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CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)

RADIATION ONCOLOGY WORKING GROUP

WORKING GROUP REPORT

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INTRODUCTION

The use of ionizing radiation for the treatment of cancer dates back to the late 19th century, remarkably soon after Wilhelm Conrad Roentgen described X-rays in 1895. Shortly after Marie and Pierre Curie discovered radium in 1898 the first brachytherapy treatments, involving implantation of radium tubes directly into tumors, emerged. These initial efforts stimulated a revolution of conceptual and technological innovations throughout the 20th century, forming the basis of the safe and effective therapies used today. Perhaps the most important of these developments has been the paradigm of fractionated dose delivery, technologic advances in X-ray production and delivery, improvements in imaging and computer-based treatment planning, and evolving models that predict how cancers and their microenvironment behave and how they should be approached therapeutically [1].

Most cancer patients in the United States receive some form of radiation therapy during the course of their disease, and its effects have been studied for more than a century. During that time, there has been tremendous progress in radiation therapy and advances in the treatment of patients. However, the rapid advancement of technology has resulted in multiple knowledge gaps in understanding the biology of the effects of radiation therapy on normal and malignant tissue. Historically, the study of radiobiology has provided key insights into DNA damage response (DDR) pathways, its implications in the etiology of cancer, and more recently, the immune effects of radiotherapy. Most of those radiobiology studies were done with cell lines and preclinical model systems, which are not always appropriate surrogates for studying the impact of irradiation in the clinical setting. Distinct from research in medical oncology, radiation biology research is less conducive to developing collaborations with the pharmaceutical industry, hampering the speed of progress. For the past two decades, the field of radiation oncology has been mainly driven by technology, focused on the delivery of precise, targeted doses of radiation anywhere in the body, with subsequent clinical trials building on advances in engineering and physics. Less research focus was placed on understanding the impact those doses have on their biologic targets in humans. Consequently, there is an urgent need to expand research on understanding the biologic implications of how different types, doses, and dose rates of ionizing radiation – whether administered locally, or systemically by radiopharmaceuticals – affect the tumor and surrounding tissues, with the goal of improving the therapeutic ratio and providing clinical benefit to patients.

The National Cancer Institute (NCI) Clinical Trials and Translational Research Advisory Committee (CTAC) formed a working group under the NCI Translational Research Strategy Subcommittee (TRSS) to address unanswered questions critical to advancing the field of radiation oncology. The *ad hoc* Working Group on Radiation Oncology was convened to survey the scientific horizons to identify translational research knowledge gaps and select the most provocative and impactful research questions to advance this form of cancer treatment. The Working Group also identified and discussed the most important opportunities for the application of new technologies to radiation oncology translational research. Members of the working group included clinicians and researchers with expertise in the field, as well as a patient advocate (Appendix A).

During their initial deliberations, Working Group members identified six topical areas on which to focus their discussions. Members of the Working Group participated in the deliberations of one or more of those subgroups charged to identify knowledge gaps and define scientific opportunities in their area. The topical subgroups met via webinar and developed draft recommendations for consideration by the

full Working Group, which held a face-to-face meeting at NCI on October 7, 2019 (Meeting Agenda, Appendix B). The six topical subgroups were:

- Mechanisms of Radiation Resistance
- Drug Development and Radiation Modalities
- Immunotherapy and Radiation
- Radiopharmaceuticals
- Proton and Particle Therapy
- Data Science / Informatics Approaches

The recommendations outlined in this report summarize the Working Group's deliberations to identify translational research opportunities with the potential to enhance knowledge in radiation biology and ultimately improve patient outcomes.

BACKGROUND

Radiation therapy (RT) is a widely used treatment modality and an essential component of cancer treatment for millions of patients annually, worldwide [2]. It is given to over 50% of patients with cancer at some time during the course of the disease. Although radiotherapy alone can be curative for early stage tumors, improvements in tumor control and survival have been realized in combination with surgery, chemotherapy, or both, for many locally advanced tumors. Radiation oncology also has an important role in palliative care for patients with widespread metastatic disease [3, 4]. The addition of concomitant chemotherapy to RT has increased the cure rate for many cancer types and, quantitatively, is one of the most significant advances in cancer care over the past 30 years [5]. It is important to recognize that RT, as most cancer therapies, does have short and long-term adverse effects. With the increase in the number of cancer survivors, in particular those treated during childhood, adolescence, and young adulthood, the genotoxic effects of RT are a major cause of morbidity and premature death [6-8].

In general, advances in radiation oncology have been driven by technological progress in delivering precise doses of radiation to the tumor while minimizing exposure to healthy surrounding tissues (e.g., intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), stereotactic ablative body radiotherapy (SABR), image-guided radiation therapy (IGRT)). The increased precision in the radiation dose distribution between tumors and normal tissues offers unique opportunities which can be exploited for drug development. Linear accelerators that produce photons and electrons remain the workhorses of external beam radiation therapy at present [9-14], but devices that generate heavy charged particle (protons and carbon ions) or ultrafast dose rates (FLASH radiotherapy) offer some intriguing possibilities for research, as do radiopharmaceuticals that produce electrons, alpha particles or Auger electrons. Technology is changing the way radiation oncologists treat patients, an example being the wider use of hypofractionation (fewer radiation fractions that drastically abbreviate the overall course of radiation treatment. Recent demonstrations of clinical benefit by radiopharmaceuticals represent a burgeoning field known as Radiopharmaceutical Therapy (RPT). Radioactive isotopes can “piggyback” on targeting molecules such as antibodies, small molecules, peptides, engineered antibodies/fragments, and nanoparticles, because they can home-in on, and potentially eradicate, metastases [15, 16]. However, unlike external beam radiation, the ability to precisely measure the dose deposition in a three-dimensional space from radiopharmaceuticals is less well understood and remains an unmet need that limits their clinical potential.

Over the past decade, substantial advances have been made in precision medicine through the development of molecularly targeted drugs. Individualized cancer therapy, predicated on genomic interrogation, is facilitating the selection of molecular targeting agents directed against driver mutations and aberrant intracellular signaling, targets in the tumor microenvironments, and genetic susceptibilities for synthetic lethality. However, the field of radiation oncology has not yet taken full advantage of this knowledge. Efforts to individualize radiation therapy on the biological characteristics of tumors and normal tissues are only just beginning to emerge. Studies showing that ionizing radiation can enhance the effectiveness of immunotherapeutic and non-immunotherapeutic targeted drugs have generated a great deal of excitement [17-22]. Mounting evidence supports testing radiotherapy (including RPT) in patients with overt and occult metastasis in combination with such drugs [23, 24].

Technological innovations in radiation technology have outpaced the convergence of our understanding of the underlying biological mechanisms in cancer to modify radiation clinical practices. Little is known about the possible impact of biology-driven radiation therapy, based on distinctive tumor markers like genomic alterations. Despite decades of studies focused on DNA lesioning and repair and a long tradition of radiation biology research, many gaps remain. The larger constellation of biological processes driven by radiation therapy, including survival pathways that radiation evokes warrants integration with distinctive tumor markers like genomic alterations or germline polymorphisms. While each irradiated patient today has an individualized radiation treatment plan, its specificity is based upon anatomical information, such as body size and shape, organ positioning, and expected movement of the target during treatment [25], along with histological type, location, volume and shape of the tumor, rather than the individual molecular or immunological profile. A key area of investigation with tremendous opportunity to expand is identifying the effects of radiation therapy in patients at the subcellular, cellular, and microenvironment levels. This would provide the foundation for treatment planning to maximize efficacy while also reducing short and long term toxicity, based on an individual patient's molecular and immunological profile.

Image-guided radiotherapy has enabled exploration of several different paradigms of radiation delivery, resulting in toxicity reduction, dose escalation, hypofractionation, voxelization, and adaptation. These already innovative trends in radiation oncology will work synergistically with other innovations in cancer management (e.g., biomarker strategies, novel systemic and local therapies) as part of the broader goal of precision medicine [26]. More research is also needed to elucidate how different radiation types (e.g., photon, charged particle), dose, or dose rate impact the biologic mechanisms related to radiation responses. Even for the most commonly used modalities like photons and electrons, our knowledge of how the physical dose translates into biological effects in humans remains limited. For other modalities of irradiation, even less is known [27]. For instance, there is some evidence that lower doses of radiation than those commonly delivered during definitive therapy have an effect on the tumor microenvironment and immune cells, which may have a downstream effect on influencing combination chemo- and immune-oncology treatments [28-30]. It is critical for optimizing cancer treatments to prioritize understanding of the underlying biological mechanisms modulated by radiation.

Radiation biologists have studied chromosomal instability, DNA repair mechanisms, radiation resistance, hypoxia, and radiation sensitivity, and to a lesser extent, the radiobiology of other cellular substrates, such as membranes. Findings from cell and animal models used to develop and test those hypotheses have often not been translatable to the clinical setting. In PDX models, for example, it is impossible to study the impact of radiation on the tumor microenvironment because these models fail to recapitulate human tumor growth in the context of a normal immune system. Better tumor models and investigational approaches are needed to translate preclinical findings into patient benefits. Some possibilities include novel *in-vitro* systems, such as organ-on-a-chip and organoids for studying normal tissue injury, humanized mouse models, and high-throughput assays to rapidly examine new drugs early in preclinical development.

Radiation and Immunity, An Emerging New Field

While the integrity of the immune system has been well known as a determinant of success of RT [31], it is only in the past twenty years that focal radiation has emerged as a valuable tool to convert the tumor into an *in situ* vaccine [32, 33]. Multiple groups are actively investigating this novel application of an established modality, with evidence suggesting that radiotherapy works through viral mimicry,

inducing both adjuvanticity through induction of interferon and antigenicity [22, 34]. Radiation immunogenicity has been shown to synergize with immune checkpoint blockade inhibitors [35]. The dependence of these synergistic effects on dose and fractionation, the choice of the field of treatment, and other variables are slowly emerging [30, 36, 37]. The role of dose rate and type of radiation (e.g., photons versus particles) also remain to be elucidated. Progress to expand this novel research area requires investment of resources and dedicated manpower. An adequate, interdisciplinary training for radiation biologists and immunologists interested in radiation combinations study will be needed to study the interaction of ionizing radiation and the immune system.

Radiation Oncology in the Era of Precision Medicine

To fundamentally change radiation oncology into a biomarker-driven field and incorporate molecular tumor characteristics and the immune-microenvironment into treatment planning, a better understanding of the biological consequences of radiation therapy in humans is required. Currently, other than clinical stage and histological descriptions, there is no reliable way to predict which patients with cancers are more or less likely to respond to radiation therapy (unless the patient has one of a handful of genetic syndromes, such as Bloom's syndrome, neurofibromatosis, or ataxia-telangiectasia), or will experience late effects related to their treatment. It remains unknown whether specific tumor signatures can be used to assess the development of resistance to treatment and determine whether the radiation type, dose, dose rate, and fractionation schedule can be modified in ways to overcome resistance. Hypoxia is a mechanism often invoked, but few biomarkers have been shown to predict outcomes in the clinic, and they are neither well-characterized nor validated [38]. Correlating any biomarker to clinical response is confounded by the dynamic temporal-spatial nature of radiation responses, the paucity of clinically annotated biospecimens, the lack of large-scale genomic profiling of pre- and post-radiation biospecimen repositories, and the lack of computational tools to help identify signatures. Overall, there is clear need to prioritize collection of these types of data, requiring development of an appropriately trained workforce for conducting these types of studies.

Nevertheless, many opportunities exist and there are immediate steps that can be taken. Nearly all patients treated with RT have had at least one biopsy to confirm their cancer before treatment. Very few of those biospecimens have been retrospectively investigated for potential association between the molecular profile characteristics and the patient's outcome. Even more scarce are studies on tumors that persisted or recurred after irradiation, while studies on biospecimens from patients during radiation therapy – to evaluate the evolution of the tumor and normal tissues during therapy – are virtually non-existent. There are indeed challenges in performing research biopsies during and after radiation in some sites, such as the brain, lung, and pancreas. However, other sites, such as the uterine cervix and the head and neck, are more accessible and could be pursued [19]. Studies have shown that research biopsies in irradiated tissues can be performed with minimal risk of complications [39]. For several malignancies (e.g., locally advanced rectal cancers, esophageal cancers, soft tissue sarcomas), radiation is routinely followed by resection of the entire tumor, yielding ample tissue for study. Only a minority of those patients demonstrate complete pathological response after irradiation. Studying irradiated tissues may be more difficult than studying non-irradiated tissues, and the field could benefit from innovative approaches. Making use of more readily obtainable fluid biospecimens and physiologic imaging, even during radiation/chemoradiation therapy, may be one such avenue. A systematic and coordinated "bedside to bench and back" approach may offer novel opportunities for rational biomarker development.

Well annotated biospecimens and images from clinical trials, and from patients receiving standard of care treatment, can provide insights into the mechanisms of resistance or response. Those biomarkers could subsequently be leveraged for tumor and patient-specific treatment planning [40]. The fields of radiomics and radiogenomics promise to unveil the relationship between the tumor genome, tumor imaging, and predicting radiation response [41, 42]. However, progress is hampered by the lack of biospecimens, easily accessible radiation and imaging data, and validated tumor-specific and/or microenvironment signatures of response.

Radiation-Drug Combination Therapy

Advances in our understanding of cancer biology over the past two decades have led to the development of a new generation of targeted treatments, but the clinical development of new radiation–drug combinations appears to be limited [43]. Very few of these newer biological agents have been combined with RT in phase III trials. Between 2006 and 2019 the FDA approved more than 130 novel drug indications in oncology, and only one drug (cetuximab) plus radiation combination received a specific FDA-approved indication [44].

Systemic agents, including immuno-oncology agents, are already being used in the clinic in combination with radiation therapy, but it is largely unknown how the dose and timing of either treatment modality can be optimized when they are used in combination. Many clinical trials have tried to improve the outcomes after radiation therapy by combining radiation and systemic agents, but only a few have shown success [45]. A recent positive phase III trial of a PD-1 inhibitor given post-chemoradiation led to an FDA approval [46]. Frequently, agents were tested because they had shown activity in patients with advanced disease, not because they addressed any specific targets or pathways responsible for radiation resistance. How changes in the dose, dose rate, fraction size, or type of radiation impact the effects of a systemic agent or the post-treatment molecular profile of the tumor remain poorly understood. A systematic approach to a better understanding of these many factors could enhance the effectiveness of combination therapies. Recent data do suggest that radiation therapy may enhance the effectiveness of some immunotherapeutic, as well as and non-immunotherapeutic, drugs [27, 40].

Preclinical studies of radiation-drug combinations can be complex, which can inhibit pharmaceutical companies from conducting or supporting them. It is important to perform these studies relatively early in the drug development process because so many patients can benefit from (or may be harmed by) such combinations. Few academic institutions possess the resources, expertise, and quality assurance mechanisms required for performing rigorous preclinical studies of radiation-drug combinations. The complexity is compounded by the need for studying different kinds of radiation (e.g., photons, protons and heavier charged particles, radiopharmaceuticals) at different dose rates and fractionation schemes, as well as studying the sequencing of the drug(s) and radiation. Another factor is that many standard of care regimens for locally advanced cancers include radiation combined with chemotherapeutic drugs, such as cisplatin [5]. High-throughput assays are needed for rapidly examining new drugs in combination with radiotherapy/chemoradiotherapy, as are algorithms for model-based-evaluation of radiation and putative radiation effect modifiers [47].

Drug–radiation trials are by definition multi-modality and hence logistically complex, creating a number of unique issues that can be sources of disagreement with, for example, scientific and ethical review boards. Another challenge for these trials is that the patient populations for non-RT and RT phase

IB trials are quite distinct. While most non-RT phase IB trials are performed in the advanced metastatic setting, for patients lacking other options, phase IB radiation trials often involve adding one or more novel agents to a first-line potentially curative therapy. An alternative approach is needed that allows for targeting tumors early in their natural history, combining precision RT with molecular agents to augment local tumor control or ablate micrometastatic or oligometastatic disease, or both. This approach has the potential to enhance time to progression and increase absolute survival for patients with cancer [23, 24]. However, establishing the best methodology to develop and implement precision radiotherapy approaches is a major clinical challenge. Fundamental to many of these issues is the lack of preclinical information with different doses and forms of ionizing radiation. In 2018 the FDA-AACR-ASTRO Clinical Development of Drug-Radiotherapy Combinations Workshop highlighted the potential for drug-RT treatment strategies and the challenges associated with bringing such combination therapies into the clinic [48].

Lagging Drug Development

Radiation oncology equipment vendors are less likely to support therapeutic clinical trials since they are not dependent on clinical trials for FDA approval. They rely instead on 510(k) clearance, demonstrating that the proposed device is substantially equivalent to an already legally marketed device (section 513(i)(1)(A) FD&C Act). Much clinical research is funded by the pharmaceutical industry, even within the NCI cooperative group networks [49]. One reason for this lack of progress may be that phase IB clinical trials with RT are often initiated late in a new drug's lifetime (i.e., close to the patent expiry date), suggesting a relative lack of interest by pharmaceutical companies to perform clinical trials with RT. The lag time in initiating clinical trials with RT for novel anti-cancer agents is a median of 6 years after the first phase I trial without RT [50]. Consequently, most of the drug development occurs within a specific time window that ends several years before patent expiration. Phase I trials without RT are much more likely to be sponsored by industry than phase IB trials with RT. The reasons for the lack of interest by the pharmaceutical industry are complex but may include a fear, which may or may not be justified, of radiation-associated toxicity. Considering the additional time required for late-phase (i.e., phase II/III) clinical trials, it becomes nearly impossible to obtain new approved indications before patent expiration. The pharmaceutical industry does not view RT combination trials as a path to drug registration. While the combination of radiation with novel agents holds much promise, such drug development is often initiated much too late into a drug's patent lifetime to make the process commercially viable. The net result is that, even if the RT-drug combination is found safe, the sponsor's enthusiasm for further studies has waned because its drug patent has expired [43, 51]. Shortening the lag time and increasing the priority for research will promote the commercial viability of developing novel RT–drug combinations and potentially provide clinical benefit to patients.

The need for rational approaches to developing drug-radiotherapy combinations are not unique to the United States. In 2009 the United Kingdom created the RT-Drug Combinations Consortium (RaDCom), a collaborative network of laboratories working in partnership with the pharmaceutical industry to generate preclinical data demonstrating that specific drugs can enhance radiotherapy treatment when used in combination. RaDCom engages with industry on a strategic level, to match appropriate expertise for the delivery of preclinical radiotherapy-drug combination work. This Consortium is an example of a successful collaboration between multiple stakeholders to change the radiation oncology research landscape. The United States currently lacks such an infrastructure to support radiation oncology research from preclinical to translational research and, ultimately, to clinical trials.

Radiopharmaceutical Therapy

Historically, radiopharmaceuticals have been important for some cancers and clinical scenarios where the target tissue was avid for the radionuclide, such as radioactive iodine for thyroid cancer and bone-targeted agents for relieving pain caused by skeletal metastases. Recent progress has rekindled considerable interest in this area of research and clinical practice. The field of targeted radiopharmaceutical therapy (RPT) has blossomed due to the ability to use monoclonal antibodies and other molecules as cancer-specific targeting agents and attach those to a variety of radionuclide emitters (i.e., alpha, beta and Auger emitters). Successes with RPT in difficult-to-treat solid tumors, such as neuroendocrine tumors (^{177}Lu-DOTATATE), have led to significant practice changes. Another example, ^{233}Ra-dichloride, prolonged the survival of metastatic prostate cancer patients and has been approved by the FDA [52, 53]. Emerging data points towards the considerable potential for RPT as an important approach for cancer treatment.

Advances in quantitative imaging of many RPT agents provide potential integral biomarkers (theranostics) for identifying patients most likely to benefit from such agents and individualizing their dose prescriptions [54-56]. Leveraging quantitative imaging and RPT could be viewed as synergistic and yield substantial benefits to patients by maximizing tumor control, while minimizing adverse effects by utilizing sophisticated tools for dosimetry. RPT has most commonly been used as a monotherapy. However, its efficacy can likely be enhanced via combinations with other forms of RPT, external beam radiation, non-radioactive drugs (such as DNA-damage response inhibitors), or immunotherapy. In addition, novel targets for precision oncology, thus far used only for standard small molecule and biologic drugs, may also provide targets for highly effective RPT. Optimizing the range and energy of the radiations emitted may even help kill neighboring cancer cells that do not express the target, while increasing the absorbed dose may preempt the development of acquired resistance by the cancer cells. However, progress has been hampered by the complexity of such preclinical studies and challenges in measuring dosimetry. While methods for data acquisition and dose estimation for radiopharmaceuticals have improved, current practice rarely employs individualized dosimetry, and data supporting the benefit to patients from individualized dosimetry remains scarce.

Workforce

In the United States there are approximately 14,000 medical oncologists but only about 4,000 radiation oncologists, most of whom only administer standard of care treatments [57, 58]. There is a paucity of personnel trained in preclinical and early-phase clinical radiation research. Unfortunately, the number of trained radiation biologists appears to be dropping [59, 60]. Even among medical oncologists there are comparatively few physicians with the skills and appropriate institutional infrastructure to perform phase IB studies of drugs plus radiation. Career development opportunities in this area are limited, and those that are available are not able to accommodate most of the applicants.

Advances in genomics, bioinformatics, and immunology are transforming oncology, and radiation oncologists and biologists are poised to contribute to those research efforts. According to department chairs, practicing radiation oncologists, and trainees, there are currently insufficient training opportunities in these areas [61]. Large amounts of data are generated for each patient during RT planning and treatment, including images, labs (including, increasingly, genomic information), and external highly granular data of four-dimensional radiation dose distributions. However, using those data

for research purposes remains a challenge due to the lack of databases and user-friendly tools for mining them, along with the paucity of biospecimens and trained personnel [62]. Similarly, advances in molecular analysis of tissues and molecular imaging require a workforce exposure to these disciplines for optimal integration into radiation-based treatments, including radiopharmaceuticals. An environment where clinical care teams can regularly interface with in-silico, in-vitro, and in-vivo researchers, is essential for advancing translational research. To accomplish this, a dedicated effort and infrastructure in radiation oncology for integrating data science and informatics into the clinical research and workflow, as well as interdisciplinary research teams to collect and use these data for improving patient outcomes are needed.

RECOMMENDATIONS

The working group considered the gaps and opportunities identified during their deliberations and developed a broad overarching recommendation, outlining specific recommendations for research capabilities that would have the greatest impact advancing the field of translational radiation oncology.

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.

SPECIFIC RECOMMENDATIONS FOR RESEARCH CAPABILTIES

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.

A foundational understanding of the mechanisms related to radioresistance and radioresponsiveness of normal and tumor tissues is required to drive the field of radiation oncology forward. Millions of patients are treated annually with different types of radiation therapy. The modalities of radiation therapies have changed over time, creating opportunities for further research and discovery. The mechanistic understanding of the biologic consequences of the various types of radiation, differences in dose rate, and dose and fractionation schedules warrant more research. Many unanswered questions remain.

Most basic and translational research has been done using standard approaches to radiation type (photons), dose, and fractionation, whereas, technological advancements, like SBRT, RPT and particle-based radiotherapy, remain relatively understudied. Working Group members discussed this paucity of mechanistic data during multiple subgroup calls, and they felt this was a major gap in the field. In particular, they discussed the impact of low-dose radiation (from photon, particle, as well as radiopharmaceutical therapy) on the tumor microenvironment and immune cells, understanding individualized dosimetry, and the mechanisms of radioresistance, along with how to overcome it. Another important area for mechanistic studies is to understand the drivers of late effects for patients of all ages, given longer overall survivals with modern treatment regimens.

Examples include, but are not limited to:

1. Study the impact of radiation type and dose on the biology of the tumor and surrounding microenvironment
    a) The impact and biology of heavy particles, both in tumors and healthy tissue
    b) The impact of low-dose radiation on normal tissue and tumor tissue

c) Understand the effect of dose rate on normal and tumor tissues
d) Understand the biological effects of radiopharmaceutical therapy (RPT)

2. Study the underlying mechanisms of the consequences of radiation
    a) Identify mechanisms and predictive markers of radiation therapy resistance or effectiveness in human specimens (e.g., molecular pathology, imaging markers)
    b) The impact of radiation therapy on the tumor microenvironment
        i. The impact of radiation therapy on the immune system (locally, regionally, and systemically)
        ii. Expanding existing research on mechanisms by which radiation can make tumors more immunogenic (make "cold" tumors "hot")
    c) Identify mechanisms of RT-induced damage to normal tissues and predictive biomarkers of adverse late effects
    d) The effect of radiation therapy on tumor heterogeneity
    e) Understand the effect of dose on circulating cells (blood) and the ability to use circulating tissue and biomolecules to gain biological insights into tumor and normal tissue radiobiology

RECOMMENDATION II

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

Clinically annotated biospecimens are needed to research the outcomes of radiation therapy. It is important to collect longitudinal samples to better understand the impact of radiation therapy on the tumor tissue and to identify markers of radioresistance or susceptibility. Available biospecimens should be well-annotated and include genomic information (when available, radiation dose and fractionation schedule, imaging, and clinical outcomes. These data are currently not readily available to researchers, partly because of the lack of longitudinal biopsies for many cancer types, and partly due to the lack of information in existing clinical trial data and tissue repositories. It is possible to collect biospecimens through the course of the standard of care therapy, where radiation treatment is followed by tumor resection, or through specially designed tissue acquisition trials. The Working Group viewed resected tumor specimens as a "low-hanging fruit" opportunity to study why some tumors respond well to irradiation while others don't, provided that, patients consent to the use of their specimens for research purposes and the samples are well-annotated.

Examples include, but are not limited to:

1. Develop clinical protocols, specifically for longitudinal biospecimen collection, for translational research studies, including those that evaluate RPT
    a) Biospecimens should be collected from multiple cancer types, including pediatric, adolescent, and young adult (AYA) cancers, as well as diverse populations
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.

Translational radiation therapy experiments to increase the pre-clinical and clinical development pipeline can be complex and costly. Moreover, there is a lack of a larger national infrastructure for this type of research. Working Group members discussed several research findings that have not been widely validated by the field, mainly due to the lack of funds, samples, equipment, and appropriately trained workforce. It might have been possible to move the most promising findings into the clinic sooner if validation of initial observations were available. Independent duplication of results will strengthen the scientific research value and accelerate progress. It can result in a rapid adoption of new scientific methods or techniques by offering broad deployment after being tested for reproducibility. There is tremendous opportunity for moving scientific advances from preclinical research of biologic mechanisms of radiation therapy into well-constructed, biomarker-rich clinical trials that translate preclinical findings into impactful changes in clinical practice. Therefore, the Working Group recommended the creation of a Centralized Validation Laboratory (CVL) as part of a coordinated and collaborative effort to accelerate and validate discovery. The findings that emerge from the CVL can be translated to novel clinical trials via convergence with the existing, robust clinical trials infrastructure of the National Clinical Trials Network (NCTN).

Examples include, but are not limited to:

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 the CVL, including during training of laboratory members and junior investigators
4. Develop expertise for translational studies of radiopharmaceutical therapy

RECOMMENDATION IV

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

Small animal models are widely used in radiation research, and they provide key insights into cancer biology. However, current models are limited. For example, findings from model studies are not easily translatable to the clinic, even when using transgenic and patient-derived xenograft (PDX) models. Moreover, there are many other unique challenges, especially in radiation research, related to the downscaling of clinical treatment dose levels and targeting. In addition, there are not dedicated animal irradiators for all radiation types (e.g., particle beam therapy [63] and RPT).

The Working Group recommended the development of animal models specific for translational and preclinical radiation research. Appropriate animal models will facilitate more reliable and rapid translation of findings into the clinic.

Examples include, but are not limited to:

1. Develop animal and preclinical model systems of adult, AYA, and pediatric tumors (e.g., 3D cell cultures and organoids)
2. Optimize model systems 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 (e.g., 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.

Radiobiology and radiation oncology can both be considered interdisciplinary fields of research, integrating biology and physics. Traditionally, radiobiologists have focused on very basic DNA repair mechanisms and clinical radiation oncologists on clinical care. Currently, there is not a large workforce that can transverse those two fields. The technological advances of clinical radiation therapy equipment have not fostered a similar change in the type of equipment radiobiology researchers use. In fact, much of the equipment used in the basic and translational research space has not changed significantly in decades. There has also not been a great investment by technology companies in translational and preclinical research, unlike in medical oncology. Therefore, in addition to the complexity of radiobiology and radiation oncology research, there has not been much stimulation or incentive from the private sector to facilitate careers in translational and preclinical radiation oncology research. This has led to a significant decrease in the number of dedicated investigators in radiation biology research over the past 20 years, a problem that remains unresolved.

In contrast to the pharmaceutical industry, the developers and vendors of radiation delivery equipment and software, have not invested in efforts to advance translational and preclinical RT research. In order to sustain research in the novel field of combining ionizing radiation with systemic cancer agents, cross training in both radiation biology (including RPT) and cancer biology (including immunology) is required. The recent plethora of RPT agents creates a significant opportunity to encourage cross-disciplinary work in radiation oncology and nuclear medicine sciences and, thus, requires immediate attention. The Working Group recommends fostering a workforce that can take findings from the bedside to the bench, and then translate those findings back into the clinic. Creating robust mechanisms to develop and sustain careers in modern radiation biology is an essential need of the discipline.

Precision radiation oncology requires imaging prior to and during treatment, and large volumes of data generated during radiation treatment need to be investigated. Few radiation oncologists and medical physicists have the requisite informatics expertise to data mine imaging information (e.g., radiomics). While radiation oncologists themselves don't necessarily need to be informaticists, it is important to develop some understanding of informatics principles to successfully collaborate with data

scientists [62]. Creating an environment where clinical care teams can regularly interface with researchers, both at the bench and in-silico, is essential to identify and advance translational research questions. Dedicated resources are needed to build and sustain interdisciplinary research teams. Among radiation oncologists surveyed, there is a perceived lack of current training opportunities in bioinformatics, genomics, and immunology. A majority of respondents reported an interest in obtaining additional training in these areas and believed that such training would provide opportunity for career advancement [61]. In addition, ongoing advances in molecular imaging and radiopharmaceutical therapy suggest that cross-fertilization with nuclear medicine and other molecular imaging specialties is very likely to be fruitful.

Examples include, but are not limited to:

1. Develop 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, medical oncology, pediatrics, 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

SUMMARY OF THE 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.

Specific Recommendations for Research Capabilities:

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.
II. Support longitudinal collection of clinically annotated biospecimens before, during, and after radiation therapy for research purposes.
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.
IV. Prioritize and support the development of animal and preclinical model systems specific for radiation therapy (normal tissue toxicity and radiation response) and utilize shared resources.
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.

CONCLUSION

The field of radiation oncology is at an inflection point due to the generation of data in massive quantities from sources such as high-resolution medical imaging, biosensors with continuous output of physiologic metrics, genome sequencing, and electronic medical records. Combined with advances in cancer biology and immunology, radiopharmaceutical therapy, and improvements in surgical and systemic therapies, the field is poised to make substantial improvements and contributions to the lives of cancer patients. Traditional approaches to research in radiation oncology have made significant progress over the past 20 years; however, this approach may be plateauing. A new research paradigm is needed to further accelerate progress.

Technological advances and clinical research over the past few decades have given radiation oncologists the capability to personalize treatments for accurate delivery of radiation dose based on clinical parameters and anatomical information. Eradication of gross and microscopic tumors with preservation of health-related quality of life can be achieved in many patients. Current state-of-the-art techniques of photon-based radiotherapy, including IGRT, IMRT, and stereotactic radiation therapy, are approaching the physical limits of shaping high doses to the target volume. The use of novel biological concepts for personalized treatment, including radiomic-biomarker-guided prescription, combined treatment modalities, integration with immunotherapy, and the adaptation of treatment during its course will result in improvements in clinical outcomes.

This report outlines recommendations instrumental to addressing immediate knowledge gaps and pressing challenges in translational radiation oncology research. To ensure continued progress and knowledge translation, multiple barriers need to be overcome, including the currently limited partnership with industry and the challenges of effectively converging multiple disciplines. A multipronged approach that will increase the science and pipeline of agents to be clinically evaluated, generate a transdisciplinary workforce, and expand the biorepository of well annotated specimens is proposed.

Although not exhaustive, these recommendations are beneficial, not only to radiation oncology, but to the entire oncology research community. They can lay the foundation for accelerating progress toward enhancing the effectiveness of radiotherapy and improving the outcome for patients receiving radiation therapy.

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APPENDIX A: RADIATION ONOCOLOGY WORKING GROUP ROSTER

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

***Ad hoc* Working Group on Radiation Oncology**

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APPENDIX B: OCTOBER 7, 2019 WORKING GROUP MEETING AGENDA

Ad hoc Working Group on Radiation Oncology
Translational Research Strategy Subcommittee
8:00 AM – 4:30 PM ET, October 7, 2019
Conference Room 2E908, NCI Shady Grove

Agenda

8:00 – 8:20 **Welcome and Overview** **Drs. Doroshow, Dicker, and Formenti**

SUBGROUP SESSIONS

8:20 – 9:20 **Immunotherapy and Radiation** **Dr. Formenti**
Drs. Blackstock, Diehn, Timmerman, Tsien and Mrs. Poteat

9:20 – 10:20 Drug Development and Radiation Modalities Dr. Curran
Drs. Blackstock, Chen, Dicker, Diehn, Hong, Sgouros, Timmerman and Mrs. Poteat

10:20 – 10:30 Break

10:30 – 11:30 **Proton and Particle Therapy** **Dr. Timmerman**
Drs. Chen, Formenti, Hong, Mankoff, and Mrs. Poteat

11:30 – 12:30 Mechanisms of Radiation Resistance Dr. Diehn
Drs. Formenti, Hong, Mankoff, and Mrs. Poteat

12:30 – 1:30 Lunch Break

1:30 – 2:30 **Radiopharmaceuticals** **Dr. Mankoff**
Drs. Chen, Dicker, Sgouros, and Mrs. Poteat

2:30 – 3:30 Informatics Approaches Dr. Dicker
Drs. Chen, Curran, Mankoff, Park, Sgouros, Timmerman, Tsien, and Mrs. Poteat

3:30 – 3:45 Break

3:45 – 4:30 **Final Recommendation and Conclusion** **Dr. Dicker**
Additional discussions, summary and next steps