

WINTER 2023

# ASTRO news

## RADIOPHARMACEUTICALS

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### **Radiation Oncology's Scope of Practice of RPTs**

*Commentary on how ROs are well positioned to play a leading role in clinical practice of RPTs.*

Page 12

### **Patient-centered RPT: A Typical Patient's Pathway**

*Exploring the essentials of care, from referral through treatment and follow-up.*



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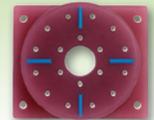
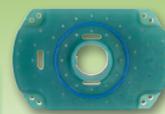
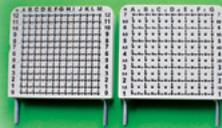


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# ASTRO news

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## RPT: The Next Frontier

**IN OCTOBER 1949**, Life Magazine ran a story headlined “Radio-iodine Halts One Type of Cancer.” It featured Bernard Brunstein, the Brooklyn shoe salesman who was “cured” of metastatic thyroid cancer with the use of radioactive iodine (RAI).<sup>1</sup> His treating physician was Montefiore Hospital’s S.M. Siedlin, MD, who confirmed that the patient’s response had been excellent, unlike others given the same treatment.

He correctly deduced that it worked as the patient had a thyroidectomy several years before, enabling the radioactivity to be taken up by the metastatic sites. Dr. Siedlin and others had built off the work of Massachusetts General Hospital’s Saul Hertz, MD, who began research on RAI for thyroid diseases in 1937, forever changing the management paradigm for thyroid diseases.

Eighty years on, the field of radiopharmaceutical therapy (RPT) has advanced to apply to a variety of other diseases, including metastatic prostate cancer, neuroendocrine tumors, neuroblastoma, etc. Interest in RPT is high among radiation oncologists and rightly so — we are best equipped to lead this collaborative effort with our knowledge of physics, radiobiology, pathophysiology, imaging, the effects of radiation on tumors and normal tissues and, most importantly, expertise and clinical competencies in oncologic decision making as well as multidisciplinary patient management.

This issue will attempt to take in the broad sweep of this rapidly developing field while exploring some of the granular details as well. We look at RO’s scope of practice for RPT (page 10), a typical patient’s pathway (page 12), how to set up an RPT program (page 15), regulatory requirements (page 20), individualized dosimetry (page 23), training and credentialing (page 31) and much more.

Many novel theranostics are under development, expected to enter clinical trials and eventually some will make it to patient care in the near future. The expansion of this novel frontier certainly is exciting but also poses key challenges. While Seidlin’s famous patient did

improve clinically, a little more than two years after the Life magazine piece, Brunstein reportedly died in 1952 from autopsy-proven anaplastic carcinoma, bringing home the point the importance of separating hype from hope. Conducting prospective randomized controlled trials and head-to-head comparison with standard-of-care treatments is paramount to generate high-level evidence.

It’s fitting that in this issue, we also pay tribute to the late Dave Larson, MD, PhD, FASTRO, a pioneer in radiosurgery who was instrumental in opening up a new frontier for the discipline (page 7).

There can be no better way to mark the new year than by looking to the future of our discipline and the ways in which we can keep improving the lives of our patients. On behalf of the *ASTROnews* editorial board, I wish all of you a very happy 2023. 🚀

*Dr. Mohideen welcomes letters to the editor at [ASTROnews@astro.org](mailto:ASTROnews@astro.org).*

### Reference

1. Radio-iodine halts one type of cancer: Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors. *Life Magazine*. 1949;27(10):54-56.

**View additional *ASTROnews* content online**

Journals Highlights, reference lists and bios of featured authors and highlights of some of the top science from the 2022 Annual Meeting, detailed by discussants of the popular Science Highlights sessions.

All this and more can be found at [www.astro.org/Winter23News!](http://www.astro.org/Winter23News!)



## CHAIR'S Update

GERALDINE JACOBSON, MD, MPH, MBA, FASTRO,  
CHAIR, BOARD OF DIRECTORS

# Working Together in 2023 to Advance Our Specialty

**GREETINGS AND WARMEST WISHES** for a happy, healthy and successful 2023!

The new year is a perfect time to consider new directions and explore the landscape of potential opportunities. The focus of this issue, expanding the use of radiopharmaceutical therapies (RPTs) in radiation oncology, exemplifies this theme. A priority that emerged from our 2017 strategic planning session was the need to expand our scope of practice, utilizing all radiation modalities for both benign and malignant conditions. We identified diagnostic and therapeutic radiopharmaceuticals as a promising area for clinical development and created an ASTRO RPT workgroup to lead this initiative. The group has published a framework for patient-centered use of RPTs,<sup>1</sup> a framework for radiopharmaceutical curriculum development for trainees<sup>2</sup> and organized highly successful Master Classes in RPT at the last four Annual Meetings.

A recent member survey attests to the level of interest among our members, with more than 30% of practices participating in RPT and a similar number planning to expand their practice in this area. With that in mind, this issue of *ASTROnews* addresses an array of topics relevant to the integration of theranostics into radiation oncology. These include patient care and logistics, radiobiology and pharmacokinetics, dosimetry, coding and billing and future directions. These and related issues will continue to unfold as we expand this area of clinical practice.

During the 2022 ASTRO Annual Meeting, I announced the formation of IRON, the International Radiation Oncology Network. This network of regional and national radiation oncology societies will serve as a vehicle for sharing information and developing closer connections to advance the field of radiation oncology. On December 6, 2022, representatives of 11 of the world's largest professional societies in cancer care, including ASTRO, signed on to Practical Arrangements on Technical Professional Society Partnerships in Cancer Care with the International Atomic Energy Agency (IAEA). The purpose of this

partnership is to coordinate programs in education and expertise to improve access and quality of radiation therapy in low- and middle-income countries. ASTRO is continuing to expand our engagement in global oncology. This provides an opportunity to share our expertise, connect with our global partners, improve the quality of global cancer care and impact global cancer policy through collaboration.

U.S. radiation oncologists are again facing significant cuts in reimbursement. There has been continual downward pressure on radiation oncology reimbursement for decades, with a 22% decrease in Medicare-allowed charges for radiation therapy services over a 10-year period. Over the same time frame, radiation oncology practices implemented shorter treatment schedules and delivered safer and more targeted care. The human and technical resources and fixed operational costs required to provide this level of quality are significant but not acknowledged in payment rates.

Radiation oncology now faces additional major cuts in the Medicare physician fee schedule due to conversion factor reductions, budget neutrality and clinical labor price updates.

ASTRO remains committed to engaging with CMS and Congress to achieve fair and stable payments for our services. We thank all our members who have joined us in advocacy so we can continue to provide access to safe, high quality radiation therapy for all patients who need our services.

Your membership and engagement are ASTRO's greatest strength. The new year will undoubtedly offer challenges and opportunities. We look forward to working together in 2023 to advance our specialty and continue to provide optimal care to our patients. 

### References

1. Buatti JM, Pryma DA, Kiess AP, et al. A framework for patient-centered pathways of care for radiopharmaceutical therapy: An ASTRO consensus document. *Int J Radiat Oncol Biol Phys*. 2021;109:913-922.
2. Kiess AP, Hobbs RF, Bednarz B, et al. ASTRO's framework for radiopharmaceutical therapy curriculum for trainees. *Int J Radiat Oncol Biol Phys* 2022;113: 719-726.



## Year in Review: 2022

**ANOTHER YEAR IS IN THE BOOKS**, and looking back, I am yet again struck by the growth of the Society's initiatives and programs. In my over 20 years as CEO, I have seen growth in terms of membership size and in the scope of the field, but one thing always holds steady: the strength of ASTRO comes directly from you, our members. Without you, we would not be able to accomplish all we did in 2022. Here's a brief recap.

ASTRO leadership began the year with a Board of Directors meeting where we held a strategic planning session to review and build on key issues and priorities for the Society in order to update ASTRO's strategic plan. In June, the Board approved an updated mission and vision statement and strategic goals. You can view these at [astro.org/strategicplan](https://astro.org/strategicplan). We are working to develop key performance indicators, which will help us measure progress toward our goals.

In February, ASTRO retained the services of Health Management Associates to conduct an analysis of the expected workforce needs in radiation oncology over the next five to 10 years. The Workforce Task Force, led by Bruce Haffty, MD, FASTRO, Pranshu Mohindra, MD, and Chirag Shah, MD, released a statement in February on issues impacting U.S. workforce. An interim report of the study, highlighting the methodology of the research, was presented during the Annual Meeting, and the highly anticipated report will be issued soon and shared with members.

As part of our efforts to support our members at every stage of their careers, ASTRO launched a new Early Career Committee in the summer with an open call for volunteers. Austin Sim, MD, JD, and Anna Paulsson, MD, were selected as chair and vice-chair of the committee. The committee is actively working to identify and develop resources to support the unique needs of this membership cohort and create a space for peer mentorship and networking, most recently establishing an early career community in the *ROhub* member forum.

Another exciting change at the governance level was the 2021 vote approval to elevate the Committee on Health Equity, Diversity and Inclusion (HEDI) to a full council with two representatives on the Board. The HEDI Council, led by Iris Gibbs, MD, FASTRO,

as chair and Curtiland Deville Jr., MD, as vice-chair will expand on the impactful work CHEDI laid the groundwork for and build on the existing programs and initiatives to increase equity and eliminate health disparities. ASTRO is dedicated to an inclusive culture and is currently undergoing internal and external cultural audits to identify areas of improvement and growth. The audit is scheduled to conclude in 2023.

The Centers for Medicare and Medicaid Services' (CMS) indefinite delay of the radiation oncology alternative payment model (RO Model) was both a disappointment and a relief. ASTRO remains hopeful that the delay offers an opportunity for CMS to work with stakeholders on a new value-based payment structure. ASTRO is developing a new proposal for an alternative payment model to share with stakeholders later this year. In addition to an emphasis on episodic payments, the new proposal will emphasize ways to help patients from economically and socially marginalized groups access and complete radiation treatments.

ASTRO published four clinical practice guidelines in 2022: Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma; Radiation Therapy for Brain Metastases; a joint guideline with the American Urological Association to update the 2017 Guideline on Clinically Localized Prostate Cancer; and Radiation Therapy for Endometrial Cancer. All ASTRO guidelines can be found in *Practical Radiation Oncology*.

2022 was the year that ASTRO's APEX became the fastest growing accreditation program for radiation oncology practices, and RO-ILS saw enrollment of more than 800 practices. ASTRO awarded nearly \$1.2 million across 13 research grants and three fellowships.

Lastly, coming together for another in-person Annual Meeting in October was such a joy. We were excited to offer a virtual component that, for the first time, livestreamed almost every session of the meeting. As our educational offerings expand, we plan to include virtual offerings as much as possible as part of the new world "post-COVID" to better accommodate the needs of our members.

Thank you for all you do for ASTRO. On behalf of the staff, I wish you a successful and happy 2023! 🇺🇸

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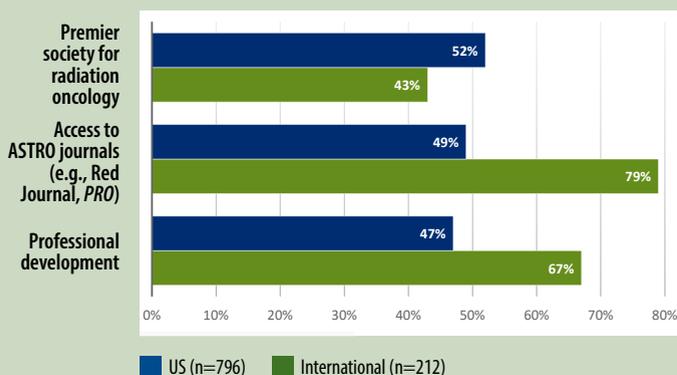
## Results of the 2022 ASTRO Member Survey

### Prior authorization remains key issue; technological innovation brings optimism

**ASTRO CONDUCTS A MEMBER SURVEY ANNUALLY** to learn more about our members' concerns and needs and how we can serve them better as a professional society. Along with the usual categories of profession and demographics, this year's survey delved into reasons for ASTRO membership as well as top concerns and reasons for being excited about the future of the field. The Member Survey was fielded for eight weeks, from May 24 through July 24, and was emailed to nearly 7,300 members. Just over 1,000 members responded, for a response rate of 14.3%, a slight decrease from 2021.

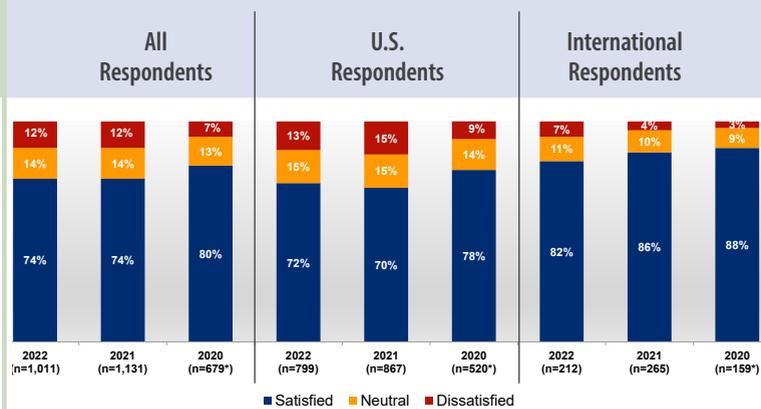
#### Top Three Reasons for being an ASTRO member

ASTRO's recognition as a premier society for radiation oncology increased among both domestic and international members from last year (48% and 34% respectively). International members valued professional development opportunities with ASTRO and access to ASTRO journals significantly more than their U.S. counterparts.



#### Satisfaction with ASTRO Membership

Overall, U.S. respondents reported a slight increase in satisfaction, with satisfaction among U.S. ROs and medical physicists holding steady. Satisfaction among international respondents dipped, attributed mainly to the cost of membership.



#### ASTRO Membership Satisfaction for Early Career Members and Residents

“Early career” is defined as eight years or fewer out of residency. Of ASTRO members who fall into this category, 63% of those surveyed are satisfied with membership. Of this same group who responded, a greater percentage (83%) of international members expressed satisfaction more than their U.S. counterparts at 59%. To better serve our early career members, ASTRO established an Early Career committee this past summer to improve the Society's support of these members and their unique needs.

U.S. residents indicated a moderate increase in satisfaction with ASTRO membership, increasing to 63% this year compared to 58% last year.

#### Importance of and Appreciation for Member Participation

Thank you to everyone who completed the 2022 ASTRO Member Survey. Your feedback is invaluable as we strategically plan ASTRO initiatives to best serve you. The survey is sent out every spring, so don't miss the 2023 Member Survey next May! Please take the opportunity to share your input.



See the complete results of the 2022 Member Survey and breakdowns on respondent demographics, including race, gender, ethnicity and profession at [www.astro.org/Winter23News](http://www.astro.org/Winter23News).

# Tribute: David Larson, MD, PhD, FASTRO

BY ARJUN SAHGAL, MD

**DAVID LARSON**, MD, PhD, FASTRO, was not only a thought leader in the broader field of radiation oncology — he was the doctor’s doctor and a world expert in radiosurgery. He was an honest and good person who cared deeply about his family, friends and patients. I had the privilege of being his last fellow at UCSF, and part of the legacy of fellows, residents, medical students and graduate students that he leaves behind, who shared in his wisdom and humor. We will miss him tremendously. His death reminds us that we need to remember those who brought us to where we are today as radiation oncologists, and to cherish the teaching moments we had with our mentors.

Dave is one of a few radiation oncologists in the world to hold a place in history as a pioneer of radiosurgery. He told us stories of treating the first AVM patients in San Francisco based on calculations from the software his team developed, and the stress and pleasure he felt in providing an option to patients who had no other treatments available. The stories of the drama surrounding the application of radiosurgery for brain metastases were remarkable and point to a special time in our profession’s history when great minds battled for what they believed was right for patients. Despite professional differences, they came together and agreed on the pivotal studies that were necessary to prove if indeed radiosurgery was beneficial in a patient population otherwise doomed to die a neurologic death. As we now enjoy the luxury of routinely performing radiosurgery for up to 10 metastases, and push the limits (as Dave would) to no matter how many metastases as long as they are targetable, we thank those visionaries on behalf of our patients.

As mainstream technology progressed to deliver radiosurgical doses with reasonable precision to extracranial targets, it was again a few courageous and highly intelligent leaders in our field that guided practice. Dave was one of those leaders there at the genesis of what we now know as stereotactic body radiotherapy (SBRT). He did more than simply adopt the technology, which was evolving in innovative and disruptive industry portfolios, as he provided much needed guidance for target dosing and tolerances to organs-at-risk like the spinal cord. Many came from



far and wide to spend time with and learn from Dave as I did, and he is credited with training many of the radiosurgical leaders of today in some shape or form. I can only say that countless patients have benefited from his dedication to radiation oncology, and his compassion for cancer patients was palpable and admirable. To learn more about his remarkable life, read his ASTRO interview at [www.astro.org/DavidLarson](http://www.astro.org/DavidLarson), and a tribute recently published in the SF chronicle.<sup>1</sup>

To know Dave was a distinct honor. I had spoken to him at least once a month for the last 15 years; he came to my wedding, he spent time with my children who call him their “Goofy” uncle and, ultimately, he had a major role in both my personal and professional life for which I can’t thank him enough. We should all be so lucky to have had a mentor and friend like him. We know Dave is in a much better place, and we will dearly miss his jokes, his simple wisdom and his heartfelt laughter. Please take a moment and celebrate his life and join us in expressing our sincere condolences to his family. 🙏

*An obituary will soon be published in the Red Journal at [www.redjournal.org](http://www.redjournal.org) in tribute to Dr. Larson and his vast contributions to the field and to UCSF.*

1. <https://www.legacy.com/us/obituaries/sfgate/name/david-larson-obituary?id=38147290>.

## Newly Elected Companies to Serve on ASTRO's Corporate Advisory Council

**ASTRO'S CORPORATE MEMBERSHIP** elected the following companies to serve on the 2023 Corporate Advisory Council: Leo Cancer Care, Novocure and Reflexion, all newly elected, and CIVCO/Qfix, which was re-elected for another term. We are also pleased to announce AstraZeneca will serve an additional term of one year. The addition of a pharmaceutical company is designed to help serve as another category of industry perspective and contribution to the work of the Council.

The Council is a smaller, representative group of the Corporate Membership-at-large, with a proportional mix of large and small companies from the Corporate Membership base. Seats on the Council are held by high-level decision makers within the corporations and represent a broad cross section of the industry.

The Council allows for collaboration between ASTRO and its Corporate Members by focusing on issues and initiatives of mutual concern in radiation oncology. Priorities include increasing awareness of radiation therapy and advancing the science and practice of cancer treatment and patient care. In cooperation with ASTRO leadership, the Council convenes several times a year via conference call and holds an in-person meeting at ASTRO's Annual Meeting. In 2022, the following topics were brought to the forefront: Industry support for new approaches to patient treatment and patient education; a report on ASTRO's workforce study; advancing the field of radiation oncology and making a greater impact on science; the Radiation Oncology Incident Learning System (RO-ILS) and its continued growth; and the many changes in health care legislation, including coding and RO Model proposed rule updates.

All corporate members can nominate their company to serve on the Council. Nominations are accepted every fall with elections conducted during the winter. For more information about the Council and/or Corporate Membership, please contact Joanne DiCesare at [joanne.dicesare@astro.org](mailto:joanne.dicesare@astro.org). 

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2022 Corporate Advisory Council

## In Memoriam

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

**David Larson, MD, PhD, FASTRO**  
San Francisco, CA

**Peter von Rottkay, MD**  
Landshut, Germany

**Diane W. Truesdale, MD**  
Lexington, South Carolina

**Frederick R. Zivnuska, MD**  
St. Louis, Missouri

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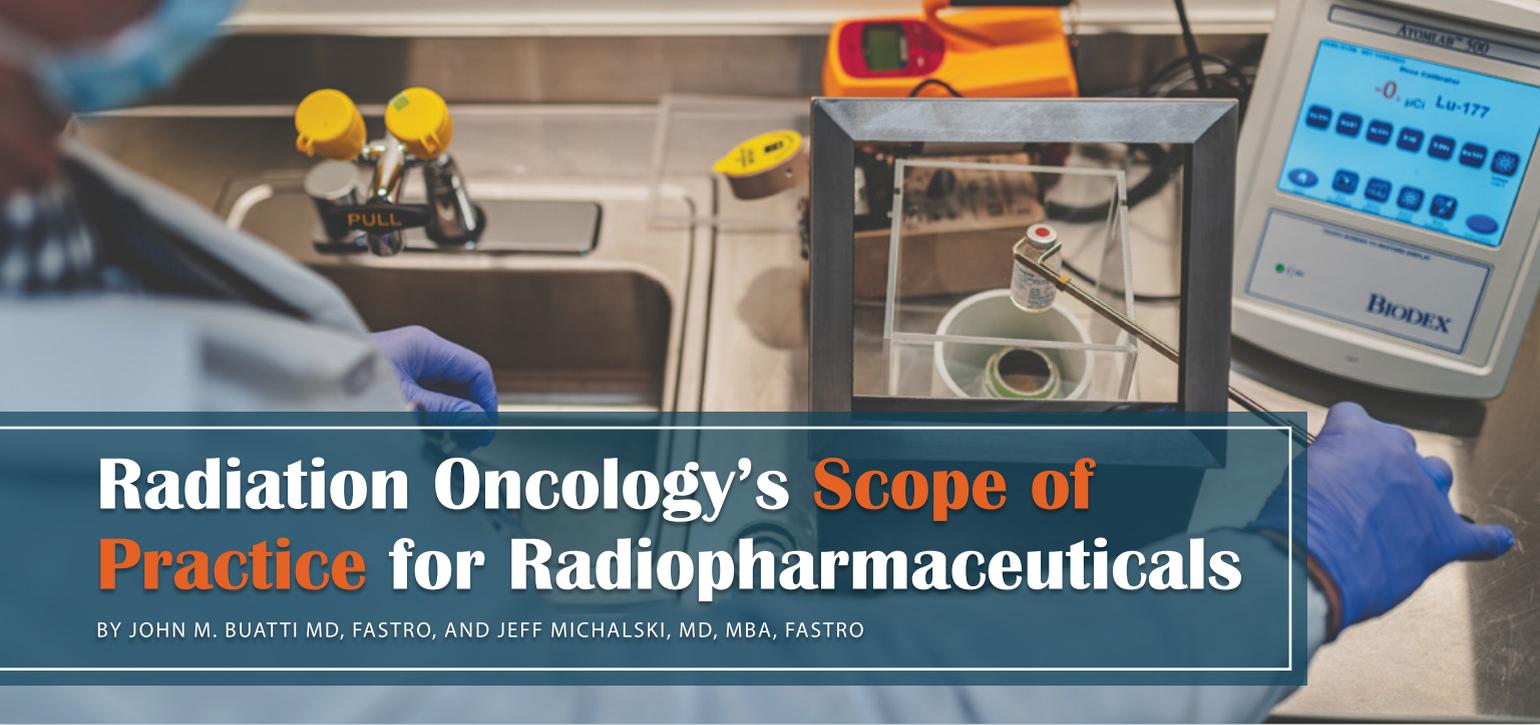
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# Radiation Oncology's **Scope of Practice** for Radiopharmaceuticals

BY JOHN M. BUATTI MD, FASTRO, AND JEFF MICHALSKI, MD, MBA, FASTRO

## **RADIATION ONCOLOGISTS ARE WELL POSITIONED**

to play a leadership role in the clinical practice of radiopharmaceutical therapy (RPT). The clinical delivery of unsealed sources has been a component of radiation oncology training and practice since its inception although the clinical applications of RPT were initially limited. The initial and most common application for many years was radioactive iodine treatment for thyroid disease. More recently, applications for lymphoma (Zevalin, Bexxar) and bony metastases from castrate resistant prostate cancer ( $^{223}\text{Ra}$ ) have been approved and shown efficacious. These humble beginnings have even more recently witnessed a continued expansion in activity centered around treatment of liver lesions with  $^{90}\text{Y}$  microspheres and  $^{177}\text{Lu}$ -DOTATATE for neuroendocrine tumors. These compounds have laid the groundwork for rapid development of small molecules labelled with radionuclides for a variety of solid tumors and most recently the FDA approved  $^{177}\text{Lu}$ -PSMA-617, which has broadened applicability significantly. Application of the new PSMA RPT has led to improved survival of patients with metastatic prostate cancer in a phase III randomized trial and opened the door for a range of new agents including alpha emitting agents. The rapid development in the chemistry for creation of novel, targeted agents with improved capacity for chelation to a variety of radionuclides has revolutionized the potential for RPT to become a substantial part of radiotherapy practice.

It is important to note that clinical practice of RPT in the U.S. has been inconsistent in terms of workflow and in many cases the treatment has been primarily

delivered by our nuclear medicine colleagues while in other cases the radiation oncologists have played a primary role. These nuclear medicine physicians are highly skilled in nuclear medicine image interpretation and have generally served as authorized users for both diagnostic studies and the limited applications of RPT previously available. However, most have limited direct patient clinical oncology experience and do not participate as equal partners in oncologic decision making and follow-up. There are also limited numbers of nuclear medicine physicians considering the upcoming demand to use these therapies as a standard treatment for significant numbers of patients. It is also important to recognize the pivotal role that quantitative imaging plays in these treatments and the opportunity to further optimize treatments through diligent use of personalized dosimetry, which will require more personnel and resources.

Radiation oncologists are well versed in radiation treatment delivery, safety and oncologic care and decision making but have been less broadly engaged in the delivery of radiopharmaceuticals in recent years. This declined as the development of external beam technologies, including intensity modulation, image guidance, brachytherapy, stereotactic radiation and MR adaptive radiotherapy, have taken a front seat in our treatment delivery methods. While this was occurring, the revolution in development of labelled targeted agents has now moved into a clinically important phase and our engagement with our colleagues is very much needed for our patients' optimal care. Our understanding of dosimetric principles and physician and physicist resources will all be needed

to optimize the potential of RPT for years to come. Developing a collaborative model of care as we have for brachytherapy and stereotactic radiosurgery will be critical to the ultimate success of this therapy.

The opportunity for collaboration that appropriately leverages the unique expertise of nuclear medicine physicians, radiation oncologists, radiation therapy physicists and nuclear medicine physicists will be critical to the success of RPT. The rapid development of effective new agents and expansion in indications will require thoughtful evaluation of the infrastructure needed to best care for our patients with this radiation therapy. Knowledge of quantitative imaging, the complexity of dose calculation for tumors and normal tissues that considers both the dose and residence time over which that dose is achieved will all be important. The radiobiologic differences in dosimetry for different radionuclides and microdosimetry considerations within organs will also be critical. The tools to adequately calculate dose to normal tissues and tumors are still very much in development and several new innovations are being developed into effective products for considering personalized dosing. While these advancements are still being tested, the likelihood that optimizing dose delivered to the tumor and normal tissues appears highly likely to be important considering the history of radiation therapy for the past decades.

Radiation oncology has an important leadership role to play in the continued therapeutic applications of RPT for our patients. We believe it will become an increasingly important part of our radiation oncology practices and that we should embrace the opportunity to deliver and improve this radiation therapy paradigm. 



*John M. Buatti, MD, FASTRO, is vice-chair of the Science Council and chair of the RPT task force. He is a physician, clinical translational scientist and professor and chair of the Department of Radiation Oncology at the University of Iowa Carver College of Medicine.*



*Jeff Michalski MD, MBA, FASTRO, is president of ASTRO and member of the RPT task force. He is the Carlos A. Perez Distinguished Professor of Radiation Oncology at the Washington University School of Medicine, St. Louis.*

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# Patient-centered Radiopharmaceutical Therapy: A Typical Patient's Pathway

BY ANA PONCE KIESS, MD, PHD

**PATIENT-CENTERED RADIOPHARMACEUTICAL THERAPY (RPT)** follows the same essential principles as patient-centered external beam radiotherapy (EBRT), with several important workflow, radiation safety and multidisciplinary considerations. In this article, we will explore a patient's typical path from referral through treatment to follow-up. There are many potential variations on this theme. Please refer to the ASTRO Framework for Patient-Centered RPT by John Buatti, MD, FASTRO, et al. for more depth.<sup>1</sup>

## Referral and Consultation

Referrals for consideration of RPT often come from medical oncology colleagues and can be managed in a similar manner as other patients, but some practices may prefer to obtain imaging such as PSMA PET/CT prior to consultation if not already done. The initial consultation includes discussion of RPT indications and potential benefits, as well as potential acute and late toxicities and risks. As in all consultations, a balanced discussion will assess the relative risks and benefits of RPT compared to alternative treatment options, and some patients may not be recommended RPT. Patient-specific factors such as imaging findings, prior therapies and baseline hematologic and renal function may influence this decision. Discussion with nuclear medicine and medical oncology colleagues should factor into the recommendations. Patients should be presented at a tumor board when applicable, and additional referrals may be appropriate. RPT logistics and radiation safety precautions are reviewed, including urine precautions. Pain and other symptom management are also discussed.

## Workup and Treatment Planning

During the workup period when labs, imaging and insurance authorization are pending, patients are counseled regarding expectations and uncertainties.

Once the workup is complete and the patient and team are ready to proceed with therapy, a clear workflow is in place for ordering RPT and labs, scheduling and ensuring that all team members are informed and prepared. The prescription for systemic RPT agents varies from weight-based activity for Ra-223 to fixed activity for <sup>177</sup>Lu-PSMA-617 or <sup>177</sup>Lu-DOTATATE. In the future, we expect that personalized dosimetry and prescriptions will be part of the standard of care for more RPTs to allow for precise treatment planning (see articles on Dosimetry, page 23 and Coding/Billing, page 24). Labs are typically reviewed within seven to 10 days prior to each cycle of therapy, and it is prudent to assess the patient's symptoms and clinical status at this time. In our practice, the referring medical oncologist is also contacted at this time for a brief update. The decision to proceed with each cycle is ideally made at least several days prior to treatment so that production and delivery can be canceled or rescheduled if needed.

## Treatment Delivery

The treatment team may vary according to each institution or practice, and this may include qualified medical physicists, radiation safety officers (RSO), specially trained nurses, technologists and authorized user (AU) physicians in radiation oncology, nuclear medicine or nuclear radiology. The RPT receipt, calibration and QA are performed on the day of treatment or the day prior (see Physics article, page 14). If the activity is not within 10% of prescribed activity, or if a dose adjustment is required for renal impairment or other reasons, there are additional workflow steps. The patient treatment room and bathroom are isolated and prepped prior to patient arrival, including potential covering of surfaces to reduce risk of contamination. The injection or infusion materials may be prepped and primed as well.

When the patient arrives, vital signs including weight and pain score are measured. In our practice, the AU physician performs a focused history and physical and discusses current symptoms and side effects prior to treatment. In many cases, adjustments in pain medications are recommended or consideration is given of additional medications for management of nausea or other symptoms. Labs and/or imaging may be reviewed, and for subsequent cycles the response to RPT may be assessed and discussed. In some practices, the physician visit(s) may occur in between cycles.

When the patient and team are ready to proceed with infusion or injection, this is performed according to the specific RPT agent dosing guide and practice operating procedures, including aseptic techniques and radiation safety precautions. A peripheral IV is placed and flushed. Treatment may include saline infusion, amino acid co-infusion and/or IV antiemetics in some cases. Radiation waste is managed appropriately (see page 16 for more detail). After completion of treatment, the patient is monitored and discharged according to the practice operating procedures. With each cycle, the written discharge instructions (especially urine safety precautions) are reviewed. A wallet card with treatment and contact information is given to the patient. The patient's schedule is confirmed for the next cycle of labs and therapy, as well as provider visits and possible imaging. The treatment note and regulatory documentation are entered into the medical record.

### Follow-up

After the last cycle of treatment, the patient's schedule is again confirmed for planned labs, imaging and provider follow-up visits. Potential acute and late toxicities and risks are reviewed and monitored. This aspect of patient-centered care will become even more important as RPTs move into earlier line and earlier stage indications. Future treatment options are discussed with the patient and medical oncologist, including other RPT and EBRT options, in the context of patient-specific disease characteristics and relevant systemic therapy options.

As the field of radiation oncology evolves to include more radiopharmaceutical therapies along with expanded metastasis-directed therapies and other palliative EBRT, longitudinal patient care will naturally be coordinated alongside our medical oncology colleagues. This essential care model is already in place in our daily practice as radiation oncologists, and RPTs such as  $^{177}\text{Lu}$ -PSMA-617 will significantly expand our practice toolkit! 



*Ana Ponce Kiess, MD, PhD, is a radiation oncologist and residency program director at Johns Hopkins University whose research focuses on new RPT agents, combination therapies, RPT dosimetry and toxicities. Her clinical practice includes RPTs for prostate cancer and other cancers, and she is a member of the ASTRO RPT task force and is active in multiple RPT education initiatives.*

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# Ensuring RPT Safety: The Role of the SOP

BY JACQUELINE ZOBERI, PHD,  
AND JOSE GARCIA-RAMIREZ, MS

**ENSURING THE SAFETY** of radiopharmaceutical therapy (RPT) patients, medical staff and the general public starts with the development of a standard operating procedure (SOP) as part of commissioning of the therapy workflow. Per 10 CFR 35.41, “For any administration requiring a written directive, the licensee shall develop, implement, and maintain written procedures...[.]” A treating center should develop and maintain a written SOP that satisfies the regulations and, in addition, follows best practice guidelines (ACR–ACNM–ASTRO–SNMMI). The SOP will serve as a resource/guide for the treatment team to perform their duties while safely handling radioactive material (RAM) and patients containing RAM.

The SOP should describe the therapy, patient population/eligibility criteria, and drug/isotope — elements typically available from the radiopharmaceutical company/manufacturer. More customized elements of the SOP are as follows. The SOP should describe the treatment administration area, its location depending on radioactive contamination and exposure risks. The treating center should identify a “restricted” area for treatment/monitoring, which should include a nearby restroom that can be isolated from general traffic and locked down for decontamination/decay purposes (10 CFR 20.1003). The SOP should address how these areas and persons in these areas will be prepared to minimize contamination and exposure.

For any RPT, it is important to keep exposures as low as reasonably achievable (ALARA) by implementing measures that employ the concepts of distance, time and shielding. Survey measurements of a calibration sample (described below) can be used to assess radiation exposure levels around these areas, then repeated during patient treatments to verify the safety of exposure levels (NCRP Reports 49,147).

The SOP should describe quality control checks prior to administration, i.e., correct patient, isotope/drug, form/route, activity amount, patient medical

preparation (e.g., thyroid protection, kidney safety, pregnancy testing). The SOP should describe the infusion process, commonly done intravenously, using either the vial the drug arrives in, or from a syringe. If needed, processes for dispensation into a syringe should be included in the SOP. The center should decide on the infusion technique and practice it via mock infusion training sessions using, for example, dyed saline in place of radioactive drug.

The SOP should include the criteria for patient release per local/national safety regulations (10 CFR 35.75) and include radiation safety instructions, which can also be reviewed with patient at time of consult to assess compliance. If the patient is hospitalized after treatment, medical staff may be required to handle inpatient scenarios under the guidance of radiation safety precautions. The SOP should address both outpatient and inpatient situations.

As one of the last commissioning steps prior to initiating therapy, the drug manufacturer should send a calibration sample that is used to calibrate activity measurement equipment. This test shipment should mimic a patient dosage, and, if so, be used as a dry run to fine-tune/validate the SOP as well as test the chain of events at the treating center, from RAM receipt to waste management (excluding actual infusion of the RAM).

As for training, the treatment team should receive radiation safety training and review the SOP as it will include their roles and responsibilities. Applicable members should also participate in hands-on sessions, e.g., mock infusion training sessions and the dry run. Beyond training, checklists should be developed and incorporated into the SOP to provide added layers of safety, e.g., an infusion checklist. Once therapy is initiated and underway, the SOP should be maintained and re-evaluated to improve robustness of the workflow. 



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# How to **SET UP** Your Radiopharmaceutical Therapy Program in **THREE STEPS**

BY GREGORY SIBLEY, MD, AND YOUSSEF CHARARA, PHD

**MOST RADIATION ONCOLOGISTS ARE WELL SUITED** to deliver radiopharmaceutical therapy given their extensive clinical experience managing cancer patients, a breadth of knowledge covering the entire range of therapeutic modalities and specific knowledge regarding ionizing radiation and radioprotection. At our facility, we administer up to 30 injections per month in a medium-sized community department, mainly Pluvicto and Lutathera. A busy, efficient and safe radiopharmaceutical program can be readily built in the community setting, and in this article, we will share our experience building a successful program.

## **Step 1: Obtain radioactive materials license authorization**

The first step is to obtain authorized user (AU) status for “Parenteral administration” of unsealed sources (see page 20 for details on how to do so). Although regulatory requirements differ by state, we will share our experience specific to the state of Virginia.

Our radiation oncologists needed preceptorship to become AUs, so we began by hiring an outside Authorized User, adding him to our license, and

amending the license to authorize the therapy procedures permitted by Virginia code of regulations 12VAC5-481-1950: Use of unsealed byproduct material for which a written directive is required (equivalent to NRC 10 CFR 35.300). Next, our radiation oncologists fulfilled the requirement to be added as an Authorized User by observing three cases treated by the outside Authorized User.

Our initial experience was with delivery of Xofigo. In January 2018, Lutathera (lutetium Lu 177 dotatate) was FDA-approved for treatment of adult patients with advanced, progressive well-differentiated neuroendocrine tumors, and we amended our license to authorize the use of <sup>177</sup>Lu as a radioactive isotope and a program was established.

Then in March 2022, Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was FDA-approved for treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC). Again, we amended our license to authorize its use and started a program.

*Continued on the following page*

## Step 2: Set up a hot lab

The total cost of setting up our hot lab was approximately \$20,000. A hot lab requires a relatively small space with controlled access. We successfully dual-purposed our underutilized block room. Our hot lab (Figure 1) includes an L-block, dose calibrator and well counter.



Figure 1: Entire footprint of the hot lab at Virginia Cancer Specialists, Fairfax, Virginia.

A new program should carefully consider radioactive waste storage. We are able to store waste for each case in a small plastic container that is labeled and stored in an organized fashion (Figure 2). The waste to be decayed includes the two needles that are placed in the vial, the IV line from the vial to patient, the IV catheter, the vial itself and miscellaneous gloves, alcohol wipes and gauze. Other materials, including chucks and IV bags, are not exposed to radiopharmaceuticals and are simply surveyed and discarded. Radiopharmaceutical waste is stored for 10 half-lives and discarded (70 days for  $^{177}\text{Lu}$  and 120 days for  $^{223}\text{Ra}$ ).



Figure 2: A cabinet for storing used vials in their lead shields (lower cabinet) and a cabinet to store radioactive waste containers (used needles, alcohol wipes, gloves, etc.). A large waste drum is available as needed.

## Step 3: Establish an injection protocol

We began our Lutathera program prior to Pluvicto and elected to use the same basic protocol for both. Our goal was to implement a workflow that minimizes the potential for spills and contamination. Specifically, a standard IV pump is used to deliver saline slowly into the vacuum-sealed radiopharmaceutical vial (100 cc/h initially) via a “short needle.” A “long needle” (spinal needle) is connected via a specialized, low volume, male-to-male IV tubing to the IV catheter in the patient’s arm. The saline infusion simply displaces the radiopharmaceutical dose until completely infused. It takes 10 minutes for Pluvicto and 30 minutes for Lutathera (Figure 3).



Figure 3: Typical injection setup.

This method eliminates the need for dose manipulation, or drawing into a syringe, by keeping the dose in the same vial in which it was received. We have not experienced a radioactive spill since the inception of our program.

We use a regular exam room for delivery of both Pluvicto and Lutathera but have purchased infusion chairs (commonly used in medical oncology) for patient comfort. A bathroom is reserved exclusively for radiopharmaceutical patients on the day of infusion and is surveyed post patient departure to ensure absence of contamination before opening again to general use. No additional shielding for staff is necessary, and we utilize a standard L-block on a cart that is used in the hot lab and rolled into the exam room for treatment. Based on film badge dosimetry, our physicist receives the highest levels of exposure, which are well below ALARA level

I (10% of maximum permissible dose). Radiation levels received to whole body and extremities for staff including nurses and physicians are negligible.

For Pluvicto treatments, patients are asked to arrive 30 minutes prior to their scheduled injection. A nurse will start their IV, and a physicist will come in with a wheeled cart with the dose vial ready for injection. The AU will attach appropriate lines and needles to the vial and will start the pump at a slow rate initially to ensure system functionality; then the rate will be increased to deliver the remainder of the dose. The entire dose will usually be delivered within 10 minutes, but the patient will stay attached to the IV line to finish 500 cc of saline (an additional 40 minutes).

The same procedure applies for Lutathera patients (drug delivered over a 30-minute period), but these patients will also receive amino acids to protect their kidneys 30 minutes prior to injection of the drug and up to four hours after the drug is delivered. We initially utilized our radiation oncology suite, but now deliver Lutathera in our medical oncology suite due to the length of the entire infusion time. When treatment is complete, the cart is wheeled back into the hot lab along with all tubing related to the infusion. The vial is assayed for residual activity and subtracted from initial assayed dose. The injection room and bathroom are then surveyed to ensure absence of contamination.

All patients receiving Pluvicto or Lutathera receive post-infusion radiation survey measurements by physics and have exposure levels of around 2 mR/hour at one meter. These exposure levels meet the criteria of acceptable exposure rate that conforms to the 10 CFR 35.75 requirement of <5 mSv exposure anticipated to other individuals. Patients are released with written radiation safety instructions on actions recommended to maintain doses to other individuals as low as reasonably achievable. 



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## Commentary: More on establishing an RPT program

I appreciate that this can be as simple as a three-step process and recognize that there will be questions and hiccups that can happen as a new theranostics program develops.

Some pearls from our experience can be grouped into a couple categories: use your resources, build the team and watch the details. Developing a radiopharmaceuticals program takes resources and can touch many outpatient and inpatient departments like the care of any oncology patient. Collaborating with radiology on PET/CT tracer availability/reads, receiving of radioactive materials, policies/procedures/protocols and even injection space will help speed up initiation of a program.

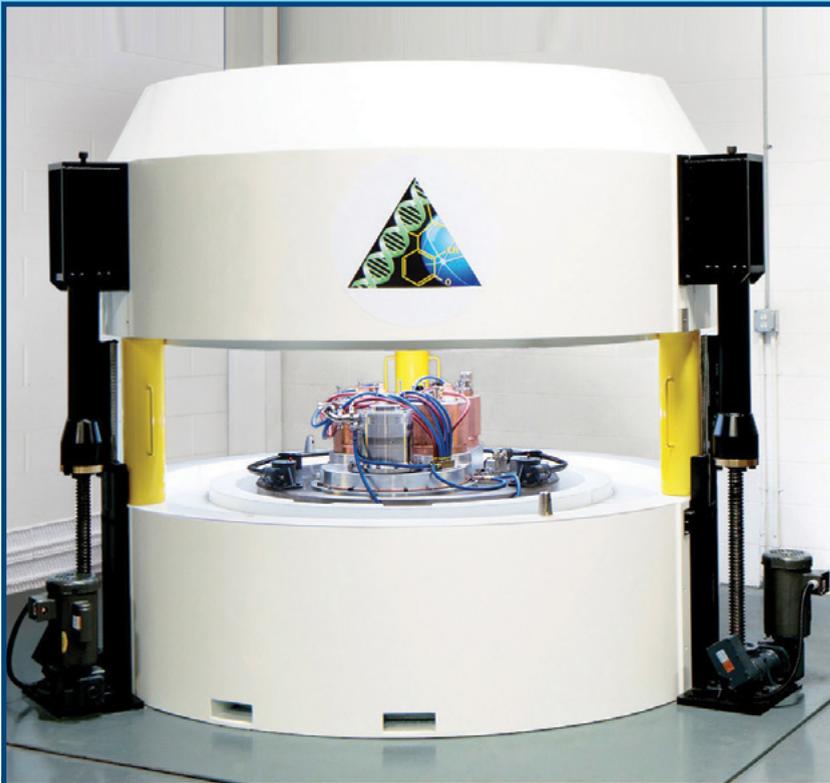
The vendors are a resource and can provide valuable training to help with staff competency and comfort.

Oncology patients benefit from multidisciplinary care and building this team when starting a program will improve the patient experience and the efficiency of the clinic. This includes someone who will provide education and outreach to the referral base who co-manage these patients with radiation oncology. They will need to know about the new treatment, possible radiation safety issues for their clinic, and how to manage toxicity along with our team. For example, if a patient requires a transfusion, how are we going to get that done?

Lastly, there are details to look after. You may need to increase your curie limit as the number of therapies and decaying radioactive materials in your department grows. Your team should help you closely monitor the revenue cycle to make sure your program is running in the black with room for investment should additional resources be needed in the future.



*Thomas Boike, MD, MMM, is a radiation oncologist based out of Michigan and leads theranostics for GenesisCare in the U.S. GenesisCare delivered the first commercial doses of Pylarify and Pluvicto.  Twitter: @tomboike*



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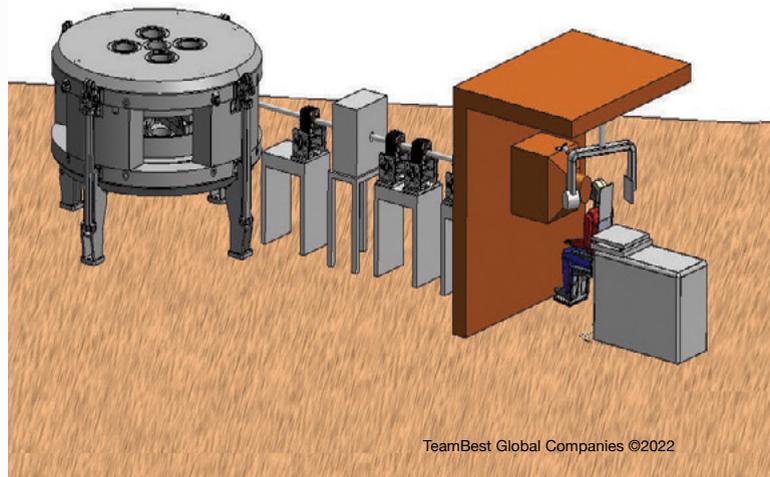
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# Bringing Radiopharmaceuticals to Your Practice: Regulatory Requirements

BY RONALD D. ENNIS, MD, FASTRO, AND CINDY TOMLINSON, MPP, SENIOR PATIENT SAFETY AND REGULATORY AFFAIRS MANAGER, ASTRO

## A PRACTICE OR FACILITY MUST BE LICENSED TO

offer radiopharmaceuticals (RPTs), and the physician must be designated as an authorized user (AU) for RPT therapy. Having the role of an AU for other therapies like brachytherapy is not sufficient.

It is important to note that while the United States Nuclear Regulatory Commission (NRC) is the ultimate regulatory body for the use of any radioactive materials, including medical uses, 39 states/regions, known as Agreement States,<sup>1</sup> have assumed primary regulatory control, under NRC aegis, for their region. For such states, a practice and physician seeking the ability to deliver RPT will apply to their state's regulatory agency while those practicing in the remaining states apply directly to the NRC. Agreement States may have different forms or requirements for obtaining a license, and we recommend familiarizing yourself with those requirements to ensure compliance. Links to state radiation protection programs, as well as links to state regulations, can be found on ASTRO's State Regulatory Library.<sup>2</sup>

## For facilities/practices

Compliance requirements differ based on whether you have a broad scope license, a limited scope license or no license at all.

If your practice or facility has a **broad scope license** and changes to the license are needed, including revisions to the list of authorized users, your radiation safety officer (RSO) can handle those in-house. Keep in mind that these changes are subject to review during regulatory inspections.

If your practice or facility has a **limited scope license**, you will need to submit the specific training and experience for each proposed AU, and the facilities and equipment available to support each proposed use, to the appropriate regulatory agency (either the NRC or the Agreement State) for review and approval. If the licensee wishes to make changes, such as adding or removing an authorized user, the regulatory agency must approve the requested change. The NRC has forms<sup>3</sup> for licensees to fill out, while agreement states may have their own forms, so it is important to contact your state's radiation protection program<sup>2</sup> to find out what forms are applicable to your situation.

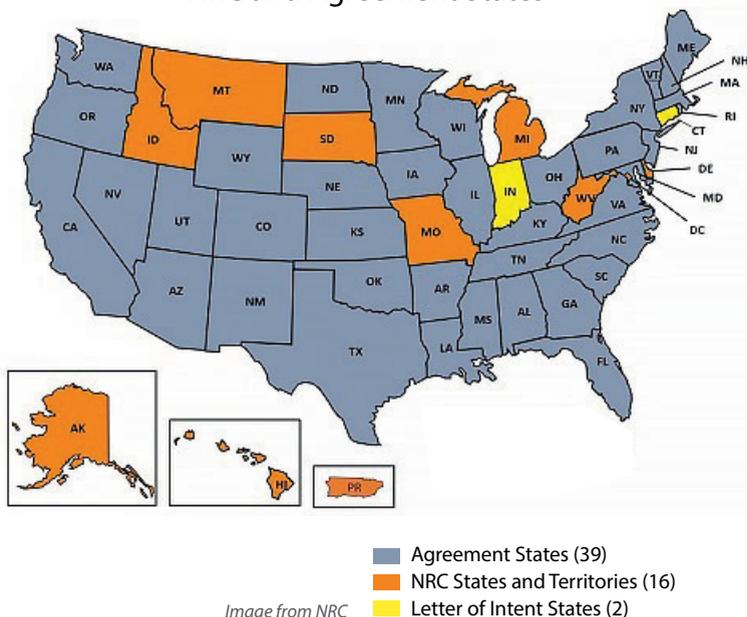
If your practice or facility is **not licensed to use radioactive byproduct material of any type**, you should begin by reviewing the facility, equipment and staffing requirements using the sources noted above. To gain approval, a facility or practice must submit an application<sup>4</sup> to the NRC or Agreement State. Fees are assigned<sup>5</sup> to each license type, and the NRC assigns a program code<sup>6</sup> for medical facilities, practices and laboratories to designate the major activity or principal use authorized in the license.

## For physicians

For physicians who received the required training and experience as part of their residency, have the "AU-Eligible" designation on their American Board of Radiology (ABR) board certification and are within seven years of training, the approval process is a relatively straightforward process of submitting forms.

For those who are more than seven years after completion of training and have never been an AU

NRC and Agreement States



# RPT Radiobiology, Theranostics Pharmacokinetics

BY RUBY MEREDITH, MD, PHD, FASTRO,  
AND ROGER HOWELL, PHD

for RPT, those without the “AU-Eligible” status on their ABR certification or those not board-certified, approval will be obtained via what the NRC terms “the alternative pathway.” For this, the application process will be more involved and likely will require obtaining documentation from one’s residency training program or other educational training program demonstrating the required training and experience. In addition, the applicant will need to perform cases under the supervision of a preceptor who will then attest to the applicant’s competency.

Prior to applying, it is important to review all training and experience requirements found in 10 CFR Part 35, *Medical Use of Byproduct Material*.<sup>7</sup> The training and experience requirements specific to radiopharmaceuticals can be found in 10 CFR 35.390, *Training for use of unsealed byproduct material for which a written directive is required*.<sup>8</sup> If you are in an Agreement State, you will also need to review any additional requirements from your state’s radiation protection program.<sup>2</sup> Reviewing the NRC’s NUREG 1556 Volume 9, Rev. 2, “Program-Specific Guidance About Medical Use Licenses”<sup>9</sup> will provide background on all the information that should be submitted to support a new license, amendment or renewal of a medical use license. The NRC’s list of frequently asked questions<sup>10</sup> and the Medical Uses Licensee Toolkit<sup>11</sup> gives invaluable information. 

*This article is provided for educational and informational purposes only and does not constitute legal advice. Each practitioner should consult with appropriate legal counsel to ensure compliance.*

## Websites\* and References for additional detail:

1. State Regulations and Legislation: NRC Agreement States <https://scp.nrc.gov/rulemaking.html>
2. ASTRO State Regulatory Library: <https://www.astro.org/Advocacy/State-Regulatory-Library>
3. NRC Forms: <https://www.nrc.gov/materials/miau/med-use-toolkit.html#forms>.
4. Licensing of Medical, Industrial, and Academic Uses of Nuclear Materials: <https://www.nrc.gov/materials/miau/licensing.html>.
5. § 170.31 schedule of fees for materials licenses and other regulatory services, including inspections: <https://www.nrc.gov/reading-rm/doc-collections/cfr/part170/part170-0031.html>.
6. License Types (Program Codes) for Medical Facilities, Practices and Laboratories: <https://www.nrc.gov/materials/miau/med-use-toolkit.html#actions>.
7. Part 35-Medical Use of Byproduct Material: <https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/index.html>
8. § 35.390 Training for use of unsealed byproduct material for which a written directive is required: <https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/part035-0390.html>.
9. Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses, Final Report. NUREG 1556 Volume 9, Rev. 2: <https://www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v9/index.html>.
10. NRC Frequently Asked Questions: <https://www.nrc.gov/materials/miau/med-use-toolkit/faqs-part35.html#9>.
11. NRC Medical Uses Licensee Toolkit: <https://www.nrc.gov/materials/miau/med-use-toolkit.html>.

\*All websites listed were accessed December 14, 2022, and subject to change.

**TRADITIONALLY**, radiation oncology training for the use of unsealed sources of radioactive material for therapy was predominantly for beta-particle emitters, with emphasis on <sup>131</sup>I for thyroid disease. The commercialization of <sup>223</sup>Ra-dichloride ushered in the use of alpha-particle emitters to the repertoire. Subsequently, the FDA has approved more beta-emitting therapeutic radiopharmaceuticals, with many alpha and beta-emitting agents in the pipeline.

More alpha emitter radioligands are expected where advantages over beta emitters can be realized. The high linear-energy-transfer (LET) of alpha particles is about 100x that of beta particles. The range of alpha particles in soft tissue is only several cell diameters (<100 μm), whereas beta particles used for therapy generally have much longer ranges (mm to cm). Therapeutically, the high-LET nature of alpha particles produces complex clustered DNA-damage in the cells through which they traverse. This damage is generally resistant to repair and leads to cell death. Thus, only a few (1-20) alpha hits to a cell nucleus are needed to kill the cell compared to hundreds to thousands required from beta particles. The cytotoxic effects of alpha particles are not diminished significantly by conditions such as hypoxia that are known to reduce the therapeutic efficacy of photon and beta particle radiation. Further, when the alpha-particle emitting radionuclide is delivered to target cells, the short-range of the emitted high-LET alpha particles has considerable therapeutic advantage over beta emitters for reduction of the absorbed dose to normal tissues while safely delivering a therapeutically effective absorbed dose to tumor cells. Clinical data has shown that radiopharmaceutical therapy with alpha-particle emitters can provide objective responses after failure of the same radiopharmaceutical labeled with the beta-particle emitter <sup>177</sup>Lu.

*Continued on the following page*

Considerable data has accumulated for normal organ tolerance to beta-particle emitting radiopharmaceuticals such that constraints derived from external beam radiation therapy (EBRT) are being replaced with more relevant values. Like EBRT, patient characteristics/medical conditions alter the tolerance to radiopharmaceuticals. Recent studies proposed redefining the relative biologic effectiveness (RBE) for alpha particles in a manner that facilitates calculation of the equieffective dose as a means to relate the expected effect of a given alpha-particle therapy to known responses to fractionated EBRT.<sup>1</sup> This approach arrives at an RBE<sub>X</sub> that is independent of the absorbed dose, a problem that has plagued the use of RBE until this time and is recommended by the International Commission on Radiation Units and Measurements in their report 96. Using this approach, an RBE<sub>2</sub> of 6.4 for mouse marrow was calculated for <sup>212</sup>Pb radiation, independent of cellularity and absorbed dose.<sup>2</sup>

### Theranostics

Theranostics applies to integrated imaging and therapy using one radionuclide for imaging (diagnostic) and a second for therapy. Using a tracer amount of the therapeutic agent, even if feasible, is often suboptimal. For several therapeutic radionuclides a diagnostic partner is needed for limitations such as short half-life, or when gamma emissions are of insufficient energy and/or abundance to provide useful biodistribution information.

Selection of diagnostic partners seeks a close match of biodistribution and pharmacokinetics of the diagnostic and therapeutic radioligands. Radioisotopes of the same element are feasible in instances such as <sup>123</sup>I/<sup>131</sup>I or <sup>203</sup>Pb/<sup>212</sup>Pb. More variance between the diagnostic and therapy distribution is expected with non-isotope partners, especially if different chelators are needed. In development of theranostic pairs, animal models allow image-based dosimetry correlation with quantitation from harvested specimens.<sup>3</sup>

Chelators continue to be developed that provide pharmacokinetics/distribution advantages and compounds that allow labeling of multiple moieties for both diagnostic and therapeutic targeting ligands. Alterations may affect aspects such as daughter retention, stability, target avidity, internalization, target retention, organ(salivary) uptake and renal transit.

Increased sensitivity of target delineation also aids accuracy. For example, in-111-pentetreotide gave way to <sup>68</sup>Ga-DOTATATE, and now <sup>64</sup>Cu-DOTATATE is available as a diagnostic partner for several therapeutic

radioligands that treat somatostatin expressing neuroendocrine tumors. Multiple research disciplines and clinical trials work to further improve aspects of radiopharmaceutical therapy. 



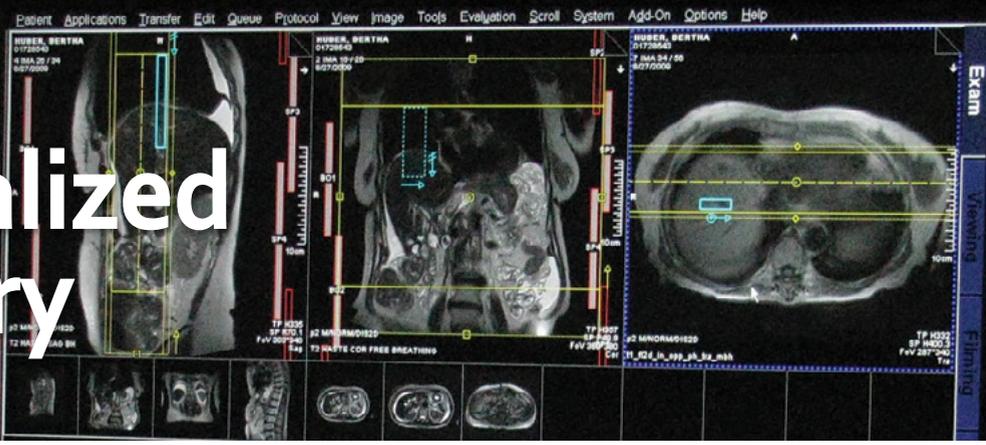
*Ruby F. Meredith, MD, PhD, FASTRO is a Professor of Radiation Oncology at the University of Alabama at Birmingham and a Senior Scientist at the UAB Comprehensive Cancer Center. She has participated in development/conduct of 50 clinical trials for targeted radionuclide therapy and served >20 years on the Medical Internal Radiation Dose committee of the Society of Nuclear Medicine and Molecular Imaging.*



*Roger Howell, PhD, is a Distinguished Professor at Rutgers University and author of over 120 publications on radiobiology and dosimetry in the context of RPTs. He is a Commissioner of the International Commission on Radiation Units and Measurements (ICRU) and sponsor/co-author of ICRU Report 96, Dosimetry-Guided RPT.*

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3. Miao Y, Figueroa SD, Fisher DR, et al. Lead-203-Labeled Alpha-Melanocyte Stimulating Hormone Peptide as an Imaging Probe for Melanoma Detection. *J Nucl Med.* 2008;49(5):823-829.



# Individualized Dosimetry

BY ROBERT HOBBS, PHD

**RADIOPHARMACEUTICAL THERAPY (RPT)** is rapidly becoming a mainstream modality. However, the manner in which the different RPTs are administered is still quite antiquated as compared to other radiation modalities. Most RPTs are administered using a fixed or simple mass-based activity and a fractionation scheme that has been optimized for a one-size-fits-all chemotherapy-type approach, e.g., 200 mCi per fraction of Lutathera. As a radiation modality, RPT would undoubtedly benefit from a more personalized approach to treatment planning, as is typical for external beam and brachytherapy.

The principles of personalized dosimetry-based RPT are:

- 1) Administer the patient with a small diagnostic-level amount of the radiopharmaceutical, or of a companion imaging/theranostic surrogate, e.g.,  $^{124}\text{I}$  for  $^{131}\text{I}$  therapy;
- 2) Use 3-D imaging (SPECT/CT or PET/CT depending on the nature of the pre-therapeutic) to image the activity distribution as a function of time in the patient;
- 3) If needed, convert the surrogate activity to therapeutic activity using the difference in half-lives; and
- 4) Convert the activity-based distributions to absorbed dose, either by voxelized Monte Carlo methods or using MIRD-based S values.
- 5) With the absorbed dose per unit activity of therapeutic calculated for both normal organs and lesions, the treating physician may optimize the amount of administered activity depending on the desired approach. As RPTs often treat metastatic disease, treating to maximum tolerated absorbed dose to the dose-limiting normal organ may be preferred. Alternatively, for a smaller number of tumors, the minimum amount of activity that delivers the target absorbed dose to the lesions may be chosen or some combination that balances efficacy and safety. As precision and confidence with the methodology and its application grow, greater activity and absorbed dose per fraction with fewer fractions may become the norm.

This approach has been used successfully, albeit anecdotally, as early as 2008 for a patient treated with  $^{131}\text{I}$  sodium iodine for differentiated papillary thyroid cancer.<sup>1</sup> More recently, Garin et al.<sup>2</sup> showed a significant increase in mean overall survival (26.6 months vs. 10.7 months) in a randomized two-arm trial for hepatocellular carcinoma patients treated with  $^{90}\text{Y}$  theraspheres, comparing the traditional “dosimetry” method with a more patient-specific dosimetric approach.

Why then are we not seeing this method of implementation in our clinics? A critical mass of consensus is building that such a personalized dosimetry-based approach would most likely benefit the patient and is preferred. Imaging availability, cost and reimbursement are all concerns. Lack of consistency in the standardization of biologically relevant dosimetry and dose reporting is also an issue. All of these considerations are being addressed.

The main concern expressed that has yet to see a satisfactory resolution and is the most challenging is the lack of standardization and consistency in dosimetric methodologies and results. As an example, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) recently published a report of a dosimetry challenge,<sup>3</sup> where participants submitted their dosimetric results for a common set of data and the results showed a very wide range of absorbed dose values (58%).

Education for medical physicists and physicians who will be performing or supervising RPT dosimetry has ramped up and is ongoing in multiple societies. The MIRD Primer 2022, the IAEA Dosimetry and the ICRU Report 96 are all recently published examples of didactic material for a new age of dosimetry-guided RPT. However, didactic material is not sufficient; increased training is also needed, in residencies and elsewhere (the 2023 AAPM Summer School will focus on RPT dosimetry).

*Continued on page 25*

# ASTRO SUPPORT OF CODING GUIDANCE FOR RADIOPHARMACEUTICAL THERAPY IMPLEMENTATION

BY GERALD WHITE, MS

## THE DESIRE TO USE RADIOACTIVE SOURCES

to enhance health dates to the earliest days of our knowledge of their existence. Many of us have seen advertisements for radium touted as a worthwhile adjunct to a “healthy” lifestyle, or a healing drug. Radium caves, radium inhalers, radium infused elixirs and many other concoctions brought radioactive patent medicines to the forefront of quackery.<sup>1</sup> The possibility of serious applications of radiopharmaceuticals became clear with the production of radioisotopes of iodine in the 1930s and the first therapeutic radiopharmaceutical treatments in 1941.<sup>2</sup> Initially, radiopharmaceuticals were produced in accelerators of various types, but the WWII-induced development of the nuclear reactor brought with it a plethora of fission product radioactive materials that could be incorporated into various chemical compounds and used in both diagnostic and therapeutic medical applications.

Foundational to current practice patterns for radiopharmaceutical therapy (RPT) are these historical applications of radioactive material, the most prominent being therapeutic applications of radioiodine to thyroid disease. Physicians specializing in radiation therapy were certainly active in treating thyroid patients with radioactive iodine, but much of the practice was in the hands of other specialties: internal medicine physicians, nuclear medicine practitioners, and most commonly, radiologists whose practice extended to nuclear medicine. Development of CPT® codes followed the practice patterns of these physicians who often acted as procedure specific players in the patient continuum of care, receiving a request to administer the radiopharmaceutical therapy (often with the desired prescription attached) but leaving the pre-treatment evaluation and post-treatment management to the referring physician.

In recent years we have seen increasing offerings of therapeutic radiopharmaceuticals available for use in cancer care.<sup>3</sup> The integration of these drug-based modalities falls within the scope of practice of a variety of physician specialties, but radiation oncologists are well prepared to provide a home for these therapeutic applications.

At the core of the radiation oncology endeavor is the understanding of the relationship between absorbed dose (Gray) and tumor response. Heretofore, administration of radiopharmaceuticals has been based on activity (Becquerel), with efficacy inferred based on analysis of tumor response based on observational studies. To use an external beam analogy, this would be much like correlating tumor response associated with linac-based treatments with the number of monitor units administered during the treatment sessions. Advances in computer technology, coupled with sophisticated modeling of absorbed dose distribution from radiopharmaceuticals as well as PET/CT and SPECT/CT quantitative imaging capabilities, now allow the calculation of absorbed dose in many radiopharmaceutical procedures. Data is accumulating that clearly demonstrates the importance of absorbed dose delivered to tumor tissue as a critical parameter in predicting favorable outcomes. This, combined with knowledge of the absorbed dose to organs at risk, will lead us to more efficacious applications of radiopharmaceuticals.

## Coding in review

Patient access to these modalities will be enhanced with appropriate coding and reimbursement processes. ASTRO is currently reviewing the typical CPT® descriptors used for radiopharmaceutical procedures. Various administration codes can be used, but it will also be important to recognize the physician work associated with the cognitive treatment planning process as well as evaluation and management and follow-up tasks provided by radiation oncologists as they provide care for patients who will receive RPTs. The technical component for the available administration codes will defray much of the expense of any additional equipment and staff time utilized in providing this service. The CMS reimbursement for this expense is higher in the Hospital Outpatient Prospective Payment System than in the Medicare Physician Fee Schedule. RO departments that wish to begin this service may find that the expense is less than for a fully featured nuclear medicine hot lab, and some existing equipment found in sealed source hot labs may well be useful for RPT modalities as well. Guidance

in using existing codes that have historically been used in association with external beam and brachytherapy procedures will be forthcoming. Further, procedure codes related to patient-specific dose modeling and calculation work may well be necessary to adequately describe services provided during these therapeutic courses.

We should look forward to advances in the science and clinical applications of RPT — advances that will be incorporated into the routine practice of radiation oncologists to the benefit of patients. Creating appropriate procedural terminology with associated RVU levels will be essential to assuring that these treatment options will be available to our patients. 



*Jerry White, MS, is a medical physicist in Colorado Springs and a past chair of the ASTRO Code Development and Valuation Sub-Committee. He has been active in the ASTRO, AAPM and ACR economics effort for several decades and is a member of the ASTRO RPT task force.*

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2. Sawin CT and Becker DV. Radioiodine and the Treatment of Hyperthyroidism: The Early History. *Thyroid*. 1997;7(2):163-76.
3. Buatti JM, Pryma DA, Kiess AP, et al. A Framework for Patient-Centered Pathways of Care for Radiopharmaceutical Therapy: An ASTRO Consensus Document. *Int J Radiat Oncol Biol Phys*. 2021;109(4):913-922.

#### Continued from **INDIVIDUALIZED DOSIMETRY**

Finally, the standard armamentarium of quality assurance methods, including checklists, error analyses, common reference data sets, quality management programs and such commonly found in radiation oncology modalities need to be adapted or developed for this discipline. This is our forte, and we are well placed to lead this aspect of RPT development and enable a more effective and rational approach to personalized RPT planning. 



*Robert Hobbs, PhD, is an Associate Professor and Medical Physicist in the Department of Radiation Oncology at Johns Hopkins and chairs the AAPM sub-committee on RPT and is a member of the ASTRO RPT task force.*

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1. Hobbs RF, et al. 124I PET-based 3D-RD dosimetry for a pediatric thyroid cancer patient: real-time treatment planning and methodologic comparison. *J Nucl Med*. 2009;50(11):1844-47.
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3. Uribe C, et al. An international study of factors affecting variability of dosimetry calculations, part 1: Design and early results of the SNMMI Dosimetry Challenge. *J Nucl Med*. 2021;62(Suppl 3):36S-47S.

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# RADIOPHARMACEUTICAL THERAPY: EMERGING HORIZONS

BY MICHAEL R. FOLKERT MD, PHD;<sup>1</sup> RAVI B. PATEL, MD, PHD;<sup>2</sup> KILIAN E. SALERNO, MD;<sup>3</sup>  
AND FREDDY E. ESCORCIA, MD, PHD<sup>4</sup>



**RADIOPHARMACEUTICAL THERAPY (RPT) HAS BEEN IN USE** since Saul Hertz harnessed radioactive iodine to treat patients with hyperthyroidism and thyroid cancers in the 1940s.<sup>1</sup> Until recently, widespread application of RPT had been limited by the lack of target specificity. While non-specific/off-target binding may be less problematic in the diagnostic setting, binding of therapeutic radiopharmaceuticals to non-target tissues can result in significant toxicity. Today, however, several clinically approved RPT agents are available — with dozens more in early phase clinical trials and many others in preclinical development — that have demonstrated the ability to direct their therapeutic payload to the clinically relevant targets. High quality prospective clinical trials demonstrating improvements in outcomes for patients has further increased enthusiasm for use of RPT.<sup>2-5</sup>

**Workforce** (also see articles on pages 10, 12, 15 and 21) First, we need to have a workforce who understands how to use the approved RPT agents, their indications and contraindications, how to administer them safely and appropriately, and how to manage adverse events. A formalized curriculum would be helpful for standardization and competency. To this end, the ASTRO RPT Workgroup proposed a framework to ensure that radiation oncology trainees have both the prerequisite didactics and hands-on exposure as part of standard residency curriculum.<sup>6</sup> Given the recent updates to the American Board of Radiology (ABR) Authorized User (AU) designations (see page 31), residency programs may wish to add qualified senior residents to their existing licenses prior to graduation to ensure that the next generation of radiation oncologists is ready and able to incorporate this important treatment modality alongside our colleagues in nuclear medicine.

## Training and Certification

To launch an independent and sustainable RPT clinical program, our specialty must recognize that we need to provide a more comprehensive experience for our trainees. This could include an in-depth nuclear medicine rotation or even extend to dual board certification in nuclear medicine and radiation oncology, a pathway that already exists in the ABR Diagnostic Radiology certification and has been explored by radiation oncology residency programs such as the Harvard and Weill Cornell/New York Presbyterian programs. Washington University in St. Louis is contemplating a launch of an intensive course along with certification program. Similarly, physicists and therapists with dual training may be needed. At the program level, metrics to ensure best practices and quality assurance should be considered. The Society for Nuclear Medicine and Molecular Imaging (SNMMI) launched Centers of Excellence designation, and ASTRO's APEX - Accreditation Program for Excellence<sup>®</sup> could include RPT accreditation as well.

## Optimization

An area of imminently accessible improvement is through optimizing the delivery of existing agents.

## Personalized dosimetry

 (Also see page 23)

With the notable exception of <sup>131</sup>I-MIBG for pheochromocytomas, administration of RPT does not currently consider patient tumor burden. Instead RPT agents are administered as flat or weight-based activity per session akin to many systemic chemotherapy regimens, with dose adjustments based on observed toxicities and not tumor burden. Accounting for tumor burden could significantly improve anti-tumor effect and mitigate toxicity. A patient with low burden of disease may saturate targets with a standard flat dose,

resulting in high excess radioligand circulating in non-target tissues, thus only contributing to toxicity and radiation safety concerns. Tumor burden may also change over time. For instance, a patient with good response may have very little tumor burden and hence uptake by last treatment. Conversely, a patient with high burden of disease may require a higher administered activity to effectively saturate targets on tumors and might have been undertreated with use of the standard activity approach.

### New indications

Expansion of RPT use in additional clinical indications is under active investigation. Several ongoing studies are moving the use of RPT agents earlier in the course of disease (e.g., neoadjuvant  $^{177}\text{Lu}$ -PSMA prior to prostatectomy, NCT04430192;  $^{177}\text{Lu}$ -PSMA in hormone sensitive prostate cancer NCT04343885, PSMAFore, PSMAddition). Evaluation for long term effects (e.g., secondary myelofibrosis, kidney damage) is of particular importance in this setting.

While prostate specific membrane antigen (PSMA) is overexpressed on prostate cancer cells, it is also expressed in the neovasculature of renal cell carcinoma<sup>7</sup> and hepatocellular carcinoma,<sup>8</sup> opening the potential utility of PSMA-targeting RPT for these indications. Similarly, somatostatin receptors (SSTRs) are also present on pituitary tumors<sup>9</sup> and meningiomas,<sup>10</sup> and therapeutic DOTATATE or DOTATOC RPT agents may have utility in these diseases.

### Combination therapy

Because monotherapy with RPT is not curative, rational combinations with external beam radiotherapy (Ra-223 with SABR, RaVENS NCT04037358;<sup>11</sup> SABR with  $^{177}\text{Lu}$ -PSMA for oligometastatic prostate cancer, NCT05079698), or systemic therapies ( $^{177}\text{Lu}$ -DOTATATE with cabozantinib, NCT05249114) such as immunotherapy ( $^{177}\text{Lu}$ -PSMA with ipilimumab/nivolumab NCT05150236;  $^{177}\text{Lu}$ -PSMA with nivolumab NCT03805594) or inhibitors of DNA damage repair pathways ( $^{177}\text{Lu}$ -PSMA with Olaparib, NCT03874884;  $^{177}\text{Lu}$ -DOTATATE with olaparib, NCT04086485;  $^{177}\text{Lu}$ -DOTATATE with DNA-PK inhibitor, NCT04750954) are active areas of exploration in clinical trials.

At the interface between existing RPT agents and novel ones, are agents that share the same targeting ligand, but are instead “armed” with  $\alpha$ -particle emitting radionuclides such as  $^{225}\text{Ac}$  or  $^{212}\text{Pb}$ , in lieu of  $\beta$ -emitting  $^{177}\text{Lu}$ . Given the higher linear energy

transfer (LET) of  $\alpha$  compared to  $\beta$  emissions, it is thought that tumors refractory to the  $\beta$ -emitting agents may still respond to the  $\alpha$ -emitting agents.<sup>12</sup> PSMA and SSTR-targeting ligands are being actively investigated and have demonstrated promising activity thus far.<sup>13-15</sup>

### Emerging targets and applications

There are many emerging targets, too numerous to present here, but among the most exciting is the fibroblast activating protein (FAP) for which imaging and therapeutic versions of inhibitors (FAPi) have been developed and are undergoing evaluation in early clinical trials.<sup>16,17</sup> Unlike SSTR or PSMA, which are tumor-selective targets with theranostics agents, FAP is expressed on cancer associated fibroblasts and is present across different tumor types, yielding a new pan-cancer targeting agent.<sup>18</sup> Additional targets being explored, such as CXCR4, B7-H3, integrins and gastrin releasing peptide receptor, are reviewed elsewhere.<sup>19-21</sup>

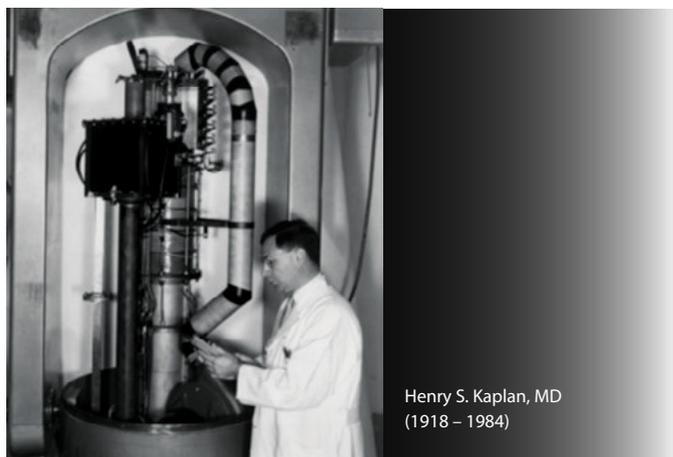
Creative applications of RPT include use as part of bone marrow conditioning for hematopoietic stem cell transplant with an anti-CD45 antibody ( $^{131}\text{I}$ -apamistamab, Iomab-B, NCT02665065) and topical beta particle emitters for non-melanoma skin cancers (NCT05135052).

### New technologies

New technologies could complement RPTs in the clinic. For example, total body positron emission tomography (PET), which has much higher sensitivity to conventional PET, could be used to better define the pharmacokinetics of a PET agent. This information could be used to prospectively calculate administered activity needed to deliver a desired absorbed dose of the RPT partner (e.g., personalized dosimetry). Similarly, the latest generation of single photon emission tomography (SPECT) scanners is now able to achieve comparable imaging quality as PET in much shorter timeframes, allowing for easier post-treatment absorbed dose estimates that may guide subsequent cycle administered activities. Additionally, the combined PET/linear accelerator could theoretically use the 511 keV photons from the positron-electron annihilation event to guide therapeutic photon delivery. Because many RPTs are first evaluated as imaging agents, this technology could expand the utility of such positron emitting agents.

*Continued on page 29*

## GIANTS OF RADIATION ONCOLOGY: BIOGRAPHICAL SKETCHES FROM THE ASTRO HISTORY COMMITTEE



**IN THE POST-WORLD WAR II ERA**, a group of visionary radiation oncologists were instrumental in establishing the specialty as an independent medical discipline, through development of dedicated clinical and research training programs, clinical discoveries and rigorous reporting of progress in the modality. Few of those visionaries have had the enduring impact on the specialty as Henry Seymour Kaplan, MD.

Born in 1918 in Chicago, Dr. Kaplan graduated from the University of Chicago at age 20, and two years later, from Rush Medical College. He served an internship in radiology at Chicago's Michael Reese Hospital and then a residency in radiology at the University of Minnesota under the tutelage of Leo Rigler, MD, one of the most influential radiologists of that era. Dr. Kaplan's father, Nathan, a Chicago dentist, and non-smoker, had died of lung cancer when Henry was only 16, and during his general radiology training he began to focus on therapeutic radiology (as it was then known) clinical care and research, being driven to cure cancer. Following completion of training, he served a fellowship at the NIH where he began his laboratory studies on radiation and viral oncogenesis, followed by three years at the Yale University School of Medicine and then a return to the NIH for an additional year. In 1948, at age 30, he was recruited to Stanford University Medical School as professor and chair of the Department of Radiology. He would remain at Stanford for the rest of his life.

During his years at Stanford, he was instrumental in orchestrating the move of the Medical School from San Francisco to the university campus in Palo Alto, for recruiting future Nobel laureates to the faculty, and for significantly improving the international reputation of the Medical School and its hospitals. In 1972, after 24 years at the helm of the radiology department, he stepped down to assume the post of Director of the Louis B. Mayer Cancer Biology Research Laboratory at Stanford. He remained active at the lab until his death in 1984, continuing his own studies in oncogenesis and monoclonal antibodies.

At Stanford, Dr. Kaplan's clinical focus became human lymphomas, especially Hodgkin lymphoma (HL), and he quickly realized that available radiation therapy systems were poorly suited to deliver the large-field, deeply penetrating, skin-sparing radiation that he needed. Aware of the klystron invention by Sigurd and Russell Varian, in his third year at Stanford he met Stanford physicist Edward Ginzton, with whom he discussed the ongoing research of the Varian brothers. Dr. Kaplan quickly recognized the potential medical applications that this new technology could bring. He joined Ginzton and together they developed the first medical linear accelerator in North America (J. Haimson, personal communication, 2022). Although development of the device had effectively been completed two years earlier, fundraising to build the facility to house the unit took two years and it was not used for clinical care until 1956. Dr. Kaplan's first patient was a 7-month old child with bilateral retinoblastoma. The child was cured of his tumors. Dr. Kaplan felt his contribution as a co-developer of this linear accelerator was one of his greatest achievements.

As Dr. Kaplan quickly augmented the Stanford radiation oncology faculty, colleagues began to utilize the linear accelerator for other sites, notably with Malcolm Bagshaw, MD, leading the genitourinary team. Much of Dr. Kaplan's lab work involved mouse lymphomas and leukemias. In 1961, Dr. Kaplan recruited Saul Rosenberg, MD, to join him to build a multidisciplinary clinical team conceptualized as a radically different management regimen for HL. This

began by using precise staging, followed by wide-field nodal irradiation employing the new medical linear accelerator, combined with multiple agent chemotherapy. The new paradigm changed HL from being effectively uniformly fatal to more than 90% curable, solidified the relevance of randomized clinical trials in cancer management, and ushered in the era of successful combined modality treatment of cancer.

In 1953, with Russell Morgan, MD, of Johns Hopkins and six other radiology thought leaders, he founded the Association of University Radiologists, and in 1955, he participated in an organizational meeting with radiation oncology colleagues that in 1958-1959 led to the founding of the American Club of Radiation Therapy, the precursor to ASTRO, of which he served as president in 1966-1967. He served as president of the Radiation Research Society in 1960, and in the same year, was appointed to the National Cancer Advisory Board, where he was a champion of scientific freedom and integrity, human rights and reduction of disparities in cancer care.

In recognition of his achievements, Dr. Kaplan received innumerable awards, including the first physician to receive the Atoms for Peace Prize (1960), the French Legion of Honor (1965), the first radiologist elected to the National Academy of Science (1972) and the David A. Karnofsky Memorial Award from ASCO (1972). In 1977, along with Juan del Regato, MD, and Gilbert Fletcher, MD, he received the first Gold Medal awarded by ASTRO, and in 1979, he was the first recipient of the General Motors Cancer Research Foundation Charles F. Kettering Prize.

In his career as a gifted clinician, inspirational teacher, mentor, motivator of faculty and trainees,

and visionary researcher, Dr. Kaplan left his mark on his own generation, and his colleagues and trainees continue that legacy. 

Read more biographies of great leaders in radiation oncology at [www.astro.org/history](http://www.astro.org/history).

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Continued from **RADIOPHARMACEUTICAL THERAPY: EMERGING HORIZONS**

#### Parting words

Radiation oncology has the expertise to advance RPT at all stages of development: from de novo design, synthesis and testing, through mechanistic studies of unique radiobiology in preclinical studies, to clinical trials of next generation molecular imaging for image-guided radiotherapy and RPT combinations with external beam and or systemic therapies.

Many exciting avenues remain yet to be explored and others yet to be defined. As we move forward, we should heed the words of esteemed computer scientist and Turing award winner Alan Kay: "The best way to predict the future is to invent it." 



View references and author bios for this article at [www.astro.org/Winter23News](http://www.astro.org/Winter23News).

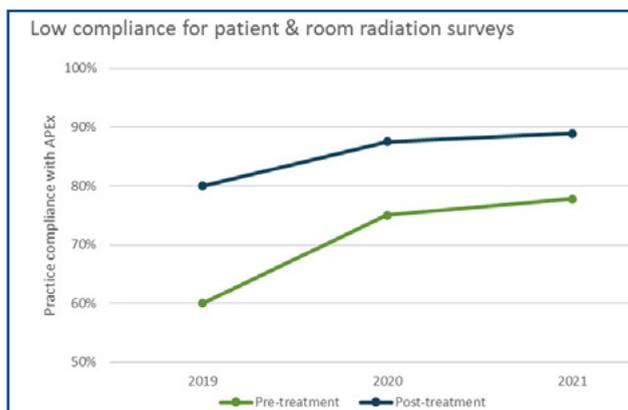
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4. Freddy E. Escorcía, MD, PhD, Molecular Imaging Branch, National Cancer Institute, Maryland

## Centering RPTs Around Quality and Safety

**RADIOPHARMACEUTICALS (RPT) ARE NOT NEW**, but with advances, interest has skyrocketed in recent years for this burgeoning field. In any new treatment option, technology or workflow, a focus on quality and safety must be at the center. Some of the new RPT agents are different enough from legacy options to require different administration, shielding requirements and involved disciplines. These variations can create new challenges for practice environments.

As with any treatment, the key to success is a strong quality management system paired with robust incident reporting. These tools provide a benchmark and expectations for all radiation oncology practices. ASTRO's APEX – Accreditation Program for Excellence® assesses the entire practice, including all team members, and evaluates the strength of quality and safety systems. APEX requires clinical standard operating procedures (SOP) for every technique offered at a practice, including RPT. This review, paired with a team interview, ensures that all team members understand their roles and responsibilities and excel at performing the procedural steps and quality assurance requirements. However, historical APEX performance data indicates that many practices delivering RPT have inconsistent documentation surrounding quality assurance activities and supervision, with an average compliance rate of less than 90%. APEX also reviews RPT safety processes such as radiation survey requirements. This metric, traditionally, has had a more significant deficiency, as shown in the graph below. Compliance has improved over the last few years, but more progress is needed.

Documentation of these important safety steps is



essential to achieving the highest possible outcome, but safety goes beyond SOPs. Incident reporting systems, like the RO-ILS: Radiation Oncology Incident Learning System®, provide a mechanism for shared learning in a secure and non-punitive environment. Practices can track radiation oncology-specific operational issues, near misses, therapeutic incidents, and unsafe conditions. Tracking this data offers practices the opportunity to find trends or process gaps and develop methods to avoid repeating them in the future. To date, 54 RPT-related events have been submitted to RO-ILS. ASTRO wants to encourage radiation oncology practices that treat with RPTs to submit safety events to the RO-ILS national database. The Radiation Oncology Health Advisory Council (RO-HAC), the radiation oncology professionals who review submitted events and develop findings, provide valuable education<sup>1</sup> to the field for other modalities and techniques, due to the large number of events reported. The more RPT data submitted to the national database, the more we can learn together and improve safety for patients receiving treatment.

With considerable interest by radiation oncology practices, ASTRO's Board of Directors is expected to commission a new Safety White Paper focused on RPT. Following the framework presented in the recently updated ASTRO Safety White Papers for stereotactic radiosurgery and stereotactic body radiation therapy,<sup>2</sup> intensity modulated radiation therapy<sup>3</sup> and image guided radiation therapy,<sup>4</sup> the RPT publication will focus on the required components of developing a robust program, training, staffing and quality assurance requirements.

The expansion of RPTs opens the door for new treatment opportunities in radiation oncology. Make sure your practice has the tools and infrastructure in place to implement RPTs with a focus on quality and safety to ensure the best outcomes for your patients. 

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## Radiopharmaceutical Training, Assessment and Credentialing

**THE ACCREDITATION COUNCIL** for Graduate Medical Education (ACGME) Radiation Oncology Review Committee (RO RC) is charged with the responsibility of defining the requirements for graduate medical education in RO, and the American Board of Radiology (ABR) has the responsibility of assessing the level of knowledge and skills attained by trainees in ACGME-approved training programs. In this regard, the specific requirements defined by the RO RC for radiopharmaceutical therapy (RPT) lack detailed guidance for the development of assessment instruments. The current program requirements indicate only that: “Residents must demonstrate competence in the use of unsealed radioactive sources.” Competence in the various aspects of radiological physics and procedural experience requirements are specified more precisely.<sup>1</sup>

While effectively being all inclusive, these requirements provide no specific granularity to guide the development of assessment instruments. To assist in the creation of its exam blueprints, the ABR looks to available literature, diplomate responses related to relevance and importance on its Continuing Certification (CC) Online Longitudinal Assessment (OLA) tool and input from volunteer clinical category committee members. Over the past several years, Initial Certification (IC) Qualifying Exam (QE) material related to the clinical applications of RPTs, as well as their physical and biological principles, has been increased.

Notwithstanding the requirements specified by the RO RC, the Training and Experience (T & E) requirements to attain authorized user (AU) status as regulated by the U.S. Nuclear Regulatory Commission (U.S. NRC) and Agreement States, as defined in 10CFR35.390, remain clear, detailed and unequivocal, and include: “completion of 700 hours of training and experience, including a minimum of 200 hours of classroom and laboratory training, in basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material requiring a written directive. Training and experience are also precisely defined and include: “oral administration of less than or equal to 1.22 gigabecquerels (33 millicuries) of sodium

iodide <sup>131</sup>I, for which a written directive is required; oral administration of greater than 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131; and, parenteral administration of any radioactive drug that contains a radionuclide that is primarily used for its electron emission, beta radiation characteristics, alpha radiation characteristics or photon energy of less than 150 keV, for which a written directive is required.”<sup>2</sup>

The regulations also define the role of the program director to indicate that: “A residency program director who affirms in writing that the attestation represents the consensus of the residency program faculty where at least one faculty member is an authorized user who meets the requirements in § 35.57, § 35.390, or equivalent Agreement State requirements, has experience in administering dosages in the same dosage category or categories as the individual requesting authorized user status, and concurs with the attestation provided by the residency program director. The residency training program must be approved by the Residency Review Committee of the Accreditation Council for Graduate Medical Education or the Royal College of Physicians and Surgeons of Canada or the Council on Postdoctoral Training of the American Osteopathic Association and must include training and experience specified in paragraph (b)(1) of this section.”<sup>2</sup> Under significant pressure from interested external physician and commercial stakeholder organizations, the NRC has committed to review the T & E requirements on a regular basis.<sup>3</sup>

In 2021, the RO RC increased the case log requirements for its non-sodium <sup>131</sup>I agent category to five cases, with this increase to be enforced effective July 1, 2023.<sup>4</sup> As previously reported, these AU requirements were promulgated by neither the RO RC nor the ABR but are regulatory mandates for any candidate anticipating application to serve as an AU. The ABR looks to the specifications of 10CFR35.390 in developing its assessment instruments.

On March 25, 2022, the ABR Board of Governors announced its intention to discontinue award of certificates that include the designation *Authorized User-Eligible* (AU-E), effective December 31, 2023.<sup>5</sup>

*Continued on page 36*



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ASTRO's Exhibit Hall provides members the chance to discover the latest and greatest technology, products and services in the radiation oncology field. As a thank you, Ambassadors and Annual Meeting sponsors enjoy a special opportunity to meet with ASTRO leadership in an Annual Meeting tradition.

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## Continued from **RADIOPHARMACEUTICAL TRAINING, ASSESSMENT AND CREDENTIALING**

For RO, the final 2023 IC exam will be administered the week of October 30; therefore, certificate awardees from that administration will be the final RO cohort to receive the AU-E designation. This ABR decision has seemingly engendered a significant amount of misunderstanding and, regrettably, misplaced consternation. The ABR-awarded AU-E designation did not confer AU status, nor did it change NRC and/or Agreement State T & E requirements. Instead, it merely served as surrogate documentation for meeting those requirements, which remain unchanged. The majority of radiation oncologists entering the workforce currently seek AU status prior to obtaining IC, because they wish to use NRC or Agreement State regulated materials immediately. These individuals now provide the required documentation to the appropriate regulatory authority (Personal communication: U.S. NRC). That practice will not change. After December 31, 2023, that process will simply become the norm for RO. Henceforth, training programs should maintain this necessary documentation and provide it to graduating trainees. 

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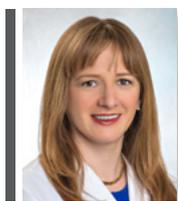
# Science

## HIGHLIGHTS

from the 2022 ASTRO Annual Meeting

### Head and Neck

BY DANIELLE MARGALIT MD, MPH,  
CHAIR OF THE H&N TRACK, 2022 ANNUAL  
MEETING SCIENTIFIC COMMITTEE



**THE HEAD AND NECK (H&N) TRACK** of the Annual Meeting Scientific Committee highlighted [abstracts with the potential](#) to influence clinical practice. An [abstract presented by Benjamin Kann, MD](#), captured the meeting's theme of artificial intelligence (AI) and its potential impact on patient care. The AI model was developed to help clinicians decide whether to recommend radiation or surgery for patients with HPV-related oropharynx cancer. With existing treatment paradigms, patients who have extranodal extension (ENE) detected after surgery are offered postoperative chemoradiation. This trimodality therapy (surgery, postoperative radiation and chemotherapy) results in increased toxicity and is preferably avoided. Therefore, an AI model to predict which patients may have ENE before surgery, may influence clinicians to recommend non-surgical management and avoid trimodality therapy.

The authors previously developed an imaging-based deep learning algorithm (DLA) to predict which patients have pathologic ENE. In the present study, they validated the DLA using data from a large multi-institutional phase II clinical trial, ECOG-ACRIN 3311. All patients in the study received surgery for HPV-related oropharynx cancer. Using the preoperative CT-scans, researchers compared the ability of specialist radiologists to predict ENE with the prediction of the

DLA. They found that the DLA outperformed the four radiologists in predicting ENE. Dr. Kann discussed next steps toward bringing the AI model closer to clinical implementation.

Another abstract addressed survivorship, a major theme in patient-centered care due to the many late effects of radiation therapy (RT). Even though H&N RT is a known risk factor for carotid artery stenosis (CAS), there are no guidelines for asymptomatic CAS screening in patients treated with RT. An abstract presented by MD-Candidate [Pranalee Patel provided useful clinical data](#) to help clinicians and patients understand the risk of CAS.

The abstract reported on more than 600 patients treated with RT for H&N cancer who were monitored with carotid ultrasounds as part of institutional practice. Patients had a mean age of 61 years, many of whom had other cardiovascular risk factors including tobacco-use, hypertension, and dyslipidemia. At five years, an estimated 17.5% of patients had asymptomatic CAS of at least 50%, including some patients with a stroke or transient ischemic attack. The risk increased with time such that at 10 years, the estimated rate of combined CAS and stroke/TIA was 31%. This is in stark contrast to the general population where the prevalence of asymptomatic CAS is approximately 2.0-2.5% in patients between 60-69 years old.<sup>1</sup>

The authors showed patients treated with neck RT have a higher risk of CAS and cerebrovascular events than the general population, and the risk increases with time, and is radiation dose dependent. This data supports current clinical trials to minimize the dose and extent of RT in H&N cancer patients. It also supports incorporating CAS monitoring in general survivorship guidelines to provide clinicians with more guidance on how to appropriately screen patients for this important late effect of treatment. 

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# Genitourinary

BY GERARD MORTON, MD,  
CHAIR OF THE GU TRACK, 2022 ANNUAL  
MEETING SCIENTIFIC COMMITTEE



**THE ASTRO 2022 ANNUAL MEETING** saw the submission of an unprecedented number of high quality, practice changing abstracts to the [GU track](#). This makes the selection of abstracts to highlight particularly difficult, but I would like to focus on two: One that provided new insight into the relative efficacy of bladder preservation for bladder cancer, and another that provided strong evidence of the efficacy of moderate hypofractionation in the management of high risk prostate cancer.

While radical cystectomy has often been considered the treatment of choice for muscle-invasive bladder cancer (MIBC), very favorable outcomes have been reported with a trimodality bladder preservation approach consisting of maximal trans-urethral resection (TURBT) followed by radiation and concurrent radio-sensitizing chemotherapy. To date, there has been limited high-quality data directly comparing these two approaches. A randomized trial from the United Kingdom failed to accrue due to patient reluctance to accept randomization and high non-compliance with the allocated arm. [Jason Efstathiou, MD, PhD, FASTRO, presented a multi-institutional propensity-score matched comparison](#) of radical cystectomy versus trimodality therapy (TMT) for MIBC. Over 700 patients with clinical T2-T4a N0 M0 MIBC were included from four academic institutions. Eligible patients had solitary tumors < 7 cm with

no or unilateral hydronephrosis and no multifocal carcinoma in situ. There was no suggestion that bladder preservation resulted in inferior clinical outcomes, and if anything, quite the opposite. Metastases-free survival probability at five years was 78% with TMT and 73% with cystectomy ( $p=0.07$ ). Cause-specific and overall survival also favoured TMT over cystectomy at 85% vs. 78% ( $p=0.02$ ) and 78% vs. 66% ( $p<0.001$ ), respectively. Radical cystectomy had a 2% mortality rate. Salvage cystectomy was performed in 13% of TMT patients for invasive local recurrence. This study provides the strongest available evidence supporting the use of bladder preservation for patients with MIBC. Trimodality therapy should be more widely adopted, sparing many patients the morbidity, risks and quality of life impact of radical cystectomy.

While several randomized trials have established moderate hypofractionation as a standard of care option for prostate-only radiation therapy, there is less consensus on how best to incorporate hypofractionation with pelvic nodal irradiation. [Tamim Niazi, MD, and colleagues presented a multicenter randomized trial](#) comparing a conventional two-phase approach with a single phase simultaneous integrated boost approach. A total of 329 patients with high and very high risk prostate cancer were randomized to receive either conventionally fractionated radiation of 46 Gy to the nodes and sequential 30 Gy boost to the prostate over 38 fractions, or a hypofractionated approach delivering 45 Gy to the pelvic nodes and simultaneously 68 Gy to the prostate over 25 fractions. All patients were prescribed 28 months of androgen deprivation therapy. At a median follow-up of seven years, no significant differences were found in biochemical recurrence-free survival (87% vs. 85%), metastases-free survival (92%), overall survival (82%) or disease-specific survival (95% vs. 96%). There were no clinically significant differences in toxicity. This clinical trial establishes moderate hypofractionation with nodal radiation therapy as an appropriate standard of care option for men with high risk disease. 

# Lung

BY INGA S. GRILLS, MD, CHAIR OF THE LUNG/THORACIC TRACK, 2022 ANNUAL MEETING SCIENTIFIC COMMITTEE



**THE LUNG SCIENCE HIGHLIGHTS SESSION** featured six abstracts, out of the [many presented on Lung/Thoracic Malignancies](#) at the 2022 ASTRO Annual Meeting. Two prospective trials from the session are discussed below.

[Salma K. Jabbour, MD, FASTRO, presented results from the timely KEYNOTE-799 trial](#) evaluating the use of pembrolizumab given concurrently with chemoradiotherapy for locally advanced NSCLC. In this phase II trial, high performing (ECOG 0-1) patients with stage IIIA-C unresectable NSCLC were assigned to one of two cohorts dependent on tumor histology (Cohort A squamous and non-squamous, or Cohort B, non-squamous only) and received one cycle of chemoimmunotherapy, followed by concurrent chemoimmunotherapy and thoracic radiation, followed by maintenance immunotherapy using pembrolizumab. Patients in cohort A received carboplatin and paclitaxel and those in cohort B cisplatin and pemetrexed. The two-year overall survival was 64% and 71% in cohorts A and B respectively, with the median overall survival (OS) not reached in either cohort; two-year progression-free survival (PFS) was 55% and 61% (median PFS 30.6 mos and not reached, respectively). Although direct trial comparisons cannot be made, the two-year OS of 64% in the carboplatin/paclitaxel cohort was similar to the two-year OS in the PACIFIC trial, while the two-year OS in the cisplatin/pemetrexed arm was numerically higher, 71%. Treatment was

generally well-tolerated, albeit with somewhat higher pneumonitis rates. Grade 5 pneumonitis was 3.6% in the concurrent carboplatin/paclitaxel group compared to 1.1% with cisplatin/pemetrexed, and 1% in PACIFIC. Grade 3 pneumonitis was 8% and 6.9% for cohorts A and B, and was 4.7% for reference, in the previously reported PACIFIC trial. KEYNOTE-799 contributes to the body of literature evaluating methods for combining upfront immunotherapy with chemoradiation and consolidation immunotherapy for stage III NSCLC. Phase III trial data are anticipated.

[Fang Peng, MD, PhD, reported a comparative analysis](#) of outcomes from two prospective single-arm phase II trials for limited stage small cell lung cancer. The more modern trial (2015-2021) used simultaneous integrated boost (SIB) IMRT for dose escalation (54 Gy) to the gross tumor volume, where the PCTV received 45 Gy in 1.5 Gy BID and PGTV was concurrently boosted to 54 Gy in 1.8 Gy BID. The earlier trial (2012-2017) used conventional IMRT, 45 Gy BID to the post-chemotherapy volume. Importantly, both trials employed concurrent chemotherapy, where radiation therapy was started with cycle 3 of cisplatin/etoposide. With a median follow-up of 34.6 mos, progression-free survival was marginally longer with dose-escalated SIB IMRT compared to conventional IMRT, 13.3 versus 11.5 mos ( $p=0.08$ ). Median and two-year overall survival, however, were significantly longer with SIB IMRT compared to conventional; median OS was 35.0 versus 20.3 mos; 2y OS 66.1% versus 38.8% ( $p=0.007$ ). Rates of baseline and surveillance brain MRI were not reported, but responders received prophylactic cranial irradiation; 67% of SIB IMRT patients had staging PET-CT. Reported results are not unlike those recently reported in the phase II trial by Grohnbeg et al. (Lancet Oncology 2021) where dose escalated BID radiation therapy to 60 Gy was associated with improved OS compared to 45 Gy BID (2-year OS 66%, median 37 mos versus 45% and 22 mos). Both reports highlight an interest in studying BID dose escalation for small cell lung cancer in future phase III clinical trials. 

# Central Nervous System

BY HELEN A. SHIH, MD, MS, MPH, FASTRO,  
CHAIR OF THE CNS TRACK, 2022 ANNUAL  
MEETING SCIENTIFIC COMMITTEE



**METASTATIC DISEASE** to the central nervous system (CNS) has remained a significant challenge. Historically, brain metastases patients indicated for whole brain radiation therapy (WBRT) accepted the known neurocognitive toxicity risk. Leptomeningeal disease (LMD) was an even more formidable diagnosis that was often not treated comprehensively with radiation due to the toxicity of craniospinal irradiation (CSI). At the 2022 ASTRO Annual Meeting, [abstracts addressing both challenges](#) offer reinvention of use of advanced radiation therapy technology to improve disease control while preserving quality of life.

With regards to LMD, [Jonathan Yang, MD, PhD, and colleagues presented exciting results](#) from a phase II randomized trial utilizing proton therapy to deliver CSI as compared to the standard of care of involved field radiation therapy (IFRT) using photons, seeking to improve CNS progression-free survival (PFS) without worsening treatment-related toxicity. Focusing on LMD in non-small cell lung cancer and breast cancer patients, Dr. Yang reported on 63 patients enrolled in 2:1 randomization between proton CSI and photon IFRT, both arms receiving 30 Gy in 10 fractions. At pre-planned interim analysis, the study was terminated because of clear benefit with proton CSI over IFRT. Median CNS PFS for proton CSI versus photon IFRT was 7.5 versus 2.3 months,  $p < .0001$ , and with no greater toxicity incurred for receiving CSI. Proton therapy is recognized for significantly reducing collateral normal tissue radiation exposure as the primary rationale for advancing this more costly and complex technology. Historically, the emphasis has been on curative treatment. With the increasing availability of proton therapy and hopeful progressively decreasing cost of treatments, this once

scarce radiation modality may offer significant clinical benefit to a patient population that is often overlooked. Arguably extension of even limited survival measured in months with preservation of quality of life are just as salient priorities in cancer care to curative treatments.

Another practice changing abstract presented pertains to optimizing management of brain metastases patients treated with WBRT. The NRG CC001 was a prospective randomized trial of 518 patients formally published in 2020 that established hippocampal avoidance whole brain radiation therapy (HA-WBRT) as a standard of care for when WBRT is used to treat brain metastases patients to decrease the risk of neurocognitive failure. HA-WBRT is relatively laborious as compared to standard WBRT with the former utilizing intensity modulated radiation therapy technology and requiring several days to create a treatment plan whereas the latter can often be initiated same day to simulation using basic 2-D or 3-D radiation planning technology. [Hua-Ren Ryan Cherg, MD, and colleagues report on a secondary analysis of NRG CC001](#), seeking to identify the subset of patients who truly benefit from hippocampal avoidance integration into WBRT. Patients surviving greater than four months with lung cancer or with baseline fewer neurocognitive symptoms based upon the MD Anderson Symptom Inventory were found to gain the most from HA-WBRT. These findings will help guide clinicians to best use of HA-WBRT, but challenge is to identify those patients who prognostically will survive long enough to benefit from it. 

## Science Highlights Recordings

For 2023, we're releasing a Science Highlight at the end of each month. Recorded during the ASTRO 2022 Annual Meeting, these highlights are the most noteworthy scientific abstracts from select tracks. They present the most important findings while featuring cutting edge research from leaders in the field.

As a new member benefit, Science Highlights are free to ASTRO members. The first Science Highlight — Central Nervous System — was available in the January 25 issue of ASTROgram and can be accessed via ASTRO Academy.

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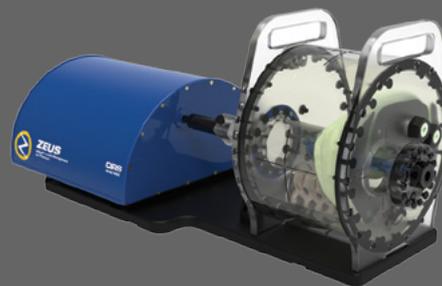
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