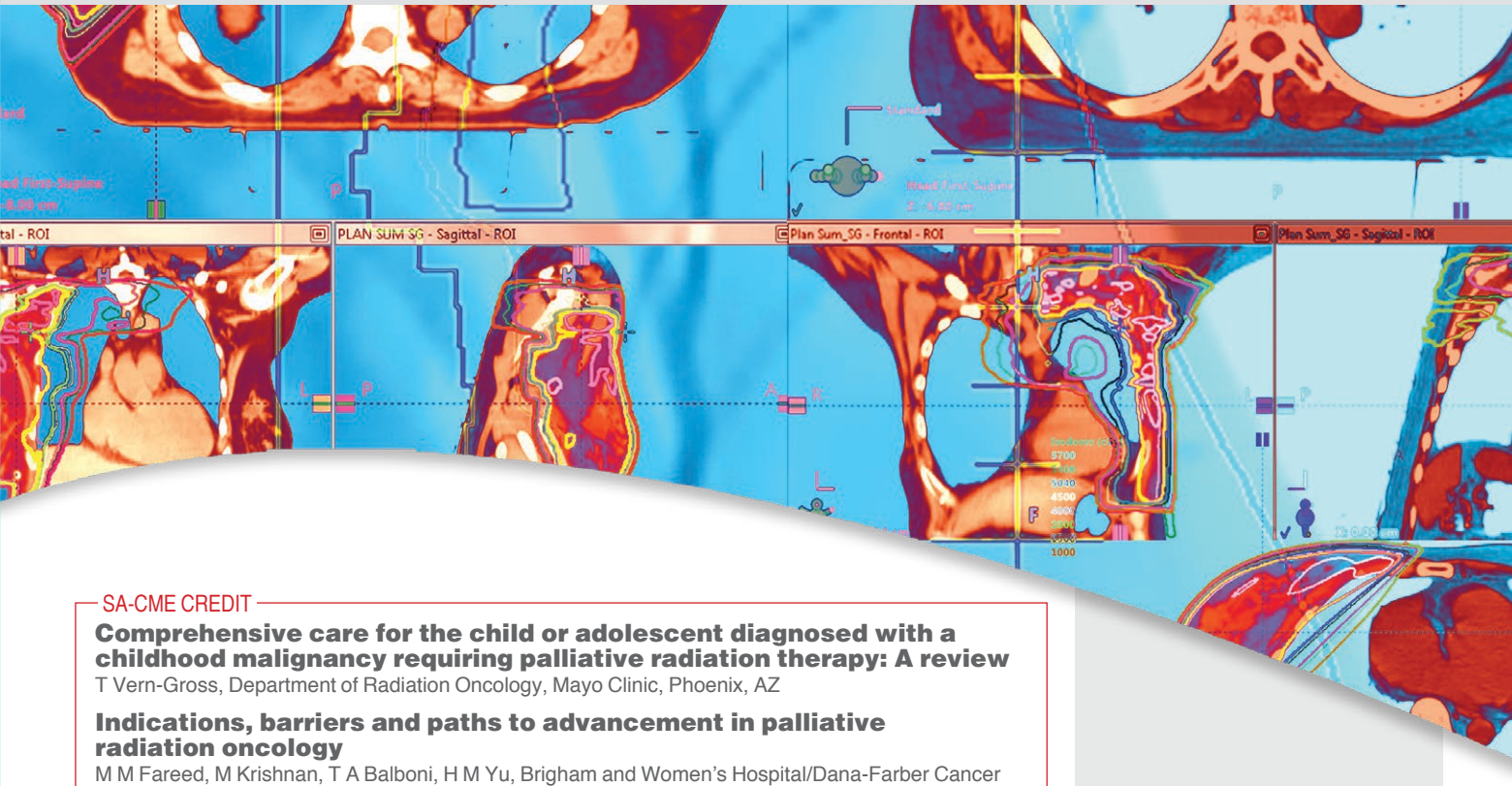
APPLIED
VOL 7 NO 2 JUNE 2018
RADIATION ONCOLOGY™



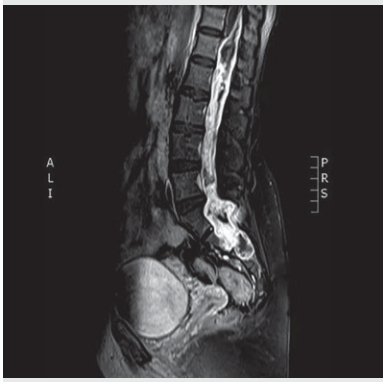
SA-CME CREDIT

Comprehensive care for the child or adolescent diagnosed with a childhood malignancy requiring palliative radiation therapy: A review
T Vern-Gross, Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ

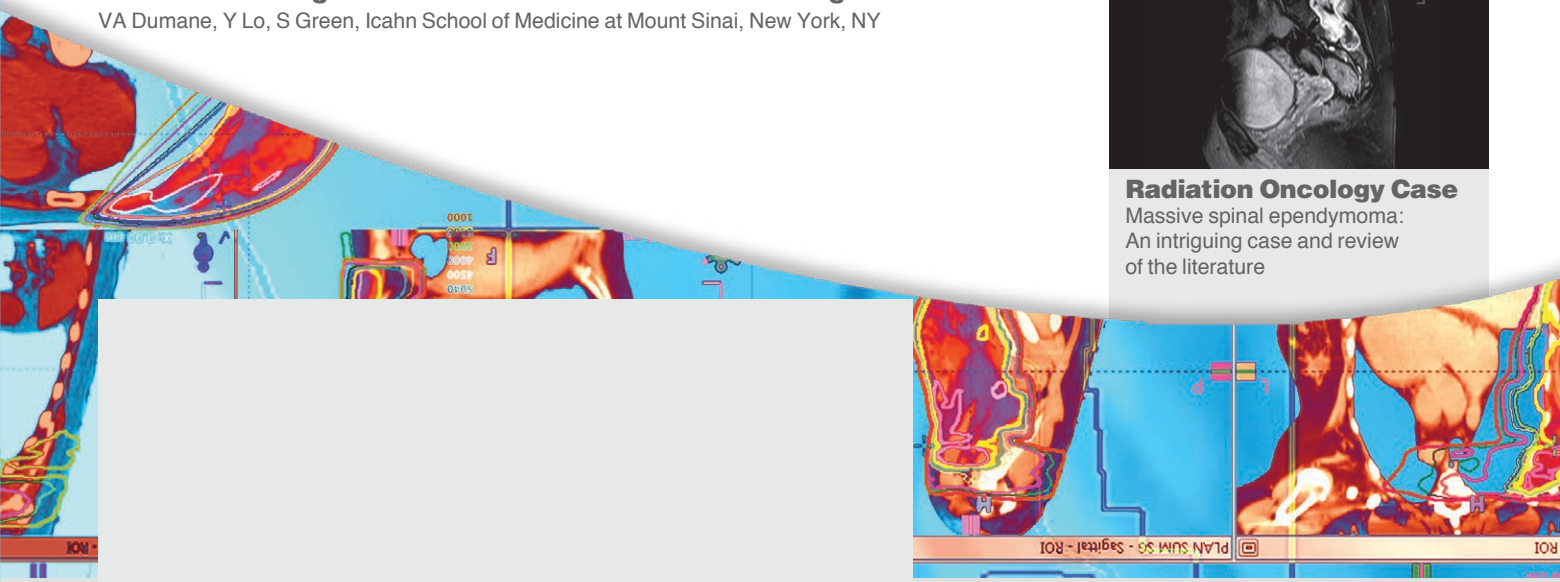
Indications, barriers and paths to advancement in palliative radiation oncology
M M Fareed, M Krishnan, T A Balboni, H M Yu, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA and H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

RTAnswers online patient education materials deviate from recommended reading levels
SA Rosenberg, RA Denu, D Francis, CR Hullett, M Fisher, JM Schuster, MF Bassetti, RJ Kimple, University of Wisconsin-Madison, WI

Combination of VMAT and PWT for improved organ sparing in a left-sided and right-sided breast cancer case receiving RNI
VA Dumane, Y Lo, S Green, Icahn School of Medicine at Mount Sinai, New York, NY



Radiation Oncology Case
Massive spinal ependymoma: An intriguing case and review of the literature



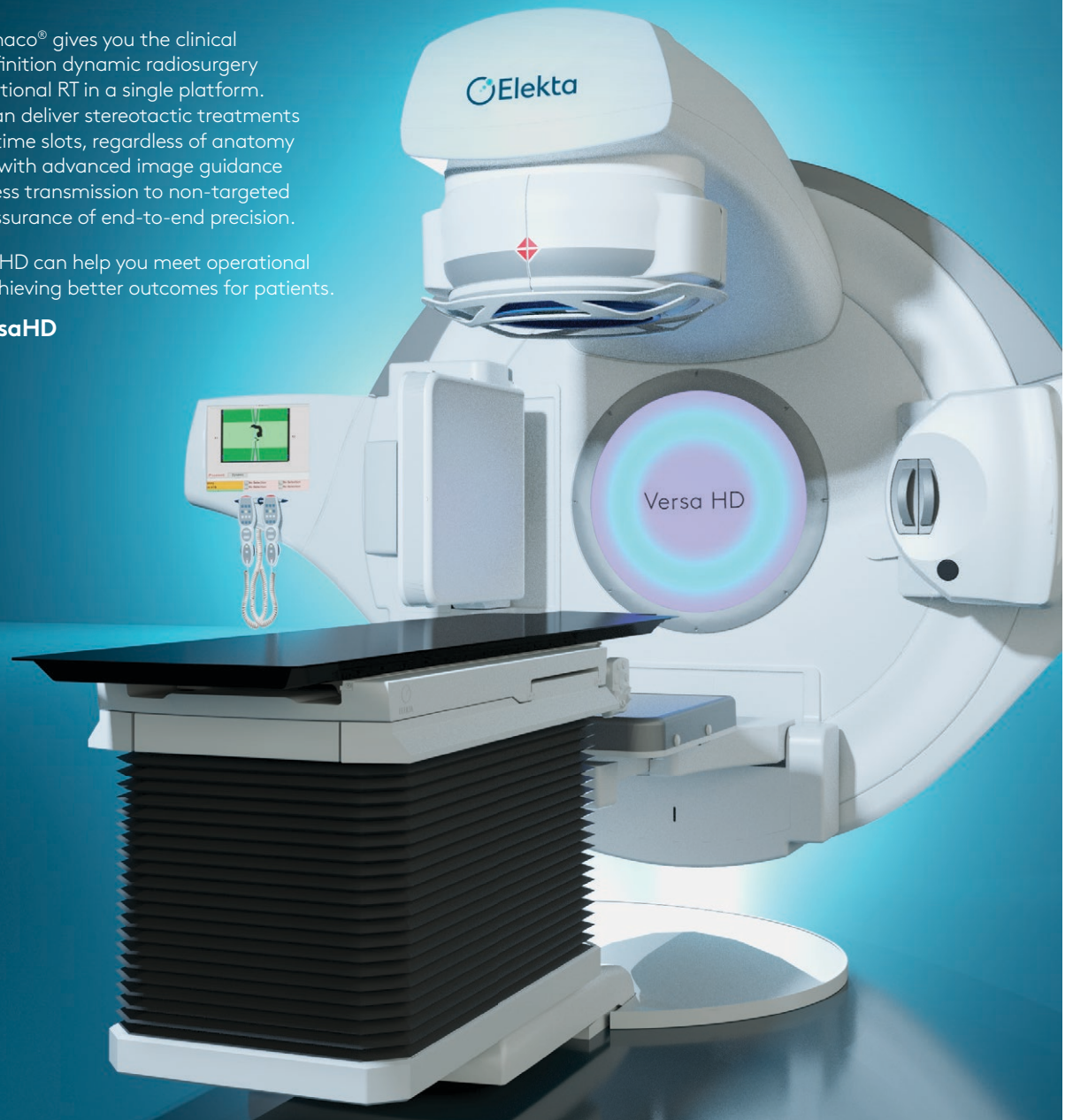
Versa HD.

Powered by high definition dynamic radiosurgery.

Versa HD™ with Monaco® gives you the clinical flexibility of high definition dynamic radiosurgery (HDRS) and conventional RT in a single platform. HDRS means you can deliver stereotactic treatments within standard RT time slots, regardless of anatomy or complexity. And, with advanced image guidance tools and up to 5x less transmission to non-targeted regions, you have assurance of end-to-end precision.

Discover how Versa HD can help you meet operational efficiencies while achieving better outcomes for patients.

elekta.com/VersaHD



Elekta

Focus where it matters.

4513 371 1539_03.17

APPLIED RADIATION ONCOLOGY™

Editor-in-Chief
John Suh, MD, FASTRO

Publisher
Kieran N. Anderson

Managing Editor
Sharon Breske

Art Director/Production
Barbara A. Shopiro

Circulation Director
Cindy Cardinal

TEL: 908-301-1995
FAX: 908-301-1997

info@appliedradiationoncology.com
www.appliedradiationoncology.com

CIRCULATION, COVERAGE and ADVERTISING RATES: Completed details of regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 30 days preceding date of issue. View our media planner at appliedradiationoncology.com/advertise.

EDITORIAL CONTRIBUTIONS: *Applied Radiation Oncology* accepts clinical-review articles, research papers, and cases that pertain to radiation oncology and related oncologic imaging procedures that will be of interest to radiation oncologists. Manuscripts and cases may be sent electronically to Sharon Breske, Executive Editor for review with our Advisory Board. The opinions and recommendations expressed herein, in articles, columns and cases, are not necessarily those of the publisher. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of the information supplied or for any opinion expressed. Before using procedures or treatments discussed or suggested by authors, clinicians should evaluate their patients' conditions, compare the recommendations of other authorities, consider possible contraindications or dangers, and review applicable manufacturer's product information. Editorial closing date is the first day of the month 3 months prior to the issue date. Review articles and cases should be geared to the practitioner and should reflect practical everyday clinical applications rather than research activity. Articles and cases may pertain to clinical management, administration, fiscal, technical, and medico-legal issues. Clinical review articles are also solicited by our Editorial Advisory Board. Any editorial submission should be original and unpublished, approximately 1500-2500 words and include the appropriate images, image captions and references. All submissions are to be submitted electronically by emailing a MS Word document, high resolution images, and selected DICOM image data sets to our Editor, Sharon Breske, for review and approval. Authors will be notified by email of acceptance or rejection and of any major recommended revisions. Prior to publication, a PDF of your article or case will be emailed to you for final approval. Manuscripts and cases should be emailed to Sharon Breske, at Sharon@appliedradiationoncology.com.

Anderson Publishing, Ltd
180 Glenside Avenue, Scotch Plains, NJ 07076
(908) 301-1995

ESSN: 2334-5446 (Online)

EDITORIAL ADVISORY BOARD

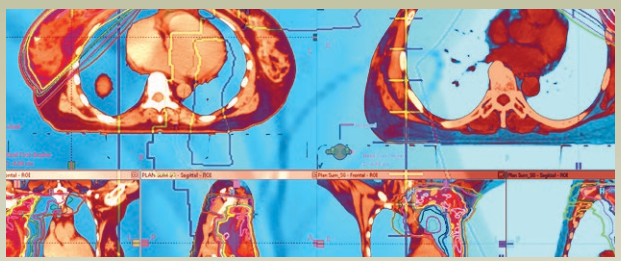
APPLIED RADIATION ONCOLOGY™

June 2018
Vol. 7, No. 2

FOCUS: PALLIATIVE RADIATION ONCOLOGY

SA-CME CREDITS

RADIATION ONCOLOGY RESEARCH



Applied Radiation Oncology *(ISSN: 2334-5446) is published quarterly by Anderson Publishing, Ltd., 180 Glenside Avenue, Scotch Plains, NJ 07076. Subscription is free of charge to all medical professionals. To update your subscription preferences, visit appliedradiationoncology.com/subscribe. Complaints concerning non-receipt of this journal should be made via email to our publisher, Kieran Anderson at kieran@appliedradiationoncology.com.*

Get the plan you want the first time, every time.

Create high quality plans quickly and efficiently.

Use the knowledge from successful treatment plans to help get more of your clinic's plans approved the very first time. That's RapidPlan™ knowledge-based planning. Leading radiotherapy teams worldwide have discovered RapidPlan's unparalleled ability to create the optimal plan for their patients—time and time again. Unlock the power of RapidPlan in your cancer center today.

Visit us at AAPM 2018 Booth #601.
Learn more about the benefits of RapidPlan at Varian.com/RapidPlan

varian

RapidPlan knowledge-based planning and its models are not intended to replace clinical decisions, provide medical advice or endorse any particular radiation plan or treatment procedure. The patient's medical professionals are solely responsible for and must rely on their professional clinical judgment when deciding how to plan and provide radiation therapy.

EDITORIAL

Comfort zone: The integral role of palliative radiation therapy

John Suh, MD, FASTRO
Editor-in-Chief

Welcome to the June issue of *Applied Radiation Oncology*! Focusing this month on palliative radiation therapy, we are pleased to offer two comprehensive review articles that examine pediatric needs and considerations, as well as challenges and opportunities in common clinical scenarios.

In treating advanced cancer, The American Cancer Society emphasizes: "Something can almost always be done to help maintain or improve quality of life."[1] Palliative radiation therapy is one such option that helps provide this much-needed comfort to patients with incurable disease.

Unfortunately for children, no consensus exists for a standard approach to palliative radiation therapy. As Dr. Tamara Vern-Gross describes, pediatric practice is extrapolated from adult palliative literature, but controversy remains regarding its appropriateness. Her thoughtful review, *Comprehensive care for the child or adolescent diagnosed with a childhood malignancy requiring palliative radiotherapy,* helps clarify differences between pediatric and adult palliative radiation therapy, while elaborating on early integration, communication, challenges, research and more.

The second review, *Indications, barriers, and paths to advancement in palliative radiation therapy*, describes evidence-based methods for advanced cancer treatment along with methods of enhancing research and education opportunities. This comprehensive update by Dr. Muhammed M. Fareed and colleagues describes ways to expand skills beyond technical areas of radiation therapy delivery to generalist palliative care competencies, including symptom management, psychosocial issues, ethical/legal issues and beyond.

In addition to a Technology Trends article on technical developments in palliative radiation therapy, we hope you enjoy an interesting array of research updates and case reports in the issue on reading levels in patient education materials, organ sparing in breast cancer treatment, gastro-esophageal junctional carcinoma, and spinal ependymoma. We're also proud to feature the impelling Resident Voice guest editorial by Dr. John Byun who stresses the need for proactive involvement in the national dialogue on health policy.

Service Recognition: Steven Feigenberg, MD

Finally, I wish to extend my deep and sincere gratitude to University of Pennsylvania's Steven Feigenberg, MD, for his more than 6 years of dedicated service on the *ARO* editorial advisory board. As one of our founding members whose time, ideas and outreach helped launch the journal in 2012, Dr. Feigenberg has authored, recruited, brainstormed and spent countless hours building the journal and refining it to its advanced online and print status today. Thank you, Steve, for your invaluable contributions!

Many thanks to our more than 5,000 subscribers as well for your continued support over the years. Please enjoy the issue, and have a safe, fulfilling summer season.

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Reference

1. American Cancer Society. *Understanding your diagnosis: Advanced cancer, metastatic cancer, bone metastasis.* https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/treatment.html. Accessed June 5, 2018.

RESIDENT VOICE

Shining light on health care policy and reform: Needs and updates

John Byun, MD

John Byun, MD

Health care policy and reform pervade our daily medical practices. Although residency training can temporarily shield trainees, the effects of national health care reforms have profound and career-long implications. The recent Patient Protection and Affordable Care Act (ACA) was signed into federal law in March 2010 and represents watershed legislation fundamentally altering healthcare in the United States.[1] The reform policies created some of the "most aggressive efforts in the history of the nation to address the problems of the [health] delivery system."[2] Furthermore, the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) introduced new reimbursement paradigms for nearly all healthcare providers.[3]

Health care policies encompass the body of local, state and national regulations, including delivery, documentation, event reporting, public health, malpractice and payment. Historically, health care resembled a "fee for service" model, linking patient or treatment volume to payment; the recent reform is creating a shift toward provider performance, quality and value. Implementation can vary state by state, so individual residencies, hospitals, and even rotations may have widely differing daily practices. For example, consider the effects of Maryland's unique all-payer rate setting in which all insurance parties pay the same for hospital-based services.[4] The implications of health policies, regardless of their temporal or provincial origins, may have significant effects on the scope in which radiation oncologists practice.

During training, policy concepts often are discussed tangentially. Familiar, but mysterious, terms include accountable care organizations (ACOs are intended to integrate inpatient, outpatient and ancillary services for Medicare patients), merit-based incentive payment systems, and alternative payment models (development ongoing, MIPS and APM change Medicare reimbursement structures to incentivize quality measurement reporting). Currently, one of these APMs, the Oncology Care Model, frames a payable episode of cancer treatment as 6 months from initiation of drug therapy; during this period, the oncologist providing the chemotherapy receives a fixed monthly payment to cover all costs for the patient, including potential radiation treatment.[5] The American Society for Radiation Oncology (ASTRO) has worked on developing an alternative payment model.[6]

These health care reforms will transform, and their downstream programs will undoubtedly change, hopefully with clinician-guided involvement, careful study and rigorous research. Importantly, these changes occur with or without input from those in practice. As our field challenges itself to grow, and we cultivate our technical skills, we must also learn to participate proactively in the national dialogue in health policy. Our future, as thoughtful clinical leaders and advocates for our patients, will rely on our engagement now.

***Dr. Byun** is chief resident, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey at the Robert Wood Johnson/Barnabas Health, New Brunswick, NJ.*

References

1. Chaikind H, Copeland CW, Redhead CS, Staman J. Congressional Research Service. R41664. PPACA: a brief overview of the law, implementation, and legal challenges. Published 2011. https://fas.org/sgp/crs/misc/R41664.pdf. Accessed May 7, 2018.
2. Blumenthal D, Abrams M, Nuzum R. The Affordable Care Act at 5 years. *N Engl J Med*, 2015;372(25):2451-2458.
3. Centers for Medicare & Medicaid Services (CMS). The Medicare Access and CHIP Reauthorization Act of 2015: path to value. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/MACRA-MIPS-and-APMs/MACRA-LAN-PPT.pdf. Accessed May 7, 2018.
4. Cohen HA. Maryland's all-payor hospital payment system. The Maryland Health Services Cost Review Commission. http://www.hscrc.state.md.us/Documents/pdr/GeneralInformation/MarylandAll-PayorHospitalSystem.pdf. Accessed May 7, 2018.
5. Centers for Medicare & Medicaid Services. Oncology care model overview. May 2018. https://innovation.cms.gov/Files/slides/ocm-overview-slides.pdf. Accessed May 7, 2018.
6. American Society for Radiation Oncology. Alternative payment models (APMs). https://www.astro.org/Daily-Practice/Medicare-Quality-Payment-Program/APM/APMs/ Accessed May 7, 2018.

SA–CME Information

COMPREHENSIVE CARE FOR THE CHILD OR ADOLESCENT DIAGNOSED WITH A CHILDHOOD MALIGNANCY REQUIRING PALLIATIVE RADIATION THERAPY: A REVIEW (PAGE 7)

Description: Because of the low incidence of pediatric malignancies, no consensus has been reached on the best practices for the delivery of pediatric palliative radiation therapy. As a result, current practice is extrapolated from adult literature and single institutional series. In addition to the technologies for palliation of pediatric patients are essential components of communication for meeting medical and psychosocial needs of the families and patients; these needs are not always addressed. A multidisciplinary approach with appropriate care and communication addressing patient questions and needs provides meaning and improved quality of life during this phase of treatment.

Learning Objectives:

After completing this activity, participants will be able to:

1. Understand and adopt principles of pediatric palliative radiation therapy treatment for the more common sites and disease-specific scenarios.
2. Adopt important considerations when caring for and treating children and families diagnosed with advanced malignancies that require palliative radiation therapy.

Author: Tamara Vern-Gross, DO, FAAP, is an assistant professor in the Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ.

INDICATIONS, BARRIERS AND PATHS TO ADVANCEMENT IN PALLIATIVE RADIATION ONCOLOGY (PAGE 18)

Description: Palliative radiation oncology is an integral part of radiation oncology practice with practical implications in common clinical scenarios including bone metastases, brain metastases, malignant spinal cord and cauda equina compression, tumor-related bleeding, fungation, obstruction and visceral metastases. Further education and research are needed as part of residency training and beyond to enhance the spectrum of care for advanced cancer patients delivered by radiation oncologists. Supportive and palliative care skills must expand beyond the technical aspects of radiation therapy delivery to generalist palliative care competencies, including symptom management basics, communication and goals of care, advance care planning, psychosocial issues, cultural considerations, spiritual needs and ethical/legal issues.

Learning Objectives:

After completing this activity, participants will be able to:

1. Implement evidence-based practice for treating advanced-cancer-related scenarios with palliative radiation oncology.
2. Identify barriers and incorporate opportunities and perspectives to advance education in palliative radiation oncology.

Authors: Muhammed M. Fareed, MD, is a fellow in the Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA. **Monica Krishnan, MD,** is an assistant professor of radiation oncology, and **Tracy A. Balboni, MD, MPH,** is an associate professor of radiation oncology, Harvard Medical School, Boston, MA. **Hsuan Michael Yu, MD,** is associate member, Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, and associate professor, Department of Oncological Sciences, University of South Florida, Tampa.

Obtaining Credits

Instructions: To earn credit, participants must complete the activity during the valid credit period. To receive SA–CME credit, you must:

1. Review this article in its entirety.
2. Visit www.appliedradiology.org/SAM.
3. Login to your account or (new users) create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

Date of release and review: June 1, 2018
Expiration date: July 31, 2020
Estimated time for completion: 1 hour for each activity

Disclosures: No authors, faculty, or individuals at the Institute for Advanced Medical Education (IAME) or *Applied Radiation Oncology* who had control over the content of this program have relationships with commercial supporters.

Accreditation/Designation Statement: The IAME is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The IAME designates each journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity. These credits qualify as SA-CME credits for ABR diplomates.

Commercial Support: None

As part of this CME activity, the reader should reflect on how it will impact his or her personal practice and discuss its content with colleagues.

SA-CME (see page 6)

Comprehensive care for the child or adolescent diagnosed with a childhood malignancy requiring palliative radiation therapy: A review

Tamara Vern-Gross, DO, FAAP

In the United States, an estimated 10 270 children ages birth to 14 years will be diagnosed with cancer in 2017, and 1190 children will die of cancer, the second leading cause of death for children following accidents.[1] Five-year survival has improved for all childhood cancers from 63% in the mid-1970s to 83% today.[2] The incidences of major childhood malignancies are shown in **Figure 1A-B**. Of these children, approximately 30% to 50%[3,4] will require radiation therapy (RT) sometime during their disease course. And of children receiving RT, approximately 11% to 18%[5-8] will require palliative radiation therapy (RT) to prevent or alleviate symptoms in the setting of incurable disease to optimize their quality of life (QOL).

Dr. Vern-Gross *is an assistant professor in the Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ.*

Disclosure: The author has no conflicts of interest to disclose and has not received outside funding for the production of this original manuscript. Prior publications/presentations on this topic are:

1. Vern-Gross TZ. Pediatric palliative radiation oncology. In Lutz S, Chow E, Hoskin P, eds. Radiation Oncology in Palliative Cancer Care. *Chichester, UK: John Wiley & Sons, Ltd.; 2013.220-234.*

2. Vern-Gross TZ, Lam CG, Graff Z, et al. Patterns of end-of-life care in children with advanced solid tumor malignancies enrolled on a palliative care service. J Pain and Symptom Manage. *2015;50(3):305-312.*

In contrast to adults diagnosed with a malignancy, the need for palliative RT is exceptionally low; most likely underestimated. Reporting differs among institutions, highlighting the variability in the definition of "palliative intent," especially within the pediatric population (**Table 1**). Radiation therapy has been initiated in the setting of "preventive palliation," where progression of uncontrolled disease could negatively impact QOL. For instance, children diagnosed with diffuse infiltrating pontine glioma (DIPG) are treated to definitive doses with the goal of achieving symptomatic relief and optimizing disease control, with cure unlikely.

Adult randomized controlled trials have demonstrated the efficacy of palliative RT in the setting of progressive primary or metastatic disease.[9-11] Because of challenges in obtaining abundant quality-controlled data, there is no consensus in the standard of care for palliative RT for pediatric and adolescent patient malignancies. Current pediatric practice is extrapolated from adult palliative literature, but controversy persists about whether current adult regimens are appropriate.

Palliative Radiation Therapy: Differences Between Pediatric and Adult Patients

Pediatric malignancies have distinctive presenting symptoms, and diverse prognostic implications, treatment options, and subsequent responses. Compared with adults, children and adolescents are more likely to present with oncologic emergencies such as spinal cord compression (SCC) and superior vena cava syndrome (SVCS) earlier in the disease process at the time of diagnosis.[12,13] For example, in a child, SCC or a mediastinal mass is frequently a sign of a new primary malignancy. It has been documented that sarcomas account for approximately 43% to 65% of SCC cases in children.[13,14] Adults develop

SA-CME (see page 6)

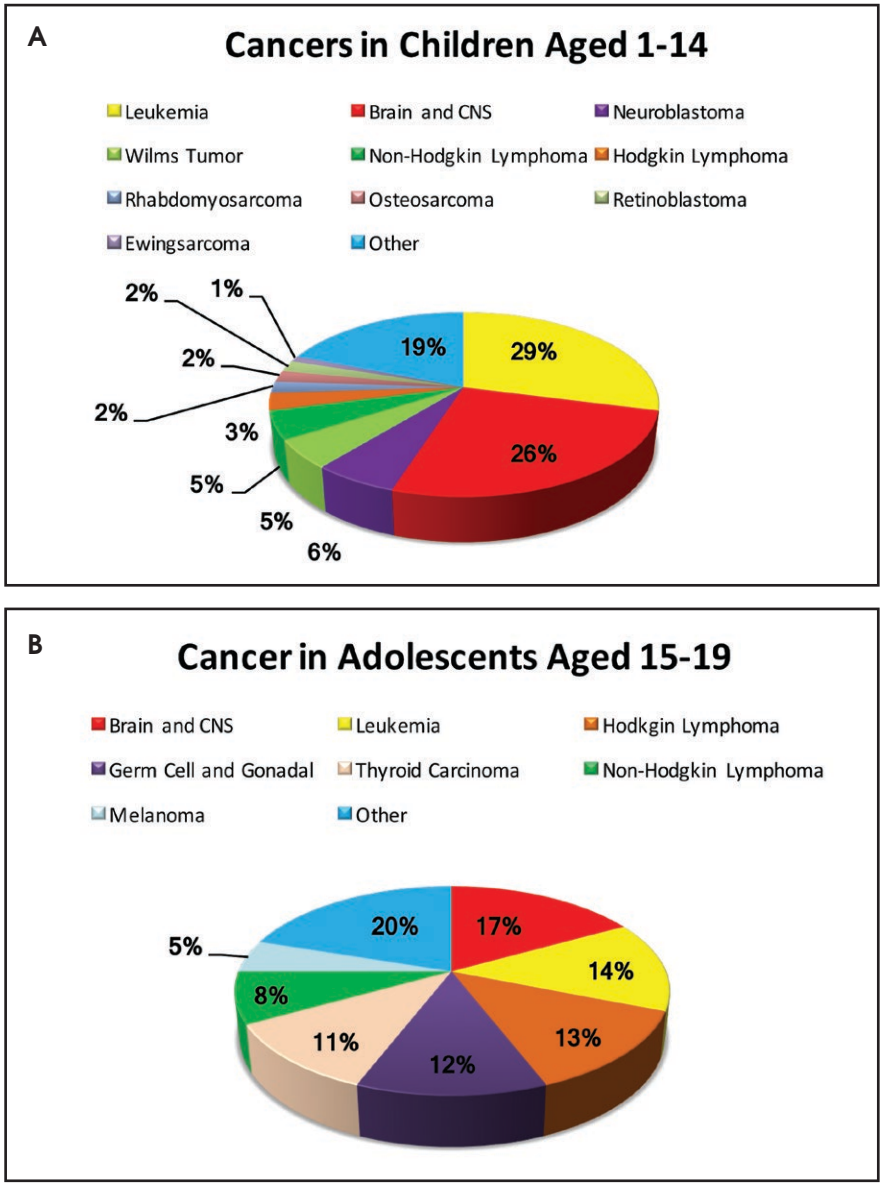


FIGURE 1. *(A and B) The incidence of major childhood malignancies.[1]*

SCC more commonly as metastatic lesions from primary lung, prostate, and breast cancer.[15,16] In the setting of SCC and paraplegia, children tend to have a more "forgiving" central nervous system (CNS) and are more likely to recover and regain ambulation with initiation of treatment compared with adults.[17-21]

Palliative RT is often not the first-line therapy in children and adolescents at the time of diagnosis, especially in those presenting with symptomatic spinal or mediastinal disease, as these tumors tend to be more chemo-sensitive compared to adult malignancies. Unlike with adults, the utilization of RT is focused more on relieving life-threatening problems, rather than palliation of unwanted symptoms.

Comprehensive Management for Children Diagnosed with Advanced Malignancies

Children with high-risk cancer and their families endure significant physical symptoms, psychosocial issues, and spiritual challenges, which impact QOL detrimentally.[22-25] Because the "hope for cure" often remains a priority, children may undergo aggressive cancer-directed therapy, overlooking the comforts and supports necessary throughout a child's illness.[26] comprehensive pediatric oncology teams collaborate with the child/family to execute high-quality care and support from initial diagnosis, throughout palliation of symptoms, and beyond the child's death.

A personalized and often creative approach is required to optimize care in managing these patients, incorporating the interdisciplinary team so patient/family needs and goals of care are appropriately met.[27-29] Pediatric palliative care (PPC) is a specialty that has gained accolades by providing an evolving backbone of support for children/families with life-threatening or life-limiting illness. It embodies total care through management of pain, complex symptoms, psychosocial and spiritual needs, coordination of care, medical decisions, and interaction with an interdisciplinary team.[26,30-34] These specialists work closely with the patient/family to enhance function, and improve QOL.[30,35,37] The World Health Organization (WHO) promotes pediatric palliative care (PPC) as an approach dedicated to "active total care of the child's body, mind, and spirit, and support for the family" (**Table 2**).

Clinical Indications for Pediatric Palliative Radiation Therapy

Palliative RT is more valuable in the setting of recurrence or metastatic disease progression, after multiple unsuccessful systemic therapies, than at initial diagnosis. The indications for palliative RT are similar for both pediatric and adult patients, depending on location, involvement of surrounding structures, overall prognosis, and ultimately patient/family goals of care (**Table 3**). Because treatment is guided to minimize acute and late toxicities, systemic therapy continues to be the optimal first-line therapy, especially in

SA-CME (see page 6)

Table 1. Definition of Patients Eligible for Pediatric Palliative Radiation Therapy

Series	Definition
Rahn et al 2015	Patients treated with palliative radiation therapy are those thought to have incurable disease at the time of treatment.
Rao AD et al 2016	Treatment intent with palliative radiation therapy is defined as having the goal to improve symptoms or to prevent impending symptoms, such as in the case of intracranial or spine involvement.
Mak et al 2017	Children diagnosed with incurable advanced cancer. Patients enrolled on protocols that called for irradiation of metastases present at diagnosis are not included within this definition, as treatment intent was not palliative.
Varma S et al 2017	Radiation therapy is considered palliative in children with advanced cancer who are ineligible for or whose disease had persisted/progressed through standard-of-care first-line therapy, in whom the goal of RT is amelioration or prevention of a specific symptom. In most cases, patients have undergone multiple unsuccessful lines of systemic, cure-directed therapy.

Adapted from references 5–7, and 147

Table 2. The WHO Definition of Palliative Care

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counseling
- Enhances quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended

Adapted from World Health Organization 2018

Table 3. Indications for Palliative Radiation Therapy

- Bone and soft tissue metastases secondary to impending or pathologic fracture, soft tissue/nerve root compression or infiltration
- Neurologic dysfunction , including cranial nerve palsies, secondary to brain or leptomeningeal disease
- Spinal cord compression
- Airway obstruction resulting in dyspnea
- Obstructions of gastrointestinal, and genitourinary tracts
- Bleeding secondary to involvement of genitourinary, gastrointestinal, or pulmonary sites
- Superior vena cava syndrome or superior mediastinal syndrome
- Hepatic metastases causing pain from capsular stretch
- Esophageal or gastric outlet obstruction

Adapted from Vern-Gross 2013

children with chemo-sensitive spinal cord tumors (eg, neuroblastoma, Ewing sarcoma, and lymphoma) in the absence of neurologic deficits.[38-43] When palliative RT is initiated, treatment focuses on reducing acute toxicities (eg, radiation dermatitis, esophagitis) and anesthesia requirements by decreasing RT dose and treatment days. Despite attempts to accurately prognosticate, children may outlive initial survival predictions, underscoring the importance of always considering the implications of long-term toxicities.[44] Although most radiotherapeutic techniques are extrapolated from the adult literature, several pediatric series have reported effective outcomes of palliative RT for various pediatric indications (**Table 4**).

Importance of biopsy prior to emergency treatment

On a new patient presentation, it is critical to obtain a tissue diagnosis to identify the primary disease and to rule out a benign or malignant process, which may require a specific treatment course. Patients may not require palliative RT, but rather a multidisciplinary approach that guides definitive treatment. If a tissue diagnosis cannot be established secondary to anesthesia risk, absence of marrow involvement,

SA-CME (see page 6)

Table 4. Patterns of Pediatric Palliative Radiation Therapy

Series	No. of Patients	Tumors Treated	Most Common Symptom at Presentation	Radiation Dose	Treatment Outcomes	Survival Outcomes
Bertsch et al[8] 1998	N = 104 115 sites	CNS-PNET gliomas (20%) Neuroblastoma (20%) Other (sarcoma, lymphoma, Wilm's, NHL, leukemia, nasopharynx, retinoblastoma, craniopharyngioma, germinoma)	Group I: SCC Group II: respiratory compromise Group III: infra-diaphragmatic distress Group IV: intracranial signs Group V: pain	Solid tumors: 1.5-4 Gy fx to a total dose of 3-55.8 Gy Leukemia/lymphoma 1.4-4 Gy fx to a total dose of 2.2-22.5 Gy	Overall response rate: 80% stabilization or improvement Group I: 85% response rate with (55%) improvement or stabilization (30%) Group III: 66% response rate; Group IV: 63% response rate; 19% stabilization; Group V: 93% overall response	N/A
Koontz et al[56] 2006	N = 21 63 sites	Ewing sarcoma	Group I: soft tissue Lung (N = 8) Brain (N = 5) Group II: bone Spine (N = 11) Pelvis/hip (N = 10) Lower extremity (N = 7)	Median RT dose 30 Gy (4.5 Gy-68.5 Gy)	Overall response rate: (84%) Median overall treatment response: 81 days (range, 0-1760 days) Group I: soft tissue CR (44%), PR (21%), NR (11%) Group II: bone CR (11%), PR (8%), NR (5%)	Median survival 1 year (range, 17 days to 6.8 years)
Rahn et al[7] 2015	N = 45 76 sites	Ewing sarcoma (20%) Osteosarcoma (16%) Rhabdomyosarcoma (13%) Neuroblastoma (13%) Brain/CNS (11%) Leukemia/lymphoma (7%) Other (20%)	Bone pain (49%) Neurologic (28%) Respiratory compromise (13%) Painful liver metastases (5%) Bleeding or painful abdomen (5%)	Bone tumors or abdominal masses: 2.5 Gy x 14 fx (35 Gy) 3 Gy x 10 fx (30 Gy) 4 Gy x 5 fx (20 Gy), 1 Gy x 8 fx (8 Gy) Leukemia: 1.5-2 Gy x 10 fx (15-20 Gy) Non-bulky lung metastases: 10 Gy x 5 fx (50 Gy), 12 Gy x 4 fx (48 Gy) Brain metastases 16-20 Gy x 1 fraction Usually treat with SRS	Overall response rate (72%) Bone pain (80%) Neurologic symptoms (58%) Dyspnea or chest pain (55%) Liver pain or ascites (100%) Bleeding (50%) No grade > 3 RTOG toxicities 7% did not complete treatment course	Median survival was 6.5 months 23% alive at last visit
Rao et al[6] 2016	N = 365* 427 sites	Neuroblastoma (20%) Leukemia/Lymphoma (15%) Rhabdomyosarcoma (14%) Brain/CNS (14%) Ewing sarcoma (8%) Osteosarcoma (12%) Other non-CNS (8%)	Pain (57%) Intracranial (16%) Spinal cord compression (10%) Respiratory compromise (9%) Abdominal distension (3%) Postop-spine (2%), Bleeding (1%) Bowel obstruction (1%), Other (1%)	N/A	Treatment was delivered to metastatic disease in 54%	N/A
Varma et al[5] 2017	N = 50 83 sites	Neuroblastoma (23%) Rhabdomyosarcoma (18%) Ewing Sarcoma (10%) Leukemia/Lymphoma (9.6%) Osteosarcoma (4.8%) Brain/CNS (3.6%), Other (26.4%)	Progression of oligometastatic disease (58%), Pain (13%) Neurologic (21%) Respiratory Compromise (10%) Other (10%)	Median RT Dose 20 Gy (1.5-59.74 Gy) Median # of fractions 6 fx (1-32)	Overall response rate (77%) asymptomatic for pain at 12 months (> 80%) neurologic symptoms success (71%) asymptomatic (100%) dyspnea (62%), other (50%)	Median survival was 124 days (1 day-1141 days) 74% had hospice care at last follow-up 10% did not complete treatment course
Mak et al[147] 2017	N = 46 76 sites	Neuroblastoma (20%) Rhabdomyosarcoma (7%) Ewing sarcoma (11%) Leukemia/lymphoma (9%) Osteosarcoma (7%) Brain/CNS (37%) Other (11%)	Progression of oligometastatic disease (39%), Pain (25%) Neurologic (43%), Spinal cord compression (1%), Leptomeningeal disease (8%), Facial mass (5%), Liver or biliary obstruction (3%), Other (1%)	Median RT dose 30 Gy (2.5 Gy-54) Median dose/fraction 2.5 Gy (1.5-4.0 Gy) Median # of fractions 12 (1-30)	During RT: 91% improved or stable 0-3 months: 73% improved or stable 3-6 months: 58% improved or stable 6-12 months: 43% improved or stable 8% did not complete treatment course	Median survival was 4.2 months 19% had hospice care at last follow-up

*Six international institutions are involved in the research consortium. Values represent the average from all institutions. Key: CNS = central nervous system, PNET = primitive neuroectodermal tumor, SCC = spinal cord compression, Gy = Gray, fx = fraction, N/A = not applicable, RT = radiation therapy, CR = complete response, PR = partial response, NR = no response, SRS = stereotactic radiosurgery, RTOG = Radiation Therapy Oncology Group, NHL= non-Hodgkin lymphoma

SA-CME (see page 6)

or lack of peripheral lymphadenopathy, systemic chemotherapy should be considered as initial therapy to stabilize the mediastinal mass and prevent further respiratory compromise.[45] While initiation of chemotherapy often is concordant with the primary malignancy, administering radiation prior to obtaining a biopsy may compromise accurate identification of the primary disease.[45,46]

Superior Vena Cava Syndrome and Superior Mediastinal Syndrome

Children and adolescents diagnosed with mediastinal tumors are at risk for developing SVCS and superior mediastinal syndrome (SMS) (12%), as a result of major vessel or airway compromise.[46-49] Acute lymphoblastic leukemia and non-Hodgkin lymphoma (NHL) are the most common causes of SVCS in children, whereas lung cancer is the chief cause in adults.[50] With a primary diagnosis of leukemia or lymphoma, which are curable and sensitive to chemotherapy, palliative RT for SVCS or SMS is often not the first line of treatment. Palliative RT is indicated for dyspnea secondary to a malignant process in the chest or mediastinum resulting in SVCS or SMS, usually in the setting of known recurrent or relapsed disease that is otherwise resistant to systemic chemotherapy.[12] RT is delivered in either standard fractionation or hypofractionation using a 3-dimensional conformal radiation therapy (3DCRT) technique. Because treatments are often based on adult literature, maintaining perspective and acknowledging the differences between child and adult is essential, especially when attempting to achieve disease control. Minimizing treatment times, reducing fractions, and using anesthesia are important considerations to decrease treatment-related toxicity.

Bone and Soft-tissue Metastases

Bone and soft-tissue metastases are one of the more common indications for palliative RT in pediatrics to reduce discomfort secondary to infiltrative lesions, tumor obstruction, and surrounding structures stretch.[51,52] Most pediatric radiation oncologists extrapolate from adult landmark studies such as the Dutch Bone Metastasis Study, the Bone Pain Trial Working Party Study, and most recently the American Society for Radiation Oncology (ASTRO) guidelines.[9,53-55] Although the benefits of palliative RT have been observed, a standardized fractionation scheme has not been established because of the variable tumor histologies and treatment responses.[5,44,55-58] One study reported characteristics of unsuccessfully completed palliative RT courses on clinical outcomes and patterns of care in children diagnosed with advanced cancer.[5] There was no difference in success rates of RT courses prescribed in ≤ 10 fractions (84%) compared with >10 fractions (94%), $P = 0.43$; the most unsuccessful median total dose delivered was 800 cGy. For children who are earlier in their disease trajectory, a short course of palliative RT can provide symptomatic relief without significant burden on the child or family. In the setting of widely disseminated or rapidly progressive disease, where life expectancy is unpredictable, the potential benefit of palliative RT may be quickly lost. Single fraction treatments of 800 cGy x 1 fraction to address an intractable focal symptom should still be considered in select situations. When anesthesia is required to deliver therapy, single-fraction courses are especially favorable to optimize comfort and to ensure appropriate immobilization during treatment. In terms of radiation treatment, fractionation schemes of 1-5 fractions are preferred to optimize QOL, especially in the setting of anesthesia requirements. Dose responses of ≥ 15 Gy and ≥ 20 Gy have been more effective in treating soft-tissue and bone metastases, respectively.[44,58]

Traditionally, bone and soft-tissue metastases have been treated using 3D conformal RT. More advanced technologies have been incorporated into the management of metastatic lesions, including intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS), radioisotopes, and radiofrequency ablation (RFA).[59-63] SBRT has been used for metastatic tumors in the palliative, curative settings and re-irradiation settings. A median dose of 40 Gy in 5 fractions (range: 16 to 50 Gy in 1 to 10 fractions) provided successful outcomes for disease control and relief of painful metastatic and recurrent osteosarcoma lesions.[61]

University of San Diego demonstrated lower response rates in the treatment of bone metastases based on histology.[7] Median dose for bone metastases treatment was 3 Gy with a median fraction of 10. Osteosarcoma had a lower response rate compared to other histologies (58% vs 87%, respectively; $P = .048$). As a result, larger palliative doses have been incorporated into practice of 6 Gy for 6 fractions.[56]

The most recent metastatic pediatric Ewing sarcoma protocol is finally evaluating SBRT for the definitive management of metastatic bone lesions.[64] Treatment doses range from 3000 to 4000 cGy in 5 fractions at 600 to 800 cGy per daily fraction. Selection of these various modalities will depend on patient prognosis, physician preference, availability, tumor location, prior treatments and response.

Spinal Cord Compression

Also rare are children diagnosed with malignancies who are at risk of developing symptomatic SCC, presenting toward the end of life (EOL) or at initial diagnosis.[65,66] Ewing sarcoma, primitive neuroectodermal tumors (PNET), soft-tissue sarcoma, and neuroblastoma are some of the most common causes of SCC in children and adolescents.[67] Presenting signs and symptoms include, but are not limited to, back and radicular

SA-CME (see page 6)

pain, motor and sensory deficits, sphincter dysfunction, and gait abnormalities.

Whether in an initial or recurrent setting, surgical intervention to prevent and/or restore neurologic deficits, initiation of systemic chemotherapy, and RT should be evaluated to optimize care management.[68] Even in the setting of neurologic compromise, surgery is often reserved for children and adolescents with a poor response to chemotherapy or RT.[69] Series have demonstrated that children presenting with disease that compromises motor function continue to be at risk for significant neurologic impairment, despite initial intervention.[43,70] Palliative RT in cases of relapsed or refractory disease has been used alone and as an adjunct to surgery to alleviate symptoms, and restore and maintain function.[65-67, 71-73]

Brain Metastases

The incidence of brain metastases in children and adolescence is significantly lower compared to adults, described at rates of approximately 1.5% to 2.5% in children diagnosed with solid tumors.[74-78] Tumors reported with the greatest metastatic potential include neuroblastoma, soft-tissue sarcoma, osteosarcoma, Ewing sarcoma, Wilm's tumor, germ cell tumor, retinoblastoma, and melanoma.[77,79,80] Depending on age, systemic disease burden, tumor histology, and prognosis, a standard treatment course of 30 to 36 Gy in 1.5 to 2.5 Gy fractions is appropriate. In the setting of previously irradiated tissue, SRS may be reasonable to consider to relieve symptom burden, optimize tumor control, and minimize risk of tissue toxicity.[77,81,82]

Symptoms and Distress in Pediatric Cancer

Children and adolescents are at risk of considerable distress as a result of tumor involvement, procedures, and treatment toxicities. Several pediatric series have demonstrated that symptoms and suffering at EOL are poorly controlled.[27,29,83] Self-reporting measures have described pain, fatigue, loss of appetite, psychological distress, and nausea as the most common symptoms.[84, 85, 87]

Symptom management at EOL is an ongoing treatment obstacle for many clinicians. Pain is one of the most commonly studied symptoms, but most challenging to manage.[84-87] An EOL study indicated that parents of dying children identified that 89% of the children suffered from at least one symptom, with pain, fatigue, and dyspnea as the most common; relief was only achieved in 27%.[29] Another study reported that 94% suffered from ≥ 3 symptoms, whereas 76% had ≥ 5 or more symptoms at EOL.[88] The most frequent complaint included pain (100%), nausea/vomiting (63%), constipation (57%), and anxiety (56%).[88] Incorporating age-appropriate communication, assessment tools, integrative therapies, and modifying factors into child or adolescent care can help alleviate the level of discomfort and improve responses to pain.[23,89-92]

To accurately assess pain level, intensity, and treatment response, age-appropriate assessment tools and baseline parental assessments are valuable when caring for these patients. Unlike older children and adolescents who may express emotion, pain, and treatment-related discomfort, younger counterparts may demonstrate pain through withdrawal and decreased activity.[89]

An assessment of distress, which can be complex, may require a comprehensive evaluation. Several scales assess symptoms: PQ-Memorial Symptom Assessment Scale (PQ-MSAS),[23,84,85] and Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL 4.0).[92]

Early Integration of Comprehensive Pediatric Palliative Care Team

To provide a supportive network for the evolving needs of the patient/family, early initiation of palliative care is recommended at diagnosis for children and adolescents with advanced malignancies. PPC focuses on the integration of expectations of life extension and disease-directed therapy, while honoring goals of comfort and QOL. Early integration of palliative care, advanced end-of-life conversations, and systematic symptom management have demonstrated improved outcomes and enhanced QOL.[30, 37]

The American Academy of Pediatrics (AAP) has provided guidelines recommending early consultation of PPC to ensure that distressing symptoms are prevented and treated, and complicated decisions at initial diagnosis are facilitated when the goals of care focus on cure.[34,93] Many patients receiving palliative RT are seeking disease-directed therapy or are enrolled in experimental therapy. A recent study from St. Jude reported that 79.4% of patients who received palliative care underwent experimental therapy, with 40.5% enrolled on a phase I trial.[25] One-third of the patients (35.5%) received cancer-directed therapy during their last month of life. Delayed palliative care (PC) (< 30 days before death) led to higher odds of death in the intensive care unit compared to a home/hospice setting for patients who received earlier PC intervention ($P < .0001$).

In addition to initiation of earlier PPC involvement, one study described the clinical outcomes of 50 children who completed 83 courses of RT and their relationship with the palliative and hospice services.[9] Of all treatment, 15 palliative RT courses were delivered to patients within the last 30 days of life, 7 of which were completed within the last 7 days of life. Treatment delivered within the last month of life had a lower success rate at palliation compared to courses delivered prior to 30 days, 28% vs 89%, respectively ($P < .0001$). Location of death for 7 patients who received palliative RT within the last 7 days of life were all within a hospital setting (inpatient floor or ICU) except for 1 patient for whom medical records

SA-CME (see page 6)

Table 5. Identifying Patient and Family Goals of Care

- Tell me about your child (as a person). What was he or she like before this illness?
- How has this diagnosis changed your child and the dynamics of the family?
- What is your understanding of your child's illness? What does the illness mean to you and your family?
- In light of your understanding, what is most important regarding your child's care?
- What are your hopes for your child? What are your fears regarding your child? What are your greatest concerns?
- Where do you find support and strength?

Adapted from Waldeman & Wolfe 2013[37]

were not available. Of the patients who received palliative RT, 28% already had PC involvement, whereas 60% were referred to the institutional PC team during their clinical course. Patients receiving palliative RT received supportive services: PC alone, hospice alone, both PC and hospice, or neither, at 14%, 18%, 46%, and 12%, respectively.[9] The median time to hospice referral was 96 days following the last palliative RT treatment (range: 0 to 924 days). With the support of the PPC, advanced care planning can assist with early delivery of home services and ensure that death takes place in the preferred location of the child/family.[88,94]

Communication

Effective communication facilitates appropriate patient, parent and team knowledge, trust, and a common goal.[95-98] Identifying the patient/family goals of care[99,100] prior to initiating palliative RT will assist communication and future medical decision-making processes, identify necessary supports, and optimize QOL (**Table 5**). Specific to radiation oncology, it is critical to identify the patient/family understanding of the illness, how much they would like to know, the associated risks/benefits, and treatment limitations, and respond to their emotions, physical presence during conversations, and high-quality care.[96,101-103] Specific to radiation treatment planning, it is essential to address patient needs based on age, sedation requirements, and management of uncontrolled symptoms to ensure treatment accuracy and safety. Child-life therapy, social work, and interpreter services are valuable resources to facilitate information sharing and improve their experience.[104]

Prognostication

When faced with a life-threatening illness, most parents prefer to be well-informed about their child's diagnosis, treatment-related complications, survival outcomes, and the potential impact on function and QOL.[105-110] If the children are diagnosed with advanced malignancies, parents often prefer cancer-directed therapy (eg, surgery, chemotherapy, biologic agents, RT) rather than more palliative therapies with an emphasis on comfort measures of prolonging life and/or relief of symptoms.[99,110,111] Parents' understanding and perception of their child's disease depends on the effectiveness of communication from the primary care team.[26,114-117] Explicit or clear sources of information regarding a parent's child, conversations with the oncologist at the time of diagnosis, or daily conversations with the oncologist and nurses, were informative approximately 73% to 85% of the time.[116] Implicit, or inherent sources of information, including "how parents feel their child is doing," or "how the oncologist appears to feel the child is doing," were informative. Parents who valued implicit information had lower prognostic accuracy, particularly when focusing on a "general sense of how my child's oncologist seems to feel my child is doing."[118] Parental preference, developmental stage variabilities, the family provider, and patient should be included in conversations about their disease and decision-making.[26,117,118] Children and adolescents are aware of their disease and prognosis as early as age 3 years; it is critical for clinicians to encourage open and honest conversations.[118,119]

Advanced Care Planning and EOL

Early introduction of PPC by the team facilitates discussions around advanced care planning EOL hospice conversations and enrollment, improved symptom control, introduction of do-not-resuscitate orders, and preparations during the child's last month of life.[88,120]

It is important to appreciate the perspective of the child, siblings, and parents regarding the emotional experience and medical-decision making, and address supports following the child's death to reduce complicated bereavement risk.[121-124] Children harbor a strong intuition and sensitivity to the experience of loneliness, anxiety, and imminent death.[28] Despite their young age, children ages 10 to 20 years who are diagnosed with advanced malignancies are competent to participate in medical-decision making, engage in EOL discussions, and understand the consequences and impact of their decisions on how their death may influence loved ones.[125]

Bereavement

The death of a child can be shattering and transformative, influencing the psychosocial and physical health of family and caregivers involved.[126-129] Bereaved

SA-CME (see page 6)

parents are at long-term risk of developing physical and psychosocial co-morbidities.[130-137] Mortality rates have been reported the highest among bereaved parents within the first 3 years following a child's death; however, some studies report no difference in morbidity or mortality rates between bereaved and nonbereaved parents.[138,139] Studies have confirmed increased chronic illnesses during the first 6 months following a child's death.[129,140] To assist with emotional and psychological adjustment prior to the child's death and to assure appropriate support throughout the deteriorating disease state, bereavement support should be initiated well before the dying phase.[27,141,142] As a radiation oncologist, acknowledgement of the evolving palliative and bereavement supports needed for the patient, siblings, and family is essential.[142]

Barriers to Pediatric Palliative Care

The low incidence of pediatric malignancies and death, differences in pediatric developmental stages, insufficient exposure of current medical school and residency programs to palliative education and competencies, lack of insurance provider reimbursement, and the limitations of prospective data on the incidence and management of symptoms are some of the major barriers to delivering high-quality comprehensive PC in children with advanced malignancies.[143] Despite attempts to provide effective comprehensive EOL care, various barriers remain, including unrealistic expectations from the family (47.5%), prognostic denial from the family (35.7%), familial conflict (30.3%), the patient's unrealistic expectations (10.1%), and prognostic denial from the patient (7.6%).[144] The growth and execution of dedicated PC may be curtailed due to the child/family requirements for additional emotional and psychosocial support; limited resources, scarcity of trained staff, and institutional budget constraints.[145] Clinical triggers for PC consultations may help facilitate earlier involvement.[31]

Barriers to Palliative Radiation Therapy

Several barriers have been identified resulting in the underutilization of pediatric palliative RT, predominately secondary to misconceptions or concerns for treatment-related toxicities. In a Canadian survey, formally trained palliative medicine physicians were more likely to refer children for palliative RT compared to responders without a palliative background (94 % vs 73 %, $p < .01$).[146] Numerous barriers include, but are not limited to, patient/family reluctance, potential benefit ignorance, potential treatment-related side effect misconceptions, short life expectancy, cancer center proximity, transportation limitations, concern for lack of improvement, and impact on QOL.[146]

A collaborative multi-institutional survey reported on the practice patterns of palliative RT in 365 pediatric patients in an international pediatric research consortium.[6] Treatment toxicity (83%) was the most common physician-reported barrier to initiation of RT, and treatment resources, insurance authorization/cost, anesthesia availability, and parental concerns were less of a deterrent.[6] A recent publication noted that the 2 most common indications for palliative RT were oligometastatic disease in asymptomatic patients (39%) and pain (25%).[147] A similar study reported only low-grade self-limiting acute toxicity outcomes of 45 children treated with palliative RT: Nausea (3.6%), dermatitis (6.0%), and fatigue (3.6%); no grade 3 or late toxicities were described.[7]

Education and innovative oncology curriculums emphasize increasing clinical exposure and didactic lectures to improve communication skills and develop a stronger knowledge base of palliative competencies. Greater clinical education and addressing parental and provider concerns may increase the appropriate consideration and implementation of palliative RT.[135,146,148,149]

Future Directions

Most palliative RT treatments are delivered using 3D-CRT, varying 41% to 63%.[6,7,147] Incorporating more advanced radiotherapeutic techniques including IMRT, SBRT, SRS, and proton beam therapy (PBT), can deliver highly conformal treatment to achieve the desired tumor response dose and spare normal tissue, while achieving symptomatic relief.[60,61,64] Current controversy centers on cost of these modalities if a child is not expected to live long enough to benefit from the therapy received; however, if a potential for decreased toxicity and local failure exists, a more conformal dose-escalated approach would be favorable, especially in the re-irradiation setting.[147,150,151]

Research

Future research direction is necessary to better define guidelines for palliative RT delivery for pediatric patients. Although there are standard guidelines for palliative RT in adults, it is well known that response rates vary depending on tumor histologies.[5] Similarly, pediatric tumors vary in histology and response specifically to RT, as described in several series.[6,7,9,44,152,153] Leukemia, neuroblastoma, and Ewing sarcoma are more likely to achieve a complete response with RT compared to CNS malignancies. There is a need to standardize doses by reducing the required treatment doses to maintain optimal local control and symptomatic relief, decrease treatment time and lower toxicity. A meta-analysis of the collective literature or a collaborative effort for a multi-institutional prospective study is warranted to evaluate optimal dose and fractionation schema specific to disease sites, symptomatic response, treatment-related toxicities, survival outcomes, and QOL measures to summarize the evidence and identify

SA-CME (see page 6)

a consensus of comprehensive care and treatment guidelines.

Conclusion

Prospective research is necessary to establish palliative RT guidelines for management of pediatric malignancies to honor preferences and maintain best practices. With more technologic advances, multidisciplinary team plan of care and communication will become extremely important in providing the correct medical, emotional and psychosocial decisions and supports for the patient and family unit.

References

1. American Cancer Society. Cancer Facts & Figures 2017. http://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. Accessed January 23, 2017.
2. Howlander N, Noone AM, Krapcho, M, et al, eds. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute, Bethesda, Maryland. http://seer.cancer.gov/csr/1975_2013. Based on November 2015 SEER data submission, posted to the SEER web site. April 2016.
3. Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy. *Acta Oncologica.* 2005;44(8):836-849.
4. Rosenschold M, Engelholm SA, Brodin PN, et al. A retrospective evaluation of the benefit of referring pediatric cancer patients to an external proton therapy center. *Pediatr Blood Cancer.* 2015;63(2):262-269.
5. Varma S, Friedman DL, Stavas MJ. The role of radiation therapy in palliative care of children with advanced cancer: clinical outcomes and patterns of care. *Pediatr Blood Cancer.* 2017;64:e26359.
6. Rao AD, Chen Q, Ermorian RP, et al. Practice patterns of palliative radiation therapy in pediatric oncology patients in an international pediatric research consortium. *Pediatr Blood Cancer.* 2017;64(11).
7. Rahn DA, 3rd, Mundt AJ, Murphy JD. Clinical outcomes of palliative radiation therapy for children. *Pract Radiat Oncol.* 2015;5(3):183-187.
8. Bertsch H, Rudoler S, Needle M, et al. Emergent/urgent therapeutic irradiation in pediatric oncology: patterns of presentation, treatment, and outcome. *Med Pediatr Oncol.* 1998;30:101-105.
9. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. *Pract Radiat Oncol.* 2017;7:4-12.
10. Scoccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. *Radiother Oncol.* 2012;102:168-179.
11. Sundstrom S, Bremnes R, Aasebo U, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: A national phase III Trial. *J Clin Oncol.* 2004 22(5):801-810.
12. Ingram L, Rivera GK, Shapiro DN. Superior vena cava syndrome associated with childhood malignancy: analysis of 24 cases. *Med Pediatr Oncol.* 1990;18(6):476-481.
13. Raffel C, Neave VC, Lavine S, McComb. Treatment of spinal cord compression by epidural malignancy in childhood. *Neurosurgery.* 1991;28(3):349-352.
14. Ch'ien LT, Kalwinsky DK, Peterson G, et al. Metastatic epidural tumors in children. *Med Pediatr Oncol.* 1982;10(5):455-462.
15. Pizzo PA, Horowitz ME, Poplack PG, et al. Solid tumors of childhood. In: DeVita VT, Hellmann S, Rosenberg SA eds: *Cancer: Principles & Practice of Oncology*, 4th ed. Philadelphia, PA: JB Lippincott, 1993:1738-1791.
16. Bruckman JE, Bloomer WD. Management of spinal cord compression. *Semin Oncol.* 1978;5:135-140.
17. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol.* 1978 3(1):40-51.
18. Rodriguez M, Dianpoli RP. Spinal cord compression: with special reference to metastatic epidural tumors. *Mayo Clin Proc.* 1980;55(7):442-448.
19. Klein SL, Sanford RA, Muhlbauer MS. Pediatric spinal epidural metastases. 1991; *J Neurosurg.* 74(1):70-75.
20. Lange B, D'Angio G, Ross AJ III, et al. Oncologic emergencies. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*, 2nd ed. Philadelphia, PA: J.B. Lippincott Co. 1993:951-972.
21. Lewis DW, Packer RJ, Raney B, et al. Incidence, presentation, and outcome of spinal cord disease in children with systemic cancer. *Pediatrics.* 1986;78(3):438-443.
22. Wolfe J, Klar N, Grier HE, et al. Understanding of prognosis among parents of children who died of cancer: impact on treatment goals and integration of palliative care. *JAMA.* 2000;284(19):2469-2475.
23. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and distress in children with advanced cancer: prospective patient-reported outcomes from the PediQUEST Study. *J Clin Oncol.* 2015;33(17):1928-1935.
24. Ullrich CK, Dussel V, Hilden JM, et al. End-of-Life experience of children undergoing stem cell transplantation for malignancy: parent and provider perspectives and patterns of care. *Blood.* 2010;115(19):3879-3885.
25. Kaye EC, Gushue CA, DeMarsh S, et al. Illness and end-of-life experiences of children with cancer who receive palliative care. *Pediatr Blood Cancer.* 2018;65(4). E26895. DOI: 10.1002/pbc.26895.
26. Himelstein BP, Hilden JM, Boldt AM, Weissman D. Pediatric palliative care. *N Engl J Med.* 2004;350(17):1752-1762.
27. Contro N, Larson J, Scofield S, et al. Family perspectives on the quality of pediatric palliative care. *Arch Pediatr Adolesc Med.* 2002;156(1):14-19.
28. Hechler T, Blankenburg M, Friedrichsdorf SJ et al. Parents' perspective on symptoms, quality of life, characteristics of death and end-of-life decisions for children dying from cancer. *Klin Padiatr.* 2008;220(3):166-174.
29. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *New Engl J Med.* 2000;342(5):326-333.
30. Liben S, Papadadou D, Wolfe J. Paediatric palliative care: challenges and emerging ideas. *Lancet.* 2008;371(9615):852-864.
31. Weaver MS, Rosenberg AR, Tager J, et al. A summary of pediatric palliative care team structure and services as reported by centers caring for children with cancer. *J Palliat Med.* 2017. DOI: 10.1089/jpm.2017.0405
32. Hain R, Heckford E, McCulloch R. Paediatric palliative medicine in the UK: past, present, future. *Arch Dis Child.* 2012;97(4):381-384.
33. Kang T, Hoehn KS, Licht DJ, et al. Pediatric palliative, end-of-life, and bereavement care. *Pediatr Clin N Am.* 2005;52(4):1029-1045.
34. Section on Hospice and Palliative Medicine and Committee on Hospital Care. Pediatric Palliative Care and Hospice Care Commitments, Guidelines, and Recommendations. *Pediatrics.* 2013;966-972.
35. Friebert S, Williams C. NHPCO's Facts and Figures. Pediatric Palliative & Hospice Care in America. National Hospice and Palliative Care Organization: 2015 Edition. 1-12. https://www.nhpco.org/sites/default/files/public/quality/Pediatric_Facts-Figures.pdf. Accessed May 10, 2018.
36. World Health Organization. Definition of Palliative Care. World Health Organization Web Site. http://www.who.int/cancer/palliative/definition/en. Accessed November 22, 2017.
37. Waldeman E, Wolfe J. Palliative care for children with cancer. *J Nat Rev Clin Oncol.* 2013;10:100-107.
38. Holgersen LO, Santulli TV, Schullinger JN, Berdon WE. Neuroblastoma with intraspinal (dumbbell) extension. *J Pediatr Surg.* 1983;18(4):406-411.
39. Kozlowski K, Beluffi G, Masel J, et al. Primary vertebral tumours in children: report of 20 cases with brief literature review. *Pediatr Radiol.* 1984;14(13):129-139.
40. Lyding JM, Tseng A, Newman A, Collins S, Shea W. Intramedullary spinal cord metastases in Hodgkin's disease: rapid diagnosis and treatment resulting in neurologic recovery. *Cancer.* 1987;60(8):1741-1744.
41. Obviatt DL, Kirshner HS, Stein RS. Successful chemotherapeutic treatment of epidural compression in non-Hodgkin's lymphoma. *Cancer.* 1982;49(12):2446-2448.
42. Ortega JA, Wharam M, Gehan EA, et al. Clinical features and results of therapy for children with paraspinal soft tissue sarcoma. *J Clin Oncol.* 1991;9(5):796-801.
43. Hayes FA, Thompson EI, Hvizdala E, et al. Chemotherapy as an alternative to laminectomy and radiation in the management of epidural tumor. *J Pediatr.* 1984;104(2):221-224.
44. Paulino AC. Palliative radiotherapy in children with neuroblastoma. *Pediatr Hematol Oncol.* 2003;20(2):111-117.
45. Kumari A, Gupta S, Singhal PP. Superior vena cava syndrome in children: a case report. *Middle East J Anesthesiol.* 2006;18(5):933-938.
46. Loeffler JS, Leopold KA, Recht A, et al. Emergency prebiopsy radiation for mediastinal masses: impact on subsequent pathologic diagnosis and outcome. *J Clin Oncol.* 1986;4(5):716-721.
47. King RM, Telander RL, Smithson WA, et al. Primary mediastinal tumors in children. *J Pediatr Surg.* 1982;17(5):512-520.

SA-CME (see page 6)

48. Arya LS, Narain S, Tomar S, et al. Superior vena cava syndrome. *Indian J Pediatr.* 2002; 69(4):293-297.
49. Ferrari LR, Bedford RF. General anesthesia prior to treatment of anterior mediastinal masses in pediatric cancer patients. *Anesthesiology.* 1990;72(6): 991-995.
50. D'Angio GJ, Mitus A, Evans AE. The superior mediastinal syndrome in children with cancer. *Am J Roentgenol.* 1975;93:537-544.
51. Foley KM. Pain syndromes in patients with cancer. *Med Clin N Am.* 1987;71: 169-184.
52. Foley KM. Acute and Chronic cancer pain syndromes. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*, 3rd ed. Oxford: Oxford University Press. 2004.
53. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol.* 1999;52(2):101-109.
54. The Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomized comparison with a multi-fraction schedule over 12 months of patient follow-up. *Radiother Oncol.* 1999;52(2):111-121.
55. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short vs long- course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97(11):798-804.
56. Koontz BF, Clough RW, Halperin EC. Palliative radiation therapy for metastatic Ewing sarcoma. *Cancer.* 2006;106(8):1790-1793.
57. Deutsch M, Tersak JM. Radiotherapy for symptomatic metastases to bone in children. *Am J Clin Oncol.* 2004; 27(2):128-131.
58. Caussa L, Hijal T, Michon J, Helfre S. Role of palliative radiotherapy in the management of metastatic pediatric neuroblastoma: a retrospective single- institution study. *Intl J Radiat Oncol.* 2011;79(1):214-219.
59. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol.* 2002;20(1):189-196.
60. Brown LC, Lester RA, Grams MP, et al. Stereotactic body radiotherapy for metastatic and recurrent Ewing sarcoma and osteosarcoma. 2014; Sarcoma: Article ID 418270:1-9.
61. Nanda R, Dhabbaan A, Janss A, et al. The feasibility of frameless stereotactic radiosurgery in the management of pediatric central nervous system tumors. *J Neurooncol.* 2014;117(2):329-335.
62. Botsa E, Poulou LS, Koutsogiannis I, et al. CT-guided radiofrequency tumor ablation in children. *Pediatr Radiol.* 2014;44(11):1421-1425.
63. Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* 1998;16(4):1574-1581.
64. DuBois S, Bender JG, Krailo M, et al. Children's Oncology Group AEWS1221- Randomized Phase II Evaluated the addition of IGF-1R monoclonal antibody Ganitumab (AMG 479, NSC#750008, IND#120449) to multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma.
65. Baten M, Vannucci RC. Intraspinal metastatic disease in childhood cancer. *J Pediatr.* 1977;90(2):207-212.
66. Punt J, Pritchard J, Pincott JR, Till K. Neuroblastoma: a review of 21 cases presenting with spinal cord compression. *Cancer.* 1980;45(12):3095-3101.
67. Pollono D, Tomarchia S, Drut R, et al. Spinal cord compression: a review of 70 pediatric patients. *Pediatr Hematol Oncol.* 2003;20(6):457-466.
68. Tachdjian MO, Matson DD. Orthopaedic aspects of intraspinal tumors in infants and children. *J Bone Joint Surg Am.* 1965;47:223-248.
69. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low dose involved field radiation after chemotherapy in advanced Hodgkin's disease: a Southwest Oncology Group randomized study. *Ann Intern Med.* 1994;120(11):903-912.
70. Simon T, Niemann CA, Hero B, et al. Short- and long-term outcome of patients with symptoms of spinal cord compression by neuroblastoma. *Dev Med Child Neurol.* 2012;54(4):347-352.
71. Bernardi BD, Pianca C, Pistamiglio P, et al. Neuroblastoma with symptomatic spinal cord compression at diagnosis: treatment and results with 76 cases. *J Clin Oncol.* 2001;19(1):183-190.
72. Shyn PB, Campbell GA, Guinto FC, Crofford MJ. Primary intracranial ependymoblastoma presenting as spinal cord compression due to metastasis. *Childs Nerv Syst.* 1986;2(6):323-325.
73. Gupta V, Srivastava A, Bhatia B. Hodgkin's disease with spinal cord compression. *J Pediatr Hematol Oncol.* 2009 31(10):771-773.
74. Allen JC. Brain metastases. In: Deutsch M, ed. *Management of Childhood Brain Tumors.* Boston, MA: Kluwer Academic Publishers. 1990;457-464.
75. Deutsch M, Albo V, Wollman MR. Radiotherapy for cerebral metastases in children. *Int J Radiat Oncol Biol Phys.* 1982;8(8):1441-1446.
76. Deutsch M, Orlando S, Wolmann M. Radiotherapy for metastases to the brain in children. *Med Pediatr Oncol.* 2002;39(1):60-62.
77. Suki D, Khoury Abdulla R, et al. Brain metastases in patients diagnosed with a solid primary cancer during childhood experience from a singlereferralcancercenter.*JNeurosurgPediatr.*2014;14(4): 372-385.
78. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol.* 2015;17Suppl4:iv1-iv62.
79. Graus F, Walker RW, Allen JC. Brain metastases in children. *J Pediatr.* 1983;103(4):558-561.
80. MacRae T, Grimard L, Hsu E, et al. Brain metastases in Wilms' tumor: case report and literature review. *J Pediatr Hematol Oncol.* 2002;24(2): 149-153.
81. King D, Connolly D, Zaki H, et al. Successful treatment of metastatic relapse of medulloblastoma in childhood with single session stereotactic radiosurgery: a report of 3 cases. *J Pediatr Hematol Oncol.* 2014;36(4):301-304.
82. Keshavarzi S, Meltzer H, Ben-Haim S et al. Initial clinical experience with frameless optically guided stereotactic radiosurgery/radiotherapy in pediatric patients. *Childs Nerv Syst.* 2009; 2(7):837-844.
83. Wolfe J, Friebert S, Hilden J. Caring for children with advanced cancer integrating palliative care. *J Pediatr Clin N Am.* 2002;49(5):1043-1062.
84. Collins JJ, Byrnes ME, Dunkel IJ, et al. The measurement of symptoms in children with cancer. *J Pain Sympt Manage.* 2000;19(5):363-377.
85. Collins JJ, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7-12. *J Pain Sympt Manage.* 2002;23(1):10-16.
86. Hedén L, Pöder U, von Essen L, Ljungman G. Parents' perceptions of their child's symptom burden during and after cancer treatment. *J Pain Sympt Manage.* 2013;46(3) 366-375.
87. Pöder U, Ljungman G, von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective longitudinal study. *J Pain Sympt Manage. 2010*; 40(5):661-670.
88. Vern-Gross TZ, Lam CG, Graff Z, et al. Patterns of end-of-life care in children with advanced solid tumor malignancies enrolled on a palliative care service. *J Pain and Sympt Manage.* 2015;50(3): 305-312.
89. Cohen LL, Lemanek K, Blount RL, et al. Evidence-based assessment of pediatric pain. *J Ped Psych.* 2008;33(9)939-955.
90. Stinson JN, Jibb LA, Nguyen C, et al. Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. *J Med Internet Res.* 2013;15(3):e51.
91. Friedrichsdorf SJ. Pain management in children with advanced cancer and during end-of-life care. *Pediatr Hematol Oncol.* 2010;27:257-261.
92. Varni JW, Burwinkle TM, Katz ER, et al. The Peds QL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *J Clin Oncol.* 2002;33(17):1928-1935.
93. American Academy of Pediatrics. Committee on Bioethics and Committee on Hospital Care. Palliative care for children. *Pediatrics.* 2000;106;351-357.
94. Dussel V, Kericbergs U, Hilden JM, et al. Looking beyond where children die: Determinants and effects of planning a child's location of death. *J Pain Sympt Manage.* 2009;37(1):33-43.
95. Pantilat SZ. Communicating with seriously ill patients. Better words to say. *JAMA.* 2009;301(12): 1279-1281.
96. Garwick AW Patterson J, Bennett FC, Blum RW. Breaking the news. How families first learn about their child's chronic condition. *Arch Pediatr Adolesc Med.* 2012;149(9):991-997.
97. Thomas, KW. Conflict and Conflict Management. Reflections and Update. J Organizat Behav, Vol. 13, No. 3, Special Issue: Conflict and Negotiation in Organizations: Historical and Contemporary Perspectives (May, 1992), pp. 265-274.
98. Thomas, KW. Conflict and Conflict Management. In: Dunnette MD, ed. *Handbook of Industrial and Organizational Psychology.* Chicago, IL: Rand McNally; 1976.
99. Hinds PS, Oakes L, Furman W, et al. Decision making by parents and healthcare professionals when considering continued care for pediatric patients with cancer. *Oncol Nurs Forum.* 1997;24(9):1523-1528.
100. Kane J, Hilden J. Tools to aid decision-making in the care of pediatric patients with cancer. *Am Soc Clin Oncol Ed Book.* 2007;188-192.
101. Masera G Chesler MA, Jankovic M, et al. SIOP Working Committee on psychosocial issues in pediatric oncology: guidelines for communication of the diagnosis. *Med Pediatr Oncol.* 1997;28(5):382-385.

SA-CME (see page 6)

102. Makoul G, Winter RJ. MSJAMA Communication skills education in medical school and beyond. *JAMA.* 2003;289(1):93.
103. Baile WF, Buckman R, Lenzi R, et al. SPIKES-A six step protocol for delivering bad news: application to the patient with cancer. *Oncologist.* 2000; 5(4):302-311.
104. Scott MT, Todd KE, Oakley H. Reducing anesthesia and health care cost through utilization of child life specialists in pediatric radiation oncology. *Intl J Radiat Oncol Biol Phys.* 2016;96(1):401-405.
105. Boman K, Lindahl A, Björk O. Disease-related distress in parents of children with cancer at various stages after the time of diagnosis. *Acta Oncol.* 2003;42(2):137-146.
106. Mack JW, Wolfe J, Grier HE, et al. Communication about prognosis between parents and physicians of children with cancer: parent preferences and the impact of prognostic information. *J Clin Oncol.* 2006;24(33):5265-5270.
107. Trask CL, Welch JJ, Manley P, et al. Parental needs for information related to neurocognitive late effects from pediatric cancer and its treatment. *Pediatr Blood Cancer.* 2009; 52(2):273-279.
108. Ringnér A, Jansson L, Graneheim UH. Parental experiences of information within pediatric oncology. *J Pediatr Oncol Nurs.* 2011;28(4):244-251.
109. Kilicarslan-Toruner E, Akgun-Citak E. Information-seeking behavior and decision-making process of parents of children with cancer. *Eur J Oncol Nurs.* 2013;17(2):176-183.
110. Mack JW, Joffe S, Hilden JM, et al. Parents' view of cancer-directed therapy for children with no realistic chance for cure. *J Clin Oncol.* 2008;26(29):4759-4764.
111. Slevin ML, Stubbs L, Plant HJ, et al. Comparing view of patients with cancer with those of doctors, nurses and general public. *BMJ.* 1990;300(6737):1458-1460.
112. Mulhern RK, Crisco JJ, Camitta BM. Patterns of communication among pediatric patients with leukemia, parents, and physicians: prognostic disagreements and misunderstandings. *J Pediatr.* 1981;99(3):480-483.
113. Mack JW, Cook EF, Wolfe J, et al. Understanding of prognosis among parents of children with cancer: parental optimism and the parent-physician interaction. *J Clin Oncol.* 2007;28(11):1357-1362.
114. Lamont EB, Christakis MA. Complexities in prognostication in advanced cancer "To help them live their lives the way they want to." *JAMA.* 2003;290(1):98-104.
115. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA.* 1998;279(21):1709-1714.
116. Sisk BA, Kang TI, Mack JW. How parents of children with cancer learn about their children's prognosis. *Pediatrics.* 2018;141(1):e20172241.
117. Young B, et al. Parents' experiences of their children's presence in discussions with physicians about leukemia. *Pediatrics.* 2011;127.e1230e1238.
118. Wiener L, Zadeh S, Wexler LH, Pao M. When silence is not golden: engaging adolescents and young adults in discussions around end-of-life care choices. *Pediatr Blood Cancer.* 2013;60:715-718.
119. Bluebond-Langner M. *The Private Worlds of Dying Children.* Princeton, NJ: Princeton University Press; 1978.
120. Wolfe J, Hammel JF, Edwards KE, et al. Easing of suffering in children with cancer at the end-of-life: Is care changing? *J Clin Oncol.* 2008;26(10): 1717-1723.
121. Gaab EM, Owens GR, MacLeod RD. Siblings caring for and about pediatric palliative care patients. *J Palliat Med.* 2014;17(1):62-67.
122. Kreicbergs UC, Lannen P, Onelov E, Wolfe J. Parental grief after losing a child to cancer: impact of professional and social support on long-term outcomes. *J Clin Oncol.* 2007;25(22):3307-3312.
123. Kreicbergs U, Valdimarsdóttir U, Onelov E, et al. Care-related distress. a nationwide study of patents who lost their child to cancer. *J Clin Oncol.* 2005;23(36):9162-9171.
124. Houlahan KE, Branowicki PA, Mack JW, et al. Can end of life care for the pediatric patient suffering with escalating and intractable symptoms be improved? *J Pediatr Oncol Nurs.* 2006;23(1): 45-51.
125. Hinds PS, Drew D, Fouladi M, et al. End-of-life care preferences of pediatric patients with cancer. *J Clin Oncol.* 2005;23(36):9146-9154.
126. Martinson IM. Improving care of dying children. *West J Med.* 1995;163:258-262.
127. Brown PG. Families who have a child diagnosed with cancer: what the medical caregiver can do to help them and them and themselves. *Issues in Compr Pediatr Nurs.* 1989;12(2-3):247-260.
128. Sloper P, While D. Risk factors in the adjustment of siblings of children with cancer. *J Child Psychol Psychiatr.* 1996;37(5):597-607.
129. Dias N, Brandon D, Haase JE, Tanabe P. Bereaved parents' health status during the first 6 months after their child's death. *Am J Hosp Palliat Care.* 2017. PMID: 29202599.
130. Rosenberg AR, Baker KS, Syrjala K, Wolfe J. Systemic review of psychosocial morbidities among bereaved parents of children with cancer. *Pediatr Blood Cancer.* 2012;58(4):503-512.
131. Hendrickson KC. Morbidity, mortality, parental grief: a review of the literature on the relationship between the death of a child and the subsequent health of the parents. *Palliat Support Care.* 2009;7(1):109-119.
132. Dyregrov A, Dyregrov K. Long-term impact of sudden infant death: a 12- to 15 year follow-up. *Death Stud.* 1999;23:635-661.
133. Saunders CM. A comparison of adult bereavement in the death of a spouse, child, and parent. *Omega.* 1979-1980;10:302-322.
134. Stroebe M, Schut H, Stroebe W. Health outcomes of bereavement. *Lancet.* 2007;370(9603): 1960-1973.
135. Kreicbergs U, Valdimarsdottir U, Onelov UVE, et al. Anxiety and depression in parents 4-9 years after the loss of a child owing to a malignancy: a population-based follow-up. *Psychol Med.* 2004; 34(8);1431-1441.
136. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. *Circulation.* 2002;106 (13):1634-1639.
137. Li J, Johansen C, Hansen D, Olsen J. Cancer incidence in parents who lost a child: a nationwide study in Denmark. *Cancer.* 2002;95(1):2237-2242.
138. Levav I, Friedlander Y, Kark JD, Peritz E. An epidemiolic study of mortality among bereaved parents. *N Engl J Med.* 1988;319;(8):457-461.
139. Harper M, O'Connor RC, O'Carroll RE. Increased mortality in parents bereaved in the first year of their child's life. *BMJ Support Palliat Care.* 2011;1(3):306-309.
140. Gilmer MJ, Foster TL, Vannatta K et al. Changes in parents after the death of a child from cancer. *J Pain Sympt. Manage.* 2012;44(4):572-582.
141. Rando TA. Bereaved parents: particular difficulties, unique factors, and treatment issues. *Soc Work.* 1985;30(1):19-23.
142. deCinque N, Monterosso L, Dadd G, et al. Bereavement support for families following the death of a child from cancer: experience of bereaved parents. *J Psychosoc Oncol.* 2006;24(2):65-83.
143. Institute of Medicine, National Research Council, National Cancer Policy Board. Foley KM, Gelband H, eds. *Improving Palliative Care for Cancer: Summary and Recommendations.* Washington, DC: National Academies Press; 2001.
144. Hilden JM, Emanuel EJ, Fairclough DL, et al. Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey. *J Clin Oncol.* 2001;19(1):205-212.
145. Hui D, Elsayem A, De La Cruz M, et al. Availability and integration of palliative care at US cancer centers. *JAMA.* 2010;303:1054-1061.
146. Tucker TL, Samant RS, Fitzgibbon EJ. Knowledge and utilization of palliative radiotherapy by pediatric oncologists. *Curr Oncol.* 2010;17(1):48-55.
147. Mak KS, Lee SW, Balboni TA, Marcus KJ. Clinical outcomes and toxicity following palliative radiotherapy for childhood cancers. *Pediatr Blood Cancer.* 2018;65(1).
148. Back AL, Arnold RM, Baile WF, et al. Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. *Arch Intern Med.* 2007;167(5):453-460.
149. Sulmasy DP, Cimino JE, HE MK, Frishman WH. U.S. medical students' perceptions of the adequacy of their schools' curricular attention to care at the end of life: 1998-2006. *J Palliat Med.* 2008;11:707-716.
150. Bakst RL, Dunkel IJ, Gilheeney S, et al. Reirradiation for recurrent medulloblastoma. *Cancer.* 2011;117(21):4977-4982.
151. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2013;56(2):277-284.
152. Halperin EC, Cox EB. Radiation therapy in the management of neuroblastoma: the Duke University Medical Center experience 1967-1984. *Int J Radiat Oncol Biol Phys.* 1986;12(10):1829-1837.
153. Chamberlain MC. Pediatric leptomeningeal metastases: Outcome following combined therapy. *J Child Neurol.* 1997;12 (1):53-59.
154. Vern-Gross TZ. Pediatric palliative radiation oncology. In: Lutz S, Chow E, Hoskin P, eds. *Radiation Oncology in Palliative Cancer Care.* Chichester, UK: John Wiley & Sons, Ltd.; 2013;220-234.

SA-CME (see page 6)

Indications, barriers and paths to advancement in palliative radiation oncology

Muhammed M. Fareed, MD; Monica Krishnan, MD; Tracy A. Balboni, MD, MPH; Hsiang-Hsuan Michael Yu, MD

Radiation therapy (RT) has been used successfully for cancer symptom palliation for more than a century in a time-efficient and cost-effective manner for palliative care delivery, even when clinicians had an incomplete understanding of its mechanism of action. Shortly after the 1895 discovery of the x-ray by Wilhelm Roentgen, radiation's paramount use became treating cancer-related symptoms.[1] Palliative radiation dose depends on overall patient condition including prognosis, performance status, prior treatment, comorbid conditions, risk of acute toxicity, and concurrent systemic therapy, and is delivered taking into account patient wishes.[2] Palliative treatment courses of 8 to 30 Gy × 1 to 10 fractions are commonly used for a wide range of scenarios, although other fractionation schemes also exist. Careful selection of dose, time and fractionation is important in palliative patients with limited life expectancies. High-dose-per-fraction or hypofractionated treatments may correlate with a higher late toxicity risk; however, per linear quadratic modeling, a single 8-Gy treatment has a lower risk of late effects than 30 to 40 Gy × 10 to 20 fractions. Similarly, higher acute toxicity is associated with a course of 30 Gy × 10 fractions compared with a single 8 Gy fraction.[3]

The benefits of palliative radiation are not limited by tumor histology or anatomic site of treatment. Tumor symptoms and signs may be relieved by RT to the central nervous system, respiratory system, gastro-intestinal tract, genitourinary system, skeleton, and skin, among other areas. Although cells of malignant melanoma and renal cell carcinoma are known to repair radiation-induced damage more efficiently than other tumors, they still respond to palliative RT.[1] **Table 1** summarizes common indications for palliative radiation treatment.

Estimating prognosis has remained difficult for clinicians caring for patients receiving palliative RT compared with colleagues in other oncology disciplines.[4] However, considerable effort has been made over the past 10 years to develop models to predict patient life expectancy. Chow and colleagues developed and validated a predictive model that determines prognosis using 3 risk factors among patients referred for palliative RT.[5] They collected potential clinical prognostic factors for 395 patients, including symptoms from the Edmonton Symptom Assessment Scale, and showed that nonbreast primary, metastases to nonbony sites, and Karnofsky performance status ≤ 60 divided patients into 3 groups (0 to 1, 2, or 3 risk factors) with remarkably different survival times. The data were further

Dr. Fareed *is a fellow in the Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA.* ***Dr. Krishnan*** *is an assistant professor of radiation oncology, and* ***Dr. Balboni*** *is an associate professor of radiation oncology, Harvard Medical School, Boston, MA.* ***Dr. Yu*** *is associate member, Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, and associate professor, Department of Oncological Sciences, University of South Florida, Tampa.*
Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

SA-CME (see page 6)

Table 1: Palliative Radiation Therapy Indications

Symptoms of Primary or Metastatic Tumor	Signs of Progressive Tumor
Pain from: • Progressive growth of primary tumor (any site) • Bone metastases • Visceral metastases • Splenomegaly (hematologic malignancies) • Recurrent tumor at primary disease site	**Status post-instrumentation for palliation of cancer:** • Orthopedic stabilization of pathologic fracture or impending pathologic fracture • Stent placement to maintain patency of airway, biliary tree, esophagus, etc. • Decompression of brain metastasis or spinal cord compression • Kyphoplasty or vertebroplasty
Neurologic symptoms from: • Brain metastases including leptomeningeal carcinomatosis • Nerve root or spinal cord compression • Brachial or lumbosacral plexopathy from tumor involvement	**Asymptomatic areas of metastatic disease or progressive primary tumors:** • Oligometastatic disease treated with stereotactic radiation therapy • Areas likely to have symptomatic progression including impending pathologic fracture, asymptomatic brain metastases, etc.
Bleeding from: • Head and neck cancers • Skin cancers • Upper and lower gastrointestinal cancers • Hematuria from genitourinary cancers • Gynecologic cancers • Hemoptysis from lung malignancy	**Bleeding from:** • Laser treatment of intracavitary disease (bronchus, biliary tree)
Obstructive symptoms from: • Cough and dyspnea related to airway obstruction • Dysphagia or odynophagia from esophageal obstruction • Gastric outlet obstruction • Biliary obstruction • Pelvic obstruction • Rectal obstruction • Superior vena cava syndrome • Urinary outlet obstruction	

validated among an additional 445 patients from the same institution and 468 patients at a separate institution. Median survivals are 31 weeks, 13 weeks and 6 weeks for patients with 0 to 1 risk factors, 2 risk factors and 3 risk factors, respectively.[6] Other prognostic models have also shown utility among patients receiving palliative RT, including the TEACHH model[7] and models among patients receiving palliative RT for specific clinical scenarios, such as brain metastases[8] and cord compression.[9,10]

Herein we discuss the most common palliative radiation oncology scenarios encountered by radiation oncologists in their routine practice: bone metastases; brain metastases; malignant spinal cord and cauda compression; and tumor-related bleeding, fungation, obstruction and visceral metastases. Next, barriers to the advancement of palliative radiation oncology, including hurdles in clinical care and research opportunities, will be considered together with strategies to overcome these barriers to benefit advanced cancer patients and their families.

Bone Metastases

External-beam RT offers the most efficient and well-tolerated therapy for painful bony metastases when combined with suitable measures such as surgical fixation, bone-strengthening agents, radiopharmaceuticals and pain medication regimens[11] with complete pain relief of 30% to 50% and partial pain relief of 60% to 80% at 3 to 4 weeks after starting palliative radiation treatment.[12] Different treatment schedules for managing uncomplicated bone metastases (ie, no reirradiation, pathological fracture or cord/cauda compression) including 30 Gy × 10 fractions; 24 Gy × 6 fractions; 20 Gy × 5 fractions; and a single, 8 Gy fraction have shown equivalent pain relief in several prospective randomized trials.[11] On average, re-treatment rates are 8% among patients receiving multifraction regimens and 20% among patients receiving a single fraction, with single-fraction treatment not showing any detrimental effect even when assessed for late spinal cord tolerance.[13] Also, pain control was not inferior after a single 8 Gy fraction compared with protracted courses in a group of patients who survived beyond a year.[14] Clinical judgment and shared decision-making with patients are recommended to determine which fractionation regimen is

SA-CME (see page 6)

appropriate. A single 8 Gy fraction is a reasonable option for patients with limited life expectancy or any patients with uncomplicated painful bone metastasis. It is not certain whether hypofractionated regimens lead to better local control or prevention of fracture compared with a single 8 Gy fraction.

Excellent palliation for painful bone metastases along with safe and effective re-treatment have been confirmed by updated analyses.[15] Expert and thorough judgment and discretion by radiation oncologists are crucial when deciding on fractionation and advanced techniques such as stereotactic body radiation therapy (SBRT) along with specific consideration for life expectancy; comorbid conditions; tumor biology; anatomy; previous radiation at or near the current site of treatment; tumor and normal tissue response to local and systemic therapies; and other factors relevant to the patient, tumor or treatment characteristics.[15] The rapid access palliative RT programs throughout Canada have helped improve patient access to RT and in-depth study of bone metastases management.[16,17] Such integrated services are becoming common, enhancing patient, family and team satisfaction and helping with prognostication, collaboration and combined decision-making.[18]

Brain Metastases

Brain metastases are common with multiple tumor types and are a significant cause of cancer morbidity and mortality. Treatment options are based on global patient factors, such as prognosis, and metastatic site-specific factors, such as site-related symptoms and number/burden of metastatic disease.[19] For example, the use of the diagnosis-specific graded prognostic index (DS-GPA) to predict life expectancy can help tailor management of brain metastases based on performance status, age, number of brain metastases, extra-cranial metastases and cancer type.[8] Thoughtful palliative care is important, as survival ranges from 2.8 to 25.3 months depending on prognostic factors. Without clear evidence of uniform preference for using local modality combinations (surgery and radiosurgery) vs whole-brain radiation therapy, it is important to consider the ideal combination for a given patient. Of note, the addition of whole-brain radiation to surgery or radiosurgery does not confer a survival advantage and can diminish quality of life and cognitive function.[20] When deciding between 30 Gy × 10 fractions and 20 Gy × 5 fractions, the shorter course seems more logical in patients with short life expectancy for optimal convenience, given that no differences in overall survival or symptom control have been shown between the regimens. In some patients, particularly those with poorer prognosis, supportive care only, with dexamethasone and pain medication, is reasonable.[3]

In the past 1 to 2 decades, stereotactic radiosurgery (SRS) has transformed brain metastases management. Randomized controlled trials have demonstrated high local control benefits after SRS for brain oligometastatic disease, and a prospective study has shown that this may be considered for up to 10 brain metastases. Its minimally invasive nature makes it a reasonable alternative to surgical resection. Furthermore, novel targeted therapies and immunotherapies with favorable side-effect profiles allow for concurrent systemic therapy delivery with radiosurgery. Possible synergistic effects have been demonstrated, thus expediting treatment of intracranial and extracranial disease.[21]

Malignant Spinal Cord and Cauda Equina Compression

Malignant spinal cord and cauda equina compression is an oncologic emergency typically resulting from extraosseous extension of tumor from bones of the spine into neural structures, although the clinical scenario also can manifest due to epidural, intradural or even intramedullary metastatic disease. Pain usually predates neurological deficits by days to months, and resultant dysfunction can include motor weakness, sensory deficits and loss of bowel and bladder function. Neurological functional losses require prompt recognition and timely intervention to prevent long-term functional deficits.[12]

Starting corticosteroids to diminish edema is the first step in managing spinal cord/cauda compression. The next step is deciding between surgical decompression followed by RT or radiation alone. In a randomized trial, Patchell et al[22] demonstrated that surgical decompression followed by RT (3 Gy × 10) leads to improved ambulation when compared with radiation (3 Gy × 10) alone for patients with a single site of metastatic epidural spinal cord compression (SCC) from different tumors and a good performance status. Patients undergoing surgical decompression were more likely to maintain ambulatory status, although that benefit decreased with age.[23] Patients treated with RT alone generally respond to multifraction regimens such as 3 Gy × 10 fractions, although recent literature suggests that patients with short life expectancy do well with a single 8 Gy dose.[3] Rades and colleagues prospectively followed a large cohort of patients treated with different dose-fractionation schemes (8 Gy × 1 or 4 Gy × 5 for short course or 3 Gy × 10, 2.5 Gy × 15 or 2 Gy × 20 for long course). The authors found that longer dose-fractionation schemes led to higher rates of local tumor control. This suggests that a higher biological equivalent dose is more likely to control spine tumors causing cord compression than a lower biological equivalent dose for patients with longer life expectancy.[10] However, no differences in motor function change or overall survival between the groups were seen, suggesting that short-

SA-CME (see page 6)

Table 2: Dose-fractionation Schedules and Response Rates for Common Palliative Radiation Scenarios[25]*

Indications	Dose	Response Rate
Uncomplicated bone metastases; equal efficacy per ASTRO guidelines;[11] longer dose fractionation scheme may have increased bone remineralization	8 Gy x 1 4 Gy x 5-6 3 Gy x 10	60%-90%
Whole-brain radiotherapy; 4 Gy x 5 generally reserved for patients with poor prognosis; may be used in conjunction with surgery and/or stereotactic radiation therapy[19]	4 Gy x 5 3 Gy x 10 2.5 Gy x 15	60%-90%
Advanced cancer in the lung causing airway obstruction, superior vena cava syndrome; longer dose-fractionation schemes may lead to longer survival[45]	7.5-8.5 Gy x 2 3 Gy x 10 2.5 Gy x 15	30%-90%
Incurable stage III non-small lung cancer patients who are candidates for chemotherapy, ECOG 0-2, life expectancy > 3 months[46]	Platinum-based doublet chemotherapy with current hypofractionated thoracic XRT of 3 Gy x 10 or 2.8 Gy x 15	1 year overall survival 50-60%
Visceral metastases causing pain, obstructive symptoms, bleeding, fungating wounds; longer dose-fractionation schemes should be reserved for patients with prognosis > 3 months	8-10 Gy x 1 3.7 Gy x 2 BID (can repeat x 2) 4 Gy x 5 3 Gy x 10 2-3 Gy x 15-30	30%-90%
SBRT, requiring advanced technologies, advanced immobilization; generally reserved for patients with good performance status (KPS > 70) with expected long prognosis and/or with few metastases; also used in the setting of reirradiation	Single fraction up to 24 Gy 10-12 Gy x 4-5	70%-90%

*Table adapted from: Sharma S, Hertan L, Jones J. Palliative radiation therapy: current status and future directions. *Semin Oncol.* 2014;41(6): 751-763. Key: ASTRO = American Society for Radiation Oncology, GY = gray, ECOG = Eastern Cooperative Oncology Group, XRT = radiation therapy, BID = twice daily radiation therapy, SBRT = stereotactic body radiation therapy, KPS = Karnofsky Performance Scale

course radiation may be appropriate for patients with a life expectancy of < 3 months. In the same population, Rades et al also developed and validated a score to predict survival after development of spinal cord compression. The score is based on histology, presence of other bone metastases, presence of visceral metastases, time from initial diagnosis of cancer to development of SCC, ambulatory status at the time of SCC, and time to develop motor deficits from the onset of SCC. The score predicts 6-month survival percentages of 16% for poor prognosis, 48% for intermediate prognosis and 81% for better prognosis patients, demonstrating the possibility of tailoring RT to anticipated survival.[9] Feasibility of spine radiosurgery for the treatment of SCC has been demonstrated by Ryu and colleagues;[24] however, additional studies are needed to determine SRS safety in this setting given the high RT dose and proximity to the spinal cord.

Tumor-related Bleeding, Fungation, Obstructive Symptoms and Visceral Metastases

Fundamental principles of RT apply for primary tumors or metastases causing symptoms in areas beyond bone and the central nervous system (CNS), and causing pain, bleeding, open wounds, or other local symptoms specific to the affected region (eg, dysphagia in the head and neck and esophagus, cough and dyspnea in the lung, etc.). Optimal dose-fractionation schemes have not been established and usually depend on the specific clinical scenario, patient's performance status and life expectancy. Short RT courses (including single-fraction) are more appropriate for patients with poor performance status and poor prognosis. For patients with intermediate prognosis, schedules such as 30 Gy × 10 fractions or more dose-intense hypofractionated regimens, such as the "quad shot RT" (4 fractions delivered twice a day

SA-CME (see page 6)

over 2 days and repeated weekly up to 2 additional times depending on performance status and response), may be suitable.[25] In patients with good performance status with no significant burden of metastatic disease and projected long survival, protracted courses of RT (eg, 40 to 60 Gy × 15 to 30 fractions) may be more appropriate. Furthermore, SBRT is increasingly being used in patients with oligometastatic disease for local control if the lesions can be treated keeping to normal tissue constraints.[25]

Table 2 summarizes dose fractionation schedules for common palliative RT cases along with estimated response rates.

Barriers and Opportunities in Advancing Palliative Radiation Oncology Practice

Several factors limit advancement in palliative RT clinical care and research. There is hesitancy in adopting evidence-based practice despite several large palliative trials by the Radiation Therapy Oncology Group (RTOG).[26,27] Generally, palliative care outcome measures are hard to define and difficult to measure. Patient-reported, validated measures are usually the most useful outcome variables, although many commonly used instruments have not been fully validated in trials. Furthermore, many palliative radiation trials suffer from missing data points as patients are not always able to fulfill follow-up appointments due to declining function or mortality.[28]

In addition, few resources are being spent on palliative radiation research compared to the number of palliative oncology patients in the United States each year as well as their symptom severity. This is reflected in part by the proportion of abstracts related to palliative care and symptom control submitted to the American Society for Radiation Oncology (ASTRO) from 1993 to 2000, which accounted for about 1.3% of overall submissions.[29] A more recent update on trends in the number of original scientific reports directly addressing palliative care outcomes in the Red and Green journals – two of the most prestigious and influential radiation oncology journals – showed minimal change in original research publications since the early 2000s.[30]

Resident Education

Approximately 30% to 40% of RT courses delivered are palliative in intent, and radiation oncologists are involved throughout the trajectory of advanced patient care from diagnosis to end of life in providing supportive and palliative care (SPC). As discussed, palliative RT is an important tool for maximizing patient quality of life in the face of incurable cancers. Hence, radiation oncologists are key members of an interdisciplinary oncology palliative care team.[32] However, despite the extent of palliative care provision within radiation oncology, radiation oncologists frequently report not having adequate competencies in palliative care.[33]

Several efforts have been made to further define and assess educational needs within SPC competencies in radiation oncology. As part of the overall competency assessment of radiation oncology resident trainees, the Accreditation Council of Graduate Medical Education (ACGME) and the American Board of Radiology (ABR) published radiation oncology competency assessment milestones that included palliative oncology care as 1 of 22 competency areas. The SPC milestone includes accurate pain and nonpain symptom assessment, independent management of toxicities and symptoms associated with RT, and developing appropriate and effective palliative care management strategies.[34,35] To define current SPC educational structures within residency programs, a survey-based study assessed program directors' perspectives of palliative care education in radiation oncology residency. This study revealed that although most of them considered SPC (93%) and palliative RT (99%) as important competencies for radiation oncology residents and fellows, only 67% of residency programs had formal educational activities in palliative and supportive care principles and practice. A formal curriculum on palliative RT applications was reported in 85% of programs and mostly focused on education regarding palliative RT to the brain, bone and spine, but less commonly for visceral or skin metastasis. The majority of programs had formal didactics of 1 or more hours on pain management (67%), neuropathic pain (65%) and nausea and vomiting management (63%), whereas initial management of fatigue (35%), spirituality assessment (33%) and advance care directives discussion (30%) were less frequently addressed.[36]

A national survey of radiation oncology residents by Krishnan and colleagues addressed residents' perspectives of their SPC education sufficiency across 8 generalist palliative care competency domains derived from national guidelines.[37] These are: symptom management (pain, nonpain), communication about goals of care, advance care planning, psychosocial issues, cultural considerations, spiritual needs, care coordination, and ethical/legal issues. The survey assessed, within these domains, residents' perceptions of: 1) the adequacy of their education, 2) competency in each domain, and 3) overall importance of palliative care competencies within radiation oncology. On average across the 8 domains, 79% of residents rated their training as "not at all," "minimally," or "somewhat" adequate. The SPC domains in which residents rated themselves as "not at all," "minimally," or "somewhat" confident were symptom management (36% pain, 44% nonpain), communication about goals of care (31%), advance care planning (48%), psychosocial issues (55%), cultural

SA-CME (see page 6)

CASE SYNOPSIS

Mr. H is a 97-year-old man with a history of multiple comorbid conditions and diffuse large B cell lymphoma (DLBCL), status post R-CHOP x 3 and involved-field radiation therapy (IFRT) (R axilla) in 2015. He transferred his care to our hospital after being admitted at an outside hospital with severe back pain without adequate control despite narcotics. Imaging evaluation showed a paraspinal mass invading the T8-10 without a compression fracture. Biopsy of this mass revealed DLBCL but was complicated by acute lower extremity weakness. Spine magnetic resonance imaging (MRI) revealed a hematoma at the epidural space at the biopsy site, without cord compression. Computed tomography (CT) of the chest, abdomen and pelvis demonstrated extensive mediastinal and retroperitoneal adenopathy. Radiation oncology was consulted for urgent palliative radiation to the lower thoracic spine. Upon assessment, the elderly patient appeared to be in very poor health and had not been ambulated due to progressive generalized weakness. His performance status was significantly declining in the last 6 months.

RECOMMENDATION:

Medical intervention with narcotic and nonsteroidal anti-inflammatory medications.

Consider a single fraction of 8 Gy to the painful paraspinal mass.

The patient refused radiation treatment, but the son, the health care proxy, wanted to pursue every possible intervention, including RT.

RECOMMENDATION:

Review cancer treatment options. Multidisciplinary discussion and communication with patient and family about prognosis and goals of care.

Communication with family members to understand medical and psychosocial concerns.

Multiple daily discussions with the inpatient team and son took place to discuss the goals of care and expected objectives to palliate symptoms. Consensus was reached with the patient proceeding to inpatient hospice care. The patient received a single 8 Gy fraction of palliative RT to the midthoracic spine.

CASE QUESTIONS

What is the frequency of complex palliative care issues, such as psychosocial, ethical and goals of care issues, relevant to our care of patients?

Parker et al[31] conducted a survey-based study of radiation oncology clinicians seeing 163 consecutive patients for urgent palliative RT. Most (82%) consults had 2 or more palliative care domains ranked as highly relevant to care that included physical symptoms (91%), care coordination (70%), goals of care (59%), and psychosocial issues (52%).

issues (22%), spiritual issues (44%), care coordination (50%) and legal/ethical issues (50%). Palliative care was perceived as an important competency for radiation oncologists by 96% of residents and greater SPC education was desired by 81%. The importance of improving generalist palliative care education in oncology has been emphasized in expert consensus recommendations.[32,38,39] Several randomized trials have demonstrated improved patient outcomes through the integration of palliative care for oncology patients.[40,41] For example, in a randomized study among 151 advanced lung cancer patients, Temel et al found that despite receiving less aggressive medical care at the end of life, early palliative care was associated with improved quality of life and survival with reduced depression.[42] Also, early palliative care is associated with reduced costs of end-of-life medical care.[43]

Incorporating specialty palliative care in oncology care is now recommended for all advanced cancer patients by the American Society of Clinical Oncology (ASCO) based on the aforementioned evidence.[32] In these guidelines, oncologists are urged to be trained in, and provide, generalist palliative care to their patients. This is necessary due to oncologists' regular role in meeting generalist palliative care needs, such as managing ongoing symptoms, discussing goals of care as part of treatment decision-making, and identifying nonadvanced cancer patients in need of palliative care specialty referrals. Additionally, at present there are insufficient specialty palliative care resources to meet the care needs as presented in the ASCO guidelines, particularly as many patients with advanced cancer are living longer due to advances in systemic therapies, such as immunotherapies. Such factors underscore the need for robust generalist palliative care education for all oncology-related disciplines, including radiation oncologists, who frequently are involved in care for patients with advanced cancers.[44] Given the frequency of patients presenting to radiation oncology with complex palliative care issues such as significant pain syndromes and difficult end-of-life medical decision-making, there is a clear need to improve education across generalist palliative oncology care domains in radiation oncology training. Likewise,

SA-CME (see page 6)

increasing the quantity and quality of radiation oncology resident training in palliative care should be emphasized.[37] Given that many radiation oncologists have no formal training in hospice and palliative care during training and residency, it is also critical that high-quality palliative RT topics be presented at radiation oncology clinical meetings.

While this article focuses on the RT aspect of palliative care, the scope of palliative care is much wider. Important aspects of palliative care practice that may be integrated into residency training include decisions on when to offer treatment, limits of palliative RT, goals of care discussion, open and empathic communication with patients and family about prognosis, and facilitation of care to hospice or a nursing facility. Working with other specialists including medical oncology and palliative care on these diverse but complicated issues offers the maximal opportunity to define optimal care for symptom management and to improve the quality of life of patients with advanced cancer and their family. A case synopsis below illustrates an approach integrating a palliative radiation plan in the overall goals of care.

Conclusion

Palliative care is an integral part of radiation oncology practice, and radiation oncologists must be facile with the best evidence-based palliative RT applications in common clinical scenarios, including bone metastases, brain metastases, malignant spinal cord and cauda equina compression, tumor-related bleeding, fungation, obstruction and visceral metastases. Further rigorous research is needed to define technical aspects of palliative RT delivery, such as in the application of advanced techniques (eg, SBRT). However, supportive and palliative care competencies must extend beyond the technical aspects of RT delivery to generalist palliative care competencies, including the basics of symptom management, communication and goals of care, advance care planning, psychosocial issues, cultural considerations, spiritual needs, and ethical/legal issues. Radiation oncologists must also interface with specialty palliative care teams, recognizing when referrals are needed, and acting as part of the interdisciplinary oncology palliative care team. Together with greater research, further education is needed both within and beyond residency training to best equip radiation oncologists to advance the care of cancer patients living with incurable disease.

References

1. Lutz S, Korytko T, Nguyen J, et al. Palliative radiation therapy: when is it worth it and when is it not? *Cancer J.* 2010;16(5):473-482.
2. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7(2):6-9.
3. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. *J Clin Oncol.* 2014;32(26):2913-19.
4. Gripp S, Mjartan S, Boelke E, Willers R. Palliative radiation therapy tailored to life expectancy in end-stage cancer patients: reality or myth? *Cancer.* 2010;116(13):3251-3256.
5. Chow E, Abdolell M, Panzarella T, et al. Predictive model for survival in patients with advanced cancer. *J Clin Oncol.* 2008;26(36):5863-5869.
6. Chow E, Abdolell M, Panzarella T, et al. Validation of a predictive model for survival in metastatic cancer patients attending an outpatient palliative radiation therapy clinic. *Int J Radiat Oncol Biol Phys.* 2009;73(1):280-287.
7. Krishnan MS, Epstein-Peterson Z, Chen YH, et al. Predicting life expectancy in patients with metastatic cancer receiving palliative radiation therapy: the TEACHH model. *Cancer.* 2014;120(1):134-141.
8. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol.* 2012;30(4):419-425.
9. Rades D, Douglas S, Veninga T, et al. Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. *Cancer.* 2010;116(15):3670-3673.
10. Rades D, Lange M, Veninga T, et al. Final results of a prospective study comparing the local control of short-course and long-course radiation therapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys.* 2011;79(2):524-530.
11. Lutz S, Berk L, Chang E, et al. Palliative radiation therapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys.* 2011;79(4):965-976.
12. Chow E, Harris K, Fan G, et al. Palliative radiation therapy trials for bone metastases: a systematic review. *J Clin Oncol.* 2007;25(11):1423-1436.
13. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiation therapy versus multifraction radiation therapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer.* 2013;119(4):888-896.
14. van der Linden YM, Steenland E, van Houwelingen HC, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiation therapy: results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol.* 2006;78(3):245-253.
15. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol.* 2017;7(1):4-12.
16. Danjoux C, Chow E, Drossos A, et al. An innovative rapid response radiation therapy program to reduce waiting time for palliative radiation therapy. *Support Care Cancer.* 2006;14(1):38-43.
17. Fairchild A, Pituskin E, Rose B, et al. The rapid access palliative radiation therapy program: blueprint for initiation of a one-stop multidisciplinary bone metastases clinic. *Support Care Cancer.* 2009;17(2):163-170.
18. Tseng YD, Krishnan MS, Jones JA, et al. Supportive and palliative radiation oncology service: impact of a dedicated service on palliative cancer care. *Pract Radiat Oncol.* 2014;4(4):247-253.
19. Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol.* 2012;2(3):210-225.
20. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037-1044.
21. Wolf A, Kondziolka D. Brain metastases: radiosurgery. *Handb Clin Neurol.* 2018;149:129-135.
22. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet.* 2005;366(9486):643-648.
23. Chi JH, Gokaslan Z, McCormick P, et al. Selecting treatment for patients with malignant epidural spinal cord compression-does age matter? Results from a randomized clinical trial. *Spine* (Phila Pa 1976). 2009;34(5):431-435.
24. Ryu S, Fang Yin F, Rock J, et al. Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. *Cancer.* 2003;97(8):2013-2018.
25. Sharma S, Hertan L, Jones J. Palliative radiation therapy: current status and future directions. *Semin Oncol.* 2014;41(6):751-763.
26. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiation therapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97(11):798-804.
27. Murray KJ, Scott C, Zachariah B, et al. Importance of the mini-mental status examination in

SA-CME (see page 6)

the treatment of patients with brain metastases: a report from the Radiation Therapy Oncology Group protocol 91-04. *Int J Radiat Oncol Biol Phys.* 2000;48(1):59-64.
28. Lutz S, Lupu D, Johnstone P, et al. The influence of the newly formed hospice and palliative medicine subspecialty on radiation oncology and end-of-life care. *J Am Coll Radiol.* 2008;5(11):1102-1105.
29. Barnes EA, Palmer JL, Bruera E. Prevalence of symptom control and palliative care abstracts presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology. *Int J Radiat Oncol Biol Phys.* 2002; 54(1):211-214.
30. Shi DD, Digiovani JD, Skamene S, et al. Patterns of symptom control and palliative care-focused original research articles in major radiation oncology academic journals. *Ann Palliat Med.* 2018; In press.
31. Parker GM, LeBaron VT, Krishnan M, et al. Burden of palliative care issues encountered by radiation oncologists caring for patients with advanced cancer. *Pract Radiat Oncol.* 2017;7(6):e517-524.
32. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2017;35(1):96-112.
33. Wei RL, Mattes MD, Yu J, et al. Attitudes of radiation oncologists toward palliative and supportive care in the United States: Report on national membership survey by the American Society for Radiation Oncology (ASTRO). P*ract Radiat Oncol.* 2017;7:113-119.
34. Weissman DE, Block SD. ACGME requirements for end-of-life training in selected residency and fellowship programs: a status report. *Acad Med.* 2002;77(4):299-304.
35. The radiation oncology milestone project. *J Grad Med Educ.* 2014;6(1 Suppl 1):307-316.
36. Wei RL, Colbert LE, Jones J, et al. Palliative care and palliative radiation therapy education in radiation oncology: a survey of US radiation oncology program directors. *Pract Radiat Oncol.* 2017;7(4):234-240.
37. Krishnan M, Racsa M, Jones J, et al. Radiation oncology resident palliative education. *Pract Radiat Oncol.* 2017;7(6):e439-448.
38. Peppercorn JM, Smith TJ, Helft PR, et al. American society of clinical oncology statement: toward individualized care for patients with advanced cancer. *J Clin Oncol.* 2011;29(6):755-760.
39. Dying in America: improving quality and honoring individual preferences near the end of life. *Mil Med.* 2015;180(4):365-367.
40. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med.* 2004;164(1):83-91.
41. Rummans TA, Clark MM, Sloan JA, et al. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. *J Clin Oncol.* 2006; 24(4):635-642.
42. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-742.
43. Scibetta C, Kerr K, McGuire J, Rabow MW. The costs of waiting: implications of the timing of palliative care consultation among a cohort of decedents at a comprehensive cancer center. *J Palliat Med.* 2016;19(1):69-75.
44. Schaefer KG, Chittenden EH, Sullivan AM, et al. Raising the bar for the care of seriously ill patients: results of a national survey to define essential palliative care competencies for medical students and residents. *Acad Med.* 2014;89(7):1024-1031.
45. Rodrigues G, Videtic GMM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. *Prac Radiat Oncol.* 2011;1(2):60-71.
46. Moeller B, Balagamwala EH, Chen A, et al. Palliative thoracic radiotherapy for non-small cell lung cancer: 2018 update of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol.* 2018;S1879-8500(18):30069-9.

RTAnswers online patient education materials deviate from recommended reading levels

Stephen A. Rosenberg, MD*; Ryan A. Denu, BS*; David M. Francis, MD; Craig R. Hullett, MD, PhD; Michael M. Fisher; Jessica M. Schuster, MD; Michael F. Bassetti, MD, PhD; Randall J. Kimple, MD, PhD

Abstract

Objective: Patients are turning to the internet more often for cancer-related information. Oncology organizations need to ensure that appropriately written information is available for patients online. The aim of this study was to determine whether the readability of radiation oncology online patient information (OPI) provided by RTAnswers (RTAnswers.org, created by the American Society for Radiation Oncology [ASTRO]) is written at a sixth-grade level as recommended by the National Institutes of Health (NIH), the U.S. Department of Health and Human Services (HHS), and the American Medical Association (AMA).

Methods: RTanswers.org was accessed and online patient-oriented brochures for 13 specific disease sites were analyzed. Readability of OPI from RTAnswers was assessed using 10 common readability tests: New Dale-Chall Test, Flesch Reading Ease Score, Coleman-Liau Index, Flesch-Kinkaid Grade Level, FORCAST test, Fry Score, Simple Measure of Gobbledygook, Gunning Frequency of Gobbledygook, New Fog Count, and Raygor Readability Estimate.

Results: A composite grade level of readability was constructed using the 8 readability measures that provide a single grade-level output. The grade levels computed by each of these 8 tests were highly correlated (SI alpha = 0.98). The composite grade level for these disease site-specific brochures was 11.6 ± 0.83, corresponding to a senior in high school, significantly higher than the target sixth-grade level ($p < 0.05$) recommended by the NIH, HHS, and AMA.

Conclusion: Patient educational material provided by RTAnswers.org is written significantly above the target reading level. Simplifying and rewording this information could improve patients' understanding of radiation therapy and improve treatment adherence and outcomes.

Dr. Rosenberg *is chief resident in the Department of Human Oncology, University of Wisconsin-Madison.* ***Mr. Denu*** *is a medical student in the University of Wisconsin School of Medicine and Public Health.* ***Dr. Francis*** *is a resident,* ***Dr. Hullett*** *is chief resident,* ***Mr. Fisher*** *is an undergraduate,* ***Dr. Schuster*** *is an assistant professor,* ***Dr. Bassetti*** *is an assistant professor, and* ***Dr. Kimple*** *is an assistant professor, all in the Department of Human Oncology, University of Wisconsin-Madison. *Co-first authors.*

Disclosure: The authors have no conflicts of interest to disclose. This project is supported by F30CA203271 to RAD and by the University of Wisconsin Carbone Cancer Center Support Grant P30 CA014520. The content is the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health (NIH). This work was presented at the 2016 ASTRO Annual Meeting, September 25-28, 2016 in Boston, MA. Abstract 2998. Rosenberg SA, Francis DM, Hullett CR, et al. "RTAnswers: Will it provide the right answer for patient information?"

Communication and education are imperative to the physician-patient relationship. The internet is a convenient source of information for patients, and nearly two-thirds of cancer patients seek information about their diagnosis online.[1-3] Cancer patients often find information about treatments and the value of receiving a second opinion, and obtain support through the internet.[3,4] Modern radiation therapy is highly personalized based on a complex interplay between patient characteristics, tumor characteristics, and previous treatments. Compared with other cancer treatments, radiation therapy is disproportionally associated with misconceptions and misunderstanding.[5] Patients often leave a consultation trying to make sense of this information deluge and turn to the internet for answers.[6] This use of online information can allow patients to more actively participate in their treatment.[7] However, it is imperative that the information be presented in a way that can be accurately comprehended by most patients. This is especially important if patients first seek information online before going to see a physician, as is increasingly becoming the case.[8]

Most of our knowledge regarding the literacy of Americans comes from the U.S. Department of Education's literacy surveys, conducted in 1982, 1992 and 2003. Most recently, the 2003 National Assessment of Adult Literacy (NAAL) assessed prose, document, and quantitative literacy in a representative sample of 19 000 adults (age 16 and older, including 1200 prisoners) from across the nation. This survey was the first to incorporate a component on health literacy, defined as "the ability of U.S. adults to use printed and written health-related information to function in society, to achieve one's goals, and to develop one's knowledge and potential." The NAAL demonstrated that 43% of American adults have basic or below basic literacy skills.[9] Regarding

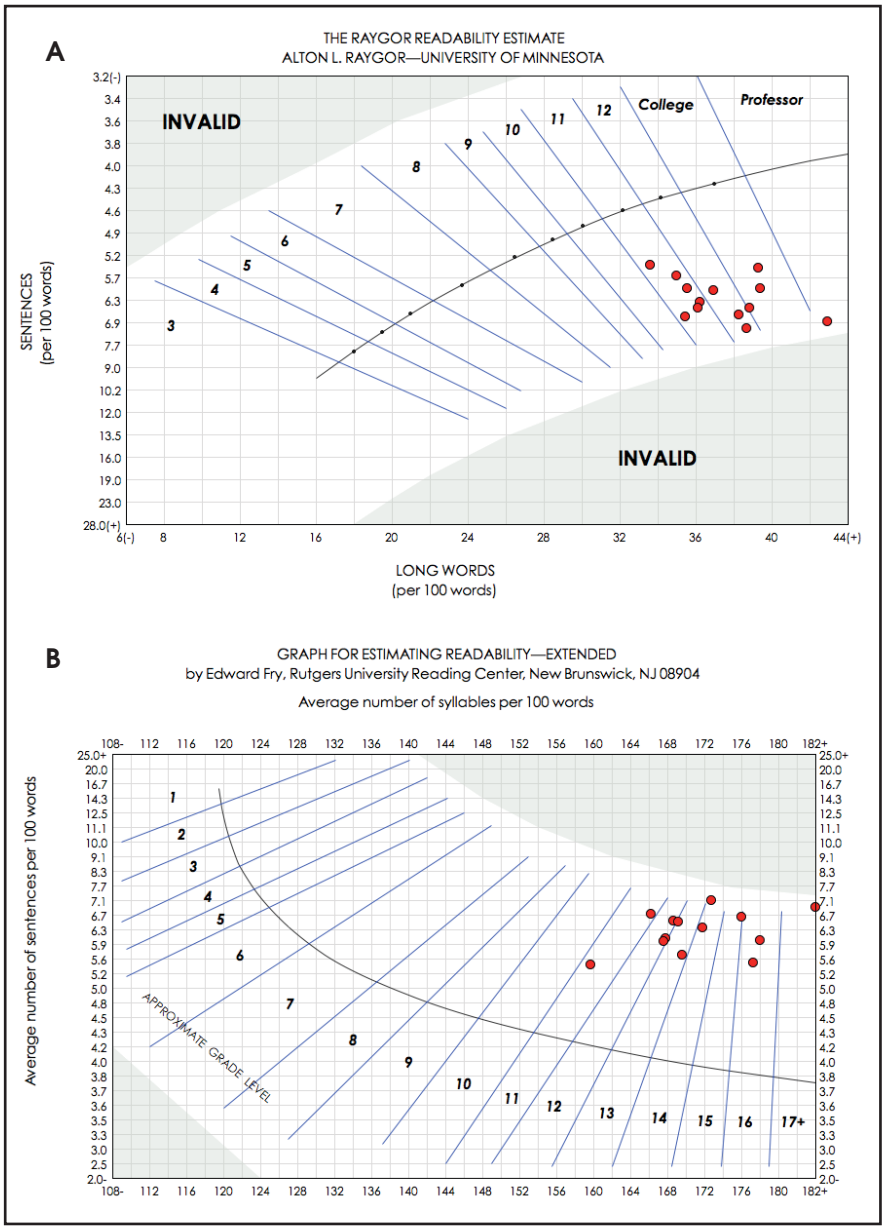


FIGURE 1. *Raygor and Fry Scores of RTAnswers online patient information. (A) The mean Raygor score was 12 (range 11-13) for all 13 disease site brochures assessed, well above the target grade level of 6 (green shading) proposed by the National Institutes of Health (NIH) and the U.S. Department of Health and Human Services (HHS). One text from RTAnswers was too difficult even for analysis and is not included in the average above. (B) The mean Fry score was 13 (range 11-16) for all 13 disease site brochures assessed, exceeding the target grade level 6 (green shading) as recommended by the NIH and HHS.*

health literacy specifically, over one-third of American adults have health literacy at or below the basic level,[10] and only 12% have proficient health literacy.[11] Health literacy is a strong predictor of the health status of an individual,[12] and those with poor health literacy demonstrate worse compliance with treatment recommendations and worse outcomes.[12,13] Based on the U.S. literacy rate, the NIH, HHS, and AMA recommend that OPI be written

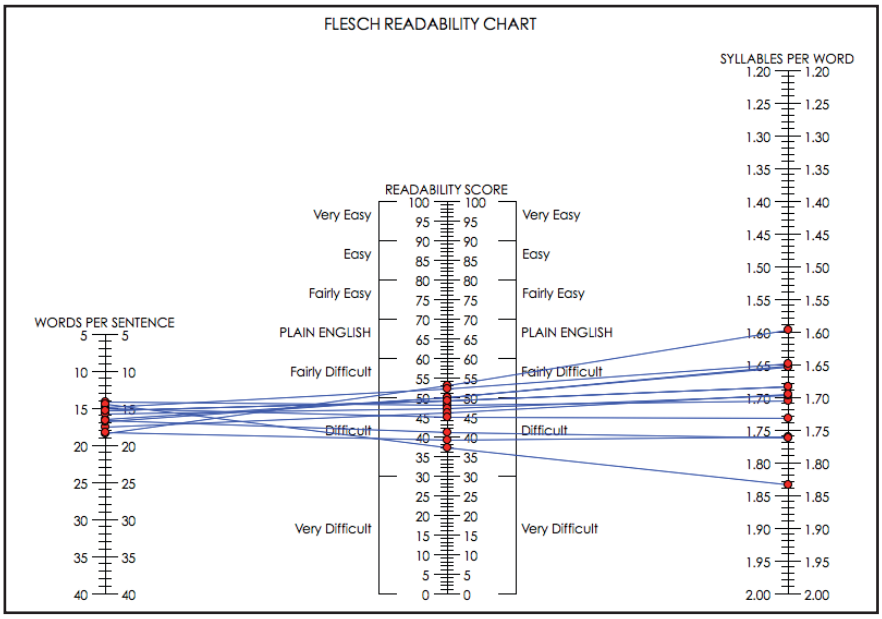


FIGURE 2. *The Flesch Reading Ease Score of online patient information (OPI). This test generates a score from 100 (very easy) to 0 (very difficult) with "plain English" corresponding to 60-70 (understood by most 13 to 15 year-olds). This test is a standard measurement of readability often used by U.S. government agencies. The mean score on this test was 47 (range 16-53), well below the target level and, therefore, well above the target level of readability.*

Table 1. Readability of Patient Information Found on RTAnswers

Reading Test	Grade Mean [min, max]
Coleman-Liau	12 [10.8, 13.6]
Flesch-Kincaid	10.9 [9.8, 12.5]
FORCAST	11.4 [10.7, 12.2]
Fry	13 [11, 16]
Gunning Fog	12.8 [11.2, 15]
New Fog Count (Kincaid)	8.9 [6.9, 11.2]
Raygor Estimate	12 [11, 13]
SMOG	12.7 [11.9, 14.1]

A composite measure of grade level was constructed using the 8 readability measures that provide a discrete grade level (above). These measures were strongly correlated and formed a reliable measure (SI alpha = 0.98). The Flesch Reading Ease and New Dale-Chall did not provide an output as a single grade but were consistent with these tests.

at a sixth-grade level.[14] These reported grade levels are derived from readability formulas, but do not necessarily indicate that an adult with a specific level of education will be able to read the text. Further, patients typically have a reading ability that is about 5 grades lower than the highest attained educational grade.[15,16] To make informed healthcare decisions, patients must have access to both accurate and understandable information.

Our team and others have demonstrated that online patient educational materials from academic radiation oncology websites, National Cancer Institute (NCI)-designated cancer websites, and cancer websites are significantly more complex than recommended.[17-20] This work has resulted in our cancer center revising online patient information. In this brief report, we hypothesized that radiation oncology patient information found on RTAnswers (RTAnswers.org, created by the American Society for Radiation Oncology [ASTRO]) is written at the recommended sixth-grade level and assessed the readability of this text using a panel of validated readability tests.

Methods and Materials

RTAnswers.org was accessed in May 2016, and OPI in the form of patient-oriented, disease-specific brochures for 13 disease sites was analyzed. Readability analysis was performed with Readability Studio version 2012.0 (Oleander Software, Hadapsar, India). Ten commonly used readability tests were employed: New Dale-Chall Test, Flesch Reading Ease Score, Coleman-Liau Index, Flesch-Kinkaid Grade Level, FORCAST test, Fry Score, Simple Measure of Gobbledygook (SMOG), Gunning Frequency of Gobbledygook (Gunning FOG), New Fog Count, and Raygor Readability Estimate. These tests are well validated and commonly used to assess readability.[21] The definition of a reading level is made on the basis of completed school years in the American school system. A composite score was constructed using the 8 tests that provide a single grade-level output (all tests except New Dale-Chall and Flesch Reading Ease Score).

Statistical analyses were performed using SPSS (IBM Corporation, Armonk, New York). All measures were compared to a sixth-grade reading level by t-tests, as this is the grade level recommended by NIH, DHHS, and AMA.[22]

Results

We analyzed the readability of 13 patient-oriented disease-specific brochures from RTAnswers. On all readability tests utilized, the readability of OPI from RTAnswers was significantly above target levels. The Raygor test, which analyzes both sentence length and the number of long words to derive a score, demonstrated a mean grade level of 12 (**Figure 1A**). Similarly, the Fry score, which incorporates sentence length and number of syllables per word, demonstrated a mean grade level of 13 (**Figure 1B**). The Flesch scale generates a score from 0-100 (with 100

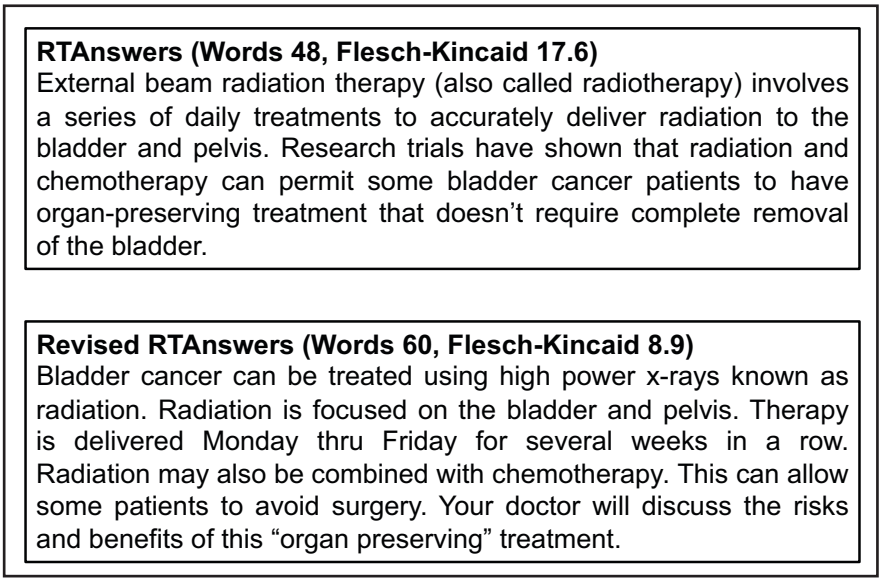


FIGURE 3. *Revising word choice and sentence structure to improve readability. (A) This figure shows a sentence from a patient brochure from RTAnswers in bladder cancer. The readability score of this paragraph is high and corresponds to at least college level. (B) By simplifying word choice and minimizing words per a sentence, we can improve the readability of the text.*

being the easiest level of readability and 60-70 corresponding to "plain English"). This test focuses on words per sentence and syllables per word and is commonly used by U.S. government agencies to assess readability.[23] The average score on the Flesch Reading Ease Scale was 47 (range 16-53) (**Figure 2**).

We then constructed a composite grade level of readability of the 13 RTAnswers brochures using the 8 readability measures that provide a single grade-level output. The readability of patient brochures for all disease sites are far from the target level as determined by these readability tests (**Table 1**). Furthermore, the grade level computed by each of these 8 tests was highly correlated (SI alpha = 0.98). When combined, the tests yielded a composite grade level of 11.6 ± 0.8, corresponding to a senior in high school, and significantly greater than the recommended sixth-grade level ($p < 0.05$).

Next, we demonstrate one example of a sentence from a bladder cancer brochure from RTAnswers that we have edited to improve the readability (**Figure 3**). This correction decreased the Flesch-Kincaid reading level from 17.6 to 8.9. We conclude that similar alterations can be made to all RTAnswers brochures and other OPI to improve readability.

Discussion

Cancer patients commonly use the internet to seek information about their diagnosis and treatment.[6] One major barrier to effectively understanding and utilizing this online information is the readability of the material. Our results indicate that online patient educational materials on RTAnswers are significantly more complex than the recommended sixth-grade level. This calculated grade level is similar to previous analyses of academic radiation oncology and NCI-designated cancer center websites.[17-19] Furthermore, our findings are consistent with the readability of other online materials (eg, WebMD, NIH, Mayo Clinic) pertaining to the most common internal medicine diagnoses.[24] This study builds on the work the work from Byun and Golden, who utilized the Flesch-Kincaid test to assess written ASTRO materials.[25] However, our analysis goes a step further by extracting and analyzing information from patient brochures by each disease site found online.

To improve patients' comprehension of radiation therapy and its role in their treatment, our analysis suggests that the language used in online patient information can be simplified to improve communication. Simple, easily understood language can reduce patient stress and anxiety, and improve the physician-patient relationship.[26,27] To accomplish this, OPI provided by RTAnswers and academic cancer centers should use simple or well-known terminology, avoid medical or technical terms, use simple phrase and sentence structure, and incorporate feedback from nonmedical personnel into developing these brochures. An example of simplifying language is shown in **Figure 3**. This shows a sentence extracted from one of the brochures on bladder cancer and our interpretation to improve it. Similar techniques can be extrapolated to other OPI.

Improving readability of OPI can have a myriad of positive outcomes. Patients typically assess website accuracy based on its endorsement by a government agency or professional organization, their own perception of the website's reliability, and their ability to understand the information presented.[28,29] Improving readability increases the likelihood that patients will follow recommendations. Furthermore, improving readability of OPI is also important for effective communication, a potential barrier to help overcome healthcare disparities.

Conclusion

The composite grade-level readability of OPI collected from RTAnswers

was 11.6, corresponding to the senior year of high school. This was significantly greater than the target sixth-grade level. These differences may prevent understanding of OPI by the general public. The readability of OPI provided by RTAnswers can be improved to enhance patient understanding and improve outcomes.

References

1. Nelson DE, Kreps GL, Hesse BW, et al. The Health Information National Trends Survey (HINTS): development, design, and dissemination. *J Health Commun*. 2004;9(5):443-460; discussion 481-444.
2. Fox S, Rainie L. Vital decisions: how Internet users decide what information to trust when they or their loved ones are sick. Washington DC: The Pew Internet & American Life Project. Vol. 2016; 2002.
3. Shuyler KS, Knight KM. What are patients seeking when they turn to the Internet? Qualitative content analysis of questions asked by visitors to an orthopaedics Web site. *J Med Internet Res*. 2003;5(4):e24.
4. Ziebland S, Chapple A, Dumelow C, et al. How the internet affects patients' experience of cancer: a qualitative study. *BMJ*. 2004;328(7439):564.
5. Hinds G, Moyer A. Support as experienced by patients with cancer during radiotherapy treatments. *J Adv Nurs*. 1997;26(2):371-379.
6. Eysenbach G. The impact of the Internet on cancer outcomes. *CA Cancer J Clin*. 2003;53(6):356-371.
7. Eysenbach G, Jadad AR. Evidence-based patient choice and consumer health informatics in the Internet age. *J Med Internet Res*. 2001;3(2):E19.
8. Hesse BW, Nelson DE, Kreps GL, et al. Trust and sources of health information: the impact of the Internet and its implications for health care providers: findings from the first Health Information National Trends Survey. *Arch Intern Med*. 2005;165(22):2618-2624.
9. Kutner M, Greenberg E, Jin Y, et al. Literacy in everyday life: results from the 2003 National Assessment of Adult Literacy; 2007.
10. White S. Assessing the nation's health literacy: key concepts and findings of the National Assessment of Adult Literacy (NAAL): American Medical Association; 2008.
11. Cutilli CC, Bennett IM. Understanding the health literacy of America: results of the National Assessment of Adult Literacy. *Orthop Nurs*. 2009;28(1):27-32; quiz 33-24.
12. Baker DW, Parker RM, Williams MV, et al. The relationship of patient reading ability to self-reported health and use of health services. *Am J Public Health*. 1997;87(6):1027-1030.
13. Friedland R. Understanding health literacy: new estimates of the cost of inadequate health literacy. In: Congress of the U.S., ed, *The Price We Pay for Illiteracy*, Washington, DC: National Academy on an Aging Society; 1998;57-91.
14. Weiss BD. Manual for clinicians. Health literacy and patient safety: Help patients understand. Chicago: American Medical Association Foundation; 2007.
15. Jackson RH, Davis TC, Bairnsfather LE, et al. Patient reading ability: an overlooked problem in health care. *South Med J*. 1991;84(10):1172-1175.
16. Ley P, Florio T. The use of readability formulas in health care. *Psychol Health Med*. 1996;1:7-28.
17. Rosenberg SA, Francis DM, Hullet CR, et al. Online patient information from radiation oncology departments is too complex for the general population. *Pract Radiat Oncol*. 2016;7(1):57-62.
18. Prabhu AV, Hansberry DR, Agarwal N. Radiation oncology and online patient education materials: deviating from NIH and AMA recommendations. *Int J Radiat Oncol Biol Phys*. 2016;96(3):521-528.
19. Rosenberg SA, Francis D, Hullett CR, et al. Readability of online patient educational resources found on NCI-designated cancer center web sites. *J Natl Compr Canc Netw*. 2016;14(6):735-740.
20. Keinki C, Zowalla R, Wiesner M, et al. Understandability of patient information booklets for patients with cancer. *J Cancer Educ*. 2016.
21. Friedman DB, Hoffman-Goetz L. A systematic review of readability and comprehension instruments used for print and web-based cancer information. *Health Educ Behav*. 2006;33(3): 352-373.
22. Assessing readability. Vol. 2016: Washington, DC: Dept of Health and Human Services; 2014.
23. Flesch R. A new readability yardstick. *J Appl Psychol*. 1948;32(3):221-233.
24. Hutchinson N, Baird GL, Garg M. Examining the reading level of internet medical information for common internal medicine diagnoses. *Am J Med*. 2016;129(6):637-639.
25. Byun J, Golden DW. Readability of patient education materials from professional societies in radiation oncology: Are we meeting the national standard? *Int J Radiat Oncol Biol Phys*. 2015;91(5):1108-1109.
26. Ha JF, Longnecker N. Doctor-patient communication: a review. *Ochsner J*. 2010;10(1):38-43.
27. Dorr Goold S, Lipkin M. The doctor-patient relationship: challenges, opportunities, and strategies. *J Gen Intern Med*. 1999;14 Suppl 1:S26-33.
28. Sbaffi L, Rowley J. Trust and credibility in web-based health information: a review and agenda for future research. *J Med Internet Res*. 2017;19(6):e218.
29. Vega LC, Montague E, Dehart T. Trust between patients and health websites: a review of the literature and derived outcomes from empirical studies. *Health Technol (Berl)*. 2011;1(2-4):71-80.

Combination of volumetric-modulated arc therapy (VMAT) and partially wide tangents (PWT) for improved organ sparing in a left-sided and right-sided breast cancer case receiving regional nodal irradiation (RNI): A technical note

Vishruta A. Dumane, PhD; Yeh-Chi Lo, PhD; Sheryl Green, MD

Abstract

Objective: Postmastectomy radiation therapy (PMRT) to the chest wall and regional nodal irradiation (RNI) in women with node-positive breast cancer is known to reduce locoregional recurrence and distant metastases, as well as improve overall survival. Standard 3-dimensional (3D) conformal techniques may not be able to provide a clinically optimal plan for treatment, especially when coverage to the internal mammary nodes is required. Although advanced delivery techniques such as volumetric-modulated arc therapy (VMAT) can be used to better spare the heart and lungs, there is an increase in low dose exposure to normal tissue compared with 3D conformal planning. In a situation where 3D conformal planning provides an acceptable dose distribution for the majority of critical organs, it may not be justifiable to use VMAT to reduce dose to a few organs, while increasing low-dose exposure to the entire patient. In such cases, a combination of VMAT and 3D can be suitable to generate a clinically acceptable dose distribution without an unnecessary increase in low dose exposure. In this report we describe a left- and a right-sided case, which have benefited from this approach.

Methods and Materials: The left-sided case was of a 59-year-old woman with stage IIIC cancer who had undergone a bilateral mastectomy requiring PMRT to the chest wall along with RNI. The right-sided case was of a 51-year-old woman with stage IIIC cancer who had undergone a lumpectomy requiring whole-breast radiation (WBI) with RNI. Computed tomography (CT) scans were acquired from the chin to the upper abdomen during free breathing at 3-mm slice spacing with the patient positioned on an angle board and head turned to the contralateral side. Contouring of the target volume was done as per Radiation Therapy Oncology Group (RTOG) guidelines. Three plans were done for each case, the first using 3D conformal planning with the partially wide tangents (PWT) technique, the second using volumetric-modulated arc therapy (VMAT) alone, and finally using a combination of 3D and VMAT. A dosimetric comparison of the plans was performed in each case.

Results: For both the left- and the right-sided cases, the PTV D95, V95 as well as the IMN D95 were comparable among all the plans; however, the hotspot in terms of the PTV D05 was found to be lower for the VMAT and the combined plan. The homogeneity index (HI) and the conformity index (CI) were best with the combined plan. For both the left- and the right-sided cases, the heart was well spared with the PWT technique. The MHD was the highest with VMAT as were the volumes covered by lower doses, namely 15 Gy and 5 Gy. However, combining VMAT and PWT did not compromise the V15 Gy and V5 Gy compared with PWT. The ipsilateral lung V20 Gy was the highest (≥ 45%) with PWT technique yielding a clinically unacceptable plan in both cases. The combination of VMAT and PWT not only maintained the ipsilateral lung V20 Gy ≤ 30%, but also kept the V5 Gy comparable to or lower than the corresponding PWT plan. The trend in the result for the total lung was similar to that of the ipsilateral lung. The contralateral breast was best spared with PWT; however, the combination plan did not compromise dose to the contralateral breast compared with the former technique.

Conclusions: Combination of VMAT and 3D was not only able to preserve the mean dose to the heart, but was able to also reduce the ipsilateral lung V20 Gy without increasing low dose to all of the organs compared to using VMAT alone.

Postmastectomy radiation therapy (PMRT) to the chest wall and regional nodal irradiation (RNI) in women with node-positive breast cancer is known to reduce locoregional recurrence and distant metastases, while improving overall survival.[1,2] The addition of RNI to whole-breast irradiation (WBI) after breast-conserving surgery (BCS) has also been shown to reduce the rate of breast cancer recurrence.[3,4] While irradiating the chest wall and internal mammary nodes (IMNs) with 3-dimensional (3D) conformal planning, the partially wide tangents (PWT) technique has been shown to provide the most appropriate balance between target coverage and normal tissue sparing.[5,6] Regardless, the requirement to irradiate the IMNs increases exposure to the heart and lungs. When standard 3D conformal planning techniques are unable to adequately reduce dose to the heart and lung, advanced treatment planning and delivery techniques such as intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) have helped improve sparing.[7-9] However, since the beams/arcs irradiate the target from many projections/angles, there is an increase in low dose exposure to normal tissue compared with 3D conformal planning. This caveat has limited the widespread application of VMAT for breast cancer treatment.

Our clinic was recently presented with a left- and a right-sided case, where in using PWT, the mean heart dose (MHD) was 2.8 Gy and 0.8 Gy, respectively; however, the ipsilateral lung V20 Gy was ≥ 45% in both cases. Hence, even though the MHD was acceptable for treatment, the ipsilateral lung V20 Gy needed to be reduced to ≤ 30% for a clinically viable plan.[10,11] If VMAT alone were used, it would increase the MHD and the spread of low dose to other critical organs. In this technical report, we describe how a combination of 3D conformal planning using PWT over the region of the heart and VMAT superior to the heart can help maintain the advantage of low mean heart dose attained with 3D while reducing dose to the ipsilateral lung, meeting the desirable dose constraint. Through a dosimetric comparison of PWT, VMAT and a combination of VMAT and PWT, we show that the combination of the 2 techniques is not only able to preserve the MHD, but will also reduce the ipsilateral lung V20 Gy without increasing low dose to all the organs as compared to using VMAT alone. In this manner, the advantages of both techniques can be preserved.

***Dr. Dumane** is assistant professor of radiation oncology; **Dr. Lo** is chief physicist and professor; and **Dr. Green** is associate professor of radiation oncology, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY.*
Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

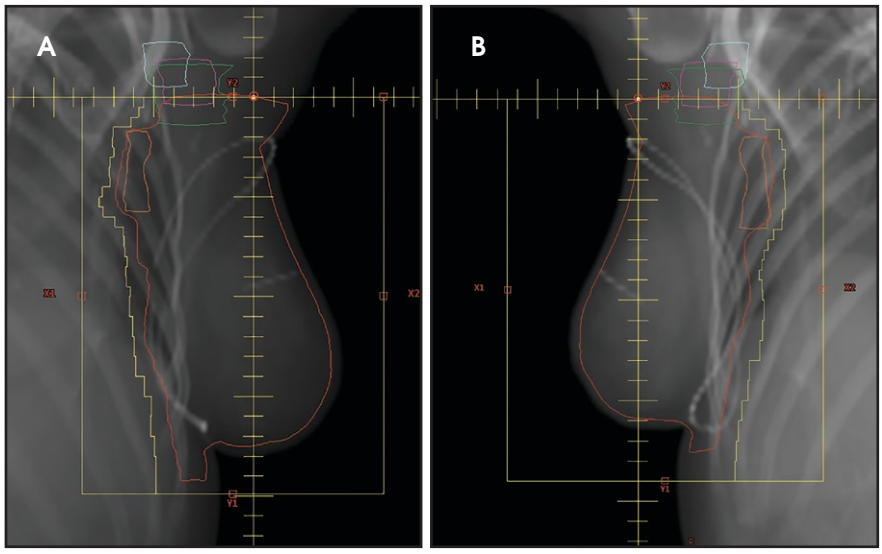


***FIGURE 1.** (A) The beam's eye view (BEV) of the lateral partially wide tangents (PWT) field covering the internal mammary nodes (IMNs) in the first 3 intercostal spaces along with some inferior portion of the axillary level I and II lymph nodes and the planning target volume (PTV). The angle board was adjusted to make the chest wall parallel to the posterior edge of the tangential field to minimize the amount of lung covered by these fields. (B) The BEV of the medial PWT field is covering the same.*

Methods and Materials

The left-sided case was of a 59-year-old woman with stage IIIC cancer who had undergone a bilateral mastectomy requiring PMRT to the chest wall along with RNI. The right-sided case was of a 51-year-old woman with stage IIIC cancer who had undergone a lumpectomy requiring WBI with RNI. Computed tomography (CT) scans were acquired from the chin to the upper abdomen during free breathing at 3-mm slice spacing with the patient positioned on an angle board and head turned to the contralateral side.

Target delineation

Contouring of the clinical target volume (CTV) chest wall/breast tissue, axillary level I, II, III, supraclavicular and IMNs was done per Radiation Therapy Oncology Group (RTOG) guidelines.[12] The planning target volume (PTV) for the left-sided case was CTV + 5 mm and included the skin as this was post-mastectomy radiation. A 5-mm bolus was used over the chest wall area for the left-sided case to adequately

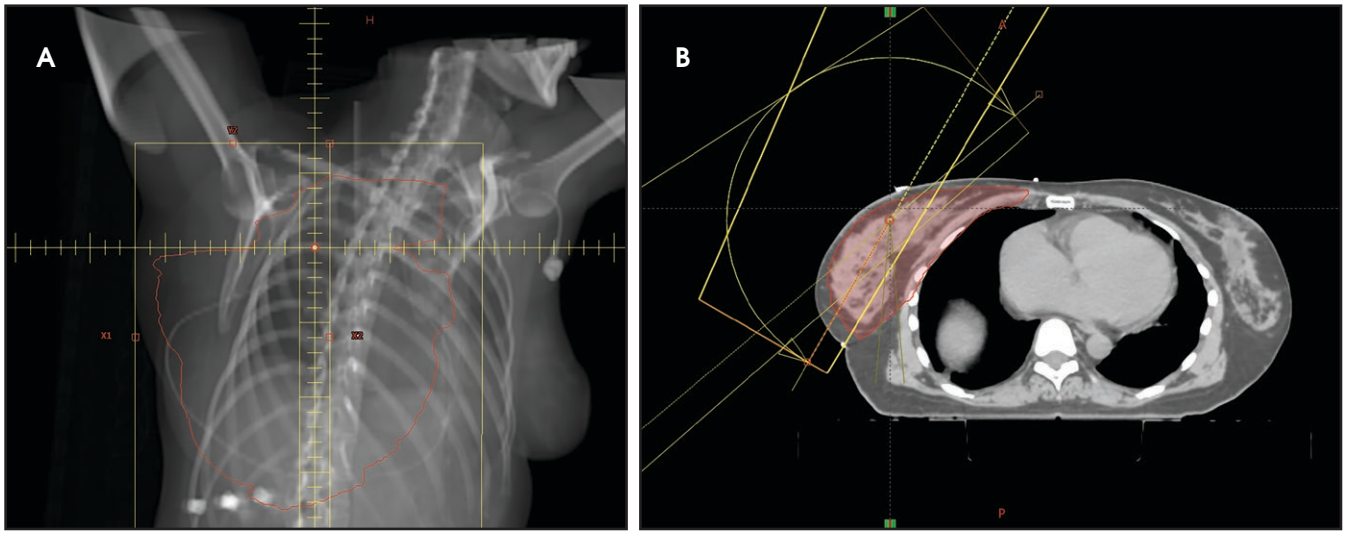


FIGURE 2. *(A) Beam's eye view (BEV) of 2 treatment fields with a 2.0-cm overlap at the isocenter at a projection of 320 degrees. The planning treatment volume (PTV) to be covered is outlined in red contour. (B) Two volumetric-modulated arc therapy (VMAT) arcs each of range 200 degrees; the angle of rotation is 50 to 210 degrees for the first arc, and 210 to 50 degrees for the second arc.*

cover the skin. For the right-sided case, the first 5 mm of the skin was excluded from the PTV, since the breast tissue was intact for this case. Critical organs contoured were the heart, ipsilateral lung and contralateral lung. The contralateral breast was also contoured for the right-sided case. Energy used for planning was 6 MV for the left-sided case, and a mix of 6 MV and 16 MV for the right-sided case due to a larger separation. Dose prescribed was 50 Gy in 25 fractions. Treatment planning for all plans was done on the Eclipse V 13.6 (Varian, Palo Alto, California).

Partially Wide Tangents (PWT) planning

A mono-isocentric technique was used where the isocenter was placed by the clavicular head, which served as the junction/matchline of the supraclavicular field with the PWT fields. The collimator angle in this technique was deliberately kept at 0 degrees to avoid divergence of the supraclavicular field into the tangents. The angle board was adjusted to make the chest wall parallel to the posterior edge of the tangential field to minimize the amount of lung covered by these fields (**Figures 1A and B**). Gantry angles were adjusted for the tangential photon fields to match the divergence of the posterior field edges of the beam. The PWT fields covered the IMNs in the first 3 intercostal spaces along with some inferior portion of the axillary level I and II lymph nodes and the PTV in the beam's eye view (BEV). The extent of the blocking was determined from the BEV of each tangential field to ensure adequate coverage of the PTV with a 7-mm margin for penumbra. Field-in-field compensation was used for planning.[13]

Volumetric-modulated Arc Therapy (VMAT) Planning

Planning with VMAT was per the technique described by Popescu et al.[9] The projection angle at which the PTV separation is the largest in the BEV was chosen. Due to the large treatment volumes involved and the limited MLC leaf travel within an individual field, which is 15 cm on a Varian linac, treatment planning required the use of at least 2 complementary arcs to cover the extent of the PTV. These arcs overlapped at the isocenter by 2 cm and the collimator angle was kept at 0° as shown in **Figure 2A**. The treatment isocenter was set in the same manner as in a mono-isocentric 3-field breast technique. Since isocenter location is typically lateral to the patient's midline, full arcs are likely to collide with the patient. In our previous study, the use of 2 complementary partial arcs within a 190-degree arc range was sufficient.[14] Increasing the arc range to 220 and 240° degrees, respectively, did not improve the PTV coverage and homogeneity, and only increased the volume of the ipsilateral lung and total lung covered by doses in the range 5 Gy to 25 Gy. Increasing the number of arcs also did not improve PTV coverage, homogeneity or critical organ dose. In this study, 2 partial complementary arcs within a 200-degree range were used (**Figure 2B**). The optimization algorithm used was the progressive resolution optimizer (PRO) and the dose calculation algorithm was the analytical anisotropic algorithm (AAA). The VMAT plan was optimized such that priority was given to cover 95% of the IMNs with at least 90% of the prescription dose (ie, 45 Gy) or more while achieving PTV D95, V95 ≥ 95% and PTV D05 ≤ 110%, followed by mean heart dose (MHD), ipsilateral lung V20 Gy, dose to the contralateral lung and breast (for the right-sided case).

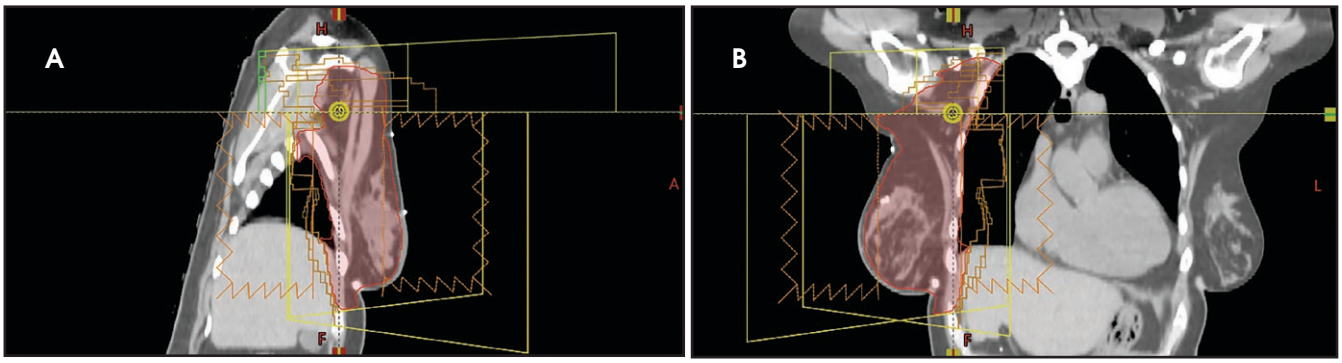


FIGURE 3. *(A) Positioning of the isocenter in the sagittal view at the matchline of the supraclavicular field; the region superior to this matchline is treated with volumetric-modulated arc therapy (VMAT) and inferior to it is treated with partially wide tangents (PWT). (B) Positioning of the isocenter in the coronal view at the matchline of the supraclavicular field.*

Volumetric-modulated Arc Therapy (VMAT) and Partially Wide Tangents (PWT) Planning

For both the left- and the right-sided cases, the PTV by the heart was adequately covered while maintaining acceptable MHD (desired to keep ≤ 3 Gy). However, the ipsilateral lung V20 Gy was unacceptably high at ≥ 45%. It is desirable to keep it ≤ 30% to reduce the likelihood of toxicity.[10,11] VMAT planning was hence used to improve the ipsilateral lung dose, over the region superior to the heart. The PTV superior to the junction was planned with VMAT and inferior to the junction with PWT. Matching of the superior and inferior plans was accomplished with the single isocenter half-beam block technique[15,16] using an asymmetric jaw. **Figure 3** demonstrates the positioning of the isocenter and the matchline. In the left-sided case, the gantry start and stop angles were 160 and 320 degrees, respectively, for the VMAT plan; for the right-sided case, they were 210 and 50 degrees, respectively. To avoid hotspots at the junction while planning with VMAT, the PTV for optimization purposes (PTV-OPT) was defined 6 mm superior from the isocenter/junction. To avoid areas of underdosing/cold spots at the junction, in this study, the slices of the PTV in between the level of the isocenter and the inferior-most slice of the PTV-OPT were constrained in the optimizer to receive at least 45 Gy, limiting the hotspot to be ≤ 105%. This dose was determined iteratively such that the PTV D95 of the combined VMAT and PWT plans was ≥ 95% and the PTV D05 ≤ 110%. The collimator angle was kept at 0 degrees for the PWT and the VMAT plan to avoid beams from both plans from diverging into each other. Blocking in the PWT plan was constructed such that the PTV was covered without compromising heart sparing. The VMAT plan was optimized with the priority given to cover 95% of the IMNs with at least 90% of the prescription dose or more while achieving PTV D95, V95 ≥ 95%, and PTV D05 ≤ 110% in the combined VMAT and PWT plans. The next priority was to minimize the ipsilateral lung V20 Gy, followed by dose to the contralateral lung and breast.

VMAT plans went through patient-specific quality assurance (QA) using portal dosimetry and 2-dimensional diode array. Absolute dose comparison was performed between the calculated and measured plans.

Results

Dosimetric comparison of the various plans for the left and the right-sided cases are shown in **Table 1**. Dose volume histograms are shown in **Figures 4A and B**, while the comparison of the dose distribution for VMAT and VMAT + PWT are shown in **Figure 5**.

Planning Target Volume (PTV) Coverage

For both the left- and the right-sided cases, the PTV D95, V95 as well as the IMN D95 were comparable among all the plans, namely, PWT vs VMAT, vs VMAT + PWT. The hotspot in terms of the PTV D05 was the least with VMAT or the combined plan. The homogeneity index (HI) and the conformity index (CI) were best with the VMAT + PWT plan.

Heart

For both the left- and the right-sided cases, the heart was well spared with the PWT technique. If VMAT alone were to be used to cover the PTV, the MHD was increased by almost 4 Gy. By combining VMAT and PWT, the advantage of low MHD achieved with PWT was not compromised**.** The V25 Gy was similar among the 3 techniques. However, volumes covered by lower doses, namely 15 Gy and 5 Gy, were highest with VMAT alone as expected. Combining VMAT and PWT did not compromise the V15 Gy and V5 Gy compared with PWT.

Ipsilateral Lung

For both cases, the PWT technique yielded a clinically unacceptable plan with the ipsilateral lung V20 Gy at ≥ 45%. VMAT alone reduced this by ≥ 20%, but the cost was an increase in

Table 1. Dosimetric Comparison of PTV coverage, IMN Coverage and Critical Organs for PWT, VMAT and VMAT + PWT for Left-sided and Right-sided case

Structure	Parameter	PWT Left-sided	VMAT Left-sided	VMAT + PWT Left-sided	PWT Right-sided	VMAT Right-sided	VMAT + PWT Right-sided
PTV	D95 (%)	100	100	100.7	98.9	98.9	101.2
	V95 (%)	99.4	99.9	100	99.1	99.9	100
	D05 (%)	114.5	109	109.4	114.1	108.1	108.8
	D_{max} (Gy)	59.8	56.8	57.8	64.1	57.8	57.1
	HI*	0.2	0.1	0.1	0.2	0.1	0.1
	CI†	1.8	1.3	1.2	1.3	1.4	1.1
IMN	D95 (%)	94.5	94	95.7	98	97.8	99.2
Heart	Mean (Gy)	2.8	7	2.6	0.8	4.9	0.6
	V25 Gy (%)	1.8	2	1.3	0	0	0
	V15 Gy (%)	3	7.4	2.3	0	1	0
	V5 Gy (%)	8.1	46	6.9	2.6	38.6	0.7
Ipsilateral Lung	Mean (Gy)	22.6	14.3	14.3	24.4	16.6	16.3
	V20 Gy (%)	45	23.1	24.5	49.7	29.6	30
	V10 Gy (%)	51.3	45.8	42.8	60.1	50.1	44.8
	V5 Gy (%)	60.4	77.5	66.1	72.4	91.1	63.7
Total Lung	Mean (Gy)	9.8	9.5	8.7	13.8	11.6	10.1
	V20 Gy (%)	19.1	10.1	10.6	27.8	16.5	16.8
	V10 Gy (%)	21.7	25	24.1	33.5	32.5	27.3
	V5 Gy (%)	25.7	65.2	52.5	40.4	70.9	44
Contralateral Lung	Mean (Gy)	0.5	5.9	4.5	0.3	5.4	2.2
	V10 Gy (%)	0	10	10.2	0	10.3	5.5
	V5 Gy (%)	0	57.6	43.2	0	46.2	18.9
Contralateral Breast	Mean (Gy)	N/A	N/A	N/A	0.3	2.2	0.2
	V4 Gy (%)	N/A	N/A	N/A	0	13.3	0
	V3 Gy (%)	N/A	N/A	N/A	1.7	22.1	0

*HI = homogenity index (D2%-D98%)/D50%; †CI = conformity index (volume of PTV X volume of prescription isodose)/(volume of PTV within prescription isodose)
Key: PTV = planning target volume, IMN = internal mammary nodes, PWT = partially wide tangents, VMAT = volumetric-modulated arc therapy, Gy = gray

V5 Gy by almost 20%. The combination of VMAT and PWT not only maintained the ipsilateral lung V20 Gy ≤ 30% at values similar to that of the VMAT plan, but also kept the V5 Gy comparable to or lower than the corresponding PWT plan.

Contralateral Lung

The contralateral lung was best spared with PWT and worst with VMAT in both cases. Doses to the contralateral lung with the combined plan were in between these 2 techniques.

Total Lung

The trend in the result for the total lung was similar to that of the ipsilateral lung. In both cases, the total lung mean dose and V20 Gy were the highest with PWT. Although using VMAT helped lower these dosimetric parameters, the cost was an increase in V5 Gy. Combining the 2 techniques helped maintain the dosimetric advantage of VMAT for the mean total lung dose and V20 Gy, while reducing the V10 Gy and V5 Gy, compared to using VMAT alone.

Contralateral Breast

For the right-sided case, the contralateral breast was spared well with PWT and was the worst with VMAT as expected due to low dose bath. The combined plan did not compromise dose to the contralateral breast.

Intensity-modulated radiation therapy (IMRT) Quality Assurance (QA)

Absolute dose comparison was performed between the calculated and

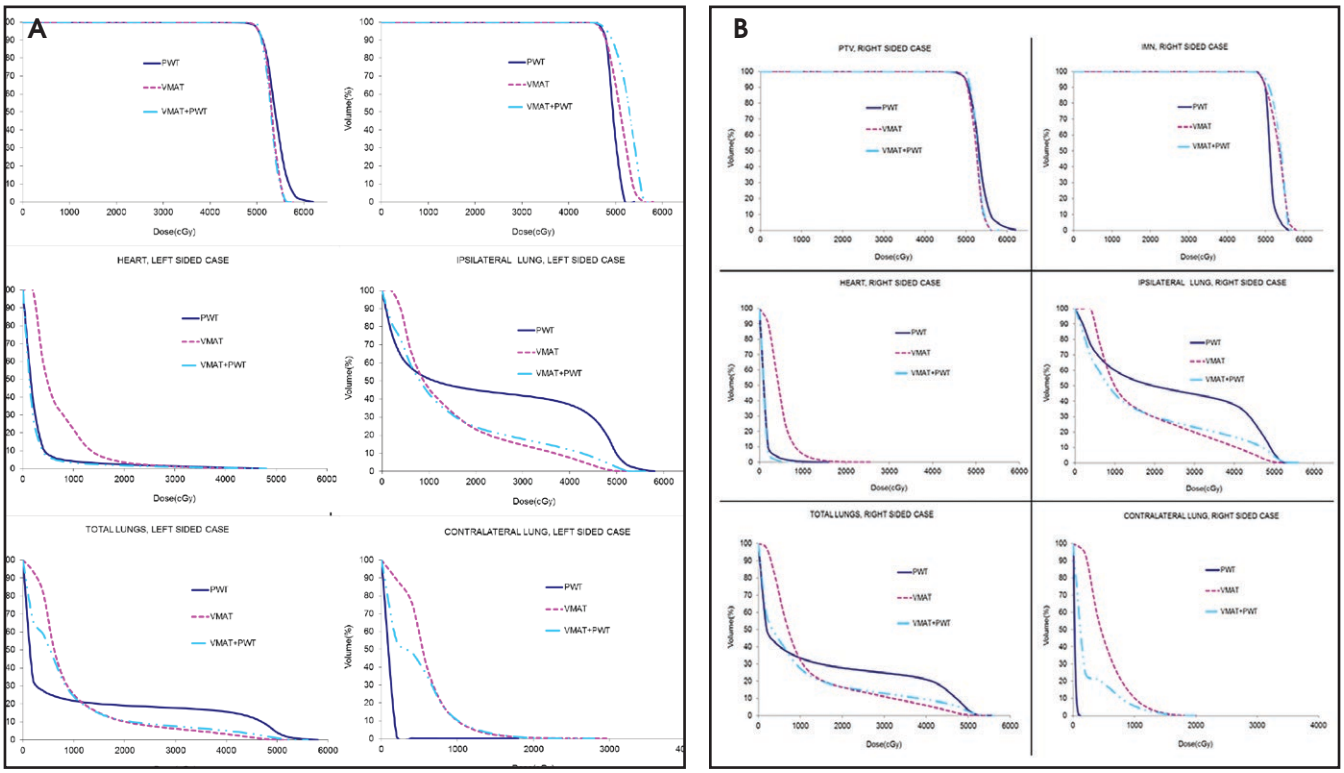


FIGURE 4. *(A) Comparison of dose volume histograms (DVHs) for the planning target volume (PTV), internal mammary nodes (IMNs), heart, ipsilateral lung, total lung and contralateral lung with partially wide tangents (PWT), volumetric-modulated arc therapy (VMAT) and VMAT + PWT for the left-sided case. (B) Comparison of DVHs for the PTV, IMNs, heart, ipsilateral lung, total lung and contralateral lung with PWT, VMAT and VMAT + PWT for the right-sided case.*

measured plans over all dose regions and > 99% of the points agreed to within 3% and 3 mm.

Discussion

With published results from the National Cancer Institute of Canada [NCIC] Clinical Trials Group MA.20 and European Organization for Research and Treatment of Cancer (EORTC) trials,[3,4] more breast cancer patients are likely to receive RNI that includes the IMNs. Including the IMNs in the treatment volume increases exposure to normal tissue. Treatment planning techniques are needed that can adequately cover the target volume while alleviating unnecessary exposure to the critical organs. In situations where the dosimetric results are not acceptable for both the heart and the ipsilateral lung, VMAT alone would suffice.[9] In this work, we have presented a left- and right-sided case in which the PWT plan met the dose constraints for the heart but not for the ipsilateral lung. Using PWT to cover the PTV in the region over the heart, and VMAT to cover the PTV superior to the heart, has helped meet the constraint for the ipsilateral lung V20 Gy without compromising heart dose or increasing the low dose as much as in the case of using VMAT alone. Studies in patients who received locoregional RT that included IMNs while maintaining the ipsilateral lung V20 Gy < 30%, showed ~6% grade 1 and 2 radiation pneumonitis (RP) and no incidence of grade 3 and 4 RP.[10,11,17] In patients for whom the V20 Gy was around 35%, the grade 1 and 2 complication rates had risen to 23% and 11.5%, respectively. These studies emphasize the importance of adhering to the constraint of the ipsilateral lung V20 Gy < 30%. In both cases reported here, we were not able to keep the ipsilateral lung V20 Gy < 30% using the PWT technique alone. However, the combination of VMAT and PWT met this constraint for both cases, while limiting the low dose.

Exposure of the heart during radiation therapy is unavoidable, especially for left-sided cases, which increases the likelihood of developing ischemic heart disease in the long term. The rates of major coronary events increase linearly with the mean dose to the heart.[18] Using VMAT alone to treat the PTV unnecessarily increased exposure to the heart, thus increasing the mean heart dose and low dose to unspecified normal tissue, both of which were lower with PWT. The influence of low dose on heart disease, specifically the volume of the heart covered by 1 to 2 Gy with radiation therapy, has been investigated in the literature.[19] No correlation has been

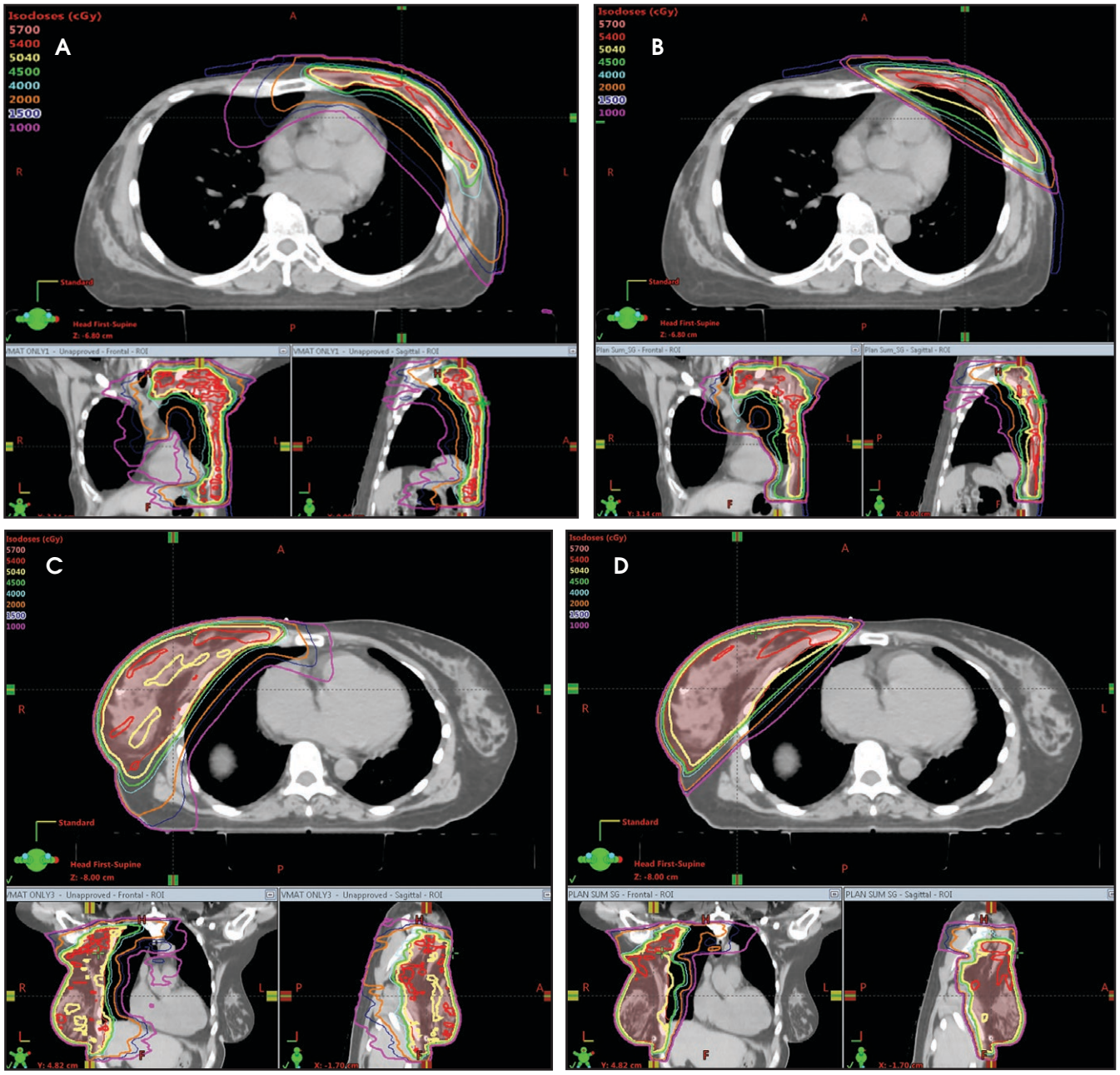


FIGURE 5. *(A) Dose distribution in the axial, coronal and sagittal plane using volumetric-modulated arc therapy (VMAT) alone for the left-sided case. (B) Dose distribution in the axial, coronal and sagittal plane using VMAT and partially wide tangents (PWT) for the left-sided case. (C). Dose distribution in the axial, coronal and sagittal plane using VMAT alone for the right-sided case. (D) Dose distribution in the axial, coronal and sagittal plane using VMAT and PWT for the right-sided case.*

found between low dose and cardiac function or perfusion defects, or worsening of these defects within a short-term follow-up (1 year after exposure). The study concluded that with average MHD < 5 Gy (1.1 to 6.1 Gy), no clinically significant defects were found after radiation therapy. Due to the absence of long-term follow-up data with respect to low dose to the heart, for patients treated with VMAT, it is optimal to keep volumes of the heart covered within all dose ranges as low as possible while maintaining adequate coverage to the target. This caveat of increased low dose prevented the use of VMAT alone for both cases, making the combination of VMAT and PWT the preferred choice.

Dose to the contralateral lung with this combination approach, however, was increased compared to PWT. Although

it was found to be less compared with VMAT, long-term follow-up again unavailable, the impact of low dose to the contralateral lung on the incidence of RP is currently unclear, although rates of grade 3 or higher RP have not been observed, even when the V5 Gy to the ipsilateral lung was 100%.[20]

Using this combination technique also increases low dose exposure to other normal tissue; however, the exposure is less compared with using VMAT alone to cover the entire PTV. The primary aim of this combination was to reduce the ipsilateral lung V20 Gy, as studies have shown that its value of > 30% is associated with increased rates of short-term radiation pneumonitis and change in short-term pulmonary function. For the right-sided case, increased exposure from the VMAT portion of the combination plan to the contralateral breast was not a concern because the PTV by that region was covered using PWT. Although the left-sided case had undergone a bilateral mastectomy, again, increased exposure from the VMAT portion of the plan to this region was not a concern for the same reason.

Both patients were treated with free breathing as they were not capable of deep inspiration breath hold. In addition to the standard PWT fields, there were 2 partial arcs to treat, each of which took 67 seconds. Hence, the treatment time required was a little over 2 minutes more than standard treatment.

Conclusion

In this technical report, we have presented a unique situation of a left- and right-sided case whereby the MHD was acceptable for treatment; however, the ipsilateral lung V20 Gy had exceeded the required dosimetric tolerance. A combination of VMAT and PWT was not only able to meet constraints for the ipsilateral lung, but did so without compromising doses to other critical organs such as the heart. This was achievable with the PWT technique and without increasing unnecessary exposure to all other organs compared to VMAT alone.

References

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366:2087-2106.
2. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014;383(9935):2127-2135.
3. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med.* 2015;373(4):307-316.
4. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med.* 2015;373(4):317-327.
5. Marks LB, Hebert ME, Bentel, G et al. To treat or not to treat the internal mammary nodes: a possible compromise. *Int J Radiat Oncol Biol Phys.* 1994;29(4):903-909.
6. Pierce LJ, Butler JB, Martel MK, et al. Postmastectomy radiotherapy of the chest wall: Dosimetric comparison of common techniques. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1220-1230.
7. Beckham WA, Popescu CC, Patenaude VV, et al. Is multibeam IMRT better than standard treatment for patients with left-sided breast cancer? *Int J Radiat Oncol Biol Phys.* 2007;69(3):918-924.
8. Popescu CC, Olivotto IA, Patenaude VV, et al. Inverse-planned, dynamic, multi-beam, intensity-modulated radiation therapy (IMRT): A promising technique when target volume is the left breast and internal mammary lymph nodes. *Med Dosim.* 2006;31:283-291.
9. Popescu CC, Olivotto IA, Beckham WA, et al. Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys.* 2010;76(1):287-295.
10. Goldman UB, Anderson M, Wennberg B et al. Radiation pneumonitis and pulmonary function with lung dose-volume constraints in breast cancer irradiation. *Journal of Radiotherapy in Practice* 2014;13:211-217.
11. Lind PA, Wennberg B, Gagliardi G, et al. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. *Breast Cancer Res Treat.* 2001;68:199-210.
12. Radiation Therapy Oncology Group. RTOG Breast Cancer Contouring Atlas. https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx Accessed September 13, 2017.
13. Kestin LL, Sharpe MB, Frazier RC, et al. Intensity modulation to improve dose uniformity with tangential breast radiotherapy: Initial clinical experience. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1559-1568.
14. Dumane VA, Hunt MA, Green S, et al. Dosimetric comparison of volumetric modulated arc therapy, static field intensity modulated radiation therapy, and 3D conformal planning for treatment of a right-sided reconstructed chest wall and regional nodal case. *J Radiother.* 2014;1-12.
15. Li JG, Liu C, Kim S, et al. Matching IMRT fields with static photon field in treatment of head-and-neck cancer. *Med Dosim.* 2005;30(3):135-138.
16. Amdur RJ, Liu C, Li J, et al. Matching intensity-modulated radiation therapy to an anterior low neck field. *Int J Radiat Oncol Biol Phys.* 2007;69(2):S46-S48.
17. Rothwell RI, Kelly SA, Joslin CA, et al. Radiation pneumonitis in patients treated for breast cancer. *Radiother Oncol.* 1985;4(1):9-14.
18. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New Engl J Med.* 2013;368(11):987-998.
19. Chung E, Corbett JR, Moran JM, et al. Is there a dose-response relationship for heart disease with low-dose radiation therapy? *Int J Radiat Oncol Biol Phys.* 2013;85(4):959-964.
20. Ho AY, Ballangrud AM, Li G, et al. Pneumonitis rates following comprehensive nodal irradiation in breast cancer patients: results of a phase I feasibility trial of intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;87(2):S48-S49.

Charting new courses in palliative radiation therapy: Technology's role

Mary Beth Massat

Although advanced cancer, such as metastatic disease, cannot often be cured, it can be treated with palliative care. Designed to resolve symptoms and make patients as comfortable and pain-free as possible, palliative treatments include surgery, chemotherapy and radiation therapy.

The American Society of Clinical Oncology (ASCO) recommends that palliative care be offered to patients within 8 weeks of an advanced cancer diagnosis. A presentation at the 2015 annual meeting of the American Society for Radiation Therapy (ASTRO) reported that a collaborative, patient-reported outcomes-based approach by radiation oncologists and palliative care teams improved symptom management and lowered costs for late-stage cancer patients and end-of-life hospitalizations.[1]

In 2017, ASTRO updated its evidence-based guidelines for palliative radiation therapy (RT) of bone metastases. The updated guidelines address the 8 questions from the initial 2011 bone metastases guidelines based on new published clinical research and literature.

***Ms. Massat** is a freelance healthcare writer based in Crystal Lake, IL.*

According to Joshua Jones, MD, MA, assistant professor, Department of Radiation Oncology, Hospital of the University of Pennsylvania, and a co-author of the updated guidelines, one of the more common treatments is managing bone metastases.

"There is a range of what is appropriate, so we need the guidelines. But fundamentally, we need to … better understand how best to tailor radiotherapy to the individual patient: When is stereotactic radiotherapy and ablative radiotherapy most appropriate in the management of bone metastases, and when are simpler techniques with lower doses most appropriate?" he asks, noting that an influx of data is expected in the next two years from randomized studies. "The key questions are: Who will most benefit from palliative radiotherapy? What dose/fractionation and technique are most appropriate with de novo palliative radiation? What dose/fractionation and technique are most appropriate in the re-irradiation setting?"

The brain is another common site for metastatic cancer. ASTRO has published guidelines on whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS), as well as combining WBRT with radiosensitizers or chemotherapy. But even with these guidelines, ambiguity remains regarding the most optimal treatment, says Charles B. Simone, MD, associate professor at the University of Maryland School of Medicine, Baltimore, and medical director of the Maryland Proton Therapy Center. Dr. Simone believes it is possible to develop standard pathways for treatments based on factors such as number and/or volume of metastatic lesions.

However, other variables can determine the number of treatment approaches, such as patient performance status, extent of extracranial disease and overall tumor burden, neurological symptoms, and other concurrent treatments being used such as chemotherapy or immunotherapy, notes Dr. Simone. "It can also be something as simple as the distance from the patient's home to the treatment facility," he says.

Current Trends

Dr. Jones notes two interesting trends in treating bone metastases: the use of more hypofractionated treatments and the movement toward advanced techniques such as stereotactic body radiation therapy (SBRT).

"It is interesting that we are moving in both directions simultaneously,"

There is great hetereogeneity among patients with metastatic cancer and considerable variability in outcomes according to primary tumor site and location, and extent of metastases.

Charles B. Simone, MD
University of Maryland School of Medicine

he says, "where we are utilizing more complex techniques and also simpler, shorter treatments."

Fundamentally, the key question remains that of local control of the metastasis. Consider a patient with a painful rib metastasis and other metastatic disease that may benefit from additional systemic therapies. Given the equivalence in pain palliation with single- and multifraction RT, a simple treatment with 1 fraction could be the best course, says Dr. Jones. On the other end, a patient with a solitary metastasis in the spine that can worsen pain and potentially lead to spinal cord compression may be best served with an ablative technique, such as SBRT.

"We have to define upfront the goal of our therapy," he explains. "We traditionally thought of radiotherapy in two categories: curative or palliative therapy. Now we see that there is an intermediary goal: a patient with metastatic disease who we don't think we can cure but [for whom] there is a strong rationale for an aggressive approach to improve local control and decrease side effects."

In addition to increased use of more advanced treatment modalities such as intensity-modulated RT (IMRT), volumetric-modulated arc therapy (VMAT), SBRT and, in some cases, proton therapy, Dr. Simone sees two other trends in palliative RT: shorter treatment courses and high variations in outcomes.

"There is a recognition that a shorter course of therapy is equally effective, more cost effective and more convenient for patients," Dr. Simone says. "Also, there is great hetereogeneity among patients with metastatic cancer [and] considerable variability in outcomes according to primary tumor site and location, and extent of metastases.

For example, widely metastatic disease differs from a single oligometastatic disease for palliation. "We need to consider not only improving the quality of life but also … progression-free survival and potentially even overall survival," he says.

Metastatic location is crucial in determining type of treatment. With rib, pelvic or extremity metastatic disease, traditional 2- or 3-dimensional RT is generally simple and effective. In the brain, SRS is often utilized. In more critical areas, and particularly for patients with oligometastatic or oligoprogressive disease, advanced modalities such as IMRT and SBRT can be considered.

While proton therapy is not broadly used, it also can be an option. A key consideration is re-irradiation of a site in cases where the clinician cannot deliver radiation again due to maximum tissue constraints of the organ or anatomic area. For instance, a patient with a large bulky thoracic recurrence that had previously been treated with definitive RT, and where retreatment with additional photon RT would be too toxic, could be a candidate for proton re-irradiation to prevent or treat cord compression, improve quality of life, or locally control disease and delay additional progression or further systemic therapy. He recalls a patient with otherwise stable disease and good performance status who had two prior courses of RT for spinal metastases. The patient was referred for a third course of treatment using proton therapy to alleviate painful compression in the spine and to prolong survival. With proton therapy, Dr. Simone stopped the dose before it reached the spinal cord, allowing for effective re-irradiation and palliation.

Adds Dr. Jones, "While location matters, part of the answer to the question is prognosis. If a patient has been through 12 courses of systemic therapy and the disease is widespread, then local control is less likely to matter, and less complex treatments are generally the right course."

In addition to local control and prognosis, the clinician must also consider the most appropriate treatment for the desired effect, such as alleviating pain, a neurologic deficit, bleeding, cough or an obstruction.

Also being explored is the role of histology in tailoring palliative radiation therapy. Dr. Jones explains that if the tumor histology is understood to be more radiosensitive or radio-resistant to RT, that can impact techniques and dose.

The most common barrier to initiating hypofractionated RT or SBRT for palliative care is the clinician's comfort level.

Joshua Jones, MD, MA
Hospital of the University of Pennsylvania

"A question I often ask is, What else is possible for that patient so we aren't just thinking about radiotherapy? If we have the option for an interventional-directed ablation, or a surgical technique or effective systemic therapy, how do we weigh those in conjunction with RT?" he poses. "While some of this was addressed in the updated ASTRO guidelines, it is an area that we are still exploring."

Benefit vs cost is a concern as well. Dr. Jones had a patient who, in her own words, had crushing medical debt and couldn't catch up. Her main concern as she approached end of life was the impact of the debt on her family.

Barriers

One barrier to providing effective palliative radiation therapy is patient pain. In Dr. Jones' practice, nearly one-third of his patients have difficulty lying flat on a treatment table due to painful spine, rib or bone metastases. To address this problem, continued development is needed for technologies that can rapidly scan and treat a patient. Dr. Jones would also like to see more innovation in treatment delivery, such a seated position for treatment.

"We have a tremendous opportunity to come up with alternative patient positioning as well as imaging modalities in palliative radiation," he stresses.

Unfortunately, the most common barrier to initiating hypofractionated RT or SBRT for palliative care is the clinician's comfort level. "They know the data and information published in the literature," says Dr. Jones, "but if they've never done it, they are hesitant."

A key predictor of using a shorter course of treatment is clinician training. While palliative RT has been used for decades, the field has evolved just as it has with curative RT. "As a society, we need to think about how we continue to make palliative care a part of our practice, including how our treatments impact our patients," he adds.

Similarly, Dr. Simone says continuing education is critical to increasing use of hypofractionated and single-fraction treatments, noting that the updated ASTRO guidelines for bone metastases cite pain relief equivalency between single and multiple fraction regimens.

"Another barrier is the misalignment between the goals of the patient and the physician," says Dr. Simone. In general, predicting overall survival remains a difficult process. Yet, while a patient may be terminally ill and desire quality of life, the clinician may hope that the course of treatment can impact survival.

"Examining quality of life should not just be the end result of symptoms but also impact how we deliver treatments," he adds. "I am definitely an advocate of a shorter course of treatment for palliation and, whenever possible, will prescribe a single or hypofraction RT treatment."

To address the need for training, Dr. Simone is hopeful that more residency programs will include dedicated curriculums for palliative care. Instituting a dedicated palliative radiation oncology service can also impact the use of single-fraction and hypofractionated radiation therapy for bone metastases, as was recently shown following initiation of the Supportive and Palliative Radiation Oncology service at the Dana-Farber/Brigham and Women's Cancer Center Department of Radiation Oncology.[2]

Fortunately, such programs have increased over the last 5 years, "While experience is still limited, the evidence shows that having a dedicated program increases referrals and the ability to study all these issues surrounding palliative care," says Dr. Jones. "I hope this trend continues, with a focus on both simple and complicated stereotactic techniques, so we can continue to explore what is best for these patients."

References

1. Read PW, Blackhall LJ, Stukenborg GJ, et al. Outcomes of a re-engineered palliative care and radiation therapy care model. *Int J Radiat Oncol, Biol, Phys.* 2016;94(1):2-3.
2. Tseng YD, Krishnan MS, Jones JA, et al. Supportive and palliative radiation oncology service: impact of a dedicated service on palliative cancer care. *Pract Radiat Oncol.* 2014;4(4):247-253.

RADIATION ONCOLOGY CASE

Massive spinal ependymoma: An intriguing case and review of the literature

Paul Ramia, MD; Khaled Alok, MD; Abeer Tabbarah, MD; Marwan Najjar, MD; Youssef H. Zeidan, MD, PhD

CASE SUMMARY

A 50-year-old previously healthy woman presented with a progressively worsening sensation of bilateral leg heaviness over the past 18 months associated with mild low back pain but no neurological deficits. Magnetic resonance imaging (MRI) of the spine revealed a 21-cm homogenously enhancing cystic lesion occupying the spinal canal from the level of T12 to S5 (**Figure 1**). Due to symptom progression, the patient was advised on debulking surgery by her neurosurgeon who performed a T12 to L5 bilateral laminectomy. Intraoperatively, the large intradural lesion was noted to be infiltrating the nerve roots, and its sacral component was not resected. Microscopic examination of this specimen revealed papillary and perivascular arrangements of epithelial cells with abundant perivascular mucin and low mitotic activity. A diagnosis of myxopapillary ependymoma (MPE) (WHO grade I) was rendered.

*All authors are from the American University of Beirut Medical Center. **Dr. Ramia** is a radiation oncology resident. **Dr. Alok** is a neurosurgery resident. **Dr. Tabbarah** is a pathologist and faculty member. **Dr. Najjar** is a neurosurgeon and faculty member. **Dr. Zeidan** is a radiation oncologist, faculty member and program director in the department of radiation oncology.*

Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

After discussing the case with the multidisciplinary tumor board, we decided to give both adjuvant radiation to the surgical bed and definitive treatment to the residual sacral mass. Both 3-dimensional conformal (3DCRT) and intensity-modulated radiation therapy (IMRT) planning were performed for evaluation. The patient was prescribed 4500 cGy in 25 fractions to the surgical bed and additional 5 boost fractions to the residual sacral disease with a 1-cm volumetric margin to a total dose of 5400 cGy. Mean dose delivered to the incision site was 2000 to 2500 cGy. Due to the more widely distributed low-dose regions affecting the kidneys and other normal structures, IMRT did not offer any normal tissue-sparing benefits. We also found no major advantage for IMRT over 3DCRT in terms of target coverage, with 95% of the low- and high-risk planning target volume (PTV) receiving > 95% of the prescribed dose; therefore, 3DCRT was utilized using 6- MV photon beams (**Figure 2**).

IMAGE FINDINGS

MRI of the spine revealed a 21-cm homogenously enhancing cystic lesion occupying the spinal canal from level T12 to S5, encasing the nerve roots and associated with scalloping of the vertebral bodies (**Figure 1**).

DIAGNOSIS

MPE status following subtotal resection

DISCUSSION

Ependymomas, the most common primary spinal cord tumors, are subclassified as myxopapillary ependymoma, classic ependymoma, and anaplastic ependymoma. Optimal treatment remains an area of investigation but typically includes surgical resection with possible adjuvant radiation therapy.[1] MPEs are a relatively rare type of spinal cord ependymoma that often arise in the conus medullaris and may progressively worsen lower extremity neurologic symptoms due to nerve root compression.[2] These tumors are often slow growing and, thus, patients suffer from such progressively worsening symptoms for years prior to diagnosis.[3] Optimal treatment for symptomatic lesions remains an area of investigation but typically includes surgical resection with consideration of adjuvant radiation therapy.[2] Several factors discourage the use of radiation therapy as the primary modality, including limited response, need for tissue diagnosis, and fear of radiation

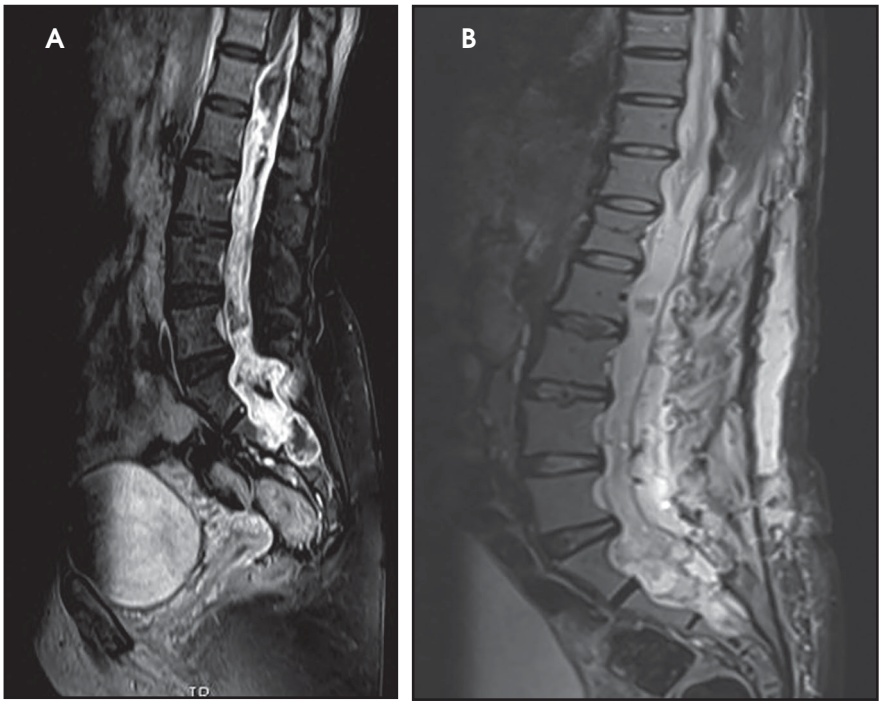


FIGURE 1. *(A) Preoperative Sagittal MRI, T2 sequence showing a large lumbosacral mass. (B) Postoperative Sagittal MRI, T2 sequence showing residual sacral mass and postoperative changes in the lumbosacral spine and paraspinal soft tissues.*

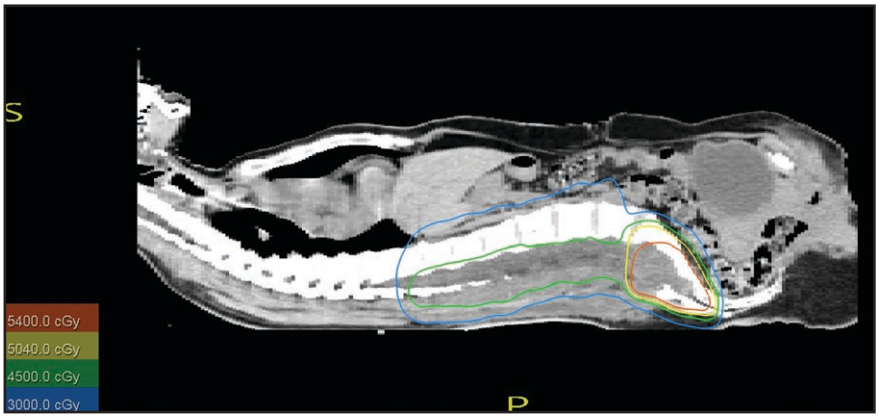


FIGURE 2. *Radiation treatment plan. The postoperative bed was treated to a dose of 4500 cGy and the residual sacral disease boosted to 5400 cGY via a 3-dimensional conformal radiation plan.*

myelopathy. The risk of myelopathy in cervicothoracic regions of the spinal cord is influenced by many factors, including total dose delivered, fractionation, and length of cord irradiated.[4] Data on dose tolerance as a function of length irradiated in the lumbo-sacral area of the spine is lacking and, therefore, we opted to treat the surgical bed with only 45 Gy as opposed to the higher dose given to the gross disease at the level of the cauda equina. Due to the rarity of this disease, there is also a paucity of randomized data comparing surgery with or without radiation for grossly resected tumors, with some studies casting doubt on the benefit of adjuvant RT.[5] However, there appears to be a local control benefit for adjuvant radiation therapy in patients with MPE regardless of the extent of tumor resection.[6,7]

MPEs are a rare variant of spinal cord ependymomas, accounting for 13%, usually originating in the filum terminale or conus medullaris and growing in the lumbosacral region. These well-encapsulated, noninvasive tumors are classified by the WHO as grade I tumors due to their slow growth, and tend to be diagnosed in the third or fourth decade of life.[8] Histologically, these low-mitotic-activity tumors display epithelial cells in papillary and perivascular arrangements with mucin around the vessels and microcystic spaces.[8] In some surgical series, complete surgical resection provides excellent long-term outcomes with median time to recurrence > 7 years.[8] Despite local therapy, it is not uncommon for these tumors to recur outside the surgical bed along the neural axis.[8]

A large retrospective study of 183 patients showed that the extent of surgical resection and use of adjuvant radiation therapy were important prognostic factors in terms of local control and progression-free survival (PFS); however, no demographic or treatment-related factors translated into an overall survival benefit on multivariate analysis. Average tumor size in this series was only 2 cm; however, tumors up to 20 cm were included[10] (**Table 1**). Interestingly, the patient population that fared worse was those younger than age 35 with a PFS below 40% at 10 years.[10] This finding is consistent with previous reports in the literature showing that despite being a low-grade tumor, MPE in the pediatric population can be aggressive.[11] In the aforementioned study, adjuvant radiation therapy at a median dose of 5040 cGy increased 10-year PFS from 40% to 70%, thus leading us to recommend more liberal use of adjuvant radiation, especially in the setting of subtotal resection.[10] Controversy remains

Table 1. Select Studies in Spinal Myxopapillary Ependymoma

Author (year)	Median Size	N (RT/ overall)	RT dose	Results (RT/No RT)
Pica et al (2009)[5]	2.5 cm (largest 11 cm)	47/85	50.4 Gy	5yr PFS 74.8%/50.4%
Sonneland et al (1985)[13]	NR	46/77	NR	LC NR /83%
Akyurek et al (2006)[6]	NR	22/35	50.4 Gy	LC 86%/46%
Weber et al (2015)[9]	2 cm (largest 20 cm)	86/183	50.4 Gy	10yr PFS 70%/40%

Key: NR = not reported, RT = radiation therapy, Gy = Gray, PFS = progression-free survival; LC = local control

concerning the presence of a dose-response relationship when ependymal tumors are treated with radiation, probably due to the heterogeneity of patient and tumor factors across the different reports.[3,12] However, there appears to be some evidence for a dose-response relationship at doses < 4500 and > 5000 cGy.[13]

CONCLUSION

In conclusion, we have presented a case of MPE, a rare spinal tumor, which to the best of our knowledge is the largest reported in the literature. This tumor was 21 cm in the craniocaudal dimension and was subtotally resected. Our patient received adjuvant radiation with a boost to gross residual disease to improve local control. Future randomized studies are needed to clarify the role of radiation therapy in managing spinal ependymomas.

REFERENCES

1. Ostrom, QT, Gittleman H, Xu J, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. *Neuro Oncol.* 2016;18:suppl5:v1-75.
2. Lee J, Parsa AT, Ames CP, MCormick PC. Clinical management of intramedullary spinal ependymomas in adults. *Neurosurg Clin N Am.* 2006;17(1):21-27.
3. Schellinger KA, Propp JM, Villano JL, McCarthy BJ. Descriptive epidemiology of primary spinal cord tumors. *J Neuro Oncol.* 2008;87(2);173-179. Schultheiss TE. The radiation dose-response of the human spinal cord. *Int J Radiat Oncol Biol Phys.* 2008;71(5):1455-1459.
4. Milano MT, Johnson MD, Sul J, et al. Primary spinal cord glioma: a Surveillance, Epidemiology, and End Results database study. *J Neuro Oncol.* 2010;98(1):83-92.
5. Pica A, Miller R, Villà S, et al. The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: a retrospective study from the Rare Cancer Network *Int J Radiat Oncol Biol Phys.* 2009;74(4):1114-1120.
6. Akyurek S, Chang EL, Yu TK, et al. Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at MD Anderson Cancer Center. *J Neuro Oncol.* 2006;80(2):177-183.
7. Bagley CA, Wilson S, Kothbauer KF, et al. Long-term outcomes following surgical resection of myxopapillary ependymomas. *Neurosurg Rev. 2009;*32(3):321-334;disc334.
8. Khan NR, VanLandingham M, O'Brien T, et al. Primary seeding of myxopapillary ependymoma: different disease in adult population? Case report and review of literature. *World Neurosurg.* 2017;99:812.e21-812.e26.
9. Weber DC, Wang Y, Miller R, et al. Long-term outcome of patients with spinal myxopapillary ependymoma: treatment results from the MD Anderson Cancer Center and Institutions from the Rare Cancer Network. *Neuro Oncol.* 2015;17(4):588-595.
10. Fassett DR, Pingree J, Kestle JR. The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. report of five cases and review of the literature. *J Neurosurg.* 2005;102(1)Suppl59-64.
11. Linstadt DE, Wara WM, Leibel SA, et al. Postoperative radiotherapy of primary spinal cord tumors. *Int J Radiat Oncol Biol Phys.* 1989;16(6):1397-1403.
12. Taylor RE. Review of radiotherapy dose and volume for intracranial ependymoma. *Ped Blood Cancer.* 2004;42(5):457-460.
13. Sonneland PR, Scheithauer BW, Onofrio BM. Myxopapillary ependymoma. a clinicopathologic and immunocytochemical study of 77 cases. *Cancer.* 1985;56(4):883-893.

Radiation therapy planning for gastro-esophageal junctional carcinoma in a paraesophageal hiatal hernia

Nilesh Tambe, MSc; Mohan Hingorani, FRCR; Andrew Beavis, PhD; Sanjay Dixit, FRCR

CASE SUMMARY

Although radiation therapy planning, including 4-dimensional (4-D) planning for gastro-esophageal cancer has become standardized, a similar standard has not been well defined for stomach and Siewert type II and III cancers. Rarely, this type of tumor is found in a fixed type II paraesophageal hiatal hernia with the stomach lying in the chest, which makes the planning parameters challenging.[1] Distorted anatomy of the stomach, displacement of the heart and lung, and temporal aliasing of the tumor caused by respiratory motion compound the uncertainties of target volume shape and position. Most of such reported cases have been treated with surgery.[2-4] Here we report radiation therapy planning for the Siewert type II cancer with the stomach lying fixed in the chest.

An 82-year-old woman with World Health Organization (WHO) performance status 1 presented with melena and anemia. A computed tomography (CT) scan showed a large hiatal hernia with the gastroesophageal junction (GEJ) and a large portion of the stomach displaced into the thorax. Endoscopic biopsy and ultrasound showed adenocarcinoma starting at the GEJ and extending to the proximal stomach with 8 cm in length (30 to 38 cm) and 2.3 cm in thickness invading the muscle without any lymphadenopathy. Positron emission tomography (PET) confirmed this tumor with SUV_{max} 40 (T3N0M0).

Surgery was discounted due to a high risk of postoperative mortality. Cognizant of her risk of significant side effects, we provided a moderate dose of radiation therapy with a reduced dose of oral capecitabine to control bleeding from the tumor and reduce the risk of dysphagia. The patient received 45 Gy in 25 fractions over 5 weeks with concomitant capecitabine.

*All authors are at Castle Hill Hospital, Hull and East Yorkshire Hospitals NHS Trust, Cottingham, UK. **Mr. Tambe** is a clinical scientist, **Dr. Hingorani** is a consultant clinical oncologist, **Dr. Beavis** is a consultant physicist, and **Dr. Dixit** is a consultant clinical oncologist.*

Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

RADIATION THERAPY PLANNING

The patient underwent a free-breathing 3-dimensional CT (3DCT) with contrast, and a free-breathing 4DCT scan (binned into 10 phases). The 3DCT, 4DCT, PET 18-fluorodeoxyglucose scan images were co-registered for the target delineation (**Figure 1**).

For clinical planning, gross tumor volume (GTV) was delineated on 3 of the 10 phases (max_inhale, max_exhale, and midphase) of the 4DCT scan using PET-CT and endoscopic ultrasound (EUS) information. The GTV from all 3 phases was then combined onto the 3D contrast scan (GTV_{Total}) and the clinical target volume (CTV) A, CTV B and PTV were produced by applying 4DCT margins as defined in **Table 1**. Both GTV_{Total} and CTV A volumes were expanded to account for any additional motion from all other 4DCT phases. The 4DCT scan showed an internal motion of 0.3 cm, 0.5 cm and 0.9 cm in lateral, anterior-posterior (AP) and superior-inferior (SI) directions, respectively.

A RapidArc (volumetric-modulated arc therapy [VMAT]) plan was produced within the Eclipse planning system (V11, Varian, Palo Alto, California) aiming 95% of the prescribed dose to cover 99% of the PTV, keeping organs at risk (OARs) below the constraints. One full arc of a 6-MV beam was used and doses were calculated using the Varian AcurosXB algorithm.

RESULTS AND DISCUSSION

In addition to the clinical plan, the effect of internal target motion on treatment volume and, hence, on OAR doses was assessed by contouring GTV on 4DCT and 3DCT scans separately (**Figure 2**). Then, 3 additional treatment plans (3D-conformal [3DCRT] and VMAT) were produced with volumes generated using 3D and 4D margins from **Table 1**, and DVH parameters for all plans were compared (**Table 2**).

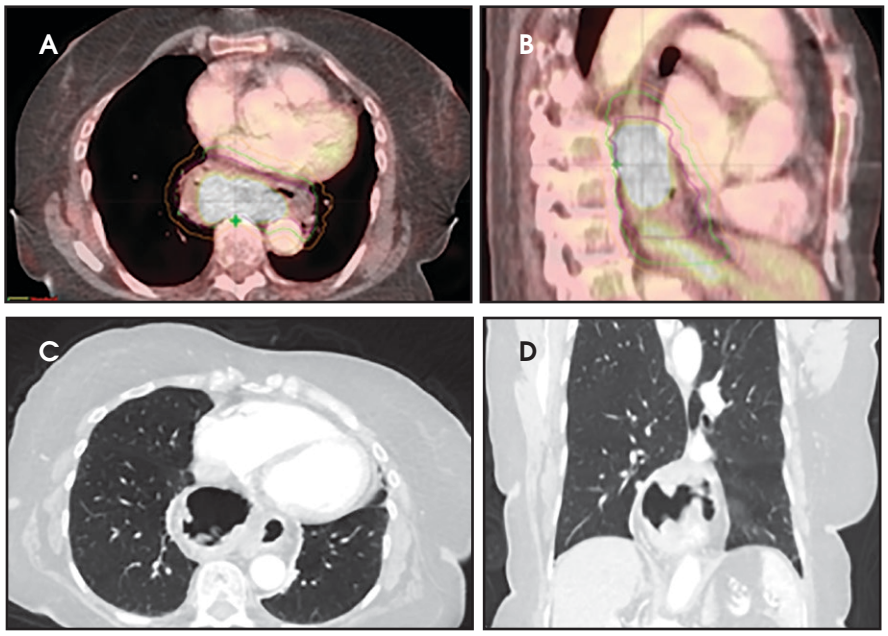


FIGURE 1. *Images A and B show gross target volume (GTV) (purple), internal treatment volume (ITV) (green), and planning target volume (PTV) (orange) on axial (A) and sagittal (B) views blended with a positron emission tomography–computed tomography (PET-CT) scan. Diagnostic images C and D show location of a hiatal hernia with a tumor and a large portion of the stomach displaced into the thorax.*

Table 1. Margins Used for 3D and 4D Volume Construction in Accordance with SCOPE 1[5] and NEOSCOPE[6] Clinical Trial Protocols

Volume	3D Margin	4D Margin
CTV A	GTV + 2.0 cm extended superiorly	GTV_{Total} + 2.0 cm manually extended superiorly and inferiorly
CTV B	CTV A + 1.0 cm circumferential. Extended manually 2.0 cm inferior. Edited for normal structures.	N/A
ITV	N/A	CTV A + 1.0cm isotropic. Extended manually 2.0 cm inferior. Edited for normal structures.
PTV	CTV B + 0.5 cm circumferential + 1.0 cm superior and inferior. Reduce posterior margin on slices where the CTV B abuts the vertebra to a minimum of 0.5 cm.	ITV + 0.5 cm isotropic

Key: CTV = clinical target volume, GTV = gross tumor volume, N/A = not applicable, ITV = internal tumor volume, PTV = planning target volume

VMAT plans produced on 3D and 4D volumes showed insignificant differences in the PTV coverage; however, a systematic increase in OAR doses was seen for the 3D volume plan. A similar trend was seen for 3DCRT plans; however; mean heart dose exceeded the tolerance dose of 26 Gy in both (3DCRT) plans (**Table 2**).

Daily free-breathing cone-beam CT (CBCT) was performed prior to each fraction (**Figure 2J**). Images were matched using bony anatomy and evaluated if the GTV defined at planning was within the PTV. All setup errors were corrected prior to treatment, and the patient completed radiation therapy without any treatment interruptions. The average (max) setup error recorded from the pretreatment CBCT matching for all fractions was 0.1 cm (± 0.7) in the lateral, 0.2 cm (± 0.6) in the anterior-posterior (AP), and -0.5 cm (± 0.7) in the SI direction.

Furthermore, interfractional tumor motion was calculated by contouring the GTV volume on all 25 CBCTs (**Figure 2**). Online registration (ie, the one used for online matching and treatment delivery) was used to transfer the volume on the planning CT. Mean (max) tumor motion was 0.59 (0.86) cm, 0.29 (0.56) cm and 0.45 (0.53) cm in the lateral, AP, and SI direction, respectively. Maximum tumor motion is greater than the margin applied to PTV (0.5 cm isotropic) illustrating the importance of daily CBCT in patients with this condition. Our case also illustrates the bigger lateral rather than SI organ motion, which is observed in the GEJ tumor[7,8] in the normally lying infra-diaphragmatic stomach.

Acute toxicities were grade 1 odynophagia, mild nausea, and grade 1 fatigue. Eight weeks following radiation therapy, the PET scan showed a significant reduction in the volume of hypermetabolic gastric tumor with residual tumor of 1.0 cm and SUV_{max} of 7 without metastases (**Figure 3**). The patient's hemoglobin improved. The patient died due to liver metastases after 7 months following the treatment. During these 7 months, the patient did not require transfusion, remained free from dysphagia and malena, and maintained performance status 1 until 2 weeks before death.

Through a PubMed search, we did not find any 4D radiation therapy treatment planning parameters in a patient with a junctional and upper stomach tumor

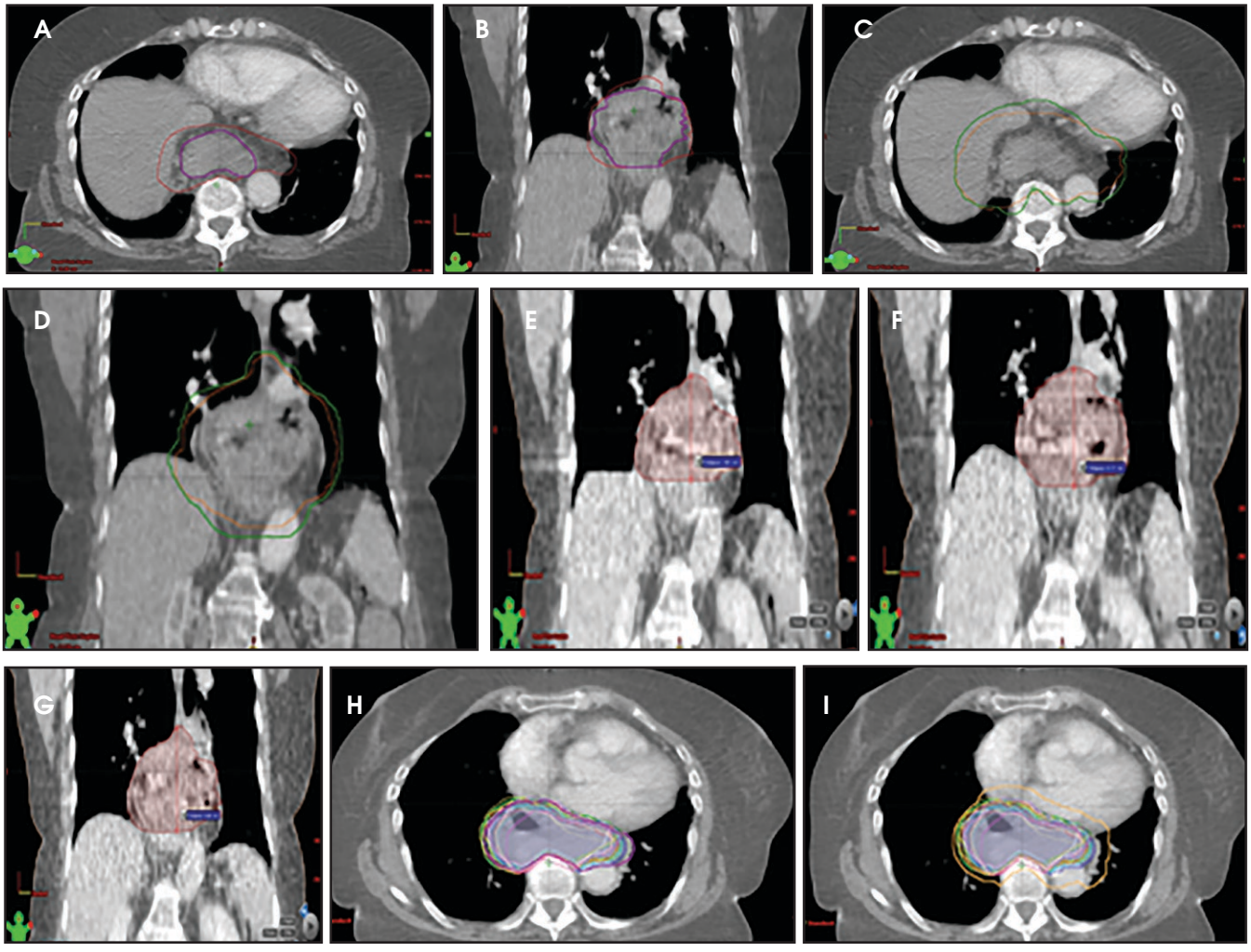


FIGURE 2. *The axial (A) and coronal (B) views show the maximum difference in the gross tumor volume (GTV) contour (3D GTV [purple] and 4D GTV [red]) near the diaphragm. Changes in the planning target volumes (PTVs) (C and D) are also shown on corresponding slices (3D PTV [green] and 4D PTV [orange]). GTV temporal aliasing can be seen on images E, F and G. Image H shows all GTVs contoured on cone-beam computed tomography (CBCT) images displayed on planning CT. I shows GTVs plus PTV in bold orange. Image J shows GTV on a CBCT image.*

associated with a large part of the stomach lying into the intrathoracic cavity.

Thoracic and abdominal tumors move with breathing, necessitating that the treatment plan account for motion during treatment planning and delivery.[7-9] Organ motion could be high for organs below the diaphragm. The stomach motion was observed mostly in the anterior, superior and left (up to 1.75 cm), toward the right and posterior (0.88 cm), and least inferiorly (0.5 cm), despite accounting for respiratory motions.[10]

In this patient, an infra-diaphragmatic organ was lying in a supra-diaphragmatic location posing difficulty in estimating organ movement and applying planning target margins as referenced in the literature. In addition, the tumor extent was not clearly visible on the CT scan, posing a planning challenge in the absence of guidelines and standards for this type and location of tumor.

Hence, we employed 4DCT imaging, which demonstrated that internal target motion could be larger compared to that observed with esophageal cancer.[7,8] With a 3D margin (**Table 1**), the PTV increased by 18.1%, resulting in higher OAR doses (**Table 2**).

CONCLUSION

Our study demonstrated that the tumor in the large hiatal hernia, which

Table 2. Dosimetric Comparison of Plans Performed Using Volumes Contoured on 3DCT and 4DCT. Margins used to produce target structures are from Table 1.

Structures (Constraints)	VMAT Plans		3DCRT Plans	
	4D volumes	3D volumes	4D volumes	3D volumes
PTV V_{95} (≥ 99%)				
PTV V_{107} (< 1.8 cc)	99.63	99.40	99.91	99.39
	0.00	0.03	0.00	0.41
Spinal Cord PRV (Max_{dose} < 45 Gy)	40.10	39.93	44.96	44.33
Lungs (V20 Gy < 35%)	25.11	29.58	28.38	29.22
(Mean Dose < 20 Gy)	11.73	12.87	12.00	11.90
Heart (V30 Gy < 46%)	19.61	23.13	31.66	32.46
(Mean Dose < 26 Gy)	20.78	22.02	26.92	27.82
Liver (V30 Gy < 30%	8.85	11.18	10.61	10.82
(Mean Dose < 28 Gy)	9.36	10.78	10.48	10.90

Key: 3DCT = 3-dimensional computed tomography, 4DCT = 4-dimensional computed tomography, VMAT = volumetric-modulated arc therapy, 3DCRT = 3-dimensional conformal radiation therapy, PTV = planning target volume , PRV = planning organ at risk volume

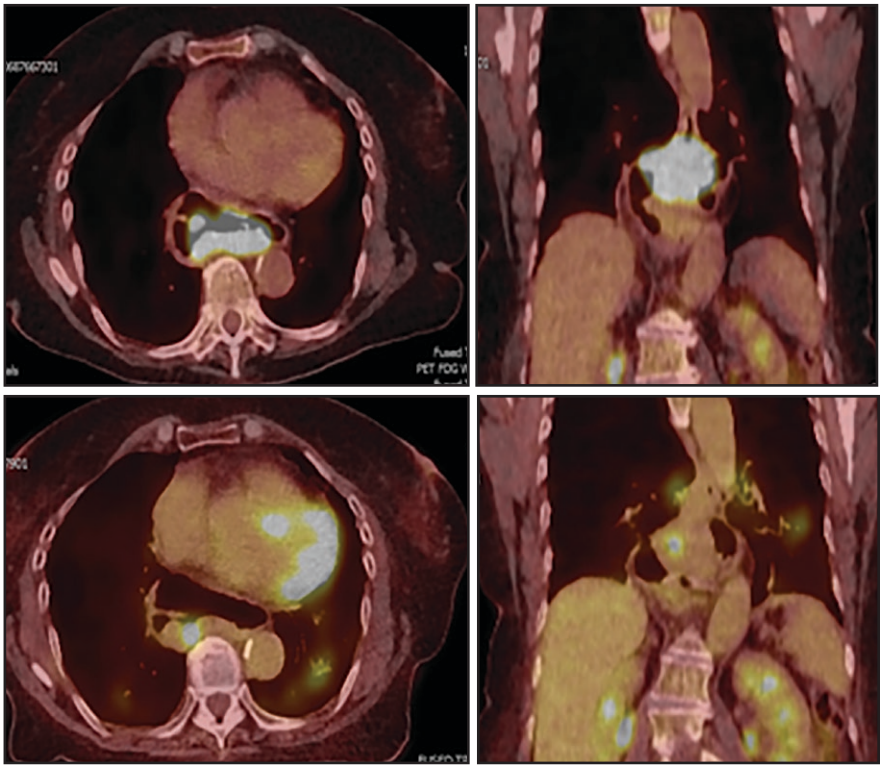


FIGURE 3. *Pretreatment (top) and post-treatment (bottom) positron emission tomography–computed tomography (PET-CT) images showing significant reduction in hypermetabolic activity.*

was displaced in the chest, can be effectively treated with chemoradiation therapy. It is, however, recommended that 4DCT be performed for target delineation to account for internal target motion, as the organ motion in this tumor does not represent that observed in patients with a GEJ tumor with normal anatomy. Our planning study demonstrated that VMAT helps minimize OAR doses. Furthermore, volumetric imaging is also recommended for larger interfractional motion, as seen in this case.

REFERENCES

1. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the diagnosis and grading of hiatal hernia. *Best Pract Res Clin Gastroenterol.* 2008;22:601-616.
2. Namikawa T, Fukudome I, Munekage E, et al. Laparoscopy‐assisted distal gastrectomy for multiple adenocarcinomas in intrathoracic upside‐down stomach. *Asian J Endosc Surg.* 2016;9:57-60.
3. Hagiwara C, Yajima K, Iwasaki Y, et al. Totally laparoscopic gastrectomy for early gastric cancer accompanied by huge hiatal hernia: a case report. *Asian J Endosc Surg.* 2016;9:61-64.
4. Gandon A, Gronnier C, Renaud F, et al. Esophageal adenocarcinoma: impact of a large hiatal hernia on outcomes after surgery. *Ann Surg.* 2016;264:862-870.
5. Crosby T, Hurt C, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. *Lancet Oncol.* 2013;14:627-637.
6. S Mukherjee, C Hurt, S Gwynne, et al. NEOSCOPE: a randomised phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. ASCO GI 2016, Oral Presentation. 2016.
7. Zhao KL, Liao Z, Bucci MK, et al. Evaluation of respiratory-induced target motion for esophageal tumors at the gastroesophageal junction. *Radiother Oncol.* 2007;84:283-289.
8. Guo YL, Li JB, Shao Q, Li YK, Zhang P. Comparative evaluation of CT-based and PET/4DCT-based planning target volumes in the radiation of primary esophageal cancer. *Int J Clin Exp Med.* 2015;8:21516-21524.
9. Wand J, Lin SH, Dong L, et al. Quantifying the interfractional displacement of the gastroesophageal junction during radiation therapy for esophageal cancer. *Int J Radiation Oncol Biol Phys.* 2012;83(2)e273-280.
10. Johnson ME, Pereira GC, El Naqa IM. et al. Determination of planning target volume for whole stomach irradiation using daily megavoltage computed tomographic images. *Pract Radiat Oncol.* 2012;2(4):e85-88.

thermoscientific

Got radiation?
See what you've been missing

Imaging in radiation environments just got easier

With superior capabilities for operating in radiation environments, the MegaRAD cameras provide excellent image quality well beyond dose limitations of conventional cameras, and are well suited for radiation hardened imaging applications

MegaRAD3 produce color or monochrome video up to 3 x 10^6 rads total dose

MegaRAD1 produce monochrome video up to 1 x 10^6 rads total dose

KiloRAD PTZ radiation resistant camera with Pan/Tilt/Zoom

In the United States:
For customer service, call 1-800-888-8761
To fax an order, use 1-315-451-9421
Email: sales.cidtec@thermofisher.com

International:
For customer service, call [01) 315-451-9410
To fax an order, use [01) 315-451-9410
Email: sales.cidtec@thermofisher.com

Find out more at **thermofisher.com/cidtec**

ThermoFisher SCIENTIFIC

INNOVATING

patient-first

CANCER TREATMENT

It is not just a tagline. It is who we are, what we do and what makes us different. We have continually introduced important cancer treatment breakthroughs that help our customers improve outcomes for patients.

PATIENT-FIRST PRECISION
Confidently delivering effective treatments with minimal side effects.

PATIENT-FIRST VERSATILITY
Making personalized treatments practical for every patient.

PATIENT-FIRST EFFICIENCY
Ensuring fewer treatments and a faster return to daily life.

VISIT US AT AAPM BOOTH #1001

#ACCURAYPATIENTFIRST

ACCURAY®

Important Safety Information
Most side effects of radiotherapy, including radiotherapy delivered with Accuray systems, are mild and temporary, often involving fatigue, nausea, and skin irritation. Side effects can be severe, however, leading to pain, alterations in normal body functions (for example, urinary or salivary function), deterioration of quality of life, permanent injury, and even death. Side effects can occur during or shortly after radiation treatment or in the months and years following radiation. The nature and severity of side effects depend on many factors, including the size and location of the treated tumor, the treatment technique (for example, the radiation dose), and the patient's general medical condition, to name a few. For more details about the side effects of your radiation therapy, and to see if treatment with an Accuray product is right for you, ask your doctor.
MKT-ARA-0118-0191