Title

Current status and recommendations for the future of research, teaching, and testing in the biological sciences of radiation oncology: report of the American Society for Radiation Oncology Cancer Biology/Radiation Biology Task Force, executive summar ...

Journal

International journal of radiation oncology, biology, physics, 88(1)

ISSN

0360-3016

Authors

Wallner, Paul E
Anscher, Mitchell S
Barker, Christopher A
et al.

Publication Date

2014

DOI

10.1016/j.ijrobp.2013.09.040

Peer reviewed

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Education Original Article

Current Status and Recommendations for the Future of Research, Teaching, and Testing in the Biological Sciences of Radiation Oncology: Report of the American Society for Radiation Oncology Cancer Biology/Radiation Biology Task Force, Executive Summary

Paul E. Wallner, DO,[*] Mitchell S. Anscher, MD,[†] Christopher A. Barker, MD,[‡] Michael Bassetti, MD, PhD,[§] Robert G. Bristow, MD, PhD,[‖] Yong I. Cha, MD, PhD,[¶] Adam P. Dicker, MD, PhD,[#] Silvia C. Formenti, MD,[**] Edward E. Graves, PhD,[††] Stephen M. Hahn, MD,[‡‡] Tom K. Hei, PhD,[§§] Alec C. Kimmelman, MD, PhD,[‖‖] David G. Kirsch, MD, PhD,[¶¶] Kevin R. Kozak, MD, PhD,[##] Theodore S. Lawrence, MD, PhD,[***] Brian Marples, PhD,[†††] William H. McBride, DSc,[‡‡‡] Ross B. Mikkelsen, PhD,[†] Catherine C. Park, MD,[§§§] Joanne B. Weidhaas, MD, PhD,[‖‖‖] Anthony L. Zietman, MD,[¶¶¶] and Michael Steinberg, PhD[‡‡‡]

***21st Century Oncology, LLC, and the American Board of Radiology, Bethesda, Maryland; [†]Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia; [‡]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; [§]Department of Human Oncology, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin; [‖]Departments of Radiation Oncology and Medical Biophysics, Princess Margaret Cancer Center/University of Toronto, Toronto, Ontario, Canada; [¶]Department of Radiation Oncology, Norton Cancer Center, Louisville, Kentucky; [#]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania; [**]Department of Radiation Oncology, New York University, New York, New York; [††]Departments of Radiation Oncology and Radiology, Stanford University, Stanford, California; [‡‡]Department of Radiation Oncology, University of Pennsylvania; [§§]Center for Radiation Research, Columbia University, New York, New York; [‖‖]Department of Radiation**

Reprint requests to: Paul E. Wallner, DO, 21st Century Oncology, LLC, and the American Board of Radiology, 5013 Cedar Croft La, Bethesda, MD 20814-3919. Tel: (301) 897-2091; E-mail: pwallner@theabr.org or paul.wallner@rtsx.com

Acknowledgments—The Task Force members wish to express their gratitude to Emily Wilson, American Society for Radiation Oncology Vice-President of Advocacy and Clinical Affairs, and former ASTRO staff members Raynard Washington, MPH, PhD, and Lindsey Mayberry, MPH, without whose support and efforts this project could not have been completed. We also wish to acknowledge the invaluable contributions of David R. Gius, MD, PhD, Feinberg School of Medicine, Northwestern University, and Michael L. Freeman, PhD, Vanderbilt-Ingram Cancer Center, Vanderbilt University, for their independent review and critique of the Task Force work product, and Francis Mahoney, PhD and Luther W. Brady, MD, for their insight into the background of the various "research plans" undertaken by and for the specialty. The Task Force is also grateful for the extraordinary support and consultation of Kevin Camphausen, MD, Chief, Radiation Oncology Branch, National Cancer Institute Center for Cancer Research and Eric Bernhard, PhD, Chief, Radiotherapy Development Branch, National Cancer Institute Radiation Research Program.

Note to readers—This document represents an executive summary of the Task Force report, approved by the American Society for Radiation Oncology Board of Directors. Scientific sections are abstracted to accommodate the length requirements for publication. The full Task Force report, including detailed materials and methods, background, discussion, complete scientific sections with appropriate citations, and appendices, are available as a White Paper on the ASTRO website: www.astro.org/biology.

Int J Radiation Oncol Biol Phys, Vol. 88, No. 1, pp. 11–17, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2013.09.040

Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; [¶¶]Department of Radiation Oncology, Duke University, Durham, North Carolina; [##]Department of Human Oncology, University of Wisconsin; [***]Department of Radiation Oncology, University of Michigan; [†††]Department of Radiation Oncology, Oakland University, Oakland, California; [‡‡‡]Department of Radiation Oncology, University of California Los Angeles, Los Angeles, California; [§§§]Department of Radiation Oncology, University of California San Francisco, San Francisco, California; [‖‖‖]Department of Therapeutic Radiology, Yale University, New Haven, Connecticut; [¶¶¶]Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

Received Aug 27, 2013. Accepted for publication Sep 20, 2013.

In early 2011, a dialogue was initiated within the Board of Directors (BOD) of the American Society for Radiation Oncology (ASTRO) regarding the future of the basic sciences of the specialty, primarily focused on the current state and potential future direction of basic research within radiation oncology. After consideration of the complexity of the issues involved and the precise nature of the undertaking, in August 2011, the BOD empanelled a Cancer Biology/Radiation Biology Task Force (TF). The TF was charged with developing an accurate snapshot of the current state of basic (preclinical) research in radiation oncology from the perspective of relevance to the modern clinical practice of radiation oncology as well as the education of our trainees and attending physicians in the biological sciences. The TF was further charged with making suggestions as to critical areas of biological basic research investigation that might be most likely to maintain and build further the scientific foundation and vitality of radiation oncology as an independent and vibrant medical specialty. It was not within the scope of service of the TF to consider the quality of ongoing research efforts within the broader radiation oncology space, to presume to consider their future potential, or to discourage in any way the investigators committed to areas of interest other than those targeted. The TF charge specifically precluded consideration of research issues related to technology, physics, or clinical investigations. This document represents an Executive Summary of the Task Force report.

Material and Methods

The Cancer Biology/Radiation Biology Task Force (TF) members were appointed by the American Society for Radiation Oncology (ASTRO) Board of Directors (BOD), and consisted of senior clinicians, clinical investigators, and basic research scientists as well as a cadre of early and mid-career basic and translational science investigators. An organizational meeting of the TF was convened at the 2011 Annual Meeting of the Society, following which activities were carried out by individual TF members, including conference calls and electronic communications, all with the continuous support of ASTRO staff. An extensive survey document was developed and circulated among radiation oncology and radiation research stakeholders. Scripted telephone interviews were conducted with oncology thought leaders. Following determination of scientific areas of critical interest, section writers developed detailed descriptions of the current state of the science, future potential to radiation oncology, and developmental requirements. TF documents and recommendations were developed through a consensus-based process within TF members.

Current Radiation Research Funding

To determine the current state of radiation oncology biology funding, 2 methods were employed to gather data. The first was a query from the ASTRO government relations staff to congress about actual radiation oncology funding levels; the second was a review of the publicly available grant system database. At ASTRO's request, Rep. Denny Rehberg (R-Mont.), chairman of the House Appropriations Health Subcommittee, submitted a written request in 2012 for the National Institutes of Health (NIH) and National Cancer Institute (NCI) to provide a report of the federal funding directed to radiation therapy specific projects for fiscal years 2010, 2011, and 2012.

In response to this Congressional request, NIH acknowledged that less than 1% of the total NIH budget in fiscal years 2010 and 2011 was spent on radiation oncology research, and just over 4% of NCI's total budget was spent on radiation oncology-specific projects in fiscal years 2010 and 2011; however, this report was not able to differentiate spending on clinical trials, physics research, and biological research. A more recent review by Steinberg et al corroborated these findings.

To differentiate biological research from clinical trials and physics research, all radiation oncology grants listed on http://report.nih.gov/ (date of search: November 2012) were hand-curated, separating the biology grants from the clinical and physics grants. Further, the biology grants were then subdivided by research topic. As shown in Figure 1, the 3 most funded subgroups were: radiosensitizers, normal tissue, and tumor micro-environment.

Proposed Areas of Scientific Concentration

Selection of the areas of scientific investigation discussed in detail below represented an iterative process that included TF members and non-TF basic scientists, clinician-scientists, and clinicians. Suggested topics that were determined to be more appropriately related to pure clinical, clinical/translational, physics, or technology were eliminated from consideration as being beyond the scope of the TF mission. No attempt was made to develop a catalogue of current areas of investigation in these areas within the active radiation research enterprise or to carry out an extensive evaluation of any ongoing projects or laboratory resources. Topics are not listed in any order of priority, nor was that issue considered

by the TF. TF scientific recommendations were not based on research endeavors that held the potential for greater prospects of successful funding from the NCI, as might be presumed by strict adherence to the list of provocative questions enumerated by that agency's leaders. Instead, selections were based on determination of those areas of investigation that demonstrated the greatest potential for direct and positive implications for radiation oncology. The topics listed do represent a consensus of the TF membership.

Clinical translation and biomarkers

A biomarker can be defined as "a measurable characteristic of a biological system that is indicative of normal function or disease state of the system or its response to an external factor such as a therapeutic intervention." At this time, the areas of study most relevant to the radiation oncology community are tumor radioresistance and normal tissue radiosensitivity. Much work has focused on DNA damage response pathways as potential targets to improve tumor radiosensitivity. An example of one such pathway is the epidermal growth factor receptor signal transduction pathway. Unfortunately, there is a paucity of other similar markers of radioresistance in routine clinical use.

Great effort has been focused on identifying biomarkers to predict normal tissue toxicity from radiation therapy, especially late toxicity, but clinical validity has not yet been achieved. Future needs include greater availability of banks of tissues and bodily fluids from which to identify candidate markers, with corresponding patient data. Expansion of bioinformatics capabilities to analyze enormous amounts of data will also be needed. Cooperation among researchers on a national and international scale will be essential to move this field forward. Partnering with industry and experienced biomarker researchers in other fields should help to speed the discovery and translation of biomarkers into the clinic.

Signaling pathways of normal and malignant tissue

The free radicals generated early and late after ionizing radiation exposure alter biological molecules so as to initiate a coordinated cascade of molecular responses through activation of signal transduction pathways. The nature of these alterations, both spatially and temporally, defines the uniqueness of the footprint of ionizing radiation. They are cell type-specific, being dependent on genetic wiring as well as lineage and differentiation status. Which signal transduction pathways are activated depend on many variables, including dose, dose−rate, and radiation quality, with the DNA damage response to double strand breaks being a major part of this "footprint."

Non-DNA modifications also contribute, in particular thiol proteome and lipid alterations. Cancer-associated mutations have a major impact on the pathways that are activated as these cause constitutive changes in signal transduction pathways, as do microenvironmental factors such as hypoxia. These pathways in large part determine the outcome of radiation exposure and are of primary importance in radiation oncology because they can be manipulated to alter cancer treatment outcomes. An understanding of how cells transmit radiation signals so as to modify their own behavior and that of others in local and distant sites would be an important contribution of radiobiology to clinical radiation oncology.

Tumor microenvironment and hypoxia

The past decades have seen a dramatic increase in our understanding of tumor microenvironment biology. These advances have reshaped our global view of cancer from a straightforward malproliferation of genetically damaged cells to a far more nuanced appreciation of cancer as a complex interplay between malignant cells and an array of host stromal cells. This knowledge theoretically offers opportunities for therapeutic exploitation. However, the process of leveraging our understanding of stromal contributions to malignant disease into advances in clinical radiation oncology is both painstaking and expensive. It is also essential for advancing our field.

Although several opportunities exist for clinical exploration, perhaps the 2 areas of interest closest to therapeutic impact are angiogenesis and tumor immunology. Despite approval of the first targeted antiangiogenic agent for human use nearly a decade ago, several key questions remain regarding how best to incorporate antiangiogenics into radiation regimens. The incorporation of immune-modulating agents with radiation is an even less mature area of research. Nonetheless, manipulation of the immune system in conjunction with radiation therapy is enormously promising. Dedicated translational research along both these lines, and others, will permit transformation of the preclinical promise of tumor microenvironment targeting strategies into improved patient outcomes.

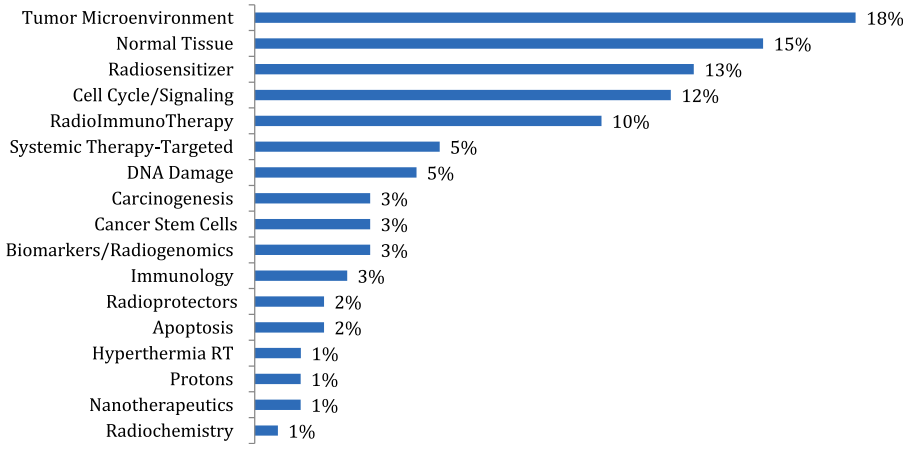

Fig. 1. Areas of Research Specialization.

Radiation sensitizers and protectors

Radiation sensitizers and protectors are agents that can modify the biologic effects of ionizing radiation; the most commonly studied and used of these are chemicals administered as drugs. At present, most radiosensitizers demonstrate independent biologic activity and exhibit spatial cooperativity rather than traditional radiosensitization. Moreover, numerous preclinical studies characterize the radiosensitizing capabilities of different drugs, but comprehensive mechanistic understanding in adequate models and rigorous clinical testing are lacking. Several resources for studies of radiosensitizers and radioprotectors are available, including the Cancer Therapy Evaluation Program, Radiation Research Program, and the pharmaceutical industry. It is anticipated that the discovery of traditional radiosensitizers and protectors may be possible with high-throughput screening techniques and novel preclinical models. Further study of these agents in clinical trials will be necessary. Importantly, understanding barriers to the use of radiosensitizers and radioprotectors in clinical radiation oncology practice will be crucial to advance this area of research.

Genomics and epigenetics

Unlike medical oncology, the field of clinical radiation oncology has not developed biomarkers to guide dose delivery. The basis of the discovery of existing markers in other fields is really genomics, differences in tumor DNA that predict drug sensitivity. Clinical radiation oncologists have a slightly different direction that is required because they need to balance both tumor kill and normal tissue toxicity, as surrounding tissues receive high doses of radiation. Ideally, there will be 2 areas in which genomics will solve problems in radiation oncology: the discovery and application of germ-line variants that predict radiation sensitivity to direct appropriate radiation dosing and the discovery of tumor-specific markers that predict altered radiosensitivity. Genomics is the best approach to answer these questions, and by allowing clinical radiation oncologists to tailor dose appropriately to the patient, we would be able to both improve cure rates as well as significantly decrease toxicity. As systemic cancer therapy improves, long-term side effects from radiation therapy will become more obvious, and more important to control, to avoid scenarios such as what we have seen in Hodgkin disease, where radiation has been slowly omitted over time because of late toxicity.

DNA repair in normal and malignant tissues

It is firmly established that DNA damage response (DDR) plays an integral part in pathogenesis of cancer as well as response of both normal and malignant tissues to cancer therapeutics. Significant bench-top research over the past decades has identified specific DNA repair pathways as well as signaling cell-cycle checkpoints, collectively referred to as DDR, and how these pathways contribute to maintaining genomic stability in response to DNA damaging agents. As a result, there has been an explosive interest in targeting DDR pathway molecules for cancer therapy and a recent focus in "personalized cancer therapy" has attempted to address the underlying molecular defects in tumor, resulting in "targeted therapy." Therefore cooperative effort by clinical radiation oncology field will be needed in following areas: early-phase clinical trials combining radiation and molecular agents, predictive assay to DNA damage response to radiation, access to preclinical drugs against DDR pathway molecules, and continued training in future physician scientist would be critical for advancement of radiation oncology in the future.

Tumor metabolism

Sixty years ago, Warburg observed that the rate of glycolysis is abnormally high in cancer cells even though the amount of glucose used for oxidative phosphorylation is much less than in normal cells. One explanation for this apparent anomaly is the large biosynthetic requirements of tumor cells for proliferation. Experimental pharmacological approaches exploiting these differences in metabolism appear promising, including those in combination with radiation. Clinical trials using drugs with extensive clinical histories such as dichloroacetate and metformin in combination with radiotherapy also appear promising. Future advances will depend on a more detailed understanding of the differences between normal and cancer cell metabolism, testing antimetabolic drugs with spontaneous animal tumors that more faithfully represent the clinical situation, and an increased experimental focus on their effects on the stromal cells of tumors including endothelial and inflammatory components. Experimental and clinical studies have demonstrated the importance of genetic factors in determining the effectiveness of the different antimetabolic treatment strategies (eg, the mutation status of TP53). Thus future clinical investigations into metabolic targeting in combination with radiation should have a genetic component in which the mutation status or polymorphisms of key genes involved in the pathway being investigated are evaluated in all consenting patients.

Molecular imaging and nanotechnology

Modern radiation oncology is dependent on imaging for treatment guidance and response assessment. Recently, several modalities dubbed "molecular imaging" have been developed to allow the detection, localization, and quantitation of molecular and physiologic events to complement imaging of anatomy currently possible through computed tomography and magnetic resonance imaging. These methods, including the use of nanotechnology and combined imaging and treatment "theranostics," are in their infancy and have clear potential to improve the administration and efficacy of radiation therapy. However, these imaging techniques are fundamentally different than those on which radiation oncologists have relied to date. A coordinated and rigorous program of basic and clinical research is therefore essential for the optimal introduction and adoption of molecular imaging into the practice of radiation oncology. This includes the identification of imaging targets of relevance to radiation treatment and radiation response, the development of specific molecular imaging probes and modalities, the incorporation of these methods into the clinical radiation therapy workflow, and the critical evaluation of the benefits of these novel technologies for patients.

Stem cell biology

Stem cells possess the unique ability to generate new stem cells by self-renewal and to differentiate into the specialized cells of an

organ. In many tissues, acute and late effects of radiation are a consequence of the depletion of resident tissue stem cells. By studying tissue-specific stem cells, it may be possible to design drugs or other therapies that prevent their depletion by radiation or promote their regeneration. In addition, a better understanding of the hierarchy of normal tissues from stem cells to differentiated cells has led to new models for understanding tumor cell heterogeneity. Although radiation biologists have long recognized that different cells within a tumor maintain different capacities for clonogenic survival after transplantation or irradiation, this concept has been adapted into the framework of stem cell biology in the cancer stem cell model. In this model, cancer heterogeneity is due to the presence of a small subset of cancer cells, which are endowed with the stem cell properties of self-renewal and the capacity to differentiate into nonclonogenic cancer cells. Importantly, several studies suggest that these cancer stem cells are resistant to radiation therapy. Targeting cancer stem cells with a drug during radiation therapy may improve rates of local control.

Immunology and inflammation

Cancer immunotherapy has been a dominant theme in oncology in recent years. Immune-modulating therapies have achieved dramatic responses across multiple solid tumor types, and despite its dubious past, immunotherapy has now gained acceptance as an effective oncologic therapy. Understanding the interaction of immunotherapies with radiation, chemotherapy, and surgery is essential to optimal care. Because of its noninvasive anatomically targetable nature, radiation has the potential to play a synergistic role with these novel immune-modulating agents. Radiation activates multiple pathways leading to inflammation, antigen release, and immune cell recruitment. Because of these potentiating effects, radiation also has the risk of serious toxicity when used with immunotherapy. Research into the differential mechanisms of immune stimulation and suppression by radiation is therefore essential for the effective use of radiation in conjunction with immune modulating agents. To ensure the best treatment available, it is necessary that radiation oncologists with an understanding of the immune response be intimately involved in the design of future investigations in this critical area of study.

Education and Testing

Developing curricula for the education of trainees in radiation oncology is the responsibility of the Radiation Oncology Residency Review Committee of the Accreditation Council on Graduate Medical Education; testing those trainees to assure their base of knowledge and skills is the responsibility of the American Board of Radiology (ABR). The Accreditation Council on Graduate Medical Education offers general requirements for radiation oncology residency programs regarding education in the biological sciences. The ABR offers a "study guide" for radiation and cancer biology on its website (www.theabr.org) to assist trainees preparing for the qualifying (written) examination in the basic sciences, but this guide essentially represents a compilation of all identified biology-related topics that might be included on any individual examination. ASTRO also has a radiation biology committee that has developed and maintains a study guide of basic science topics. No attempts are made in any of these outlines to prioritize listed topics, weight by "value," or to regularly eliminate topics that are diminishing in scientific or clinical relevance.

The ABR has independently taken significant steps forward to facilitate the development of a cadre of clinician-scientists within the profession by creation of the Holman Research Pathway (HRP) for initial ABR certification. The HRP has been highly successful in increasing the likelihood that trainees who have completed the program will pursue academic, research-oriented careers, but as with the primary area of federally funded research grants (R-01), candidate research projects are investigator-initiated and may lack cohesiveness with the overarching needs and direction of the specialty. Career research development among the HRP trainees and other, non-HRP clinician-scientists may be significantly hampered by the general lack of postgraduate laboratory commitment within departments and by the typical requirement that these clinician-scientists supplement their incomes via clinical care activities. Nonphysician radiation scientists are not subjected to specific organizational curricular constraints outside of their parent training institutions and, as such, form a disparate group that must somehow be developed in a more focused direction to meet the long-term needs of the specialty.

Primary responsibility for education of postresidency radiation oncology practitioners falls to specialty societies such as ASTRO and the Radiological Society of North America. These organizations have developed significant programming in the clinical and technical aspects of the specialty, but the focus on biological investigation has remained a secondary topic. The Radiation Research Society (RRS) has a Scholars-in-Training Program that organizes a 1-day workshop before its Annual Meeting, and the meeting also has a series of early morning educational review lectures. A new RRS initiative is a development fund that aims to support young investigators and junior faculty by providing funding for short-term sabbatical training and pilot/bridge grants. Because of the biological focus of RRS members, most of these efforts are directed at radiobiology.

Recommendations

It was not within the scope of the TF mandate to develop strategies to operationalize the recommendations made nor to enumerate the policy-making steps necessary to move those recommendations forward although that effort was debated. To move forward with any or all recommendations of the TF will require collaboration between multiple stakeholders, development of strategic plans and budgets, and determination of policy agendas. Attempts to prioritize areas of scientific investigation presume foreknowledge of research outcomes and the assignment of "value" to specific projects. Operational planning was not within the mandate of the TF and ranking of scientific efforts, all of which were felt to be critical to the specialty, was determined to be inappropriate.

These recommendations represent a consensus of the TF members and are not presented in any specific order of priority.

1. The TF believes that the areas of scientific investigation identified represent critical lines of investigation for the radiation oncology enterprise over the next decade and should be actively pursued by our basic science laboratories. No attempt at prioritization was deemed to be appropriate. This attempt at "trend-spotting" should in no way serve to detract from ongoing research efforts in existing programs or from the value of those efforts.
2. The TF believes that the ABR HRP should, if feasible, be expanded, as should other innovative methods of encouraging

trainee research projects and careers. The research careers and achievements of HRP and non-HRP clinician scientists will be significantly hampered if opportunities for research-only or research-focused postdoctoral opportunities are not made available. It is incumbent on leadership of the specialty that these experiences be encouraged and supported.

3. Basic science testing of residents for initial certification by the ABR should be expanded to include the areas of emerging science noted in this report. As a critical element of this expansion, areas of science felt to be more limited in current clinical relevance should be reduced in emphasis. A critical element of any increase in resident research is stable access to funding and infrastructure support necessary to enable successful implementation and completion of resident-developed projects.
4. A coordinated effort to attract PhD-level scientists to the radiation research-related areas of scientific endeavor must be established and resources for these scientists to flourish must be identified and secured.
5. The TF believes that in pursuit of these areas of investigation, a coordinated and strategic policy effort should be made within the federal research funding programs to increase support for the training, infrastructure, and projects necessary to pursue these endeavors. ASTRO and other interested stakeholders may pursue policy efforts designed to increase funding for the "general" radiation research enterprise, but in addition, efforts should be actively pursued to improve the potential for funding of specific high-value, high-quality projects and the supporting individual institutional infrastructure necessary to develop or enhance centers of excellence in radiation-related cancer biology and radiation biology. Currently, grant submissions in radiation biology as considered by the TF are evaluated and scored for funding by the NCI, Center for Scientific Review, Radiation Therapeutics and Biology Study Section. This review section considers applications involving therapeutic interactions of ionizing radiation, radionuclides, electromagnetic radiation, and heat at the molecular, cellular, organ, and patient levels. The study section roster includes physicists, imaging experts, and other reviewers not felt to be authoritative in the depth and breadth of radiation biology applications submitted. The nature of these reviews and reviewers is felt to negatively impact the scoring and potential funding of radiation biology applications, and revision of the evaluation system should become a significant ASTRO policy initiative.
6. The TF believes that the current NIH, and other federal agency methods of reporting funding for radiation-related research, significantly impedes efforts at development of cohesive policies and research strategies of interest to the specialty. A methodology by which investigators can self-designate research activities as "radiation research-related," designate relationship to a radiation oncology department, or other appropriate nomenclature should be encouraged, as should the ability to evaluate funding by this categorization.
7. The TF believes that in support of these recommendations, there should be an intensive effort to strengthen the basic cancer biology/radiation biology curricula of postgraduate training programs to better prepare residents in radiation oncology to understand and expeditiously adapt new scientific discoveries into their clinical practice and to encourage research efforts in these areas of investigation. Because many smaller training programs have limited resources available for education in every aspect of emerging areas of science, it would be worthwhile to consider a broad variety of innovative training pathways, such as online courses and centralization of some portions of resident education in the basic sciences. Where possible, trainees committed to basic research should have access to institutional funding to support participation in national and international basic science meetings. Mentoring of trainees committed to basic research must be improved and critical assistance with early career investigators grant submissions must be provided. Especially in smaller training programs, this mentorship and review may be necessary from investigators in other departments or institutions if senior mentorship is not internally available. The TF advises that grant applications from early career investigators should undergo critical and constructive senior mentor review before submission. Concurrent with adoption of emerging areas of scientific investigation into training program curricula, the ABR should update its cancer and radiation biology qualifying examination to include these new areas of investigation. Concurrent with increase in the number of potential investigators, the specialty must seek progressive growth in infrastructure and stable funding mechanisms.
8. The TF believes that ASTRO's Annual Meeting Scientific Program Committee should be encouraged to actively seek to provide podium sessions and courses on the scientific topics identified. Where the Society Annual Meeting is not felt to be an appropriate venue for focused and in-depth consideration of specific topics, development of smaller regional meetings should be considered. The nature of these designated areas of investigation are of such complexity that expansion of innovative opportunities for joint programming between ASTRO and other scientific organizations such as the American Association for Cancer Research and the Radiation Research Society should be considered. Rather than pursuing joint meetings between the various societies, which has been attempted in the past with limited success, efforts should focus on incorporation of individual speakers and/or panels, dealing with highly selected scientific topics, into regional and national meetings. Whenever possible, ASTRO should attempt to include international radiation research investigators in its programming.
9. The 5-year period following completion of residency training is critical in the establishment of research-oriented careers. This transitional period is especially important for ABR HRP trainees and other non-Holman individuals who have already exhibited a commitment to research. Just as trainees in medical oncology or pediatric oncology receive mentored basic science training for 3, 4, or more years at the postgraduate level, the TF believes that opportunities to extend protected time for mentored research training beyond the research-oriented residency or HRP are needed so that current trainees in radiation oncology have the skills, experience, and publication track record to successfully compete with oncologists from other fields when they become independent investigators. The TF recommends that ASTRO investigate expansion of a "bridge fund" program to assist these young investigators during the period before they can establish successful laboratories and attain independent research funding.
10. Radiation oncology is a relatively small specialty with a limited number of committed investigators and finite resources. As such, optimizing the work of individuals and value of resources is critical. The TF believes that a "clearinghouse" of personnel, projects, and resources should be developed and made available to interested individuals, and that ASTRO

should create a variety of opportunities for research-committed individuals to network.

11. The TF believes that the tasks enumerated in this report are of a critical concern to the Society and the specialty, such that all stakeholder organizations, including, but not limited to ASTRO, the Society of Chairmen of Academic Radiation Oncology Programs, the Association of Program Directors of Radiation Oncology Programs, the Association of Residents in Radiation Oncology, the ABR, American Association for Cancer Research, and RRS, should convene a high-level "summit" to develop a strategic plan that includes budgets and timelines to operationalize these goals. The recommendations of that summit should be incorporated into ASTRO's strategic plan and communicated to the leadership of the various funding agencies.
12. It was apparent from TF interviews that the breadth and depth of current activities in cancer biology and radiation research within the radiation oncology enterprise are little known or recognized outside of the profession. Efforts should be made to aggressively and widely "market" the activities of these researchers, especially those early in their careers.
13. The nature and rapidity of scientific progress and discoveries are such that any periodic review carried out at intervals of 5 or more years runs a significant risk of irrelevance or lack of timeliness. The TF recommends that a "Scientific Advisory Board" be convened and supported by ASTRO, with membership consisting of influential scientists and clinicians from inside the radiation oncology community and from outside that enterprise, and including individuals from outside the United States. This committee should meet periodically to review and update ASTRO scientific programs and recommend proposed policy changes. Committee members must represent a variety of scientific disciplines and career and funding levels, and, where possible, should have access to national research funding and development policy-makers.

Conclusions

The TF charge from the ASTRO BOD was to focus on the future of radiation biology research in its role of advancement of the clinical specialty of radiation oncology. In its deliberations, the TF made no effort to evaluate the merits of current radiation research centers, investigators, or projects, and none of the TF recommendations should be perceived as disparagement of those facilities, personnel, or projects. Translational (phase 1) and phase 2 or 3 clinical investigations as well as physics and technical research were not considered by the TF, except for considerations of how basic, preclinical investigation might impact those endeavors. In its discussions, the TF did consider several inexorable facts that weighed heavily on its ultimate recommendations. These included:

- Radiation oncology is, and will remain, a relatively small specialty with limited resources to support dedicated basic research efforts, but with an inordinate degree of benefit to cancer patients.
- Although the ability to deliver higher and more accurate doses of radiation has advanced the treatment of many cancers, maximizing further improvements in the outcome of cancer patients treated with radiation therapy will likely not depend on technological improvements in dose delivery, but instead will depend on advances in understanding and using the effect of radiation as a potent modulator of genetic and cellular activity.
- The nature of the radiation research enterprise is such that it will survive and flourish only if its efforts are directed primarily in support of clinical radiation oncology, rather than simply attempting to adapt agents developed by and for medical oncology to radiation-related use. The research and systemic agent needs of clinical radiation oncology are such that government funding efforts will relate more directly to answering broader scientific questions, and pharmaceutical company initiatives will focus on fulfilling more significant commercial implications. The responsibility of developing unique agents that will impact radiation effect will fall primarily on our own laboratories and investigators.

As charged, the TF has made recommendations in support of its findings, but developing operational strategies or tactics, or definition of resources necessary to bring its recommendations to fruition, were beyond the scope of the TF mission. No attempt was made to prioritize areas of scientific investigation or recommendations, but the TF does recommend that these issues be considered concurrently rather than sequentially by ASTRO policy-makers and other stakeholders.