R01 CA202761: Investigating Radiation-Induced Injury to Airways and Pulmonary Vasculature in Lung SAbR

Amit Sawant, PhD University of Maryland, School of Medicine, Baltimore, MD

Robert Timmerman, MD University of Texas, Southwestern Medical Cer Dallas, TX



Disclosures

Ongoing Research Support from

- The National Institutes of Health (R01 CA169102, R01 CA202761)
- Varian Medical Systems
- Vision RT Ltd.

SOUTHWESTERN



Research Team

Pranshu Mohindra



Amit Sawar rsity of Maryland, Baltimor

Funding Mechanism Overview



Funding Mechanism Overview

Academic Industrial Partnerships are different from "regular" R01s TU-E-225BCD – NIH Grant Writing Workshop

- Emphasis on true partnership i.e., project should not be possible without either partner
- Innovation defined differently for AIPs "a coherent translational plan to deliver emerging or new capabilities for preclinical or clinical use that are not yet broadly employed in preclinical or clinical settings"

"innovation may be considered as delivery of a new capability to end users"

Special emphasis review panel – does not repeat!

Clinical Significance - Motivation

- Current treatment planning paradigms view the lung as a uniform parallel functioning organ • V_{20} MLD are quite small in SAbR and do not seem adequate to predict toxicity, e.g., MLD \approx 6 Gy, $V_{20} \approx 5\%$
- In reality, the lung consists of branching serial structures (BSS airways and vessels) which divide progressively and ultimately end in a parallel parenchyma
- Radiation damage to these BSS can cause airway stenosis, atelectasis and fibrosis, <u>often</u>, <u>distant from the intersection of the beams</u>



<section-header><section-header><text>





Relevant Experience/Expertise

- Based on virtual bronchoscopy clinically validated technique widely used in interventional pulmonology
- Strong team: Physician (Timmerman) + Physicist (Sawant) co-Pls — Physician – Nationally and internationally recognized expert



 Physicist – Experience in lung imaging, motion management, advanced treatment planning

2. Investigator(s): Strengths

on SAbR (RTOG 0236)

 Excellent clinical expertise involved in the conduct of this study. Dr. Timmerman in particular is a world-recognized expert in this topic. Dr. Sawant is also well able to lead this effort.

R01 SUBMISSION – Specific Aims

<u>Overall Hypothesis</u>: Anatomically variable radiation injury to the bronchial tree and pulmonary vasculature is an important determinant of post-SAbR pulmonary toxicity and residual pulmonary function

<u>Aim 1</u> - Perform a prospective clinical study with 40 NSCLC patients to assess the relationship between dose and radiation injury to segmental elements of the BSS <u>Hypothesis</u>: Radiosensitivity of BSS elements is variable and depends on a variety of factors such as segment anatomy, branch level and lumen diameter.

<u>Aim 2</u> - Investigate the impact of radiation injury to BSS elements on localized lung function, as characterized by SPECT ventilation/perfusion imaging <u>Hypothesis</u>: Radiation injury to BSS causes localized and predictable impairment of lung function.

<u>Aim 3</u> – Investigate treatment planning based on novel dose-sculpting strategies and/or higherdimensional optimization in order to minimize dose to BSS while achieving conventional SABR dosimetric objectives.

Hypothesis: Novel 3D and 4D radiation dose-sculpting strategies can reduce dose to BSS elements below levels that are likely to cause injury Arm Saw

Outcome of Submission #1

| Principal Investigator SAWANT, AMIT PHD TIMMERMAN, ROBER | s (Listed Alphabetic (Contact) RT D MD | ally): | | | | | | |
|--|---|---|-----------|--|--|--|--|--|
| Applicant Organization: UT SOUTHWESTERN MEDICAL CENTER | | | | | | | | |
| Review Group: | ZRG1 SBIB-D (57) Center for Scientific PAR Panel: Acaden | c Review Special Emphas nic Industrial Partnership | is Panel | | | | | |
| Meeting Date: | 05/28/2015 | RFA/PA: | PAR13-169 | | | | | |
| Council: | OCT 2015 | PCC: | 5PDI | | | | | |
| Requested Start: | 12/01/2015 | | | | | | | |
| | | Dual IC(s): | EB | | | | | |
| Project Title: | Investigating Radiation-Induced Injury to Airways and Pulmonary Vasculature in Lung SABR | | | | | | | |
| SRG Action: | Impact Score: 31 | Percentile: 18 # | | | | | | |

SNG Action: Impact Score: 31 Percentile: 18 # Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm Human Subjects: 30-Human subjects involved - Certified, no SRG concerns Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Amit Saw

Strategizing the Response

The Glide-Hurst Method



The Sawant Solution



Amit Sav ly of Maryland, Baltin

Submission #2

Responses to Key Critiques

"Reviewers generally considered the approach to the research as outstanding", "They stated that the investigator team and their environments are outstanding for conducting the proposed research." and "Despite (some) concerns, the reviewers considered the overall impact of this proposed research as excellent."

Major changes include:

- Significantly stronger preliminary data: 26 patients compared to 6 in the original proposal (Aim 1, Sec. D.2.1). These findings will be reported at the 2015 ASTRO annual meeting in the <u>Best in Physics</u> session.
- Revised clinical study protocol that explicitly accounts for respiratory motion during pre- and post-treatment SPECT and CT imaging
- <u>Addition of Specific Aim 4</u>, which focuses on clinical translation.

Amit Sav

Responses to Key Critiques

"Reviewers generally considered the approach to the research as outstanding", "They stated that the investigator team and their environments are outstanding for conducting the proposed research." and "Despite (some) concerns, the reviewers considered the overall impact of this proposed research as excellent."

Major changes include:

- Significantly stronger preliminary data: 26 patients compared to 6 in the original proposal (Aim 1, Sec. D.2.1). These findings will be reported at the 2015 ASTRO annual meeting in the <u>Best in Physics</u> session.
- Revised clinical study protocol that explicitly accounts for respiratory motion during pre- and post-treatment SPECT and CT imaging
- Addition of Specific Aim 4, which focuses on clinical translation.

Amit Sawa itv of Marvland. Baltimo

Responses to Key Critiques

"Reviewers generally considered the approach to the research as outstanding", "They stated that the investigator team and their environments are outstanding for conducting the proposed research." and "Despite (some) concerns, the reviewers considered the overall impact of this proposed research as excellent."

Major changes include:

- Significantly stronger preliminary data: 26 patients compared to 6 in the original proposal (Aim 1, Sec. D.2.1). These findings will be reported at the 2015 ASTRO annual meeting in the <u>Best in Physics</u> session.
- Revised clinical study protocol that explicitly accounts for respiratory motion during pre- and post-treatment SPECT and CT imaging Addition of Corpetition for the forume or clinical translation
- Addition of Specific Aim 4, which focuses on clinical translation

Amit Sawa

Responses to Key Critiques

"Reviewers generally considered the approach to the research as outstanding", "They stated that the investigator team and their environments are outstanding for conducting the proposed research." and "Despite (some) concerns, the reviewers considered the overall impact of this proposed research as excellent."

Major changes include:

- Significantly stronger preliminary data: 26 patients compared to 6 in the original proposal (Aim 1, Sec. D.2.1). These findings will be reported at the 2015 ASTRO annual meeting in the <u>Best in Physics</u> session.
- Revised clinical study protocol that explicitly accounts for respiratory motion during pre- and post-treatment SPECT and CT imaging
- <u>Addition of Specific Aim 4</u>, which focuses on clinical translation.

Amit Sav

Responses to Key Critiques

"Reviewers generally considered the approach to the research as outstanding", "They stated that the investigator team and their environments are outstanding for conducting the proposed research." and "Despite (some) concerns, the reviewers considered the overall impact of this proposed research as excellent."

Major changes include:

- Significantly stronger preliminary data: 26 patients compared to 6 in the original proposal (Aim 1, Sec. D.2.1). These findings will be reported at the 2015 ASTRO annual meeting in the <u>Best in Physics</u> session.
- Revised clinical study protocol that explicitly accounts for respiratory motion during pre- and post-treatment SPECT and CT imaging
- Addition of Specific Aim 4, which focuses on clinical translation.

Amit Sawai itv of Marvland, Baltimor

| Principal Investigator SAWANT, AMIT PHD FIMMERMAN, ROBER | rs (Listed Alphabet (Contact) RT D MD | cally): | | | | |
|--|---|---------------------------------------|-------------------------|--------|--|--|
| Applicant Organizatio | on: UT SOUTHWES | TERN MEDICAL | CENTER | | | |
| Review Group: | ZRG1 SBIB-D (57) Center for Scientif PAR Panel: Acade | ic Review Specia mic Industrial Pa | al Emphas artnership | is Pan | | |
| Meeting Date: | 10/15/2015 | | RFA/PA: | PAR1 | | |
| Council: Requested Start: | JAN 2016 04/01/2016 | | PCC: | 5PDI | | |
| | | D | ual IC(s): | EB | | |
| Project Title: | Investigating Radi Lung SABR | ation-Induced In | jury to Air | ways a | | |
| SRG Action: | 1: Impact Score: 20 Percentile: 6 # | | | | | |
| Next Steps: | Visit http://grants. | nih.gov/grants/n | ext steps | htm | | |
| Human Cubicator | 20 Luman aubiaat | involved Cort | ified no C | BC as | | |
| | | | | | | |
| | | | 11- | | | |

Key Scientific Outcomes







Airway Dose Response Curves





IMRT Planning For Different Relative Weights of Dose Avoidance to Airways



Future Research Directions



AAPM 2019 BEST IN PHYSICS - Wed: 1.45 pm - 3.45 pm; Room 301 Accounting for Respiration-induced

Motion of Peripheral Airways in Virtual **Bronchoscopy-guided Lung Stereotactic** Ablative Radiotherapy Planning

Esther Vicente¹, Arezoo Modiri¹, Kun-Chang Yu², Henky Wibowo², Yulong Yan³, Robert Timmerman³, Amit Sawant¹ Ulong tent, source training Baltimore, Baltimore, MD ¹Broncis Medical, Inc., San Jose, CA ¹UT Southwestern Medical Center, Dallas, TX evicente@som.umaryland.edu (601 CA202761)

MOTIVATION

 Geometric and dosimetric errors will be more pronounced in the presence of high dose gradients, large amounts of motion, and small structures.



 $Pr_{collapse} = \frac{1}{1 + e^{-(\alpha_1 + \alpha_2 \cdot d + \alpha_3 \cdot D_{max})}}$

nax = **D**_{0.01cc}: Minimum dose to a voxel within the 0.01 cc volume that has received the highest dose.

Grant Advice for AAPM Members



- Significance Differentiate yourself from the crowd

 Unmet clinical need that reviewers can understand and appreciate
 New technology or novel application of an existing technology
- Team Find partners that "work". Develop and nurture relationships
 - Complementary expertise (e.g., physicist + physician + engineer + radiobiologist)
 Clear communication and expectations from each other
- Persistence Develop a thick skin (academically speaking!)
 - Review and scoring process is "noisy" panels do try to be considerate, especially to new investigators
 - Even successful grantees get new grants rejected/unscored
 - Don't stop working on your science after you submit you can use new results/publications when you resubmit.

QUESTIONS?

asawant@som.umaryland.edu

Amit Sawant