



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

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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

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Response-based adaptive therapy

a transition from
optimizing "a" treatment plan

to
optimizing and adapting each patient's course of treatment

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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

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Response-Based Adaptive Therapy

- Assess pretreatment the patient's tumor and normal tissues
 - + Genetically (SNPs, μ RNAs)
 - + 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

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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.

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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

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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.

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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.

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UM P01 Shared Resource Cores

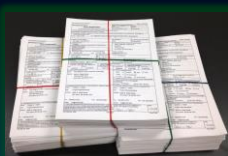
- Core Component A:** *Administration and Statistics.*
- Core Component B:** *Treatment Verification and Treatment Plan Refinement,* supports the clinical application of optimized adaptive therapy planning and delivery.
- Core Component C:** *Quantitative Image Analysis, Processing, and Management,* 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
 - + A1 Resubmission January, 2013
 - * 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

- P01CA059827-16:
 - + ~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

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Midtreatment PET/CT-Adapted RT for NSCLC

JAMA Oncology | Original Investigation

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

Feng-Ming Kong, MD, PhD; Randall K. Ten Haken, PhD; Matthew Schipper, PhD; Kish A. Frey, MD, PhD; James Hayman, MD; Milton Gross, MD; Nithya Ramnath, MD; Khaled A. Hassan, MD; Martha Matuszak, PhD; Timothy Ritter, PhD; Nan Bi, MD, PhD; Wei Wang, MD, PhD; Mark Oringer, MD; Kemp B. Cease, MD; Theodore S. Lawrence, MD, PhD; Gregory P. Kalenkerian, MD

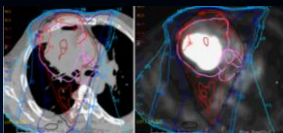
JAMA Oncol 3:1358-65, 2017. DOI: 10.1001/jamaoncol.2017.0982

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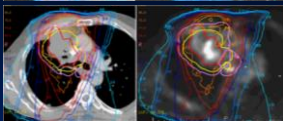


Midtreatment PET/CT-Adapted RT for NSCLC

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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Kong, et al. JAMA Oncol 3:1358-65, 2017



RTOG 1106

NRG ONCOLOGY
American College of Radiology Imaging Network

RTOG 1106/ACRIN 6697

RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Current PET Adaptive Lung Study:
Only residual PET disease targeted after adaptation; Minimize functional lung irradiated

Initial Treatment Plan from Pre-Treatment Imaging

Adaptive Treatment Plan from Mid-Treatment Imaging

Lung Perfusion (SPECT) overlaid on Planning CT

Metabolic Tumor (PET) overlaid on Planning CT

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Machine learning for dose adaptation

Deep reinforcement learning for automated radiation adaptation in lung cancer

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Randall K. Ten Haken and Issam El Naqa¹⁾
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

Med Phys 44:6690-6705, 2017. DOI: 10.1002/mp.12625

2018 Farrington Daniels Award Winner

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Machine learning for dose adaptation

- 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 training 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.

RADIATION ONCOLOGY Tseng, et al. Med Phys 44:6690-6705, 2017

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Machine learning for dose adaptation

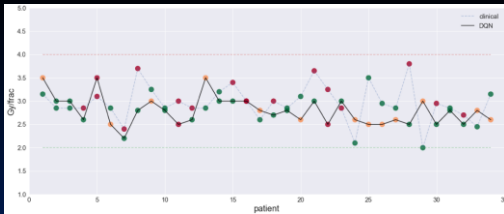
- This multicomponent reinforcement learning approach was benchmarked against real clinical decisions that were applied in an adaptive dose escalation clinical protocol.
 - + In which, 34 patients were treated based on avid PET signal in the tumor and constrained by a 17.2% normal tissue complication probability (NTCP) limit for RP2.
- The uncomplicated cure probability (P+) was used as a baseline reward function in the DRL.

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Tseng, et al. Med Phys 44:6690-6705, 2017



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.

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Tseng, et al. Med Phys 44:6690-6705, 2017



Multi-factorial outcome modeling in NSCLC

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

Yi Luo,[®] Daniel L. McShan, Martha M. Matuszak, Dipankar Ray, Theodore S. Lawrence, and Shruti Jolly
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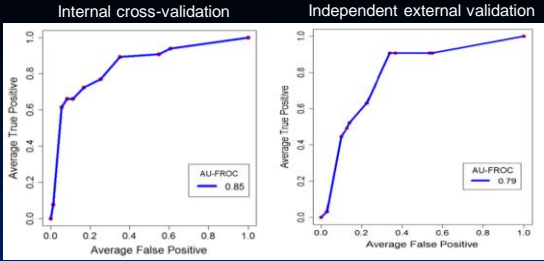
Randall K. Ten Haken and Issam El Naqa
 Department of Radiation Oncology, The University of Michigan, Ann Arbor, MI 48103, USA

Med Phys 45:3980-3995, 2018. DOI: 10.1002/mp.13029

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Multi-Objective Bayesian Network (MO-BN)



RADIATION ONCOLOGY Luo, et al. Med Phys 45:3980-3995, 2018 MICHIGAN MEDICINE UNIVERSITY OF MICHIGAN

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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| Kelly Younge, PhD | |

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Program Project Grant information

Funding Opportunity Announcement (FOA) Number

PAR-18-290

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

<https://grants.nih.gov/grants/guide/pa-files/par-18-290.html>

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