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MINI-FOCUS ISSUE: RADIATION AND CARDIOVASCULAR DISEASE

PRIMERS IN CARDIO-ONCOLOGY: HOW TO

How to Manage Patients With Cardiac Implantable Electronic Devices Undergoing Radiation Therapy

Michael G. Fradley, MD,[a] Bénédicte Lefebvre, MD,[a] Joseph Carver, MD,[a] Jim W. Cheung, MD,[b] Steven J. Feigenberg, MD,[c] Rachel Lampert, MD,[d] Jennifer Liu, MD,[e] Bharath Rajagopalan, MD,[f] Daniel J. Lenihan, MD[g]

Improved monitoring and treatment options have led to dramatic progress in the treatment of cardiovascular disease and cancer. Because of shared risk factors, a substantial number of cancer patients also have pre-existing cardiovascular disease when starting cancer treatment. It is projected that in 2021, there will be almost 1.9 million new cancer diagnoses, and approximately 50% of patients will undergo radiation therapy (RT) as part of their treatment plan (1). It is also estimated that by 2035, >45% of the U.S. population will have some form of cardiovascular disease. Annually, almost 1 million pacemakers and implantable cardioverter-defibrillators (ICDs) are inserted (2). Ionizing radiation, especially thoracic RT, can damage a cardiac implantable electronic device (CIED), and occasionally, a device can interfere with RT delivery. Therefore, a collaborative multidisciplinary approach is necessary to provide effective and safe RT for patients with existing CIEDs.

BASICS OF RADIATION THERAPY

RT is administered for a variety of reasons, including palliation, definitive treatment, and adjuvant therapy following surgery. RT planning starts with the patient undergoing a computed tomography simulation in the treatment position where the target and all nontarget normal tissues are identified. The radiation dose (measured in Grays), duration of treatment (number of fractions), and level of sophistication of treatment are determined by many clinical factors, including the urgency of treatment, the sensitivity of the tumor to RT, and the ultimate goal of therapy. Treatments are designed to conform the highest dose to the tumor volume while decreasing the dose to the surrounding uninvolved normal tissues. Precision RT can be further individually optimized through advanced imaging, mitigating tumor motion, or adjusting treatment delivery. In general, electrons are used to treat superficial tumors (<4 cm deep from the skin), whereas photons are used to treat deeper tumors. Recently, there has been increased interest in the use of proton therapy, which is currently available only at select institutions, for its ability to treat deeper tumors using selective energy deposition. This approach has an advantage over photon-based techniques by reducing areas receiving low RT doses and decreasing the integral dose of irradiation received by normal tissues. Based on available

From the [a]Cardio-Oncology Translational Center of Excellence, Division of Cardiology and Abramson Cancer Center, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [b]Weill Cornell Medicine, Department of Medicine, New York, New York, USA; [c]Department of Radiation Oncology, Perelman Center for Advanced Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [d]Department of Medicine (Cardiovascular Disease/Electrophysiology), Yale School of Medicine, New Haven, Connecticut, USA; [e]Cardiology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Department of Medicine, Weill Cornell Medical College, New York, New York, USA; [f]Prairie Heart Institute, Springfield, Illinois, USA; and the [g]Cardio-Oncology Center of Excellence, Washington University in St. Louis, St. Louis, Missouri, USA.

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ABBREVIATIONS AND ACRONYMS

CIED = cardiac implantable electronic device

ICD = implantable cardioverter-defibrillator

RT = radiation therapy

clinical data, protons display promising outcomes and toxicity profiles for several neoplasms, including intrathoracic malignancies. When a patient has a CIED, RT planning should ensure that no radiation beam is directed at or through the device to minimize the absorbed dose. Another important issue during RT is the occurrence of nuclear reactions within the linear accelerator causing neutron contamination, which is especially damaging to CIEDs (3). This occurs with increasing energy photons (>10 MV) and electrons (>20 MeV) or with proton therapy (4-6).

CASE

A 68-year-old man with left upper lobe non-small-cell lung cancer was to receive RT as part of his treatment plan. He had a history of hypertension and complete heart block requiring dual-chamber pacemaker placement in the left upper chest. Prior interrogations showed 100% ventricular pacing, with the battery approaching the elective replacement interval in 6 months. Cardio-oncology consultation was requested for device management during RT.

DEVICE MANAGEMENT BEFORE STARTING RT. Radiation oncologists should work with a cardiologist familiar with CIEDs, most often an electrophysiologist, when developing a treatment plan. This can often be completed via e-consults or telehealth if the institution RT does not have an onsite cardiologist or electrophysiologist. In all patients, before initiating therapy, a complete cardiovascular history should be obtained including CIED type, with review of the most recent device interrogation or remote transmission noting the device's lower rate limit. It is advisable to turn off the rate-responsive settings to avoid the possibility of RT-induced changes in the upper sensor rate (7). A follow-up evaluation is recommended with any changes in the patient's clinical situation.

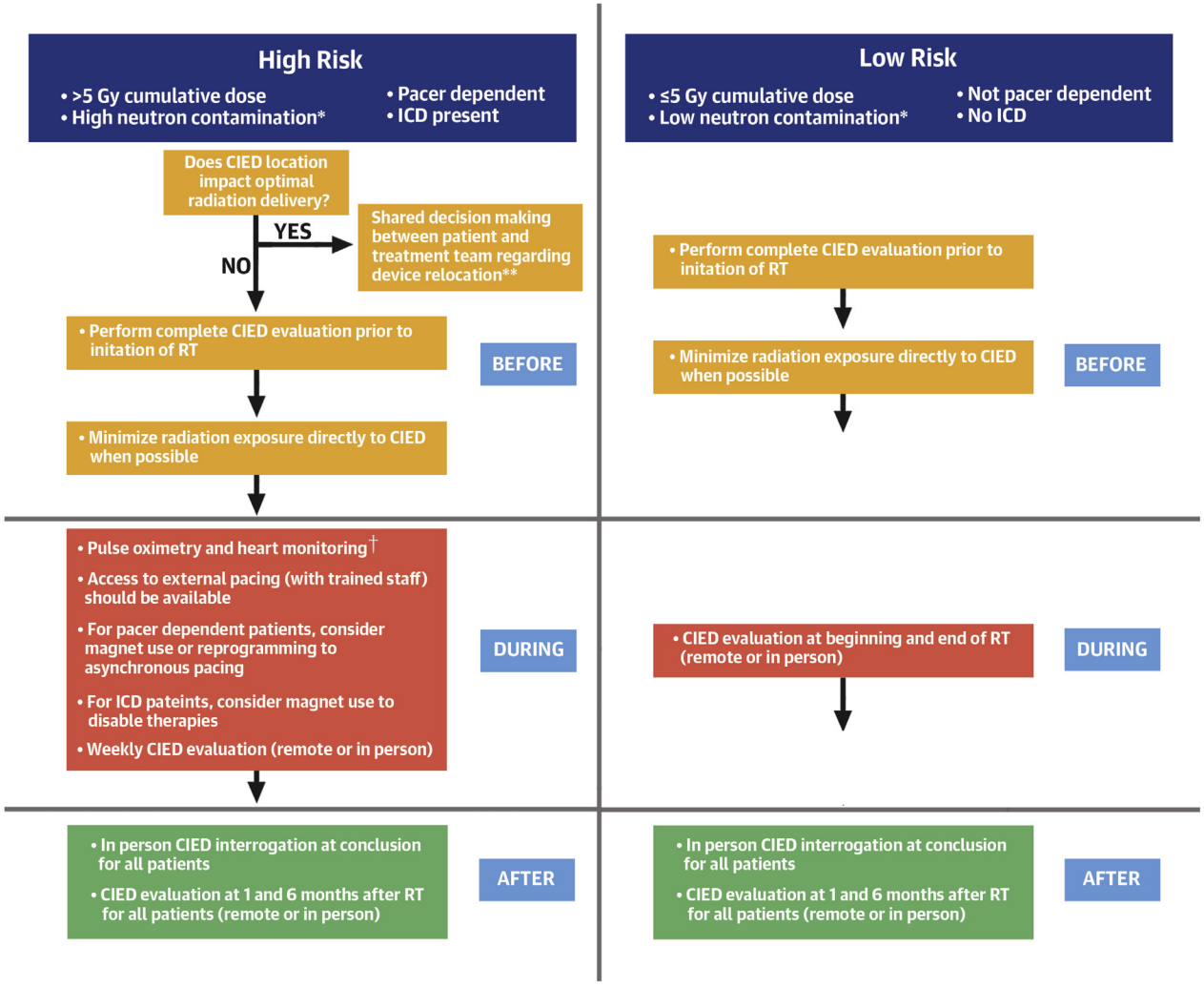
It is essential to determine patient-specific risk before initiating RT (**Figure 1**). Although current guidelines and recommendations have a 3-tier system of low, intermediate, or high risk, we often use a simplified approach, categorizing patients as either low or high risk. In our view, this streamlines decision making, particularly when onsite cardiology or electrophysiology consultation is not available, because the majority of recommendations for intermediate-risk patients overlap with those categorized as high risk. Patients with high-risk features require close monitoring of device function during radiation.

To assess the risk, a multidisciplinary team should consider each of the following questions (4,5,7,8):

- Is the device a pacemaker or ICD?
  - ICDs are more sensitive to ionizing radiation than pacemakers and are considered higher risk for malfunction because of the increased amount of boron in the internal circuitry (6). In addition, an elevated RT dose rate can lead to oversensing and inappropriate ICD shocks, with dose rates of <0.01 Gy/min considered low risk.
- Is the patient pacemaker dependent?
  - Pacemaker dependency (defined as a lack of spontaneous ventricular activity or intrinsically low heart rate that is not clinically tolerated) is considered a high-risk scenario, given the potential for RT to interfere with pacing leading to asystole. For all patients, particularly those with cardiac resynchronization therapy, it is important to assess underlying rhythm and pacemaker dependency.
- What is the absorbed dose to the device?
  - The medical physicist should estimate the absorbed dose to the device as part of treatment planning. In general, risk to the device is increased when the absorbed dose exceeds 5 Gy, which primarily occurs when the planned target for radiotherapy includes the thorax, neck, or proximal upper extremity. In general, the dose to the device is <2 Gy if the radiation field is ≥5 cm away from the device.
- What is the planned energy of the RT?
  - Radiation energies that lead to neutron contamination are the most likely to damage devices even when directed at distant sites below the diaphragm. Photon energy of >10 MV, electron energy of >20 MeV, and proton therapy are considered high risk for device malfunction because of the potential for neutron contamination, even if the absorbed dose is relatively low.

Device relocation should be considered only when the CIED position affects adequate delivery of RT, such as when the tumor is directly posterior to the device. CIED relocation can be associated with complications including infection, especially if lead revision is necessary. Moreover, because CIED malfunction primarily occurs with neutron contamination, moving the device to the contralateral side is not necessarily protective because neutrons can penetrate significant distances (3). Limited data are available regarding RT risk to subcutaneous cardiac devices or leadless pacemakers; device manufacturer instructions should be followed. Finally, this is an

FIGURE 1 Management Algorithm for Cardiac Implantable Devices During Radiation Therapy



*Radiation treatment associated with high neutron contamination: photons >10 MV; electrons >20 MeV; proton therapy. **Device relocation not recommended for ≤5 Gy cumulative dose. †Continuous electrocardiogram monitoring during radiation treatment may be considered in patients with ICDs who have had prior treatments for ventricular arrhythmias. ICD = implantable cardioverter-defibrillator.

opportunity for shared decision making about permanent device deactivation or removal, with a focus on the patient's goals of care and cardiovascular and oncologic prognoses.

CASE CONTINUED

Based on multidisciplinary conversations, the patient was considered high risk for adverse events should device malfunction occur during RT, given the lack of intrinsic ventricular activity. The pulse generator was outside of the direct treatment field and would not impede delivery of RT to the tumor. As such, device relocation was not necessary. The pacemaker was interrogated before the first treatment, and baseline parameters were recorded.

DEVICE MONITORING DURING RT. Device malfunction during RT can be classified as either soft errors (those affecting device software) or hard errors (those affecting device hardware). Although device malfunction during RT is rare, soft errors occur more frequently than hard errors. Soft errors include power-on reset or reversion to backup factory settings, temporary increased sensor or pacing rate, temporary oversensing, or inappropriate ICD

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operation. Hard errors comprise complete device failure and early battery depletion resulting in permanent damage, ultimately requiring device replacement (4,7).

During RT, staff should be able to directly visualize and communicate with all patients throughout the entirety of treatment. Data are lacking on the need and benefit of magnets or reprogramming of pacemakers or ICDs during thoracic RT. Although device manufacturer instructions suggest device reprogramming if the device is in close proximity to the radiation beam, professional societies differ in their recommendations (4,5,7,8). Patients in whom magnets or reprogramming may be considered include those who are pacer dependent, those whose device battery is nearing end-of-life, or those with ICDs. In addition, higher-risk patients should have continuous heart rate monitoring via pulse oximetry with immediate access to a 12-lead electrocardiography machine, external pacing, and defibrillation devices, as well as advanced cardiac life support/cardiopulmonary resuscitation-trained personal should an emergency arise. Continuous electrocardiographic monitoring during RT is not generally necessary but may be considered in patients with ICDs who have had prior treatments for ventricular arrhythmias.

Current consensus statements (4) recommend weekly CIED evaluations for patients undergoing treatment associated with neutron contamination and pacemaker-dependent patients (**Figure 1**). For most devices, remote monitoring may permit complete evaluation, which would obviate the need for additional clinic visits. Remote transmission can be sent manually, as well as automatically based on prespecified alerts indicating ICD therapies or potential lead or device malfunction. In general, the use of remote monitoring systems has been shown to improve clinical outcomes and patient satisfaction for patients with CIEDs. It is our opinion that remote monitoring should be used as much as possible, with in-person evaluations reserved for patients not enrolled in remote monitoring services or those in whom malfunction is identified.

CASE CONTINUED

On treatment day 1, standard audiovisual and pulse oximetry monitoring was initiated, and a magnet was placed over the device during RT. The patient had no arrhythmias, and the device was interrogated post-RT with no change from baseline parameters. He completed all planned fractions with the magnet in place during RT without any cardiac events. The device was interrogated in person at RT completion, with remote transmissions reviewed at 1 and 6 months post-RT without any change from baseline parameters.

DEVICE MONITORING AFTER COMPLETION OF RT. At the conclusion of RT, a complete in-person evaluation of the CIED is warranted for all patients, regardless of the type, location, dose, or energy of the radiation (4). Additionally, remote CIED evaluation at 1 month and 6 months following RT should be performed (**Figure 1**) (3,7). Although CIED malfunction is very rare and usually not clinically significant, oversensing, pacing threshold change, lead impedance change, premature battery depletion, and electrical/power-on reset can occur. Current data suggest that the likelihood of late CIED malfunction following RT is very low. In one retrospective study of 215 patients with CIEDs undergoing RT, no delayed malfunctions were directly attributed to RT (9).

In addition to the potential late effects of RT on CIED function, changes to the skin and underlying tissue exposed to RT can have implications for device generator changes, upgrades, revisions, or reimplantation if the surgical site lies within or is in close proximity to the treated area. Cellular depletion, microvascular changes, and cytokine and growth factor dysregulation during the delivery of RT can then lead to long-term effects of fibrosis and impaired wound healing (10). Whether or not the late effects of RT result in increased risks of CIED infection or other complications merits investigation.

CONCLUSIONS

Although damage to CIEDs is infrequent, pacemaker dependency, the presence of an ICD, exposure to neutron contamination, and increased absorbed dose because of proximity of the device to the radiation field warrant enhanced monitoring during and after therapy. In general, these higher-risk patients should have pulse oximetry monitoring in addition to standard audiovisual monitoring and magnet application during RT and routine weekly device interrogations (in person or via remote monitoring). A multidisciplinary approach with radiation oncologists, cardio-oncologists, and electrophysiologists is necessary to ensure the safety of patients with CIEDs receiving RT.

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ADDRESS FOR CORRESPONDENCE: Dr Michael G. Fradley, Perelman School of Medicine at the University of Pennsylvania, 2-355E PCAM3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: Michael.fradley@pennmedicine.upenn.edu. Twitter: @Dr_Mike_Fradley, @drjcheungep, @jliu_MSKCardOnc, @penncardiology.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33.

2. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–e528.

3. Miften M, Mihailidis D, Kry SF, et al. Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: a report of the AAPM TG-203. *Med Phys*. 2019;46(12):e757–e788.

4. Indik JH, Gimbel JR, Abe H, et al. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. *Heart Rhythm*. 2017;14(7):e97–e153.

5. Ohno T, Soejima T, Sekiguchi Y, et al. JASTRO/JCS guidelines for radiotherapy in patients with cardiac implantable electronic devices. *J Radiat Res*. 2021;62(1):172–184.

6. Elders J, Kunze-Busch M, Smeenk RJ, Smeets JLRM. High incidence of implantable cardioverter defibrillator malfunctions during radiation therapy: neutrons as a probable cause of soft errors. *Europace*. 2013;15(1):60–65.

7. Zecchin M, Severgnini M, Fiorentino A, et al. Management of patients with cardiac implantable electronic devices (CIED) undergoing radiotherapy. *Int J Cardiol*. 2018;255:175–183.

8. Hurkmans CW, Knegjens JL, Oei BS, et al. Management of radiation oncology patients with a pacemaker or ICD: a new comprehensive practical guideline in the Netherlands. *Radiat Oncol*. 2012;7(1):198.

9. Grant JD, Jensen GL, Tang C, et al. Radiotherapy-induced malfunction in contemporary cardiovascular implantable electronic devices: clinical incidence and predictors. *JAMA Oncol*. 2015;1(5):624–632.

10. Haubner F, Ohmann E, Pohl F, Strutz J, Gassner HG. Wound healing after radiation therapy: review of the literature. *Radiat Oncol*. 2012;7(1):162.

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