APPLIED RADIATION ONCOLOGY™
VOL 9 NO 1 MARCH 2020

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Noninvasive Cardiac Radioablation at Washington University: Past, Present and Future Directions for the Treatment of Ventricular Tachycardia
P Samson, G Hugo, K Moore, N Knutson, P Cuculich, C Robinson, Washington University, St. Louis, MO

Cardiotoxicity and Radiation Therapy: A Review of Clinical Impact in Breast and Thoracic Malignancies
EM Nichols, A Modiri, P Mohindra, University of Maryland School of Medicine, Baltimore, MD

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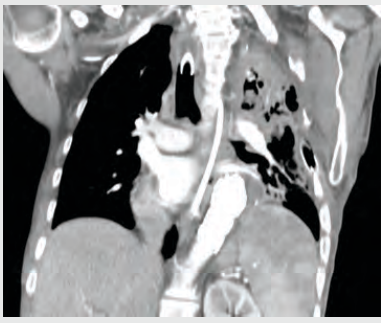
Healing Hearts: Evolution and Growth in Cardiac Radioablation
MB Massat



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March 2020
Vol. 9, No. 1

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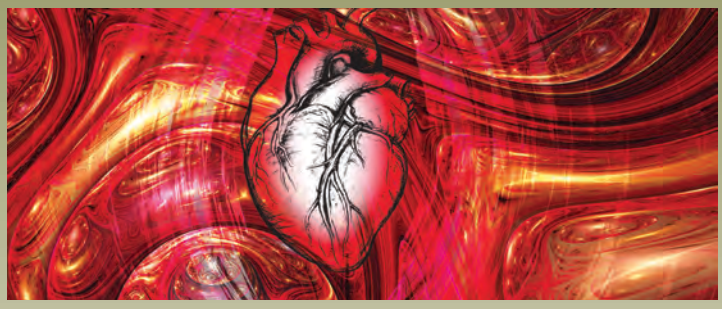

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EDITORIAL

Minimizing Potential Radiation-Related Cardiotoxicity and Treating Ventricular Tachycardia with Radioablation — Current Trends

John Suh, MD, FASTRO, FACR
Editor-in-Chief

Since heart disease and cancer are the leading causes of death in the US, research is focused on utilizing a variety of techniques to minimize potential cardiac toxicity, particularly for treatment of breast and thoracic malignancies with radiation therapy. To better understand the burden of and management options for preventing radiation-induced cardiotoxicity (RIC), we are pleased to present *Cardiotoxicity and Radiation Therapy: A Review of Clinical Impact in Breast and Thoracic Malignancies*. This SA-CME-approved article offers a thorough examination of current literature on the clinical impact of RIC in cancers of the breast, lung and esophagus, as well as mediastinal lymphomas.

A second SA-CME review article, *Noninvasive Cardiac Radioablation at Washington University: Past, Present and Future Directions for the Treatment of Ventricular Tachycardia (VT)* examines the innovative use of radiation to treat VT. The authors discuss early clinical trials demonstrating the use of noninvasive cardiac radioablation with SBRT as a potentially safe, effective, and durable salvage treatment for patients with VT in which standard management has failed. This excellent review describes key lessons from the ENCORE-VT trial, usage and workflow details, and future directions for this promising modality.

The Technology Trends article, *Healing Hearts: Evolution and Growth in Cardiac Radioablation,* complements the ENCORE-RT report to provide further insight into this emergent treatment approach, offering added perspectives on its roots, efficacy, challenges and goals.

Beyond cardiac care, we are pleased to feature two research articles on residency websites and SRS trends for glioblastoma, two case reports, and two thought-provoking editorials.

Contest Winners

I would like to congratulate the winners of the *ARO* 2019 Article of the Year contests as determined by the *ARO* advisory board for their well-written and enlightening work:

- 2019 Review Article of the Year: *The safety and efficacy of combined immunotherapy and radiation therapy* by Shwetha Manjunath, MD; Jacob E. Shabason, MD, MTR
- 2019 Research Article of the Year: *Effect of radiation dose escalation on overall survival in ependymoma: A National Cancer Database analysis* by Jennifer Vogel, MD; Sriram Venigalla, MD; Sonam Sharma, MD, et al
- 2019 Case Report of the Year: *Abscopal effect of radiation therapy in monotherapy in a patient with malignant melanoma* by Catarina Martins Silva, MD; Carlos Fardilha, MD; Diana Freitas, MD, et al.

As we enter the journal's ninth year, we extend our deepest gratitude to the authors, advisory board, and expanding peer review panel whose expertise and commitment help position *Applied Radiation Oncology* as a respected and useful resource in the field. To our dedicated readers, a tremendous thank you for your continued support!

***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.*

A Message for Our Readers During the Coronavirus Crisis

Anderson Publishing, Ltd., publishers of Applied Radiation Oncology, *wish to sincerely thank the millions of healthcare professionals around the world who manage the frontlines every day, no matter what comes through your doors. Your commitment, passion, sacrifice and resilience during this pandemic are truly appreciated as you continue to provide the best care possible to a growing number of citizens affected by COVID-19. For that, we are eternally grateful to each of you.*

On behalf of the entire Applied Radiation Oncology *team and our Editorial Advisory Board, we wish you and your families the very best of health and safety during these challenging and uncertain times. Thanks for being a hero and providing hope for patients.*

Sincerely,

Kieran N. Anderson
Vice President & Group Publisher
Anderson Publishing, Ltd.

John Suh, MD, FASTRO, FACR
Editor-in-Chief
Applied Radiation Oncology

RESIDENT VOICE

Countering the Rise of Administrators: Overcoming Cultural Disconnects and Optimizing Patient Care

Austin J. Sim, MD, JD

Austin J. Sim, MD, JD

A seminal analysis by Goodall demonstrated the positive effect of physician-leaders on hospital performance, as evidenced by *U.S. News and World Report* scores. The presence of physician leadership significantly increased quality scores when examining top institutions in cancer, digestive health, and cardiac health. Additionally, a significant majority (16/21) of high-performing institutions in the "Honor Roll" were also led by physicians.[1]

Despite the historical norm of physician-led hospitals, increasing complexity and paradigm shifts toward business-like models in the 1980s gave rise to clinical directorates. Although many physicians entered these roles, this signaled the rise of administrators.[2] The increasing "metrification" of health care that accompanied these structural changes, shifting administrators' focus away from patients, has led to loss of physician autonomy, exacerbating a cultural disconnect. At the same time, administrative costs have ballooned from $294.3 billion in 1999 (representing 31% of total health care expenditures)[3] to $812 billion in 2017 (representing 34.2% of total expenditures).[4] This was over 4% of our entire nation's GDP in 2017.[5]

In such an imperfect system, truly optimizing patient care requires systemic change. A full inventory of such solutions is beyond the scope of this piece, but increasing physician knowledge and skills in emotional intelligence and leadership is a critical first step. Some physicians perceive mismanagement from nonclinical administrators and either seek or are thrust into these roles. On the other hand, many administrators feel that clinicians lack management and leadership skills. Despite awareness of these shortcomings, clinicians feel that resources are lacking to acquire these skills.[6]

Nevertheless, physicians who have succeeded are able to wield these skills to benefit patient care. Shanafelt et al also demonstrated reduced burnout and increased satisfaction with more effective physician leadership.[7] Another meta-analysis conducted by Clay-Williams et al recapitulated some evidence of this benefit. They noted that multiple studies analyzing institutional board compositions showed better service quality and lower morbidity rates with more physicians taking part. Other studies showed better outpatient care with physician-led accountable care organizations, but also a harder time fully adopting managerial roles.[2]

Throughout our training, emphasis has centered on individual accomplishments and has not traditionally highlighted leadership and managerial skills, despite leader-

***Dr. Sim** is a resident physician (PGY-3), Department of Radiation Oncology, Moffitt Cancer Center & Research Institute, Tampa, FL.* *Acknowledgement: Many thanks to Stephen A. Rosenberg, MD, MS, for editorial support.*

Even without official leadership roles, we as radiation oncologists lead a team of dosimetrists, physicists, nurses and other allied health professionals with the patient at the center.

ship roles inherent in being a physician, both perceived and actual. Even without official leadership roles, we as radiation oncologists lead a team of dosimetrists, physicists, nurses and other allied health professionals with the patient at the center. Other pieces have highlighted leadership programs within radiation oncology resdiency,[8] and we are doing our part. At Moffitt Cancer Center, we recently completed a unique longitudinal, case-based leadership development course exploring topics such as emotional intelligence, conflict management and negotiations, with practical application and guest lectures from executives.

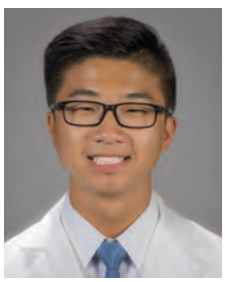
Although more widespread efforts for formal training and opportunities for leadership growth are lacking in radiation oncology, offerings like the Foundations in Leadership course through the European Society for Radiotherapy & Oncology (ESTRO) have begun this process.[9] Organizations such as the Association of Residents in Radiation Oncology (ARRO), American Society for Radiation Oncology (ASTRO), American College of Radiation Oncology (ACRO), and Canadian Association for Radiation Oncology (CARO) should follow suit and create content to provide practical skills and knowledge valuable to radiation oncologists at all stages of their careers.

References

1. Goodall AH. Physician-leaders and hospital performance: is there an association? *Soc Sci Med.* 2011;73(4):535-539.
2. Clay-Williams R, Ludlow K, Testa L, et al. Medical leadership, a systematic narrative review: do hospitals and healthcare organisations perform better when led by doctors? *BMJ Open.* 2017;7(9):e014474.
3. Woolhandler S, Campbell T, Himmelstein DU. Costs of health care administration in the United States and Canada. *N Eng J Med.* 2003;349(8):768-775.
4. Himmelstein DU, Campbell T, Woolhandler S. Health care administrative costs in the United States and Canada, 2017. *Ann Intern Med.* 2020.
5. GDP (current US$) - United States. The World Bank. https://data.worldbank.org/indicator/NY.GDP.MKTP.CD?locations=US. Accessed January 14, 2020.
6. Keller EJ, Giafaglione B, Chrisman HB, et al. The growing pains of physician-administration relationships in an academic medical center and the effects on physician engagement. *PloS One.* 2019;14(2):e0212014.
7. Shanafelt TD, Gorringe G, Menaker R, et al. Impact of organizational leadership on physician burnout and satisfaction. *Mayo Clinic Proc.* 2015;90(4):432-440.
8. Campbell SR. Leadership development: why is it important for radiation oncology residents? *App Radiat Oncol*. 2019;8(4):6-7.
9. ESTRO. Foundations of Leadership in Radiation Oncology. https://www.estro.org/Courses/FOUNDATIONS-OF-LEADERSHIP-IN-RADIATION-ONCOLOGY-EN. Accessed January 14, 2020.

GUEST EDITORIAL

In the Mix: Fostering Mentorship Through a Student and Faculty Research Mixer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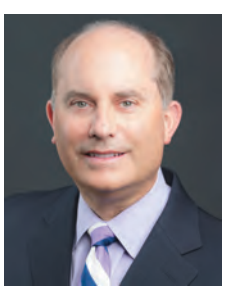
Louis Harrison, MD

***Mr. Song** is a third-year medical student at USF Morsani College of Medicine, Tampa, Fl. **Dr. Hoffe** is the section head of Gastrointestinal Radiation Oncology, **Dr. Johnstone** is the vice chair of the Department of Radiation Oncology, **Dr. Harrison** is the Deputy Physician in Chief and Chair, Department of Radiation Oncology, at Moffitt Cancer Center, Tampa, FL.*

Although radiation oncology has become a highly competitive specialty, early exposure remains elusive. With the increasing role of oncology interest groups to positively impact medical student learning about oncology and specialty choice,[1] we developed a novel method to introduce students to radiation oncology with pathways for mentorship.

Partnering with the Moffitt Cancer Center Department of Radiation Oncology, the University of South Florida Radiation Oncology Interest Group (ROIG) organized a wine and cheese research mixer during the first months of the medical school year. Interested medical students would submit their resume in advance and receive access to a project database with physician research interests and ongoing projects.

After welcoming remarks from the department leadership, students would rotate to tables arranged by disease site where they would interact with faculty physicians, physicists, and residents. At the end of each rotation and before moving to the next table, attendees shared contact information to set up a more formal future meeting time. The event concluded with a group photo that was posted on social media to heighten awareness.

Mentorship has been identified by medical students, residents, and faculty as an important component of research productivity in radiation oncology.[2,3] Previously established undergraduate medical education mentorship programs in radiation oncology were also shown to strongly affect medical student career choice, as a majority of participants pursued radiation oncology as a specialty.[2] Similarly, in residency, the Radiation Oncology Academic Development and Mentorship Assessment Project (ROADMAP) study identified that mentorship positively influences the academic productivity and career direction of residents.[4]

Along with increased exposure to radiation oncology, this event was also able to foster important research and career mentorships that have resulted in presentations at national/international meetings and peer-reviewed manuscripts. Early opportunities like this could boost the visibility of radiation oncology as a career choice to first- and second-year medical students.

References

1. Sherwood M, Rioux D, Knight R, et al. Increasing undergraduate exposure to oncology: the role of oncology interest groups. *J Cancer Educ.* 2019.
2. Boyd GH, Rand AE, DeNunzio NJ, Agarwal A, Hirsch AE. The Radiation Oncology Mentorship Initiative: analysis of a formal mentoring initiative for medical students interested in radiation oncology. *J Cancer Educ.* 2019.
3. Hirsch AE, Agarwal A, Rand AE, et al. Medical student mentorship in radiation oncology at a single academic institution: a 10-year analysis. *Pract Radiat Oncol.* 2015;5(3):e163-168.
4. Holliday EB, Jagsi R, Thomas CR, Jr., Wilson LD, Fuller CD. Standing on the shoulders of giants: results from the Radiation Oncology Academic Development and Mentorship Assessment Project (ROADMAP). Int *J Radiat Oncol Biol Phys.* 2014;88(1):18-24.

SA–CME Information

NONINVASIVE CARDIAC RADIOABLATION AT WASHINGTON UNIVERSITY: PAST, PRESENT AND FUTURE DIRECTIONS FOR THE TREATMENT OF VENTRICULAR TACHYCARDIA

Description

Noninvasive cardiac radioablation using stereotactic body radiation therapy (SBRT) techniques has emerged as a potential salvage treatment option for patients with ventricular tachycardia who have either failed procedural or medical management, or have contraindications to receive those therapies again. The recently published phase I/II Electrophysiology-Guided (EP) Noninvasive Cardiac Radioablation for Ventricular Tachycardia trial (ENCORE-VT, NCT02919618) demonstrated early safety and efficacy of this novel use of SBRT. This article reviews the lessons learned from ENCORE-VT, current use and workflow for treatment refractory ventricular tachycardia patients, and future directions for this emergent treatment modality.

Learning Objectives

After completing this activity, participants will be able to:

1. Identify the patient population that may be considered for noninvasive cardiac radioablation as a salvage therapy.
2. Understand the anatomical and electrophysiological data that must be obtained prior to noninvasive cardiac radioablation and how targets are identified in collaboration with an electrophysiologist.
3. Increase awareness of potential short- and long-term toxicities from noninvasive cardiac radioablation.

Authors

***Pamela Samson, MD, MPHS**, is a PGY-5 resident, **Geoff Hugo, PhD,** is a professor, **Nels Knutson, PhD,** is an assistant professor, and **Dr. Robinson** is a professor, Department of Radiation Oncology, Washington University, St. Louis, MO. **Kaitlin Moore, BSN,** is a clinical nurse II , and **Philip Cuculich, MD,** is an associate professor, Division of Cardiology, Department of Internal Medicine, Washington University in St. Louis School of Medicine.*

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Noninvasive Cardiac Radioablation at Washington University: Past, Present and Future Directions for the Treatment of Ventricular Tachycardia

Pamela Samson, MD, MPHS; Geoff Hugo, PhD; Kaitlin Moore, BSN; Nels Knutson, PhD; Philip Cuculich, MD; Clifford Robinson, MD

Among the many types of cardiac arrhythmias, ventricular tachycardia (VT) represents a potentially fatal arrhythmia in the setting of abnormal anatomical and physiological pathways of the heart. Specifically, these aberrant pathways result from cardiac injury to the ventricles, either by ischemic causes (post-myocardial infarction) or nonischemic causes (inflammatory or secondary to other systemic pathologies). Regardless of the underlying etiology, these arrhythmias are associated with a high mortality rate. Gold standard therapies for VT include catheter ablation and medical therapies. Catheter ablation is a procedure performed over several hours under anesthesia in which vascular access is obtained, the location of the ventricular arrhythmia is mapped using the catheter, and electrical tracts are ablated using thermal ablation, essentially converting a functional scar into a nonfunctional scar. Anti-arrhythmic drugs generally work by affecting the repolarization phases of the heart through sodium, potassium and/or calcium channels to slow the conduction rate. While these are effective for many patients with VT, both approaches can be associated with significant toxicities. For example, a recent national retrospective analysis including more than 4600 patients receiving catheter ablation for ischemic VT showed the overall rate of any in-hospital complication was 11% with an in-hospital mortality of 1.6%.[1] The cornerstone of medical management has been amiodarone, which unfortunately can cause pulmonary fibrosis, hypothyroidism, and other systemic effects. Even for patients who can tolerate procedural and medical management, these therapies are not always durable and can result in treatment refractory VT.[2-4] For patients with refractory disease, one series exploring noncatheter ablation salvage such as transcoronary alcohol ablation, epicardial window, and cryoablation demonstrated a 25% complication rate and 10% 30-day mortality.[5]

In a similar lineage to other applications of stereotactic body radiation therapy (SBRT), noninvasive cardiac radioablation has emerged as a potential salvage treatment option for patients who have either failed procedural or medical management, or have contraindications to receive those therapies again. The recently published phase I/II Electrophysiology-Guided (EP) Noninvasive Cardiac Radioablation for Ventricular Tachycardia trial (ENCORE-VT, NCT02919618) demonstrated early safety and efficacy of this novel use of SBRT.[6] In this review, we will discuss the lessons learned from ENCORE-VT, our current use and workflow for treatment refractory ventricular tachycardia patients, and future directions for this treatment modality.

Dr. Samson *is a PGY-5 resident,* ***Dr. Hugo*** *is a professor,* ***Dr. Knutson*** *is an assistant professor, and* ***Dr. Robinson*** *is a professor, Department of Radiation Oncology, Washington University, St. Louis, MO.* ***Ms. Moore*** *is a clinical nurse II , and* ***Dr. Cuculich*** *is an associate professor, Division of Cardiology, Department of Internal Medicine, Washington University in St. Louis School of Medicine.*

Disclosure: Dr. Robinson and Dr. Hugo are consultants for Varian and Dr. Cuculich is a consultant for Varian and Medtronic related to the work presented here. Dr. Samson and Ms. Moore have no relevant disclosures related to this manuscript. 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.

Development of Noninvasive Cardiac Radioablation

Prior to implementing noninvasive cardiac radioablation in humans, preclinical studies laid the groundwork for this treatment approach.[7-10] Previous work by Zei and colleagues demonstrated the effectiveness of using SBRT to target

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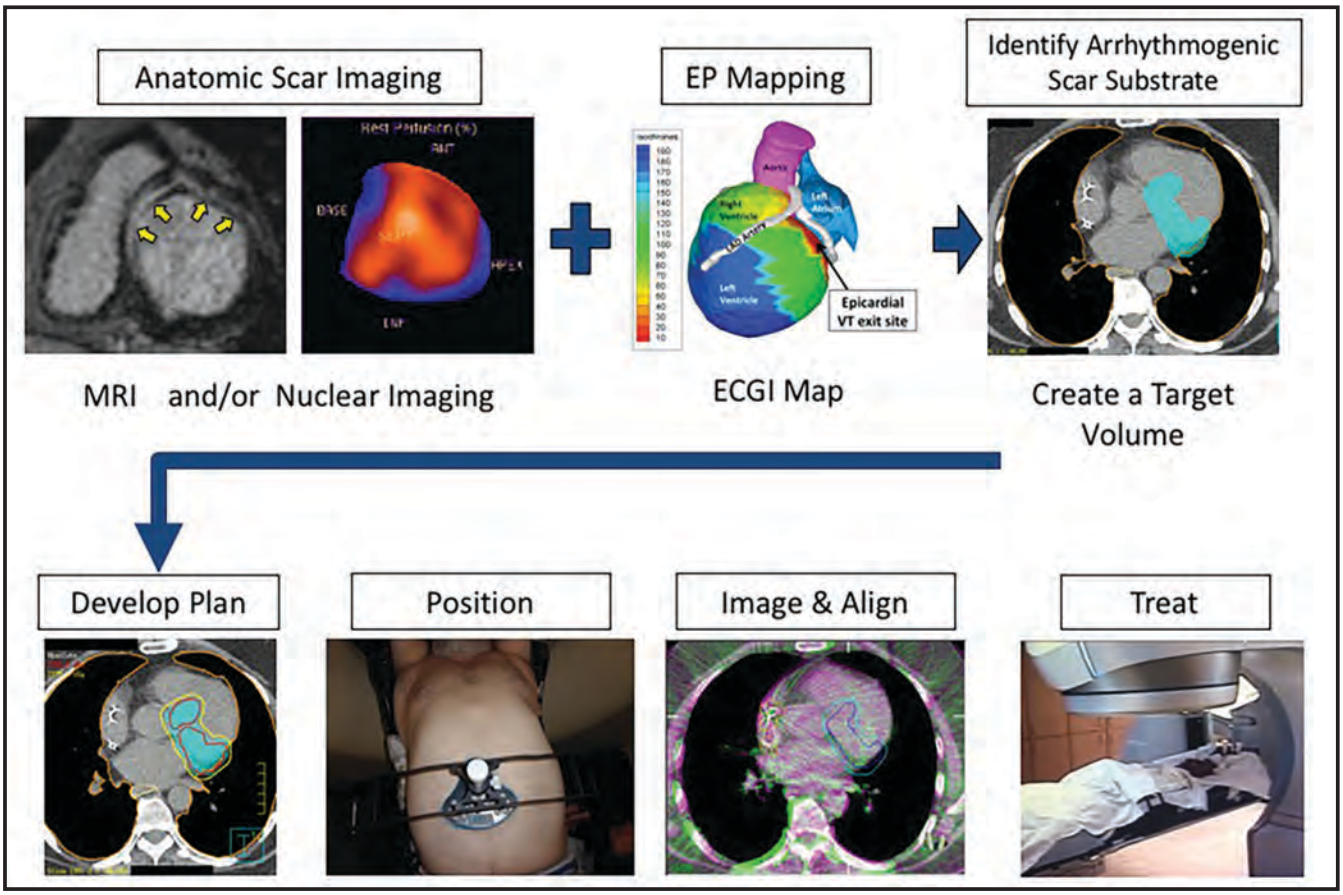

FIGURE 1. *Multimodality imaging including radiologic studies and electrophysiologic mapping are used offline to identify the target volume in patients with monomorphic ventricular tachycardia for treatment planning.*

the superior pulmonary veins (as done in atrial fibrillation ablative procedures) with 25 Gy.[11] Similarly, Packer and colleagues demonstrated the effectiveness of creating a complete atrioventricular nodal block using 25 Gy in a single fraction in a porcine model.[12] Additionally, these animal models were monitored for 3 to 6 months following the procedure, with no evidence of collateral injury found at the time of histopathological assessment at study conclusion. Of note, these preclinical studies were done in animal models with structurally normal hearts and were found to create fibrotic changes in the distribution of the target volume, over a period of months from the time of treatment. This mechanism of ablation is fundamentally different from catheter-based approaches, which use radiofrequency energy to cauterize the arrhythmogenic circuit, over the period of days to weeks.[13] However, no preclinical studies to date have examined electrophysiologic and histologic changes in models with aberrant conduction pathways due to intrinsic cardiac disease and, therefore, it is unknown how the latent period and tissue changes may differ from healthy models.

While these studies demonstrated the feasibility of cardiac radioablation to alter electrical conduction, use in humans was limited because the arrhythmogenic pathways in the ventricular muscle needed to be mapped so a treatment volume could be appropriately delineated. With conventional catheter ablation, the mapping and treatment are done as one procedure, as the catheter can be used to both map the arrhythmogenic circuit and then provide ablation to that delineated area. Therefore, the attractiveness of a noninvasive cardiac radioablation option was significantly limited as the patient still needed a catheter-based mapping procedure. If the catheter is already placed directly at the target, one can see the willingness to ablate (or re-ablate), vs ending the procedure without direct treatment at that time. While conventional imaging tests such as cardiac MRI, single photon emission computed tomography (SPECT), positron emission tomography (PET), and echocardiogram can provide some gross/anatomical features of areas of fibrosis in which the arrhythmia likely originates, it gives us no electrical information to delineate the actual pathway of the arrhythmia. One development able to bridge anatomical information with aberrant electrical

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pathways normally obtained by invasive catheter mapping is electrocardiographic imaging (ECGI).[14,15] During this procedure, the patient wears a vest containing 256 electrodes that individually capture electrocardiograms based on their distance and orientation from the heart. While still wearing the vest, the patient also undergoes a CT scan to generate anatomical coordinates for each of the electrodes in relation to the heart. With the anatomical and electrical mapping, an algorithm is used to translate the body surface potentials back to the electrical potentials on the epicardial surface.[16] This technology has now been formally developed as the CardioInsight Noninvasive 3D Mapping System (Medtronic).

With the integration of electrocardiographic imaging to identify the VT substrate externally, the stage was then set for an entirely noninvasive cardiac radioablation workflow. On the ENCORE-VT phase I/II trial, we elected to deliver linac-based SBRT (Edge, Varian) as this would allow us to take advantage of a well-established thoracic workflow in terms of motion control, treatment planning, on-board fluoroscopy, and minimization of neutron exposure for implantable cardioverter defibrillators (ICDs). This workflow and dosimetric objectives were recently described by Knutson et al.[17] Briefly, the treatment target (here, a gross target volume [GTV]), is compiled upon review of all available radiologic imaging and electrophysiologic data including 12-lead ECG and ECGI. A respiratory correlated 4-dimensional CT (4D-CT) with abdominal compression is acquired and co-registered to a free-breathing CT to assess target motion. Recently, we upgraded our CT simulator to perform a respiratory 4D-CT with ECG-gated imaging to assess cardiac motion (Siemens). With this summation of respiratory and cardiac movement, an internal target volume (ITV) is then generated. Of note, ITV delineation for cardiac radioablation planning presents a new challenge for radiation oncologists who may be used to contouring based on excursion of a mass. For this, we have noticed that superimposing a 5-mm grid directly onto the CT images during ITV delineation helps document the extent of target movement and provide appropriate coverage boundaries. Initially, a 5-mm expansion was done to create the planning target volume (PTV) from the ITV, although with additional experience we have now decreased our PTV margin to 2 to 3 mm. A dose of 25 Gy in a single fraction is then delivered (with allowance of up to a 35 Gy hotspot within the ITV). Our current institutional workflow for noninvasive cardiac radioablation is shown in **Figure 1.**

In July 2016, ENCORE-VT was opened to evaluate safety and efficacy of noninvasive cardiac radioablation in patients with refractory VT, defined as failure of ≥ 1 antiarrhythmic medications and ≥ 1 catheter ablation or having a contraindication to catheter ablation.[6] The primary safety endpoint was defined as the rate of ≤ 90-day serious adverse events (SAE, ≥ grade 3) and the primary efficacy endpoint was defined as the number of subjects with any reduction in the number of ICD therapies, including shocks and/or antitachycadia pacing (ATP). The results of this clinical trial demonstrated low risk of SAEs, significantly decreased VT episodes in 95% of patients, decreased use of amiodarone and dual-antiarrhythmic medications, and significant improvements in quality-of-life metrics.

Current Use of Noninvasive Cardiac Radioablation for Refractory Ventricular Tachycardia

A substantial clinical need for patients with refractory VT has led to continued off-label use of noninvasive cardiac radioablation in select patients as we await opening of the next prospective trial. As of February 2020, we have now treated 39 patients. As more patients are treated and our follow-up becomes longer, our focus is shifting to continued improvements in workflow, close monitoring for long-term toxicities, and collaboration with other centers planning to use noninvasive cardiac radioablation.

In examining our treatment planning patterns over time, we have seen evidence of a learning curve during the course of ENCORE-VT. Specifically, we saw with the more recent cohort of patients a significant decrease in PTV volume, which was reflective of smaller GTV volumes as there was no changes in motion management or PTV margins during the clinical trial.[17] Subjective decreases in the R50 (ratio of the volume of the 12.5 Gy isodose to the PTV), gradient measure (average distance between the 12.5 Gy equivalent spherical volume and the 25 Gy equivalent spherical volume), homogeneity index (ratio of the maximum dose to the prescription dose), and treatment time were also observed in this small group of patients (n = 16), but this did not reach significance. These findings have helped establish a new range of objectives in treatment planning and evaluation that are now implemented in our clinic. For example, examining the clinical outcomes and target volume size, we saw that no patients with a PTV > 200 cc lived to 1 year.[18] An association between SAEs and PTVs was not found, suggesting that the mortality rate with large volumes was more likely a surrogate for more severe heart disease/dysfunction rather than cardiac toxicity from radiation therapy. However, this value now serves as a possible prognostic factor for early mortality.

As our follow-up of patients participating in ENCORE-VT lengthens, we continue to become aware of possible short- and long-term toxicities. In the longer-term follow-up presented at ASTRO 2019, we have now described 2 cases of late-grade 3 pericarditis (both occurring > 2 years from the time of radiation, treated with steroids) and

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1 patient with a grade 4 gastropericardial fistula (2.4 years after radiation) requiring surgical intervention.[19] In reviewing the plan of the patient who developed the gastropericardial fistula, we did see that the target was in the apex of the left ventricle – the portion of the heart closest to the anterior left diaphragm and stomach. Currently, any targets including the left ventricular apex are now planned to optimize on the stomach, and the patient is consented regarding the risk of gastric ulceration and fistula. Diligent clinical follow-up for these patients will be crucial in the years to come. From the ENCORE-VT trial, we documented that the left anterior descending artery (LAD), which is the major blood supply to the left ventricle for the majority of the population, received a median dose of 10 Gy (IQR 10.7, EQD2 26.4 Gy). Similarly, the left circumflex artery received a median dose of 9.2 Gy (IQR 6.3, EQD2 22.4 Gy).[17] While we have yet to see any direct evidence of radiation-related coronary adverse events among treated patients, these late effects could take years to develop. This will be crucial to document and understand as durable control of ventricular arrhythmias improves survival to a point that radiation late effects must be considered.

With this demonstration of clinical efficacy for salvage therapy, international interest in this therapy continues to develop. To date, the recently formed Center for Noninvasive Radioablation (CNCR, pronounced "Conquer") at our institution has collaborated with 27 domestic and international hospitals to remotely review patient cases, target mapping, and treatment planning. Similarly, other groups have initiated collaborative work to treat and manage patients receiving noninvasive cardiac radioablation such as the Standardized Treatment and Outcome Platform for Stereotactic Therapy of Re-entrant Tachycardia by a Multidisciplinary Consortium (StopStorm), representing the efforts of radiation oncologists, electrophysiologists and physicists from 7 European countries.

Noninvasive Cardiac Radioablation: Going Forward

The future of noninvasive cardiac radioablation involves many potential avenues for research: elucidation of the mechanisms of radiobiologic effectiveness, continued refinement of target delineation, dose finding studies, diligent monitoring for late toxicities, and scalability of this workflow to centers regardless of geography. Ultimately, multi-institutional phase II and III trials to compare noninvasive cardiac radioablation against repeat catheter ablation for refractory ventricular tachycardia will help further delineate the role of this therapy. These trials will only be possible through continued collaboration on both the institutional level (electrophysiology, radiation oncology and medical physics) and through cooperative groups with specific end-to-end testing metrics, quality control, and central plan review. Another question that will be addressed in the future is understanding the relative benefits and risks of various treatment modalities that could deliver this modality. While intensity-modulated proton therapy (IMPT) could offer dosimetric advantages to organs at risk including nontarget heart tissue, potential issues include neutron scatter that could damage ICDs/pacemakers in patients who depend on these devices, significant sensitivity to motion, and changes in volume status of the patient from the time of simulation to the time of treatment. In ENCORE-VT, most patients had class III or IV heart failure, and as such may have had significant changes in weight and cardiac filling from week to week. Another challenge to proton therapy would be confirming target localization on the day of treatment — in our current workflow process we use both a cone-beam CT and fluoroscopy to adjust positioning immediately prior to treatment if required. It is also possible that intrafraction cone-beam imaging could be of benefit in complex anatomical targets and/or targets immediately adjacent to the esophagus or diaphragm/stomach.

Another treatment approach could involve MR-guidance, which would offer the benefit of real-time imaging during treatment. However, while a benefit of MR-guided therapy in cancer therapy is the ability to gate tumor targets relative to surrounding soft tissue through continuous real-time imaging, this has not yet been shown to apply to cardiac targets as there is no discernable difference between the treatment volume and the nontarget heart tissue. Therefore, gating would have to occur based on the entire heart or a surrogate structure in the thorax, which may not offer a clear benefit compared to a standard ITV approach. However, we have described the use of MR-guided therapy for a case in which VT was being caused by a cardiac fibroma where the mass was visible and able to be tracked.[20]

Conclusions

Similar to SBRT use for other malignancies, early clinical trial work has shown that noninvasive cardiac radioablation for VT is a potentially safe, effective, and durable salvage treatment for a patient population that has exhausted procedural and medical management options. However, understanding the threshold of potential benefit and long-term risk of toxicities will be crucial in delineating the patient population that should receive this treatment. Future endeavors in radiobiology mechanisms, clinical trial development, and quality improvement will facilitate the continued development of this new application of SBRT.

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References

1. Palaniswamy C, Kolte D, Harikrishnan P, et al. Catheter ablation of postinfarction ventricular tachycardia: ten-year trends in utilization, in-hospital complications, and in-hospital mortality in the United States. *Hear Rhythm.* 2014;11(11):2056-2063. doi:10.1016/j.hrthm.2014.07.012
2. Wolf M, Sacher F, Cochet H, et al. Long-term outcome of substrate modification in ablation of post-myocardial infarction ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2018;11(2):e005635. doi:10.1161/CIRCEP.117.005635
3. Yokokawa M, Desjardins B, Crawford T, Good E, Morady F, Bogun F. Reasons for recurrent ventricular tachycardia after catheter ablation of post-infarction ventricular tachycardia. *J Am Coll Cardiol.* 2013;61(1):66-73. doi:10.1016/j.jacc.2012.07.059
4. Kumar S, Romero J, Mehta NK, et al. Long-term outcomes after catheter ablation of ventricular tachycardia in patients with and without structural heart disease. *Heart Rhythm.* 2016;13(10):1957-1963. doi:10.1016/j.hrthm.2016.07.001
5. Kumar S, Barbhaiya CR, Sobieszczyk P, et al. Role of alternative interventional procedures when endo- and epicardial catheter ablation attempts for ventricular arrhythmias fail. *Circ Arrhythmia Electrophysiol.* 2015;8(3):606-615. doi:10.1161/CIRCEP.114.002522
6. Robinson CG, Samson PP, Moore KMS, et al. Phase I/II trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia. *Circulation.* 2019;139(3):313-321. doi:10.1161/CIRCULATIONAHA.118.038261
7. Zei PC, Wong D, Gardner E, Fogarty T, Maguire P. Safety and efficacy of stereotactic radioablation targeting pulmonary vein tissues in an experimental model. *Heart Rhythm.* 2018;15(9):1420-1427. doi:10.1016/j.hrthm.2018.04.015
8. Sharma A, Wong D, Weidlich G, et al. Noninvasive stereotactic radiosurgery (CyberHeart) for creation of ablation lesions in the atrium. *Heart Rhythm.* 2010;7(6):802-810. doi:10.1016/j.hrthm.2010.02.010
9. Lehmann HI, Richter D, Prokesch H, et al. Atrioventricular node ablation in Langendorff-perfused porcine hearts using carbon ion particle therapy: methods and an in vivo feasibility investigation for catheter-free ablation of cardiac arrhythmias. *Circ Arrhythm Electrophysiol.* 2015;8(2):429-438. doi:10.1161/CIRCEP.114.002436
10. Lehmann HI, Graeff C, Simoniello P, et al. Feasibility study on cardiac arrhythmia ablation using high-energy heavy ion beams. *Sci Rep.* 2016;6:38895. doi:10.1038/srep38895
11. Zei PC, Wong D, Gardner E, Fogarty T, Maguire P. Safety and efficacy of stereotactic radioablation targeting pulmonary vein tissues in an experimental model. *Heart Rhythm.* 2018;15(9):1420-1427. doi:10.1016/j.hrthm.2018.04.015
12. Lehmann HI, Deisher AJ, Takami M, et al. External arrhythmia ablation using photon beams. *Circ Arrhythmia Electrophysiol.* 2017;10(4):1-8. doi:10.1161/CIRCEP.116.004304
13. Tung R, Boyle NG, Shivkumar K. Catheter ablation of ventricular tachycardia. *Circulation.* 2010;122(3):e389-391. doi:10.1161/CIRCULATIONAHA.110.963371
14. Wang Y, Cuculich PS, Zhang J, et al. Noninvasive electroanatomic mapping of human ventricular arrhythmias with electrocardiographic imaging (ECGI). *Sci Transl Med.* 2011;3(98):98ra84. doi:10.1126/scitranslmed.3002152
15. Ghanem RN, Jia P, Ramanathan C, Ryu K, Markowitz A, Rudy Y. Noninvasive electrocardiographic imaging (ECGI): comparison to intraoperative mapping in patients. *Heart Rhythm.* 2005;2(4):339-354. doi:10.1016/j.hrthm.2004.12.022
16. Cheniti G, Puyo S, Martin CA, et al. Noninvasive mapping and electrocardiographic imaging in atrial and ventricular arrhythmias (CardioInsight). *Card Electrophysiol Clin.* 2019;11(3):459-471. doi:10.1016/j.ccep.2019.05.004
17. Knutson NC, Samson PP, Hugo GD, et al. Radiation therapy workflow and dosimetric analysis from a phase 1/2 trial of noninvasive cardiac radioablation for ventricular tachycardia. *Int J Radiat Oncol Biol Phys.* 2019;104(5):1114-1123. doi:10.1016/j.ijrobp.2019.04.005
18. Samson PP. S-PO01-001 to S-PO01-175. *Heart Rhythm.* 2019;16(5):S93-S141. doi:10.1016/j.hrthm.2019.04.014
19. Robinson CG, Samson P, Moore KMS, et al. Longer term results from a phase I/II Study of EP-guided Noninvasive Cardiac Radioablation for Treatment of Ventricular Tachycardia (ENCORE-VT). *Int J Radiat Oncol Biol Phys.* 2019;105(3):682. doi:10.1016/j.ijrobp.2019.08.032
20. Gach HM, Green OL, Cuculich PS, et al. Lessons learned from the first human low-field MRI guided radiation therapy of the heart in the presence of an implantable cardiac defibrillator. *Pract Radiat Oncol.* 2019;9(4):274-279. doi:10.1016/j.prro.2019.02.003

SA–CME Information

CARDIOTOXICITY AND RADIATION THERAPY: A REVIEW OF CLINICAL IMPACT IN BREAST AND THORACIC MALIGNANCIES

Description

Cardiotoxicity can be an unfortunate side effect from cancer therapies including chemotherapy, hormonal therapy, and radiation therapy (RT). Sub-acute cardiotoxicity can occur during systemic therapies but is often considered a late effect from RT. This manuscript reviews the current literature regarding the clinical impact of radiation-induced cardiotoxicity in the setting of breast cancers and thoracic malignancies including lung cancer, esophageal cancer and mediastinal lymphomas.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the clinical impact of radiotherapy-induced cardiotoxicity in breast cancers.
2. Understand the clinical impact of radiotherapy-induced cardiotoxicity in lung/esophageal cancers.
3. Understand the clinical impact of radiotherapy-induced cardiotoxicity in hemato-lymphoid malignancies.
4. Apply management approaches for radiotherapy-induced cardiotoxicity.

Authors

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Date of release and review: March 1, 2020
Expiration date: February 28, 2022
Estimated time for completion: 1 hour

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.

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Cardiotoxicity and Radiation Therapy: A Review of Clinical Impact in Breast and Thoracic Malignancies

Elizabeth M. Nichols, MD; Arezoo Modiri, PhD; Pranshu Mohindra, MD, MBBS

Cardiotoxicity can be an unfortunate side effect from cancer therapies including chemotherapy, hormonal therapy, and radiation therapy (RT). Subacute cardiotoxicity can occur during systemic therapies but is often considered a late effect from RT. Several different clinical conditions can result from radiation-induced cardiotoxicity (RIC): cardiomyopathy, myocarditis, pericarditis, acute coronary syndrome, congestive heart failure, and valvular disease. Cardiac injury remains multifactorial, however, with some patients receiving radiation dose to the heart and never experiencing a resultant clinical condition while others can be severely affected and even die. Data have shown that the existence of heart conditions (hypertension, diabetes, prior myocardial infarction, etc.) prior to therapy can result in a synergistic effect of cardiac injury.[1] In addition, receiving systemic therapy agents during or in close chronologic proximity to RT also can have a synergistic effect.[2-5] To date, no "protective" agent, except for decreased radiation dose, has been identified to minimize risk from RT.

A variety of imaging modalities are available to assess cardiac function, including multigated acquisition scans, single-photon emission computed tomography, echocardiography (and derivatives thereof), cardiac magnetic resonance imaging, and invasive procedures such as cardiac catheterization. Other cardiac imaging assessments can also be performed, such as CT angiography (CTA) and assessment of coronary calcifications; however, these do no assess cardiac function. To date the "best" modality has not been determined; each modality has strengths and weaknesses, and costs vary widely, as described in detail by several publications.[6,7] Table 4 in Lancellotti et al's review article gives a thorough and concise summary of imaging techniques for RIC diagnosis.[8] Additional work is needed to develop a standard method of assessing RIC. The pathophysiology of RIC is primarily associated with fibrosis and chronic inflammation. The mechanisms of action as currently understood have been described in previous publications. What remains lacking are models that can integrate the role of other medical comorbidities (hypertension, diabetes mellitus, hyperlipidemia, etc.) with cardiotoxic systemic effects.[9,10] **Table 1** describes several clinical conditions associated with RIC and the incidence as described in the literature.

The focus of this manuscript is to review the current literature regarding the clinical impact of RIC in the setting of breast cancers and thoracic malignancies including lung cancer, esophageal cancer and mediastinal lymphomas.

Impact by Disease Site

Breast Cancers

Three large cohort studies have shown a correlation between increased radiation dose to the heart and incidence of cardiac morbidity for women treated for breast cancer. The first study, by Darby et al, was published in 2013 and showed a linear 7.4% increased incidence of major coronary events per gray of radiation to the mean heart.[11] This study was a population-based, case-control study in which the incidence of major coronary events (including myocardial infarction, coronary revascularization, or death from ischemic heart disease) was counted in 2168 women who underwent breast radiation between 1958 and 2001. The average mean dose to the heart was 4.9 Gy. The study showed the risk of cardiovascular events to begin within the first 5 years following RT completion and continue to increase up to 30 years

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Table 1. RIC Endpoints and Their Reported Incidence, Severity and Time Course

RIC Endpoints	Incidence/Severity/Time Course as Reported in Relevant Studies
Hearth failure and death from any RT-induced cardiotoxicity[3,11,13,15,18,23,3133,38,39,41,42,44,51-55]	The risk of a fatal cardiac event in patients with any cancer type is 1.5-3 times higher in those treated with TMRT compared to those not treated with RT. Age at first treatment is inversely correlated with standardized mortality ratio of myocardial infarction but directly correlated with absolute excess risk of death from myocardial infarction. The statistically significant increase in the risk of myocardial infarction mortality stays for 25 years post-RT. Supradiaphragmatic RT and cardiotoxic chemotherapy (anthracyclines or vincristine) independently increase this risk. A 25-year cumulative risk of heart failure is associated with dose to LV.
Symptomatic myocardial infarction[3,11,12,43]	The median interval between treatment and myocardial infarction (or angina pectoris requiring intervention) is 19.0 years. There is a 2.5-fold increased risk for patients receiving a mean TMRT dose of 20 Gy to the heart, compared with patients not treated with TMRT. The excess incidence risk seems to decrease with each tertial of age at treatment. Having an existing cardiac risk factor directly impacts incidence risk; a high level of physical activity inversely impacts this risk.
Vessel/artery damage and conduction disorder[11,39,40,44,56-58]	Coronary artery atherosclerosis and fibrotic build-up in the tunica media may develop 5-20 years post-TMRT and initially tend to be asymptomatic but can lead to myocardial infarction. The left internal mammary artery, preferred for coronary artery bypass grafting, can be damaged due to TMRT-induced stenosis. The right bundle branch is likely to be damaged by RT as well.
Ischemia[11,12,23,32,44,46,59]	Ischemia incidence is seen as early as 6 months post-RT with an increased rate at 24 months post-RT. Heart mean dose, dose homogeneity, male sex, and age are significant predictors.
Pericarditis and effusion[32,39,40,42,60-63]	Acute pericarditis is caused after > 40 Gy TMRT. Patients may present with chest pain, possibly a fever, electrocardiogram abnormalities, and mild elevations in cardiac markers within days to weeks of therapy. Many patients with pericarditis have effusion or constrictive diseases that, on average, present about 3-5 years post-RT. Some patients may be asymptomatic or develop progressive shortness of breath before a pericardial effusion that is detectable by imaging months post-RT. Constrictive pericarditis is usually the most severe form of pericarditis and commonly presents 10 years post-RT as congestive heart failure.
Valvular damage[15,39,40,42,44,47,48,64-70]	A large percentage of patients receiving TMRT experience valvular damage. A few such patients require valve surgery for symptomatic valvular disease, while the majority have mild valvular diseases. RT progressively degenerates the valvular tissue for many years. Valvular damages include isolated aortic valve disease, isolated mitral disease and combined aortic and mitral valve diseases.
Cardiomyopathy[23,40,58,71,72]	Cardiomyopathy (LV ejection fraction < 50%) is more common in survivors treated with RT than those without. Five-year survival after cardiac transplantation due to radiation-induced restrictive cardiomyopathy is found less than in those not exposed to RT.
Autonomic dysfunction and arrhythmia[44,73-75]	The incidence of abnormal heart rate recovery times is 3.5 times more in patients who received TMRT compared to those who did not. This becomes more important when considering the increase in 3-year all-cause mortality in patients with abnormal heart rate recovery. In children treated with TMRT, persistent sinus tachycardia is common.

Also see Table 2 in Bhattacharya et al[76] and Table 3 in Lancellotti et al[8] review articles.
Key: RT = radiation therapy, TMRT = thoracic/mediastinal RT, LV = left ventricular.

after treatment. They found no difference in proportional increase in the rate of major coronary events per radiation dose unit in women with or without known cardiac risk factors at the time of RT. Criticisms of this study include changes across the eras of RT delivery as well as changing diagnosis and treatment of cardiac disease/events. Patients in this study did not undergo CT-based planning, and mean heart doses were estimated from 2-dimensional techniques. Concern was thus raised about the accuracy of the prediction model. The strength of this study, however, was the long-term data provided.

In 2017, van den Bogaard et al published a study looking at 910 women treated at a single institution with RT following breast-conserving therapy.[12] The primary endpoint of the study was to evaluate the incidence of acute coronary events (ACE). The investigators evaluated mean heart doses as well as

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dose to cardiac substructures, including the right and left atria and ventricles, to determine whether dose to a particular cardiac substructure correlated with more risk. All patients underwent CT-based planning. The mean heart dose was 2.37 Gy, with a median follow-up of 7.6 years. Three percent of patients experienced an ACE. This study showed a risk of 16.5% increased incidence of ACE per gray of RT to the mean heart within the first 9 years after RT, with a c-statistic of 0.79 that ultimately validated Darby's model. When evaluation by cardiac substructure was performed, the volume of the left ventricle receiving 5 Gy was the most important predictor of acute coronary events, with increasing doses predicting increased risk. Based on their statistical analysis, a threshold of mean value of 16.85% was associated with no ACE while a mean value of 29.4% was associated with an ACE. Of note, however, increasing doses of RT to the left ventricle were associated with increasing risks of an ACE. The authors also evaluated risk by decade of life at diagnosis (40s, 50s, 60s, 70s, 80s) and showed the highest risks for women in their eighth decade compared to the fourth decade. They also evaluated incidence by cardiac risk factor and found patients with a prior history of ischemic heart disease to have an exponentially worse risk of ACE compared to those with prior histories of hypertension or diabetes. The strengths of this analysis include the CT-based planning nature of their study with exact heart dosimetry and dosimetry to cardiac substructures, modern methods of diagnosis and treatment of ACEs, and moderately long follow-up. Weaknesses include the shorter nature of follow-up (compared to Darby et al). The incidences would likely continue to increase, with a slight modification of the risk ratio over time.

Taylor et al performed a systematic review of individual patient data published from 2010 to 2015.[13] Their analysis included more than 40 000 patients, with a median follow-up of 10 years. Estimates of heart doses were used in this study rather than individual dosimetric data. They found an increased risk of cardiac mortality with an increased risk ratio of 1.3 (95% confidence interval [CI], 1.15 to 1.46) and a 0.04 excess rate ratio of cardiac mortality per gray of whole-heart dose. Their study found a history of ischemic heart disease and smoking to be confounding factors for risk of cardiac death. The fact that this study focused on cardiac death as opposed to cardiac events likely resulted in the lower correlation of mean whole-heart dose per gray.

Some feel the risk ratios presented by the Darby and van den Boggard analyses may be overestimated.[14] For example, a study of > 70 000 Dutch stage I to III breast cancer patients showed that only death due to valvular heart disease was more frequent in these patients compared to the general Dutch population.[15] Further work is needed to clarify the best dosimetric parameters to use regarding heart and/or cardiac substructures and subsequent treatment planning goals, although a general consensus targets achieving the lowest dose possible to the mean heart and left ventricle. The ongoing multicenter, prospective MEDIRAD EARLY HEART study seeks to identify and validate new cardiac imaging and circulating biomarkers of RIC focusing on changes arising within first 2 years of breast cancer RT.[16] Patients receiving chemotherapy will be excluded. With plans to accrue 250 patients in the age group of 40-75 years, the data generated will also allow an opportunity to explore risk models correlating dose metrics of cardiac structures with the studied biomarkers while incorporating patient-specific risk factors. In a preliminary retrospective study, RT planning based on risk models that included patient age, smoking status, and existing cardiac risk factors at the time of RT was assessed.[17] The risk models were developed using published multi-institutional data. In 39 patients with left-sided breast cancer treated with comprehensive postlumpectomy locoregional conformal RT planning, median total decrease achieved in mortality or recurrence was 0.4% (range = 0.06 to 2.0%) and 0.5% (range = 0.11 to 2.2%) without and with existing cardiac risk factors, respectively.

Based on available data, a clear relationship exists between whole-heart dose and risk of cardiac events following RT for breast cancer with a significant increase in risk for left-sided breast cancer patients.[15,18] The clinical reality is that, as radiation oncologists, we are often unaware of the cardiac events our patients may experience. In addition, great heterogeneity in the length and frequency of patient follow-up for breast cancer contributes to this underappreciation. Patients, with a particular focus on those with left-sided disease, should be evaluated for cardiac-sparing techniques, including but not limited to deep-inspiration breath hold (DIBH), gating, prone positioning, and/or proton therapy, to achieve the lowest dose possible. Partial-breast irradiation can also be considered for suitable patients to decrease heart exposure. In addition to dose–volumetric parameters, radiation oncologists also must engage in smoking cessation counseling as well as education and discussion of the synergistic risks of other cardiac risk factors. As a result of the available data showing the confounding nature of cardiac risk factors, additional care should be taken when delivering RT for women with a history of ischemic cardiac disease.

Thoracic Malignancies (Lung and Esophageal Cancers)

Because of the overall higher mortality, evaluation of RIC in lung and esophageal cancers has proven more problematic than in breast cancer. Most patients do not live long enough to develop a cardiotoxicity. Nevertheless, recent recommendations for early screening of high-risk populations (ie,

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Table 2. RIC Endpoints with Known Dosimetric Correlates by Site

Primary Malignancy	Patient Population	Study Institution /Type	Dosimetric Parameter	Outcome
Breast cancer	Stage I-III (receiving RT)	Multi-institutional, retrospective[11]	Mean heart dose, left ventricle V5	Acute coronary/cardiac events: 7.4% increased risk per Gy of mean heart dose
Lung cancers	Stage I-II NSCLC	Multi-institutional, retrospective[31]	Maximum dose on the left atrium and dose to 90% of the superior vena cava	Noncancer death: Median 6.5 Gy EQD2, range = 0.009-197, HR = 1.005, $p = 0.035$ and median 0.59 Gy EQD2, range = 0.003-70, HR = 1.025, $p = 0.008$, respectively
	Stage III NSCLC	RTOG 0617, prospective[27]	Heart V5 and V30 Gy	Overall survival
	Stage III NSCLC	Tianjin Medical University Cancer Institute, retrospective[22]	Mean Heart Dose < 10 Gy, ≥ 10-20 Gy, and > 20 Gy	2-year competing-risk adjusted RIC rates 4%, 7% and 21%, respectively
	Locally Advanced NSCLC	Washington University, retrospective[26]	Heart V50 Gy < 25% vs ≥ 25%	2-year overall survival 45.9% vs 25%, $p < 0.0001$
Lymphoma	HL and NHL survivors	French-British cohort analysis[41]	Cardiac dose 5-14.9 Gy vs > 15 Gy	Relative risk of death: 12.5 vs 25.1, a linear relationship between the average cardiac radiation dose and the risk of cardiac mortality (estimated excess RR at 1 Gy = 60%)
	Multiple childhood cancers	Childhood Cancer Survivor Study, retrospective[42]	Cardiac dose > 15 Gy	2- to 6-fold increased risk of cardiac events
	HL	Princess Margaret Hospital, retrospective[46]	V5 of left anterior descending artery, and V20 of left circumflex artery	Ischemic Cardiac Events: HR = 0.98, $p = 0.003$ and HR = 1.03, $p < 0.001$
	HL	National Research Council of Italy, retrospective[47]	V25 Gy of left atrium, V30 Gy of left ventricle and V30 Gy of right ventricle	Mtral, aortic and tricuspid valvular disease
	HL	Analysis of prospective EORTC-LYSA trials[44]	Mean heart dose	Increased cardiovascular disease risk with each 1 Gy increase in dose, HR 1.015 [95% CI = 1.006-1.024], $p = 0.0014$

Key: Vx = the percentage volume receiving ≥ x Gy, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, CI = confidence interval, HR = hazard ratio.

smokers) have increased the probability of diagnosing lung cancer at an earlier stage with longer life expectancy and less comorbidity.[19] A 2019 statistical analysis of 11 3945 stage III non-small cell lung cancer (NSCLC) patients treated in 2004 to 2013 showed that 28% of the patients were younger than 60 years.[20] Similarly, another 2019 study of 44 498 stage IV NSCLC patients treated in 2013 to 2014 showed that 31% of the patients were younger than 60 years.[21] These findings highlight the importance of detecting and avoiding survival-compromising secondary complications in lung cancer RT as well as other types of thoracic RT. One study estimated the risks of RIC in lung cancer survivors to be as high as 33%.[22,23] Another analysis of 127 stage III NSCLC patients treated between 1996 and 2009 showed that 2-year competing risk-adjusted RIC rates for patients with a heart mean dose of < 10 Gy, ≥ 10 to 20 Gy, and > 20 Gy were 4%, 7%, and 21%, respectively.[22,24] Stam et al performed a study in 469 locally advanced NSCLC patients that showed a significant inverse correlation between increasing heart dose and survival.[25] A retrospective single-institutional multivariate analysis of 251 patients with locally advanced NSCLC from Washington University, St. Louis, Missouri, for which cardiac structures were recontoured, increasing heart V50 (Vx: the percentage volume receiving ≥ x Gy), was independently associated with survival (2-year overall survival increased from < 25% for V50 ≥ 25%, to 45.9% for V50 < 25%, $p < 0.0001$).[26]

In the more recently published RTOG 0617 study, RT dose to the heart was found to be prognostic for likelihood of death. On both univariate and multivariate analysis, V5 and V30 of

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heart were associated with increased risk of death.[27] In a secondary analysis reported subsequently, the incidence of grade 3+ cardiovascular events were lower with intensity-modulated RT (IMRT) vs 3-dimensional conformal RT (3D-CRT) (11% vs 21%, $p = 0.131$).[28] It was postulated that heart dose might best explain inferior outcomes in the 74 Gy arm. While there were recommended constraints for heart, this was not a compliance criterion. Expectedly, to limit lung doses, an incidental increase in cardiac dose may have been seen in both groups.[29] An important realization from the RTOG 0617 study was the significance of heart doses in a patient population with a median follow-up of < 24 months. This may become even more relevant in the modern era of consolidation immunotherapy, which is associated with a small risk of cardiac-related deaths.[30] Dose to heart (sub) structures has also been linked with noncancer death in early stage NSCLC patients treated with stereotactic body RT (SBRT).[31] In an analysis of 803 patients, at a median follow-up of 34.8 months, multivariate analysis identified maximum dose on the left atrium (median 6.5 Gy EQD2 [equivalent dose in 2 Gy fractions], range = 0.009 to 197, hazard ratio [HR] = 1.005, $p = 0.035$), and the dose to 90% of the superior vena cava (median 0.59 Gy EQD2, range = 0.003-70, HR = 1.025, $p = 0.008$) were significantly associated with noncancer death.

As in lung cancer, the risks of esophageal cancer RIC have previously been underreported because of poor overall prognosis. Beukema et al conducted a retrospective analysis of patients receiving definitive concurrent chemoradiation.[32] Grade 3 or higher cardiac events such as ischemia, effusions and heart failure were noted with a median follow-up of 26.1 to 57 months with an incidence ranging from 5.8 to 11.1%. Molenaar et al performed a Surveillance Epidemiology and End Results (SEER) analysis of patients receiving RT for esophageal cancer from 1973 to 2013.[33] They analyzed 6514 patients, of whom 53% received RT and 44% did not. Nine percent of 5-year survivors experienced cardiac death: 336 who received RT compared to 254 who did not, with mean times to death of 25.3 and 32.2 years, respectively. On multivariate analysis, risks were highest in patients diagnosed prior to 1995 and in those with squamous cell carcinoma. Increased cardiac death in 1995 was likely partially the result of older RT techniques.

In both lung and esophageal cancers, RT techniques have progressed so that the majority of these patients are now treated with IMRT rather than 3D-CRT.[34-36] IMRT has the ability to spare high doses of RT to smaller heart volumes at the cost of spreading lower doses over larger volumes. It remains unclear which is most important in avoiding RIC with data to support negative impact of both dosimetric parameters (**Table 2**). Not having data to guide the decision, both lowering mean dose to whole heart and limiting high dose values to small volumes should be emphasized during treatment planning. The risk of RIC in both lung and esophageal cancers is heavily confounded by age as well as risk factors. The risk factors inherent in disease development are also risk factors for cardiac disease; as such, these patient populations are at even higher risk for RIC. In addition, many patients have been diagnosed with cardiac disease prior to their cancer diagnosis, highlighting an even greater need for heart avoidance. Because of the anatomic proximity of these cancers to the heart, however, radiomodulatory techniques such as DIBH or gating may not be as helpful in reducing heart dose; thus, other techniques, such as proton therapy, may be needed.

Lymphoma

RT continues to play an integral role in the management of Hodgkin lymphoma (HL) and is still used in select cases of non-Hodgkin lymphoma (NHL). Both diagnoses involve treatment with cardiotoxic systemic agents that further enhance cardiac risks of RT.[37] Cardiac-related death is the third most common cause of death among lymphoma survivors, who have a 5.3 to 7.3 times increased risk of cardiac mortality compared to the general population.[38] Among HL survivors, the risk of fatal myocardial infarction has been found to be 2.5 times higher than in the general population.[3] Most of the cardiotoxicity data is derived from childhood survivors of HL, a highly curable disease, with toxicities including valvular heart disease (21% to 41%), coronary heart disease (17% to 23%), heart failure (8% to 17%), conduction disorders (12%) and pericardial abnormalities (10%).[39]

Data regarding relative contribution of doxorubicin-based chemotherapy and RT in causing RIC are heterogeneous. In a single-institutional analysis of 615 HL patients from Princess Margaret Hospital, Toronto, Canada, it was shown that while the rate of cardiac morbidity was highest among patients treated with both doxorubicin and mediastinal RT (HR = 2.77, $p < 0.0001$), mediastinal RT without chemotherapy also significantly increased this risk (HR = 1.82, $p < 0.038$).[5] In a report from the German-Austrian Pediatric Hodgkin's Disease Study Group, a longitudinal follow-up analysis of 1132 HL survivors who received treatment before 18 years of age in consecutive trials between 1978 and 1995, cumulative incidence of RIC after 25 years dropped with reduced radiation dose (21% with 36 Gy RT vs 3% with no RT, $p < 0.001$).[40] Valvular defects were diagnosed most frequently, followed by coronary artery diseases, cardiomyopathies, conduction disorders, and pericardial abnormalities. A similar linear dose-response relationship was noted in another French-British cohort analysis of 4122 children, including HL and NHL survivors treated in 8 cancer treatment centers in France and the United Kingdom.[41] Cumulative anthracycline dose

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and average radiation dose to the heart increased the risk of death from cardiac diseases (anthracycline RR [relative risk] = 4.4, cardiac dose 5 to 14.9 Gy RR = 12.5, cardiac dose > 15 Gy RR = 25.1) with a linear relationship between the average cardiac radiation dose and the risk of cardiac mortality (estimated excess RR at 1 Gy = 60%). A Childhood Cancer Survivor Study from 26 institutions evaluated 14358 5-year survivors of cancer diagnosed under age 21 and noted a 2 to 5 times increased risk of congestive heart failure, pericardial disease, and valvular abnormalities compared with untreated sibling survivors.[42] Cardiac radiation exposure > 15 Gy also resulted in a 2- to 6-fold increased risk of the above cardiac events. A Dutch case-control study of HL patients diagnosed before age 51 years who had a 5-year follow-up showed a higher mean left ventricular dose (MLVD) (16.7 Gy vs 13.8 Gy, $p = 0.003$).[43] The risk of heart failure was also correlated with MLVD (MLVD 1 to 15 Gy, 16 to 20 Gy, 21 to 25 Gy, and ≥ 26 Gy: RR of heart failure 1.27, 1.65, 3.84, and 4.39, respectively, $P_{trend} < 0.001$). Further, this risk was increased with anthracycline use (MLVD 0 to 15 Gy, 16 to 20 Gy, and ≥ 21 Gy: Cumulative risk of heart failure was 4.4%, 6.2%, and 13.3%, respectively, without anthracycline and 11.2%, 15.9%, and 32.9%, respectively, with anthracycline). The largest analysis of prospective data comes from EORTC-LYSA trials for patients with HL.[44] Dose to the heart and carotids was reconstructed to a demonstrated increased risk of cardiovascular disease with an increased mean heart dose (per 1 Gy increase in dose, HR = 1·015 [95% CI, 1·006-1·024], $p = 0·0014$). Dose to carotid arteries did not correlate with a similar risk.

A major limitation of such survivorship studies is lack of details on true 3D cardiac dose and treatment with conventional large-field treatments including mantle/mini-mantle, total body radiation or use of cobalt-60 machines. With the evolution of more modern treatment planning principles of reduced treatment dose targeting smaller involved-site and involved-nodal regions combined with increasing use of modern treatment technologies such as IMRT and proton therapy, dose to cardiac substructures may become more relevant than whole cardiac dose.[45] In a random sample of 125 HL patients treated with mediastinal RT, 44 cardiac events were documented, of which 70% were ischemic.[46] In a subanalysis of ischemic cardiac events, V5 of the left anterior descending artery (HR = 0.98, $p = .003$), and V20 of the left circumflex artery (HR = 1.03, $p < .001$) were found to be significant predictors. In a modern cohort analysis, 56 patients undergoing cytotoxic chemotherapy and involved-field 3D-CRT for HL were retrospectively analyzed.[47] V25 Gy of left atrium, V30 Gy of left ventricle and V30 Gy of right ventricle correlated with mitral, aortic and tricuspid valvular disease, respectively, yielding 32.1% of patients developing valvular regurgitation and/or stenosis after a median follow-up of 70.5 months. In a more recent prospective analysis, 179 consecutive asymptomatic patients with HL were evaluated with coronary CTA.[48] With a median follow-up of 11.6 years, 26% survivors demonstrated CTA abnormalities, with 15% of patients demonstrating changes within 5 years and 6.7% demonstrating severe stenoses requiring surgical procedures. Radiation dose to the coronary artery origins was noted to be prognostic.

Ongoing efforts will require continued monitoring of 3D dose-distribution to cardiac substructures in the era of modern radiation planning and delivery principles to refine the dosimetric constraints. Equally important will be efforts toward cardiac rehabilitation.

Treatment and Management of Radiation-Induced Cardiotoxicity

To date, no treatment is available to reverse or treat the effects of RIC. The focus of treatment paradigms has been on optimizing medical management of other cardiac risk factors, such as hypertension and diabetes, and preventing disease through education toward a smoke-free and heart-healthy lifestyle. Smoking cessation and counseling have played critical roles in reducing risk.

Over the last several years, the field of cardio-oncology has emerged as a multidisciplinary field of cardiologists, medical oncologists, and sometimes radiation oncologists specializing in both temporary and long-term effects of oncology-related cardiotoxicity with a goal of improving the quality of life of cancer survivors.[49] A pilot project in lymphoma patients undergoing stem cell transplant demonstrated improved exercise levels and physical functioning with guided cardiac-rehabilitation exercises.[50] Similar efforts should be initiated for patients receiving cardiac exposure from RT. The indications for patient referral for this field vary by institution/locale. In some cases, any patient at potential risk for cardiotoxicity may be referred for consultation and subsequent follow-up. In others, patients may be referred only when they begin to show signs of cardiotoxicity (eg, a patient who develops a decreased ejection fraction while on trastuzumab). As the number of cancer survivors continues to increase, the role of cardio-oncology becomes more important, with a call for a greater number of providers.

Conclusion

RIC is a known late effect of breast and thoracic RT in childhood cancer survivors. Population-based and institutional analyses in recent years have provided some dosimetric correlates to better predict the risk of RIC in relationship to cardiac radiation exposure. However, assessments are limited by lack of 3D anatomical data, use of conventional treatment planning and delivery technology, and relative lack of dosimetric significance of dose to various cardiac substructures. Furthermore, true assessment of RIC is limited

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by lack of follow-up, cancer-related mortality, pre-existing conditions and age-related changes. In the absence of an approved treatment for RIC, reducing the clinical impact of RIC focuses on minimizing dose to the heart through advanced RT delivery techniques, smaller RT volumes and/or decreased doses of RT. Treatment paradigms also focus on preventing cardiac risk factors. With the evolution of more modern treatment planning principles of reduced treatment dose targeting smaller involved-site and involved-nodal regions combined with increasing use of modern treatment technologies such as IMRT and proton therapy, dose to cardiac substructures may become more relevant than whole cardiac dose. All radiation oncologists should be aware of RIC, with a call to action to support advanced delivery techniques. Although these techniques may sometimes come at an increased short-term cost, reducing RIC will lead to long-term gains for patients, for the scientific understanding of cardiac toxicity, and for the medical establishment.

References

1. Bloom MW, Hamo CE, Cardinale D, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. *Circ Heart Fail.* 2016;9(1):e002661.
2. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood.* 2007;109(5):1878-1886.
3. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Nat Cancer Inst.* 2007;99(3):206-214.
4. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev.* 2012;(4):Cd006243.
5. Myrehaug S, Pintilie M, Tsang R, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. *Leuk Lymphoma.* 2008;49(8):1486-1493.
6. Awadalla M, Hassan MZO, Alvi RM, Neilan TG. Advanced imaging modalities to detect cardiotoxicity. *Curr Probl Cancer.* 2018;42(4):386-396.
7. Akhter N, Murtagh G, Yancy C. Strategies for early detection of cardiotoxicities from anticancer therapy in adults: evolving imaging techniques and emerging serum biomarkers. *Future Oncol.* 2015;11(14):2093-2013.
8. Lancellotti VT, Nkomo, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging.* 2013;14(8):721-740.
9. Sylvester CB, Abe JI, Patel ZS, Grande-Allen JK. Radiation-induced cardiovascular disease: mechanisms and importance of linear energy transfer. *Front Cardiovasc Med.* 2018;5:5.
10. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. *Front Oncol.* 2015;5:39.
11. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New Eng J Med.* 2013;368(11):987-998.
12. van den Bogaard VA, Ta BD, van der Schaaf A, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol.* 2017;35(11):1171-1178.
13. Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol.* 2017;35(15):1641-1649.
14. Schneider U, Ernst M Hartmann M. The dose-response relationship for cardiovascular disease is not necessarily linear. *Radiat Oncol.* 2017;12(1):74.
15. Boekel NB, Schaapveld M, Gietema JA, et al. Cardiovascular disease risk in a large, population-based cohort of breast cancer survivors. *Int J Radiat Oncol Biol Phys.* 2016. 94(5):1061-1072.
16. Walker VA, Crijns, Langendijk J, et al. Early detection of cardiovascular changes after radiotherapy for breast cancer: protocol for a european multicenter prospective cohort study (MEDIRAD EARLY HEART Study). *JMIR Res Protoc.* 2018;7(10):e178.
17. Stick LB, Vogelius IR, Modiri A, et al. Inverse radiotherapy planning based on bioeffect modelling for locally advanced left-sided breast cancer. *Radiother Oncol.* 2019;136:9-14.
18. Boero IJ, Paravati AJ, Triplett DP, et al. Modern radiation therapy and cardiac outcomes in breast cancer. *Int J Radiat Oncol Biol Phys.* 2016;94(4):700-708.
19. Final Research Plan for Lung Cancer: Screening. 2018. https://www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan/lung-cancer-screening1. Accessed February 15, 2020.
20. Vyfhuis MAL, Bentzen SM, Molitoris, JK, et al. Patterns of care and survival in stage III NSCLC among black and latino patients compared with white patients. *Clin Lung Cancer.* 2019;20(4):248-257.e4.
21. Foster CC, Sher DJ, Rusthoven CG, et al. Overall survival according to immunotherapy and radiation treatment for metastatic non-small-cell lung cancer: a National Cancer Database analysis. *Radiat Oncol.* 2019;14(1):18.
22. Ming X, Feng Y, Yang C, et al. Radiation-induced heart disease in lung cancer radiotherapy: a dosimetric update. *Medicine (Baltimore).* 2016. 95(41):e5051.
23. Hardy D, C.C. Liu, et al. Cardiac toxicity in association with chemotherapy and radiation therapy in a large cohort of older patients with non-small-cell lung cancer. *Ann Ocol.* 2010;21(9):1825-1833.
24. Wang K, Eblan MJ, Deal, MA, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol.* 2017. 35(13):1387-1394.
25. Stam B, van der Bijl E, van Diessen J, et al. Heart dose associated with overall survival in locally advanced NSCLC patients treated with hypofractionated chemoradiotherapy. *Radiother Oncol.* 2017;125(1):62-65.
26. Speirs CK, DeWees TA, Rehman S, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. *J Thorac Oncol.* 2017;12(2):293-301.
27. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 2015;16(2):187-199.
28. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol.* 2017;35(1):56-62.
29. Thor M, Deasy JO, Hu C, et al. The role of heart-related dose-volume metrics on overall survival in the RTOG 0617 clinical trial. *Int J Radiat Oncol Biol Phys.* 2018;102(3):S96.
30. Antonia SJ, A. Villegas, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *New Engl J Med.* 2018. 379(24):2342-2350.
31. Stam B, Peulen H, Guckenberger M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. *Radiother Oncol.* 2017;123(3):370-375.
32. Beukema JC, van Luijk P, Widder J, Langendijk J, Muijs CT. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? *Radiother and Oncol.* 2015;114(1):85-90.
33. Molenaar RJ, Radivoyevitch T, Hulshof M, Van Laarhoven HWM. Cardiac death rates after irradiation for esophageal cancer: an epidemiologic study among esophageal cancer survivors. *J Clin Oncol.* 2017;35(15_suppl):4049.
34. Peng J, Pond G, Donovan E, Ellis PM, Swaminath A. A comparison of radiation techniques in patients treated with concurrent chemoradiation for stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2020.
35. Koshy M, Malik R, Spiotto M, et al. Association between intensity modulated radiotherapy and survival in patients with stage III non-small cell lung cancer treated with chemoradiotherapy. *Lung Cancer.* 2017;108:222-227.

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36. Haque W, Verma V, Butler EB, Teh BS. Utilization of neoadjuvant intensity-modulated radiation therapy and proton beam therapy for esophageal cancer in the United States. *J Gastrointest Oncol.* 2018;9(2):282-294.
37. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol.* 2003;21(18):3431-3429.
38. Boyne DJ, Mickle AT, Brenner DR, et al. Long-term risk of cardiovascular mortality in lymphoma survivors: a systematic review and meta-analysis. *Cancer Med.* 2018;7(9):4801-4813.
39. Ratosa I, Pantar MI. Cardiotoxicity of mediastinal radiotherapy. *Rep Pract Oncol Radiother.* 2019;24(6):629-643.
40. Schellong G, Riepenhausen M, Bruch C, et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. *Pediatr Blood Cancer.* 2010;55(6):1145-52.
41. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol.* 2010;28(8);1308-1315.
42. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Brit Med J.* 2009;339:b4606.
43. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of hodgkin lymphoma. *J Clin Oncol.* 2015;34(3):235-243.
44. Maraldo MV, Giusti F, Vogelius IR, et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials. *Lancet Haematol.* 2015;2(11):e492-502.
45. Hoppe BS, Bates JE, Mendenhall NP, et al. The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern radiation therapy era. *Pract Radiat Oncol.* 2019.
46. Hahn E, Jiang H, Ng A, et al. Late cardiac toxicity after mediastinal radiation therapy for Hodgkin lymphoma: contributions of coronary artery and whole heart dose-volume variables to risk prediction. *Int J Radiat Oncol Biol Phys.* 2017;98(5):1116-1123.
47. Cella L, Liuzzi R, Conson M, et al. Dosimetric predictors of asymptomatic heart valvular dysfunction following mediastinal irradiation for Hodgkin's lymphoma. *Radiother Oncol.* 2011;101(2):316-321.
48. Girinsky T, M'Kacher R, Lessard N, et al. Prospective coronary heart disease screening in asymptomatic Hodgkin lymphoma patients using coronary computed tomography angiography: results and risk factor analysis. *Int J Radiat Oncol Biol Phys.* 2014;89(1):59-66.
49. Koutsoukis A, Ntalianis A, Repasos E, et al. Cardio-oncology: a focus on cardiotoxicity. *Euro Cardiol.* 2018;13(1):64-69.
50. Rothe D, Cox-Kennett N, Buijs DM, et al. Cardiac rehabilitation in patients with lymphoma undergoing autologous hematopoietic stem cell transplantation: a cardio-oncology pilot project. *Can J Cardiol.* 2018;34(10 Suppl 2):S263-s269.
51. Raghunathan D, Khilji MI, Hassan SA, Yusuf SW. Radiation-induced cardiovascular disease. *Curr Atheroscler Rep.* 2017;19(5):22.
52. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *J Am Med Assoc.* 2013;309(22):2371-2381.
53. Fidler MM, Reulen RC, Henson K, et al. Population-based long-term cardiac-specific mortality among 34 489 five-year survivors of childhood cancer in Great Britain. *Circulation.* 2017;135(10):951-963.
54. Boerma M, Sridharan V, Mao X-W, et al. Effects of ionizing radiation on the heart. *Mutat Res.* 2016;770(Pt B):319-327.
55. van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood.* 2017;129(16):2257-2265.
56. Heidenreich A, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol.* 2007;25(1):43-49.
57. Brown ML, Schaff HV, Sundt TM. Conduit choice for coronary artery bypass grafting after mediastinal radiation. *J Thorac Cardiovasc Surg.* 2008;136(5):1167-1171.
58. Totterman KJ, E. Pesonen, Siltanen P. Radiation-related chronic heart disease. *Chest.* 1983;83(6):875-878.
59. Marks LB, Yu X, Zhou S-M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys.* 2005;63(1):214-223.
60. Mousavi N and A. Nohria, Radiation-induced cardiovascular disease. *Curr Treat Options Cardiovasc Med.* 2013;15(5):507-517.
61. Veinot J and W.D. Edwards, Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum Pathol.* 1996.27(8):766-73.
62. Yusuf SW, Sami S, Daher IN, et al. Radiation-induced heart disease: a clinical update. *Cardiol Res Pract.* 2011;2011:317659.
63. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. *Circulation.* 1999;100(13):1380-1386.
64. Brosius FC 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med.* 1981;70(3):519-530.
65. Bijl JM, Roos MM, Leeuwen-Segarceanu EM, et al. Assessment of valvular disorders in survivors of hodgkin's lymphoma treated by mediastinal radiotherapy +/- chemotherapy. *Am J Cardiol.* 2016;117(4):691-696.
66. Heidenreich A, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol.* 2003;42(4):743-749.
67. Cella L, Liuzz R, Conson M, et al. Multivariate normal tissue complication probability modeling of heart valve dysfunction in Hodgkin lymphoma survivors. *Int J Radiat Oncol Biol Phys.* 2013;87(2):304-310.
68. Paven E, Cimadevilla C, Urena M, et al. Management of radiation-induced valvular heart disease due to Hodgkin's lymphoma in the modern era. *EuroIntervention,* 2018;13(15):e1771-e1773.
69. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *J Am Med Assoc.* 2003;290(21):2831-2837.
70. Cutter DJ, Schaapvel M, Darby SC, et al. Risk for valvular heart disease after treatment for hodgkin lymphoma. *J Nat Cancer Inst.* 2015;107(4).
71. Mulrooney DA, Armstrong GT, Huang S, et al. Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional study. *Ann Internal Med.* 2016;164(2):93-101.
72. Al-Kindi SG, Oliveira GH. Heart transplantation outcomes in radiation-induced restrictive cardiomyopathy. *J Cardiac Failure.* 2016;22(6):475-478.
73. Groarke JD, Tanguturi VK, Hainer J, et al. Abnormal exercise response in long-term survivors of Hodgkin lymphoma treated with thoracic irradiation: evidence of cardiac autonomic dysfunction and impact on outcomes. *J Am Coll Cardiol.* 2015;65(6):573-583.
74. Adams MJ, Lipshultz SE, Schwartz C, Fajardo LF, Coen V, Constine LS. Radiation-associated cardiovascular disease: manifestations and management. *Semin Radiat Oncol.* 2003;13(3):346-356.
75. Wu S, Tam M, Vega RM, Perez CA, Gerber NK. Effect of Breast irradiation on cardiac disease in women enrolled in BCIRG-001 at 10-year follow-up. *Int J Radiat Oncol Biol Phys.* 2017;99(3):541-548.
76. Bhattacharya S, Asaithamby A. Ionizing radiation and heart risks. *Sem Cell Develop Biol.* 2016;58:14-25.

An Assessment of the Comprehensiveness of Radiation Oncology Residency Websites

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Abstract

Objective: Medical students rely on the internet as a resource to gather information about residency programs, although little data exist on the quality or completeness of these websites. Therefore, we sought to evaluate the accessibility of educational and recruitment content of radiation oncology residency websites in the US.

Methods and Materials: The names of radiation oncology residency programs were obtained from the Electronic Residency Application Service. Websites were evaluated for the presence of 20 unique features related to categories of application process, work incentives, educational instruction, research, clinical training, and program leadership introduction. Programs were organized by geographic location, size and ranking for further analysis. Univariate logistic regression was performed to assess predictors of matching in the 2019 cycle.

Results: A total of 92 analyzable websites were identified. Individual program websites contained a mean (SD) of 9.75 (3.8) of the 20 factors sought (49%). Ten (11%) program websites had at least 75% of the 20 features. In addition, 37 (40%) programs had less than 50% of the features listed on their websites. When evaluated by geographic region, no differences in the amount of information available on each website were noted ($p = 0.102$). Furthermore, there was no significant difference in mean number of features reported by large or small programs (10.80 vs 9.15, $p = 0.114$) and by ranking (9.96 vs 9.68, $p = 0.760$). Large programs were more likely to fill all their spots in the 2019 match (OR 3.85, $p = 0.013$) and there was a nonsignificant trend in increased likelihood of matching with 6 to 15 features on program websites (OR 2.07-2.14).

Conclusion: With the recent high unmatched rate in radiation oncology residency programs, methods to improve the recruitment process are of even greater importance. Many radiation oncology residency websites appear to be incomplete. Improvement in the comprehensiveness and accessibility of radiation oncology websites may improve the recruitment process and allow for medical students to make more informed decisions.

Medical students interested in obtaining a radiation oncology residency position often use the internet as a resource to gather information about residency programs. Although there have been no surveys specific to radiation oncology applicants, studies in other medical specialties have confirmed the importance of online program information.[1-8] Therefore, it is important for residency programs to maintain informative and comprehensive websites for prospective radiation oncology applicants.

Prior studies in other medical specialties have demonstrated that residency program websites are often suboptimal and that missing information can be crucial for applicants to determine which programs are a better "fit" for them.[9,10] Given that program websites may be the only novel program-specific resource medical students have before applying, completeness of program information may be a significant factor in allowing residency programs to remain competitive for applicants, particularly with the

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Table 1. List of 20 Features and the Percentage of Total Programs That Included the Feature on Their Website

Feature	Percent of Programs with Feature Included on Website
Application Process	
Contact e-mail	98
Link to ERAS	54
Number of spots for match	33
Selection criteria	32
Work Incentives	
Benefits	41
Information on surrounding area	41
Salary	36
Parking information	9
Educational Instruction	
Description of didactics	63
Research	
Research rotations/opportunities	86
Active/past research projects	58
Clinical Training	
Comprehensive faculty listing	82
Equipment description	76
Current residents	73
Rotation schedule	51
Medical student electives	47
Alumni job placement	42
Call schedule	15
Introduction to Program Leadership	
Message from program director	36
Message from chairperson	24

Key: ERAS = Electronic Residency Application Service

recent increase in unmatched radiation oncology program spots in 2019.[11]

Previous studies in other medical specialties have found deficiencies in online content on residency program websites; however, similar information regarding the availability and quality of current radiation oncology residency website content is not available. We sought to evaluate the accessibility of educational and recruitment content of radiation oncology residency websites in the US.

Methods and Materials

A list of US radiation oncology residency programs was obtained from the Electronic Residency Application Service (ERAS). All websites were publicly available. This study did not require institutional review board approval per the SUNY Downstate Medical Center.

The program websites were accessed through the link provided by ERAS or through an online search. Websites were evaluated for the presence of 20 unique features related to categories of application process, work incentives, educational instruction, research, clinical training, and program leadership introduction (**Table 1**). The 20 features were derived from published studies in other specialties evaluating residency websites and were considered to be relevant to the field of radiation oncology by the authors.[4,5,12] Inclusion of information required its presence directly on the radiation oncology residency or department website. However, information on salary, benefits, parking, and faculty listing was considered present if it was accessible by a direct link from the residency website.

Programs were organized by geographic location and residency size for further analysis. Programs were divided into institutions based in the Northeast (Maryland, Pennsylvania, Delaware, New Jersey, New York, Connecticut, Massachusetts, Vermont, Rhode Island, New Hampshire, Maine, and the District of Columbia), South (Virginia, Kentucky, Arkansas, Oklahoma, Texas, North Carolina, South Carolina, Georgia, Florida, Louisiana, Mississippi, Alabama, Tennessee), West (New Mexico, Colorado, Washington, Oregon, Nevada, Utah, Arizona, California, Hawaii), and Midwest (Nebraska, Kansas, Minnesota, Iowa, Missouri, Wisconsin, Illinois, Michigan, Indiana, Ohio, West Virginia). States/territories without programs included Alaska, Wyoming, Montana, Idaho, North Dakota, Puerto Rico, and South Dakota. Program size was determined by the median number of residents in the programs, with ≤ 7 residents considered to be small and ≥ 8 considered large. Programs were then categorized by the ranking of the cancer program per *US News and World Report* as a "Top 25" vs a "Not Top 25" program and further categorized using the National Resident Matching Program data as having filled or not filled in the 2019 cycle. Chi-square and Mann-Whitney/Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively. Univariate logistic regression was performed to assess predictors of matching in the 2019 cycle. SPSS version 21.0 (IBM Inc., Armonk, New York) was used for statistical analysis.

Results

A total of 94 radiation oncology residency programs was obtained from ERAS. Of the 94 programs, 92 websites

Table 2. Average Number of Features Included on Program Websites Based on Program Size and Geographic Location

Feature	Number of Features on Programs' Websites, Mean (SD)	*p*-value
Overall	9.75 (3.8)	
Size of program		0.114
Small	9.15 (3.7)	
Large	10.80 (3.2)	
Location of program		0.102
Midwest	11.32 (3.2)	
West	10.83 (3.3)	
Northeast	8.93 (3.9)	
South	8.56 (4.0)	
Ranking		0.760
Not Top 25*	9.68 (4.05)	
Top 25	9.96 (2.96)	

Key: SD = standard deviation; *Top 25 was determined by *US News and World Report*

Table 3. Univariate Logistic Regression for the 2019 Match

Feature	OR (95% CI)	p-value
Number of website features		
0-5	1	
6-10	2.07 (0.41-10.36)	0.378
11-15	2.14 (0.41-11.26)	0.368
16-20	1.00 (0.13-7.57)	1.000
Size of program		
Small	1	
Large	3.85 (1.34-11.11)	0.013*
Location of program		
Midwest	1	
West	1.77 (0.28-11.04)	0.544
Northeast	0.38 (0.10-1.45)	0.155
South	0.71 (0.17-2.95)	0.633
Ranking		
Not Top 25*	1	
Top 25	2.56 (0.68-9.67)	0.166

Key: OR = odds ratio, CI = confidence interval; *Top 25 was determined by *US News and World Report*

were evaluated (2 websites were inaccessible or nonexistent). Individual program websites contained a mean (SD) of 9.75 (3.8) of the 20 factors sought (49%).

Only 10 (11%) of the program websites had at least 75% of the 20 features. In addition, 37 (40%) programs had < 50% of the features listed on their websites. Websites ranged from having 15% of the features to as much as 90%. Most sites had contact e-mail (98%), research opportunities (86%), and a comprehensive faculty listing (82%), while fewer than a quarter of programs had a message from the chairperson (24%), call schedule (15%), or parking information (9%) (**Table 1**).

After organizing by geographical location, the Northeast contained 29% of programs, the South 29%, the West 19%, and the Midwest 23%. There were no differences in the amount of information available on each website based on geographic region ($p = 0.102$). There were 45 large programs and 47 small programs, and there was no significant difference in mean number of features reported by large or small programs (10.90 vs 9.15, $p = 0.114$). Comparison of Top 25 vs Not Top 25 programs by the US News and World Report found no difference in mean number of features reported (9.96 vs. 9.68, $p = 0.760$) (**Table 2**).

There were 88 programs that entered the NRMP in 2019 of which 22 (25%) did not fill all positions. On univariate logistic regression, large programs were more likely to fill their spots in the 2019 match (OR 3.85, $p = 0.013$) and there was a nonsignificant trend in increased likelihood of matching with 6 to 15 features on program websites (OR 2.07-2.14)(**Table 3**).

Discussion

The 2019 Match Day results, with 22 programs (25%) going unfilled for the first time in many years, was a surprising development after years of a competitive match in radiation oncology. The decline in applications is likely multifactorial, with causes including an anticipated future oversupply of radiation oncologists and a much higher-than-usual failure rate on the 2018 radiation biology and physics qualifying board examinations.[13,14]

As future generations of medical trainees undoubtedly will continue to use the internet as a resource for investigating residency specialties and individual programs, having comprehensive program websites will continue to grow in importance. In this study, we evaluated current program websites based on 20 criteria and note that on average, programs met about half of these predefined criteria. Furthermore, the geographical location and program size were not related to website completeness, implying that the issue is widespread and overlooked among a variety of programs.

While the deficiencies in online content available for other medical

specialties has been reported extensively,[1-8] information on availability and quality of online information regarding radiation oncology programs is limited.[12] We found that important information for prospective residents, including the number of match spots, selection criteria, and alumni job placement, is omitted in the majority of websites. Previous studies have noted that websites influence prospective applicants' decisions[5,7] and that an easily navigable site may be an important factor in deciding where to apply.[3] The lack of information on radiation oncology residency websites may leave applicants with insufficient information with which to gauge their interest in a particular program.

It is likely that another resource programs use is social media, which may be used in recruitment. A survey study of prospective anesthesia residents showed that the majority (52.8%) felt a residency-based social media account impacted their evaluation of programs. Specifically, the most popular platforms included Doximity and Facebook.[15] With an increasing Twitter presence in oncology,[16] its utilization by programs may also be an emerging trend in resident recruitment.

This study has several limitations. First, the choice of program website features by the study team was completed through extensive literature review of desired features in other specialties as well as consensus on factors specific to radiation oncology; however, additional factors of interest to medical students may not have been included. Second, due to website variability, available features may have been overlooked despite thorough review. There was also no official way to verify the accuracy of the information posted on the websites. Furthermore, intangible factors such as website design and ease of use were not assessed in this study. Nonetheless, these results highlight several areas for potential improvement.

Conclusion

The recent match results indicate that individual residency programs, and even our field as a whole, cannot be complacent when it comes to attracting the best medical students. We demonstrate that residency program websites, a medical student's first and sometimes final look at a program, often lack completeness. Enhancing the quality and completeness of residency program websites may be a very high-yield first step toward optimizing future matches and reversing the recent concerning increase in unfilled radiation oncology residency spots.

References

1. Mulcahey MK, Gosselin MM, Fadale PD. Evaluation of the content and accessibility of web sites for accredited orthopaedic sports medicine fellowships. *J Bone Joint Surg Am.* 2013;95(12):e85.
2. Chu LF, Young CA, Zamora AK, et al. Self-reported information needs of anesthesia residency applicants and analysis of applicant-related web sites resources at 131 United States training programs. *Anesth Analg.* 2011;112(2):430-439.
3. Mahler SA, Wagner M, Church A, Sokolosky M, Cline DM. Importance of residency program web sites to emergency medicine applicants. *J Emerg Med.* 2009;36(1):83-88.
4. Kumar A, Sigal Y, Wilson E. Web sites and pediatric residency training programs in the United States. *Clin Pediatr (Phila).* 2008;47(1):21-24.
5. Gaeta TJ, Birkhahn RH, Lamont D, Banga N, Bove JJ. Aspects of residency programs' web sites important to student applicants. *Acad Emerg Med.* 2005;12(1):89-92.
6. Reilly EF, Leibrandt TJ, Zonno AJ, Simpson MC, Morris JB. General surgery residency program websites: usefulness and usability for resident applicants. *Curr Surg.* 2004;61(2):236-240.
7. Embi PJ, Desai S, Cooney TG. Use and utility of web-based residency program information: a survey of residency applicants. *J Med Internet Res.* 2003;5(3):e22.
8. Hansberry DR, Bornstein J, Agarwal N, et al. An assessment of radiology residency program websites. *J Am Coll Radiol.* 2018;15(4):663-666.
9. Svider PF, Gupta A, Johnson AP, et al. Evaluation of otolaryngology residency program websites. *JAMA Otolaryngol Head Neck Surg.* 2014;140(10):956-960.
10. Skovrlj B, Silvestre J, Ibeh C, Abbatematteo JM, Mocco J. Neurosurgery residency websites: a critical evaluation. *World Neurosurg.* 2015;84(3):727-733.
11. National Resident Matching Program, Results and Data: 2018 Main Residency Match. National Resident Matching Program, Washington, DC. 2018.
12. Wakefield DV, Manole BA, Jethanandani A, et al. Accessibility, availability, and quality of online information for US radiation oncology residencies. *Pract Radiat Oncol.* 2016;6(3):160-165.
13. Pan HY, Haffty BG, Falit BP, et al. Supply and demand for radiation oncology in the United States: updated projections for 2015 to 2025. *Int J Radiat Oncol Biol Phys.* 2016;96(3):493-500.
14. Royce TJ, Katz MS, Vapiwala N. Training the radiation oncology workforce of the future: course correction to supply the demand. *Int J Radiat Oncol Biol Phys.* 2017;97(5):881-883.
15. Renew JR, Ladlie B, Gorlin A, Long T. The impact of social media on anesthesia resident recruitment. *J Educ Perioper Med.* 2019;21(1):E632.
16. Sedrak MS, Attai DJ, George K, Katz MS, Markham MJ. Integrating social media in modern oncology practice and research. *Am Soc Clin Oncol Educ Book.* 2018;38:894-902.

National Trends in the Use of Stereotactic Radiosurgery for Glioblastoma

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Abstract

Background: Glioblastoma (GBM) is a high-grade intracranial malignancy with a propensity to progress. We analyzed the National Cancer Database (NCDB) to examine trends in the use of stereotactic radiosurgery (SRS).

Methods: We queried the NCDB for patients with GBM receiving intracranial radiation. Odds ratios were used to determine SRS predictors. Cox regression was used to determine predictors of overall survival (OS).

Results: We identified 62681 patients meeting eligibility criteria. Predictors of SRS use were increased age, government insurance, lower comorbidity score, treatment at an academic facility, metropolitan location, and earlier years of treatment. Increased age, lack of chemotherapy, higher comorbidity score, and earlier year of treatment predicted worse OS. SRS utilization decreased from 3% in 2004 to 1% in 2014.

Conclusion: SRS use in the initial management of GBM has steadily decreased.

Glioblastoma (GBM) is the most common primary malignancy of the brain in adults, affecting close to 30000 patients per year in the United States.[1] A locally aggressive tumor, GBM has a high propensity for intracranial progression despite multimodality therapy including maximal safe resection succeeded by adjuvant chemoradiation.[2] Given high rates of local failure, attempts have been made to explore the use of escalated doses of radiation, ultimately showing no benefit.[3-5] Initially developed by Swedish neurosurgeon Lars Leksell, stereotactic radiosurgery (SRS) represents an advanced method of delivering high-dose-per-fraction radiation treatments in a tightly conformal manner.[6] With SRS, conformal dose escalation is achievable and has been investigated in the pre-temozolomide era in RTOG 9305.[7] In this trial, patients were treated with an initial SRS boost followed by a course of fractionated external-beam radiation (EBRT). Ultimately, no discernible benefit was observed. It is conceivable that upfront SRS use in GBM management would decline after penetrance of the RTOG 9305 findings; however, data supporting this conclusion are lacking. As such, we examined data from the National Cancer Database (NCDB) to analyze trends and potential predictors for the use of SRS in the treatment of GBM.

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Methods

The methods for performing an analysis of the NCDB have been described previously.[8,9] We conducted a retrospective review using data from the NCDB, which is de-identified and thus exempt from Institutional Review Board oversight. The NCDB is a tumor registry jointly maintained by the American Cancer Society and the American College of Surgeons for more than 1500 hospitals accredited across the United States by the Commission on Cancer (CoC). It is estimated that this database captures up to 70% of newly diagnosed malignancies each year across the country. We queried the NCDB from 2004-2014

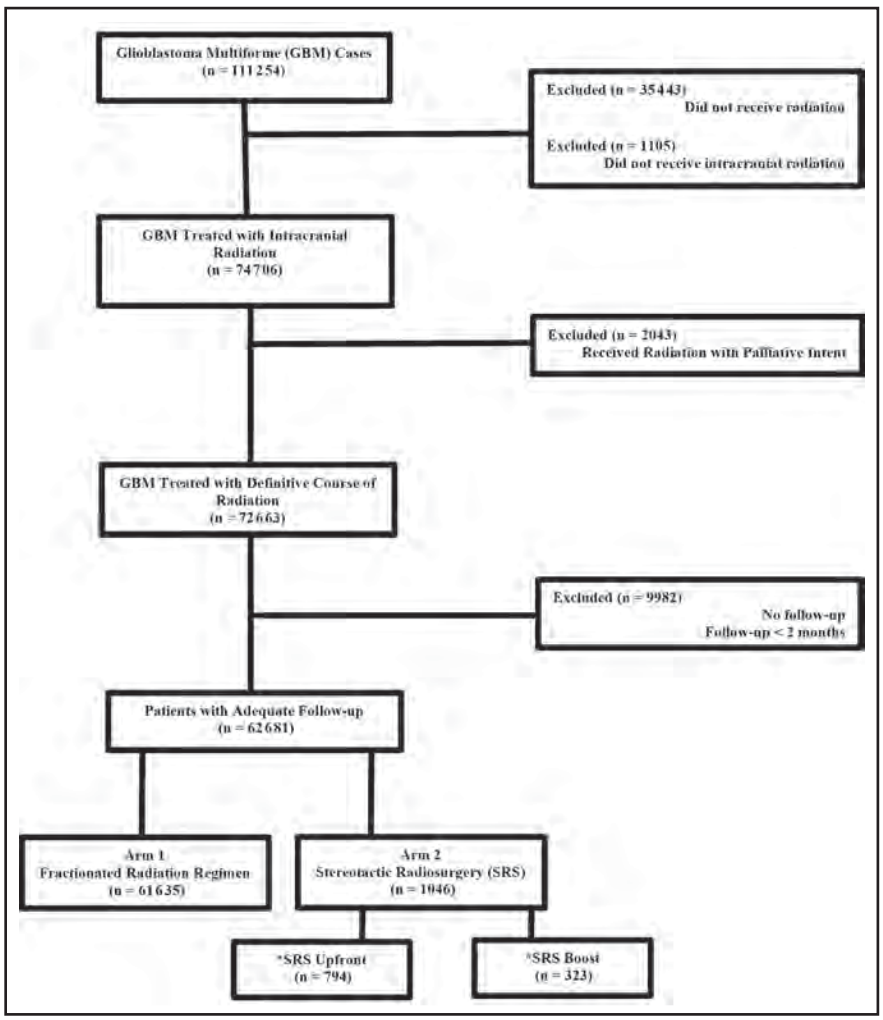

FIGURE 1. *A CONSORT (Consolidated Standards of Reporting Trials) diagram outlines the selection criteria and inclusion/exclusion. *Seventy-one patients were coded as receiving stereotactic radiosurgery (SRS) both upfront and as a boost.*

for patients with GBM who had external-beam radiation to the brain delivered with nonpalliative intent (a variable that is recorded within the NCDB). Patients had to have at least 2 months of follow-up. SRS is coded as a specific radiation technique within the NCDB and used to identify those patients. **Figure 1** shows a CONSORT (Consolidated Standards of Reporting Trials) diagram outlining the selection criteria and inclusion/exclusion.

Race was broken down into three broad categories: Caucasian, African American, or other. Comorbidity was quantified using the Charlson/Deyo comorbidity index.[10] Stage was defined according to the 7th edition of the American Joint Committee on Cancer's clinical group. Socioeconomic data in the patients' residence census tract was provided as quartiles of the percentage of persons with less than a high school education and median household income. The facility type was assigned according to the CoC accreditation category. Locations were assigned based on data provided by the US Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Data were analyzed using MedCalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables and c^2 tests compared sociodemographic, treatment, and tumor characteristics between the treatment groups. Overall survival was calculated in months from time of diagnosis to date of last contact or death, which is the standard way this data is recorded in the NCDB. Kaplan-Meier curves were used to calculate cumulative probability of survival.[11] Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative proportions across groups. A Cox proportional hazards model was used for multivariable survival analysis.[12] Due to the large nature of the dataset, factors significant on univariable Cox regression were entered using a stepwise backward elimination process. Adjusted hazard ratios and 95% confidence intervals are reported, using an α level of 0.05 to indicate statistical significance.

Propensity score-adjusted survival analysis was used to account for indication bias due to lack of randomization between patients receiving standard external-beam radiation and SRS.[13] Multivariable logistic regression was used to calculate a propensity score indicative of conditional probability of receiving standard radiation or SRS. The propensity model included observable variables associated with treatment selection on multivariable logistic regression. A Cox proportional hazards model was then constructed incorporating the propensity score, but also excluding factors included in the propensity score calculation to avoid overcorrection. The assumption of balance was further

Table 1. Patient Demographics and Clinical Characteristics at Baseline (n = 62 681)

Characteristics	No. (%)
Sex	
Male	36752 (59)
Female	25929 (41)
Race	
White	57105 (91)
African American	3376 (5)
Other	2200 (4)
Comorbidity Score	
0	47280 (75)
1	9785 (15)
≥2	5616 (10)
Insurance	
Not insured	2098 (3)
Private payer	31741 (50)
Government	27927 (44)
Unrecorded	915 (3)
Education %	
≥29	8297 (13)
20 to 28.9	14438 (23)
14 to 19.9	20881 (33)
<14	17670 (28)
Not Recorded	1395 (3)
Treatment Facility Type	
Community cancer program	3366 (6)
Comprehensive community cancer program	22404 (38)
Academic/research program	33716 (56)
Treatment Facility Location	
Metro	49746 (83)
Urban	9071 (15)
Rural	1148 (2)
Income, US dollars	
<30000	8473 (14)
30000-35000	13610 (22)
35000-45999	16881(28)
46000	22289 (36)

Characteristics	No. (%)
Distance to Treatment Facility, Miles	
≤12 miles	29951 (48)
>12 miles	32730 (52)
Age Distribution, Years	
≤62	32852 (52)
>62	29829 (48)
Year of Diagnosis	
2004-06	14419 (23)
2007-09	16437 (26)
2010-12	18462 (29)
2013-14	13363 (22)
Upfront Stereotactic Radiosurgery (SRS)	
No	61635 (98)
Yes	1046 (2)
Tumor Size	
≤3 cm	12026 (19)
>3 cm	38093 (61)
Not recorded	12562 (20)
Extent of Surgery	
None	3924 (6)
Biopsy	6071 (10)
Subtotal resection	7710 (12)
Gross total resection	11072 (18)
Not recorded	33904 (54)
Karnofsky Performance Score (KPS)	
80-100	2546 (4)
50-70	1300 (2)
0-40	264 (1)
Not recorded	58571 (93)
MGMT Status	
Unmethylated	3251 (5)
Methylated	2205 (4)
Not Recorded	57225 (91)
Chemotherapy	
Yes	55217 (88)
No	7464 (12)

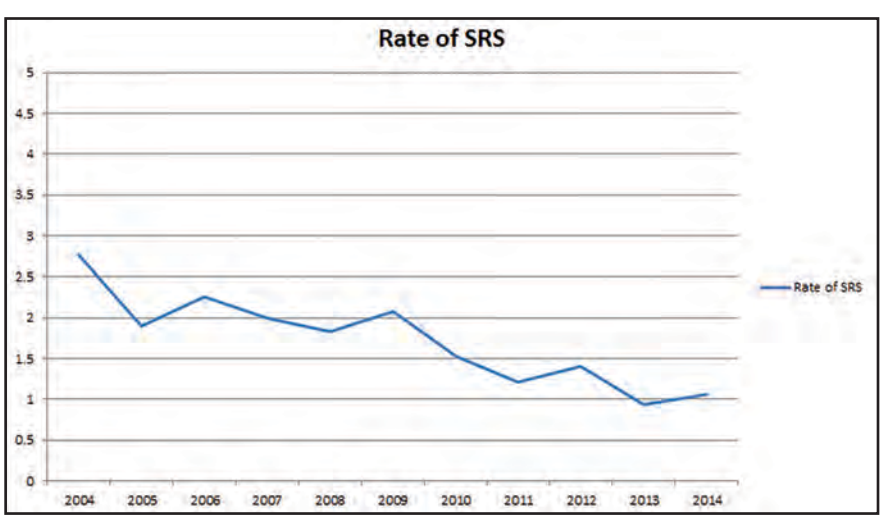

FIGURE 2. *Rate of stereotactic radiosurgery (SRS) use in a frontline setting for glioblastoma by year.*

validated by stratifying the data into propensity score-based quintiles, and confirming that the difference in propensity score mean per quintile was <0.10.

Results

We identified 62681 patients meeting the above eligibility criteria, with 1046 patients receiving SRS as part of initial treatment. **Table 1** displays patient characteristics of the population. Of note, Karnofsky Performance Status (KPS) and MGMT (O6-methylguanine-DNA methyltransferase) methylation status were only documented after 2010, with data present in < 10% of cases. As such, these were recorded in **Table 1**, but not used for statistical

Table 2. Comparative Use of Upfront SRS by Baseline Characteristics in Patients Receiving Brain Radiation for GBM

Characteristic	Standard Radiation (n = 61,635) (%)	Upfront Stereotactic Radiosurgery (SRS) (n = 1,046) (%)	Odds Ratio	95% CI	*p*
Sex					
Male	36146 (59)	606 (58)	1	Reference	
Female	25489 (41)	440 (42)	1.03	0.91-1.17	0.64
Race					
White	56136 (91)	969 (93)	1	Reference	
African American	3328(5)	48 (5)	0.84	0.62-1.12	0.23
Other	969 (4)	29 (2)	0.77	0.53-1.12	0.18
Comorbidity Score					
0	46454 (75)	826 (79)	1	Reference	
1	9651 (15)	134 (13)	0.78	0.65-0.94	0.0084
≥ 2	5530 (10)	86 (8)	0.87	0.70-1.09	0.24
Age					
≤ 62	32338 (52)	514 (49)	1	Reference	
> 62	29297 (48)	532 (51)	1.14	1.01-1.29	0.0327
Insurance					
None	2074 (3)	24 (2)	1	Reference	
Private Payer	31223 (50)	518 (50)	1.43	0.95-2.16	0.0863
Government	27442 (45)	485 (46)	1.52	1.01-2.31	0.0441
Unknown	896 (2)	19 (2)	1.83	0.99-3.36	0.0505
Education					
≥ 29%	8161 (13)	136 (14)	1	Reference	
20 to 28.9	14222 (24)	216 (21)	0.91	0.73-1.13	0.40
14 to 19.9	20522 (34)	359 (35)	1.05	0.86-1.28	0.63
< 14	17367 (29)	303 (30)	1.05	0.85-1.28	0.66
Facility Type					
Community cancer program	3325 (6)	41 (4)	1	Reference	
Comprehensive cancer program	22082 (38)	322 (33)	1.18	0.85-1.64	0.31
Academic/research program	33095 (56)	621 (63)	1.52	1.11-2.09	0.0097
Facility Location					
Metro	48933 (83)	813 (82)	1	Reference	
Urban	8906 (15)	165 (17)	1.12	0.94-1.32	0.21
Rural	1139 (2)	9 (1)	0.48	0.25-0.92	0.0272
Income, US Dollars					
< 30000	8335 (14)	138 (14)	1	Reference	
30000-35,000	13374 (22)	236 (23)	1.07	0.86-1.32	0.56
35000-45999	16609 (28)	272 (27)	0.99	0.80-1.22	0.92
>46000	21921 (36)	368 (36)	1.01	0.83-1.24	0.89
Distance to Facility					
≤ 12 miles	29493 (48)	458 (44)	1	Reference	
> 12 miles	32142 (52)	588 (56)	1.18	1.04-1.33	0.0091
Year of Diagnosis					
2004-06	14086 (22)	333 (32)	1	Reference	
2007-09	16114(26)	323 (31)	0.85	0.73-0.99	0.0366
2010-12	18206 (30)	256 (24)	0.59	0.50-0.70	< 0.0001
2013-14	13229 (22)	134 (13)	0.43	0.35-0.52	< 0.0001
Tumor Size					
≤ 3 cm	11725 (24)	301 (37)	1	Reference	
> 3 cm	37570 (76)	523 (63)	0.54	0.47-0.63	< 0.0001
Chemotherapy					
No	7240 (12)	224 (21)	1	Reference	
Yes	54395 (88)	822 (79)	0.49	0.42-0.57	< 0.0001
Extent of Surgery					
None	3846 (14)	78 (23)	1	Reference	
Biopsy	6007 (21)	64 (19)	0.52	0.38-0.73	0.0002
Subtotal resection	7620 (27)	90 (27)	0.58	0.43-0.79	0.0005
Gross total resection	10969 (38)	103 (31)	0.46	0.34-0.62	< 0.0001

Note: Education is quartiles of the percentage of persons with less than a high school education in the patients' residence census tract. Income is median household income in the patients' residence census tract.

Table 3. Multivariable Cox Proportional Hazards Models for Overall Survival in Patients Receiving Radiation for Glioblastoma Multiforme

Significant Characteristic	Hazard of Death (95% CI) Cox Model Without Propensity Score	*p*
Age		
≤62	Reference	
>62	1.45 (1.42-1.48)	<0.0001
Chemotherapy		
No	Reference	
Yes	0.63 (0.62-0.65)	<0.0001
Comorbid Score		
0	Reference	
1	1.13 (1.10-1.16)	<0.0001
≥2	1.28 (1.24-1.32)	<0.0001
Distance		
≤12 miles	Reference	
>12 miles	0.97 (0.95-0.99)	0.0157
Extent of Surgery		
None	Reference	
Biopsy	0.65 (0.62-0.68)	<0.0001
Subtotal resection	0.61 (0.59-0.64)	<0.0001
Gross total resection	0.50 (0.48-0.52)	<0.0001
Facility Type		
Community cancer program	Reference	
Comprehensive community cancer program	0.98 (0.94-1.02)	0.30
Academic/research program	0.88 (0.86-0.90)	<0.0001
Education, %		
≥29	Reference	
20-28.9	1.06 (1.03-1.09)	0.0001
14-19.9	1.07 (1.04-1.11)	<0.0001
<14	1.08 (1.04-1.12)	<0.0001
Income, US Dollars		
<30000	Reference	
30000-35000	1.00 (0.97-1.03)	0.80
35000-45999	0.93 (0.91-0.96)	<0.0001
>46000	0.87 (0.84-0.89)	<0.0001
Insurance		
None	Reference	
Private	1.00 (0.95-1.05)	0.96
Government	1.20 (1.17-1.22)	<0.0001
Location		
Metropolitan	Reference	
Urban	1.03 (1.00-1.06)	0.0154
Rural	1.05 (0.99-1.12)	0.0799
Race		
Caucasian	Reference	
African American	0.87 (0.84-0.91)	<0.0001
Other	0.79 (0.76-0.83)	<0.0001
Sex		
Male	Reference	
Female	0.92 (0.90-0.93)	<0.0001
Size		
≤3 cm	Reference	
>3 cm	1.11 (1.09-1.14)	<0.0001
Year		
2004-06	Reference	
2007-09	0.94 (0.92-0.96)	<0.0001
2010-12	0.85 (0.81-0.89)	<0.0001
2013-14	0.81 (0.77-0.85)	<0.0001

analyses. In addition, isocitrate dehydrogenase (IDH) status is not recorded in the NCDB and thus not tabulated. Almost 90% of patients received chemotherapy. SRS use was sparse, and decreased over time, from 3% in 2004 to approximately 1% in 2014 (**Figure 2**). Predictors of SRS were increased age, government insurance, lower comorbidity score, treatment at an academic facility, metropolitan location, increased distance to facility, smaller tumor size, lack of surgery, no chemotherapy, and more distant year of treatment (**Table 2**). In addition, multivariable logistic regression identified lack of chemotherapy, increased distance to facility, smaller tumor size, treatment at an academic center, and lack of surgery. The median dose in the SRS group was 40 Gy (interquartile range: 16.2 to 66.2 Gy). The median dose in the standard arm was 60 Gy (interquartile range: 59.4 to 60 Gy). The median time to start of radiation was 32 days (interquartile range: 24 to 42 days) and 28 days (interquartile range: 17 to 40 days) for standard radiation and SRS, respectively. The median time to start of chemotherapy (if given) was 30 days (interquartile range: 20 to 42 days) and 30 days (interquartile range: 19 to 46 days) for standard radiation and SRS, respectively.

The median follow-up for the entire group was 12.6 months (range: 2 to 155 months). Median follow-up for standard radiation was identical to that of the entire group. Median follow-up in the SRS cohort was 12.6 months as well (range: 2 to 126). Median overall survival was 13 months for all patients, with a 5-year survival of 7%. On univariable analysis, median overall survival was 12.9 months with SRS, compared to 13.1 months with standard fractionated EBRT ($p = 0.28$) Five-year overall survival was 7% in both groups. On multivariable analysis, increased age, lack of chemotherapy, higher comorbidity score, extent of surgery, treatment at nonacademic facilities, less

Table 4. Multivariable Cox Proportional Hazards Models for Overall Survival in Patients Receiving Radiation for Glioblastoma Multiforme with Propensity Score Adjustment

Significant Characteristic	Hazard of Death (95% CI) Cox Model Without Propensity Score	*p*
Education, %		
≥ 29	Reference	
20-28.9	1.05 (1.02-1.09)	0.0001
14-19.9	1.08 (1.05-1.11)	< 0.0001
< 14	1.08 (1.04-1.11)	< 0.0001
Income, USD		
< 30000	Reference	
30000-35000	0.99 (0.95-1.02)	0.47
35000-45999	0.93 (0.91-0.95)	< 0.0001
> 46000	0.86 (0.84-0.89)	< 0.0001
Insurance type		
None	Reference	
Private	1.00 (0.95-1.05)	0.98
Government	1.57 (1.54-1.59)	< 0.0001
Race		
Caucasian	Reference	
African American	0.84 (0.80-0.87)	< 0.0001
Other	0.78 (0.74-0.82)	< 0.0001
Sex		
Male	Reference	
Female	0.94 (0.92-0.95)	< 0.0001
Propensity Score	12117.94 (4964.54-29578.60)	< 0.0001

education, government insurance, urban location, Caucasian race, male gender, larger tumor size, and more distant year of treatment predicted for worse overall survival (**Table 3**). Use of SRS was not a significant predictor of survival on this multivariable Cox regression. As described in methods, a logistic regression was used to generate a propensity score. The logistical regression model included age, chemotherapy, comorbidity score, distance to facility, surgery, facility type, location, tumor size, and year. Multivariable analysis with propensity score included was then used to determine predictors of outcome (excluding factors used to generate propensity score). On propensity-adjusted multivariable analysis, decreased education, less income, government insurance, Caucasian race, and male gender predicted for worse survival (**Table 4**).

Discussion

The results of our NCDB analysis confirm a decrease in the use of SRS in the initial management of GBM. In 2004, a limited number of patients (3%) received SRS, with a further decrease to < 1% by 2014. The results of the previously discussed studies support our findings of decreased national use of SRS in the upfront treatment of GBM. In addition, the present analysis did not show any difference in survival between patients treated conventionally and those receiving SRS, which is consistent with previous reports. Regardless, SRS remains an important tool in the retreatment of GBM after local failure as evidenced by multiple contemporary studies.[14-16] Furthermore, based upon the national patterns of SRS use observed in our study, it may be reasonable to consider SRS in elderly patients, patients residing far from treatment facilities, or patients with logistical issues relating to transportation.

Despite advances in imaging, surgery, radiation, and systemic therapy, GBM continues to have disappointing outcomes with 5-year survival in the realm of 10%.[1,2,17] The current standard of care for patients with reasonably good performance status is maximal safe resection followed by adjuvant temozolomide-based chemoradiation.[18] Despite this aggressive multimodality approach, local failure represents a significant challenge. An investigation by Dobelbower et al assessed survival outcomes and patterns of failure in nearly 100 GBM patients treated with reduced radiation field sizes.[4,5] Patients ultimately received a conventional fractionated radiation dose of 60 Gy; however, nearly 90% of patients in this cohort experienced recurrence within the radiation field or marginally. Similarly, a group from Italy reported on outcomes in > 100 patients treated to 60 Gy with concurrent temozolomide.[19] Corroborating the findings of Dobelbower et al, progression occurred centrally, in-field, or marginally in approximately 90% of cases.[19]

Given the exceedingly high rates of local failure, there was considerable interest in the use of higher doses of radiation using EBRT. One of the earliest investigations was that of the RTOG 9803.[3] This phase I study utilized conventionally fractionated EBRT (ie, 2 Gy daily fractions) with concurrent chemotherapy in the form of biodegradable carmustine (BCNU).[3] Following an initial 46 Gy, patients were dose escalated to 66, 72, 78, or 84 Gy. Median survival was greatest in patients receiving 84 Gy (ie, 14 to 19 months depending on tumor volume) and lowest in the 66 Gy arm. Of note, no dose-limiting toxicities were observed. The authors concluded that dose escalation was feasible and safe; thus, they suggested a potential larger future role with technologic and therapeutic advances. A more recent study from Washington University compared outcomes in patients < 70 years of age who received 60 Gy or > 60 Gy with concurrent temozolomide.[20] More than 200 patients were analyzed with the authors identifying age, performance status, and extent of

resection as prognosticators of survival. No difference in overall survival was observed at 5 years between the conventional dose and dose-escalated arms; therefore, the authors concluded that dose escalation with temozolomide did not improve outcomes.

Given the highly conformal nature of SRS and its ability to deliver high-dose-per-fraction radiation treatments, it was naturally explored as a potential solution for dose escalation. One of the initial investigations using SRS for dose escalation was RTOG 9305, a randomized multiple institutional study.[7] A total of 203 patients were randomized to SRS followed by EBRT to a dose of 60 Gy with concurrent BCNU or conventional treatment with EBRT to a dose of 60 Gy with concurrent BCNU.[7] With 5 years of follow-up the median survival in both arms was 13 months, with no difference in failure patterns. A more recent study (RTOG 0023), explored postoperative radiation treatment. Patients were treated with EBRT to a dose of 50 Gy succeeded by SRS delivered once per week at 5 to 7 Gy fractions for a total of 4 weeks.[21] Patients also received BCNU for 6 cycles in this study. Seventy-six patients were evaluable and median OS was 12.5 months, thus comparable to historical controls. Of note, both aforementioned studies were in the pre-temozolomide era. More recently, other groups have experimented with hypofractionation with concurrent temozolomide as a means of dose escalation. One study examined outcomes in 24 patients treated with 60 Gy in 10 fractions with temozolomide.[22] As expected, most patients progressed (71%) but of those, only 50% were central, in-field, or marginal. The median overall survival of 33 months was slightly improved compared to historical controls.

The present study is not without limitations, many of which are intrinsic to the NCDB, including the retrospective nature of data collection and analysis which inevitably contributes to selection bias. Furthermore, the NCDB lacks important data on outcomes such as toxicity, local failure, type of chemotherapeutic agent(s), and number of treatment cycles completed, all of which play an important role in determining outcome for GBM. Moreover, salvage therapy is also not recorded in the NCDB, which is an important player in long-term outcomes for GBM patients given the high likelihood of failure. Also, KPS and MGMT status were not well recorded in the NCDB (as well as IDH status), and may be areas in which SRS could have potential value (ie, poor performance patients or those who are MGMT unmethylated).

Conclusions

Utilization of SRS in the management of GBM has decreased over time, likely reflecting penetrance of multiple prospective and retrospective studies demonstrating no survival benefit. Concordant with previous findings, overall survival was not improved with SRS in our investigation.

References

1. Black PM. Brain tumors. Part 1. *N Engl J Med.* 1991;324:1471-1476.
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10:459-466.
3. Tsien C, Moughan J, Michalski JM, et al. Radiation Therapy Oncology Group T: phase I three-dimensional conformal radiation dose escalation study in newly diagnosed glioblastoma: Radiation Therapy Oncology Group Trial 98-03. *Int J Radiat Oncol Biol Phys.* 2009;73:699-708.
4. Dobelbower MC, Burnett III OL, Nordal RA, et al. Patterns of failure for glioblastoma multiforme following concurrent radiation and temozolomide. *J Med Imaging Radiat Oncol.* 2011;55:77-81.
5. Gebhardt BJ, Dobelbower MC, Ennis WH, et al. Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. *Radiat Oncol.* 2014;9:130.
6. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand.* 1951;102:316-319.
7. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys.* 2004;60:853-860.
8. Hasan S, Renz P, Turrisi A, Colonias A, Finley G, Wegner RE. Dose escalation and associated predictors of survival with consolidative thoracic radiotherapy in extensive stage small cell lung cancer (SCLC): a National Cancer Database (NCDB) propensity-matched analysis. *Lung Cancer.* 2018;124:283-290.
9. Hasan S, Renz P, Wegner RE, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (PCR) in locally advanced rectal cancer: a National Cancer Database (NCDB) Analysis. *Ann Surg.* 2018.
10. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613-619.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
12. Cox DR. Regression models and life - tables. *J Royal Statist Soc.* 1972;34:187-220.
13. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998;17:2265-2281.
14. Gigliotti MJ, Hasan S, Karlovits SM, Ranjan T, Wegner RE. Re-irradiation with stereotactic radiosurgery/radiotherapy for recurrent high-grade gliomas: improved survival in the modern Era. *Stereotact Funct Neurosurg.* 2018:1-7.
15. Hasan S, Chen E, Lanciano R, et al. Salvage fractionated stereotactic radiotherapy with or without chemotherapy and immunotherapy for recurrent glioblastoma multiforme: a single institution experience. *Front Oncol.* 2015;5:106.
16. Torok JA, Wegner RE, Mintz AH, Heron DE, Burton SA. Re-irradiation with radiosurgery for recurrent glioblastoma multiforme. *Technol Cancer Res Treat.* 2011;10:253-258.
17. Hottinger AF, Pacheco P, Stupp R. Tumor treating fields: a novel treatment modality and its use in brain tumors. *Neuro Oncol.* 2016;18:1338-1349.
18. Blumenthal DT, Gorlia T, Gilbert MR, et al. Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. *Neuro Oncol.* 2017;19:1119-1126.
19. Minniti G, Amelio D, Amichetti M, et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. *Radiother Oncol.* 2010;97:377-381.
20. Badiyan SN, Markovina S, Simpson JR, et al. Radiation therapy dose escalation for glioblastoma multiforme in the era of temozolomide. *Int J Radiat Oncol Biol Phys.* 2014;90:877-885.
21. Cardinale R, Won M, Choucair A, et al. A phase II trial of accelerated radiotherapy using weekly stereotactic conformal boost for supratentorial glioblastoma multiforme: RTOG 0023. *Int J Radiat Oncol Biol Phys.* 2006;65:1422-1428.
22. Reddy K, Gaspar LE, Kavanagh BD, Chen C. Hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy may alter the patterns of failure in patients with glioblastoma multiforme. *J Med Imaging Radiat Oncol.* 2014;58:714-721.

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Editor's note: Please see related article, *Noninvasive Cardiac Radioablation at Washington University: Past, Present and Future Directions for the Treatment of Ventricular Tachycardia,* on page 10.

Healing Hearts: Evolution and Growth in Cardiac Radioablation

Mary Beth Massat

Stereotactic body radiation therapy (SBRT) may be more than a tool to target and destroy cancerous cells throughout the body. Data from a phase I/II prospective trial presented at ASTRO 2019 by clinicians at Washington University School of Medicine in St. Louis, Missouri, show promise for using SBRT to ablate cardiac tissue in patients with arrhythmias—including ventricular tachycardia (VT)—where other treatment options have failed.

The study of Electrophysiology (EP)-guided Noninvasive Cardiac Radioablation (ENCORE) for the Treatment of Ventricular Tachycardia is being led by Clifford Robinson, MD, associate professor of radiation oncology and cardiology, and Phillip Cuculich, MD, associate professor of cardiology and radiation oncology, at Washington University in St. Louis. They reported long-term follow-up data on 19 patients demonstrating a 78% reduction in VT episodes more than 2 years after the cardiac radioablation procedure. Overall survival was 74 percent after 1 year and 52 percent after 2 years. Six patients died from cardiac events and 3 died from noncardiac events.[1]

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Previously, Cuculich et al reported a 94% reduction in VT episodes in the first 6 months after cardiac radioablation treatment in a small cohort of 5 patients. The average treatment time was under 15 minutes and most of the patients stopped their antiarrhythmic medications a few weeks after treatment. The therapy combines electrocardiogram (ECG) data with computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging data to identify the precise area of the patient's heart causing the arrhythmia and then targets it with a single high dose of SBRT.[2] (**Figure 1**)

In a news release from the American Society for Radiation Oncology (ASTRO), Dr. Robinson said, "The results are very promising. The use of noninvasive radiation therapy is providing new hope for patients with life-threatening ventricular arrhythmias and limited treatment options." The cardiac radioablation technique could potentially help tens of thousands of people who suffer from arrhythmias and have tried other treatments without success.[3]

Current treatments to correct arrhythmias include medication, cardiac ablation using a catheter to scar or destroy the heart tissue causing the abnormal heart rhythm, and an implantable cardioverter defibrillator (ICD)—a small battery-powered device that detects irregular heartbeats and sends electric shocks to the heart to correct the problem.

ICDs do not prevent arrhythmias or VT, the most dangerous and life-threatening type of arrhythmia. The shocks also can be painful and frightening. Cardiac ablation, meanwhile, comes with high risks and may not provide long-term results, with success rates between 50% and 75%.[3,4] Additionally, cardiac ablation is not always an option because in some patients the catheter cannot reach the site in need of treatment, explains Paul C. Zei, MD, PhD, director, Comprehensive Atrial Fibrillation Program, Cardiac Arrhythmia Service, Brigham and Women's Hospital, and associate professor of medicine at Harvard Medical School, both in Boston, Massachusetts. For this patient population, cardiac radioablation can provide a real clinical need.

"The biggest benefit of cardiac radioablation is that it is a noninvasive

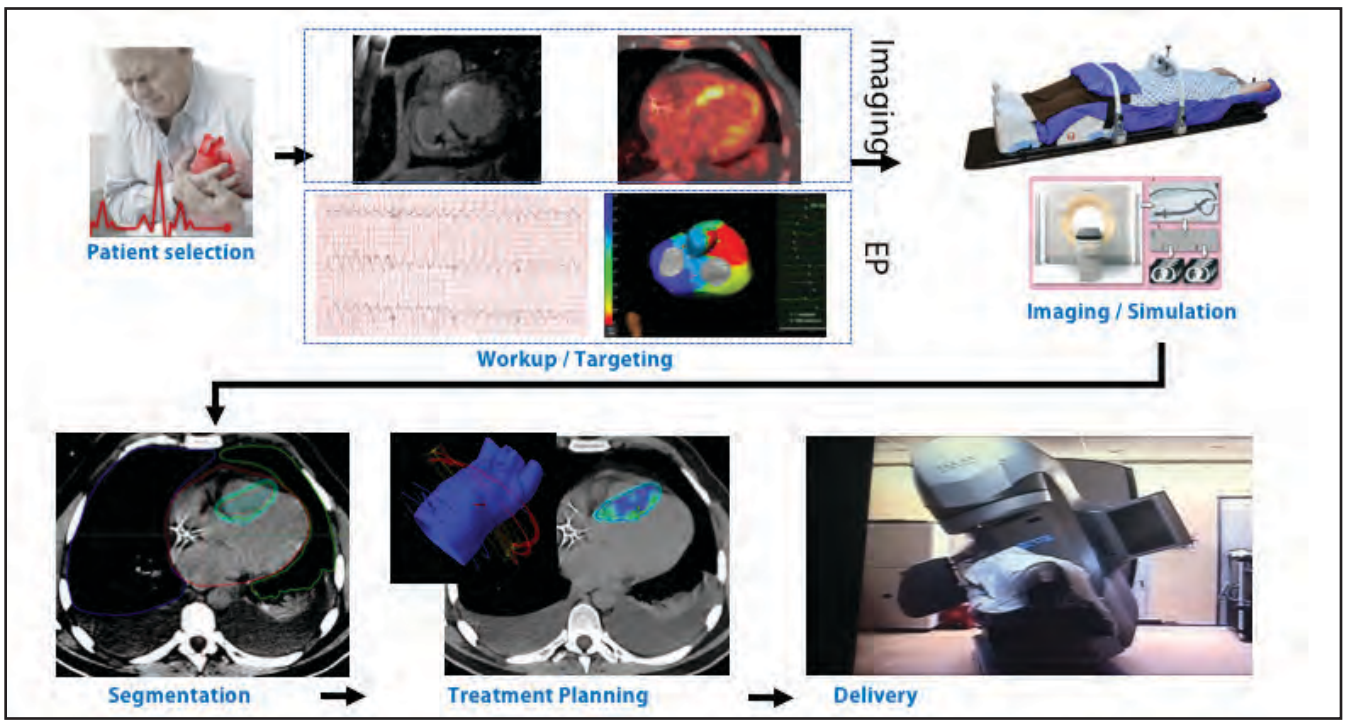

FIGURE 1. *Electrophysiology (EP)-guided noninvasive cardiac radioablation (ENCORE) fuses electrical electrocardiogram and imaging data to pinpoint scar tissue in a patient's heart responsible for the arrhythmias, then targets it with a single dose of stereotactic body radiation therapy. Used to treat ventricular tachycardia, ENCORE requires no general anesthesia and patients can return home immediately after treatment.*[3] *Credit: Clifford Robinson, MD*

technique and has a much shorter procedure time than catheter ablation," Dr. Zei says. "The tradeoff is there may be longer-term toxicity from the radiation; however, the procedural risk is vastly improved. The other big advantage is that it can address the shortcomings of catheter ablation by overcoming the barrier of getting ablative energy to the treatment site or treating a larger amount of tissue."

Additional Roots

While at Stanford University in California in 2012, Dr. Zei was one of the first clinicians to use CyberHeart's noninvasive method for performing cardiac radioablation on a patient under an Institutional Review Board-approved, compassion-use protocol. At that time, CyberHeart partnered with Accuray Inc. (Sunnyvale, California) to develop the technology for performing cardiac radioablation. In May 2019, Varian (Palo Alto, California) acquired CyberHeart and its intellectual property.

Dr. Zei and his colleagues at Stanford published data on the first CyberHeart procedure on a man in 2015, demonstrating feasibility of the technique. While the patient's VT returned, it was less frequent—52 episodes per month, 2 to 9 months postprocedure, compared to 562 episodes in the 2 months before the procedure. The cycle length was also slower: from 380-411 ms before the procedure, to 470 ms after the procedure.[5]

Of note, the complexity of planning this case went beyond the traditional considerations of using SBRT in the heart.

"In our planning, we had to consider cardiac motion in addition to respiratory motion in this patient," Dr. Zei explains. "There were also logistical challenges. Traditionally, a cardiologist or electrophysiologist doesn't work closely with a radiation oncologist. So that was a new working relationship with the added complexity of getting the patient in for pretreatment imaging, meeting to create the plan, and then scheduling the treatment."

After Dr. Zei left Stanford to lead the Comprehensive Atrial Fibrillation Program at Brigham and Women's Hospital, he continued to explore the potential for treating atrial fibrillation and VF on a Varian Edge radiosurgery system. Six patients have been treated at Brigham and Women's and he has also worked with groups in Texas, Japan, Mexico and Taiwan interested in performing the procedure, treating approximately 20 patients with this technique.

"One to 4 weeks after the procedure, we can see a real effect and that is quite consistent across the publications and in our own experience as well," Dr. Zei says. One limitation for cardiac radioablation, however, is the implanted ICD, which creates artifacts in the MR images of the heart used for treatment planning.

Gaining Momentum

At Allegheny General Hospital in Pittsburgh, Pennsylvania, radiation oncologists Athanasios (Tom) Colonias, MD, and Mark G. Trombetta, MD, were

"The biggest benefit of cardiac radioablation is that it is a noninvasive technique and has a much shorter procedure time than catheter ablation."

Paul C. Zei, MD, PhD, director, Comprehensive Atrial Fibrillation Program, Cardiac Arrhythmia Service, Brigham and Women's Hospital, and associate professor of medicine at Harvard Medical School

intrigued by results reported by Dr. Robinson in the initial 2017 *New England Journal of Medicine* article regarding SBRT to treat patients with refractory cardiac arrhythmias.[2] To learn more, Dr. Trombetta attended a September 2019 symposium at Washington University.

"There was tremendous interest compared to what I expected—approximately 300 people were in attendance," Dr. Trombetta says. "All over the world there are groups working to put this program together to offer it to their patients. However, most have not treated patients as it takes time to develop the technology and the planning."

Drs. Trombetta and Colonias identified a patient who could benefit at Allegheny General Hospital: a man who spent 30 days in the ICU with an uncontrolled heart rhythm. However, approximately 1 week before the procedure, the patient converted to a controlled heart rhythm and has remained in good condition.

"These are the highest risk patients whose alternative is sudden cardiac arrest and death," Dr. Trombetta says.

Vendor Updates

Interest in this procedure has also surfaced in Elekta's (Stockholm, Sweden) MR Linac Consortium, where Dr. Colonias is helping to spearhead a working group.

The Consortium group estimated that 100 patients worldwide have been treated with this procedure. While that number may have increased since the meeting, there is significant interest in exploring the use of Elekta's Unity for this procedure.

"Compared to CT-based planning, cardiac MRI with the right sequences will be a better modality to visualize the heart because of its superior imaging of infarcted soft tissue," Dr. Colonias says.

Adds Dr. Trombetta, "With a dedicated cardiac MRI system, we can see the area of infarct. That capability, or sequencing, is what we are working on to add to the Unity system. The procedure also requires electrical mapping, which can be done with intracardiac electronic mapping and intracardiac electrocardiography or by placing a vest on the patient that contains more than 200 electrode receivers. We need to identify the areas of involvement of the arrhythmia to target the therapy."

According to Dr. Colonias, cardiac radioablation is similar to other uses of SBRT in the body, with some minor adjustments. Drs. Colonias and Trombetta are working with their colleagues at Allegheny General Hospital to fuse the electrical data from the heart with the images used for treatment planning. Since intracardiac electronic mapping data are not DICOM compatible, the hospital team is looking at software revisions that could accomplish this task.

The DICOM-converted intracardiac electronic mapping data comes out in a mesh file providing graphic information that can then be overlaid on cardiac MR images to provide a more detailed vessel analysis that includes electrical activity. Sometimes, erratic heart pulses will go around a tightly ablated area, requiring the entire area to be treated with precision rather than using tiny pinpoint fields. This "fusing" of the electronic mapping and imaging data provides the information needed for radiation treatment planning.

Although there is much excitement surrounding cardiac radioablation, Drs. Colonias and Trombetta caution that more results on efficacy, toxicity and side effects are needed.

"These patients will die without intervention; however, we anticipate there will be significant toxicity and we need to quantify the side effects," says Dr. Colonias.

The good news is that most modern linacs using image guidance with appropriate immobilization devices should be able to deliver cardiac radioablation. Since most treatment planning systems rely on CT simulation data, Dr. Trombetta is working on a protocol to convert these treatments to the Elekta Unity once the system is installed at Allegheny General Hospital.

Although preliminary data are intriguing, many questions remain regarding long-term response and optimizing precision in the delivery and workflow of cardiac radioablation. Elekta is investing resources to explore the technique, both with conventional linacs and the company's MR linac, Elekta Unity, including the working group with Dr. Colonias.

"We were blown away by the initial results presented in both the *New England Journal of Medicine* article and at the ASTRO session last year," says John Christodouleas, MD, vice president of Medical Affairs and Clinical Research, Elekta. "Currently, the most important work is happening at the individual institutions but there are at least a few multi-institutional registries gathering data on disease control and toxicity."

From a research and development standpoint, Elekta is focused on building a foundation of knowledge for radiation oncologists and cardiologists to create a strategy addressing challenges in clinical workflow.

"For this to be successful, it will require the expertise of both communities—radiation oncology and cardiology," he adds. "Both communities will also need to collaborate clinically and technically to make this option available to patients who have very few options left."

Although a conventional linac was used by Washington University in St. Louis, Dr. Christodouleas sees potential for MR linacs. The downside of a conventional linac is it doesn't visualize soft tissue very well and can't visualize the tissue while the beam is on. With the high doses being delivered in the reported cases, soft-tissue visualization and motion management will likely be key to avoiding healthy heart tissue. Dr. Christodouleas points out that in addition to cardiac and respiratory motion, the heart may drift while the beam is on and that could be the most important type of motion to manage as the heart may not drift back to its original position.

"The promise of Elekta Unity is to use soft-tissue diagnostic quality imaging to target the region of interest and to continue imaging the patient while the treatment beam is on," Dr. Christodouleas explains. "If there is a change in position, the provider can hold the beam or track it."

MRI could also potentially be used to assess biologic response, particularly if fractionated treatments are used in the future. The plan used at Washington University in St. Louis was not fractionated, rather it was conducted in 1 treatment session.

According to Deepak Khuntia, MD, senior vice president and chief medical officer at Varian, after acquiring the assets to CyberHeart, Varian created a business entity for cardiac radioablation.

"With the CyberHeart asset and intellectual property, we are looking to create an SBRT solution for cardiac radioablation," Dr. Khuntia says. "This is different from most products Varian has brought to market because it is considered by the FDA to be class III and, therefore, has a more stringent regulatory pathway."

First, however, Varian is focused on assembling the right team to develop an end-to-end solution that addresses technical and workflow considerations as well as regulatory and reimbursement requirements.

"Our cardiac radioablation technique will require a different set of solutions than what currently exists," Dr. Khuntia explains. The institutions that have performed cardiac radioablation have utilized a variety of platforms and have developed in-house solutions for the technique.

"If we want a technology that is available to all clinics and not just academic or large tertiary care institutions, then we need to develop a commercial-grade, scalable solution," he adds.

Dr. Khuntia expects that electrophysiologists will drive this technique, including identifying patients who would benefit, requiring Varian to examine treatment planning from their perspective. Radiation oncologists are accustomed to looking at targeting tools and software with cross-sectional anatomic slices; electrophysiologists, however, view anatomy 3-dimensionally, prompting the need for software updates that provide information in a familiar form.

"This information is not just the electrical signals but also the anatomic and physiologic information," he explains. "Sometimes, a PET scan is used in evaluating arrhythmias. So, how we take that information along with a 12-lead EKG and possibly 4D-gated MR, and reconstruct it into a tool that can help an electrophysiologist target the area of abnormality, still needs to be determined."

While additional multisite, prospective studies and longer-term results are needed to validate the safety and efficacy of cardiac radioablation, patients who have run out of treatment options for their arrhythmia or VT and have undergone cardiac radioablation are reported to be doing well.

"We are on the heels of something quite exciting," Dr. Khuntia says.

References

1. Robinson CG, Samson P, Moore KMS, et al. Longer term results from a phase I/II study of EP-guided noninvasive cardiac radioablation for treatment of ventricular tachycardia (ENCORE-VT). *Int J Radiat Oncol Biol Phys.* 2019;105(3):682.
2. Cuculich PS, Schill MR, Kashani R, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med.* 2017;377:2325-2336.
3. American Society for Radiation Oncology. Noninvasive radiation treatment offers long-term benefits to patients with high-risk heart. September 15, 2019. https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2019/Noninvasive-radiation-treatment-offers-long-term-b. Accessed February 14, 2020.
4. WebMD. Cardiac Ablation Procedure (Heart Ablation) for AFib. https://www.webmd.com/heart-disease/atrial-fibrillation/what-is-cardiac-ablation#1. Accessed February 14, 2020.
5. Loo BW, Soltys SG, Wang L, et al. Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. *Circ Arrhythm Electrophysiol.* 2015;8:748-750.

RADIATION ONCOLOGY CASE

External-beam Radiation Therapy for Aspergilloma-associated Hemoptysis

Donald J. Bastin, MSc; Andrew J. Arifin, MD; Brian P. Yaremko, MD, FRCPC, MSc, PEng

CASE SUMMARY

A 51-year-old man with an extensive history of left lung aspergilloma and hemoptysis was referred to radiation oncology for treatment-refractory hemoptysis. His past medical history included hypertension, multiple surgeries for congenital coarctation of the aorta, and bronchiectasis. A diagnosis of aspergilloma in the left upper lobe was made in the mid-1990s and the patient experienced bouts of hemoptysis intermittently ever since. The aspergilloma had been treated with multiple rounds of antifungal medications, including intravenous and intracavitary itraconazole, amphotericin and voriconazole. Computed tomography scans demonstrating aspergilloma in the left upper lobe are shown in **Figure 1**.

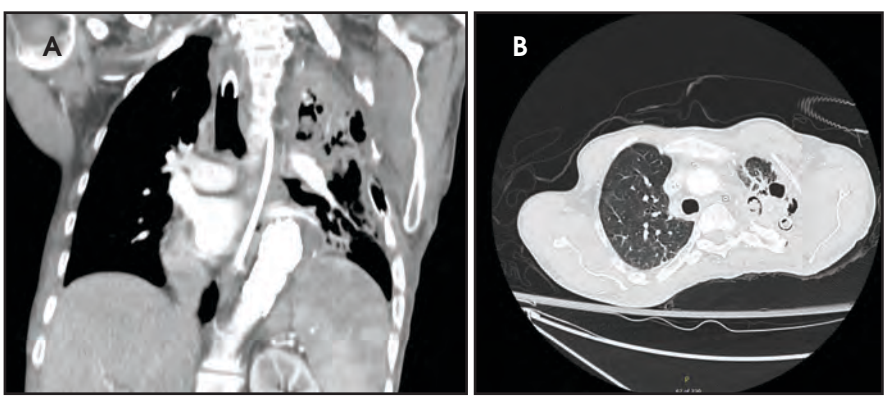

FIGURE 1. *Diagnostic computed tomography images with representative coronal (A) and axial (B) sections showing an aspergilloma in the left upper lobe.*

Prior to a consultation with radiation oncology, all standard-of-care options had been exhausted. He remained on voriconazole with no improvement of his hemoptysis. Further surgical efforts were precluded due to a descending aortic graft being plastered to the left hilum from his previous aortic surgeries. Interventional radiology was unable to embolize the left bronchial artery. Based on previous case reports describing the use of external-beam radiation therapy in treating hemoptysis secondary to fungal infection of the lung, the patient was referred to radiation oncology.

The mycetoma was contoured as the gross tumor volume (GTV). The clinical target volume (CTV) was defined as the GTV plus a 1-cm uniform expansion. To account for variation in setup and penumbra, a 1-cm margin was added to the CTV to establish the field edges. Radiation was delivered by a two-beam opposed-oblique technique at a dose of 7 Gy at 3.5 Gy per week, prescribed to the midplane with 6 MV photons (**Figure 2**). It was our intention to repeat the treatment every 7 days until hemoptysis resolved. The anterior and posterior beams were designed to cover the CTV with multileaf collimators set to spare healthy lung and extrapulmonary tissue. The first treatment was well tolerated and the hemoptysis resolved over the following week. A second dose was delivered to improve durability of effect. The patient was discharged after several days of monitoring.

Four months after receiving radiation therapy, voriconazole was discontinued

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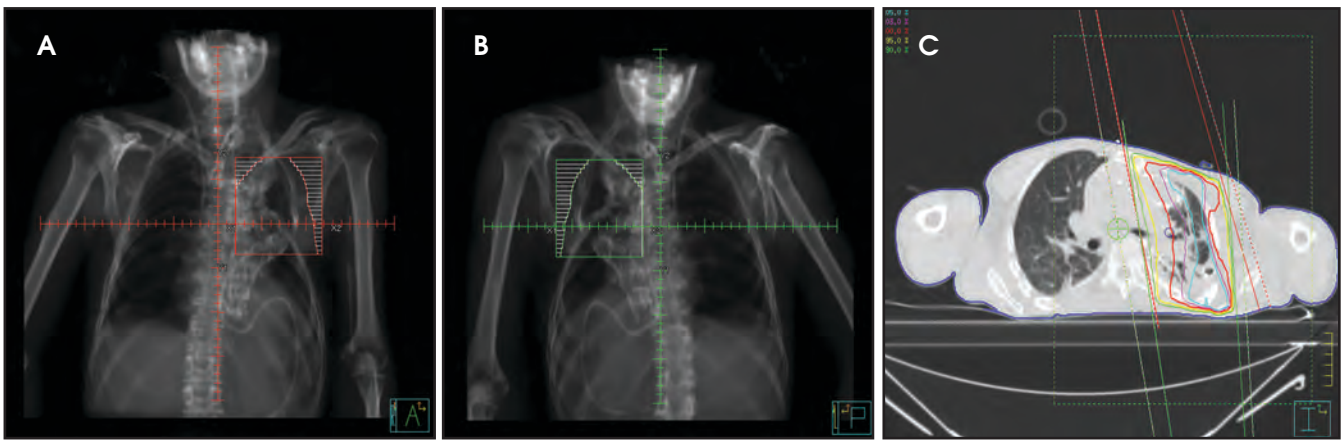

FIGURE 2. *Digitally reconstructed radiographs of a parallel-opposed pair anterior (A) and posterior (B) beams. Representative axial cross section (C) showing isodose lines. Light blue represents 105% of normal, magenta 103%, red 100%, yellow 95% and green 90%.*

because of apparent liver toxicity. Three months later, the patient experienced a recurrence of hemoptysis with a superimposed pseudomonas infection. This improved on oral ciprofloxacin. Several months later, he was readmitted to the hospital for worsening respiratory status despite oral ciprofloxacin and was treated with intravenous ertapenem. The patient improved after 6 days on intravenous antibiotics and was discharged home. Unfortunately, he died two weeks later after recurrence of massive hemoptysis.

IMAGING FINDINGS

Computed tomography scans of the aspergilloma in the upper lobe reveal a soft-tissue mass surrounded by air.

DIAGNOSIS

Pulmonary aspergilloma causing hemoptysis

DISCUSSION

Pulmonary aspergilloma is a condition in which Aspergillus fungi, immune cells and debris form a mass in the lung. This can develop in patients with predisposing conditions such as tuberculosis, cancer and bronchiectasis.[1] The standard treatment for aspergilloma-associated hemoptysis includes pharmacologic therapies, surgical removal of the affected area and, more recently, embolization strategies.[2] Surgical resection, however, requires that the patient be sufficiently healthy to endure the procedure and can be accompanied by high morbidity and mortality. Furthermore, the efficacy of embolization procedures is often transient and drug therapies may not be sufficient in many cases.[1] For patients who fail these treatments, options are limited.

External-beam radiation therapy is accepted as the standard of care for palliation in patients with hemoptysis secondary to lung cancer.[3] Radiation has been shown to be effective at promoting coagulation, thereby stopping bleeding in multiple sites of malignancy including the lung.[4] The mechanism of how radiation promotes resolution of hemoptysis in benign diseases such as aspergilloma is unclear. It has been suggested that radiation affects the small blood vessels surrounding the mycetoma rather than the fungal ball itself, promoting swelling, necrosis and thrombosis.[5]

This case contributes to a nascent body of literature suggesting a role for radiation in this context. A 1980 case report was published detailing the treatment of a single patient with hemoptysis following allergic bronchopulmonary aspergillosis and aspergilloma using an initial dose of 20 Gy followed by another 10 Gy on relapse.[6] A more recent report in 2011 described resolution of hemoptysis with radiation in a woman diagnosed with an aspergillosis mycetoma that was refractory to standard-of-care treatments. In this case, a cumulative dose of 28 Gy at 3.5 Gy per fraction delivered weekly was used, similar to the regimen used in our case.[7]

Reports involving multiple patients are sparse. In a 5-patient series for patients with a history of hemoptysis who were ineligible for standard-of-care therapies, patients were treated with varying cumulative doses of radiation therapy ranging from 7 to 14 Gy depending on the dose required to sustain symptom alleviation delivered at 3.5 Gy per fraction weekly. This appeared safe and effective at 6-month follow-up.[5] We followed this regimen, delivering 3.5 Gy per fraction weekly until symptom alleviation. Two of the patients in this series required 7 Gy to resolve hemoptysis as did our patient, while others required a higher dose to achieve resolution. It is unclear whether a higher dose produces a more durable response in patients who experience symptom relief at a lower dose. A single-institution retrospective analysis of 21 Brazilian patients who received radiation therapy for aspergilloma-mediated hemoptysis following a diagnosis of tuberculosis demonstrated a failure-free survival rate of 82%.[8] Patients received

2 Gy daily up to 34 Gy, with most patients receiving 20 Gy via a cobalt-60 source. This was the only case series with follow-up > 8 months (median 25 months), making estimated duration of benefit unclear.

While the aforementioned reports suggest that external-beam radiation therapy shows potential in treating hemoptysis following aspergilloma, we are limited by the small number of patients studied and the lack of a standardized dosing regimen. The studies describe different dosing regimens and sometimes were forced to adjust doses depending on patient response. Even in hemoptysis secondary to malignancy, controversy remains regarding optimal radiation dosing.[9] This fact as well as the experience described herein highlight the need for larger-scale studies to optimize delivery of these treatments to realize their full potential. Currently, one randomized early phase clinical trial (NCT02878447) is aiming to recruit 40 patients with hemoptysis following aspergillomata, and we await how these results will inform the management of this rare, difficult-to-treat condition.[10] This trial uses the same fractionation scheme as our case, and treats all affected lung tissue. Until we have more evidence to guide practice, proper patient selection and consent will be important in this novel use of radiation.

CONCLUSIONS

We present the case of a 51-year-old man with treatment-refractory aspergilloma-related hemoptysis who received a total of 7 Gy in 2 fractions delivered weekly and had resolution of his hemoptysis. Seven months after discharge, hemoptysis recurred, and the patient died. We demonstrate that while this treatment modality shows promise for benign causes of hemoptysis, our current state of knowledge is limited. Future studies will be important to guide proper patient selection and optimal dosing.

REFERENCES

1. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev*. 2011;20(121):156-174.
2. He G, Liu W, Gao Z, Gao Z, Gao H, Wang Y. Intervention treatment on massive hemoptysis of pulmonary aspergilloma. *Exp Ther Med*. 2017;13(5):2259-2262.
3. 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. *Pract Radiat Oncol*. 2011.
4. Rasool MT, Manzoor NA, Mustafa SA, Maqbool LM, Afroz F. Hypofractionated radiotherapy as local hemostatic agent in advanced cancer. *Indian J Palliat Care*. 2011.
5. Falkson C, Sur R, Pacella J. External beam radiotherapy: a treatment option for massive haemoptysis caused by mycetoma. *Clin Oncol*. 2002;14(3):233-235.
6. Shneerson JM, Emerson PA, Phillips RH. Radiotherapy for massive haemoptysis from an aspergilloma. *Thorax*. 1980;35(12):953-954.
7. Samuelian JM, Attia AA, Jensen CA, Monjazeb AM, Blackstock AW. Treatment of hemoptysis associated with aspergilloma using external beam radiotherapy: a case report and literature review. *Pract Radiat Oncol*. 2011;1(4):279-281.
8. Sapienza LG, Gomes MJL, Maliska C, Norberg AN. Hemoptysis due to fungus ball after tuberculosis: a series of 21 cases treated with hemostatic radiotherapy. *BMC Infect Dis*. 2015.
9. Ma JT, Zheng JH, Han CB, Guo QY. Meta-analysis comparing higher and lower dose radiotherapy for palliation in locally advanced lung cancer. *Cancer Sci*. 2014.
10. University of Stellenbosch. The utility of radiotherapy in the management of haemoptysis secondary to aspergillomata and structural lung diseases.

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RADIATION ONCOLOGY CASE

A Rare Case of Recurrent Paget's Disease of the Vulva and Gluteal Region Treated with Radiation Therapy

Mirza Athar Ali, MD; M. Babaiah, MD; Prabhakar Mariappan, MD; Sudha Sinha, MD; KR Muralidhar, PhD, RSO; Srinivas Ponaganti, Post MSc; Pranav Ashwin Shah, MD; Sujana Priya Vuba, MD; Arun Kumar Reddy Gorla, MD, FANMB; Deepak Koppaka, MD, DM

CASE SUMMARY

An 80-year-old woman presented to us in May 2018 with a large cutaneous growth involving the vulva and gluteal region (**Figure 1**). A detailed clinical history revealed that in 2012, she initially noticed a nonhealing growth over the vulva and gluteal region for which she underwent wide local excision with skin grafting. The histopathology report was suggestive of Paget's disease, and her surgeon advised close follow-up. In 2015, local recurrence was detected and she underwent a second surgery. Histopathology showed features of extramammary Paget's disease (EMPD) with focal stromal invasion. The patient was again advised for close follow-up.

In May 2018, local recurrence was again detected. Biopsy showed poorly differentiated carcinoma with pagetoid spread to the epithelium. Immunohistochemistry (IHC) showed features consistent with Paget's disease with extensive pseudoepitheliomatous hyperplasia. The patient's primary surgeon deferred any further surgical intervention and recommended radiation therapy. A positron emission tomography – computed tomography (PET-CT) scan was performed to detect nodal involvement and to rule out synchronous malignancy. The PET-CT scan showed iliac and inguinal nodal metastasis but did not show evidence of synchronous malignancy.

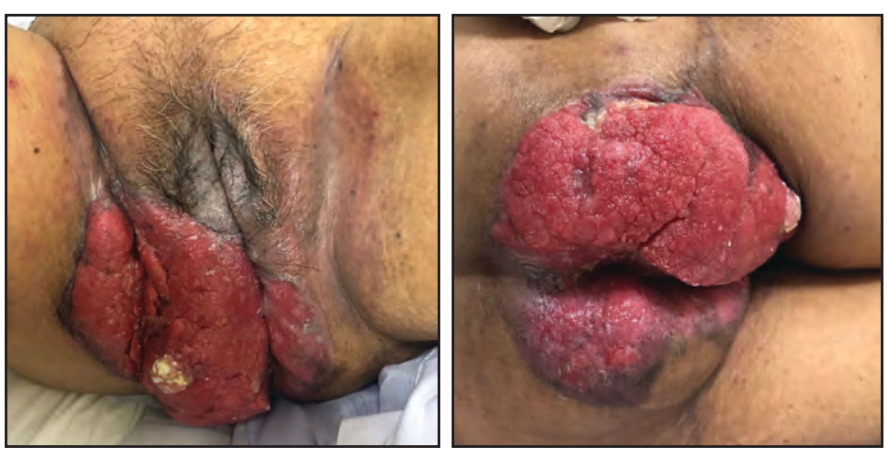

FIGURE 1. *Clinical presentation with cutaneous lesions involving the vulva, perineum and gluteal region.*

The patient was treated with volumetric-modulated arc therapy (VMAT) (RapidArc; Varian, Palo Alto, California) using 6-MV photons in a sequential manner to a total dose of 56 Gy in 28 fractions, 2 Gy per fraction, delivered 5 days per week (**Figure 2**).

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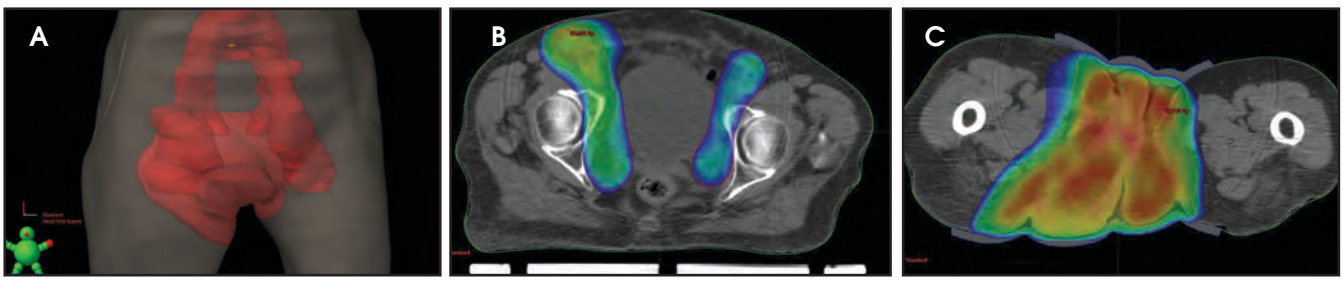

FIGURE 2. *Radiation therapy treatment volumes (A). Volumetric-modulated arc therapy (VMAT) plan showing dose in color wash covering the primary and nodal target volumes (B, C).*

Treatment plan details include:

- The clinical target volume (CTV) primary = the gross tumor volume (GTV) primary (based on clinical examination and PET-CT) + a 2-cm margin. The CTV node = the bilateral common + external + internal iliac + bilateral inguinal nodal region.
- PTV = CTV + 5 mm.
- Phase 1: PTV primary + Node: 42 Gy in 21 fractions, 2 Gy per fraction.
- Phase 2: PTV primary + gross nodal volume [(GTV) node + 5 mm]: 12 Gy in 6 fractions, 2 Gy per fraction.
- Phase 3: Planning target volume (PTV) primary: 2 Gy in 1 fraction, 2 Gy per fraction.

A 5-mm gel bolus was placed over the primary tumor site for dose build-up over the cutaneous surface. The patient also received concurrent oral capecitabine 500 mg twice daily as a radiation sensitizer. Considering her age and frail general condition, the medical oncologist preferred oral capecitabine (in low dose as a radiation sensitizer) over other more toxic chemotherapy options. The patient tolerated the treatment well with grade 3 acute skin and mucosal reactions over the ano-genital region. These acute effects recovered well within 4 weeks of completing treatment. Disease response assessment performed at a 2-month and 5-month follow-up visit showed good local control and the patient symptomatically felt much better. **Figure 3** shows clinical response during and after treatment. PET-CT performed at a 1-year follow-up showed no evidence of residual locoregional disease (**Figure 4**).

IMAGING FINDINGS

Pre-radiation therapy whole-body PET-CT (**Figure 4**) showed a large metabolically active growth involving the skin of right gluteal region, extending anteriorly up to the inguinal region, perianal region and vulva with a standard uptake value (SUV) max of 7.73. Mildly F-18 fluorodeoxyglucose (FDG)-avid enlarged bilateral common iliac, bilateral external iliac and right inguinal lymph nodes, the largest measuring 3.8 × 1.6 cm with an SUV Max of 3.34, suggestive of nodal involvement. There was no distant metastasis. Post-treatment PET-CT (at 1-year follow-up) showed complete locoregional radiological and metabolic response.

DIAGNOSIS

EMPD of the vulva and gluteal region

The differential diagnosis in the ano-genital area includes neurodermatitis, psoriasis, seborrheic dermatitis, lichen simplex, lichen planus, mycosis fungoides, Bowen's disease and perioriificial tuberculosis.[1] Histopathologically, the differential diagnosis includes pagetoid Bowen's disease and pagetoid malignant melanoma in situ.[2]

DISCUSSION

EMPD is a rare dermatologic condition that frequently presents in areas where apocrine sweat glands are abundant such as the vulva, perineum, scrotum and penile skin. EMPD has a female predominance and usually occurs in the sixth to eighth decade of life.[3]

The common presenting symptoms include pruritus, bleeding, oozing, tenderness, a painful burning sensation or hypopigmented lesions.[4] Lesions clinically present as erythematous, well-demarcated plaques that may become erosive, ulcerated, scaly or eczematous.[5] There are usually 3 patterns of EMPD: (1) an in situ epithelial form without associated carcinoma; (2) an epithelial form with associated adnexal carcinoma; and (3) a form associated with visceral malignancy of the genitourinary or gastrointestinal tract.[1] There is a strong association between the presenting anatomical site of EMPD and the underlying visceral carcinoma.[6]

Due to the histologic extension beyond the clinically abnormal area, local recurrence of EMPD is relatively common. EMPD cells have the potential to invade the dermis and to metastasize. Hard nodules and regional lymph node enlargement may develop, resulting from underlying carcinoma. "Underpants-pattern erythema" is a specific clinical aspect of genital EMPD.[3]

Surgery is the gold standard treatment for patients with EMPD. Other therapies include radiation therapy, curettage, topical fluorouracil (5-FU), and cryosurgery.[5] Systemic chemotherapy (vincristine, docetaxel, carboplatin, 5-FU, mitomycin-C, etoposide) can be used if there are contraindications to surgery and radiation therapy.[3] Radiation treatment can be utilized for inoperable lesions. A systematic review of

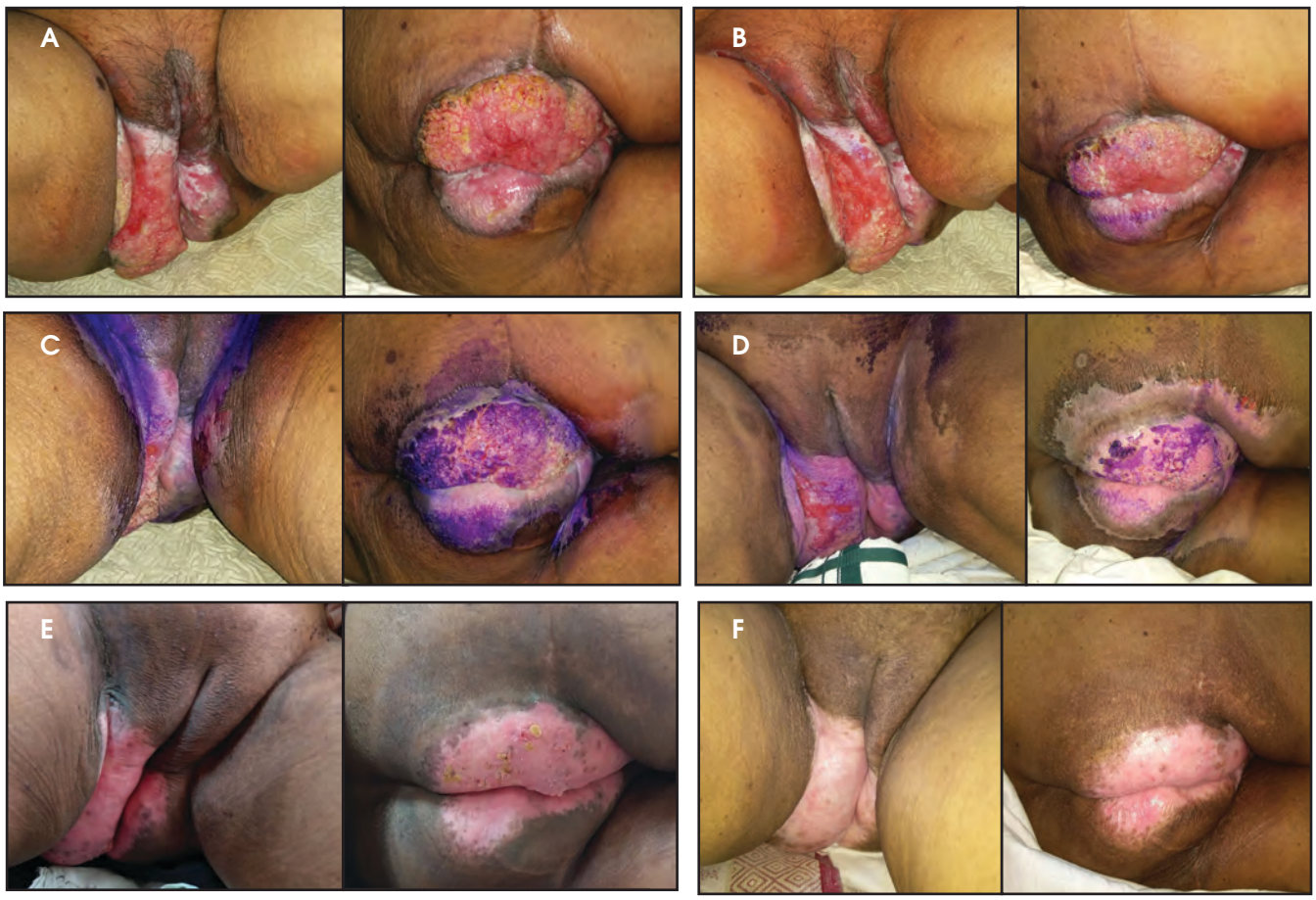

FIGURE 3. *Clinical photograph at the third week of treatment (A), fourth week of treatment (B), fifth week of treatment (C), post-treatment 2-week follow-up (D), 2-month follow-up (E), 5-month follow-up (F).*

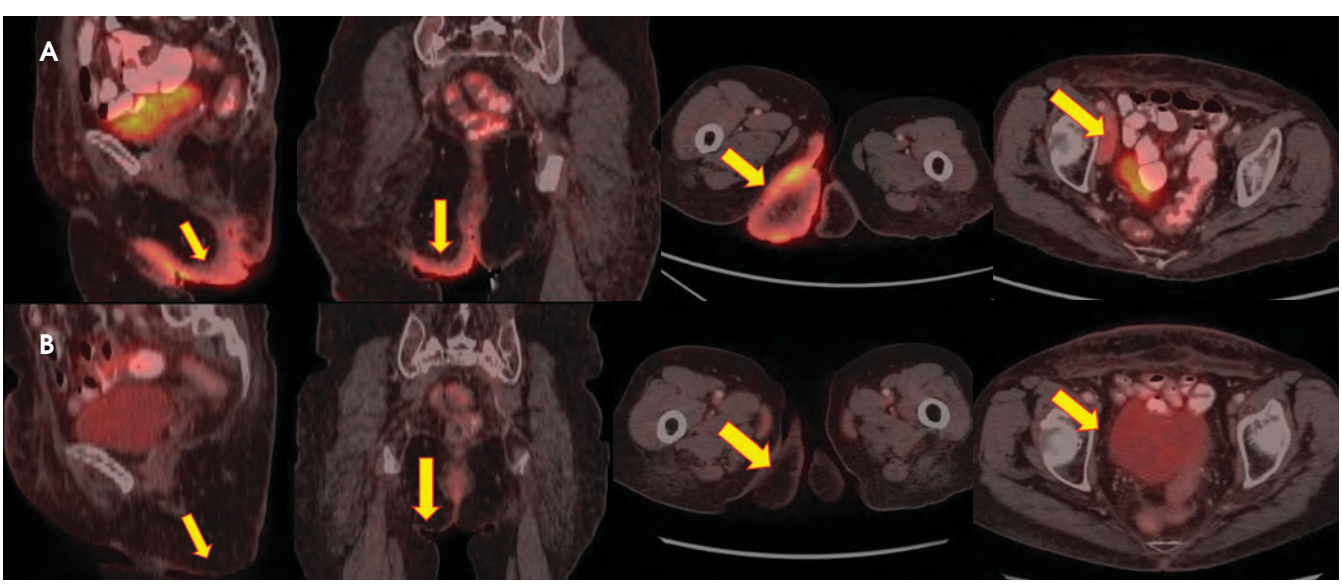

FIGURE 4. *Positron emission tomography – computed tomography (PET-CT) (pre-treatment) showing a large area of metabolically active diffuse cutaneous thickening involving the right gluteal region extending anteriorly up to inguinal region, perianal region, and vulva with pelvic lymphadenopathy (yellow arrow) (A). Post-treatment PET-CT shows complete locoregional response (yellow arrow) (B).*

the role of radiation therapy in EMPD evaluated 19 articles published from 1991 to 2015.[7] Radiation therapy was used in different clinical settings, namely the definitive, postoperative adjuvant, salvage and preoperative settings. The doses were 30 to 80 Gy in 3 to 43 fractions for gross disease, 32 to 64.8 Gy in 20 to 30 fractions for adjuvant treatment, and 40 Gy in 20 fractions for preoperative treatment. For definitive and salvage radiation therapy, response rates were 50% to 100% with 0% to 80% relapse rates. The dose-response relationship suggested a dose of at least 60 Gy for treating gross disease. A report on long-term outcomes of EMPD treated with definitive radiation therapy with doses of 40 to 56 Gy in 10 to 28 fractions showed an initial complete remission rate of 85%. The local relapse rate was 28.6% at a median follow-up of 6 years.[8]

A study by Hata et al reported the outcomes of radiation therapy for 41 patients of genital EMPD.[9] Radiation therapy doses of 45 to 80.2 Gy (median 60 Gy) in 23 to 43 fractions were utilized. Local progression-free survival and disease-free survival were 88% and 55% at 3 years and 82% and 46% at 5 years, respectively. Tumor invasion into the dermis and nodal metastasis were significant prognostic factors for distant metastasis and survival.

A literature review from the Cochrane Register of Controlled Trials, MEDLINE and the EMBASE database up to September 2015 concluded that radiation therapy alone is an alternative therapeutic approach for extensive inoperable disease.[10] High-risk features warranting adjuvant radiation therapy (after primary surgery) include dermal invasion, lymph node metastasis, close or positive surgical margins, large tumor diameter, multifocal lesions, coexisting histology of adenocarcinoma or vulvar carcinoma, high Ki-67 expression, adnexal involvement, and overexpression of HER-2/neu. A case report of suprapubic EMPD treated with electron-beam radiation therapy to a dose of 60 Gy in 30 fractions showed excellent local response.[11] Debabrata et al reported a case of EMPD of the vulva treated with surgery followed by adjuvant radiation therapy with good local control at 20 months' follow-up.[12] Seok-Hyun et al reported their experience in treating 3 cases of EMPD of the vulva with definitive radiation therapy (54 to 78 Gy in 1.8 Gy per fraction) and found complete response in all cases.[13] A case report on EMPD of the vulva treated with surgery followed by adjuvant radiation therapy (50.4 Gy in 28 fractions) with concurrent weekly cisplatin (40 mg/m^2) showed good local control at 15-months' follow-up.[14] Leslie et al from the Mayo Clinic Cancer Center reviewed cases of metastatic EMPD treated from 1998-2012 and supported use of local radiation therapy for bulky disease sequentially with chemotherapy (carboplatin and paclitaxel or irinotecan).[15]

This case report adds to the existing slim body of literature on the role of definitive radiation therapy in EMPD of the vulva. It demonstrates how effective and safe radiation therapy can be in controlling even grossly bulky disease. Concurrent capecitabine as a radiation sensitizer can be considered in elderly frail patients not considered suitable for other more toxic chemotherapy regimens. Treatment planning with VMAT helps to deliver a conformal dose distribution to the irregular target geometry, which includes the primary cutaneous site and nodal region Hence, radiation therapy can be considered as an effective and safe alternative to surgery in such cases.

CONCLUSION

EMPD is a rare cutaneous disease of elderly patients. Clinical and radiological evaluation is of paramount importance to detect underlying visceral malignancy. Surgery is the preferred primary treatment; however, local recurrences are common. Repeat surgery (which is often extensive) in the elderly population subset is difficult and carries significant morbidity. Radiation therapy is a safe and effective nonsurgical treatment modality for these patients. Even for bulky disease, radiation therapy can result in gratifying local control as demonstrated in this case report.

REFERENCES

1. Helwig EB, Graham GH. Anogenital (extramammary) Paget's disease. a clinicopathologic study. *Cancer.* 1963;16:387-403.
2. Kirkham N. Tumours and cysts of the epidermis. In: Elder D, Elenitsas R, Jaworksy C, Johnson B Jr, eds. *Lever's Histopathology of the Skin.* 8th ed. Lippincott- Raven; 1997:736-738.
3. McDaniel B, Brown F, Crane JS. Extramammary Paget disease. [Updated 2019 December 17, 2019]. In: *StatPearls* [Internet]. StatPearls Publishing; 2019. https://www.ncbi.nlm.nih.gov/books/NBK493224/. Accessed on December 19, 2019.
4. Balducci L, Crawford ED, Smith GF, Lambuth B, McGehee R, Hardy C. Extramammary Paget's disease: an annotated review. *Cancer Invest.* 1988;6:293-303.
5. Banerjee S, Chatterjee M, Chand K. Extramammary Paget's disease. *Indian J Dermatol Venereol Leprol.* 2005;71:417-420.
6. Chanda JJ. Extramammary Paget's disease: Prognosis and relationship to internal malignancy. *J Am Acad Dermatol.* 1985;13:1009-1014.
7. Tagliaferri L, Casa C, Macchia G, et al. The role of radiotherapy in extramammary Paget disease: a systematic review. *Int J Gynecol Cancer.* 2018;28(4):829-839.
8. Tackenberg S, Gehrig A, Dummer R, Navarini AA. External beam radiotherapy of extramammary Paget disease. *Cutis.* 2015;95:109-112.
9. Hata M, Koike I, Minagawa Y, et al. Radiation therapy for extramammary Paget's disease: treatment outcomes and prognostic factors. *Ann Oncol.* 2014;25(1):291-297.
10. Tolia M, Tsoukalas N, Sofoudis C, et al. Primary extramammary invasive Paget's vulvar disease: What is the standard, what are the challenges and what is the future of radiotherapy? *BMC Cancer.* 2016;16:563.
11. Valle L, Deig C, Wright R, High W. An advanced case of extramammary Paget disease: safe and effective treatment in an inoperable elderly patient using extensive en face electron irradiation. *JAAD Case Rep.* 2019;5:72-74.
12. Barmon D, Kataki AC, Imchen L, Sharma JD. Extramammary Paget's disease of vulva. *J Mid-life Health.* 2012;3:100-102.
13. Son S, Lee J, Kim Y, et al. The role of radiation therapy for extramammary Paget's disease of the vulva; experience of three cases. *Cancer Res Treat.* 2005;37(6):365-369.
14. Inayama Y, Abiko K, Miyamoto T, et al. Invasive Paget's disease of the vulva treated with a combination of surgery and concurrent chemoradiotherapy: a case report. *Molec Clin Oncol.* 2018;9:489.

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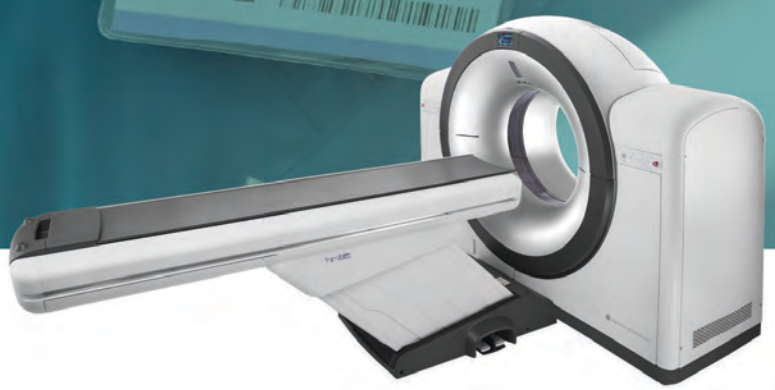

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