Disclosures

Ongoing Research Support from

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

Academic Industrial Partnerships are different from “regular” R01s

- 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
- \( V_{20} \) and \( MLD \) are quite small in SABR and do not seem adequate to predict toxicity, e.g., \( MLD = 6 \text{ Gy}, V_{20} = 5\% \)
- 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, often distant from the intersection of the beams

- \( \text{Pre-SABR} \)
- \( \text{Post-SABR} \)
Radiation-Induced Injury to the Bronchial Tree in Lung SBRT

**Key Idea:** Image and incorporate the bronchial tree and lung vasculature into the SBRT treatment planning process

Retrospective Study - NSCLC patient, LUL, GTV~ 5cm

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Relevant Experience/Expertise

- Based on virtual bronchoscopy - clinically validated technique widely used in interventional pulmonology
- Strong team: Physician (Timmerman) + Physicist (Sawant) co-PIs
  - Physician – National and internationally recognized expert on SAbR (RTOG 0236)
  - Physicist – Experience in lung imaging, motion management, advanced treatment planning

2. Investigator(s):
   Strengths
   - 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

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

**Aim 1:** Perform a prospective clinical study with 40 NSCLC patients to assess the relationship between dose and radiation injury to segmental elements of the BSS.

**Hypothesis:** Radiosensitivity of BSS elements is variable and depends on a variety of factors such as segment anatomy, branch level and lumen diameter.

**Aim 2:** Investigate the impact of radiation injury to BSS elements on localized lung function, as characterized by SPECT ventilation/perfusion imaging.

**Hypothesis:** Radiation injury to BSS causes localized and predictable impairment of lung function.

**Aim 3:** Investigate treatment planning based on novel dose-sculpting strategies and/or higher-dimensional 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.

Outcome of Submission #1

Principal Investigators (Listed Alphabetically):
- AMIT SAWANT, MD (Contact)
- ROBERT D TIMMERMAN

Applicant Organization: UT SOUTHWESTERN MEDICAL CENTER

Review Group: ZRG1 SBIR-D (37)

Center for Scientific Review Special Emphasis Panel
PAR Panel: Academic-Industrial Partnership

Meeting Date: 05/30/2015
Panel: PAR13-169
Council: 10/30/2015
PCORNI: 5PD

Requested Start: 12/01/2015

Hypothesis: Investigating Radiation-Induced Injury to Airways and Pulmonary Vasculature in Lung SABR

SRG Action: Impact Score: 31

Percentile: 16.8


Human Subjects: 30 humans subjects involved - Certified, no SRG concerns

Animal Subjects: 10-20 live vertebrate animals involved for collecting astr.
Strategizing the Response

The Glide-Hurst Method

The Sawant Solution
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 Best in Physics 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.
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Amit Sawant
University of Maryland, Baltimore
Key Scientific Outcomes

Risk Model for Post-Treatment Airway Injury

\[ P(\text{Collapse} | \text{Diameter}) = \frac{1}{1 + e^{-\theta_0 - \theta_1 \text{Diameter} - \theta_2 \text{Diameter}^2}} \]
Airway Dose Response Curves

IMRT Planning For Different Relative Weights of Dose Avoidance to Airways

Future Research Directions
Accounting for Respiration-induced Motion of Peripheral Airways in Virtual Bronchoscopy-guided Lung Stereotactic Ablative Radiotherapy Planning

Esther Vicente, Arezoo Modiri, Kun-Chang Yu, Henky Wibowo, Yulong Yan, Robert Timmerman, Amit Sawant

1University of Maryland in Baltimore, Baltimore, MD
2Broncus Medical, Inc., San Jose, CA
3UT Southwestern Medical Center, Dallas, TX

Motivation

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

\[ P_{\text{collage}} = \frac{1}{2 \pi \sigma^2 (\langle x^2 \rangle + \langle y^2 \rangle + \langle z^2 \rangle) / \sigma_{\text{max}}} \]

\[ D_{\text{max}} = D_{0.01\text{cc}} \]: 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?  

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