



## Original Article

# Assessment of Radiation-Induced Malfunction in Cardiac Implantable Electronic Devices

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## ABSTRACT

**Background:** Radiation therapy (RT) is a standard cancer treatment modality, and an increasing number of patients with cardiac implantable electronic devices (CIEDs) are being referred for RT. The goals of this study were as follows: (i) to determine the incidence of CIED malfunction following RT; (ii) to characterize the various types of malfunctions that occur; and (iii) to identify risk factors associated with CIED malfunction following RT.

**Methods:** A retrospective study of patients with CIEDs who received RT between 2007 and 2018 at 4 Canadian centres (Sunnybrook Health Sciences Centre, Kingston General Hospital, Hamilton Health Sciences

## RÉSUMÉ

**Contexte :** La radiothérapie (RT) est une modalité standard de traitement du cancer, et un nombre croissant de patients porteurs de dispositifs cardiaques électroniques implantables (DCEI) doivent recevoir un traitement de RT. Les objectifs de cette étude étaient les suivants : (i) déterminer l'incidence d'une défaillance du DCEI après une RT; (ii) caractériser les différents types de défaillances qui se produisent; (iii) déterminer les facteurs de risque associés à la défaillance du DCEI après une RT.

**Méthodologie :** Une étude rétrospective des patients avec un DCEI ayant reçu une RT entre 2007 et 2018 dans quatre centres canadiens

Radiation therapy (RT) is a standard cancer treatment modality, and an increasing number of patients with cardiac implantable electronic devices (CIEDs) diagnosed with cancer are referred for RT. Ionizing radiation used in external beam radiation therapy can damage heart rhythm devices, including pacemakers (PMs) and implantable cardioverter-defibrillators

(ICDs).<sup>1</sup> The primary mechanism causing device malfunctions is ionizing radiation damage to the device semiconductor microelectronics, resulting from accumulated dose or neutron-causing single-event upsets.<sup>2,3</sup> An estimated 2.9 million patients received permanent PMs in the United States from 1993 to 2009, and overall use increased by 55.6%.<sup>4</sup> Nearly 1% of patients receiving RT have a CIED (79% PMs, 21% ICDs).<sup>5</sup> Given the increasing global burden of cancer and the concurrent rise in CIED implantations, the identification of risk factors associated with RT-induced device malfunction is of increasing concern.<sup>6,7</sup>

Cardiac device malfunctions are identified in 2%-7% of patients receiving RT.<sup>8</sup> Although proposed risk factors associated with device-malfunction severity and frequency have included RT treatment modality, total device radiation dose, and anatomic location of the treated site, recent studies

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**Ethics Statement:** This retrospective cohort study was approved by the local ethics committees at the 4 participating sites and did not require patient-level consent.

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See page 1442 for disclosure information.

Centre, and University of Ottawa Heart Institute) was conducted. Patients underwent CIED interrogation after completion of RT, to assess for late damage to the CIEDs. Data on demographics, devices, and RT were compared for the primary outcome of device malfunction.

**Results:** Of 1041 patients with CIEDs who received RT, 811 patients with complete data were included. Device malfunctions occurred in 32 of 811 patients (4%). The most common device malfunctions were reduced ventricular/atrial sensing (in 13 of 32 [41%]), an increase in lead threshold (in 9 of 32 [22%]), lead noise (in 5 of 32 [16%]), and electrical reset (in 2 of 32 [6%]). Higher beam energy ( $\geq 10$  MV) was associated with malfunction ( $P < 0.0001$ ). Radiation dose was not significantly different between the malfunction and non-malfunction groups (58.3 cGy vs 65 cGy, respectively,  $P = 0.71$ ).

**Conclusions:** Although RT-induced CIED malfunctions are rare (occurring in 4% of patients with a CIED who undergo RT), collaborative efforts between radiation oncologists and cardiac rhythm device clinics to optimize CIED monitoring are needed, to detect and manage CIED malfunctions. Malfunctions are more common in patients receiving higher-beam energy ( $\geq 10$  MV) RT.

have compellingly indicated that neutron-producing radiation, with its associated photon beam energy (the extent of radiation penetration, in megavolts [MV]), is the single strongest predictor of CIED malfunction in contemporary devices.<sup>9</sup>

Despite the increasing proportion of patients with CIEDs undergoing RT, 28% of cardiologists are unfamiliar with radiation limits for CIEDs.<sup>10</sup> In fact, a survey from Europe found that only 39% of radiation oncology departments have policies regarding CIEDs, and 18% manipulate CIEDs without collaboration with cardiac electrophysiologists.<sup>11</sup> The goals of this study were as follows: (i) to determine the incidence of CIED malfunction; (ii) to characterize the various types of malfunctions that occur; and (iii) to identify risk factors associated with CIED malfunction following RT.

## Methods

### Radiation therapy concept review

Radiation is the cornerstone for the treatment of various types of cancer. Up to 50% of malignancies require RT for either curative or palliative intent.<sup>12</sup> Radiation doses used in cancer therapy are measured in grays (1 Gy = 1 joule of absorbed energy of ionizing radiation per 1 kg of matter). RT is delivered based on individualized treatment strategies, which commonly consist of several treatments over days or weeks, with daily fractions of typically 1.8-2 Gy. Cumulative doses of up to 80 Gy are given in curative RT for solid tumours, with a total radiation dose of approximately 50 Gy for breast cancer and 60-66 Gy for lung cancer.<sup>13,14</sup>

(Sunnybrook Health Sciences Centre, Kingston General Hospital, Hamilton Health Sciences Centre et Institut de cardiologie de l'Université d'Ottawa) a été menée. Le DCEI des patients a été interrogé après la fin de la RT, pour en évaluer les dommages tardifs. Les données sur les caractéristiques démographiques, les dispositifs et la RT ont été comparées pour le paramètre d'évaluation principal, soit la défaillance du dispositif.

**Résultats :** Sur les 1 041 patients avec un DCEI ayant reçu une RT, 811 patients avec des données complètes ont été inclus. Des défaillances du dispositif sont survenues chez 32 des 811 patients (4 %). Les défaillances les plus fréquentes du dispositif étaient une détection ventriculaire/atriale réduite (chez 13 des 32 patients [41 %]), une augmentation du seuil de la sonde (chez 9 des 32 patients [22 %]), un bruit provenant de la sonde (chez 5 des 32 patients [16 %]) et une réinitialisation électrique (chez 2 des 32 patients [6 %]). Une énergie de faisceau plus élevée ( $\geq 10$  MV) était associée à une défaillance ( $p < 0,0001$ ). La dose de rayonnement ne présentait pas de différence significative entre le groupe où une défaillance a été constatée et l'autre groupe (58,3 cGy vs 65 cGy, respectivement,  $p = 0,71$ ).

**Conclusions :** Bien que les défaillances du DCEI causées par la RT soient rares (survenant chez 4 % des patients avec un DCEI qui subissent une RT), une collaboration est nécessaire entre les radio-oncologues et les cliniques de dispositifs de gestion du rythme cardiaque, afin d'optimiser la surveillance du DCEI et de détecter et de gérer ces défaillances. Les défaillances sont plus fréquentes chez les patients recevant une énergie de faisceau plus élevée au moment de la RT ( $\geq 10$  MV).

Several forms of RT are used in the treatment of malignancies. Most commonly, photons or electrons are generated and delivered by a linear accelerator. The radiation beams are characterized by their depth dose curves. By increasing the beam energy of the linear accelerator, the depth of the maximal delivered radiation dose increases. Hence, photons in the MV range (commonly 6-20 MV) are used for more deeply located tumours, whereas electrons are typically used for superficially located tumours, owing to their sharp fall-off with increasing depth and hence limited range. Kilovolt (kV) photons are also often used for superficial lesions, such as skin cancer.<sup>15</sup>

### Study population and data collection

Patients included in this study were those receiving the following: (i) external beam radiation therapy in the following treatment modalities: megavoltage electron therapy, megavoltage photon therapy, and kilovoltage (kV) photon therapy; or (ii) both external beam radiation therapy and brachytherapy (classified according to the external beam radiation therapy modality type). Patients receiving only brachytherapy treatments were excluded. Most of the patients in the cohort received MV photon therapy employing the following radiation delivery techniques: 2-4 field, intensity-modulated radiation therapy, volumetric modulated arc therapy, stereotactic body radiation therapy, stereotactic radiosurgery, and tomotherapy. All MV photon treatments were delivered using photons in the 6-18 MV energy range. If both photons and electrons were applied, the treatment was classified as photon RT.

Ten major centres in Ontario, Canada were approached for the existing databases inclusive of prespecified criteria. The study

was feasible and was inclusive of the data at 4 tertiary centres (Sunnybrook Health Sciences Centre, Kingston General Hospital, Hamilton Health Sciences Centre, and University of Ottawa Heart Institute). Clinical and device-related data were collected, for all patients with CIEDs retrospectively who underwent RT for cancer between 2007 and 2018, from electronic medical records and from the treatment-planning system software. Collected data included clinical characteristics, device type and manufacturer, total device radiation dose and fractionation scheme, RT treatment modality and technique,<sup>16,17</sup> beam energy of therapeutic radiation,<sup>18-21</sup> and anatomic location of malignancy and RT treatment site. CIED malfunctions were categorized as minor or serious. Serious malfunctions included premature battery depletion and electrical reset that resulted in total malfunction with subsequent battery replacement. Other malfunctions were considered minor. All episodes of device malfunction were documented, including changes in patients' physical status during RT. All patients were evaluated after completion of RT to assess for late damage to their CIEDs. Occurrences of device malfunction were identified at CIED clinic follow-up visits per individual site protocol. At each of the 4 CIED implantation sites in Ontario, data were collected by a trained research coordinator, a cardiac electrophysiologist, and a cardiology fellow and were entered into a real-time, password- and firewall-protected web database. Data quality was continually assessed.

Protective measures were built into the protocols employed by each cancer clinic and were based on guidelines from the literature. These measures typically require that the device be outside of the treatment field and that the radiation beams in the treatment plan be configured in such a way as to minimize the dose to the device. Many clinics are also aware of the risk associated with neutrons and so will aim to reduce the use of higher-energy photon beams during radiation treatment planning.<sup>15</sup>

### Radiation data

Total radiation dose to the device was obtained using one of the following 3 techniques, depending on the proximity of the device to the treatment field and on technique complexity: (i) American Association of Physicists in Medicine report TG-36 data if the device was not located within the RT planning computed tomography simulation scan<sup>22</sup>; (ii) dose estimation from the RT treatment planning system commissioning data if the device was located within the computed tomography simulation scan; and (iii) dose measurement on the patient's first treatment fraction for complex photon treatment techniques (intensity-modulated radiation therapy, volumetric modulated arc therapy, stereotactic radiosurgery, and tomotherapy) for which the PM or ICD was within 10 cm of the nearest radiation field edge.

The anatomic regions were classified as follows: head and neck, chest, esophagus, abdomen and pelvis, spine, and skin. If 2 anatomic regions were treated simultaneously, the region closest to the PM/ICD generator was recorded.

### Ethics

This retrospective cohort study was approved by the local ethics committees at the 4 participating sites and did not require patient-level consent.

### Statistical analysis

Only variables with < 10% of data missing were included. Continuous variables were reported as mean  $\pm$  standard deviation. Data on clinical characteristics, RT, and devices were compared for patients that did vs did not have RT-induced device malfunctions. A univariable analysis was performed to compare variables. Continuous, normally distributed variables were compared with the Student *t* test. For continuous non-normally distributed variables, the Wilcoxon rank-sum test was used. Associations between categorical variables were assessed with the  $\chi^2$  test or the Fisher exact test when 25% of cell counts were < 5.

## Results

### Patients

Of 1041 patients with CIEDs who received RT, 811 patients with available data were included (Fig. 1). The mean age for patients with CIEDs who underwent radiation therapy was  $78.4 \pm 9.4$  years for CIEDs with normal function, and  $79.3 \pm 11.5$  years for CIEDs with malfunction. A majority of patients with CIED malfunction were male (5.2%); women had only 2 CIED malfunctions out of 236. Data on clinical characteristics, devices, and RT are presented in Table 1.

### Device malfunctions

Device malfunctions occurred in 24 PMs (of a total of 624 PMs; 3.8%) and 8 ICDs (of a total of 185 ICDs; 4.3%). The most common device malfunctions were reduced ventricular/atrial sensing (41%), an alteration in lead threshold/impedance (22%), lead noise (16%), and electrical reset (6%; Table 1). Manufacturers of devices that experienced malfunctions are presented in Figure 2. Serious malfunction occurred in the devices of 4 of 32 patients, and included 2 cases each of electrical reset and premature battery depletion.

### Predictors of device malfunction

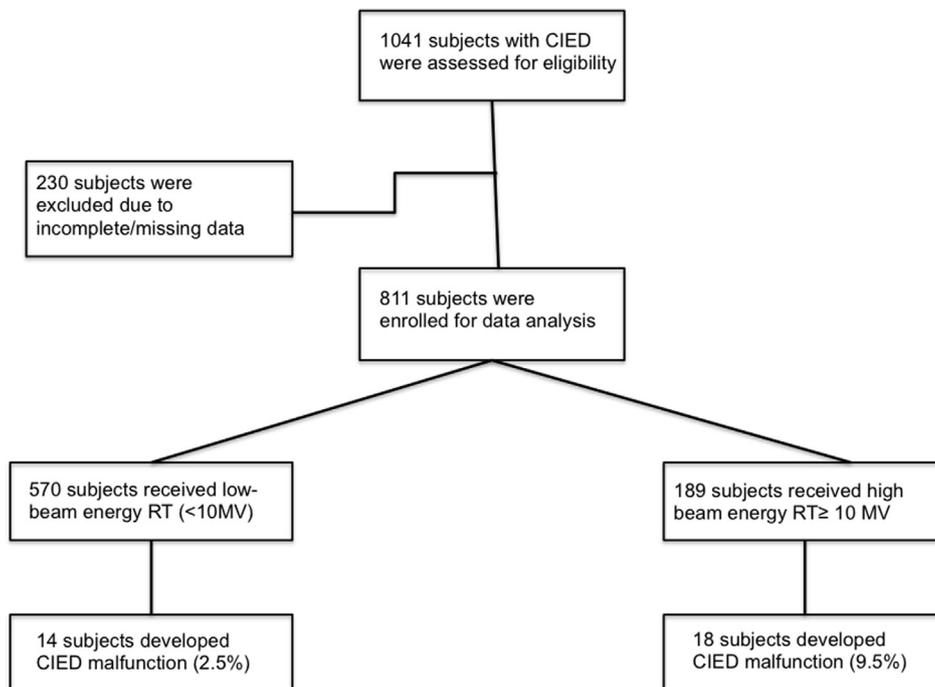
The mean device radiation dose was not statistically different in the malfunction vs non-malfunction groups ( $65$  vs  $58.3$  cGy,  $P = 0.71$ ). Device malfunctions occurred more commonly in men than in women. Occurrence of CIED malfunctions was equal between PMs and ICDs. The photon beam energy of the RT was significantly higher in the malfunction group ( $\geq 10$  MV vs  $< 10$  MV,  $P = 0.0001$ ; Table 1). Device malfunctions distribution by radiation target locations are presented in Figure 3.

### Device relocation

A total of 11 PMs (1.8%) required relocation owing to close proximity of the CIED to the targeted cancer and potential interference with therapy. None of the ICDs required relocation.

## Discussion

To our knowledge, this is largest published series investigating CIED malfunctions in patients receiving RT. The 4%



**Figure 1.** Flowchart for patient enrollment in this study. CIED, cardiac implantable electronic device; RT, radiation therapy.

incidence of CIED malfunction and the lack of association between radiation dose and malfunction are consistent with results of prior reported studies.<sup>10,15,23-26</sup> The results of this study suggest that CIED malfunctions are uncommon in centres that follow an algorithm of risk assessment for device management post-radiation therapy. Furthermore, our results support the recent studies and expert consensus statements that have compellingly indicated that neutron-producing radiation and the associated beam energy are the strongest predictors of CIED malfunction.<sup>3,15,18,23,24</sup> The 2017 Heart Rhythm Society expert consensus statement specifically states that non-neutron-producing treatment is

preferred over neutron-producing treatment in patients with a CIED, to minimize the risk of device reset; however, the statement does not address specifically whether/when to avoid beam energy  $\geq 10$  MV.<sup>9</sup> In light of the growing evidence, specific consideration for beam energy should be implemented as a part of the initial assessment for patients with CIEDs who are undergoing RT.

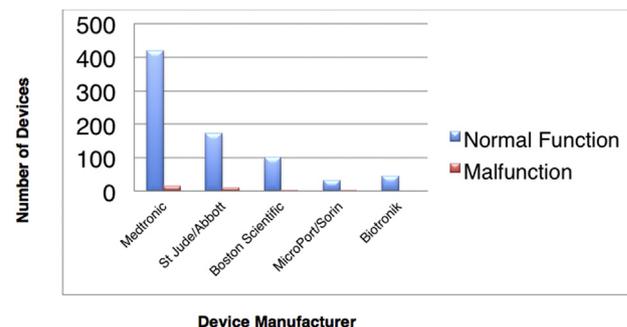
However, major variations are present in the manufacturer recommendations among the various tertiary cancer centres regarding patient management precautions.<sup>27</sup> CIED manufacturers have differing opinions regarding the thresholds at which a CIED can tolerate radiation. The Medtronic CIED (Medtronic, Minneapolis, MN) was the most common cardiac device to be implanted in our study. Medtronic reports that the dose tolerance is 5 Gy for PMs and 1-5 Gy for ICDs, with the dose tolerance being specific to the type of ICD. These recommendations may need to be challenged, as it is only beam energy that appears to be a significant factor

**Table 1.** Outcomes of patients with cardiac implantable electronic devices with radiation-induced malfunction compared to those for patients with devices with normal function

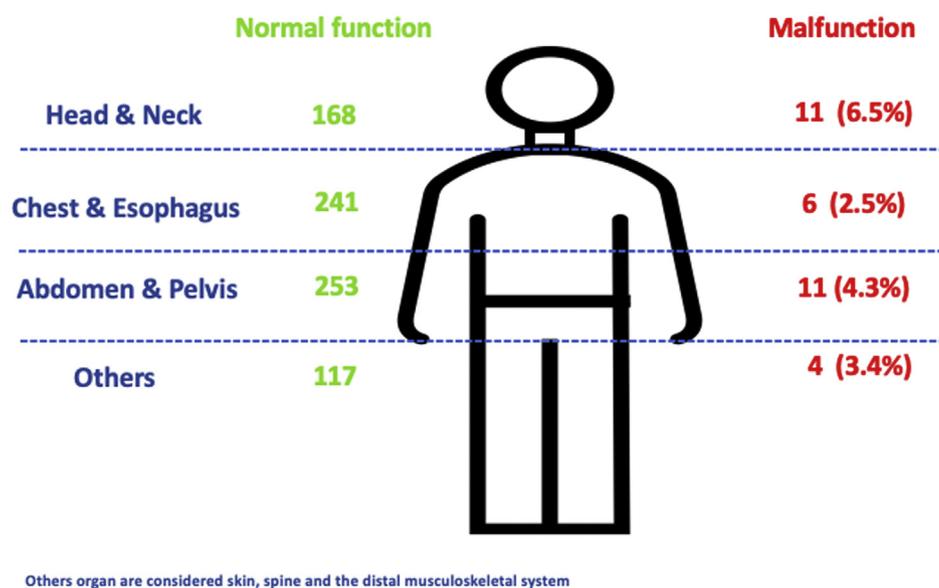
Characteristic	All patients	Normal function	Malfunction	P
Sex				
Male	575	545	30 (5.2)	
Female	236	234	2 (0.8)	0.004
Age, y		78.4 ± 9.4	79.3 ± 11.5	0.7
CIED type				
PM	624	600	24 (3.8)	
ICD	185	177	8 (4.3)	0.77
ILR	1	1	0	
Beam energy, MV				
≥ 10	189	171	18 (9.5)	< 0.0001
< 10	570	556	14 (2.5)	
Mean device radiation dose, cGy		65 ± 73	58.3 ± 288	0.71

Values are n, n (%), or mean ± standard deviation, unless otherwise indicated.

CIED, cardiac implantable electronic device; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; PM, pacemaker.



**Figure 2.** Incidence of cardiac implantable electronic device malfunction and normal function among devices from various manufacturers.



**Figure 3.** Incidence of cardiac implantable electronic device malfunction and normal function among body regions.

associated with malfunctions. Moreover, as radiation therapy has become common for patients with CIEDs, consideration should be given to mandatory device pre-marketing testing by the manufacturer so as to develop a better-defined recommendation. As with magnetic resonance imaging conditioning, one can foresee radiation being conditioned on CIEDs for elderly patients and those with known malignancies.

Whether to relocate a CIED in patients undergoing RT is a challenging issue, given the risks of surgical complications.<sup>28-30</sup> The rate of device relocation in the literature varies between 3.5% and 31%.<sup>19</sup> In our series, 11 PMs (1.8%) required either relocation or extraction, due to the proximity of the CIED to the targeted cancer and hence potential interference with therapy; this may explain the lower incidence of CIED malfunction in the chest and esophagus region. None of the ICDs in this cohort required relocation. However, there are no widely accepted criteria to use to assess the appropriateness of surgically moving the device. Recommendations for preventative device relocation based on radiation dose are vague, such as a cumulative radiation dose exceeding 2-10 Gy for PMs, and generally lower doses for ICDs.<sup>8</sup>

Although rare, the clinical consequences of RT-induced CIED malfunctions can vary from the asymptomatic to hemodynamic instability. Grant et al. described symptoms in 6 patients with a CIED parameter reset in the context of RT: 3 experienced hypotension and/or bradycardia, 2 experienced abnormal chest pounding consistent with PM syndrome, and 1 developed congestive heart failure.<sup>3</sup> None of the CIED malfunctions led to clinical symptomatology or harmful events in our cohort group.

### Study limitations

Given the study design, the typical limitations of using retrospective data apply. Moreover, institutional differences among the participating centres with regard to CIED relocation and magnet application during radiation treatment could have affected outcome events.

Our study group reflects experience with only tertiary centres with a high level of expertise in both the radiation and CIED management areas. In these institutions, CIED clinics are readily available for immediate interrogation; monitoring and final outcomes of many of the malfunctions were not available in the database. These factors may limit the applicability of our conclusions.

### Conclusions

With longer life expectancy, the volume of patients who have both a CIED and malignancy is increasing; cardiologists are expected to care for a growing number of patients with CIEDs who undergo RT. A standardized protocol for collaboration between the radiation oncology and cardiology departments is essential to ensure the safety of patients with CIEDs undergoing RT. CIED malfunctions are uncommon in real-world patients and are associated with either no or minor clinical events. The use of close CIED monitoring during and after RT may improve CIED event detection, especially in patients receiving high-energy beam RT.

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### Disclosures

The authors have no conflicts of interest to disclose.

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