

Clinical Trials and Translational Research Advisory Committee
Translational Research Strategy Subcommittee (TRSS)
Overview and Update

October 5, 2020

Today's Agenda

1:00 Call to order and opening remarks

Dr. Dang
Dr. Davidson

1:05 TRSS Overview

Dr. Doroshov
Dr. Ujhazy

1:15 Radiation Oncology Working Group Report

Dr. Dicker
Dr. Formenti

2:00 Discussion: Future Role of TRSS

Dr. Dang
Dr. Davidson

2:25 Wrap-up and next-steps

Dr. Dang
Dr. Davidson

2:30 Adjourn

TRSS Mission Statement

Survey scientific horizons broadly and provide broad advice to NCI's advisory boards (BSA, CTAC, and NCAB) and NCI leadership on enhancing and broadening the overall translational research portfolio.

1. Help identify the most provocative and impactful translational research questions
2. Examine and identify the most important opportunities for application of new technologies to translational research
3. Identify translational research knowledge gaps

TRSS Working Groups

Glioblastoma

Co-Chairs:

- Walter J. Curran, Jr., M.D., F.A.C.R
- Chi V. Dang, M.D., Ph.D.

- Roster:
<https://deainfo.nci.nih.gov/advisory/ctac/workgroup/GBM/Roster.pdf>

Radiation Oncology

Co-Chairs:

- Adam Dicker, M.D., Ph.D., F.A.S.T.R.O.
- Silvia Formenti, M.D.

- Roster:
<https://deainfo.nci.nih.gov/advisory/ctac/workgroup/RO/Roster.pdf>

Working Group Updates – Glioblastoma

- **July 8, 2019**
 - TRSS accepted the Working Group report for submission to CTAC
- **July 17, 2019**
 - CTAC approved the Working Group report
- **May 12, 2020**
 - BSA approved an RFA to establish the NCI Glioblastoma Therapeutics Network (GTN) to enhance support for discovery and development of glioblastoma therapies
- **August 27, 2020**
 - RFA released for the GTN: <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html>

Working Group Updates – Radiation Oncology

- **October 5, 2020**
 - Presentation of the Working Group activities and report to TRSS
 - Propose motion to accept the Working Group report for submission to CTAC
- **November 4, 2020**
 - Presentation of the Working Group report to CTAC

TRSS Future Business

- Now that the reports of the *ad hoc* Working Groups on Glioblastoma and Radiation Oncology have been received, the plan is for TRSS to advise on:
 - The success and value of this approach
 - Whether this process should be used to look at other diseases or modalities

Translational Research Strategy Subcommittee
Ad hoc Working Group on Radiation Oncology
Working Group Report

Drs. Adam Dicker and Silvia Formenti

Today's Topics

- Radiation Oncology Working Group Overview
- Background & Rationale
- Recommendations

Radiation Oncology Working Group Mission Statement

Survey the scientific horizons broadly to:

1. Identify radiation oncology translational research knowledge gaps
2. Help identify the most provocative and impactful radiation oncology translational research questions to advance cancer treatment
3. Examine and identify the most important opportunities for application of new technologies to radiation oncology translational research

Radiation Oncology Working Group Membership

Co-Chairs: Adam Dicker, M.D., Ph.D.
Thomas Jefferson University

Silvia C. Formenti, M.D.
Weill Cornell Medical College

Members

Arthur W. Blackstock Jr., M.D.
Wake Forest School of Medicine

Ronald C. Chen, M.D., M.P.H.
University of Kansas

Walter J. Curran, M.D.
Emory University School of Medicine

Maximilian Diehn, M.D., Ph.D.
Stanford University School of Medicine

Theodore Sunki Hong, M.D.
Massachusetts General Hospital

David A. Mankoff, M.D., Ph.D.
University of Pennsylvania

Catherine C. Park, M.D.
University of California, San Francisco

Susan Poteat
Kidney Cancer Coalition

George Sgouros, Ph.D.
Johns Hopkins Medicine

Robert Timmerman, M.D.
University of Texas, Southwestern
Medical Center

Christina J. Tsien, M.D.
Johns Hopkins University

Ex Officiis

Kevin A. Camphausen, M.D.
National Cancer Institute

James H. Doroshov, M.D.
National Cancer Institute

Bhadrasain Vikram, M.D.
National Cancer Institute

Executive Secretary

Samantha L. Finstad, Ph.D.
National Cancer Institute

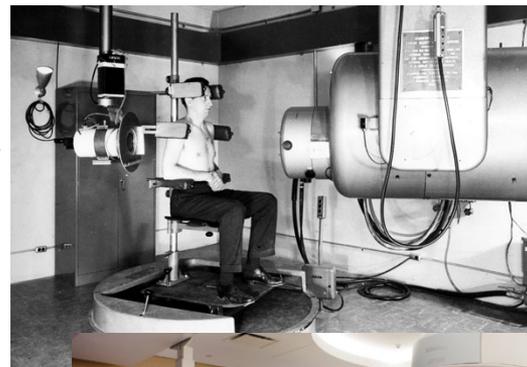
Radiation Oncology Working Group Activities Timeline

- May – October 2019: Working Group discussions by topic areas
 - Mechanisms of radiation resistance (Dr. Diehn)
 - Drug development and radiation modalities (Dr. Curran)
 - Immunotherapy and radiation (Dr. Formenti)
 - Radiopharmaceuticals (Dr. Mankoff)
 - Proton and particle therapy (Dr. Timmerman)
 - Informatics and data science (Dr. Dicker)
- October 7, 2019: In-person Working Group meeting
 - Reviewed current research landscape, identified gaps and opportunities, and developed draft recommendations

Radiation Oncology Background & Challenges

Radiation Therapy (RT)

- Used to treat cancer patients for nearly 100 years
- RT is given to over 50% of patients with cancer at some time during the course of the disease
- RT alone can be curative for early stage tumors, improvements in tumor control and survival in combination with surgery, chemotherapy, or both, for many locally advanced tumors
- The addition of concomitant chemotherapy to radiation therapy has increased the cure rate for many cancer types and, quantitatively, is one of the most important advances in cancer care over the past 30 years



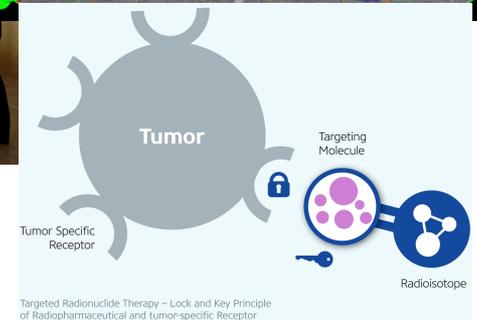
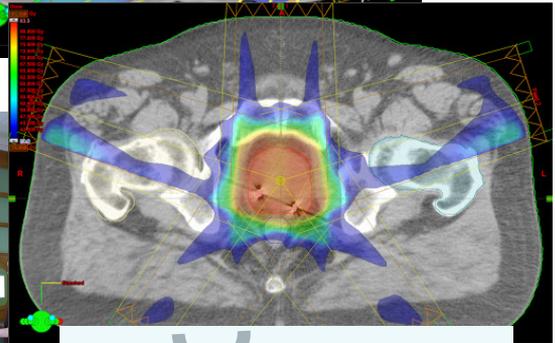
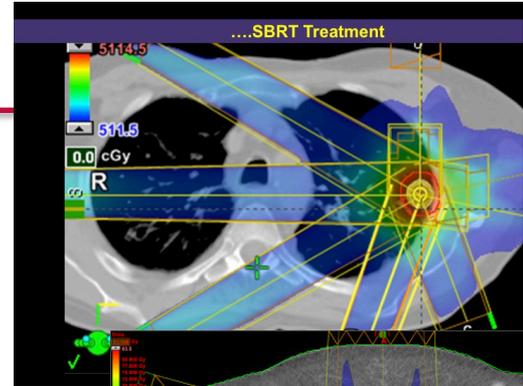
Field of Radiation Oncology is Broad

Innovation has largely been driven by device makers (physics & engineering) and not by biology or the drug industry

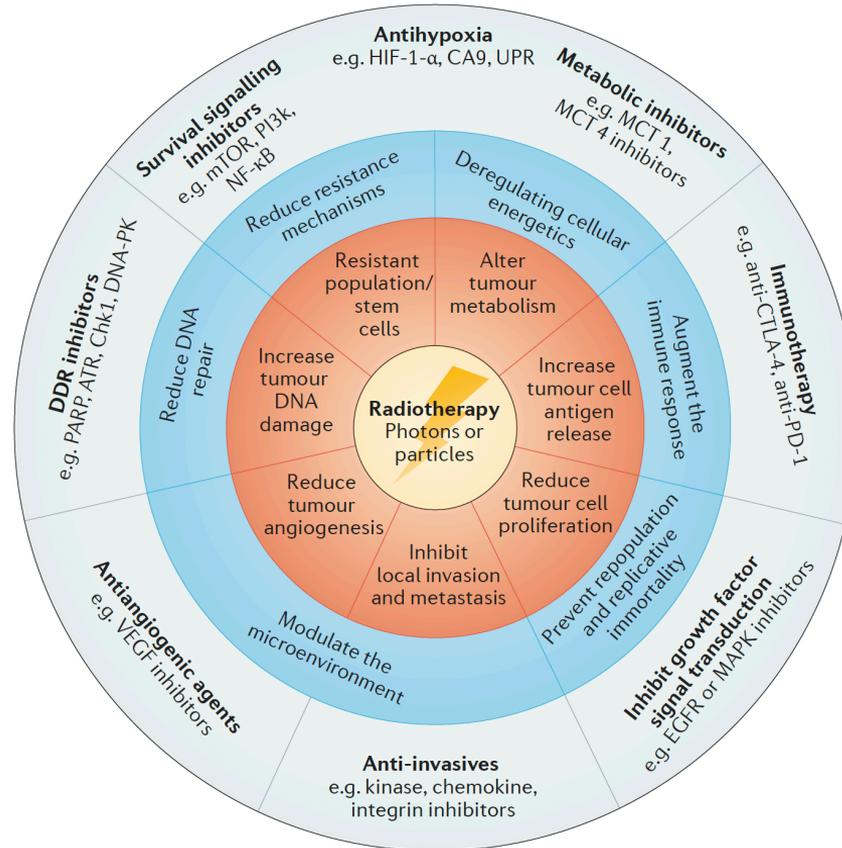
- *Stereotactic RT (radiosurgery)*
- *Intensity Modulated RT*
- *Proton and Particle Therapy*
- *Brachytherapy*

Special case:

- *Radiopharmaceutical Therapy*
(*tumor heterogeneity and companion diagnostics*)



Combination strategies to augment the biological effects of radiation



Understanding the Biological Effects of Radiation Therapy

- Major knowledge gaps remain in understanding the effects of RT on normal and malignant tissue in humans
 - *Most radiobiology studies done with established cell lines*
 - *Clinical focus has been on the precise physical delivery of radiation rather than on understanding the biological impact of that radiation*
- For precision medicine a better understanding of the biological consequences of RT is required to incorporate molecular tumor characteristics and the immune-microenvironment into treatment planning
 - *Unknown whether specific tumor signatures can be used to predict the development of resistance, and determine how the radiation type, dose, dose-rate, and fractionation schedule can be modified to preempt/overcome resistance*
 - *Need for tumor samples pre/post RT for research studies*

Testing Novel Drugs in Combination with Radiation

- Preclinical studies of radiation-drug combinations can be complex
 - *Few biological agents have been combined with radiotherapy in phase III trials*
 - *No strong support from drug or device companies to conduct trials*
- Few academic institutions possess the resources, expertise, and quality assurance mechanisms to conduct the studies
 - *Largely unknown how the dose, timing, fractionation, etc. can/should be modified when used in combination*
- Crucial to conduct these studies earlier in the drug development process

Artificial Intelligence in Radiation Oncology

2000-2010

2010-2020

2020-2030

CLINICAL SUCCESSES



Automated tumor segmentation



Inverse Treatment Planning

CURRENT DEVELOPMENTS



Personalized Outcome Prediction



Quality Improvement & Symptom Management

FUTURE DIRECTIONS



Prospective Clinical Validation



Data Sharing & Federated Learning



Interpretability & Vulnerability Studies

Need for Interdisciplinary Training in the Workforce

- Large volumes of data are generated during RT
 - *Imaging, dosimetry, fractions, etc.*
 - *Integrated with EMR data*
 - *Opportunities for collaborations with data scientists*
 - *Challenges integrating data streams*
- Among radiation oncologists, there is a perceived lack of training opportunities in bioinformatics, genomics, and immunology
- Radiomics: Advances in molecular imaging and radiopharmaceutical therapy suggest cross-fertilization with nuclear medicine and other molecular imaging specialties is very likely to be fruitful

Recommendations

Overarching Recommendation

Establish an agile and effective, coordinated, national effort for radiation oncology, to advance the study of the biologic mechanisms of radiation therapy through preclinical research and translational research studies to develop promising radiotherapeutic approaches to advance cancer care.

Recommendation I

Prioritize and support research to investigate the translational mechanistic interactions and biologic consequences of ionizing radiation to facilitate bench to bedside and back research.

Examples:

1. Study the impact of radiation type and dose on the biology of the tumor and surrounding microenvironment
2. Study the underlying mechanisms of the consequences of radiation

Recommendation II

Support longitudinal collection of clinically annotated biospecimens before, during, and after radiation therapy for researcher purposes.

Examples:

1. Develop clinical protocols, specifically for longitudinal biospecimen collection, for translational research studies, including those that evaluate radiopharmaceutical therapy (RPT)
2. Develop mechanisms for the use of clinical biospecimens for research purposes, including surgical samples of patients who have received radiation for cancer treatment

Recommendation III

Develop a coordinated infrastructure to support translational research, that could include a centralized validation laboratory, designed to leverage expertise of investigators, accelerate discovery, and validate key findings.

Examples:

1. Develop an accelerated translational research pipeline to the clinic by bringing together radiation oncology research investigators to conduct hypothesis-driven, biomarker-rich preclinical research (RTRT= rapid translation research trials)
2. Validate key preclinical findings in a designated, centralize laboratory before results publication, and disclose their successful validation in the manuscript
3. Maintain interaction and collaboration with a centralized validation laboratory (CVL), including training of laboratory members and junior investigators
4. Develop expertise for translational studies of radiopharmaceutical therapy

Recommendation IV

Prioritize and support development of animal and preclinical model systems specific for radiation therapy (normal tissue toxicity and radiation response) and utilize shared resources

Examples:

1. Develop animal and preclinical model systems of adult and pediatric tumors (e.g., 3D cell cultures and organoids)
2. Optimize model systems and methods to permit validated standard operating procedures or protocols for the collection of biospecimens and imaging before, during, and after radiation therapy
3. Develop models or algorithms to predict clinical outcomes in patients, including RT and systemic agents (chemotherapy, immunotherapy and RPT)

Recommendation V

Develop a multidisciplinary workforce and engage stakeholders with the expertise to conduct studies in translational, preclinical, and clinical radiation oncology, including leveraging data science and informatics approaches.

Examples:

1. Developing educational and outreach opportunities for the integration of radiation oncology sciences with computational imaging and computational biology
2. Training opportunities for radiation scientists to work with both human tissues and preclinical models, embracing the complexity of multidisciplinary therapies by employing modern statistics and state-of-the-art informatics approaches
3. Training opportunities for radiation oncologists and medical physicists to develop skills in techniques of radiomics and outcome prediction algorithms
4. Training opportunities for cross-disciplinary work in radiation oncology and nuclear medicine sciences
5. Training opportunities to allow scientists to study the new interfaces of radiation biology to other areas of science, such as immunology, data science, molecular imaging and other imaging sciences, pharmaceutical science (including radiopharmaceuticals), space-biology, and single-cell methodologies
6. Leverage existing funding mechanisms to provide additional funding to sustain radiation biology programs and cores

Discussion



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