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

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NIH NATIONAL CANCER INSTITUTE

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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.
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Silvia C. Formenti, M.D.
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Members

Arthur W. Blackstock Jr., M.D.
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Walter J. Curran, M.D.
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Executive Secretary

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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
- October 5, 2020: Presentation of Working Group report to TRSS
- November 4, 2020: Presentation of Working Group report to CTAC

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

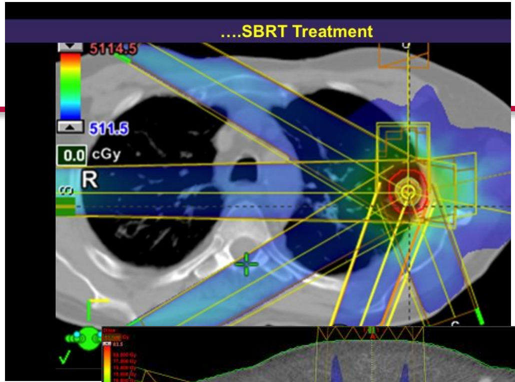
Innovation has largely been driven by device makers (physics & engineering) and not by biology or the drug industry

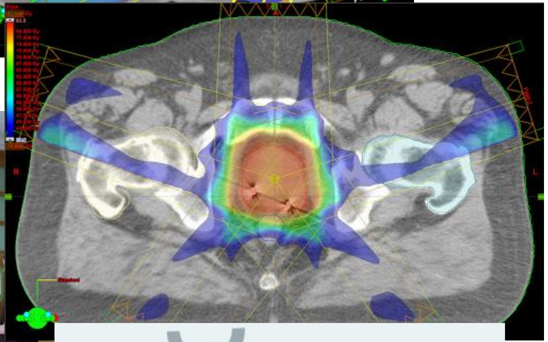
- *Stereotactic RT (radiosurgery)*
- *Intensity Modulated RT*
- *Proton and Particle Therapy*
- *Brachytherapy*

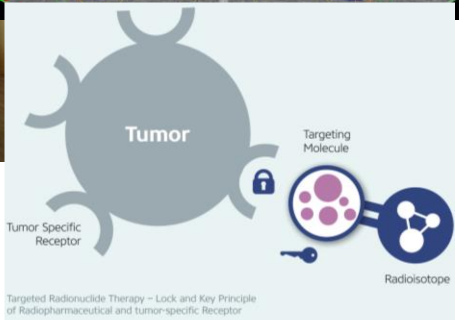
Special case:

- *Radiopharmaceutical Therapy*

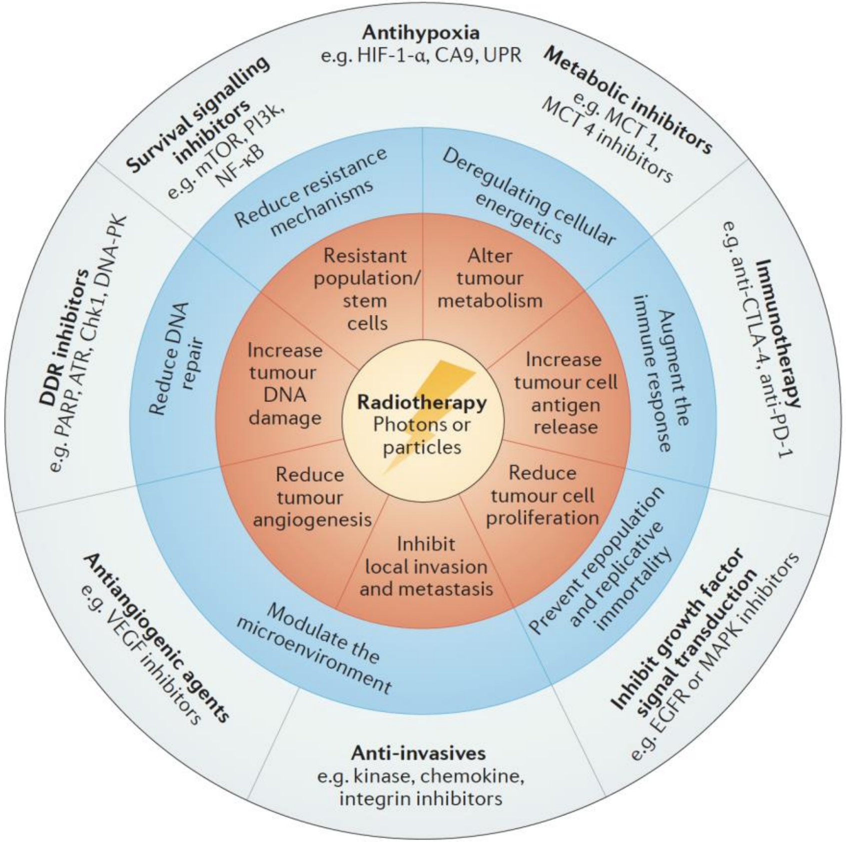
  (tumor heterogeneity and companion diagnostics)







Combination strategies to augment the biological effects of radiation



Sharma et al, Nature Reviews 2016

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*
  - *Understanding the drivers for immediate and late effects of RT regimens*
- 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	**CURRENT DEVELOPMENTS**	**FUTURE DIRECTIONS**
Automated tumor segmentation	Personalized Outcome Prediction	Prospective Clinical Validation
Inverse Treatment Planning	Quality Improvement & Symptom Management	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
   - *Specifically understanding the impact of variations in dose and type of RT*
2. Study the underlying mechanisms of the consequences of radiation
   - *Mechanisms and predictive markers of RT resistance or effectiveness*
   - *The impact of RT on the tumor heterogeneity, tumor microenvironment, and the immune system*
   - *Mechanisms of RT-induced damage to normal tissues and predictive biomarkers of adverse late effects*

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

Biospecimens should be collected from multiple cancer types, including pediatric, adolescent, and young adult (AYA) cancers, and diverse populations

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, centralized 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, AYA, 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 new multidisciplinary workforce to develop stakeholders with the expertise to conduct studies in translational, preclinical, and clinical radiation oncology.

Examples:

1. 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
2. Training opportunities for radiation oncologists and medical physicists to develop skills in techniques of radiomics and outcome prediction algorithms
3. Training opportunities for cross-disciplinary work in radiation oncology and nuclear medicine sciences, including pharmaceutical science (radiopharmaceuticals)
4. Training opportunities to allow scientists to study the new interfaces of radiation biology to other areas of science, such as immunology, molecular imaging, and pathology (single-cell methodologies, etc.)
5. Leverage existing funding mechanisms to provide additional funding to develop and sustain modern radiation biology programs and cores

QUESTIONS?

Proposed Motion: Accept the Radiation Oncology Working Group Report

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