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Current version: 5/21/2015

Title of Protocol:
Definitive Re-Irradiation with Proton Beam Radiotherapy for Patients with Recurrent Thoracic Cancers

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1.0 INTRODUCTION

Title	*Definitive Re-Irradiation with Proton Beam Radiotherapy for Patients with Recurrent Thoracic Cancers*
Short Title	*Proton Re-Irradiation in the Thorax*
Protocol Number	
Phase	*Pilot Study*
Methodology	*Single Arm Open-Label*
Study Duration	*3 years*
Study Center(s)	*University of Washington Medical Center/SCCA Procure Proton Center*
Objectives	*To utilize proton radiation to safely treat patients with tumors in the thorax, who have previously received radiation to the chest. We will assess the efficacy and toxicity of treatment.*
Number of Subjects	*20 evaluable subjects*
Diagnosis and Main Inclusion Criteria	*Patients diagnosed with tumors in the thorax, who have previously received radiation to the chest, such that the current radiation treatment fields are likely to overlap with the prior radiation fields.*
Study Product, Dose, Route, Regimen	*Proton radiation to the thorax*
Duration of administration	*Radiation treatment regimens will be at the discretion of the treating radiation oncologist, BED_{2Gy} at least 60 Gy*
Statistical Methodology	*We expect to see <25% grade 3 toxicity attributable to radiation, and ≥80% local tumor control at 3-months post-treatment*

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

2.0 BACKGROUND

2.1 Study Disease

Lung cancer is the most common cause of cancer related mortality in the US. Radiation therapy is a main treatment modality for lung cancer: for resectable tumors, radiation can be given pre-operatively or post-operatively to improve local tumor control and outcomes; for unresectable tumors, radiation can be given as definitive treatment for the cancer, either alone or in combination with chemotherapy.

Local recurrence remains a significant cause of treatment failure in lung cancer. For stage III lung cancer treated with definitive chemoradiation, local failure rates range from 30% to 50% [1, 2]. At the time of lung cancer recurrence, patients often present as a heterogeneous group, with a mixture of local as well as systemic disease, and varying time intervals to recurrence. Outcomes are generally poor with recurrence, however, various treatments are often given to either prolong life or palliate symptoms. Depending on specific patient characteristics such as age, stage, histology, and performance status, aggressive treatments can sometimes be pursued with superior outcomes to supportive care alone.

External beam radiation is often given to patients with recurrent lung cancer to provide local tumor control and palliate symptoms. This can be challenging in patients who have previously received

radiation to the chest, usually as part of the initial cancer treatment. Radiation oncologists are guided by normal tissue tolerances, which is the standard of care radiation dose that is felt to be safe for specific organs in the body. Typically, for patients who have already received thoracic radiation, many organs in the area have already received a significant radiation dose. Therefore, it is often assumed that thoracic radiation cannot be repeated. Even when repeat radiation is given, it is typically for palliative doses, due to concerns about toxicity if higher radiation doses were attempted, as well as concerns over patient life expectancy [3].

Recent technological advances in radiation therapy and imaging have led to more interest and more feasibility in the role of repeat radiation for a select group of recurrent cancer patients. For patients with symptomatic locally recurrent tumors, or patients with good systemic disease control but persistent or progressive local disease, repeat radiation with moderately high radiation doses can provide lasting tumor control and symptom palliation. Multiple clinical series have been published on thoracic re-irradiation, showing safety and efficacy [4-10]. However, the series are typically retrospective or prospective registry trials, with no prospective guidelines in terms of radiation dose limits for normal organs. Radiation doses and fractionation varies widely. Toxicity and efficacy information are often incomplete. Table 1 summarizes some of the best published clinical data on repeat irradiation in the thorax. As systemic treatments improve for lung cancer, local control will also become more critical for this patient population, and prospective guidelines to safely deliver repeat radiation must be developed.

Table 1. Summary of Recurrent Thoracic Radiation

Study	Institution	# of patients	Radiation Technique	Toxicity	Local Control
Kelly et al. IJROBP 2010[8]	MD Anderson	36	SBRT (10 Gyx4 fractions or 10 Gyx5)	33% grade 3. No grade 4 or 5.	92% at 2 years
Trakul et al. JTO 2012[9]	Stanford	17	SBRT (dose fractionation varies)	13% grade 3. No grade 4 or 5.	65.5% at 1 year
Seung et al. J Cancer Therapy 2011[10]	Oregon Clinic	8	SBRT (8-20 Gy x3-5 fractions)	100% grade 2 pneumonitis. No grade 3 or higher.	86% at 1.5 years

In addition to recurrent lung cancers, other malignancies can also result in the need for repeat irradiation of the chest. For example, recurrent thymomas that were previously treated with radiation therapy can still have a relatively long disease course. In unresectable localized recurrences that show no evidence of dissemination, in patients with good performance status and life expectancy, it would be reasonable to consider repeat radiation. Patients with one thoracic cancer can also develop a second primary malignancy in the chest (i.e. esophageal cancer that was treated with radiation years ago, now with lung cancer; or breast cancer treated previously, now with lung cancer). Since radiation planning is guided by normal organ dose limits, this patient population would follow similar radiation guidelines as recurrent lung cancer patients, in terms of normal organ radiation constraints.

2.2 Rationale for Use of Proton Radiation

Proton radiation has unique physical properties compared with photon-based radiation due to the Bragg peak[11]. For the more widely available photon-based radiation, the radiation beams enter the

patient's body, deposits energy and causes tissue damage, and exists through the body on the other side. In comparison, proton radiation beams enter a patient's body, deposits a relatively small amount of energy along the path, until the beam weakens to the point when it deposits all of its energy immediately before the proton particles come to rest. This is called the Bragg peak. This physical characteristic of proton therapy has the potential for less normal tissue exposure to radiation, and therefore less toxicity. Multiple publications have shown that proton radiation have superior normal tissue sparing compared with photon-based radiation [12-14].

2.3 Clinical Data to Date

Proton radiation has been increasingly used for treating lung and other thoracic malignancies in the recent years, with multiple published patient series showing safety and efficacy [15-17]. Multiple clinical series have also been published on thoracic re-irradiation, showing safety and efficacy [4-7]. However, the series are typically retrospective or prospective registry trials, with no prospective guidelines in terms of radiation dose limits for normal organs. Radiation doses and fractionation varies widely. Toxicity and efficacy information are often incomplete.

2.4 Risks/Benefits

The benefit for patients enrolled in this trial is to receive proton radiation treatment to the thorax for recurrent tumors, which adheres to strict radiation normal organ dose limits that has been developed after thorough literature review and multiple radiation oncology specialists.

The potential harm for patients enrolled in this trial is the radiation toxicity related to re-irradiation.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

To assess the grade 3 toxicity associated with thoracic re-irradiation with proton therapy, with prospectively applied normal organ radiation dose limits.

Hypothesis: With the normal tissue dose limits listed in this protocol, repeat radiation to the chest can be delivered safely without grade 3 or greater toxicity exceeding 25%.

3.2 Secondary Objective

To assess the efficacy of thoracic re-irradiation with proton therapy.

Hypothesis: We will achieve >80% local tumor control at 3-months post-treatment inside the radiation field.

4.0 STUDY DESIGN

4.1 General Design

This is a pilot study to utilize proton radiation to safely treat patients with tumors in the thorax, who have previously received radiation to the chest. We have set out specific radiation guidelines for normal tissue dose limits and tumor coverage.

4.2 Endpoints

4.2.1 Primary Endpoint
Grade 3 or greater toxicity attributable to radiation treatment.

4.2.2 Secondary Endpoint

- Local control (Failure: tumor progression per RECIST criteria – at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions inside the full dose radiation field.)
- Overall survival (Failure: death due to any cause)
- Grade 2 toxicity attributable to radiation treatment

5.0 SUBJECT SELECTION

5.1 Inclusion Criteria

5.1.1 Patients >18 years old.

5.1.2 Women of child-bearing age must have a negative pregnancy test.

5.1.3 Patients must have received prior radiation treatment to the chest. Records of prior radiation treatment must be available.

5.1.4 Patients must have received prior chest radiation at least 3 months prior to enrollment in this trial. Radiation treatment to other body sites not overlapping with current radiation fields are allowed within the 3 months period (example, brain radiation is allowed).

5.1.5 Patients must have a prior diagnosis of cancer inside the thoracic cavity. Both primary thoracic malignancies (such as lung cancer) as well as metastatic lesions (such as metastatic breast cancer or colorectal cancer to the lungs) are allowed. Patient must have pathologic confirmation of the recurrent thoracic tumor, or have an enlarging thoracic mass (as seen on two CT scans at least 6 weeks apart, with either a >25% or >5 mm increase in longest dimension).

5.1.6 Patients must have a life expectancy of > 6 months.

5.1.7 Patients must have measurable disease to be treated with proton radiation (minimum tumor dimension at least 10 mm on CT imaging).

5.1.8 Patients should have either non-metastatic cancer of the thorax, or metastatic cancer to the thorax and candidate for definitive radiation dose to the thoracic tumor (not palliative intent), tumor radiation dose to at least BED_{2Gy} 60 Gy.

5.1.9 Patients must be able to receive proton radiation treatment.

5.1.10 All stages of cancer are eligible.

5.1.11 There are no limits on prior therapy. Patients are allowed to have prior chemotherapy and surgery. Patients are allowed to have concurrent chemotherapy with radiation treatment. Patients are allowed to have chemotherapy or surgery after radiation treatment.

5.1.12 Patients are allowed to be on another study concurrent with this protocol.

5.1.13 Ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1 Patients who have never received radiation to the chest.

5.2.2 Patients who received radiation to the chest within the past 3 months (in a region that overlaps with current radiation fields).

5.2.3 Patients with life expectancy < 6 months.

5.2.4 Pregnant women.

5.2.5 Patients unable to provide informed consent.

5.2.6 Prisoners.

5.3 Recruitment

Subjects will be recruited from investigator clinical practices and include men and women with recurrent thoracic cancer who will be receiving radiotherapy to at least BED_{2Gy} 60 Gy. Subjects will undergo an informed consent process in accordance with GCP. Informed consent will be obtained prior to the performance of any screening procedures.

6.0 SUBJECT REGISTRATION

Subjects will be registered by the FHCRC/UW Study Coordinator and entered into the Protocol Accrual Tracking System (PATS). Information regarding the PATS system is available at http://www.cancerconsortiumorg/rto/protocol_office/pats/. A complete, signed, study consent and HIPAA consent are required for registration.

7.0 TREATMENT PLAN

All patients will receive radiation treatment per standard of care, adhering to the normal organ radiation dose constraints outlined in this protocol. The only additional procedure related to this protocol is informed consent at enrollment.

The standard treatment outline for patients receiving radiation treatment, which also applies to patients on this protocol, begins with an initial consultation, including history and physical. Patients' prior radiation records will be obtained and reviewed. If patients are eligible and consent to repeat irradiation, they are scheduled for a radiation simulation scan, to be used for radiation treatment planning. Physicians will delineate the target tumor volume as well as normal organs to be protected in the region. A radiation plan will be generated that meets the normal organ dose limits outlined in this protocol. The plan undergoes quality assurance checks, and patients then start treatment. During treatment, patients are seen at least once weekly by the physician to assess for toxicity. After completion of radiation, patients are seen typically 3 months post-treatment with CT chest to assess for treatment response and toxicity. Additional imaging or follow up visits may take place per routine medical standard of care. Research staff will review clinical record at 3 months post-treatment. See Table 1 below for summary.

Table 2. Study Calendar.

	Screening	Prior to Start of Radiation Treatment	Weekly During Radiation Treatment	3-Months*** Post-Radiation Treatment End
Informed Consent	X*			
Physical Exam	X		X	X
Medical History	X		X	X
Pulmonary Function Tests (PFTs)		X		X
CT Chest	X			X
Serum Pregnancy Test**	X			

* Denotes a Research Procedure, all others are standard of care
** For women of child bearing potential only
*** Exact time of follow up can vary depending on clinical judgment. Patients are typically seen at 3 months after treatment, but this can vary between 2-6 months as judged appropriate by treating physician.

7.1 Radiation Treatment Parameters

7.1.1 Localization, Simulation, and Immobilization

Body cradle or similar immobilization device(s) must be utilized. A treatment planning CT scan is mandatory. CT scan thickness should be 0.5 cm or smaller (preferably ≤0.3 cm) through the treatment volume. Intravenous contrast is recommended in patients who do not have a contraindication to it. MRI and/or PET scans with image fusion also may be helpful in treatment planning, particularly if these scans can be performed with the same immobilization device as was used for the planning CT scan. 4D CT scan with respiratory motion tracking is strongly preferred for lung tumors. Any tumors moving more than 1 cm with respiration must be considered for motion management for radiation treatment, which can include but not limited to: abdominal compression, respiratory gating, and active breathing control. These are all standard of care for lung radiation treatment.

7.1.2 Volume Definitions

Gross Tumor Volume (GTV): This is the region of interest that is known to contain gross cancer. This will include all gross tumor as based upon the planning CT scan. This also may include areas that appear "normal" by the planning CT scan but are known to harbor cancer based on the MRI, PET, physical examination, endoscopy, etc.
Clinical Tumor Volume (CTV): The CTV is defined to be the GTV plus a margin as appropriate to account for microscopic tumor extension. The exact CTV margin to be used is at the discretion of the treating physician, and can be as low as 0 mm if microscopic extension is not felt to be of concern in a particular patient situation.
Internal Target Volume (ITV): If 4D CT scans are used to assess for breathing motion, the ITV will be used to encompass the CTV and all respiratory motion.
Planning Tumor Volume (PTV): This includes the CTV (or ITV if appropriate) plus a margin to compensate for various uncertainties, such as systematic treatment setup variables, organ motion (especially with respiratory motion), and organ displacement. A minimum of 5 mm around the CTV is required in all directions, except where the CTV is immediately adjacent to a critical organ such as the spinal cord (in which case, the margin from CTV to PTV may be as small as 1 mm).

7.1.3 Treatment Planning Dose Constraints

- A composite radiation plan that includes the prior thoracic radiation must be generated.
- Minimum PTV dose should be 90% of the prescription dose and 95% of the PTV should receive the prescription dose, unless PTV overlaps with a critical normal organ. In that case, the portion of PTV not overlapping with the critical organ should meet the constraint above. Min PTV dose <80% will be a major violation, volume of PTV receiving prescription dose <90% will be a major violation.
- Minimum prescription dose to PTV must be at least BED_{2Gy} 60 Gy.
- Spinal cord: max point dose 50 Gy (<0.03 cc) or BED equivalent (BED_{2Gy} 83 Gy) from proton radiation plan. Composite maximum spinal cord dose must not exceed BED_{2Gy} 90 Gy. For patients who received radiation > 3 years prior, the cord constraint can be increased with PI approval.
- Normal lung: mean dose < 20 Gy and volume receiving 20 Gy (V20) < 35% for proton radiation plan.
- Esophagus: mean dose <34 Gy and max dose < 66 Gy for proton plan. Composite max point dose < BED_{2Gy} 140 Gy.
- Heart: mean dose < 40 Gy and max dose < 66 Gy for proton plan. Composite max point dose < BED_{2Gy} 140 Gy.

7.1.4 Treatment delivery

All patients will have daily imaging guidance for setup and positioning prior to proton radiation delivery. This is typically done with port films.

7.1.5 R.T. Quality Assurance Reviews

All patients treated on this protocol will undergo standard review in the Department of Radiation Oncology. At least two physicians will review the patient history, imaging findings, tumor contours, and radiation plan.

7.1.6 Radiation Toxicity

Toxicity will be graded based on CTCAE 4.0. Grade two and above adverse events will be recorded.in a Redcap database. The AE's will be followed for three months post-treatment.

7.2 Criteria for Removal/Withdrawal from Treatment

Patients will be withdrawn from treatment if their clinical conditions decline so they are no longer able to tolerate proton radiation, or are unlikely to clinically benefit from further therapy.

Patients will still receive follow up care per standard of care even if they withdraw from the study. If a subject withdraws consent to participate in the study or aspects of the study, attempts will be made to obtain permission to record at least survival data up to 6 months post-treatment.

8.0 DATA AND SAFETY MONITORING PLAN

Oversight for this study at the SCCA and UWMC will be provided by the Principal Investigator with delegation of appropriate responsibilities to sub-investigators and designated study personnel. They will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events are performed according to the IRB-approved protocol.

8.1 Early Stopping Rules

In the event of a grade 5 event occurring within ≤ 30 days after the end of treatment , there will be a temporary cessation in patient enrollment for event review If the event is defined as possibly, probably, or definitely related to treatment (per CTCAE, v.4.0), early stopping of this trial will occur permanently. All Grade 3 and 4 AE's will be immediately monitored and reviewed by PI.

8.2 Interim Data Review

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented or published. In general, the interim reports will contain the following information:

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Frequencies and severity of adverse events
- Compliance rates of treatment delivery

9.0 ASSESSMENT OF EFFICACY

9.1 Efficacy Parameters

Tumor response will be assessed using the RECIST criteria.

For tumors targeted by radiation:

- Complete Response (CR): Disappearance of all target lesions
- Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort will be made to document the objective progression even after discontinuation of treatment.

9.2 Method and Timing

Tumors will be measured on axial CT chest images. The radiation treatment planning scan will be used as baseline. The 3-months post-treatment scan will be used for comparison.

9.3 Toxicity Profile

Toxicity will be measured by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

10.0 STATISTICAL CONSIDERATIONS

The primary objective of this protocol is to provide a preliminary evaluation of the safety and efficacy of re-irradiation with proton beam radiotherapy in patients with recurrent thoracic cancer. Ideally this therapy should have a grade 3 toxicity rate of < 25% and a local control rate of > 80%.

Twenty patients will be enrolled. If 7 or more of the 20 patients experience grade 3 toxicity, then we would be at least 80% confident that the true toxicity rate exceeds 25%; conversely, if 3 or fewer of the 20 patients experience grade 3 toxicity, then we would be at least 80% confident that the true toxicity rate is less than 25%. An intermediate result, 4-6 patients with grade 3 toxicity, would be regarded as inconclusive.

With regard to efficacy, if the therapy results in 14 or fewer of the 20 patients with local tumor control, then we would be at least 80% confident that the true local control rate is less than 80%; conversely, if 18 or more of the patients have local tumor control, then we would be at least 80% confident that the true local control rate exceeds 80%. An intermediate result, 15-17 patients with local tumor control, would be regarded as inconclusive.

An early stopping rule will be imposed for grade 5 adverse events, and the protocol will stop should any patients experience a grade 5 AE as described in Section 8.1. If the true rate of grade 5 AE is 10%, then there is an 88% chance that this stopping rule will be triggered.

11.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

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