidence supports the use of hypofractionated stereotactically delivered radiation therapy to control lung cancer with acceptable toxicity profiles.

Thus we propose to increase the doses of radiation to residual masses of NSCL to a BED >100 Gy by the addition of 2-3 fractions of stereotactically delivered boost radiation therapy to residual disease post-conventional chemoradiation to at least 59.4 Gy in 180 cGy fractions. Using the linear quadratic equation to model doses of radiation therapy, 59.4 Gy would have a BED of approximately 70 Gy. Single fraction stereotactic body radiation therapy (SBRT) of 10 Gy would have a BED of approximately 20 Gy. Thus the addition of two fractions of 10Gy of SBRT to limited volumes of PET residual disease would theoretically result in higher degrees of local control of lung cancer masses, achieving a minimum cumulative BED of approximately 110Gy-equivalent.

2.0 Objectives

Primary

1. to determine the toxicity of the SBRT boost dose by estimating the proportion of subjects enrolled who develop pneumonitis

Secondary

1. to determine response rates of the residual primary tumor following SBRT boost

3.0 Eligibility

1. Histological confirmation of non-small cell lung cancer (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchoalveolar cell carcinoma, or non-small cell carcinoma NOS) by either biopsy or cytology.
2. Clinical AJCC stage IIA (T1N1M0), IIB (T2,N1M0, T3,N0,M0) or IIIA (T1-3, N1-2,M0)/selected IIIB. In all cases, patients may be included at the discretion of the treating radiation oncologist if it will be likely the disease can be encompassed by the stereotactic boost.

3. Patients with non-bulky (<2.0-3.0 cm) hilar or mediastinal lymphadenopathy determined by pre-treatment CT scan, PET or mediastinoscopy
4. Must have completed a standard course of chemoradiation in accordance with NCCN Guidelines
5. One month following definitive chemoradiation, CT or PET-CT revealing limited volume residual disease within the site of primary tumour mass (post-chemo/RT mass </= 7.0 cm). Patients with a CR and no obvious target are not eligible.
6. must be able to fit into the Civco stereotactic immobilization device.
7. Patients must be ≥ 18 years of age.
8. The patient's ECOG performance status must be 0-2.
9. Women of childbearing potential and male participants must use an effective contraceptive method.
10. Patients must sign a study-specific consent form.

3.1 Exclusion Criteria

1. Any other active cancer.

2. No prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or other cancer from which the patient has been disease-free for 5 years.

3. Patients with other systemic illness, or have not recovered adequately from their primary treatment or who have evidence of progression of their lung cancer prior to therapy that, in the investigators opinions, would preclude their inclusion

4. Plans for the patient to receive other concomitant antineoplastic therapy while on this protocol, except at disease progression. Patients may be allowed to use bisphosphonates for hypercalcemia.

5. Pregnant or lactating women

4.0 PRETREATMENT EVALUATIONS

(All lab tests and radiographic studies should be done at approximately 3 weeks post chemoradiation)

4.1 Complete history, physical examination, and evaluation of Zubrod Performance Status.

4.2 Pathological *(biopsy)* or cytologically proven non-small cell lung cancer.

4.3 Postchemoradiation CT with contrast or PET/CT (preferred)of chest and upper abdomen to include the liver and adrenals; baseline brain MRI or CT scan.

4.4 Bone scan, only if the patient has bone pain and/or and elevated alkaline phosphatase.

4.5 Pulmonary function tests - including DLCO and FEV1

4.6 CBC; serum chemistry tests to include alkaline phosphatase, glucose, creatinine, electrolytes, AST *(SGOT*), and total bilirubin,

5.0 Treatment Plan

5.1 Radiation Therapy - Primary chemoradiation

All initial chemoradiation must be planned and delivered with CT-based 3-d planning. Like any radiation oncology boost therapy, as part of the pre-SBRT boost therapy assessment, complete and detailed dosimetry from the primary chemoradiation must be made available. The purpose is to ensure dose constraints on normal tissues are respected. The recommended radiation plan format is elucidated below and follows standard radiation oncology practice. Detailed chemoradiation plan must be reviewed during planning of the SBRT boost.

Volume and ICRU Reference Point Definitions

The definitions of volumes will be in accordance with the 1993 ICRU Report #50:45 Prescribing, Recording and Reporting Photon Beam Therapy.

5.1.1 *Gross Tumor Volume (GTV)* is defined by the physician as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor *(GTV-P)* and abnormally enlarged regional lymph nodes > 1.0 cm *(short axis*

measurement) (GTV-N).46,47,48,49 These volume*(s)* may be disjointed. Note ICRU Report #50 also defines a clinical target volume *(CTV)* which may include the area of subclinical involvement around the GTV.

5.1.2 *Planning Target Volume (PTV)* will provide margin around the GTV to compensate for variabilities in daily treatment setup and internal CTV motion due to breathing or motion during treatment. The PTV for which dose escalation will be occurring must include the entire GTV plus a minimum 3D margin of 10mm. More margin may be necessary if the tumor movement is increased because of physiologic movement which should be checked, in most cases by fluoroscopy.

5.1.3 The *ICRU Reference Point* is to be located in the central part of the PTV. Typically this point should be located on the beam axis or at the intersection of the beam axes *(isocenter)*.

5.2 3D Planning

5.2.1 *Planning Volume (PTV)* - The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures.

5.2.2 *Dose Specification* : Radiation therapy: Patients will be have CT planning designed to encompass all known disease. While mediastinal coverage is recommended, fields will be at discretion of the treating physician in accordance with standard therapy. Recommended plans will give patients initial fields using AP:PA plans to approximately 3960cGy, followed by off cord boost to a final dose of 5940 cGy or higher. Alternative plans respecting dose limiting organ tolerances would be acceptable. All patients will be treated at 180-200 cGy/day on minimum 6 mV linear accelerators or higher energies. All attempts are to be made to cover contoured GTV's by minimum a 95% of prescribed dose.

5.2.3 All patients will have 3-d planning with attention to dose limiting organs. Complete dose volume histograms must be provided and include (at a minimum) spinal cord, esophagus, brachial plexus as appropriate, combined lung volumes (to estimate V_{20}), heart, gross tumour volume (may have separate GTV's for primary tumour and nodes), planning target volume (GTV+ 1.0-2.0 cm at the discretion of the treating physician)

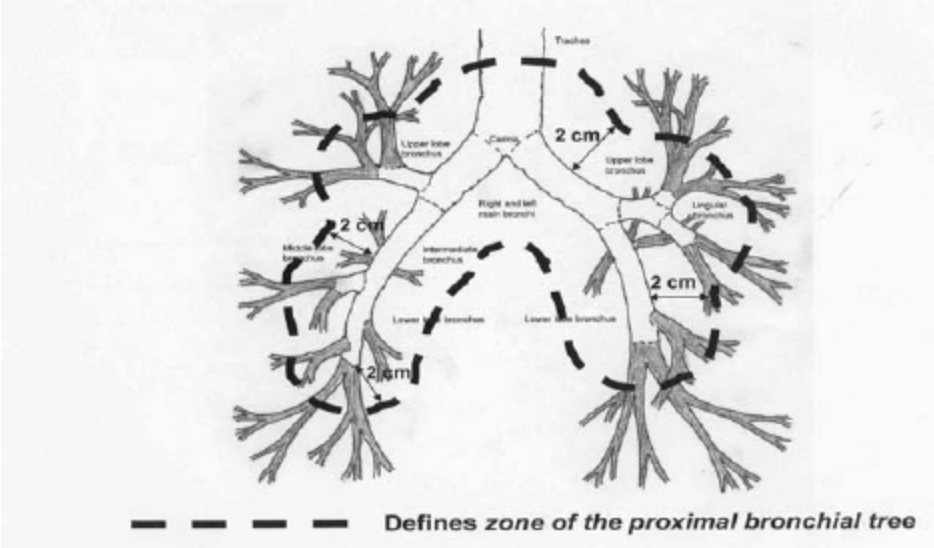
5.3 Normal Tissue Volume and Tolerances

5.3.1 The tolerance of the lungs is related to the volume of the organ*(s)* irradiated. Data from the Washington University (12) reported that high-grade acute pneumonitis did not occur when the V20 was </= approximately 30%. The incidence and the grade or severity of pneumonitis was clearly related to the V20. Total lung volume is defined as the lung volume of both lungs minus the PTV. In the Washington University data, maximum dose *(with conventional fractionation)* was not related to acute pneumonitis. For this protocol all eligible patients the goal is to attempt to have the V20 < 30% although higher percentages are acceptable at the discretion of the treating physician. It is expected that the dose to the lungs will be the primary dose-limiting structure. Every effort to keep the total lung dose to a minimum should be performed. Since most lung tumors are localized to one lung, efforts to keep the contralateral lung at a minimum should also be performed. The patient's overall lung function is evaluated by the FEV1 and DLCO should also be evaluated in determining an individual's lung function reserve and thus the ability to radiate.

5.3.2 When planning the beam arrangement to the PTV, the heart, esophagus, and spinal cord should be out of the field to the extent possible. The dose per fraction to the lungs, heart, esophagus, and spinal cord should be maintained at 2 Gy or less per fraction to the extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangements should be used.

5.3.3 Tumors will be classified as being either medial or peripheral based on the planning CT scan obtained for treatment planning. This definition will be based on the same designation for RTOG 0813: including any tumor within the zone of the proximal bronchial tree", which is a 2 cm radius around the main tracheo-bronchial tree: trachea;

left and right main stem bronchi; right upper, middle, and lower lobe bronchus; and left upper, lingular, and lower lobe bronchus. This can be represented in the figure below:



5.3.4. *General considerations for organ tolerances*

ORGAN	*VOLUME*	*TOLERANCE DOSE TD 5/5*	*END POINT*
Lung	Ipsilateral whole lung Contralateral lung *(only if necessary)*	25 Gy 20 Gy	Clinical Pneumonitis
Esophagus	1/3 2/3 3/3	65 Gy 58 Gy 55 Gy	Clinical Stricture and Perforation
Brachial Plexus	point dose	60 Gy	Clinically Manifested Nerve Damage
Spinal Cord	5 cm 10 cm 20 cm	50 Gy 50 Gy 47 Gy	Myelitis Myelitis Myelitis
Heart	1/3 2/3 3/3	66 Gy 50 Gy 40 Gy	Clinical Pericarditis Clinical Pericarditis Clinical Pericarditis
Liver	1/2 2/2	35 Gy 30 Gy	Clinical Hepatitis Clinical Hepatitis

6.0 Stereotactic Dose Specifications

6.1.1 Stereotactic Targeting and Treatment

Targeting, planning, and directing of therapy will be accomplished using beams of radiation along any trajectory in 3-D space focusing on the target, which will be of known 3-D coordinates. A fixed 3-D coordinate system defined by fiducials will be

used. This coordinate system will be directly related to the radiation producing device in a reproducible and secure fashion and will be used to define the position of the target(s) within the patient. Each treatment is designed to direct the radiation toward an isocentre according to known 3-D coordinates determined during treatment planning. In this study, the fiducials will be radio-opaque markers placed at known locations within a frame adjacent to the patient.

6.1.2 Patient Positioning

The patient's position must be accurately reproducible from treatment to treatment. Uncomfortable positions should be avoided to prevent movement during treatment. The immobilization system used in this trial will be a stereotactic frame that surrounds the patient on three sides and references the stereotactic coordinate system. Within this frame, the patient will be positioned on large, rigid pillows that conform to patients' external contours.

6.1.3 Inhibition of Effects of Internal Organ Motion

Reliable abdominal compression (the effectiveness of which will be checked via fluoroscopy) will be used to minimize the effect of internal organ motion (i.e. breathing, etc.) on target positioning and reproducibility. This will be performed such that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e. <5%).

6.1.4 Localization

Immediately before each treatment, isocentre port localization films (anterior/posterior and lateral) will be obtained on the treatment unit to ensure proper alignment of the isocentre.

6.2 Treatment Planning/Target Volumes

6.2.1 Image Acquisition

Treatment planning will utilize Computed Tomography (CT). The planning CT will be obtained with the patient in the body frame to allow simultaneous view of the patient's anatomy and the fiducial system. To better delineate between tumor and adjacent vessels or atelectasis, IV contrast will be used during planning CT acquisition unless

contraindicated (i.e. the patient has poor renal function or allergy to contrast media). 3.0mm thick axial slices will be obtained with the gantry at 0 degrees. An appropriately trained physician will outline the target lesion and designate it as the Gross Tumor Volume (GTV). This will be accomplished using pulmonary windows or soft tissue windows with contrast. Only abnormal density on CT consistent with gross tumor will be included in the GTV, with no enlargement of the target for "margin" to account for presumed microscopic extension (i.e. GTV and Clinical Target Volume (CTV) are to be identical). The Planning Treatment Volume (PTV) will consist of the GTV with an additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal (cranio-caudal) plane.

6.2.2 Dosimetry

Each case will have three-dimensional non-coplanar (and occasionally coplanar) beam arrangements custom designed to deliver highly conformal prescription dose distributions per the UK institutional standard. 7 or more beams (minimum 7 beams) with roughly equal weighting will be used, with more beams being used for larger lesions. The isocentre will be defined as the common point of gantry and couch rotation for the treatment unit. The isocentre in stereotactic coordinates will be determined from system fiducials and translated to the treatment record. The field aperture size and shape will correspond nearly identically to the projection of the PTV along a beam's eye view, except when observing the minimum field dimension of 3.5 cm in the treatment of small lesions. Prescription lines covering the PTV will generally be the 80% line. Hotspots will be manipulated to occur within the target and not within adjacent normal tissue.

The prescription dose of **with inhomogeneity correction** to the 80% isodose line times 2 fractions will be delivered to the margin of the PTV covering a minimum of 95% of the PTV. For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body, including lung, will be assumed to have unit (water) density (no correction for tissue heterogeneity).

6.2.3 Dose and Fractionation

The dose and fractionation scheme utilized will be based on the location of the patient's residual disease. For patients with:

Peripheral Tumors: Treatment will consist of 2 fractions of radiation, with a minimum of 40 hours separating each fraction. Two fractions of 10 Gy with inhomogeneity

correction will be delivered to the prescription line at the edge of the PTV for a total of 20 Gy. This will yield a total BED of 110 Gy.

Medial Tumors: Treatment will consist of 3 fractions of radiation, with a minimum of 40 hours separating each fraction. Three fractions of 6.5 Gy with inhomogeneity correction will be delivered to the prescription line at the edge of the PTV for a total of 19.5 Gy. This will yield a total BED 102.2 Gy.

6.3 Technical Factors

6.3.1 Physical Factors

Treatment radiation will consist of photon (x-ray) beams produced by linear accelerators. 6MV energies will be used under most circumstances, with energies of 15-16MV used only in a limited number (maximum of 2) beams that must travel a cumulative distance of more than 10cm through soft tissue (not lung) to reach the isocentre.

6.3.2 Minimum Field Aperture (Field Size) Dimension

A minimum field dimension of 3.5 cm is required for any field used for treatment delivery. If the minimum field exceeds the technical requirements for small lesions (<2.5 cm axial GTV dimensions or < 1.5 cm cranio-caudal GTV dimension), the prescription dose is still prescribed to the edge of the defined PTV.

6.3.3 Critical Organ Dose-Volume Limits

All critical organ dose volume limits must take into account the initial dose delivered during chemoradiation. All initial chemoradiation must have been planned with 3-d CT planning. Typically, chemoradiation is given to 59.4-66 Gy and organs such as spinal cord and esophagus reach significant doses of radiation. Commonly the tolerance of spinal cord is considered to be 50 Gy (180-200cGy/fraction). Prior to boost stereotactic radiotherapy, all previous radiation plans must be reviewed with dose-volume histogram analysis to determine critical organ doses. In considering the stereotactic plan, if a minimum of 7 beams are used, each is contributing only approximately 140cgy of the

total prescribed dose. If any beam traverses a critical organ, the dose delivered will be considered and a maximum point dose to any organ considered.

Table 5.3.3 lists maximum dose limits to a point or volume within several critical organs to be considered when standard (180-200cGy) fractionation is given. Size of fraction delivered to each organ during stereotactic treatments must be considered, since not all beams will either enter or exit through a structure. Every attempt to keep entrance and exit doses of each fraction of SBRT traversing a critical organ to as close to a **maximum** of 200 cGy as possible to help estimate critical structure doses. All critical organs will be contoured and doses calculated in a standard fashion. Composite plans incorporating the initial radiotherapy and the stereotactic boost must be created to accurately assess tolerances.

7.0 Patient assessments

Assessments	**Pre-Study entry[a]**	**1mo[f] Post SBRT**	**3mo[f] Post SBRT**	**Follow Up[g]**	**As Indicated**
History/physical	X	X	X	X	
Pregnancy test[b]	X				
Toxicity eval[c]		X	X	X[c]	
PET-CT	X				X
CXray/CT		X[d]	X[d]	X[d]	X
PFT's[e]	X	X	X		X
CMP/CBC	X				

a. Pre-study evaluations typically done 3-4 weeks after completion of primary chemoradiation. CT simm typically done approximately 1 week following study entry, with SBRT delivery done approximately 1 week after CT simm.
b. Pregnancy test if indicated and not done prior to chemo-RT
c. Toxicity evaluation through 6 months
d. Ideally alternate CT/Chest rays on routine visits post-treatment
e. Pulmonary function tests to include spirometry, lung volumes and diffusion capacity
f. Approximate timeframe
g. Routine follow-up visits scheduled as per institutional standard (strict FU scheduled not required).

8.0. Criteria for Evaluation

8.1. Response determination – This protocol will use a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors

(RECIST) Committee (JNCI 92(3): 205-216, 2000). Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as defined below.

8.2 Baseline documentation of Target and Non-target lesions

The longest diameter (LD) for the target lesion will be calculated from the treatment planning CT scan using pulmonary windowing and reported as the baseline LD. The baseline LD will be used as the reference by which to characterize the objective tumor response. For follow-up assessment, diagnostic CT scans using lung windows are the preferred modality. Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult e.g. patchy consolidation.

All other lesions which appear or enlarge after treatment e.g. regional lymph nodes and distant metastses should be identified as non-target lesions and should be recorded at the time of their appearance/suspicious enlargement. Patients who have suspicious CT scans may have PET/CT to assess local failure/distant metastasis as per clinical judgment.

8.2.1. Post treatment followup **-** Followup evaluation will be performed approximately 30 days after completion of all protocol treatment to assess toxicity and tumor response. Follow-up for evaluation of toxicity will continue for 6 months following SBRT delivery. Additional follow-up for local control and survival will continue until death or study withdrawal.

8.3 Response Criteria

8***.3.1 Evaluation of Target Lesions***

Complete Response (CR) – disappearance of the target lesion, ideally on PET/CT although assessment by CT is acceptable.

Partial Response (PR) – At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD. Ideally this determination will be on CT evaluation.

Stable Disease (SD) – Neither sufficient shrinkage to qualify for CR/PR as above, nor sufficient increase to qualify for LE as below, taking as reference the smallest LD since treatment started.

Local Enlargement (LE) – At least a 20% increase in the LD of the target lesion

with respect to the LD based on followup

Local Failure (LF) – refers to the primary treated tumor after protocol treatment and corresponds to meeting both of the following criteria: 1. increase in tumor dimension of 20% as defined for the above LE; 2. The measurable tumor with criteria meeting LE should be avid on PET/CT with uptake of similar intensity as the pretreatment staging PET/CT

9.0 Data and Safety Monitoring Plan

The study principal investigator has primary responsibility for monitoring the safe conduct of this study. Additionally, the Markey Cancer Center Quality Assurance Committee (QAC) provides oversight and monitoring of all cancer clinical trials. The Committee is responsible for reviewing data to identify patient safety and protocol compliance issues. The Markey Protocol Review Committee (PRC) assigns studies a QAC review timeline based on the phase, origination of the study and known safety issues.

The members of the QAC consist of Medical Oncologists, a Pharmacist, a Nurse Manager, a Certified Clinical Research Professional and a Reporter. These members were selected based on their experience, reputation for objectivity and knowledge of clinical trial methodology. All members should view themselves as representing the interest of the study patients and not that of the institution.

At each meeting, representatives for each study on the agenda present their study data to the QAC for review. The Principal Investigator, CRA and/or Study Coordinator present the following data for active patients: treatment issues, serious adverse events (SAEs) per FDA's definition, dose levels, dose modifications, and responses as applicable.

The QAC will reviews protocols to assure the following:

- progress of the trial and safety of participants,
- compliance with requirements regarding the reporting of severe adverse events,
- that any action resulting in a temporary or permanent suspension of this NIH-funded clinical trial is reported to the responsible NIH grant program director, and

- data accuracy and protocol compliance.

The QAC, the Protocol Review Committee (PRC), the responsible disease-specific Clinical Care and Research Team (CCART) and/or the UK/VA IRB are empowered to immediately suspend accrual to any study under its purview for any of the following:

- Failure to comply with AE/SAE reporting requirements,
- poor study enrollment,
- protocol violations, or
- issues related to patient safety.

10.0 Statistical Considerations

10.1. Sample size justification :

In this pilot protocol, it is anticipated that 37 patients will be enrolled to receive boost therapy. This number of patients will provide a 10% level of precision (half-width of a 90% confidence interval) for the true (unknown) proportion of subjects that will experience toxicity-limiting pneumonitis. The investigators believe this proportion will be no greater than 20% and have used this number in the sample size justification based on the 90% confidence interval width.

10.2 Stopping rules for severe pneumonitis:

We anticipate that pneumonitis may be the most common radiation-related side effect, and patients will be closely monitored for development of severe pneumonitis in this study. An historical rate of severe pneumonitis rate has been documented to be as high as 15% but varies depending on the volume of lung being irradiated (12). Treatment of most stage III lung cancers carry risks in the 15% and higher range due to volumes of lung irradiated. As such, the protocol will be stopped if sufficient evidence exists suggesting that, among patients receiving therapy, the true incidence of severe pneumonitis exceeds 15%. Sufficient evidence will be statistically defined in the form of an estimate for the severe pneumonitis rate (binomial proportion) whose lower 90% confidence limit exceeds 15%, and these estimates will be made after every 5th enrolled patient to the study. Operationally, any of the following observed ratios (# experiencing severe

pneumonitis of total number observed) would lead to exceeding such a limit: 3 or more of the first 5; 4 or more of the first 10; 5 or more of the first 15; and 6 or more of the first 20.

If the true probability of severe pneumonitis incidence is 10%, the probability of stopping the study under these rules is less than 1% after enrollment of 5 patients on the study, <1.3% after enrollment of the first 10, and roughly <1% after enrollment of 20 patients on the study. If the true probability is 20%, then the probability of stopping after 5, 10, and 20 patients is 6%, 12% and 19%, respectively. If the true probability is 40%, the probability of stopping after 5, 10, and 20 patients is approximately 32%, 62%, and 88%, respectively.

11. Reporting Toxicity

11.0 All patients will be assessable for toxicity, and those with measurable disease will be assessable for response. All grade 4 or grade 5 toxicities that are attributable to radiation therapy will be reported to the DSMB and Institutional Review Board within 24 hours of discovery. The boost therapy is given in a two to three day period, and definitions of acute vs. late effects are used as below. Monitoring of late effects of radiation therapy (most commonly pneumonitis) will continue for 6 months following completion of the boost therapy.

11.1 *Acute Radiation Toxicity Monitoring*: Acute (≤ 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).

11.2 *Late Radiation Toxicity Monitoring*: Late (> 90 days from RT start) side effects will be documented using the NCI Common Toxicity Criteria version 3.0.

11.3 Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment, will be reported directly to the DSMB and IRB

12.0 Criteria for Study Withdrawal

Patients will be removed from the study for the following:

1. Noncompliance with protocol requirements.

2. Patient withdrawal of consent.

13.0 References.

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