JNCI Cancer Spectrum (2021) 5(4): pkab046

doi: 10.1093/jncics/pkab046
First published online 17 May 2021
Commentary

Moving Forward in the Next Decade: Radiation Oncology Sciences for Patient-Centered Cancer Care

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Abstract

In a time of rapid advances in science and technology, the opportunities for radiation oncology are undergoing transformational change. The linkage between and understanding of the physical dose and induced biological perturbations are opening entirely new areas of application. The ability to define anatomic extent of disease and the elucidation of the biology of metastases has brought a key role for radiation oncology for treating metastatic disease. That radiation can stimulate and suppress subpopulations of the immune response makes radiation a key participant in cancer immunotherapy. Targeted radiopharmaceutical therapy delivers radiation systemically with radionuclides and carrier molecules selected for their physical, chemical, and biochemical properties. Radiation oncology usage of "big data" and machine learning and artificial intelligence adds the opportunity to markedly change the workflow for clinical practice while physically targeting and adapting radiation fields in real time. Future precision targeting requires multidimensional understanding of the imaging, underlying biology, and anatomical relationship among tissues for radiation as spatial and temporal "focused biology." Other means of energy delivery are available as are agents that can be activated by radiation with increasing ability to target treatments. With broad applicability of radiation in cancer treatment, radiation therapy is a necessity for effective cancer care, opening a career path for global health serving the medically underserved in geographically isolated populations as a substantial societal contribution addressing health disparities. Understanding risk and mitigation of radiation injury make it an important discipline for and beyond cancer care including energy policy, space exploration, national security, and global partnerships.

The scope, breadth, depth, complexity, technology, underlying science, and societal opportunities for radiation oncology have expanded dramatically over the last decade. In 2018, co-authors from the National Institutes of Health (NIH), National CancerInstitute's (NCI) Radiation Research Program (RRP), and CERN/ICTR-PHE (European Organization for Nuclear Research/ International Conference for Translational Radio-oncology-Physics for Health) jointly described emerging opportunities for the radiation sciences including but also well beyond cancer care in "Accurate, Precision Radiation Medicine" (1). It emphasized the addition of accurate physical targeting to biological targeting in a patient-centeredprecision medicine approach. It described the multifaceted composition of radiation sciences including basic physics, technology, biology, health care, energy, space exploration, and mass casualty preparedness with multiple crossroads coming together in a "radiation rotary." Since that publication, substantial advances have been achieved. An entire new dimension for radiation oncology had opened by defining dose in both biological and physical terms in an NCI Workshop ("Defining the Shades of Gy: Utilizing the Biological Consequences of Radiotherapy in the Development of New Treatment Approaches") (2). This articulated the need to define what happens biologically and physiologically to tumors and normal tissues as dose, fractionation, and type of radiation vary and the tissues rapidly adapt. This further highlights the critical need to define and measure dose delivered (3) in the

Received: 25 March 2021; **Revised:** 15 April 2021; **Accepted:** 23 April 2021

laboratory and the clinic as radiation oncology's technical ability to physically deliver radiation externally and systemically rapidly grows. Accompanying these dramatic advances in science and opportunities for what the field can bring to cancer care and society led to our field taking a broad look at career opportunities in the expanding horizon (4) including the need for our expertise in disaster preparedness (5).

The Radiation Research Program: Radiation Oncology in a Changing World

With the decade of the 2020s beginning, herein, the RRP faculty provides an overview and collective vision of the scope of the scientific opportunities encountered in the research portfolio. This is not an in-depth review and uses a limited number of key references highlighting the intersection of opportunities. Specifically, this is not an NCI research plan but an overview of emerging science for those outside of radiation oncology whose work interacts with the radiation sciences. This explanation is critical so that readers within our field understand that their work may be mentioned, but not necessarily specifically referenced. The opportunities are depicted in Figure 1.

Clinical Care Innovation

A key concept for the clinical application of radiation sciences is that it is where physics and biology merge. The current ability to physically localize radiation treatments is spectacular including external beam shaping, depth delivery of charged particles, and brachytherapy. That a target is hit requires accounting for motion, and it is recognized that even for superbly shaped fields, normal tissues are included from the margin for incorporating potential routes of spread including regional lymph nodes, transit dose to reach the tumor target, dose falloff from internal sources, and circulating and diffusing signaling molecules from the radiated tissue responding to the radiation stress. Radiopharmaceutical therapy (RPT) requires dosimetry: routes of agent distribution, elimination, and excretion. External beam techniques are being developed, which: 1) purposely aim for heterogeneity (ie, lower and higher doses within the target with spatially fractionated radiotherapy) (6); 2) use highly focused large doses with stereotactic body radiation therapy; and 3) FLASH (7), which is radiation delivered in a short pulse in a fraction of a second the biology, physiology, efficacy, and toxicity of which are being defined.

Adding biological perturbation as a component of the physical energy deposited (in SI units of Joule/kg called the gray [Gy]) provides both complexity and opportunities. Having coined the term *focused biology* years ago, we view radiation "as a drug" where the pharmacokinetics and pharmacodynamics matter (2). Dose size, radiation type, timing, and biological impact matter and are exploitable variables. As with all cancer therapies, the more they are used the better they are understood. Therefore, the initial proposed mechanisms may not be what is operative with time. That the relative biological effectiveness (RBE) at the end or edge of a particle beam matters greatly for potential toxicity with proton therapy was recognized after treatments had been administered for years (8). Our future is now exceptional technology, induced biological changes and multimodality treatments with regulatory (https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k#), and clinical implementation that require broad understanding of safety and short- and long-term efficacy as

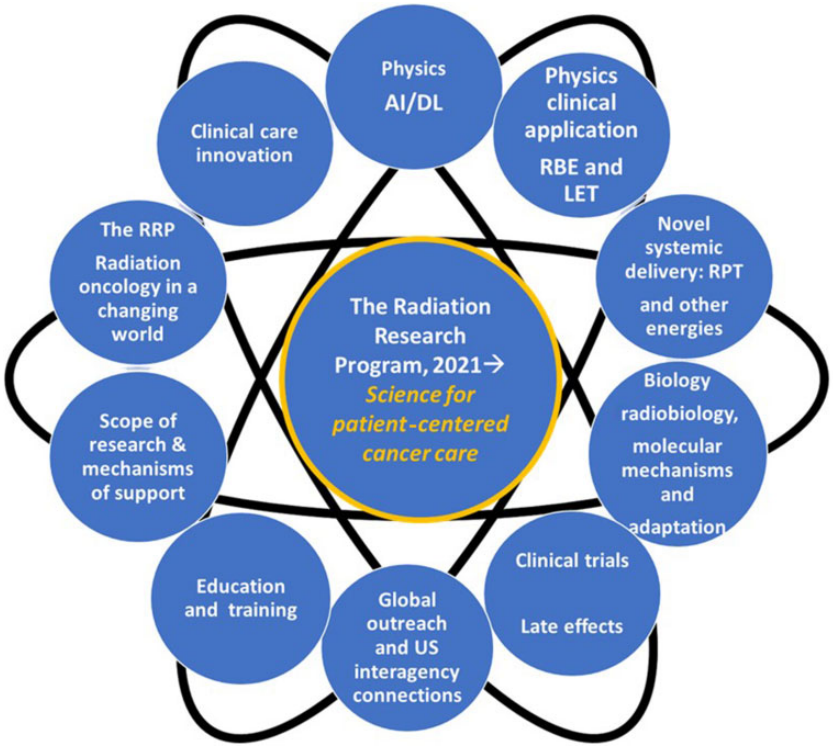

Figure 1. The Radiation Research Program, 2021: Science for patient-centered cancer care. Each circle is prepared by members of the RRP who are leading the efforts in that area. The report proceeds clockwise from "RRP: Radiation oncology in a changing world." AI = artificial intelligence; DL = deep learning; LET = linear energy transfer; RBE = relative biological effectiveness; RPT = radiopharmaceutical therapy; RRP = Radiation Research Program.

they move from research into routine clinical practice. The scope of the regulatory process is beyond this paper and the domain of the US Food and Drug Administration (FDA). The introduction of new treatments into clinical practice requires one to be cognizant of what the new treatment can cause (9). Radiation physics and biology have extraordinary opportunities to alter the next generation of cancer treatment with biological effects now being discovered.

Physics

Artificial Intelligence and Deep Learning

The successful application of artificial intelligence (AI) to computer vision, object recognition, and discovery extraction in massive datasets has found a niche in radiation oncology. Although AI has not yet been implemented in routine clinical practice, researchers are continuously developing AI tools, and more and more use cases using these tools are being reported in the literature. Advanced AI techniques of decision trees, neural networks in all their flavors, and various AI learning algorithms have been applied to clinical problems in the field (10). Recent accomplishments include fast, efficient contour autosegmentation that can drastically reduce the tedium and error rate brought about by simple reliance on voxel intensities of radiology images (11). Deep learning algorithms have been employed to generate optimal dose distributions almost on the fly, with promising potential for adaptive radiotherapy. Classifiers have been used on radiomics features as possible imaging biomarkers to correlate with underlying pathology and treatment outcomes. The integration and cross-correlation of various omics databases are now being attempted to discern biological signatures underlying the treatment response of irradiated organs and tissues. The overarching goals of these AI applications are to assist practitioners in routine tasks and free up time for patient management, to mine the enormous data generated from clinical experience for trends, and to extract hitherto unrecognized determinants of patient outcome.

Challenges and opportunities arise from these AI efforts. It is known that performance of AI algorithms such as deep learning depends on the size of the underlying data. Big data and the accompanying analytics are therefore natural desiderata, and many academic institutions, consortia, and government entities have embarked on building the necessary information technology infrastructure to harmonize, pool together, and share individual datasets sitting in institutional silos. The NCI has created the publicly accessible Cancer Research Data Commons (https://datascience.cancer.gov/data-commons) with huge repositories of genomics, proteomics, digital pathology, radiological images, and so forth. These data archives are test beds for data mining and discovery extraction. For clinical text reports, there is a challenge not just of big data, but more so, good quality data. Several task forces and working groups in many professional societies like the American Association of Physicists in Medicine, American Society for Radiation Oncology, American College of Radiology, American Society of Clinical Oncology, Healthcare Information and Management Systems Society, and others in tandem with electronic medical record providers like Epic, Cerner, and GE Healthcare's Centricity have been created precisely to address this need.

A hurdle to this data aggregation is the expense incurred in private health information anonymization to ensure required data privacy by the Health Insurance Portability and Accountability Act (https://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html), General Data Protection Regulation (https://gdpr.eu/), and other legal entities. The cost and infrastructure hampers institutions from uploading and sharing data. An alternative approach is a federated learning network, where data never leave the institution, as the machine learning model is locally installed, optimized, and continuously updated by a master server without exchanging underlying data. It has been shown that this federated approach performs close to 99% accuracy as that in the centralized, pooled data repository. Also, this data aggregation could be done per institution, so that a patient electronic health record could contain all clinical data from genomics, pathology, psychometrics, radiation treatment, and so on. Finally, new AI algorithms are emerging that have good performance even with small data such as generative adversarial networks, naïve Bayesian networks, transfer learning networks, deep reinforcement learning networks, and one-shot few-shot techniques where human experts' knowledge is embedded in the algorithm.

Applying Physics to Therapeutic Dose: RBE

Integral to modern radiation oncology are methods to measure and plan the delivery of radiation physical dose in Gy. Visualization tools, modern volumetric imaging input, computationally intense plan optimization, and an infrastructure of devices and tools allow sophisticated and precise dose deliver to any location in the human body.

Dose has always been related to biology where the clinician strives to optimize the therapeutic ratio—improving the probability of tumor control and/or reducing the likelihood of normal tissuetoxicity. Early researchers, while studying the radiobiology of protons and incorporating a linear fit of preclinical data points across published data, defined the RBE of protons to be 1.1, meaning protons were 10% more biologically powerful than photons if the same energy in Joules was delivered to the same tissue (12). Looking ahead in particle therapy, ions heavier than protons (eg, carbon, oxygen, helium) have higher and spatially variable RBEs as shown in Figure 2 (13,14).

Further investigation has shown that 1.1 is not absolute and that the RBE of protons is variable across space and tissue type (15). Research is currently underway to better understand and model RBE for different particle types to plan using biologic data that is contextual for patient factors, clinical context, and tissue type. As such, RBE currently requires a specific tissue measurement and is not yet able to be calculated because the biology is not fully understood with radiation alone or in combination with other agents.

In addition to particle dosimetry, ultra-high dose rate (defined as more than 40 Gy/s) biology is of potential high impact for the field and is called FLASH radiotherapy. Early data suggest that very rapid dose delivery may spare normal tissue more than standard dose rate radiotherapy. At the time of this article, FLASH radiation therapy was just getting underway across the globe with many physical, biological, and preclinical questions to be defined and explored (16). A recent special issue of *Radiation Research* provides background information (17,18).

Moving from prescribing radiation in physical dose terms and adding contextual biological considerations, accurate precision medicine is the field's next grand challenge (19). As these research advances are in progress, an intermediate step has been developed using the linear energy transfer (LET) that

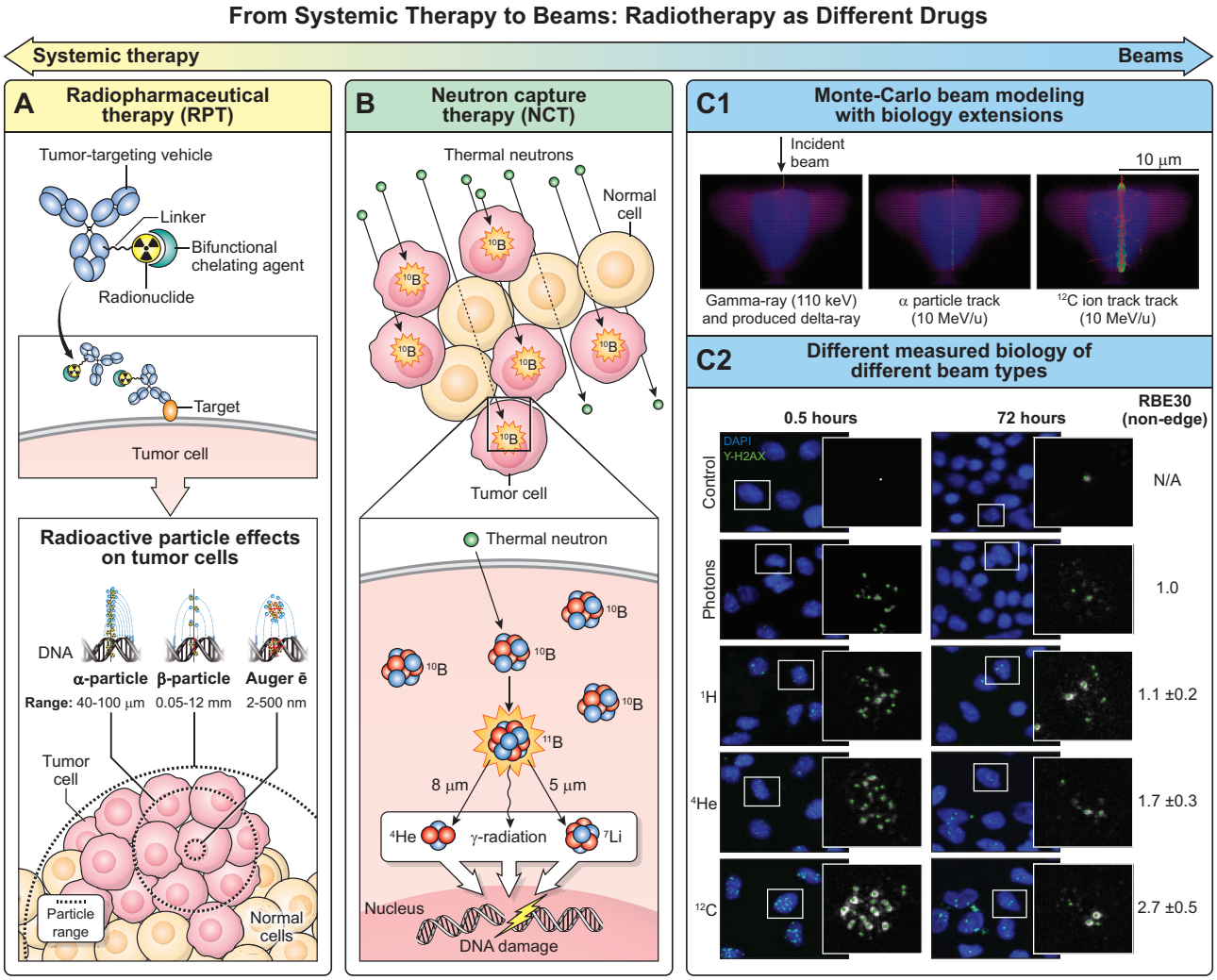

Figure 2. The conceptual similarity between systemic therapy and radiation: How tissues can experience radiation as different drugs. The figure illustrates the different scales of radiation therapy from pharmaceutical injection to external beam made up of photons or particles moving at upwards of 0.7c. Given the vast differences in the effects and scale of radiation therapy, it is fair to consider different forms of radiation as being like different drugs. **Panel A** represents the biology of RPT and notes how beta, alpha, and Auger electrons can be employed to cause DNA damage. In **Panel B**, the combination of beam and pharmaceutical processes involved in neutron capture therapy are shown. In **Panel C1**, TOPAS-nBIO (TOol for PArticle Simulations is extended to model radiobiological date) (https://gray.mgh.harvard.edu/research/software/258-topas-nbio) images show how computational modeling via Monte Carlo simulation is able to accurately model cellular events. This capacity to expand world-leading physics code that is easy to use with biology is of critical importance to the field and is actively supported by the National Cancer Institute's Informatics Technology for Cancer Research (https://itcr.cancer.gov/) program. In **Panel C2**, each image shows the resulting signal from 1 Gy of physical dose that was delivered to cells. These measurements were carried out in DAPI-labeled background (nuclear staining) to count H2AX foci. Relative biologic effect relative to Cobalt 60 beams is noted for 30% survival (RBE30) in the third column. Raw cell images and RBE values were provided by Ivana Dokic and Amir Abdollahi and were used with permission (14). The simulation images were provided to us for use in this figure by the TOPAS (http://www.topasmc.org/) team (with special thanks to Joseph Perl and Jose Ramos Mendez) (72).

varies along the beam path in protons and heavier ions but not photons. LET, crucially directly calculable, may deliver additional insight into the correct way to prescribe particles (14,20). Ultimately, it may be possible to model RBE relatively well via the use of LET, patient-specific factors like genomics, and biomarkers of radiation response that currently do not exist.

Radiopharmaceutical Therapy

RPT presents an alternative way to irradiate tumors by systemic delivery of radioactive nuclides, emitting cytotoxic alpha or beta radiation, targeted to tumor cells (21). A major advantage is the potential to eradicate an unlimited number of metastases, including those too small to be detected, with minimal toxicity to normal tissues. Currently, 7 radiopharmaceuticals are FDA approved, most notably Xofigo (^{223}radiumdichloride, the first commercially available radiopharmaceutical emitting alpha particles) for bone metastases and Lutathera (^{177}Lu-labelled DOTATATE) for neuroendocrine tumors. Additional clinical trials are in different stages of development.

New research suggests that the efficacy of RPT may be increased by combining radiopharmaceuticals with different characteristics, for instance, the difference in the clearance (elimination) routes—renal vs hepatic; the use of different carriers (peptide- and antibody-based radiopharmaceuticals); and the combination of alpha and beta emitters that have different killing ranges to allow possibly improved tumor cell killing for both small and large lesions.

An individualized treatment plan, based on assessment of radiation doses delivered to the tumor and normal tissues and an understanding of the response of these tissues to the radiation dose deposited in them, is crucial to fully utilize the potential of RPT (22). It will also facilitate combination of RPT with other cancer treatment modalities such as immunotherapy, molecularly targeted therapies, and external beam radiotherapy. Ultimately, properly optimized RPT could replace some indications for large-volume radiotherapy. RPT could also be used in salvage scenarios when chemotherapy and traditional external beam therapy are felt to either lack efficacy or come with too much toxicity (23).

Other Types of Energy Delivery Therapies

Neutron Capture Therapy (NCT). External irradiation can be used to activate cytotoxic events in tumor cells. One example is NCT, which is based on the ability of a nonradioactive isotope capturing thermal neutrons resulting in a nuclear reaction emitting cytotoxic radiation. If these reactions are selectively triggered in tumor cells, micrometastases invading normal tissues can be destroyed without damaging the surrounding healthy tissues (24). Although the efficacy of NCT has not been confirmed in randomized phase 3 trials, several reports showed promising results for glioblastoma (25,26) and head and neck cancers (27) including a recent phase 2 trial (28) of boron neutron capture therapy for recurrent or locally advanced head and neck cancer that lead to a recent approval of NCT devices by the Japanese counterpart of the FDA. In addition, there are new critical developments that might improve the chance of successful trials of NCT: 1) the introduction of an accelerator-based neutron source that allows location of NCT facilities in hospitals (29); 2) progress in boron delivery agents and formulations, including nanotechnology (30); and 3) possible use of other nuclides and their combinations (31,32) to be activated by neutrons (33).

Hyperthermia and Photodynamic Therapy (PDT). Other types of physical energy delivery are being explored to treat patients. Heat can be effective and is challenging to use (34,35). Light is being used in PDT to treat not only shallow lesions but also at depth via catheter methodologies with planning systems and new agents that respond at greater depths (36,37). Both electrical and magnetic fields show promise in treating tumors with and without the use of nanoparticles (38,39). Histotripsy (focused ultrasound, acoustic energy) for liver lesions has been used in humans with promising results (40).

Biology

Radiobiology

The impact of radiation dose, dose rate (eg, FLASH), and fractionation on the various components of the tumor microenvironment includes 1) normal cell response with repair and intrinsic tolerance to radiation cell killing; 2) tumor cell and cancer-associated stroma response with apoptosis, clonogenic, and immunogenic cell death; and 3) tumor cells evading killing by various means potentially through the selection of resistant subclones, adaptation of the tumor to the treatment regimen and proliferation of surviving cells (41,42). There is extensive interest on the effect of local radiation on immunogenic response and on causing an immune-related cell death for cancer cells not in the radiation field by the abscopal effect (43). Figure 2 illustrates the complexity and some of the opportunities for tumor cell killing by radiation therapy used in conjunction with systemic therapy for immunotherapy generally requiring an immunotherapy agent (44) and molecular targeted therapy. While radiation can enhance immune response, radiation can also produce an immune suppressive effect. Furthermore, local radiation therapy can fail to control tumors because of tumor burden, induction of prosurvival pathways, and increased proliferation (2,41,42,45) (Figure 3).

Tumor Adaptations That Impact Cancer Treatment

A major challenge is a comprehensive understanding of the molecular mechanisms that drive cancer cell resistance to radiation and other therapies such that strategies to anticipate and abate disease recurrence can be deployed. Cancer cells exposed to radiation therapies share a pervasive feature of living systems in surroundings that undergo fluctuations, chiefly the capacity to persist through evolutionary bottlenecks for repopulation after the cessation of stress. The 2 prevailing viewpoints on cancer cell resistance, which are not mutually exclusive, are that positive selection operates on a pool of cancer cells that harbor intrinsic preexisting resistance traits and that therapy induces new adaptations among select cancer cells, so-called acquired resistance. Resistance is favored in a larger tumor volume where the probability of a cancer cell within a population either having (intrinsic) or finding (acquired) a solution to cytotoxic radiation stress is increased (46). It therefore follows that heterogeneity is intertwined with therapy resistance. The advent of genomic sequencing technologies has helped define evolutionary patterns associated with radiation treatment. For example, a longitudinal analysis of glioblastoma patients suggests that the dominant clones associated with relapse were distinct from those at diagnosis and typically existed more than a decade before the commencement of radiation therapy (47). While these data credential the importance of long-standing intrinsic mutations in clonal emergence following selection pressures imposed by treatment, heterogeneity and resistance can also operate at the phenotypic level in a process known as stochastic switching (48). Stochastic switching in cancer cells involves complex relationships between metabolism, morphological dynamics, and epigenetic control of stemness (adaptive process that determines if a cell retains the property of a stem cell) and occurs on short time scales relative to processes wed to irreversible intrinsic genetic mutations. Research efforts that leverage modification of radiation dose and fractionation scheduling regimens in a manner that has potential to counter anticipated tumor adaptative responses and/or induce an adaptation that have potential for exploitation in synthetic lethality strategies are areas of interest (ie, identify responses that make the cell and/or the tumorsensitive to a molecular targeted therapy).

Clinical Trials

The opportunities for clinical trials are changing as the classification of cancer evolves from anatomical to biological. The move toward precision biological approaches, as in the Molecular Analysis for Therapy Choice trials, will become increasingly effective and open further opportunities for radiation-plus drug trials utilizing the biological perturbations from radiation (49) and radiation as part of immunotherapy (50). Table 1 includes considerations for current opportunities.

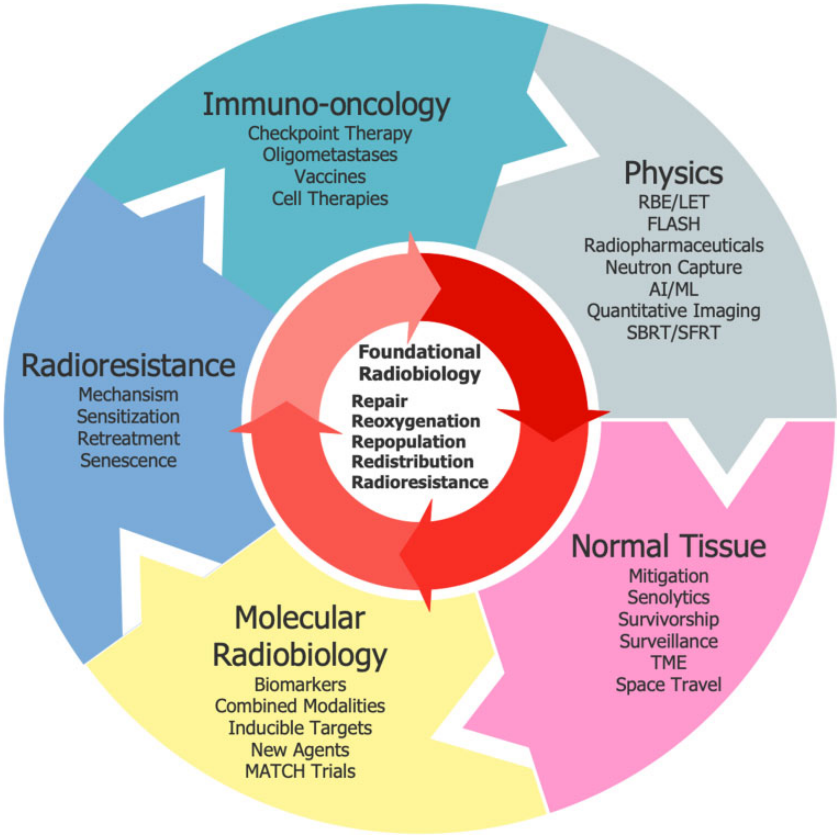

Figure 3. The spectrum of radiation biology research and clinical application. Being at the interface between physics and biology, radiation dose can be targeted for tumor cell killing and for inducing perturbations that are exploitable in a range of sequences using chemotherapy, molecular-targeted therapy, and immunotherapy. Foundational radiation biology built on clinically and laboratory-derived mathematical models and well-documented observations is at the core. Advances in knowledge in any of the components lead to improved understanding of tumor and normal tissue biology and novel treatments, done in partnership with a broad range of partners and collaborators. AI = artificial intelligence; LET = linear energy transfer; MATCH = Molecular Analysis for Therapy Choice; ML = machine learning; RBE = relative biological effectiveness; SBRT = stereotactic body radiation therapy; SFRT = spatially fractionated radiotherapy; TME = tumor microenvironment.

Late Effects

Late effects occur due to many causes and are tissue-specific heterogenous complex stress responses, often linked to reactive oxygen species (ROS), in an attempt to heal or reprogram the cellular injury. For example, when normal fibroblasts accumulate extracellular matrix proteins during differentiation after radiation therapy, fibrosis may occur in the lungs, driven by ROS via several pathways (51,52). Similarly, ROS can contribute to cardiovascular disease (53). Elevated oxidative stress in the brain can result in cognitive dysfunction stemming from neuroinflammation, a decline in neurogenesis, and degradation of neuronal structural and synaptic integrity (54).

Radiation doses of more than 0.1 Gy carry long-term risks of developing secondary cancers that generally increase linearly with dose (55). Several factors, including sex and age at exposure, modulate this risk (56). Cancer treatments also induce senescence, which is the loss of proliferation potential, in both normal cells and cancer cells and is an active area of research because of its diverse role in tumor suppression, resistance to therapy, immune escape, neoplastic transformation, and normal tissue effects.

Cancer survivors are a growing population worldwide, making the mitigation and early detection of late effects a priority (57). Some examples of currently funded research programs that include radiation therapy include the Children's Cancer Survivorship Study (58) and the National Wilms Tumors Study (59). Further, the potential systemic long-term tissue injury impact of the pandemic SARS-CoV-2 offers an opportunity for cross-disciplinary efforts to improve outcomes for millions of patients. Efforts to develop radiation injury biomarkers (60) and mitigators (57,61) have seen limited success (eg, mitigation of fibrosis) but are vanguards of new paradigms in understanding and mitigating late effects of treatment such as senescent cells noted above.

Global Outreach and US Interagency Collaborations

Although cancer is often considered a disease of high-income countries, the majority of cancer deaths are already occurring in low- and middle-income countries (62,63). The impact in disparity of access to health care has become even more apparent during the SARS-CoV-2 crisis. Access to radiation in low- and middle-income countries is dismal with some countries having almost no availability or only outdated technology. The argument against radiation therapy being "too expensive" has been made by the Global Taskforce for Radiation for Cancer Control (64) showing it is good for health and the economy. Led in large measure by the new generation of radiation oncologists, global health interest has increased, with it being the theme of the 2020 American Society for Radiation Oncology meeting (65).

The opportunity for basic, translational, and clinical research in global health is plentiful including the linkages

Table 1. General considerations for clinical trials with radiation therapy (RT)[a]

Clinical setting	Tumor types	Issues to address
Early stage: often cured by radiation alone or in combination with surgery	HNC, NSCLC, breast, prostate, cervix, medulloblastoma, Ewing sarcoma, Hodgkin disease, thymoma, and others	Identifying subgroups that do not need full-dose radiotherapy (HPV+ HNC; subtypes of medulloblastoma, etc) or any radiotherapy (breast DCIS, low-risk prostate cancers, etc). For those who do need radiotherapy reducing adverse events that impair quality of life.
Locally advanced cancers: only some can be cured by RT, usually in combination with surgery and/or systemic therapies	HNC, NSCLC, breast, prostate, cervix, medulloblastoma, Ewing sarcoma, rhabdomyosarcoma, anal cancer, rectal cancer, Hodgkin disease, other lymphomas, thymoma, osteosarcoma, and others	Understanding why some are cured and others are not (in relation to mechanisms proposed in biology and adaptation) by studying biospecimens and images before, during, and after RT. Applying that knowledge to logically study dose escalation, novel drugs and devices (immunotherapeutic agents, protons and heavier charged particles, radiopharmaceuticals, FLASH, etc).
Metastatic and other "incurable" cancers	GBM, DIPG, metastases to brain, bone, liver, lung, and other sites	Understanding which, if any, patients can be cured by focal radiotherapy. Refining and investigating immunotherapeutic approaches, novel drugs, devices, and radiopharmaceuticals, alone or in combination with "traditional" therapies.

[a]DCIS = ductal carcinoma in situ; DIPG = diffuse intrinsic pontine gliomas; GBM = glioblastoma; HPV = human papillomavirus; HNC = head and neck cancer; NSCLC = non-small cell lung cancer.

between infectious diseases, environment and diet, and non-Western genetic backgrounds. Opportunities exist for new approaches via application of telecommunications and distributed planning with cost-effective technology and networking (66). Global health enables trainees to learn many aspects of cancer care not readily available in high-income countries (67). This includes prevention (eg, human papilloma virus vaccination), early diagnosis (eg, detection and treatment of cervical intraepithelial neoplasia to prevent cervical cancer), and cost-effective, short-course treatment.

RRP, in collaboration with the NCI Center for Global Health, has supported affordable cancer technology (https://www.cancer.gov/about-nci/organization/cgh/research/affordable-cancer-technology) projects that may facilitate both cost-effective treatment and trials. Examples include a device for intensity modulated radiation therapy that reduces the cost of the hardware from hundreds of thousands to just a few hundred dollars. In keeping with radiation sciences having a broad reach and impact, global oncology provides a career opportunity for a broad range of experts and collaborators (68).

To address the challenges and opportunities presented herein, the RRP collaborates with many agencies within the US government including the Department of Health and Human Services (DHHS) (ie, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, Centers for Disease Control and Prevention, FDA, Office of the Secretary of DHHS, trans-NIH with the National Institute of Allergy and Infectious Disease, National Institute of Biomedical Imaging and Bioengineering, and National Center for Advanced Translational Sciences) and other agencies across the US government such as Defense Advanced Research Projects Agency, Department of Defense, Department of Homeland Security, Department of Energy (DoE), Environmental Protection Agency, White House Office of Science and Technology Policy, National Aeronautics and Space Agency (NASA), National Nuclear Security Agency, Nuclear Regulatory Commission, and Radiation Emergency Assistance Center/Training Site. International collaborators include CERN, International Atomic Energy Agency, World Health Organization, and other related entities listed in Supplementary Table 1 (available online).

Education and Training

Radiation biology (69) is more than 100 years old since x-rays were discovered in 1895 by Roëntgen. As the field started to understand radiation's interaction with cellular structures, physicists studied radiation's biological effects, becoming a pillar of radiation biology. In most of the 20th century, radiation biologists who were teaching radiation oncology residents had substantial physics backgrounds. Mathematically based foundational models remain both useful for safe clinical application and informative for understanding the cellular, molecular, and immunological biologies that are advancing new radiation biology concepts, just as pharmacology remains relevant to medical oncology. The teaching of radiation biology expanded with the growth of molecular biology, cellular biology, and immunology. Going forward, radiation biology education faces 2 major issues: as traditional physicist-turned-radiation biologists are retiring, there is a scarcity of foundational radiation biology mentors and training programs, and teaching radiation biology must incorporate the current understanding of molecular, cellular, and immune-biological concepts.

In an initial attempt, these 2 challenges were addressed by NCI funding an educational course, Integration of Biology and Physics into Radiation Oncology (70) to Wayne State University, whereby 240 clinicians and researchers in the radiation sciences discipline were trained over 5 years. More innovative approaches, including the NCI T32 mechanisms, are being considered to increase the necessary teaching force to educate the next generations of biologists and clinicians.

Scope of Research: Mechanisms of Support

The RRP manages a portfolio of approximately 170 active awards that is dominated by the R01 (70%) and, to a lesser extent, R21 (20%) funding mechanisms. The vast majority of research grant applications with an RRP referral are submitted as unsolicited proposals. The primary locus of review for radiation research is in the Radiation Therapeutics and Biology (https://public.csr.nih.gov/StudySections/DTCS/OTC1/RTB) study section empaneled by the NIH Center for Scientific Review; however, numerous other standing study sections and special emphasis panels may review an application given the broad range of scientific topical areas in which radiation research questions are addressed. Members of the radiation research community have raised the issues of the percentage of total NCI funding for radiation research grants, which can be complicated into how projects are "counted" in terms of the topic and field to which the research is attributed (71). As with other NCI programs, the RRP endeavors to assist with opportunities for novel topics; however, the issue of funding is more appropriately discussed at venues other than this overview. A "word cloud" of the research topics is in Supplementary Figure 1 (available online).

Conclusion: Advancing Clinical Cancer Research With Our NCI and NIH Partners

The opportunities for radiation oncology science included in Figure 1 present field-changing opportunities for multimodality cancer care, health disparities, and further advances into medical technology, energy, space exploration, policy, and global partnerships that will provide the field the opportunity to be central players in technology development, data management, and health-care systems beyond cancer. Many career opportunities are rapidly emerging, including formal collaborations within NCI, NIH, and DHHS; other US federal agencies (eg, DoE and NASA); international agencies (Supplementary Table 1, available online); academia; professional societies; and unique industry partnerships. We posit that radiation oncology has the responsibility to expand the definition of radiation dose to more formally include contextual biology and to use the skills, experience, and breadth to help address the enormous economic, environmental, and societal challenges facing us in this decade where rapid change is expected and novel solutions to recalcitrant problems are required.

To achieve these goals, the field must target a set of core goals with some general consideration of next steps related to recent workshops and new funding opportunities. A first goal is to expand the definition of dose to include the physical dose and biological dose. This will include exploring optimization of treatment based on biologic and physical dose along with potential biomarkers, including imaging, to assess the response of tumor and normal tissues to radiation. Closely related is the second goal to carefully integrate innovative technology into practice with the requisite quality assurance, safety, efficacy, and long-term assessment. This applies to external radiation sources (eg, FLASH and systemic radionuclides) both of which require dosimetry and biological mechanisms in addition to clinical outcomes.

To apply the first 2 goals requires a third goal of expanding the research models available for combined modality therapy while understanding the multiple cellular targets within a tumor and normal tissues. Rapidly emerging techniques in single-cell analysis can help define heterogeneity of responses within tumors.

A fourth goal is to build the necessary workforce, which includes educating, mentoring, and building a global community of scientists and medical professionals. The scope of expertise needed includes foundational radiobiologists, medical physicists, radiation oncologists, immunologists, medical oncologists (or clinical oncologists trained in both radiation and medical oncology), mathematicians, chemists, synthetic biologists, preclinical-model creation experts, engineers, computer scientists, biochemists, data scientists, materials scientists, social scientists, patient advocates and many more. Expanding the necessary workforce will enhance the needed research and expand the reach of radiation therapy into underserved populations globally to greatly improve lives and create opportunities to expand knowledge of cancer biology and environmental impact on treatment outcome.

The cancers we are not curing now and the late effects we are seeing are complex problems and require large teams of collaborating scientists, innovative thinking, and the utilization of both our most robust methodologies and our newest technologies to make progress.

Funding

No funding was used for this commentary.

Notes

Role of the funder: Not applicable.

Disclosures: The authors have no disclosures.

Author contributions: Conceptualization: CNC, JCB; Writing—original draft: CNC, JCB, PGSP, JC, CO, MGE, MMA, JAH, BV; Writing—review & editing; Supervision: CNC, JCB.

Acknowledgements: Thank you to Alicia Livinski, NIH Library, for assistance with editing and formatting this manuscript.

Disclaimers: This manuscript is the personal opinion of the authors and does not represent opinion or policy of the National Cancer Institute, National Institutes of Health, or US Department of Health and Human Services.

DataAvailability

No additional data applicable for this manuscript other than that referenced.

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