

# ASTRO *news*

WINTER 2016

## NEW DIRECTIONS IN RADIATION TREATMENT

*How biologically based therapies are opening a world of possibilities*

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Tribute to John "Jack" Francis Fowler,  
DSc, PhD, FASTRO

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2016 Member Survey Results

**+ MORE**

# Best<sup>®</sup> Particle Therapy

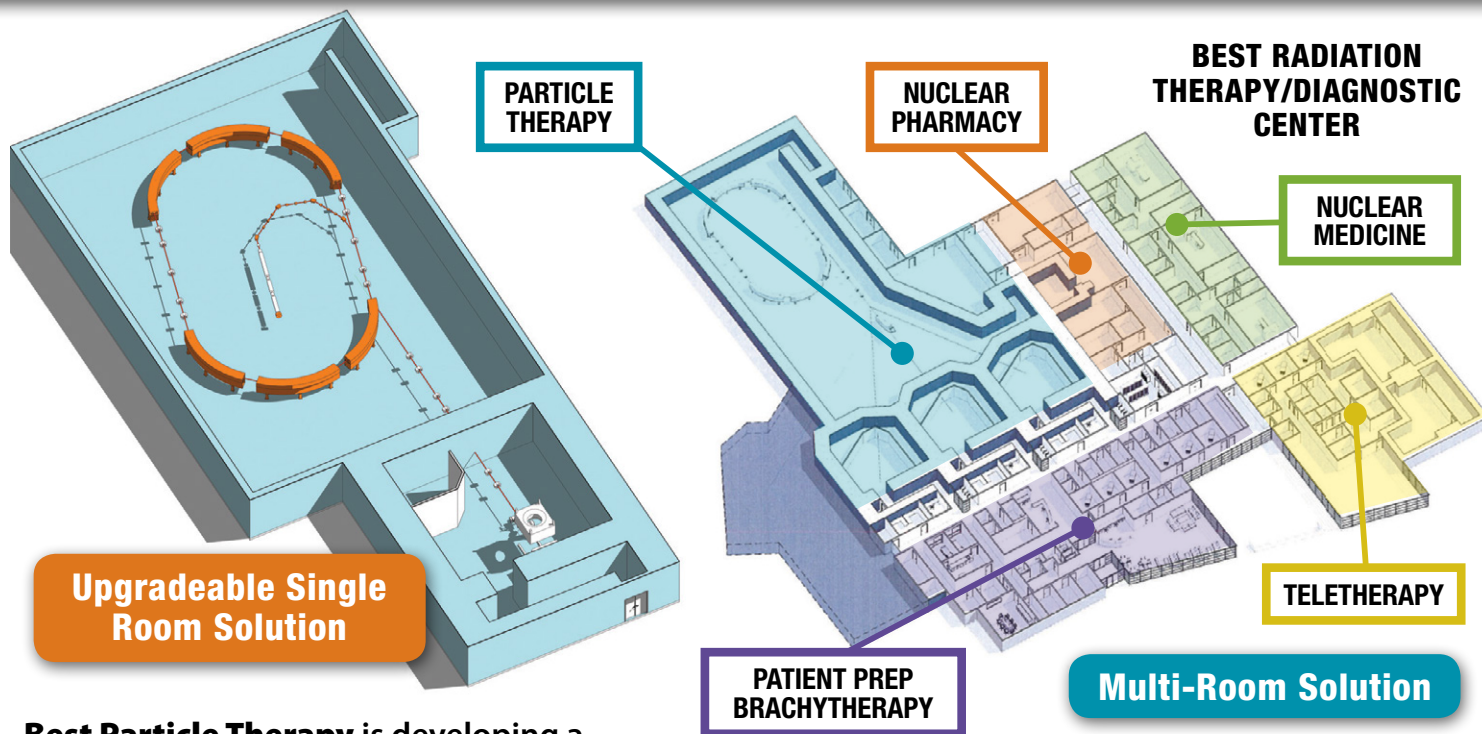


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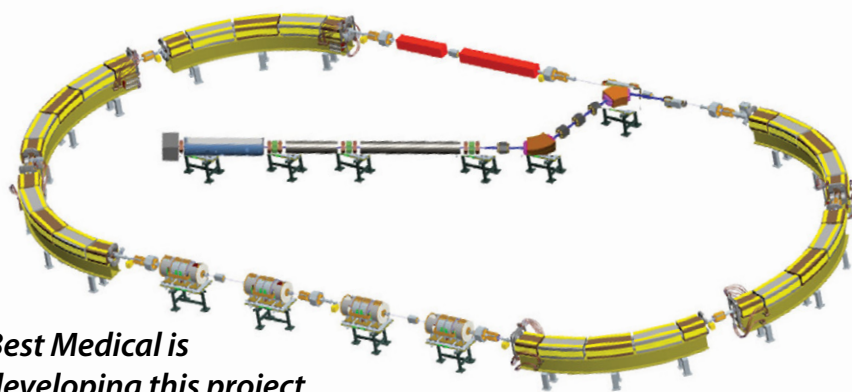


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# ASTRO news

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

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## THE PROMISE OF PERSONALIZED MEDICINE IN RADIATION ONCOLOGY

GREETINGS, FELLOW ASTRO MEMBERS, and a Happy New Year to all of you. It is my distinct pleasure and honor as the incoming editor of *ASTROnews* to present you with our latest issue.

When the ASTRO Board of Directors offered me the opportunity to helm the magazine, I knew I would be following in the footsteps of some illustrious predecessors—Lisa Kachnic, Tom Eichler, Phil Devlin, Tim Williams and the inimitable Prabhakar Tripuraneni—all of whom have had a hand in making sure *ASTROnews* kept evolving along with our specialty. It is my endeavor to make sure that this process continues and the able assistance of Anna Arnone, our new managing editor Leah Kerkman Fogarty and the freshly constituted editorial board has been, and will be, invaluable toward that end.

I am also pleased that the Board has voted to reinstate print editions of *ASTROnews* in 2017, so look for our next edition in your mailbox this spring.

But back to the present: We have a packed issue! One of our main stories deals with exploring, expanding and combining radiation research with cancer genomics and immunology. Technological advances over the past two decades have given radiation oncologists the capability to tailor doses based on clinical parameters and anatomical information. Cancer genomics holds out the promise of novel biological concepts being used for personalized treatment. Medical oncology has greatly benefited from using this genetic information. For example, it is now routine to identify driver mutations and narrow down potential responders to various forms of targeted medical therapies. Some of these responses are nothing short of miraculous.

Take the case of a man in his mid-60s—let's call him Mike—with metastatic lung cancer. He received thoracic radiation and stereotactic radiation for brain metastases under my care but subsequently developed rather unusual small-bowel vascular

metastatic lesions that bled continuously through standard chemotherapy.

Though parts of the small bowel were operated on to remove the tumor and stem the bleeding, the tumor recurred aggressively in a separate part of the bowel within a matter of weeks. At this point, Mike needed four units of packed cell transfusions weekly. After undergoing three surgeries in a span of four months, he had enough.

It was at this low point that one of the checkpoint inhibitors received FDA approval for squamous cell lung cancer. The medical oncologist, who was swiftly running out of options, placed Mike on this regimen. Within two weeks, his bleeding slowed and then ultimately stopped. A year later he is in clinical remission and displays no evidence of disease on PET imaging. "I'm lucky to be alive," Mike said recently on a follow-up visit. "If I had this disease two years ago, I would be dead by now."

While cancer genomics currently has relatively less impact on our choice of radiation treatment, there is the promise of further expanding the therapeutic window using this new biological information. In a stimulating lead article, Simon Powell and Amato Giaccia suggest that radiation strategies must account for other aspects of cancer biology and genomics (other than hypoxia) and refocus on key radiobiological targets and pathways. They argue that physicians "need to study how to use both tumor biology/genomics and normal individual variations in radiation sensitivity, radio genomics, to plan treatment."

We have been familiar with the abscopal effect—the concept of utilizing localized radiation therapy to elicit out-of-target tumor responses—for more than 50 years now. Over decades, many investigators have further elucidated the abscopal mechanism including Formenti and Demaria, who demonstrated

*Continued on next page*

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## “Cancer genomics holds out the promise of novel biological concepts being used for personalized treatment.”

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that this process was likely mediated by the immune system resulting in immunogenic tumor cell death<sup>1,2</sup>. In patients with metastatic disease, it has been widely accepted that the standard treatment for distant disease is the administration of either chemotherapy, hormonal therapy or biologically targeted agents. Arta Monjazeb and Jonathan Schoenfeld explore the possibility of transforming the use of radiation-enhanced immunotherapy from isolated case reports to wider applications through clinical trials. Encouragingly, dozens of trials are investigating combinations of radiation therapy and immunotherapy, and more are in the offing! The meld of radiotherapy with immunotherapy could potentially shift the focus from direct tumor kill to immunomodulation in patients with metastatic disease, creating a real possibility of shifting the treatment paradigm yet again for radiation oncologists.

As David Beyer states in his Chair’s Update: “We must be seen as leaders in the research and basic science that is exploding around us.” The future of any specialty is in the hands of a cadre of brilliant physician-scientists and researchers, and in that area we are particularly privileged to have such amazing talent—some of whom are profiled by Sewit Teckie. Paul Wallner and Amato Giaccia also offer a piece on how this new biology will find its way into the training syllabus and ABR examination in Radiation Oncology.

President Donald J. Trump was inaugurated as the 45th President of the United States after a contentious campaign season. With the Republican Party controlling the White House, the House and Senate, much may get done in the beginning of the year. President Trump has vowed broad-based tax reform, a repeal of numerous executive orders and a roll back of financial and health care regulations. While it is pretty much a given that the Affordable Care Act (ACA) won’t survive a Trump presidency and the republican Congress in its current form, there are sweeping implications in reversing a law that has already reached into our health care system in so many ways. Will the ACA exchanges go away? What will happen to health insurance prices? What happens to the coverage of pre-existing conditions? What about

the changes and payment reform efforts initiated partly because of the ACA? Hopefully all will become clearer soon.

One thing that I do not (at this point) foresee changing, however, is the new set of Medicare rules we come under this year. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) repealed the Sustainable Growth Rate (SGR) in order to replace it with the Quality Payment Program (QPP), which further consists of both the Merit-based Incentive Payment System (MIPS) and the Alternative Payment Model (APM) programs. Under the QPP, the focus of Medicare payments has shifted from the current volume-based, fee-for-service payment structure, to a more value-driven and quality-based payment system. MIPS and APMs went into effect on January 1, 2017, and participation this year will be used to determine Part B payments in 2019. ASTRO’s Quality Improvement staff outline the QPP’s requirements—it’s a must-read for those looking to be fully compliant.

Last but not least, Jack Fowler died in December of this past year. Paul Harari and Albert van der Kogel pay fitting tribute to this doyen of radiation oncology. Jack and the amazing scientific talent at the Gray Lab made pioneering contributions to our field in normal and tumor tissue radiobiology—work that helped pave the foundations of our practice. As we stand on the cusp of developments in genomics and immunology, it is inspiring to recall the feats of a man whose career spanned the entire modern history of our field, and whose time in it was noted as much for his charm, kindness and mentorship as for his staggering academic achievements.

*Dr. Mohideen is the senior editor of ASTROnews and attending physician of the Department of Radiation Oncology at Northwest Community Hospital in Arlington Heights, Illinois. He welcomes letters to the editor at [astronews@astro.org](mailto:astronews@astro.org).* 

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## MORE THINGS THAT CHANGE

**WE HAVE BEEN LIVING THROUGH A PERIOD OF ENORMOUS CHANGE.**

We have spent the past few years trying to figure out the dramatic and ongoing changes in the American health care system. If that were not enough, the recent election adds yet more uncertainty to our professional lives. Having little choice, somehow we have learned to live with that.

It is fitting that, as we speak, the ASTRO Board of Directors is engaged in creating a new strategic plan. Every few years, we need to look at what ASTRO does and ensure that it is aligned with what it needs to do for both the specialty and for individual practitioners. Focus groups held at the 2016 Annual Meeting in September got us started with a variety of different viewpoints actively sought and heard.

Each of the councils that make up the varied expertise and interests

within ASTRO have also given their input. With Board input and a professional moderator, we hope to have a dynamic plan and document to guide us for the next several years.

We have previously created and used strategic plans to make sure that ASTRO is serving the real needs of its members. In years past, we have also examined the scope of practice for radiation oncologists. We think we know what we do, but there is wide variation from practice to practice.

Some of us spend our days doing brachytherapy, others SRS or SBRT, radiopharmaceuticals or what some consider just bread-and-butter radiation oncology practice. As part of our board certification, there are many skills we are expected to demonstrate. But our practices are more than just the fund of knowledge we prove to the ABR.


I have long advocated that our scope of practice needs to keep us involved in all aspects of the care of cancer patients. Direct clinical care and managing symptoms put us in the center of the team of cancer specialists—and not as a consultant in the basement who is sought out as an afterthought. Being a clinician and not merely a technician is not only good medical care; it is vital to the survival of the specialty.

We now find ourselves faced with dramatic changes in our biologic understanding of cancers, and with new therapies available to our patients. I graduated from medical school with a solid understanding of immunology and

genetics as it was then understood. It was interesting but there were no therapies nor any treatment decisions to influence the course of care and scope of practice in radiation oncology.

That appears to be changing and it will be up to us to decide how we want to manage this change. Do we see this as something to include in our scope of practice? Will we expect practicing physicians to become knowledgeable and incorporate these advances in our clinics? Or will we be satisfied to allow other specialists to use these tools and make decisions for our patients?

I think the answer must be clear. We must be seen as leaders in the research and basic science that is exploding around us. These new therapies will be part of someone's practice. They will be tested and used in conjunction with some cancer treatments. Will radiation be integral in these new therapeutics or will we be on the periphery waiting our turn to see these patient referrals?

I hope the answer will be that we are going to develop and embrace new skills to enhance our scope of practice and take advantage of these advances. And I expect that a decade from now, when your Board of Directors embarks on another strategic planning session, they will recognize a growing specialty that has embraced new therapeutics in the scope of practice for our specialty. 



## COMMUNICATION AND COLLABORATION: ASTRO'S 2016 YEAR IN REVIEW

AS ASTRO BOARD OF DIRECTORS Chair David C. Beyer rightly states in his Chair's Update, 2016 has been a year of change for ASTRO and its members. Yet ASTRO has emerged stronger and better than ever—thanks to our ability to remain flexible, form collaborations and communicate our Society's message—both inside and outside of our field.

Toward the end of 2015, ASTRO launched its first open-access journal, *Advances in Radiation Oncology*. The open-access format allows us to be nimbler, getting research to readers more quickly. This outlet has been incredibly popular and more successful than we could have hoped—we published 52 papers in 2016, with 126 total submissions last year alone.

Also in 2016, the [ASTRO Accreditation Program for Excellence®](#) (APEX) accredited its first practices. As of press time, there were 26 APEX-accredited facilities in eight states. This independent radiation oncology practice accreditation program builds upon and integrates ASTRO's quality improvement initiatives. Over the course of the year, we've made adjustments and improvements to the program to streamline the process for participating practices.

We're also starting the third year of our RO-ILS: [Radiation Oncology Incident Learning System®](#). More than 250 practices are using RO-ILS as their error-reporting system, including major academic institutions. Through RO-ILS, we're learning lessons that will help us create relevant and timely guidelines and education for our members.

ASTRO unveiled a redesigned website, [ASTRO.org](#), in April. To reflect member priorities, our staff members worked with the ASTRO Communications Committee to design a site that's responsive and boasts a robust search engine. Website visitors can also pick a user profile, such as radiation oncologist, researcher or patient, to quickly find relevant content. We also produced several new patient education videos to assist patients and their families in learning more about radiation therapy.

In addition to a new virtual home, ASTRO headquarters found a new physical home. In May, ASTRO moved to Crystal City, a Northern Virginia suburb just outside Washington, D.C., to



strategically locate us closer to the nation's capital and the legislative activities that affect our members. Our new home is also near public transportation and Reagan National Airport, making us more conveniently located for members to visit and hold meetings. Read more about the design awards our new space has won in Society News on page 13.

Additional collaborations are forming with our colleagues in Washington, too. ASTRO met with leadership at the newly created Food and Drug Administration's [Oncology Center of Excellence](#) this past year. We began a dialogue about how ASTRO can best engage with the FDA. Many potential opportunities to work together were discussed, including sending ASTRO members FDA email alerts about drug approvals and other news relevant to our field, working with them on our upcoming [Immunotherapy Workshop](#) at the National Cancer Institute this summer and potentially holding a briefing for their staff on key research presented at our Annual Meeting.

Over the past year, ASTRO has also worked to get radiation therapy on the agenda of the Obama administration's [Cancer Moonshot Initiative](#) (CMI). Former Chair of ASTRO's Board of Directors Bruce G. Haffty, MD, FASTRO, attended a CMI event in October on behalf of the Society following months of encouragement by ASTRO for the initiative to broaden its focus and integrate radiation oncology more fully into the Moonshot effort. With the passage of the 21st Century Cures Act in December—which includes funding for the CMI—there is a bright future for those pursuing some of the areas highlighted in their recommendations.

But there is still more work to be done to raise the profile of radiation oncology within the cancer community. In order to pool our efforts, ASTRO has forged collaborations with other medical societies in 2016, and I anticipate several more in the new year. One way we have partnered with others is by cosponsoring meetings, such as the upcoming [Multidisciplinary Thoracic Cancers Symposium](#). These partnerships, like with the American Society of Clinical Oncology (ASCO) and The Society of Thoracic Surgeons, help us meet our members' needs by getting new research out to them quickly.

In addition to meetings, we have also worked in cooperation with other societies to ramp up the publication of clinical practice statements. In 2016, we published seven guidelines, clinical practice statements and white papers, two of which we partnered with other societies on. These statements and guidelines are very labor intensive, so partnering with others helps us do more, faster.

Another partnership that we're pursuing with ASCO is for their online depository of oncological data, CancerLinQ. This collaboration could help our members better serve their patients by giving them access to clinical data shared by fellow oncologists. We will share more information with members on this exciting development as it becomes available. The collaborations with ASCO and other societies will help all of our members in the long term. If we can use talent from different programs and not duplicate work, we can all make more progress. Here's to a 2017 full of forward progress! 🚀

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# SOCIETY NEWS

## ASTRO launches new webinar series in 2017

THIS YEAR, ASTRO WILL LAUNCH A NEW WEBINAR SERIES called Clinical Controversies. These webinars will present timely topics in radiation oncology in a point-counterpoint format. Other planned webinars for 2017 include: eContouring, coding, health policy, guidelines, ASTRO-ARRO Journal Clubs for residents and others.

Three Clinical Controversies webinars will feature relevant issues in radiation oncology debated by leaders in the field. The first of these webinars was held Wednesday, January 25. Paul Nguyen, MD, moderated as W. Robert Lee, MD, MS, MEd, FASTRO, and Anthony D'Amico, MD, PhD, FASTRO, discussed "Should hypofractionation be the standard of care for prostate cancer?"

On Thursday, April 27, 2017, Lilie Lin, MD, will moderate Eleanor Elizabeth Harris, MD, and Gary Freedman, MD, on "Throw 'caution' to the wind? Discussion of challenging cases for accelerated partial

breast irradiation." Cases will be presented for this webinar with different treatment approaches for each.

In the fall of 2017, John Suh, MD, FASTRO, and Eric Chang, MD, FASTRO, will discuss the pros and cons of whole brain radiotherapy (WBRT) versus stereotactic radiosurgery (SRS) for brain metastasis. Dr. Suh and Dr. Chang have previously debated on this topic—it should be a lively and informative event.

Participants can earn SA-CME for attending these webinars. The number of credits available varies by webinar. Each live webinar will also be recorded and made available on ASTRO's website on-demand. Further your education by joining faculty leaders and your peers for one of ASTRO's new webinars.

For more information about ASTRO webinars, please visit <https://www.astro.org/Meetings-and-Education/Education/MOC/CME/webinars> or contact [Education@ASTRO.org](mailto:Education@ASTRO.org). 📧

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## 21st Century Cures Act becomes law

### *Cancer Moonshot Initiative receives funding for cancer research*

GOOD NEWS FOR CANCER RESEARCHERS. Former president Barack Obama signed into law the 21st Century Cures Act during a lame-duck session in December 2016. It was the largest piece of health care legislation to emerge from Congress in 2016 and it devotes \$1.8 billion to cancer research. That amount is earmarked for former Vice President Joe Biden's Cancer Moonshot Initiative (CMI), which ASTRO supported in October 2016 by attending an event hosted by Biden.

At that event, the then-Vice President released a report outlining the CMI progress to date and roadmap for its four remaining years. Former Chair of ASTRO's Board of Directors Bruce G. Haffty, MD, FASTRO, attended on behalf of the Society following months of encouragement by ASTRO for the

initiative to broaden its focus and integrate radiation oncology more fully into the Moonshot effort.

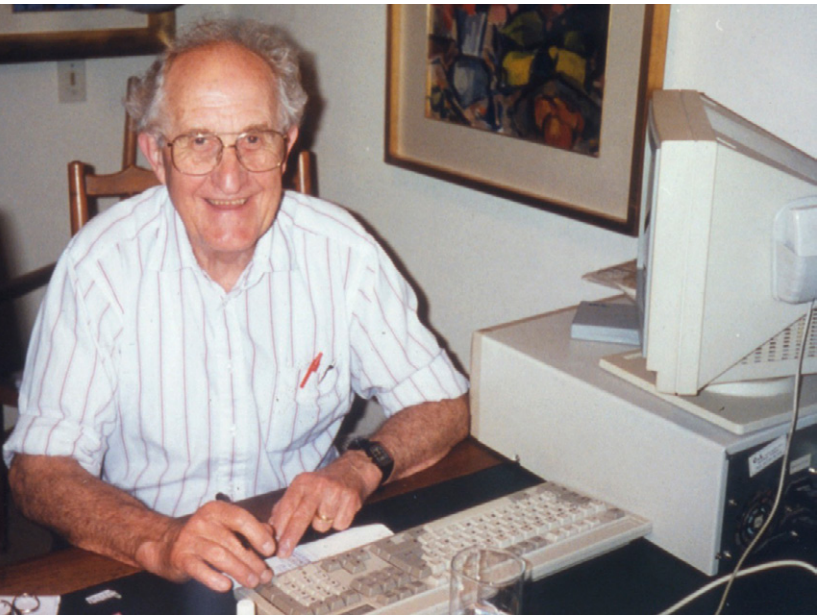
In addition to many other ASTRO-backed provisions, the 21st Century Cures Act will provide \$4.8 billion to the National Institutes of Health for biomedical and precision medicine projects and \$500 million to the Food and Drug Administration.

The bipartisan bill was overwhelmingly passed by the House of Representatives on November 29, 2016, and by the Senate on December 7, 2016. ASTRO ensured its support was heard by Congress by activating its grassroots network. Members of Congress heard from more than 40 ASTRO members from around the country in a single day expressing support for the 21st Century Cures Act. 📧

## SPECIAL *tribute*

BY PAUL M. HARARI, MD, FASTRO, AND ALBERT J. VAN DER KOGEL, PHD

### JOHN “JACK” FRANCIS FOWLER, DSC, PHD, FASTRO



**JACK FOWLER, A 1995 ASTRO GOLD MEDALIST,** perhaps best known for his contributions to fractionation in radiation oncology, passed away on December 1, 2016. He died peacefully at his home in London, in the arms of his beloved wife Anna, at the age of 91.

Jack enjoyed a long and colorful professional career. He was a prolific thinker, writer and speaker during his career, which spanned many decades. Although his academic career was launched strongly in physics—his bachelor's, master's and PhD, all from the University of London, were in physics—he earned his doctorate of science in radiation biology in 1974. By mid-career, he was highly engaged in cancer biology with a subsequent interest in radiation oncology fractionation schedules and clinical outcomes.

Jack served as director of the Gray Laboratory at Mount Vernon Hospital in Northwood, United Kingdom, from 1969–1988. As director, he followed in the footsteps of founding director Hal Gray and Oliver Scott at the lab, known as the world's first radiobiological institute. During Jack's tenure, the Gray Lab, now known as the Oxford Institute

for Radiation Oncology, boasted a robust cadre of scientific talent including: Gerald Edward “Ged” Adams, Adrian Begg, Julie Denekamp, Michael Joiner, Barry Michael, Fiona Stewart, Boris Vojnovic, Peter Wardman and George Wilson.

Significant contributions to tumor and normal tissue radiobiology emerged during this period and Jack was integral to much of this work. The Gray Lab attracted many bright students, fellows and faculty during this era including Eli Glatstein, Lester Peters, Elizabeth Travis and others who interacted with and learned from Jack. With increasing focus on radiation fractionation, Jack was engaged in animal studies as well as consultation on the design of human fractionation trials that would occupy his interest for much of his latter career.

Soon after “retirement” from the Gray Lab, Jack joined the faculty at the University of Wisconsin as a visiting professor, where his contributions continued to flourish. Freed from administrative duties, Jack could focus his energies on reading, writing, teaching and collaborating with researchers at the university and across the globe. He also held extended teaching engagements in Leuven, Belgium, and Umeå, Sweden, during this timeframe.


This was an enormously productive phase of Jack's career. His passion for linear-quadratic modeling and alpha/beta discourse, combined with his ability to illuminate these concepts logically, made Jack a coveted adviser, speaker and analyst of clinical fractionation schedules across the globe. Fortunately, he enjoyed excellent health, loved to travel and made his way around the world for various collaborations during this period. Although Jack was famous for devoting his undivided attention to any student, he also loved interactions with other leading radiobiology and mathematical thinkers, including Howard Thames, Rod Withers, Eric Hall, Herman Suit, Jolyon Hendry and many others throughout the years.

*Continued on next page*

Jack was a very prolific writer with more than 550 papers listed on his curriculum vitae. He published a book at the age of 89 on fractionation and overall treatment time in radiation oncology. He earned many awards and medals during his brilliant career. These include the Röntgen Prize of the British Institute of Radiology (1965), Breur Award of ESTRO (1983), Juan A. del Regato Gold Medal (1984), Gold Medal of the Gilbert H. Fletcher Society (1986), Gold Medal of ASTRO (1995) and Radiation Research Society Failla Award (2002), among many others.

A signature trait of Jack's was his remarkably upbeat, enthusiastic and energetic style. Jack routinely met or beat deadlines, provided rapid and in-depth feedback to scientific queries and made it very clear to colleagues that he was genuinely excited about "their" research. This style triggered widespread interest on the part of many to work with Jack.

Jack was the father of seven children and grandfather to a cadre of grandchildren and great-grandchildren. His wife since 1992, Anna Edwards Fowler, was a beautiful match and companion to Jack for almost 25 years.

The broad contributions made by Jack Fowler to the discipline of radiation oncology are compelling and we are very fortunate to have had this talented and enthusiastic researcher, teacher, friend and colleague in our midst. 

**Log on to [ASTRO.org](http://ASTRO.org) to read the History Committee's interview with John "Jack" Francis Fowler about his early career:**  
[www.astro.org/About-ASTRO/History/John-F-Fowler/](http://www.astro.org/About-ASTRO/History/John-F-Fowler/)

## *In Memoriam*

ASTRO has learned that the following members have passed away. Our thoughts go out to their family and friends.

**John F. Fowler, DSc, PhD, FASTRO,**  
London

**Michael Goitein, PhD, FASTRO,**  
Windisch, Switzerland

**William Harms Sr.,**  
St. Charles, Missouri

**Michael R. Manning, MD,**  
Tucson, Arizona

**Daniel Ochs, MD,**  
Demarest, New Jersey

**Wolfgang Wagner, MD,**  
Osnabruck, Germany

**Mayer Zaharia, MD,**  
Lima, Peru

The Radiation Oncology Institute (ROI) graciously accepts gifts in memory of or in tribute to individuals. For more information, visit [www.roinstitute.org](http://www.roinstitute.org).

## Submit your news to ASTRO

Every month, ASTRO reports [People in the News](#), featuring updates about your colleagues' awards, promotions, media coverage and other announcements. We encourage ASTRO members to submit items of interest to [communications@astro.org](mailto:communications@astro.org) for inclusion in the online feature.







## ASTRO releases updated breast cancer guidelines

DURING THE SECOND HALF OF 2016, ASTRO released three new guidelines related to radiation therapy for breast cancer, either on its own or jointly with other societies.

ASTRO issued an update to its clinical practice statement for accelerated partial breast irradiation (APBI) for early-stage breast cancer in November. The [executive summary and full guideline](#) are available now in *Practical Radiation Oncology*. The updated guideline reflects findings that greater numbers of patients can benefit from accelerated treatment, including younger patients and those with low-risk ductal carcinoma in situ (DCIS). The update also provides direction for the use of intraoperative radiation therapy (IORT) for partial breast irradiation.

This updated guideline has received attention in the press, including the CBS daytime program [The Doctors](#). The guideline update also was covered by Reuters Health and featured in several medical news outlets, including [MedPage Today](#) and [Medscape Medical News](#).

Along with the Society of Surgical Oncology (SSO) and the American Society of Clinical Oncology (ASCO), ASTRO issued a [consensus guideline](#) for physicians treating women who have DCIS treated with breast-conserving surgery with whole breast irradiation. The new guideline has the potential to save many women from unnecessary surgeries while reducing costs to the health care system.

The groups concluded, “The use of a two millimeter margin as the standard for an adequate margin in DCIS treated with whole breast radiation therapy (WBRT) is associated with low rates of recurrence of cancer in the breast and has the potential to decrease re-excision rates, improve cosmetic outcome, and decrease health care costs. Clinical judgment should be used in determining the need for further surgery in patients with negative margins less than two millimeters. Margins more widely clear than two millimeters do not further reduce the rates of recurrence of cancer in the breast and their routine use is not supported by evidence.”

The same three organizations—ASTRO, ASCO, and SSO—issued a joint clinical practice guideline update in September for physicians treating women with breast cancer who have undergone a mastectomy. The update provides additional considerations for physicians to determine which patients might benefit from [postmastectomy radiotherapy](#) (PMRT).

The guideline update states that there is strong evidence showing that PMRT reduces the risk of breast cancer recurrence. It provides evidence-based recommendations for the use of PMRT in: patients with T1-2 tumors (tumors smaller than 5 cm) and 1 to 3 positive lymph nodes; patients undergoing neoadjuvant systemic therapy; and patients with T1-2 tumors and a positive sentinel node biopsy. The Expert Panel also addressed technical aspects of radiotherapy, such as the optimal extent of regional nodal irradiation.







## New office wins design awards

SIX MONTHS AFTER MOVING IN, the interior design accolades are stacking up for ASTRO's new office. In November 2016, the Northern Virginia chapter of NAIOP, the Commercial Real Estate Development Association, presented ASTRO with their Award of Excellence in the Interiors category of its 2016 design awards. In October 2016, Commercial Real Estate Women (CREW) of Washington, D.C., honored the Society with its Best Interiors Award.


"These awards echo what ASTRO staff and members have already been saying about our new space: the open environment, collaborative meeting areas and glass-walled offices create an atmosphere that's cooperative and integrated—and on the cutting-edge of interior design," said Laura I. Thevenot, chief executive officer of ASTRO.

The Best of NAIOP Northern Virginia Awards recognize and celebrate significant new contributions to Northern Virginia by the commercial, industrial and mixed-use real estate community. At the Chapter's premier event, the awards program recognizes the outstanding individuals who provide contributions to the

design environment. CREW DC's annual awards celebrate real estate achievements in the commercial real estate industry, including recognitions in the areas of developments and interiors work that demonstrate excellence, impact and vision within Washington-area's real estate industry.

"These awards are some of the most prestigious recognitions in the architecture and design industry," said Jay Choi of Davis Carter Scott (DCS), lead architect on the project. "They are also a recognition of ASTRO, who gave us their support and trusted our vision for their new space. It was truly a team effort, and these awards reflect that collaboration."

The office is located in Crystal City, an urban community just minutes from Washington, D.C., and adjacent to Reagan National Airport.

"We now have an inviting, convenient space where we can meet with our Society members for meetings, board education, programs and other Society business," said Thevenot. "And, importantly, it is a work environment that our staff members love. ASTRO is most grateful to the entire design, construction and management team for creating the space for us." 







# A New Look at Radiobiological Targets

*Cancer genetics, tumor microenvironment and immunotherapy are emerging treatment options in radiation therapy*

BY AMATO GIACCIA, PHD, AND SIMON POWELL, MD, PHD, FASTRO

It's a brave new world, full of promise for personalized cancer treatment using genomic testing. Yet its full impact is still to be realized in radiation oncology.

Radiation therapeutic choices have been determined by the presence or absence of hypoxia, the top radiobiological concern for the past 70 years. Fractionated therapy has reduced the impact of hypoxia. Tumors that are hypoxic still have a worse local and distant outcome, suggesting both local resistance<sup>1</sup> and a propensity to metastasize<sup>2</sup>.

However, the evidence is beginning to suggest that radiation strategies need to take into account other aspects of cancer biology and genomics. The philosophy of treatment has been to give radiation doses that eradicate as many tumors as possible with acceptable side effects. The definition of acceptable has shifted with time, since the impact of intensity-modulated radiation therapy (IMRT) to reduce side effects for head and neck cancer or prostate cancer results in a greater expectation of quality of life as an outcome.



Where do we go from here? We need to study how to use both tumor biology/genomics and normal individual variations in radiation sensitivity, radiogenomics, to plan treatment. We have known since the 1980s that each tumor type has a significant range of radiosensitivity<sup>3,4</sup> but attempts to measure this intrinsic variation have been limited by technical difficulties. The Cancer Genome Atlas (TCGA) and related studies have revealed the prevalence of mutations in DNA repair genes and there are preliminary studies suggesting the DNA repair-defective tumors have a better result with chemotherapy<sup>5</sup>. Strategies to turn the vulnerabilities revealed from cancer genomic studies into improved results from therapy are needed.

Here are key radiobiologic targets and pathways to be studied in the next five years.

### DNA repair defects

DNA repair defects found in cancers can be classified into meaningful groupings. Mismatch repair (MMR) defects and alterations in DNA polymerase function result in the accumulation of point mutations in large numbers throughout the cancer genome. These tumors were found as part of Lynch Syndrome, but TCGA shows that MMR-defective cancers are prevalent across a variety of cancers. The therapeutic strategy for this type of DNA repair defective cancer was not clear until recently, when multiple reports have shown a high response to immunotherapy<sup>6,7</sup>. Studies should determine whether this can be observed when radiotherapy is used as part of the immunotherapeutic strategy. The response of MMR-defective cancers to DNA damaging agents was otherwise mixed, with MMR defects also promoting a lack of damage signaling and a reduced response relative to repair proficient tumors.

The ability of a tumor to express methyl-guanine methyl transferase (MGMT) corresponds with its response to short alkylating agents, such as temozolamide. Multiple studies have shown that methylation of MGMT, or suppressing the expression of the DNA repair enzyme, results in a better outcome to temozolamide and radiation<sup>8</sup>. The DNA lesions produced by temozolamide can be repaired by MGMT, but can also be repaired by base-excision repair, which removes the entire nucleotide. Thus, the impact of methylation status of MGMT could be

amplified significantly by the use of concurrent poly-ADP ribose polymerase (PARP) inhibitors. Trials to test this hypothesis are ongoing.

Homologous recombination (HR) is a major pathway of DNA double-strand break repair, especially in human tumors, where control of HR is relatively de-repressed. Homologous recombination deficiency (HRD) is now recognized to be very common in human cancers, not just associated with hereditary breast and ovarian cancer. HRD can be diagnosed with a combination of target HR gene sequencing and verified by a pattern of structural rearrangements seen throughout the genome. In most cases of HRD, there are biallelic genetic mutations of a homologous recombination gene. Single allelic events are often not functionally significant, but there remains the possibility that clustering of single allele events may be significant<sup>9</sup>. Once HRD is found in a cancer, we believe cisplatin with ionizing radiation exploits the repair deficiency.

In other words, for all the extensive use of platinum and radiation, the patients who benefit the most from this combination are those with tumors showing HRD. PARP inhibitors have been used in the treatment of hereditary ovarian and breast cancer, so there is an obvious reason to determine whether the combination of ionizing radiation with these is beneficial in HRD cancers. Beyond PARP inhibitors, there are many developing strategies for exploiting synthetic lethality in HRD cancers, which includes many of the demonstrated back-up DNA repair pathways.

One interesting recent observation is whether ATM or Mre 11 complex mutations behave like HRD human cancers. In cell lines, ATM-deficient cells are not significantly sensitive to PARP inhibitors<sup>10</sup>, but determining whether tumors with ATM or NBN mutations—found with significant frequency—are usefully treated by these agents still needs to be determined. New agents entering phase I studies include ATM, DNA-PK and ATR inhibitors; the first two are most likely to be effective in concert with DNA damaging agents and ionizing radiation in particular. The challenges in introducing these agents to clinical trials include the extent of radiosensitization (up to 2-3-fold sensitization) and also the differential sensitization of tumor cells relative to normal cells.

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“Improving the efficacy of radiotherapy through understanding cancer genetics, tumor biology and immunology is paramount for the future of our discipline.”

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As the prevalence of gene sequencing increases, previously unrecognized patterns of DNA repair defects are being discovered, such as the presence of APOBEC mutations<sup>11</sup>. APOBEC enzymes are responsible for deamination of cytidine to uridine. The presence of uridine provokes excision repair, which promotes the formation of single-strand breaks in significant numbers. In this context, they produce a form of replication stress, which makes these tumors vulnerable to agents that exacerbate the condition, such as ATR inhibitors. Each of these scenarios requires clinical testing. The effect of new DNA repair inhibitory agents, the most appropriate cancer genomic profile and therapeutic ionizing radiation make a triad of interesting variables that must be studied to optimize radiation oncology.

### **Radiation therapy and T cell checkpoint therapy**

Combining radiotherapy and T Cell checkpoint therapy has drawn a great deal of preclinical and clinical interest. The major mechanism in which radiation induces cell death is through the introduction of DNA double strand breaks in tumor cells. However, evidence exists that, for some tumor models, the immune system can reduce the dose needed to control tumor growth, and that animals immunosuppressed through thymectomies and loss of T cells, required higher doses to be effective<sup>12</sup>. At the time they were published, these did not move the needle far in seeking new ways to enhance radiotherapy by manipulating the immune system. However, with the now-widespread testing of T cell checkpoint therapies in tumors of different histological origins, and the potential contribution of T cells to tumor control in preclinical models, academic and pharma interest has grown for combining radiation with T cell checkpoint inhibitors in the clinic.

Although recent reviews describe the current landscape for preclinical and clinical studies<sup>13-15</sup>, certain points need to be emphasized. From preclinical studies, the finding that T cells reduce the dose needed to control solid tumors suggests that T cell modulation be used as an adjuvant to enhance the efficacy of radiotherapy. However, most

current combination studies use radiotherapy as an adjuvant to enhance the efficacy of T cell checkpoint therapy, for example through the generation of neoantigens<sup>16</sup>. While both possibilities are feasible clinical development strategies, it seems that studies focusing on determining how immune regulation can enhance the efficacy of radiotherapy should have more straightforward endpoints such as local control and survival compared with those in which radiation is used as an adjuvant for immunotherapy, where the endpoints and biological correlates will require significant more effort and sample collection.

Furthermore, a major problem with T cell checkpoint therapies is the limited response of tumors in which T cells are excluded or found only at the periphery<sup>17</sup>. A fundamental question is whether radiation can enhance the infiltration of T cells into tumors in which they are initially excluded. The design of trials to optimize the combination of radiotherapy and immunotherapy will be the subject of much debate.

Preclinical and clinical studies investigating the combination of radiotherapy and T cell checkpoint therapy involve immunogenic models, which use different radiation doses and fractionation schedules<sup>13</sup>. Preclinical models for testing radiation and immune effects need to be considered with regard to mouse models used in future studies, as well as developing immune-deficient mice with transplanted human immune system components to test patient-derived biopsy material. In fact, tumors that do and do not attract host-infiltrating T cells will need to be developed for different sites. Much attention has also been focused on doses and fractionation schedules used in testing radiation and T cell checkpoint combination therapy. In preclinical studies, most studies have used only single doses, whereas most human tumors are still treated with some sort of fractionated schedule.

Also, most solid tumors are characterized by genomic instability and heterogeneity, and it has yet to be determined how much tumor heterogeneity affects T cell recruitment and antitumor activity. Another consideration relates to the surrounding normal stroma and infiltrating cells of a tumor, and how they respond to different doses of radiation, as

well as to different fractionation schedules. The choice of dose and fractionation schedule is critical as it may change radiation from a pro-immunogenic therapy to an anti-immunogenic therapy.

## Mitigating hypoxia


The tumor microenvironment, especially hypoxia, theoretically presents two types of problems for radiation and T cell checkpoint combination therapy. First, hypoxia will act as a dose-modifying factor for radiation and will have a more significant impact on single large radiation doses than on fractionated schedules<sup>1</sup>. Second, hypoxia can stimulate the expression and excretion of factors that act to promote immune resistance<sup>18</sup>.

Therefore, both preclinical and clinical studies should at least measure tumor hypoxia either by molecular imaging or in biopsies using hypoxia markers to see how changes in oxygenation affect the T cell response before and after irradiation<sup>19</sup>. Perhaps hypoxia alone could be a major mechanism for T cell exclusion in some tumors, a question that has yet to be rigorously addressed. In addition to microenvironmental changes, there is a significant gap in our understanding of how stromal cells, such as fibroblasts and endothelial cells, affect radiation and immune responses. These cells could have both direct effects as well as indirect effects in secreting factors that can enhance or inhibit the immune response of tumors.

While the combination of radiotherapy with T cell checkpoint therapy has received the most attention, the potential to use radiation in combination with other immune modulators such as vaccines, adjuvants, cytokine therapy and potentially even adoptive T cell transfer should be considered. While preclinical studies support radiation with these different combinations, the opportunity to test these combinations in the clinic is warranted and needed.

Reversing tumor hypoxia through metabolic radiosensitization is the newest concept in addressing this. Radiobiological principles predict that hypoxia becomes more relevant as dose per fraction increases, potentially inhibiting the ability of a hypofractionated radiation protocol from eradicating a tumor<sup>20</sup>. Results with clinical trials of hypoxia modifying agents have been disappointing. Hypoxia, especially for hypofractionated protocols, needs new approaches.

One new approach based on the concept that reducing oxygen consumption at the cellular level is a potentially efficient means of reducing tumor hypoxia<sup>21</sup>. The major oxygen-consuming organelle in the cell is the mitochondria. In tumor cells under both oxic and hypoxic conditions, HIF-1 inhibits mitochondrial metabolism through a variety of targets<sup>22</sup>. However, inhibiting HIF would not necessarily be a good idea as it could lead to increased mitochondrial activity, oxygen consumption and further exacerbate hypoxia. While the Warburg effect is often used to describe the increased levels of aerobic glycolysis and decreased levels of mitochondrial activity found in solid tumors, the levels of mitochondria activity are still quite robust in tumor cells and consume a great deal of oxygen. By inhibiting mitochondrial activity completely in both the oxic and hypoxic regions of tumors, tumors will become more responsive to radiation. Therefore, a search for mitochondrial inhibitors that work in most tumor cells is a prime new research direction<sup>23,24</sup>.

Improving the efficacy of radiotherapy through understanding cancer genetics, tumor biology and immunology is paramount for the future of our discipline. 

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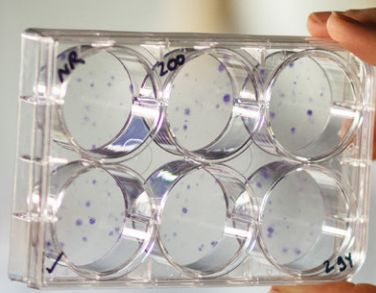
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# CORPORATE AMBASSADORS

ASTRO PROUDLY RECOGNIZES THE ONGOING COMMITMENT OF OUR CORPORATE AMBASSADORS FOR THEIR OUTSTANDING YEAR-ROUND LEADERSHIP AND PROMOTIONAL SUPPORT OF RADIATION ONCOLOGY.





# RT RESEARCH: THE NEXT GENERATION

***New advances can only come from new research. Look out for these up-and-coming researchers who are working on the latest treatment innovations in radiation therapy.***

BY SEWIT TECKIE, MD

WITH THE PASSAGE OF THE 21ST CENTURY CURES ACT IN DECEMBER 2016, a huge financial commitment was made to cancer research—a commitment that just might signal a major turning point in how radiation oncologists treat cancer in the future. The bipartisan legislation earmarked \$1.8 billion for former Vice President Joe Biden's Cancer Moonshot Initiative (see Society News on page 9 for more) and \$1.5 billion for former President Barack Obama's Precision Medicine Initiative, which is aimed at tailoring treatments to people based on their genes and lifestyles.

That's all promising news for the following researchers, who are all looking at novel ways of using radiation therapy in the treatment of cancer. Read on for the latest innovations coming out of their labs.



**CARMEN BERGOM, MD, PHD**  
*Bergom Laboratory, Medical College of Wisconsin in Milwaukee*

**Research areas:** In our translational research laboratory, we use unique genetic animal models and next-generation sequencing technologies to identify genes in the tumor microenvironment that improve the response of breast cancers to radiation therapy. Our research aims to use these tumor microenvironment targets to identify patients who are at higher risk of radiation side effects to better tailor therapy in order to limit long-term sequelae of treatment. We also attempt to predict which tumors

are less sensitive to radiation therapy in order to personalize radiation treatment by changing dose or administering adjunct therapies to improve tumor responses.

**Project Highlights:** We are utilizing a newly developed Consomic Xenograft Model, the first experimental genetic tool to map the effect of germline variants in the tumor microenvironment on radiation responsiveness. Consomic rats are those in which a chromosome from one inbred rat strain is selectively substituted into another inbred rat strain. In this model, we manipulate the genetic backgrounds of rat strains while keeping the tumor cells the same, enabling us to assess the effect of host tumor microenvironment differences on radiation responses of human tumor xenografts and syngeneic tumors. Because the genetic background of the host is altered, but the tumor cells stay the same, any differences seen in tumor growth or treatment responses are due to host factors. These studies have shown that host factors on rat chromosome 3 can lead to differences in radiation sensitivity. In addition to genetic mapping, we are also utilizing a species-specific RNA sequencing method that determines changes in gene expression between human tumor cells and the rat non-malignant tumor microenvironment. Using these techniques, we have a number of putative candidate genes that influence tumor radiosensitivity in the tumor microenvironment that are currently being tested.

*Continued on next page*

**Clinical Applications:** Our projects aim to identify genes that can both enhance the tumor response to radiation and reduce the side effects to normal organs. This information may ultimately allow for more personalized radiation therapies that improve cancer outcomes and minimize long-term side effects for cancer survivors.



**MARKA CRITTENDEN, MD, PHD**  
*Director of Translational Radiation Research, Integrated Therapies Laboratory, Earle A. Chiles Research Institute and The Oregon Clinic, Providence Portland Medical Center in Portland, Oregon*

**Research Areas:** Run by Michael Gough, PhD, and Marka Crittenden, the Integrated Therapies Laboratory is focused on understanding how to integrate immunotherapy with conventional therapies such as radiation, chemotherapy and surgery. In particular, our research focuses on how radiation can enhance or limit innate and adaptive immune responses to cancer, focusing on the immune consequences of radiation-induced cancer cell death, and the T cell responses to antigens in cancer cells. We are particularly interested in how best to integrate existing immunotherapy agents with radiation and to find novel agents for translation into clinical studies.

**Project Highlights:** Radiation as a single therapy rarely results in systemic immune responses capable of curing distant tumors. This demonstrates that cancer cell death caused by radiation is extremely poor at initiating effective systemic immunity. In one

project, we have focused on the tumor macrophage, an abundant cell in the tumor environment, which drives an immune suppressive response following interaction with cancer cells killed by radiation. We have demonstrated that this limits the ability of T cells to clear residual cancer cells. By preventing the macrophage suppressive response, or blocking their interaction with dying cells, we have demonstrated dramatically improved tumor control by radiation therapy. We believe therapies targeting macrophages will combine well with the well-studied T cell targeting immunotherapies to increase the proportion of patients responding to treatment.

**Clinical Applications:** Preclinical studies provide an opportunity to rapidly answer questions about dose, timing, sequencing and mechanism that would take years or decades to answer in patients. We have demonstrated in preclinical studies that the timing of immunotherapy used in clinical studies may not be optimal, and have demonstrated in patients that fractionated chemoradiation may not be the optimal partner for immunotherapy. Rapid translation of preclinical findings and close analysis of clinical studies will help the field develop optimal treatment combinations for patients.



**SCOTT FLOYD, MD, PHD**  
*Associate Professor, Floyd Laboratory, Department of Radiation Oncology, Duke University School of Medicine in Durham, North Carolina*

**Research Areas:** For patients with brain tumors, radiation therapy is particularly important as many chemotherapies do not enter the brain well. We are therefore interested in how brain cancer cells and normal brain cells respond to DNA damage caused by radiation. More specifically, our laboratory investigates the effects of molecules that modify chromatin, such as epigenetic writers and readers, on the signaling network that senses DNA damage and initiates repair, cell cycle arrest and/or cell death. We use cell culture and mouse models to study these effects, and to develop strategies to modulate these epigenetic writers and readers to alter the DNA damage response and improve brain cancer treatment.

**Project Highlights:** Previous work in our lab has identified the epigenetic chromatin reader BRD4

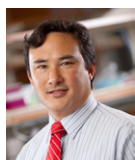
## PARTNER UP

The Bergom Laboratory has begun collaborating with Dr. Randy Kimple's laboratory at the University of Wisconsin in Madison to utilize this genetic animal model to identify genes in the tumor microenvironment that alter head and neck cancer growth and treatment responses. (See page 21 for more on Dr. Kimple's work)



as a modulator of the DNA damage response. This molecule is particularly exciting, as several new drugs targeting BRD4 are currently in clinical trials as treatment for cancer. Work in our lab demonstrates that combining BRD4 inhibitors with radiation therapy can be a powerful combination to kill certain brain tumor cell types. However, the molecular makeup of DNA damage response components in these cells is critical to determining whether they will respond to this radiation/BRD4 inhibitor combination. We are currently working on how the molecular connection between BRD4 and DNA damage response operates, and how best to predict and modulate this response.

**Clinical Applications:** Our work implicates BRD4 in the cellular response to radiation-induced DNA damage. Determining which cancers will respond best to radiation combined with drugs targeting BRD4 is an important part of our current studies. These can lead to new molecular diagnostics to predict for response. With drugs that target BRD4 already in clinical trials, we are hopeful that our work will lead to novel effective combinations of BRD4-inhibiting drugs with radiation therapy.



**RANDALL (RANDY) J. KIMPLE, MD, PHD**  
*Kimple Lab, Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Carbone Cancer Center in Madison, Wisconsin*

**Research Areas:** Our research goal is to improve the care of cancer patients. We study how we can customize care to each individual patient and their specific cancer. Much of our work relies on a model system that involves growing human cancers donated by patients in animal hosts. Over the past five years we have reported key studies describing how HPV (human papillomavirus) makes cancer more sensitive to radiation therapy. Projects in my lab focus on one of two key questions. First, how do cancers become resistant to standard treatments? Do they activate alternative survival pathways? Do they alter metabolism or activate stress response? Second, in cancers caused by HPV, how does the virus affect tumor growth, spread and response to treatment?

**Project Highlights:** A project funded by the American Cancer Society is studying how treatments regulate a cell stress response called autophagy. EGFR is a pro-growth protein that is expressed at high levels in head and neck cancer, and it is the target of chemotherapy used in treating these cancers. Recent work has shown that EGFR plays a key role in autophagy, which, in head and neck cancer, is turned on by either cetuximab or radiation. We are investigating the role of therapy-activated autophagy in resistance to these treatments. In addition, we will use novel drugs that block autophagy to learn if turning off autophagy can improve cancer response to standard treatments.

**Clinical Applications:** The goal of everything we do is to improve the lives of cancer patients. We rely on patients who volunteer to donate a sample of their tumor so that we can develop the translational model systems used in our studies. By using actual patient tissues, we hope to accelerate the translation of our findings back into the clinic with the ultimate goal of improving cancer care for our patients.



**ANDY MINN, MD, PHD**  
*Assistant Professor, Department of Radiation Oncology, Assistant Investigator, Abramson Family Cancer Research Institute, University of Pennsylvania in Philadelphia*

**Research Areas:** My research interests focus on understanding how cancer cells interact with stromal and immune cells of the tumor microenvironment to acquire resistance to both conventional therapies and to immunotherapies. To better understand the mechanistic basis for this, we incorporate high-dimensional data approaches by integrating various data types from animal models, molecular biology, genome-wide profiling, immune profiling, clinical data mining and computational modeling. We are particularly interested in how signaling pathways that are typically associated with an antiviral response, yet broadly expressed across common human cancers, orchestrate response and resistance to conventional therapies and to immune checkpoint blockade.

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**Project Highlights:** One research project in the laboratory studies the molecular determinants of response and resistance to the combination of radiation and immune checkpoint blockade for metastatic cancer. We are examining how these therapies mechanistically interact in nonredundant ways to improve response. Conversely, we are also investigating how the tumor can co-opt critical signaling pathways to promote immunosuppression that limits response and/or favors relapse.

**Clinical Applications:** An important goal of our research is to facilitate the design and implementation of clinical trials. Through parallel studies in mice and early-phase clinical trials, my lab—as part of a multidisciplinary team at the University of Pennsylvania—has a series of ongoing or completed clinical trials investigating the combination of radiation and immune checkpoint blockade for various cancer types. We hope that this mechanistically informed and rational approach to clinical trial design will facilitate the successful use of radiation to improve upon the promise of immune checkpoint blockade for metastatic cancer.




**TERENCE WILLIAMS, MD, PHD**  
*Associate Professor and Director of  
Translational Research, Williams  
Laboratory, The Ohio State University  
in Columbus*

**Research Areas:** Our laboratory research interests center around thoracic and gastrointestinal (GI) malignancies, including pancreatic cancer and non-small cell lung cancer. We are interested in the molecular biology and genetics of DNA damage response, those pathways which dictate tumor aggressiveness, such as invasion and metastasis, and those factors governing response to treatment from chemotherapy, molecularly targeted agents and radiation. A large focus of the lab is on developing treatment strategies incorporating novel molecularly targeted agents and nanotherapeutics targeting DNA repair, the immune system and apoptosis with standard radiation or chemoradiation. We are also interested in elucidating novel DNA repair pathways and their relationship to cancer development and therapeutic response. Additionally, we perform

molecular profiling of human tissues from patients to identify genetic factors that confer prognosis or predict response from treatment. Finally, we are also interested in the role of stromal elements and their relationship to tumorigenesis, metastasis and resistance to therapy.

**Project Highlights:** We are studying RAS pathway-mediated radiation resistance. RAS is a small GTPase residing in the cytoplasm involved in cellular proliferation, differentiation and survival, and consists of three isoforms, KRAS, NRAS and HRAS. RAS normally shuttles between an “on” and “off” state. KRAS is the most commonly mutated RAS isoform in human cancer, and mutations cause uncontrolled activation of RAS. Mutations in KRAS occur in 90 percent of pancreatic cancer, 40 percent of colorectal cancer and 20 percent of lung cancer. Earlier studies indicate that activating RAS mutations promote radiation resistance, but whether this occurs through altered DNA repair or through other mechanisms has been poorly understood. Our studies suggest that RAS mutations orchestrate and promote an environment typified by accelerated DNA repair, through heightened double-strand break repair after radiation. We have identified a number of nuclear DNA repair intermediates up-regulated by KRAS, and are working to better delineate how their function is altered in RAS-transformed cells. Finally, we are testing novel inhibitors and nanotherapeutics targeting these components to subvert RAS radioresistance.

**Clinical Applications:** Our initial work has been translated into a phase 1 clinical trial for patients with locally advanced rectal cancer. Patients are treated with 5-fluorouracil, radiation, and a MEK-1/2 inhibitor (a signaling intermediate downstream of RAS) prior to surgery. So far, our data suggests that the combination is safe and tolerable, with encouraging signs of efficacy. Our continued work is building upon these findings and developing novel strategies to directly and indirectly target RAS and RAF kinases in combination with radiation and/or chemotherapy. The goal of our research is to improve response rates and long-term cancer control rates with novel therapeutic approaches using radiation and rationally driven molecular approaches. 

# Treating Cancer by Combining Immunotherapy and Radiation Therapy

## *Future treatment options with the synergistic use of radiation and immunotherapy*

BY ARTA M. MONJAZEB, MD, PHD, AND JONATHAN D. SCHOENFELD, MD, MPH

**IMMUNOTHERAPY IS RAPIDLY CHANGING** the practice of oncology. Over the last several years, immune checkpoint inhibitors have been integrated into the treatment of patients with metastatic melanoma, renal cell carcinoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck and Hodgkin lymphoma. Anti-tumor vaccine approaches have demonstrated benefit in patients with metastatic melanoma and castrate-resistant prostate cancer.

With this potential, it is estimated that immunotherapy, and specifically inhibitors of the PD-1 immune checkpoint receptor or its ligand, PD-L1, will account for a greater than \$22 billion market by 2022<sup>1</sup>. And it is very likely that indications for immunotherapy will continue to expand—a significant number of new therapeutic clinical trials in United States are testing immunotherapy approaches.

In general, immunotherapy seeks to either engender anti-tumor immune responses or overcome suppressive mechanisms that tumors have exploited to evade immune attack. To this end, immune checkpoint inhibitors interfere with the functioning of inhibitory receptors present on the surface of T cells. Uninhibited, these T cells can then potentially mediate immunologic tumor cell death and give rise to systemic immune responses. Two immune checkpoint receptors in particular, CTLA-4 and PD-1, as well as the PD-L1 ligands, have been successfully targeted by drugs that are able to activate anti-tumor responses in multiple types of cancers.

Mechanistic and preclinical data strongly support a potential for radiation and immunotherapy to have synergistic effects<sup>2</sup>. Targeted radiotherapy has complex immunologic effects, some of which may enhance immune recognition and anti-tumor immune responses. For example, by causing an immunologic cell death, radiation may lead to an increased recognition of tumor proteins by the immune system

and may also alter the tumor microenvironment to allow for more efficient infiltration by T cells. Conversely, by killing immune cells or causing non-specific inflammation, radiation can also inhibit tumor-specific immune responses. However, these inhibitory effects could potentially be overcome with immune checkpoint inhibitors or other forms of immunotherapy.

Indeed, animal experiments have suggested that the combined use of radiotherapy and immunotherapy could offer a number of potential benefits. In these experiments, activation of immune responses has enhanced the local efficacy of radiotherapy. Excitingly, in some cases the use of targeted radiotherapy has also improved the systemic efficacy of immune therapy, leading to disease eradication and improved survival<sup>3</sup>. This so-called abscopal effect has also been anecdotally described in patient case reports and clinical series<sup>4,5</sup>. Unfortunately, the increased efficacy of radiotherapy with checkpoint inhibitors has yet to be confirmed in a prospective clinical trial—which may speak to the complexity of optimally combining radiotherapy and immunotherapy<sup>6</sup>.

Given the dramatic expansion of indications for immunotherapy, and promising preclinical and retrospective data, exploring combinations with radiotherapy in prospective clinical trials is of prime interest. In general, radiation immunotherapy trials can fit into three general categories: 1) Adding immunotherapeutic agents to standard of care radiation approaches; 2) Adding radiation to clinical scenarios where immunotherapy has become standard; and 3) Evaluating novel combinations or scenarios to capitalize on synergistic effects.

This first approach—adding immunotherapeutic agents to standard of care radiation—is now being tested in populations of patients with locally advanced tumors who commonly receive radiation or chemoradiation with curative intent. At least two



large, multicenter randomized trials are evaluating the addition of a PD-1 or PD-L1 inhibitor to cisplatin/radiation therapy for patients with intermediate- or high-risk head and neck cancers. Additional single institution studies are currently evaluating the combination of intensity-modulated radiation therapy (IMRT), cetuximab and the CTLA-4 immune checkpoint inhibitor ipilimumab.


Many patients for whom immunotherapy approaches are now indicated, such as patients with metastatic melanoma, renal cell carcinoma and non-small cell lung cancer, frequently receive palliative radiotherapy. Promising outcomes have already been reported in patients treated with immunotherapy who have also received radiation. A few recently reported early phase clinical trials have demonstrated reassuring safety profiles and suggestion of immune activity with the combination of palliative, hypofractionated or stereotactic body radiotherapy and the CTLA-4 inhibitor ipilimumab in patients with metastatic melanoma<sup>3,7,8</sup>.

Several studies are now evaluating the combination of radiation and PD-1 or PD-L1 inhibitors in melanoma and other populations such as metastatic non-small cell lung cancer and head and neck cancer, where PD-1/PD-L1 inhibitor monotherapy might otherwise be employed. Response rates and the percentage of patients who demonstrate durable benefit from PD-1/PD-L1 inhibitor monotherapy have been modest in these disease types; therefore, the hope is the combination of radiation and checkpoint blockade will better stimulate the immune system and improve response rates.

Preclinical data suggest that the combination of radiation and immune therapy might achieve favorable results even in scenarios where either treatment alone is of limited value, such as in patients with tumor types that have not generally responded to immune checkpoint blockade or in patients with metastatic disease who have previously progressed on immune therapy. Adding radiation to immunotherapy combinations, such as combined inhibition of CTLA-4 and PD-1/PD-L1, may be particularly appealing, as preclinical models have shown promise. The use of radiation in these settings is currently being explored in prospective clinical trials. In collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) PD-L1 project team, we have developed a multicenter randomized phase 2 study that will evaluate the addition of radiation to

combined CTLA-4/PD-L1 inhibition in patients with metastatic colorectal or non-small cell lung cancer. This study includes a comprehensive set of biomarkers that will attempt to further define the immunologic effects of radiation to guide future trials.

The great promise of immunotherapy has opened up new potential, both to improve on current results of radiotherapy and to expand the use of radiotherapy to new horizons that capitalize on immunologic effects that were, until recently, largely unrecognized. According to a recent review, there are currently approximately 81 trials investigating radiation therapy and immunotherapy combinations, with many more being planned<sup>9</sup>.

Unlike combining cytotoxic therapies, combinatorial strategies involving immunotherapy may be exquisitely sensitive to issues of dosing, fractionation, sequencing, irradiation of draining lymph nodes, field size and other factors. As new immunotherapy agents continue to be developed and tested, there is an urgent need for rigorous preclinical, clinical and translational studies to evaluate their effects when given in combination with radiotherapy to ensure that future trials are rationally designed and the optimal combinatorial strategies can be delivered to our patients. 

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# GET READY, SET, GO!

## HOW YOU CAN BE MIPS READY IN 2017

BY ANGELA KENNEDY AND KSENJIA KAPETANOVIC, [MIPS@ASTRO.ORG](mailto:MIPS@ASTRO.ORG)

The Centers for Medicare and Medicaid Services (CMS) has issued final regulations for the new Quality Payment Program (QPP) established under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). The QPP represents a significant change in the way all physicians, including radiation oncologists, will be paid by Medicare starting in 2017 and requires immediate attention and action.

The QPP has two components: the Merit-based Incentive Payment System (MIPS) and the Alternative Payment Model (APM) program. ASTRO, along with other specialty societies, submitted letters to CMS with concerns that the changes were too much, too fast. Following some positive changes, radiation oncologists have multiple options to avoid penalties and receive bonuses but will need to start preparing in 2017 to participate in MIPS.

### What is MIPS?

MIPS combines the Meaningful Use, Physician Quality Reporting System (PQRS) and Value-based Modifier (VM) programs into one comprehensive program. Clinicians receive a composite score based on performance across four categories: Quality, Advancing Care Information (ACI), Improvement Activities (IA) and Cost. Medicare Part B

reimbursements will be adjusted up or down based on the composite score. Reimbursements will be adjusted two years after the reporting period, so adjustments in 2019 will be based on your composite score during the 2017 performance period. The positive and negative adjustments will increase over time.

### Who is eligible to participate in MIPS?

CMS set the MIPS participation threshold for eligible clinicians at a minimum of 100 Medicare Part B-enrolled patients AND \$30,000 in Medicare Part B-allowed charges. Individual clinicians and group practices must meet both of these requirements to participate in the MIPS program. CMS will send eligibility letters and launch a website for clinicians to check their eligibility.

### How do eligible clinicians comply with MIPS in 2017?

2017 is a transition year to allow for more flexibility and time to prepare. In 2017, the MIPS composite score will be based on only three of the four categories: Quality, ACI and IA. The chart below details each of the categories, the points available and the category weight used for determining the composite score.

### SUMMARY OF 2017 MIPS PERFORMANCE CATEGORIES

Performance category	2017 MIPS category weight
<b>Quality:</b> Clinicians choose six measures to report* to CMS that best reflect their practice. One of these measures must be an outcome measure or a high-quality measure. Radiation oncologists can choose to report the radiation oncology specialty measure set, which contains four measures. *Clinicians can use the <a href="#">PQRSwizard</a> to report measures in 2017.	60 percent
<b>Advancing Care Information:</b> Clinicians will submit a minimum of four out of five required measures. Many hospital-based physicians will be exempt and some may qualify for a hardship exemption.	25 percent
<b>Improvement Activities:</b> Clinicians can choose up to four measures to report* and attest to their completion. *Clinicians participating in RO-ILS and/or APEx can meet one or more measures.	15 percent
<b>Cost:</b> CMS will collect cost data based on adjudicated claims.	0 percent

*Continued on next page*

## PICK YOUR REPORTING PACE AND PAYMENT ADJUSTMENT FOR 2017

An eligible clinician's 2019 reimbursement can be adjusted upward or downward by as much as 4 percent, depending on MIPS participation and performance in 2017. Eligible clinicians who choose not to participate in MIPS will receive the -4 percent adjustment. During this transition year, eligible clinicians have three options for MIPS performance category reporting:


**1 Test pace = Neutral payment adjustment**  
Eligible clinicians can submit, at a minimum, a single measure in the Quality category OR a single activity in the IA category OR the required measures in the ACI category to avoid a negative payment adjustment in 2019.

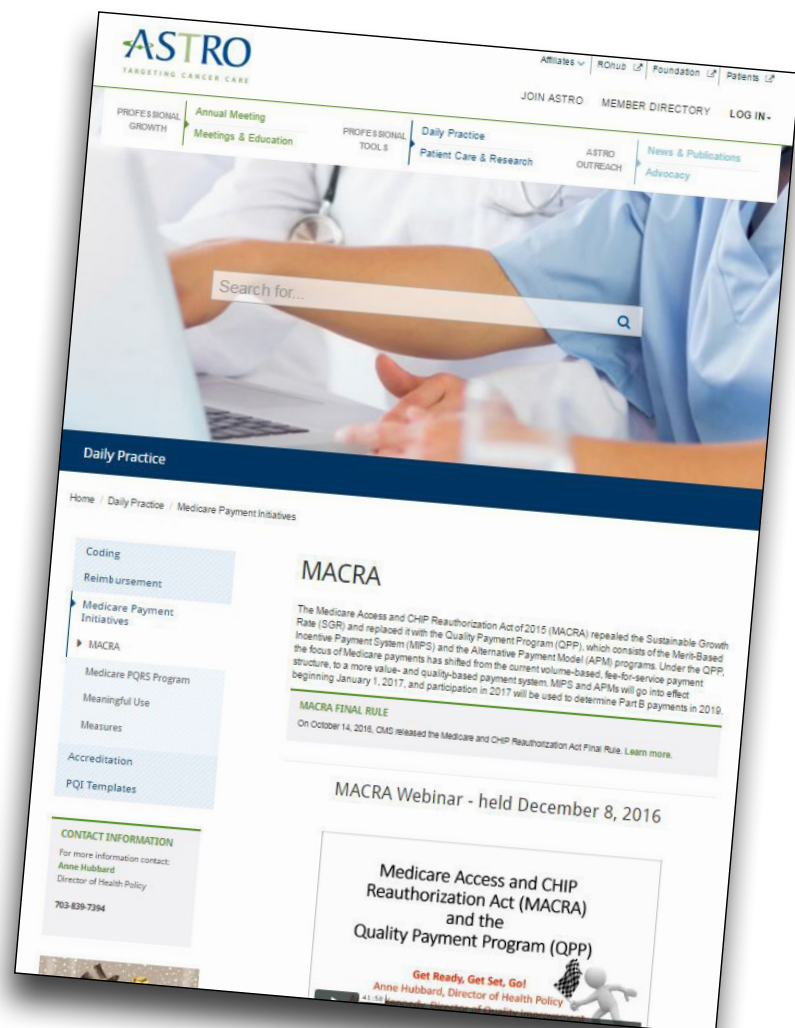
**2 Partial participation = Possibility of a positive payment adjustment**  
Eligible clinicians can report for a minimum of 90 consecutive days on more than one measure in the Quality category OR two activities in the IA category OR more than the required measures in the ACI category to avoid the negative payment adjustment and possibly receive a small positive adjustment.

**3 Full participation = Possibility of a positive payment adjustment**  
Eligible clinicians ready to report in all categories, as described in the previous table, can submit reports for a full calendar year. These eligible clinicians maximize their chances to qualify for a positive payment adjustment, including an exceptional performance adjustment, in 2019.

*Note:* Clinicians participating in ASTRO's RO-ILS: Radiation Oncology Incident Learning System® and/or Accreditation Program for Excellence (APEX) can meet one or more measures in the IA category.

It is important to note that CMS continues to provide updates often on how it will implement MIPS. Information in this article was accurate at the time of publication and is subject to change.

ASTRO will provide detailed education programs on the QPP and each MIPS performance category to inform radiation oncologists on the reporting requirements. More information, including a free webinar on the QPP, can be found on the ASTRO MACRA website at [www.astro.org/MACRA](http://www.astro.org/MACRA). 





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# Thank You

## IN APPRECIATION OF ASTRO'S 2016 CORPORATE AMBASSADORS AND ANNUAL MEETING SPONSORS

Attendees visiting the Exhibit Hall at ASTRO's 58th Annual Meeting were treated to a fantastic display of products and services in radiation oncology and cancer care. As ASTRO leadership visited with the many companies who sponsored the Annual Meeting, they enjoyed networking and sharing their new products and advancements. These visits are just one of the many benefits associated with sponsorship. If you are interested in learning more or would like to see us visit you next year in San Diego, please find the 2017 Annual Meeting Sponsorship Opportunities by [clicking here](#).



### 1. Accuray Inc.

Ron R. Allison, MD, Rahul R. Parikh, MD, and Ravi Bhasker Patel MD, PhD, thank Andy Kirkpatrick, Lionel Hadjadjeba, Scott Chapman, Birgit Fleurent, Kelly Londy and Susan Hopkins for their Corporate Ambassadorship.



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Members of ASTRO leadership thank Stanley Rosenthal, PhD, Don Melson, Lionel Bouchet, PhD, Joe Jachinowski, Scott Soehl, Yoel Bakas and Chris Dodge for their Gold Level Sponsorship.



## 8. PHILIPS

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# Thank You

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## 12. Siemens Healthineers

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## 14. Vertual Ltd.

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# Satisfaction Remains High Among ASTRO Members

*Results from the 2016 Membership Survey reveal the increasing importance placed on education*

BY ANNA ARNONE, VICE PRESIDENT, MEMBER RELATIONS AND COMMUNICATIONS, [ANNA.ARNONE@ASTRO.ORG](mailto:ANNA.ARNONE@ASTRO.ORG) AND TIM SANDERS, RESEARCH ANALYST, [TIM.SANDERS@ASTRO.ORG](mailto:TIM.SANDERS@ASTRO.ORG)

THE ASTRO MEMBERSHIP SURVEY is our yearly look into how you feel about your membership and the Society’s initiatives, direction and programs. This year’s survey was fielded from May 10 to June 20, 2016, among all active, affiliate, international and associate members, as well as members-in-training. A total of 1,775 ASTRO members completed the survey for a response rate of 20.5 percent, which is up slightly from 2015’s survey.

## RESPONDENT AND PRACTICE DEMOGRAPHICS

This year’s respondents were highly representative of ASTRO’s membership as a whole in terms of profession and primary employer. Nearly two-thirds of respondents were radiation oncologists, with medical physicists and radiation oncology residents as the next most common occupations (*see Figure 1*).

Geographically, most respondents practice in North America (77 percent), followed by Asia (12 percent) and Europe (7 percent). A total of 60 countries across six continents were represented in the survey, most commonly the United States (71 percent), Japan (5 percent), Canada (5 percent), Brazil (2 percent) and India (2 percent).

Just under half (48 percent) of the respondents practice in an academic or university system, while 41 percent are employed in a private practice/community-based system. Approximately four out of five respondents described their primary work setting as hospital-based, and the remainder reported working primarily in freestanding/satellite clinics. Work setting and primary employer did vary somewhat among domestic and international respondents (*see Figures 2 and 3*).

**Figure 1: Demographics—Profession**

PROFESSION	PERCENT OF RESPONDENTS
Radiation Oncologist	64.1%
Medical Physicist	18.8%
Radiation Oncology Resident	10.9%
Administrator	1.1%
Oncology Nurse	0.9%
Clinical Oncologist	0.9%
Medical Dosimetrist	0.6%
Radiation Biologist	0.6%
Radiation Therapist/Technologist	0.5%
Other	0.5%
Nurse Practitioner	0.4%
Veterinarian	0.3%
Diagnostic Radiologist	0.2%
Medical Oncologist	0.1%
Physician Assistant	0.1%
Surgical Oncologist	0.1%

A variety of practice sizes were represented, most frequently medium-sized practices (with 33 percent of respondents working at practices serving 500–999 unique patients per year), followed by small (28 percent working at practices serving 0–499 patients), large (22 percent working at practices serving 1,000–1,499 patients) and jumbo (17 percent working at practices serving more than 1,500 patients).

Medical director respondents reported an average of 6.5 radiation oncologists and 4.7 medical physicists employed at each practice. Staff sizes were substantially larger in academic settings compared with private practices, and international respondents, on average, reported roughly one additional radiation oncologist per practice (*see Figure 4*).

*Continued on next page*

## SATISFACTION AND ENGAGEMENT WITH ASTRO

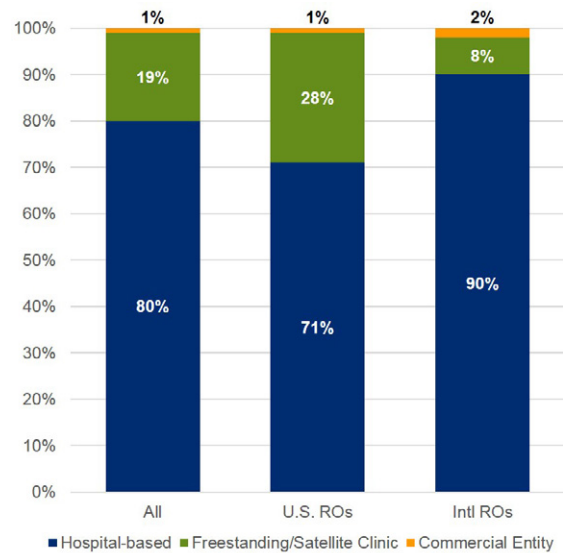
Overall, nine out of 10 respondents agreed that participation in ASTRO is a good use of their time. This satisfaction level has held steady over the past two years. International respondents were slightly more likely to report satisfaction with their ASTRO membership (see Figure 5).

Respondents in the United States reported that the most important functions that ASTRO performs are publishing scientific and practice journals (the [Red Journal](#), [Practical Radiation Oncology](#) and [Advances in Radiation Oncology](#)), providing education and professional development opportunities for members of the treatment team and educating Congress and regulators about radiation oncology. Compared with 2015, the largest increase in perceived importance was for education and professional development. International respondents also rated ASTRO's journals as the most important function performed by the Society, followed by hosting the Annual Meeting. All of ASTRO's functions were rated as important, with the lowest rating being 5.5 out of 7 (see Figure 6).

Responses indicate that members rely on a variety of communication channels to stay informed about ASTRO activities, benefits and services. The Annual Meeting remains the most popular information source, followed by ASTRO's [website](#), the weekly [ASTROgram](#) e-newsletter and the quarterly [ASTROnews](#) magazine. ASTRO's social media channels, including our [Twitter](#), [Facebook](#) and [LinkedIn](#) pages and [blog](#), also gained some traction among members looking to stay informed (see Figure 7).

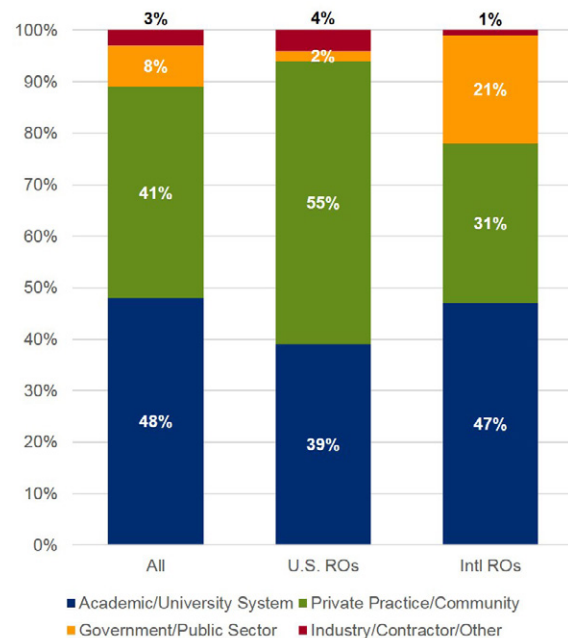
As in previous years, satisfaction with ASTRO's educational programs is strong, with 84 percent of respondents reporting that they are satisfied with the Society's educational offerings. Live, in-person meetings remain the most popular format for education among both U.S. and international respondents, followed by online SA-CMEs, journal SA-CMEs and on-demand webinars. Moreover, preference for self-paced/on-demand education available online has increased since 2014 (see Figure 8).

Figure 2: Demographics–Work Setting



Most respondents work in hospital-based settings, especially among international radiation oncologists.

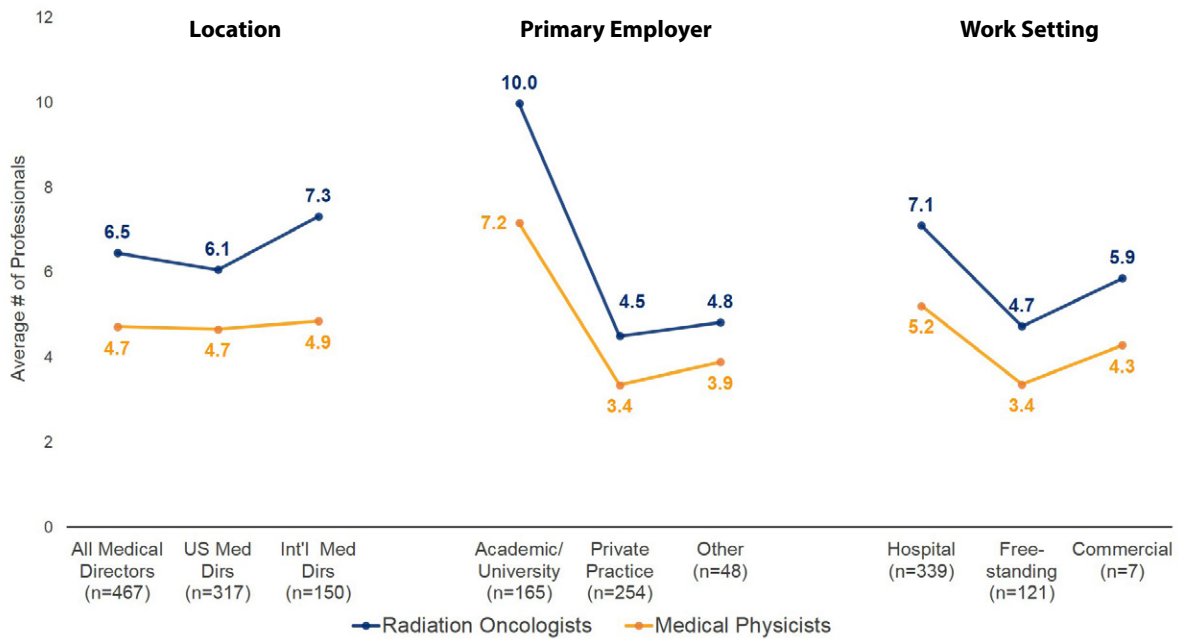
Figure 3: Demographics–Primary Employer



Respondents are split more evenly among primary employer groups, with international respondents more likely to work for government/public sector employers than respondents in the United States.

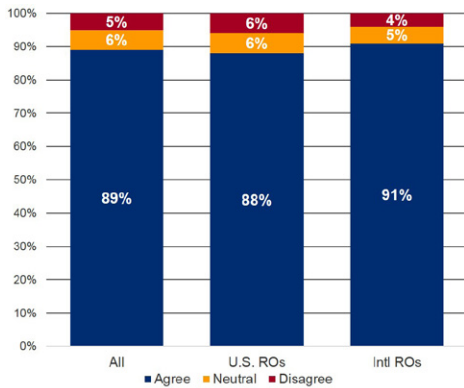


**Figure 4: Practice Demographics—Medical Professionals**



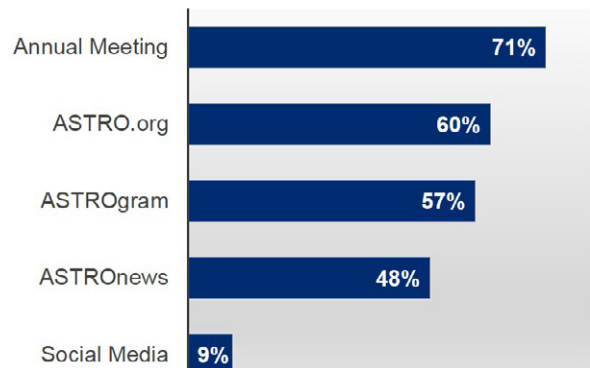
The average numbers of radiation oncologists and medical physicists vary by practice location, setting and employer, with universities boasting the highest average staff size.

**Figure 5: Satisfaction with ASTRO Volunteering**



Overall, approximately 9 out of 10 respondents feel that participation in ASTRO is a good use of their time.

**Figure 7: Communication Channels**



Members use a variety of communication channels to stay informed about ASTRO.

**Figure 6: Importance of ASTRO Functions**

	ALL U.S.	ALL INT'L
Publish scientific and practice journals	6.34	6.38
Provide education and professional development	6.32	5.88
Educate Congress/regulators	6.30	N/A
Advocate for appropriate reimbursement	6.29	N/A
Host the Annual Meeting	6.15	6.04
Raise public awareness of radiation oncology	6.14	5.73
Provide guidance on regulatory issues	6.10	N/A
Advance science through research and innovation	6.09	5.96
Support safe and effective patient care	6.06	5.89
Host specialty meetings	5.77	5.52

While all functions were rated highly on the seven-point importance scale (with 1 being least important and 7 being most important), ASTRO journals were considered most important among both domestic and international respondents.

## ISSUES AFFECTING MEMBERS AND THEIR PRACTICES

Nearly half of all medical directors reported a change to their practice's organizational structure within the past two years. Leadership and staffing changes were most common, though many respondents also reported changes due to practice acquisitions. Respondents also shared insight into barriers that impact their research efforts. Only 7 percent of respondents reported that they experience no road blocks. The most pervasive barriers by far were insufficient time and funding, and these road blocks inhibit nearly two-thirds of the respondents' practices from doing research. Challenges related to infrastructure, partnerships and collaborations and the approval process/IRB also affected more than a quarter of respondents.

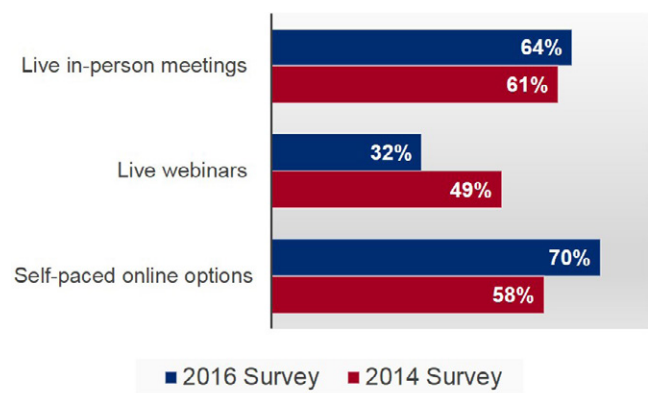
While previous years' surveys have found that ASTRO members are embracing the value of technology in their practices, U.S. reported interoperability of electronic health records (EHRs) was surprisingly low, with 39 percent of respondents reporting data sharing between hospitals and departments. International respondents reported that 46 percent of practices had some kind of data sharing—but 21 percent also reported having no EHRs at all. That's compared with only 3 percent of respondents who reported their American practices had no EHRs (see Figure 9).

## SUMMARY

As in previous years, the 2016 membership survey indicates that ASTRO members consider the Society to be a good use of their time and that they find the variety of education offerings and communication channels that ASTRO provides to be valuable. Survey results also point to a few areas where we can continue to improve. Your feedback will help guide the Board of Directors as they embark on a strategic planning effort in 2017.

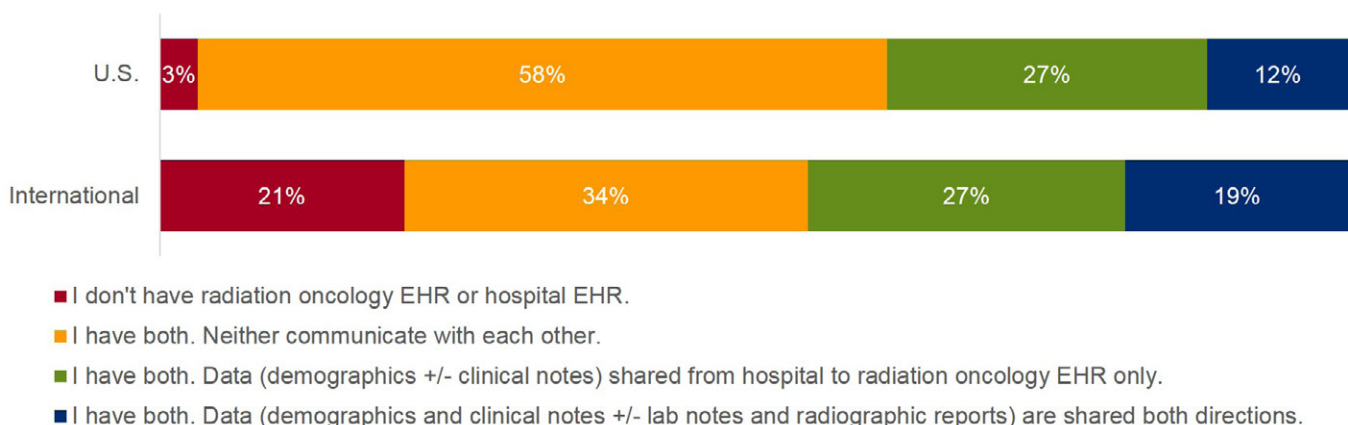
Thank you to everyone who took the time to complete the 2016 survey. The survey is sent out every spring, so don't miss it this year! Your input is essential to make ASTRO work best for you. [A](#)

Figure 8: Educational Format Preference



Compared with 2014, popularity has dropped for live webinars but grown for self-paced online options.

Figure 9: EHR Interoperability



Fewer than half of respondents report data sharing between a hospital EHR and radiation oncology EHR.

## USING BIG DATA TO MAKE A DIFFERENCE FOR RADIATION ONCOLOGY



**MEDICAL PHYSICIST TODD MCNUTT, PHD, FOUND INSPIRATION IN AN UNLIKELY SPOT** when creating a big dataset for radiation oncology: he looked to the stars. While working on a cross-disciplinary team at Johns Hopkins University in Baltimore, Dr. McNutt learned about the

Sloan Digital Sky Survey (SDSS), which uses high-resolution pictures and advanced imaging processing software to construct a three-dimensional map of the sky. The SDSS collects and analyzes a large and accurate amount of data that has resulted in hundreds of new discoveries in astrophysics, and all of the data is shared through an online portal called SkyServer.

But instead of mapping the sky, Dr. McNutt recognized the immense potential of using a database of clinical data to create more personalized treatment plans for radiation therapy patients. Over the past ten years, Dr. McNutt and his team have built Oncospace, a database and website that assembles data from the radiation oncology treatment planning system and patients' clinical records.

"We initially focused on building tools to collect the data as part of the normal workflow so that every radiation oncology patient can be treated as if they are in a clinical trial," says Dr. McNutt. Three additional institutions have started using the Oncospace platform and have joined Johns Hopkins to form a consortium in which patient data can be easily shared while still maintaining patient privacy and institutional control over the data.

Now that a large amount of data—more than 1,500 head and neck cancer patients alone—has been amassed in the Oncospace system, Dr. McNutt and his team are starting to use big data analysis and machine learning techniques to find patterns in this data that are clinically useful and could improve practice. The Radiation Oncology Institute (ROI)

recently awarded Dr. McNutt with a \$200,000 grant to use the data from head and neck cancer patients in Oncospace to build machine learning models that make personalized, evidence-based predictions of treatment toxicities related to weight loss. Dr. McNutt and his team will then begin to develop a decision support tool that will assist with treatment planning and clinical interventions based on these predictions. For this project, Dr. McNutt will collaborate with radiation oncologist Harry Quon, MD, who specializes in treating head and neck cancers and has provided a critical link to the clinical setting throughout the development of Oncospace.

A focus of the ROI-funded work is to better understand how the spatial distribution of the radiation dose influences toxicities. Current toxicity prediction models are based on factors associated with outcomes, such as patient demographics and clinical assessments, and dose volume histograms (DVH), which assume that all parts of a critical structure are equally important to its function and equally sensitive to radiation.

Dr. McNutt and his team will harness the advanced computing power available to develop better prediction models that incorporate the current factors, along with image-based features of a given structure's anatomy and more complex spatially dependent features of the dose distribution based on dose gradient, symmetry and analysis of which regions of the structure have the most influence on function.

"Our ultimate goal is to integrate these predictive models into a tool for decision support that can extract data on a new patient from the clinical system, apply the predictive models and present the results to a physician to assist with clinical decisions," says Dr. McNutt. "All of the data from that patient, including his or her outcomes, then become part of the knowledge base that the next patient's predictions are based on. Oncospace is designed to support a

*Continued on page 37*



## INTEGRATION OF “NEW SCIENCE” INTO ABR CERTIFICATION EXAMINATION PROCESS

SINCE WORLD WAR II, ADVANCES IN THE BASIC SCIENCES related to the clinical practice of oncology have been extraordinary. Progress in scientific discoveries often leaves educators with uncertainty as to precisely what aspects of these developments should be taught to trainees. Assessors of knowledge and skills, such as the American Board of Radiology (ABR), are faced with a similar dilemma regarding what level of emerging knowledge should be routinely assessed.

Responsibility for curriculum development in postgraduate medical education resides with the Accreditation Council for Graduate Medical Education (ACGME) and its constituent discipline-related review committees (RCs). For radiation oncology (RO), that responsibility lies with the RO RC, which has defined a requirement for radiation research personnel within accredited training programs, embedded within the ACGME Program Requirements for Graduate Medical Education in Radiation Oncology<sup>1</sup>. These requirements indicate the following: “The faculty must include at least one full-time radiation biologist or cancer biologist (PhD level or equivalent) who devotes the majority of his or her professional time to laboratory-based cancer research and is at the primary clinical site or at an integrated site to provide a scholarly environment of research, and to participate in the teaching of radiation and cancer biology.”

However, the RO RC has remained silent on the type of research these scientists must pursue, leaving open the potential that their research endeavors may be unrelated to clinical radiation oncology.

ACGME curriculum requirements in radiation and cancer biology are equally vague: “The program must provide instruction in radiation and cancer biology that includes the molecular effects of ionizing radiation and radiation effects on normal and neoplastic tissues, as well as the fundamental

biology of the causes, prevention, and treatment of cancer.” The requirements further state the following: “Graduating residents are expected to “demonstrate competence in their knowledge of . . . radiation and cancer biology.”<sup>1</sup>

As the entity responsible for assessing the level of knowledge and skills attained by postgraduate trainees at the completion of their RO residencies, it becomes incumbent upon the ABR to determine which elements of scientific advances will be assessed and when they should be included on examinations. To assist in this process, the ABR creates a blueprint for examination development in each area of assessment, based on its consideration of recent developments in clinical and basic science. In radiation and cancer biology, the trustees and staff of the ABR are guided by a committee of distinguished scientists and clinician-scientists.

These volunteers confer on a regular basis to review basic and translational scientific developments. In addition to incorporating new concepts into the Initial Certification (IC) item inventory, they continuously review the existing inventory to discard items related to scientific concepts that may have been discredited or lack current relevance. In fact, the pool of questions has almost completely turned over in the past five years, reflecting both the increase in knowledge of gene and pathway functions in cancer and radiation biology and the need to derive more thought-provoking questions on the subject matter.

While the fundamental principles of radiation biology have not changed, the volunteers have taken on the task of making the questions more relevant to clinical oncology. To assist program directors and instructors in the development of departmental didactic programming and to aid candidates in examination preparation, the committee prepares and regularly updates a detailed study guide that defines their current thinking<sup>2</sup>. Examination content is then

crafted from this blueprint. Topics that are considered “pure” research are avoided in item development. At this time, broad blueprint categories include the following:

- Interaction of radiation with matter
- Molecular and cellular damage and repair
- Cellular responses to radiation
- Linear energy transfer and oxygen effect
- Tumor biology and microenvironment
- Cancer biology
- Radiobiology of normal tissues
- Dose delivery
- Radiation modifiers
- Late effects and radiation protection

After each IC examination pool for radiation and cancer biology has been completed, items are reviewed by clinician volunteers to ensure timeliness and relevance and to assign Angoff scores to each item. A description of the Angoff scoring system is beyond the scope of this article, but details have been well-established, validated and reported. The system utilizes item-based criteria to evaluate each item independently, with grading based on an individual’s performance unrelated to the group (e.g., no scoring curve)<sup>3</sup>. Members of the Radiation and Cancer Biology Committee participate in the Angoff scoring for those items, but to ensure fairness, the majority of input is performed by clinicians.

To remain on the cutting edge of oncologic scientific development, an understanding of the basic sciences that underpin clinical decision making and progress is essential. The ABR has developed its assessment tools and support material to guide educators in preparation of curricula and to aid trainees in a clear understanding of its expectations.



## References

- <sup>1</sup> Accreditation Council for Graduate Medical Education ACGME Program Requirements for Graduate Medical Education in Radiation Oncology. [http://www.acgme.org/Portals/0/PFAAssets/ProgramRequirements/430\\_radiation\\_oncology\\_2016.pdf](http://www.acgme.org/Portals/0/PFAAssets/ProgramRequirements/430_radiation_oncology_2016.pdf). Accessed November 14, 2016.
- <sup>2</sup> American Board of Radiology Initial Certification Study Guide for Cancer and Radiation Biology. <https://www.theabr.org/ic-ro-study-bio>. Accessed November 16, 2016.
- <sup>3</sup> Wikipedia, Standard Setting in Professional Examinations. [https://en.wikipedia.org/wiki/Standard-setting\\_study](https://en.wikipedia.org/wiki/Standard-setting_study). Accessed November 15, 2016.

learning health system in which outcomes improve over time as the system learns with each new patient. Eventually, we want to be able to make these types of tools available to any physician through our web portal.”

Although projects like Oncospace hold considerable promise to change the practice of radiation oncology and improve outcomes for cancer patients, traditional research funding sources often do not support them. Dr. McNutt has kept the Oncospace program going through a variety of industry grants, but funding from other sources such as the National Cancer Institute has been elusive. “The ROI award is great because a peer review recognized the value of what we are trying to do,” says Dr. McNutt. His proposal was selected for funding from 16 applications that were submitted in response to ROI’s “Leveraging Big Data to Optimize Quality Assurance and Patient Care Improvement Initiatives” request for proposals that sought to encourage research in this emerging field.

Dr. McNutt is optimistic about the future of big data in medicine: “We can collect far more detailed data than traditional clinical trials and machine algorithms can do far more than standard analytical methods. Big data can really make a difference in radiation oncology. If we do it right and have good predictive models, it can serve the world.”

## 2016 ANNUAL MEETING UNRESTRICTED EDUCATIONAL GRANT SUPPORTERS

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## DEVELOPING A RISK-BASED QUALITY MANAGEMENT PROGRAM FOR RADIATION THERAPY

WHEN THE U.S. [INSTITUTE OF MEDICINE](#) PUBLISHED THE REPORT, “To err is human: building a safer health system,” more than 17 years ago, it was a wake-up call for the entire health care community. While none of us comes to work with the intention of compromising patient care, the enormity of human consequences on poor-quality medicine was brought home dramatically with this publication. Although we, in radiation oncology, take both care and pride in providing accurate and effective treatment for cancer patients, our field has seen its share of catastrophic misadministration—and that’s based just on incidents that make it to the public domain. In the areas of safety and quality, physicists have been in the fore for many years, devoting countless hours to ensuring that increasingly sophisticated treatment planning and delivery equipment is both functioning correctly and used appropriately. Of course, safe, high-quality radiotherapy is predicated on accurately calibrated and properly maintained equipment. But evidence has been building that most of the problems faced in achieving the levels of quality and safety that patients deserve are attributable to human performance failures and not inherent weaknesses in equipment design and maintenance.

In 2003, the American Association of Physicists in Medicine (AAPM) became concerned with the rapid technological evolution of radiotherapy planning and delivery equipment and the associated quality assurance requirements of these new devices. The recommendations of AAPM Task Group 40 from 1994, which addressed quality assurance of the devices in use at that time, required expanding and updating to reflect advances in technology and clinical practice. Out of this concern, Task Group (TG) 100 was formed. Comprised of 10 physicists, one industrial engineer and one radiation oncologist, the TG started by considering how it might best help the medical physics and broader radiation oncology community.

During early deliberations, the TG recognized that merely adding to the current number of safety and quality tests to accommodate the increasing complexity of equipment and practice was likely to create resource problems without achieving the larger goal of enhancing the quality and safety of radiotherapy. Not only were physics resources unlikely to expand sufficiently to fully meet the demand for a larger suite of quality assurance tests, but many of the safety and quality problems being reported in radiation oncology were not directly attributable to inadequate equipment quality assurance. Rather, they were attributable to the human contribution to the radiotherapy process. Against that background, the members of TG 100 recommended that a radically new approach to quality and safety in radiation oncology was needed. The following is a key statement from the mandate of TG 100 and it was meeting this objective that consumed most of TG 100’s effort: *Identify a structured systematic QA program approach that balances patient safety and quality versus resources commonly available and strike a good balance between prescriptiveness and flexibility.*

The Task Group communicated in person, by teleconference and email during the 13 years of its deliberations. This effort culminated in the publication in 2016 of “The report of Task Group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management. Medical Physics 43, 4209 – 4262. 2016.” In this brief note, we outline the methodology recommended in the report.

The ultimate aim of the exercise is to develop a Quality Management (QM) program that provides the patient with confidence that the highest standards of quality and safety will be reached. The QM program is built on three components: Process Mapping, Failure Modes and Effects Analysis and Fault Tree Analysis. We will briefly describe each of these three components.



## PROCESS MAPPING

Process Mapping is familiar to many of us. It is the process of describing, usually diagrammatically, the major steps and sub-steps undertaken in order to provide a patient with treatment. Process maps are best generated by a multidisciplinary team to ensure that all key and critical activities are included. As well as being the first step in TG 100's methodology, process maps have other significant benefits for the clinical radiotherapy operation. A process map is a graphical representation of a Standard Operating Procedure, and it is widely recognized that standardizing procedures has the ability to enhance both quality and safety. However, process maps can quickly become very complicated structures, so it is advisable to restrict their scope to the purpose for which they are intended. It is also important that all users of the process map have the same understanding of the words used to describe the various major- and sub-steps.

## FAILURE MODES AND EFFECTS ANALYSIS

Armed with a process map, the next phase in TG 100's methodology starts with the selection of a step in the process for further analysis. It is usually advised that, rather than attempt to examine the total patient pathway, one critical step is selected for the first Failure Modes and Effects Analysis (FMEA). Having selected a step, this question is posed: What could possibly go wrong at this step? The answer(s) to this question are the Failure Modes (FM) associated with this step. Having identified one or more FMs, the group performing the analysis then estimates how likely it is that an event would occur that could lead to the postulated Failure. This is the Occurrence value. Next, an estimate is made of the severity of the FM should it reach the patient. This is the Severity value. The last judgment the group is called upon to make is the probability that the pathway leading from the originating event will not be intercepted before reaching the patient. This is the Detectability. In the TG 100 approach, Occurrence, Severity and Detectability are all scored between 1 and 10. Multiplying these three estimates together yields the Risk Priority Number (RPN). The process is repeated for all identified FMs. The output of this analysis, an RPN for each FM, provides the opportunity for

ranking FMs from the most to the least significant, and can help determine how to direct resources to the issues presenting the greatest potential hazards to the patient. Prioritizing interventions can also be based on the Severity scores of the FMs, or, indeed, setting thresholds for action on both Severity and RPN.

## FAULT TREE ANALYSIS

A more detailed examination of the pathways that can lead to Failures at patient treatment can be helpful in designing an appropriate Quality Management program. Fault Tree Analysis (FTA) is a technique commonly employed to delve deeper into pathways to failure. A Fault Tree links events and circumstances through "and" and "or" gates to the FM. It can be thought of as a hypothetical Root Cause Analysis (RCA). In an RCA, an actual incident is traced back to causes and contributing factors, frequently being illustrated on a cause-and-effect diagram. In FTA, it is not an actual incident that starts the tree but rather a postulated failure. Because the RCA attempts to describe actual events and their relationships, gates are not necessary—there is no "or" gate in an RCA—because we believe we know the chain of events. However, visually an FTA looks similar to an RCA. The value of FTAs, in the context of prospective risk management, is that they can help identify where best to place barriers in the possible failure pathways and, once a few FTAs have been designed, systemic safety improvement measures, such as increased training or better documentation, become readily apparent.

The overall objective of this exercise is to develop a Quality Management program for the process, or at least that part of the process under consideration. FMEA helps us to prioritize those FMs that pose the greatest hazard to the patient and hence require the most urgent attention. FTA can highlight those systemic infrastructure issues that have the greatest potential to compromise quality and safety and also provides a basis for decisions on where to place barriers to error propagation. Information obtained from the application of these three tools can then be used to develop a risk-based quality management program.


The Quality Management program developed out of the application of the TG 100 methodology will

*Continued on next page*

be specific to the clinical operation under study. Thus, the TG 100 approach customizes QM to individual radiation oncology departments reflecting their unique ways of doing things and is definitely not a one-size-fits-all solution to quality and safety.

There is undoubtedly a learning curve associated with the application of the techniques outlined here. However, experience has shown that, with a stable, committed multidisciplinary group, confidence and competence in the use of these tools can be quickly acquired. Working toward the goal of developing a more effective QM program not only enhances the safety culture of the organization but also cements relationships between the various professionals in the clinic, thus building a more cohesive clinical team.

There are two complementary classes of approach to the enhancement of quality and safety in the

clinic. In the retrospective approach, we look back on our experience, and that of others, of what has gone wrong and institute actions to prevent recurrences. This is incident learning and is exemplified by systems such as RO-ILS: Radiation Oncology Incident Learning System®. The complementary approach is prospective and is based on postulating what might go wrong in the future and developing a quality program to minimize the chances of failure. It was this latter approach that was adopted by TG 100. An important footnote at this point is that the TG 100 methodology was never intended to replace the prescriptive quality assurance protocols, such as the AAPM's TG 142 and similar documents, which have served us so well over the years. However, it is likely that, in the future, prescriptive protocols will be more and more influenced by risk assessments of the type proposed by TG 100. Time will tell. 



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# JOURNALS

# HIGHLIGHTS

## HIGHLIGHTS FROM INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY • BIOLOGY • PHYSICS

**July 15, 2016**

### Randomized Phase 3 Trials of Accelerated Partial Breast Irradiation: A Trickle Before the Deluge

*Khan and Belkacemi*

Although Accelerated Partial Breast Irradiation (APBI) has become a recognized and approved alternative to whole-breast irradiation, it still lacks randomized data to prove equivalence. That is about to change with many international trials maturing. Breast cancer editors Khan and Belkacemi take a look at three recently published trials, the GEC-ESTRO and smaller studies from Spain and Italy. The message is consistent. APBI and whole-breast irradiation appear equivalent in terms of local control with five years of follow-up.

**August 1, 2016**

### The Stagnation and Decay of Radiation Oncology Resources: Lessons from Nigeria

*Irabor et al.*

In this Around the Globe article, Irabor details the troubles facing the Nigerian economy, political culture and medical system. Unlike most African nations, in which oncology services are slowly on the rise, Nigeria is heading in the reverse direction. Nigeria was an early adopter of radiation therapy, yet this specialty is now in a state of contraction, with established machines becoming obsolete and radiation oncologists practicing in other specialties.

**September 1, 2016**

### Safety and Efficacy of Radiation Therapy in Advanced Melanoma Patients Treated with Ipilimumab

*Qin et al.*

Ipilimumab and radiation therapy (RT) are now standard treatments for advanced melanoma, and preclinical models suggest the potential for synergy. In a retrospective analysis, these authors found that both ablative and conventionally fractionated RT can be safely administered with ipilimumab without a clinically apparent increase in toxicity. Patients who received ipilimumab before RT appeared to have an increased duration of irradiated tumor response.

**October 1, 2016**

### Fractionation Spares Mice from Radiation-Induced Reductions in Weight Gain but Does Not Prevent Late Oligodendrocyte Lineage Side Effects

*Begolly et al.*

Begolly and colleagues studied the role of fractionation in reduced white matter side effects of stereotactic dose radiation in adult mice. Although fractionation (36Gy in 6 fractions) reduced some effects on weight gain when compared to a single dose of 20Gy, the patterns of early and late oligodendrocyte progenitor cell depletion, and late white matter pathology and dysfunction, were very similar. This indicates that fractionation fails to reduce late white matter side effects of radiation in this particular mouse model.

**November 1, 2016**

### 18F-Fluorodeoxyglucose Positron Emission Tomography Can Quantify and Predict Esophageal Injury During Radiation Therapy

*Niedzielski et al.*

This study investigated the ability of mid-treatment 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) research to objectively, and spatially, quantify esophageal injury in vivo from radiation therapy given for non-small cell lung cancer. FDG-PET uptake was normalized to each patient's low-irradiated region (<5Gy) of the esophagus, as a radiation-response measure. Increasing normalized standardized uptake value was related to esophagitis severity. It can objectively, and noninvasively, quantify esophagitis during radiotherapy, and predict eventual symptoms among asymptomatic patients. Normalized uptake may provide patient-specific dose-response information not discernible from dose.



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**November 15, 2016**

## **From Röntgen Rays to Carbon Ion Therapy: The Evolution of Modern Radiation Oncology in Germany**

*Lischalk et al.*

Beginning with the discovery of X-rays in 1895, German scientists and clinicians were instrumental in establishing the fields of diagnostic and therapeutic radiology, creating the first peer-reviewed journal for radiation therapy and holding the first international oncologic conference. These authors explore the evolution of radiation therapy in Germany, from the groundbreaking establishment of Bismarck's health care system to a modern view of radiation therapy practice.

### **HIGHLIGHTS FROM PRACTICAL RADIATION ONCOLOGY**

**July–August 2016**

## **Partial Orbit Irradiation Achieves Excellent Outcomes for Primary Orbital Lymphoma**

*Binkley et al.*

Primary radiation therapy achieves excellent local control and overall survival when treating localized orbital lymphoma. However, evidence supporting irradiation of partial orbit volumes to spare nearby critical structures is lacking. The authors sought to investigate outcomes for patients with localized orbital lymphoma treated with partial orbit irradiation. Their findings indicate that the use of partial orbit irradiation in treating low-grade, localized orbital lymphoma achieves excellent survival with low rates of local failure, contralateral orbit recurrence or progression.

**September–October 2016**

## **Bladder dose–volume parameters are associated with urinary incontinence after postoperative intensity modulated radiation therapy for prostate cancer**

*Son et al.*

Urinary incontinence is a potential side effect of prostatectomy and intensity modulated radiation therapy (IMRT) for prostate cancer. There are limited data on dosimetric parameters that may predict for poor continence recovery in men who receive postoperative IMRT. There was no significant change in patient-reported urinary continence scores after postprostatectomy IMRT. Bladder V70 Gy was independently associated with a decrease in urinary continence scores. Further evaluation is necessary to optimize quality of life in these men.

**November–December 2016**

## **Can Surface Imaging Improve the Patient Setup for Proton Post-Mastectomy Chest Wall Irradiation?**

*Batin et al.*

For post-mastectomy radiation therapy by proton beams, the usual bony landmark-based radiograph

setup technique is indirect because the target volumes are generally superficial and far away from major bony structures. The surface imaging setup technique of matching chest wall surface directly to treatment planning computed tomography was evaluated and compared to the traditional radiograph-based technique. The use of surface imaging allows post-mastectomy chest wall patients to be positioned more accurately and substantially more efficiently than radiograph-based techniques.

### **HIGHLIGHTS FROM ADVANCES IN RADIATION ONCOLOGY**

**January–March 2016**

## **Long-term Benefit of Electron Beam Radiation Therapy in the Treatment of Scleredema of Buschke**

*Skrepnik et al.*

Scleredema of Buschke is a rare connective tissue disorder presenting with woody thickening and induration of the nuchal and shoulder regions, resulting in progressive decrease in the range of motion of the neck. Treatment options include several forms of systemic therapy with variable results. Local radiation therapy is often thought of as a secondary form of therapy. Few reports exist in the literature about the durability of its benefit. The authors present a case report with the longest known follow-up after primary treatment with electron beam radiation therapy.

**April–June 2016**

## **Clinical Application of Lying-on-the-Floor Total Skin Electron Irradiation for Frail Patients with Cutaneous Lymphoma: An Emphasis on the Importance of In Vivo Dosimetry**


*Evans et al.*

Total skin electron irradiation (TSEI) is an effective option for cutaneous T cell lymphoma (CTCL). The authors report clinical implementation of this technique in a nonambulatory patient with progressive CTCL, with particular emphasis on the critical importance of in vivo dosimetry.

**July–September 2016**

## **Neutron Radiation Therapy for Advanced Thyroid Cancers**

*Chapman et al.*

The authors reviewed institutional outcomes for advanced thyroid cancers treated with fast neutron radiation therapy (FNRT) and photon radiation therapy. Outcomes in this study are in line with historical results. There is an apparent detriment in overall survival (OS) with FNRT for well-differentiated histologies and a trend toward improved OS with medullary and anaplastic histologies that warrants further investigation. 

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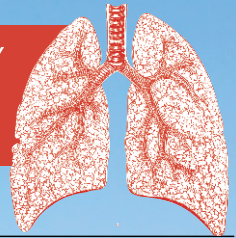
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