

# UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

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Title of Protocol:

**Pulmonary Functional Imaging for Radiation Treatment Planning for Lung Cancer**

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## 1.0 INTRODUCTION

Title	<i>Pulmonary Functional Imaging for Radiation Treatment Planning for Lung Cancer</i>
Short Title	<i>SPECT/CT for Radiation in Lung Cancer</i>
Phase	<i>Pilot Study</i>
Methodology	<i>Single Arm Open-Label</i>
Study Duration	<i>2 years</i>
Study Center(s)	<i>University of Washington Medical Center</i>
Objectives	<i>To utilize SPECT/CT imaging with <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA to accurately identify functional lung in patients receiving radiation treatment for lung cancer, and characterize tissue response to radiation. The long-term goal being to use functional imaging to guide radiation treatment planning, so functional lung tissue can be preferentially avoided, which will reduce radiation induced pulmonary toxicity allowing for increased dose delivery to the primary tumor.</i>
Number of Subjects	<i>20 evaluable subjects</i>
Diagnosis and Main Inclusion Criteria	<i>Patients diagnosed with non-metastatic lung cancers receiving radiation treatment, with impaired pulmonary function</i>
Study Product, Dose, Route, Regimen	<i><sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA SPECT/CT scans</i>
Duration of administration	<i>Drug administration will consist of 3 SPECT/CT scans with <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA (one baseline scan which is standard of care, two follow up scans which are experimental and paid for by departmental research funds). The two experimental scans will be at mid-radiation treatment and approximately 3 months post-treatment.</i>
Statistical Methodology	<i>Outside the radiation field, normal lung tissue ventilation and perfusion over serial imaging will be assessed for stability using regression analysis, Pearson correlation, and Dice coefficient. Inside the radiation field, dose response curves will be developed for radiation dose versus changes in ventilation and perfusion. Gradient search algorithm in MIM 6.0. will be used to identify perfused and ventilated lung.</i>

This document is a protocol for a human research study. This study is to be conducted according to US and international regulations, 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 main 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]. Escalating radiation dose is one approach that may improve local control [3-5]. However, this approach has seen little success in recent dose escalation trials [6]. One potential limitation to radiation dose escalation is radiation induced toxicity. In the thoracic region, pulmonary toxicity is one major source of dose limitation. Many lung cancer patients are smokers and have poor baseline pulmonary function secondary to pulmonary co-morbidities, such as COPD. Moderate to severe radiation induced pulmonary toxicity occurs in 10-20% of patients receiving definitive treatment to a therapeutic dose of 60Gy and is fatal in 2-3% of these patients.[7]

Due to the prevalence of tobacco use in the lung cancer population, a significant percentage of patients have underlying parenchymal lung disease, which frequently has heterogeneous involvement. Differences in perfusion and ventilation leads to regional variations in pulmonary function. Perfusion imaging is an established technique to identify functional and non-functional zones within normal lung and is routinely used to predict post-operative pulmonary function in patients planned for pulmonary resection [8]. Current radiation treatment planning treats the lung as a homogeneously functioning organ and does not take regional variances in pulmonary function into account. Recent advances in radiation treatment planning and delivery, such as 3-D conformal radiation therapy and intensity modulated radiotherapy allow for preferential sparing of anatomic substructures in close proximity to the primary tumor. Other radiation treatment modalities, such as proton radiation therapy, provide greater ability to carefully choose radiation beam path, to selectively avoid lung regions.

## **2.2 Rationale for Use of SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA Scans**

SPECT imaging is a sensitive method of detecting regional lung function such as ventilation and perfusion. Radiation has been shown to affect both lung ventilation and perfusion. Data from Duke University and NKI using SPECT imaging have suggested a dose-response relationship between decrease in lung ventilation and perfusion and radiation dose delivered [9]. With more advanced imaging methods and the addition of CT scan to SPECT imaging, it is possible to improve contrast resolution relative to planar scintigraphy, and quantitative accuracy from attenuation correction [10, 11]. By integrating SPECT/CT scans into the radiation planning process, it is also possible to obtain scans in the radiation treatment position, allowing for more accurate calculation of radiation dose and functional image intensity at the voxel scale, leading to more precise dose-response characterization.

## **2.3 Clinical Data to Date**

SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA scans are both in use clinically for evaluating lung perfusion and ventilation, respectively. A landmark study showed that intravenous <sup>99m</sup>Tc macroaggregates were shown to accurately predict functional loss (FEV 1) 3 months postpneumonectomy [12]. Radionuclide-labeled tracers for perfusion scanning remains the gold standard for predicting postoperative lung function [13]. The radiation oncology community has not adopted the use of functional imaging to aid in radiation planning. The standard of care in radiation oncology is to treat all lung tissue as identical when calculating radiation dose and probability of complications.

## **2.4 Risks/Benefits**

The only risk to patients in this study is the risk associated with the two additional SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA scans. The radiation treatment patients receive will be standard of care. Risks associated with the two SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA scans include: patient time; radiation dose from radioactive tracers and scans (~ 30 mSv per session, which is about 0.1% of the usual

radiation dose for lung cancer treatment, typically around 60 Gy), and intravenous injection and potential for bleeding, pain, infection, and injection site reaction. Please see consent form for further details on potential risks.

The benefit gained from this study is the knowledge of whether SPECT/CT  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA scans can identify functional lung tissue that remains ventilated and perfused over time. If we are able to reliably identify functional lung tissue, we can preferentially protect those lung regions from radiation, which can decrease radiation induced lung injury. We will also learn about the effect of radiation on the spatial and temporal dynamics of lung ventilation and perfusion, which can better help us design radiation treatments to safely treat tumors while minimizing lung toxicity.

## 3.0 STUDY OBJECTIVES

### 3.1 Primary Objective

To utilize SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA to identify functional lung on serial imaging in patients receiving radiation treatment for lung cancer, as well as to characterize reproducibility of perfusion and ventilation in non-irradiated lung tissue.

Hypothesis: For lung tissue outside the radiation field, perfusion and ventilation as defined by SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA will exhibit smaller changes over time than tissue inside the radiation field. Compared to the pre-radiation scan, lung tissue receiving radiation dose below the 20<sup>th</sup> percentile of total lung will have perfusion and ventilation that remain constant or increase at the mid-radiation treatment scan and 3-months post-treatment scans. By contrast, lung tissue receiving radiation dose above the 80<sup>th</sup> percentile of total lung will have perfusion and ventilation that decrease at the mid-radiation treatment scans and 3-months post-treatment scans.

### 3.2 Secondary Objective

a) To estimate the dose response relationship on multiple spatial scales (global lung, regional lung, lung image voxel) between radiation dose and changes in lung ventilation and perfusion, both acutely (mid-radiation treatment) and long term (3 months post-treatment), using SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA.

Hypothesis: Compared to the current models of radiation dose response for lung tissue, using CT in addition to SPECT imaging acquired in the radiation treatment position, a more accurate regional dose response relationship between radiation dose and changes in lung function can be generated with superior volumetric and quantitative data.

b) To estimate the degree of radiation response in lung tissue with varying levels of function (i.e. compare radiation dose response of well ventilated and well perfused tissue against lung tissue with poor perfusion and ventilation). This may establish a threshold of lung tissue that would be “safe” to treat without significantly affecting lung function.

Hypothesis: Well-perfused and ventilated lung tissue has a different radiation dose response curve than lung tissue that receives poor ventilation and perfusion (upper quartile versus lower quartile of perfused and ventilated tissue image intensity distributions). The dose-response relationship can be modeled either as a linear or sigmoid function.

### 3.3 Exploratory Objective

To evaluate proton radiation therapy for functional lung sparing in lung cancer through treatment planning comparisons to conventional photon radiation therapy.

Hypothesis: Unique physical characteristics of proton radiation allow for fewer external radiation beam pathways through normal tissue to achieve similar tumor dose coverage with photon radiation, leading to superior functional lung sparing.

## 4.0 STUDY DESIGN

### 4.1 General Design

This is a pilot study of utilizing SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA to accurately identify functional lung tissue on serial imaging in patients receiving radiation treatment for lung cancer. The long-term goal being to use functional imaging to help with radiation planning, which can preferentially spare functional lung tissue, leading to reduced pulmonary toxicity. Conversely, this has the potential for allowing increased radiation dose to the tumor while keeping normal tissue dose the same as conventional photon radiation therapy.

Patients will have a total of 3 SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA. The first scan will be routine medical care (not experimental) and will take place prior to initiation of radiation treatment. Two follow up scans will be part of the protocol, one at mid-radiation treatment, and one about 3 months post-radiation treatment.

### 4.2 Endpoints

#### 4.2.1 Primary Endpoint

In this study, patients with lung cancer will undergo SPECT/CT imaging with  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -DTPA at the time of radiation treatment planning. All image datasets will be imported into MIM 6.0, and fused with the radiation treatment planning CT and radiation plan. Lung tissue will be divided into tissue outside the radiation field (dose < 20<sup>th</sup> percentile of total lung dose) and tissue inside the radiation field (dose > 80<sup>th</sup> percentile of total lung dose). This process will be repeated for the mid-treatment scan and 3 months post-treatment scan. Lung tissue outside the radiation field will be compared on serial scans and their perfusion and ventilation quantified. There should be insignificant changes in perfusion and ventilation in >80% of lung tissue outside the radiation field. Lung tissue inside the radiation field will also be compared, and should yield significant differences in ventilation and perfusion between pre, mid, and post-treatment scans.

We will analyze the perfusion and ventilation data through multiple methods. Image sets from all 3 time points (before radiation, mid-radiation, 3-months post-radiation) will be fused using rigid registration. Regions of interest within the lung will be defined using automated and semi-automated methods, including simple thresholds and gradient-search algorithms. For each tracer, uptake value will be calculated for each voxel. For lung tissue outside the radiation field, summary statistics such as total regional uptake and mean regional uptake by lobe will be compared across the time points using parametric and non-parametric statistical testing. Voxel-based correlation, including Pearson linear and Spearman rank, will be performed to measure the stability of uptake between time points. Lastly, metrics of ventilation and perfusion volume overlap between time points will be estimated using the Dice coefficient.

## 4.2.2 Secondary Endpoint

For the second aims (a) and (b) looking at lung tissue inside the radiation field, the images will be processed similar to primary endpoint. For lung tissue inside the radiation field, changes in tracer uptake at the global lung, regional lung, and lung image voxel scales (compared to baseline scan) will be plotted against the radiation dose at the same scales to generate multiscale radiation dose response curves. These curves will be fit to linear and sigmoid dose-response functions. We will also separate out lung regions in the upper quartile and lower quartile of ventilation and perfusion, and generate separate radiation dose response curves per region, to assess for potential differences in radiation dose response of functional lung versus non-functional lung.

## 4.2.3 Exploratory Endpoint

Comparison planning with proton radiation will also be performed, to explore whether superior functional lung sparing can be achieved with proton radiation, compared with conventional photon radiation therapy. Two planning paradigms will be utilized: (1) fixed tumor dose objectives and comparison of normal tissue dose sparing, (2) fixed normal tissue objectives and comparison of tumor dose escalation.

# 5.0 SUBJECT SELECTION

## 5.1 Inclusion Criteria

- 5.1.1 Lung cancer patients receiving radiation treatment to the thorax to at least 45 Gy. Both non-small cell and small cell patients are eligible. Patient must have pathologic confirmation of diagnosis, or have an enlarging lung mass on at least two scans spaced 3 months apart, and FDG avidity on PET scan.
- 5.1.2 All stages of lung cancer are eligible, but patients must be planned for at least 45 Gy of radiation.
- 5.1.3 Patients are not required to have measurable disease. Post-operative patients (patients who have had surgical resection of lung cancer) are eligible.
- 5.1.4 Patients must have pulmonary function as defined below:
  - 5.1.4.1 Abnormal pulmonary function test within 3 months of study entry
  - 5.1.4.2 Prior radiation to the lungs
  - 5.1.4.3 Prior surgical resection of lung tissue (i.e. wedge resection, lobectomy, or pneumonectomy)
  - 5.1.4.4 Clinical diagnosis of COPD or emphysema
  - 5.1.4.5 Ongoing oxygen use
- 5.1.5 There are no limits on prior therapy. Patients are allowed to have prior chemotherapy, radiation therapy, and surgery. Patients are allowed to have concurrent chemotherapy with radiation treatment. Patients are allowed to have chemotherapy after radiation treatment. Patients are not allowed to have planned lung resection after radiation.
- 5.1.6 Patients >18 years old.
- 5.1.7 Ability to understand and the willingness to sign a written informed consent document.

- 5.1.8 Patients will typically be enrolled on this trial prior to beginning the radiation treatment course. However, if a patient has had a SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA scan as part of routine medical care within 6 weeks prior to initiation of radiation treatment, he/she is eligible for trial enrollment up to the last day of the radiation treatment course.

## **5.2 Exclusion Criteria**

- 5.2.1 Patients must not be planned for lung resection after radiation therapy.
- 5.2.2 Patients receiving < 45 Gy radiation.
- 5.2.3 Patients who received radiation to the chest within the past 6 months.
- 5.2.4 Patients unable to tolerate a SPECT/CT <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA scan.
- 5.2.5 Patients who are not planning to adhere to the required follow up schedule as outlined in this protocol.
- 5.2.6 Pregnant women
- 5.2.7 Women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception.
- 5.2.8 Patients unable to provide informed consent.

## **5.3 Recruitment**

Subjects will be recruited from investigator clinical practices and include men and women with lung cancer who will be receiving radiotherapy to at least 45 Gy. Subjects will undergo an informed consent process in accordance with GCP (see section 11 Ethical Considerations). 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/](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. As part of this study, all patients will undergo 3 SPECT/CT scans: 1) first scan will be at the time of radiation treatment planning, in the treatment position. This scan will be standard of care clinically for patients with compromised lung function (such as COPD); 2) second scan will be mid-radiation treatment (up to 1 week post-completion of radiation is acceptable), to assess the acute response of functional lung to radiation; 3) third scan will be 3 months post-radiation (up to 6 months is acceptable), to assess the longer term response of functional lung tissue. Follow up of all patients will occur via standard clinical follow-up by treating physician. This clinical follow-up may include clinical exam, pulmonary function test (PFT), and FDG PET/CT scan. Research staff will review clinical record at 3 months post-treatment. See Table 1 below for summary.

**Table 1. Study Calendar.**

	<b>Screening</b>	<b>Prior to Start of Radiation Treatment</b>	<b>Mid-Radiation Treatment</b>	<b>3-Months Post-Radiation Treatment End</b>
<b>Informed Consent</b>	X*			
<b>Physical Exam</b>	X		X	X
<b>Medical History</b>	X			X
<b>Pulmonary Function Tests (PFTs)</b>	X			X
<b>Serum Pregnancy Test**</b>	X			
<b>FDG PET/CT Scan</b>	X***			X, X#
<b>SPECT/CT with <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA</b>		X	X*	X*

\* Denotes a Research Procedure, all others are standard of care

\*\*For women of child bearing potential only

\*\*\*FDG PET/CT simulation scan preferred over CT simulation scan, but both are acceptable

#CT scan only is also acceptable in the follow-up period

## **7.1 Imaging Protocol**

SPECT/CT with <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA will be performed per standard protocol, which is currently in routine clinical use. The imaging session is comprised of an inhalation of the <sup>99m</sup>Tc-DTPA tracer and SPECT static acquisition, followed by intravenous injection of the <sup>99m</sup>Tc-MAA tracer and second SPECT static acquisition. This rapid serial process ensures the efficient imaging of ventilation and perfusion in the same imaging session. An initial scan at the time of radiation planning will identify functional lung that is ventilated and perfused. This scan will be in the radiation treatment position which can be fused precisely with the radiation treatment planning scan, and will be used to identify functional lung tissue both inside and outside the radiation fields. Two follow up scans will track lung response to radiation (one scan at mid-treatment for acute radiation response, and one scan at 3-months post-treatment for longer term assessment). Detailed ventilation and perfusion dose response curves will be generated from this data. Comparison planning with proton radiation will be performed to evaluate the feasibility of improved functional lung sparing with proton beam radiation.

## **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 SPECT/CT with <sup>99m</sup>Tc-MAA and <sup>99m</sup>Tc-DTPA. They will be withdrawn from treatment if they are enrolled with hospice.

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 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.

## 9.0 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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