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Radiotherapy-induced Cardiac Implantable Electronic Device Dysfunction in Patients with Cancer

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Running title: Radiotherapy-induced CIED dysfunction

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Abstract

Radiotherapy can affect the electronic components of a cardiac implantable electronic device (CIED) resulting in malfunction and/or damage. We sought to assess the incidence, predictors and clinical impact of CIED dysfunction (CIED-D) following radiotherapy for cancer treatment. Clinical characteristics, cancer and different types of CIEDs as well as radiation-dose were evaluated. The investigation identified 230 patients; mean age 78±8 years and 70% were male. A total of 199 (86%) patients had pacemakers (59% dual-chamber), 21 (9%) cardioverter-defibrillators and 10 (4%) resynchronizators/defibrillators. The left pectoral (n=192, 83%) was the most common CIED location. Sixteen (7%) patients experienced 18 events of CIED-D after radiotherapy. Reset to back-up pacing mode was the most common encountered dysfunction, and only 1 (6%) patient of those with CIED-D experienced symptoms of atrio-ventricular dys-synchrony. Those who had CIED-D had a shorter device-age at the time of radiotherapy compared to those who did not (2.5±1.5 vs. 3.8±3.4 years, *P*=0.005). The total dose prescribed to the tumor (66±30 vs. 42±23 Gy) was significantly higher among those who had CIED-D (P<0.0001). Multivariable logistic regression analysis identified the total dose prescribed to the tumor as the only independent predictor for CIED-D (odds ratio: 1.19 for each increase in 5 Gy, 95% confidence interval: 1.08-1.31, P=0.0005). In conclusion, in this large population of patients with CIEDs undergoing radiotherapy for cancer treatment, the occurrence of newly diagnosed CIED-D was 7%, and the reset to back-up pacing mode was the most common encountered dysfunction. The total dose prescribed to the tumor was a predictor of CIED-D. Importantly, although the unpredictability of CIEDs under radiotherapy is still an issue, none of our patients experienced significant symptoms, life-threatening arrhythmias or conduction disorders.

Key-words: radiotherapy - cancer - pacemaker - implantable defibrillator - malfunction

Introduction

Radiotherapy is a well-established treatment in oncology and about two-third of the patients with cancer undergo radiotherapy.[1-4] Importantly, the GLOBOCAN series of the International Agency for Research on Cancer estimated that 14.1 million of new cancer cases were diagnosed in 2012 worldwide, with incident rates expected to increase, and a projected number of 22.2 million by 2030.[3, 5, 6] It is therefore expected that the number of patients requiring radiotherapy for cancer treatment will continue to rise. Notably, together with the rapidly ageing population, the implantation of cardiac implantable electronic devices (CIED) is also increasing.[7, 8] Ionizing radiation can affect the electronic components of CIED resulting in transient or permanent malfunction, but is unforeseeable.[9-12] Previous small studies reported an incidence of CIED dysfunction (CIED-D) that widely varies from 3% up to 79%.[12-17] Therefore, identifying patients at risk of developing CIED-D would be of high clinical relevance in the current cardio-oncology era. Hence, the aims of this study were to assess the incidence, predictors and clinical impact of CIED-D in a large cohort of patients undergoing radiotherapy for cancer treatment.

Methods

Between February 2007 and November 2013, a total of 23100 patients underwent a course of radiotherapy for cancer treatment at the Radiation Oncology Center, Quebec University Hospital Centre. Of these, 262 patients were found to have previous CIED and 32 of them were excluded due to incomplete data, leading to a study population of 230 patients. Baseline clinical and echocardiographic data, cancer types and CIEDs types were retrospectively evaluated. In order to further assess the potential impact of different cancer's location, cancers were divided based on the mid-line of the body as left side, right side or center. Zones of radiation-exposure were classified from the head to the lower limb (Figure 1).

Radiotherapy was delivered using photons and/or electrons beams. The majority of treatments were delivered by a medical linear accelerator (LINAC) and only few cases involved an x-ray tube (orthovoltage treatments) or Cobalt-60 radiation source. Techniques used to treat patients were 3DCRT, IMRT, VMAT and orthovoltage. None of the patient was treated with a CIED exposed to the primary radiation field. Lead shielding was used according to medical physicists' recommendations.

Electronic devices were interrogated at the beginning, mid-period and/or at the end of treatment depending on the planned fraction number. All CIED interrogations were performed by experienced electrophysiology technicians and supervised by a cardiologist at the pacemaker-clinic. In the case of any CIED-D, the date was recorded, and then allocated to the correspondent phase of treatment where the disturbance was discovered (i.e. mid or end of radiotherapy). An experienced cardiologist (VG) unaware of clinical and radiotherapy data performed a thorough interrogatory in order to assess for patients' symptoms and its correlation with CIED-D. Data were prospectively collected in a dedicated file, then retrospectively analyzed for the purpose of this study. Device relocation before the initiation of radiotherapy was performed when the maximum tolerated dose to the CIED would not be respected due to a direct or close (<3 cm) to the radiation beam. Upon recommendations,[18] in order to assess for potential transient CIED-D that can be detected in a "real-time" manner, patients were placed under telemetry for remote monitoring during each fraction treatment done by a dedicated nurse at the coronary care unit. Finally, the cardiologist prescribed installation of a magnet over the CIED during radiation treatment (usually in patients with ICDs) as needed.

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as n (%). Comparison of continuous variables was performed using the two-sided

Student's t-test or Welch's unequal variances t-test when appropriated, and categorical variables were compared using the Exact Chi-square test. Odds ratios (OR) and their 95% Wald confidence intervals were calculated. Bonferroni corrected method was used for multiple comparisons to analyze the differences between types of cancer. A stepwise logistic regression analysis including variables with a P-value <0.05 in the bivariate analysis were used to identify the independent predictors of CIED-D. Odds ratios estimates were adjusted for confounders, such as the total dose prescribed to the tumor in a logistic regression model. Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminatory power of the independent predictor of CIEDs, and to calculate an optimal cut-off value and its respective sensitivity and specificity percentages using Youden's index. All statistical tests were two-tailed and differences were considered statistically significant when a P-value was <0.05. Data analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The mean patient's age was 78±8 years and 70% were male. A total of 199 (86%) patients had pacemakers (59% dual-chamber and 28% single-chamber), 21 (9%) ICDs, and 10 (4%) ICD-resynchronization therapy. Sick sinus syndrome (n=107, 47%) followed by advanced and/or third degree atrio-ventricular block (n=95, 41%) were the most common underlying causes for CIED implantation, and 76 (33%) patients were pacing-dependent. A total of 21 (9%) patients underwent device relocation prior to the initiation of radiotherapy treatment. The left pectoral was the most common location (n=192, 83%) of CIED and 51 (22%) patients received a magnet over their CIED during radiotherapy session. The zone 3 was the most common (n=106, 46%) zone exposed to radiotherapy and most of cancers were centre-located (n=117, 51%). The mean

total dose prescribed to the tumor was 43.3±24.2 Gray (Gy). The remaining characteristics of the study population are presented in Table 1.

A total of 16 (7%) patients experienced 18 events of CIED-D, and the reset to back-up pacing mode was the most common encountered dysfunction. These findings were discovered at the end-of-the-treatment CIED interrogation visit in two-third of the patients. No transient CIED-D was detected while patients were under telemetry monitoring. Only 1 (6%) patient of those with CIED-D experienced symptoms compatible with atrio-ventricular dys-synchrony. Characteristics of patients with and without new-onset CIED-D are shown in Table 2. There were no differences between types of CIED. Patients who experienced CIED-D after radiotherapy had a shorter device-age at the time of radiotherapy initiation (2.5±1.5 vs. 3.8±3.4 years, P=0.005); however, this could not be confirmed in the multivariable analysis. There was a trend towards to be pacing-dependent among those who had CIED-D (56% vs. 31%, P=0.054). Patients experiencing CIED-D more often underwent device relocation before the initiation of radiotherapy (25% vs. 8%, P=0.045). Notably, CIED-D occurred more frequently with a higher total dose prescribed to the tumor (66±30 vs. 42±23 Gy, P<0.0001). The mean prescribed dose was higher for patients in whom CIEDs were relocated prior to the initiation of radiotherapy (55.7±29.9 vs 42.1±23.3 Gy, P=0.013). Logistic regression analysis showed an association of CIED relocation before radiotherapy with CIED-D (OR: 3.86, confidence interval [CI]: 1.12-13.29, P=0.032); however, not statistically significant after adjusting for the total dose prescribed (OR: 2.65, CI: 0.69-10.23, P=0.16). Total dose prescribed to the tumor was identified as the only independent predictor for CIED-D (OR: 1.19 for each increase in 5 Gy, 95% CI: 1.08-1.31, P=0.0005). A dose of ≥44.5 Gy was identified as the optimal cut-off point with a sensitivity of

0.88 and specificity of 0.56 for the prediction of CIED-D, with an area under the ROC curve of 0.76 (95% CI: 0.65-0.87, P<0.001, Figure 2) and a negative predicted value of 0.98.

Discussion

In this large contemporary cohort of patients with previous CIED undergoing radiotherapy for cancer treatment, radiotherapy-induced new-onset CIED-D was 7%. The reset to back-up pacing mode was the most common encountered dysfunction, and only 1 (6%) patient of those with CIED-D experienced symptoms such as atrio-ventricular dys-synchrony. A higher prescribed dose to the tumor was the strongest predictor of CIED-D. Notably, none of the patients experienced significant symptoms, life-threatening arrhythmias or conduction disorders.

Old-generation CIEDs were manufactured with simple electronic circuitry and thus, ionizing radiation had no or little harmful effect. With the evolving technology, newer-generation of CIEDs comprise more sophisticated and complex electronics components such as, complementary metal-oxide semiconductors in the integrated circuitry.[3, 10, 12, 14, 18, 19] When these semiconductors are exposed to ionizing radiation, the damage affects the silicon leading to the oxidation of insulators within the semiconductor.[10, 12, 20-22] In our study, a shorter device age was associated with higher likelihood of CIED-D in the univariate analysis, however, not supported by multivariate analysis. In this regard, while some studies support the fact of newer-generation devices being more sensitive, others do not and in fact, state that are more resistant to radiotherapy-exposure.[9, 14, 19, 23] The cumulative dose, location of the device, and type of radiation have been associated with CIED-D.[1, 10, 13, 14, 21, 22, 24, 25] Interestingly, previous studies have shown that device malfunction can occur even at very low[13, 26] accumulated doses whilst others tolerate much higher accumulated doses before its point of failure.[9, 14] The threshold for the cumulative dose to a CIED is incremental above 2 Gy as suggested by the American Association of

Physicists in Medicine guidelines.[10] Further, Hurkmans et al.,[1] classified patients receiving an estimated dose to their CIED of <2 Gy as low risk (unless pacing dependent since then they were medium risk), between 2-10 Gy as medium risk, and >10 Gy as high risk.

The cancer location/radiation zone seems to be an important factor. Indeed, patients receiving radiotherapy from the lower portion of the neck up to the upper portion of the thorax (Figure 1, zones 2 and 3) are at higher-risk of CIED-D as suggested by the Dutch[1] and German guidelines.[3] Moreover, if cancer/radiation-exposure is associated with an estimated dose to the CIED that exceeds >10 Gy, CIED relocation is then recommended.[1, 3] Of note, it has been reported that when radiotherapy is applied to the abdomen, pelvis or lower extremities, patients experienced higher rates of CIED-D.[27-29] In our study, neither the radiated zone, nor cancer location side was associated with increased rates of CIED-D. Importantly, no studies to date have specifically reported the relocation of CIED as a protective factor for device malfunction after radiotherapy. The results of the present study suggest that CIED relocation did not protect the occurrence of CIED-D. It should be noted that our analysis between relocation and dysfunction was adjusted for prescribed dose. Thus, if the relocation had really been protective, then for a fixed prescribed dose, we would have seen an OR lower than 1 for relocation. Indeed, even though not statistically significant after adjustment, the obtained OR was 2.65. These results further support that several other mechanisms, such as type of energy and scattered radiation, may contribute to CIED-D beyond direct exposure to ionizing radiation.[13, 27-30] Therefore, this fact needs to be further explored since the avoidance of CIED relocation may contribute to improve logistics, resources, saving costs, and also unnecessary risks inherent to the relocation procedure per-se. Hence, future prospective randomized studies may confirm these results and would let determine if the current practice of CIED relocation will remain recommended.

Recommendations[18] for remote monitoring may differ from the different companies and are, indeed, quite vague; ultimately deferring to the radio-oncology and cardiologist the task for an individualized assessment. Pacing-dependent patients are at higher-risk of sudden cessation of pacing and may result in severe bradycardia and/or hemodynamic instability, as well as those with ICDs, would be a subject of patients that will benefit for continuous cardiac monitoring during each fraction/session of radiotherapy. Two-third of our patients who experienced CIED-D, events were encountered at the end-of-the-treatment device-interrogation visit, highlighting therefore that an earlier visit to the pacemaker-clinic would be advisable. Particularly, to identify patients who experienced any CIED-D, that although asymptomatic, require reprogramming, mostly patients with dual-chamber CIED and/or ICDs. Importantly, although the unpredictability of radiotherapy on CIED function remains an important issue, none of our patients experienced significant symptoms, life-threatening arrhythmias or conduction disorders.

The present study has several limitations. The main lies with the retrospective nature of the study; therefore, the crude effect of certain variables that appeared to account more frequently in some group might be affected by confounding variables. Bivariate analyses in this context can be used to verify the presence of association with CIED-D, but not to establish a causal effect relationship. The estimated dose to the device and different beam energy (high or low) or type (photons or electrons) were not collected, precluding the availability to perform further analyses. Finally, late follow-up beyond the end of radiotherapy treatment (i.e. months) was not systematically performed; thus, impeding the capture of potential long-term and/or delayed effects of radiotherapy on CIED.

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Figures legends

Figure 1. Cancer zones. Zone 1, upper head: virtual line including nose-ears. Zone 2, lower head and neck: virtual line below nose-ears and up to the neck. Zone 3: chest and pectoral including shoulders and upper third of the arms. Zone 4: abdomen and including medium third of the arms. Zone 5: pelvis and including lower third of the arms and upper third of the lower limb. Zone 6: medium and lower thirds of lower limb.

Figure 2. Receiver-operating characteristic (ROC) curve showing the sensitivity and specificity of the total prescribed dose to the tumor that best predicted the occurrence of cardiac implantable electronic device dysfunction.

Table 1. Baseline clinical characteristics and cancer-related variables of the study population

Clinical characteristics	**n=230**
Age (years)	78±8
Male sex	160 (70%)
Body mass index (kg/m^2)	26±4
Diabetes mellitus	57 (25%)
Hypertension	171 (74%)
History of heart failure	62 (27%)
Chronic atrial fibrillation/flutter	111 (48%)
Previous myocardial infarction	66 (29%)
Previous percutaneous coronary intervention	38 (17%)
Prior coronary artery bypass grafting	47 (20%)
Cerebrovascular disease	21 (9%)
Peripheral vascular disease	30 (13%)
Chronic obstructive pulmonary disease	44 (19%)
Estimated glomerular filtration rate (mL/min/1.72m^2)	79±30
Chronic kidney disease	49 (21%)
Echocardiographic data	
Left ventricular ejection fraction (%)	50±16
Left ventricular ejection fraction <40%	34 (28%)
Pulmonary artery systolic pressure (mmHg)	32±10
Underlying conduction disorder or disease	
Sick sinus syndrome	107 (47%)
Second or third-degree atrio-ventricular block	95 (41%)
Bifascicular block plus first-degree atrio-ventricular block	2 (1%)
Sudden cardiac death prevention and/or advanced heart failure	26 (11%)
Cardiac implantable electronic devices data	
Permanent pacemakers	
Dual-chamber	135 (59%)
Single-chamber	64 (28%)
Cardioverter defibrillators	21 (9%)
Cardioverter defibrillators and resynchronizators	10 (4%)
Age of the device at time of radiotherapy (years)	3.7±3.4
Pacemaker dependency*	76 (33%)
Device localization regarding radiation field	
Left pectoral	192 (83%)

Right pectoral	32 (14%)
Abdominal	6 (3%)
Device relocation before radiotherapy	21 (9%)
Magnet over the CIED	51 (22%)
New-onset cardiac electronic device dysfunction	16 (7%)
Type of cancer	
Brain/cranial	10 (4%)
Oto-rhino-laryngological	17 (7%)
Esophageal and gastric	11 (5%)
Lung and pleural	57 (25%)
Breast	35 (15%)
Colorectal	13 (6%)
Prostate	48 (21%)
Lymphoma	11 (5%)
Multiple myeloma	7 (3%)
Uro-genital	13 (6%)
Bone	2 (0.9%)
Skin	3 (1.3%)
Other	3 (1.3%)
Radiation-exposure zone*	
1	13 (6%)
2	22 (10%)
3	106 (46%)
4	21 (9%)
5	83 (36%)
6	2 (1%)
Cancer localization side**	
Left side of the body	57 (25%)
Right side of the body	61 (27%)
Center	117 (51%)
Radiotherapy data	
Total prescribed dose to the tumor (Gray)	43.3±24.2

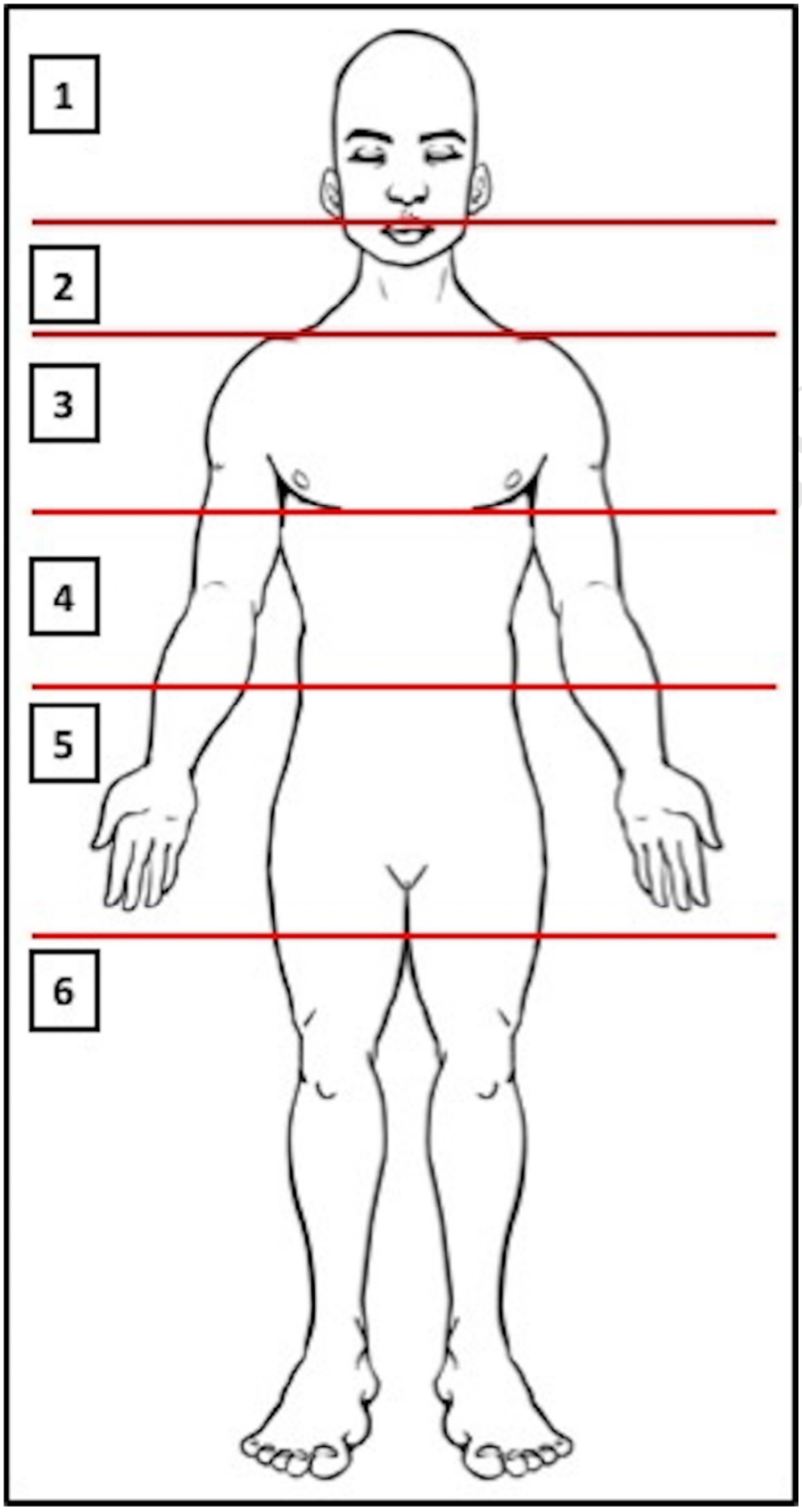
Values are expressed as mean±SD or n (%) unless otherwise noted. CIED: cardiac implantable electronic device. Chronic kidney disease: estimated glomerular filtration rate <60 mL/min/1.72m^2. Some percentages may not add up to 100 because of rounding. *Pacemaker dependency: absence of an intrinsic rhythm above 30-35 beats/min after switching off the pacemaker and therefore, needing a back-up pacing. Some percentages may not add up to 100 because of rounding and/or because 17 patients had 2 affected adjacent zones* and 5 patients had 2 affected sides**.

Table 2. Baseline clinical characteristics and cancer-related variables of patients with new-onset cardiac implantable electronic device dysfunction

Clinical characteristics	New-onset CIED dysfunction		*P*-value
	YES (n=16)	NO (n=214)	
Age (years)	77±7	78±8	0.61
Male sex	9 (56%)	151 (71%)	0.26
Body mass index (kg/m^2)	27±3	26±4	0.63
Diabetes mellitus	4 (25%)	53 (25%)	1.00
Hypertension	13 (81%)	158 (74%)	0.58
History of heart failure	3 (19%)	59 (28%)	0.58
Chronic atrial fibrillation/flutter	9 (56%)	102 (48%)	0.61
Previous myocardial infarction	7 (44%)	59 (28%)	0.25
Previous percutaneous coronary intervention	4 (25%)	34 (16%)	0.48
Prior coronary artery bypass grafting	6 (38%)	41 (19%)	0.10
Cerebrovascular disease	1 (6%)	20 (9%)	1.00
Peripheral vascular disease	3 (19%)	27 (13%)	0.70
Chronic obstructive pulmonary disease	3 (19%)	41 (19%)	1.00
Estimated glomerular filtration rate (mL/min/1.72m^2)	76±29	79±30	0.78
Chronic kidney disease	6 (38%)	43 (20%)	0.12
Echocardiographic data			
Left ventricular ejection fraction (%)	44±16	50±15	0.25
Left ventricular ejection fraction <40%	4 (36%)	30 (27%)	0.73
Pulmonary artery systolic pressure (mmHg)	35±9	32±10	0.38
Underlying conduction disorder or disease			
Sick sinus syndrome	9 (56%)	98 (46%)	0.75
Second or third degree atrio-ventricular block	5 (31%)	90 (42%)	
Bifascicular block plus first-degree atrio-ventricular block	0	2 (1%)	
Sudden cardiac death prevention and/or advanced heart failure	2 (13%)	24 (10%)	
Cardiac implantable electronic devices data			
Permanent pacemakers			0.29
Dual-chamber	10 (63%)	125 (58%)	
Single-chamber	4 (25%)	61 (29%)	
Cardioverter defibrillators	1 (6%)	20 (9%)	
Cardioverter defibrillators and resynchronizators	2 (13%)	8 (4%)	
Age of the device at time of radiotherapy (years)	2.5±1.5	3.8±3.4	0.005
Pacemaker dependency*	9 (56%)	67 (31%)	0.054

Device localization regarding radiation field			
Left pectoral	11 (69%)	180 (84%)	
Right pectoral	3 (19%)	29 (14%)	0.58
Abdominal	2 (13%)	5 (2%)	
Device relocation before radiotherapy	4 (25%)	17 (8%)	0.045
Magnet over the CIED	5 (31%)	46 (22%)	0.53
Type of cancer			
Brain/cranial	0	10 (5%)	1.00
Oto-rhino-laryngological	1 (6%)	16 (7%)	1.00
Esophageal and gastric	1 (6%)	10 (5%)	1.00
Lung and pleural	3 (19%)	54 (25%)	1.00
Breast	6 (38%)	29 (14%)	0.27
Colorectal	0	13 (6%)	1.00
Prostate	5 (31%)	43 (20%)	1.00
Lymphoma	0	11 (5%)	1.00
Multiple myeloma	0	7 (3%)	1.00
Uro-genital	0	13 (6%)	1.00
Bone	0	2 (0.9%)	1.00
Skin	0	3 (1.4%)	1.00
Other	0	3 (1.4%)	1.00
Radiation-exposure zone*			
1	0	13 (6%)	0.61
2	1 (6%)	21 (10%)	0.72
3	9 (56%)	97 (45%)	0.44
4	1 (6%)	20 (9%)	1.00
5	5 (31%)	78 (36%)	0.79
6	0	2 (0.9%)	1.00
Cancer localization side**			
Left side of the body	4 (25%)	53 (25%)	1.00
Right side of the body	6 (38%)	55 (26%)	0.38
Center	7 (44%)	110 (51%)	0.61
Radiotherapy data			
Total prescribed dose to the tumor (Gray)	66±30	42±23	<0.0001

Values are expressed as mean±SD or n (%) unless otherwise noted. CIED: cardiac implantable electronic device. Chronic kidney disease: estimated glomerular filtration rate <60 mL/min/1.72m^2. Some percentages may not add up to 100 because of rounding. *Pacemaker dependency: absence of an intrinsic rhythm above 30-35 beats/min after switching off the pacemaker and therefore, needing a back-up pacing. Some percentages may not add up to 100 because of rounding and/or because 17 patients had 2 affected adjacent zones* and 5 patients had 2 affected sides**.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