P01 CA059827
Optimization of High Dose Conformal Therapy
(y16 - y20)
Response-Based Adaptive Therapy

P01 - an integrated, team-based approach to solving problems
- Optimization of High Dose Radiotherapy
  - 04/1993: Benedick Fraass, PI
  - 09/2000: Benedick Fraass, PI
  - 07/2006: Benedick Fraass, PI
  - 04/2011: Randall Ten Haken, PI
  - 05/2014: Randall Ten Haken, PI; Theodore Lawrence (MPI)
- All cases - 4 Projects (3-2 Physics; 1-2 Clinical)
  - 4 Shared Resource Cores (Administration + 3 Physics)
- Now, response-based adaptive therapy

Response-based adaptive therapy
a transition from
optimizing “a” treatment plan
to
optimizing and adapting each patient’s course of treatment
## Standard Radiation Therapy
- Treatment based on a population estimate of what might control a tumor
- Estimated risk of normal tissue damage based on the most sensitive 5% of the population
- Treatment delivered to the initially prescribed dose
  - Stop only for unacceptable acute toxicity

## Response-Based Adaptive Therapy
- Assess pretreatment the patient's tumor and normal tissues
  - Genetically (SNPs, μRNAs)
  - With functional and molecular imaging
  - With plasma cytokines
- Determine during treatment
  - If (and what parts) of the tumor are responding
  - If (and what parts) of the normal tissues are being injured
- Adapt therapy to the individual patient’s response

## Program Premise
- We hypothesized that a treatment design that:
  - Integrates pre-treatment patient factors
  - With an adaptation strategy that uses the first part of treatment to assess tumor and normal tissue sensitivity
- Would permit us to optimize therapy for the individual patient rather than giving a population-averaged treatment that is likely to be less effective.
Program Premise

- To investigate this new paradigm we proposed that we needed to:
  - perform clinical investigations at sites likely to benefit from adaptation,
  - establish how information extracted from imaging studies could be reliably utilized
  - enhance decision support mechanisms to help account for all of the multitude of interacting issues.
- An integrated, team-based, approach; a P01

UM P01 Scientific Projects

Projects 1 & 2, Response-driven Treatment of Cancers within Volume Effect Organs, for tumors in the liver or lung, uses physiological imaging and other methods to individualize dose redistribution in normal tissues to lower toxicity while also heterogeneously irradiating tumor subvolumes to improve outcome.

UM P01 Scientific Projects

Project 3, Imaging based Assessments of Response, establishes the spatial and temporal precision of imaging-based methods for both tumor targeting and normal tissue response.

Project 4, Response-driven, Knowledge-based, Adaptive Plan Optimization, develops, investigates, and improves decision support tools and optimization strategies to take advantage of predictive models for adaptive therapy patient management.
**UM P01 Shared Resource Cores**

**Core Component A:** Administration and Statistics.

**Core Component B:** Treatment Verification and Treatment Plan Refinement, supports the clinical application of optimized adaptive therapy planning and delivery.

**Core Component C:** Quantitative Image Analysis, Processing, and Management, provides acquisition, registration, fusion, and analysis of all imaging data.

**Core Component D:** Computer Software Support, designs, develops, tests and implements data handling and software.

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**UM Program Project Grant funding timeline**

- **P01-CA059827-16:**
  - Initial competitive renewal application September, 2011
  - Notice of “likely not funded” spring, 2012
  - 4 Projects, 4 Shared Resource Cores
  - >15 RO faculty, 11 other UM faculty
  - 11 RO staff, 5.5 GSRA/Post Docs
  - 452 pages of paper per copy

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**UM Program Project Grant funding timeline**

- **P01-CA059827-16:**
  - Favorably reviewed June, 2013
  - Just in Time (JIT) request 7-9/2013
  - Just more info, no guarantees
  - Government shutdown 10/2013
  - Program “approved” December, 2013
  - Many NIH snow days Dec-Feb
  - 2nd JIT request late February, 2014
  - Notice of Award (i.e., $) May 15, 2014
**Midtreatment PET/CT-Adapted RT for NSCLC**

Effect of Midtreatment PET/CT-Adapted Radiation Therapy With Concurrent Chemotherapy in Patients With Locally Advanced Non-Small-Cell Lung Cancer
A Phase 2 Clinical Trial

Kong Ming Kong, MD, PhD; Varadharaj, Tan; Holman, PhD; Matthew Schopp, PhD; Kirk A. Frey, MD, PhD; James Hayman, MD; Milton Gross, MD; Ville Hartman, MD, Unlimited A. Hussen, MD; Martha Manczuk, PhD; Timothy White, PhD; Yee S. MD, PhD; Neil King, MD, PhD; Mark Orange, MD; Kent B. Cousar, MD; Theodore S. Lawrence, MD, PhD; Gregory P. Kalaher, MD


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**Midtreatment PET/CT-Adapted RT for NSCLC**

Pre-RT PET/CT
Based plan
70 Gy; NTCP 17%

During-RT PET/CT
Based adapted plan
86 Gy; NTCP 17%

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**RTOG 1106**

NRG Oncology
American College of Radiology Imaging Network
RTOG 1106/ACRIN 6697

Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using Midtreatment PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)
Machine learning for dose adaptation

Deep reinforcement learning for automated radiation adaptation in lung cancer

Huan Hsin Tseng, Yi Lu, and Susan Cui
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA
Jin-Tzung Chen
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA
Department of Electrical and Computer Engineering, National Taiwan University, Taipei, Taiwan
Randall K. Ten Haken and Hassan El Nagi
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA


2018 Farrington Daniels Award Winner

In a retrospective population of 114 NSCLC patients who received radiotherapy, a three component neural networks framework was developed for deep reinforcement learning (DRL) of dose fractionation adaptation.

- First, a generative adversarial network (GAN) was employed to learn patient population characteristics necessary for DRL learning from a relatively limited sample size.
- Second, a radiotherapy artificial environment (RAE) was reconstructed by a deep neural network (DNN) utilizing both original and synthetic data (by GAN) to estimate the transition probabilities for adaptation of personalized radiotherapy patients' treatment courses.
- Third, a deep Q-network (DQN) was applied to the RAE for choosing the optimal dose in a response-adapted treatment setting.
Machine learning for dose adaptation

- This multicomponent reinforcement learning approach was benchmarked against real clinical decisions that were applied in an adaptive dose escalation clinical protocol.
  - In which, 24 patients were treated based on avid PET signal in the tumor and constrained by a 17.2% normal tissue complication probability (NTCP) limit for RP2.
- The uncomplicated cure probability (P+) was used as a baseline reward function in the DRL.

DQN lung cancer application

Automated dose decisions given by DQN (black solid line) vs. clinical decision (blue dashed line) with RMS error = 0.5 Gy. An evaluation of good (green dots), bad (red dots) and potentially good decisions (orange dots) are labeled according to our own evaluation.

Multi-factorial outcome modeling in NSCLC

A multiobjective Bayesian networks approach for joint prediction of tumor local control and radiation pneumonitis in non-small-cell lung cancer (NSCLC) for response-adapted radiotherapy

Yi Lai,1,2,3 Daniel L. McShan, Martha M. Motszik, Dipenkar Ray, Theodore S. Lawrence, and Dilmit Iulty
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2Feng Hsing Kong
3Department of Radiation Oncology, Indiana University, Indianapolis, IN 46292, USA
4Randal H. Ten Haafen and Isaac D. Naaps
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Besides dosimetric information such as Lung_gEUD and Tumor_gEUD, each patient had two kinds of features:

- **Basic/Time-independent data:**
  - Clinical Factors: 12
  - Single-nucleotide polymorphisms (SNPs): 60
  - miRNAs: 62

- **Sequential/Time-dependent data for pre-, week2, week4 treatments:**
  - Cytokines:
    - pre-treatment: 30
    - week2 treatment: 30
    - week4 treatment: 30
    - Total: 90
  - PET tumor radiomics:
    - pre-treatment: 43
    - week2 treatment: 43
    - week4 treatment: 43
    - Total: 129

A multi-objective Bayesian network (MO-BN) approach was developed to identify important features for joint LC/RP2 prediction using:

- extended Markov blankets as inputs to develop a BN predictive structure,
- Cross-validation (CV) to guide the MO-BN structure learning.

Area under the free-response receiver operating characteristic (AU-FROC) curve was used to evaluate joint prediction performance.

Can be used to predict multiple radiation outcomes (LC and RP2) simultaneously.
Hallmarks of this type of P01

- A clear, important, overall common goal: telling an effective story
- A highly synergistic relationship among the projects and cores:
  - The clinical projects employ results from the physics-oriented projects, with clinical study designs that utilize technical improvements in planning and delivery of optimized radiation treatments.
  - Similarly, the main thrusts of the physics projects are the study and evaluation of improved techniques that are driven by the needs of the clinical protocols.
  - The shared resource cores are likewise heavily incorporated with all the projects, as well as with each other.
- Beyond economies of scale, a Program Project makes this all possible.

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National Cancer Institute Program Project Applications
(P01 Clinical Trial Optional)