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META-ANALYSIS

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A systematic review and meta-analysis on oncological radiotherapy in patients with a cardiac implantable electronic device: Prevalence and predictors of device malfunction in 3121 patients

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Abstract

Background: The number of patients with cardiac implantable electronic devices (CIEDs) undergoing radiotherapy (RT) for cancer treatment is growing. At present, prevalence and predictors of RT-induced CIEDs malfunctions are not defined.

Methods: Systematic review and meta-analysis conducted following the PRISMA recommendations. PubMed, Scopus and Google Scholar were searched from inception to 31/01/2022 for studies reporting RT-induced malfunctions in CIEDs patients. Aim was to assess the prevalence of RT-induced CIEDs malfunctions and identify potential predictors.

Results: Thirty-two out of 3962 records matched the inclusion criteria and were included in the meta-analysis. A total of 135 CIEDs malfunctions were detected among 3121 patients (6.6%, 95% confidence interval [CI]: 5.1%–8.4%). The pooled prevalence increased moving from pacemaker (PM) to implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy and defibrillator (CRT-D) groups (4.1%, 95% CI: 2.9–5.8; 8.2% 95% CI: 5.9–11.3; and 19.8%, 95% CI: 11.4–32.2 respectively). A higher risk ratio (RR) of malfunctions was found when neutron-producing energies were used as compared to non-neutron-producing energies (RR 9.98, 95% CI: 5.09–19.60) and in patients with ICD/CRT-D as compared to patients with PM/CRT-P (RR 2.07, 95% CI: 1.40–3.06). On the contrary, no association was found between maximal radiation dose at CIED >2 Gy and CIEDs malfunctions (RR 0.93; 95% CI: 0.31–2.76).

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Conclusions: Radiotherapy related CIEDs malfunction had a prevalence ranging from 4% to 20%. The use of neutron-producing energies and more complex devices (ICD/CRT-D) were associated with higher risk of device malfunction, while the radiation dose at CIED did not significantly impact on the risk unless higher doses (>10 Gy) were used.

KEYWORDS
cancer, cardiac implantable electronic devices, implantable cardioverter defibrillator, pacemaker, radiation therapy, radiotherapy

1 | INTRODUCTION

The total number of cardiac implantable electronic devices (CIEDs) implanted every year is constantly growing.[1] Similarly, the incidence of cancer patients is expected to increase with population aging.[2] In this context, a rising number of CIED patients will require radiotherapy (RT) for cancer treatment. Therefore, careful patient evaluation and appropriate planning of the RT course planning is crucial to prevent any possible interference with the device. RT-induced CIED malfunctions have been reported with varying prevalence, ranging between 0% and 25%,[3] and can be life-threatening particularly in pacemaker (PM)-dependent and implantable cardioverter defibrillator (ICD) patients.[3,4] At present, only small-scale studies addressed this issue and robust predictors of device malfunction or failure are lacking. Most national and international guidelines and consensus documents[3–6] on this topic suggest a personalized approach to patient management, based on classes of risk for device malfunction. In this regard, several factors related to patient profile (e.g., PM-dependency, prior ICD interventions for ventricular tachyarrhythmias), device type (e.g., PM or ICD) and RT characteristics (e.g., beam energies and radiation dose at CIED) are usually being considered, but most of the recommendations are based on expert opinion, highlighting the need for more solid up-to-date scientific evidence.

The aim of the present systematic review and meta-analysis is to describe the prevalence of RT-induced CIEDs malfunction and to identify potential risk factors, based on data reported so far in the literature.

2 | METHODS

We conducted the present metanalysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations[7,8] and the study protocol was registered with PROSPERO (CRD42022308152).

Highlights

- This is the first meta-analysis investigating the prevalence of RT-related CIEDs malfunctions and its risk factors.
- The pooled prevalence of RT-related CIEDs malfunctions is variable (4%–20%).
- The use of neutron-producing energies is associated with a higher risk of CIED malfunctions as compared to non-neutron-producing energies.
- Similarly, ICD/CRT-D showed a higher risk of malfunctions as compared to PM/CRT-P.
- High radiation dose at CIED (>2 Gy) did not confer a significantly higher risk of CIED malfunctions.

2.1 | Search strategy, study selection, data extraction and quality assessment

We searched multiple electronic records (Pubmed, Scholar and Scopus) for publications from inception to 31/01/2022. The following search terms were used: ("implantable cardioverter defibrillator" OR pacemaker OR CIED OR "cardiac implantable electronic device" OR "cardiac resynchronization therapy") AND (radiotherapy OR radiation OR electromagnetic OR interference). The corresponding MeSH terms are reported in Appendix S1, no language restriction was applied. All titles and abstracts were screened by two independent reviewers (AT and VLM). Studies eligible for full-text evaluation were identified and data extracted on a prespecified spreadsheet for subsequent statistical analysis. Potential disagreements were resolved by a third independent reviewer (JFI). Study inclusion criteria were as follows: (i) original studies including at least four CIED patients (only in vivo studies), (ii) patients implanted with PM or ICD or cardiac resynchronization therapy and pacing (CRT-P)/cardiac resynchronization therapy

and defibrillator (CRT-D) before RT for cancer treatment, and (iii) availability of follow-up data on CIEDs malfunctions. Case reports, paediatric populations and in vitro studies were excluded. Whenever available, the following data were extracted: baseline characteristics of the patients, cancer site, type of CIED implanted, beam energies (neutron- or non-neutron-producing radiation), radiation dose at CIED, and study design. Neutron-producing energy was defined according to the definition provided in each single study. In case it was not clearly stated, the definition provided by Zecchin et al.[3] was used (photon beam energy >6 MV, electron beam energy ≥20 MeV). The risk of bias for each study was assessed using The Newcastle-Ottawa scale for non-randomized cohort studies. We evaluated the following domains: study group selection, study group comparability and outcome assessment; a score ≥7 identified high-quality studies.

2.2 | Endpoints

The endpoints of the present meta-analysis were to describe the prevalence of RT-induced CIED malfunctions and to identify potential predictors of malfunction.

2.3 | Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are reported as counts and percentages.

Two different meta-analysis techniques were used. With the aim to describe the standardized prevalence of malfunction, we conducted a meta-analysis of proportions. Prevalences were transformed using logit transformation and were pooled with the inverse variance method; tau was estimated with the restricted maximum-likelihood (REML) method. To evaluate the presence of potential confounders, we performed a subgroup analysis based on the type of CIED implanted (PM/CRT-P, ICD, CRT-D). We also conducted a multivariable meta-regression using study-level year of publication, device investigated (PM/CRT-P, ICD, CRT-D) and sample size as covariates.

In order to explore potential risk factors for CIEDs failure, we made three pairwise meta-analyses comparing the type of CIED (ICD/CRT-D vs. PM/CRT-P), beam energy (neutron- vs. non-neutron-producing energy) and radiation dose at CIED (>2 Grey [Gy] vs. ≤2 Gy). In order to evaluate also higher dose limits, we performed a proportion and a binary meta-analysis comparing ≤5 Gy vs. >5 Gy and ≤10 Gy vs. >10 Gy doses to the device. Subgroup analysis comparing retrospective and prospective studies was performed. Results were reported as risk ratio (RR) and 95% confidence interval (CI). All meta-analyses were modelled with a random-effect approach and results were graphically reported by forest plots. The I^2 statistic was employed to measure heterogeneity among the studies for each analysis. The following thresholds were applied: low heterogeneity if $I^2 < 25\%$, moderate if I^2 between 25% and 75% and high if $I^2 > 75\%$. If I^2 was >25% we performed a sensitivity analysis using the "leave-one-out" technique. Meta-regression analyses according to study-level year of publication and publication bias was assessed by visual inspection of funnel plots and also using the Egger's test. Data were analysed using R v.4 (R Core Team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing. URL http://www.R-project.org/) with the packages *meta*[9] and *metafor*.[10] A p-value < .05 was considered significant. Reporting of the study conforms to broad EQUATOR guidelines.[11]

3 | RESULTS

3.1 | Study selection and quality of study assessment

A total of 3962 records were obtained through the literature search. Relevant citations were assessed following the Patient/Population, Intervention, Comparison, Outcomes (PICO) process. Thirty-two papers matched the inclusion/ exclusion criteria and were included in the present meta-analysis.[12–43] Figure 1 summarizes the study selection process. The quality assessment performed using the Newcastle-Ottawa scale showed an overall high quality of the studies included (Table S1). Eighteen (56%) studies scored ≥7/9 points,[14,15,19,21–24,26,28,30,32,34,36–41] 12 (38%) studies scored 4–6 points,[12,16–18,20,25,29,31,33,35,42,43] and only 2 (6%) studies scored ≤3 points.[13,27]

3.2 | Studies and patient characteristics

Among the 32 studies considered, 13 (41%) were prospective[12,14–19,21,22,24,33,37,40] and 19 (59%) were retrospective.[13,20,23,25–32,34–36,38,39,41–43] With regard to CIED type, PM/CRT-P were considered in 28 studies,[13,14,16–21,23–26,28–43] ICD in 29 studies[12,13,15,16,19–43] and CRT-D in 12 studies.[22,24,25,28–30,32–34,37,39,43] Publication years ranged from 2002 to 2021. The main characteristics of the included studies are summarized in Table 1.

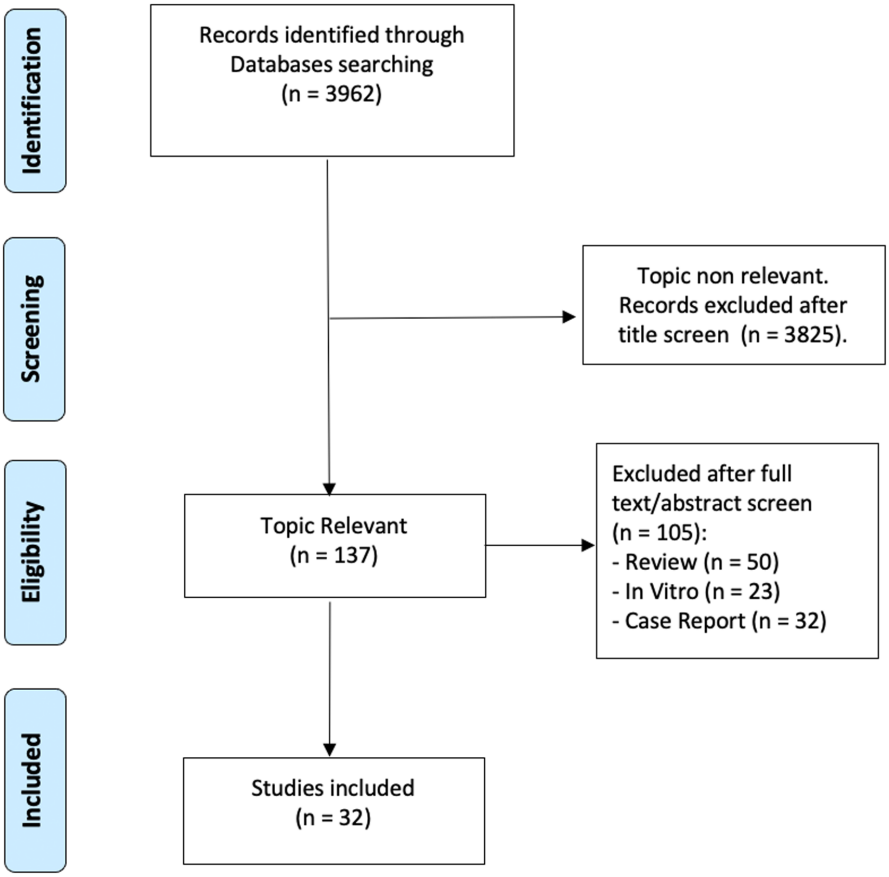

FIGURE 1 Flow diagram showing the study selection process

3.3 | RT-induced CIED malfunctions

3.3.1 | Proportion of malfunctions

A total of 135 CIED malfunctions were detected among 3121 patients (pooled prevalence: 6.6%, 95% CI: 5.1%–8.4%), with a moderate degree of heterogeneity ($I^2 = 41\%$). When analysing data according to the type of CIED, 84 malfunctions were observed among 2359 PM/CRT-P patients across 28 studies (pooled prevalence: 4.1%, 95% CI: 2.9–5.8), 39 malfunctions among 675 ICD patients in 29 studies (pooled prevalence: 8.2% 95% CI: 5.9–11.3) and 12 malfunctions among 87 CRT-D patients in 12 studies (pooled prevalence:19.8%, 95% CI 11.4–32.2), with statistical significance for the difference among subgroups ($p = .0003$) (Figure 2).

Only three malfunctions were reported as potentially life-threatening (two inappropriate shocks and one ventricular tachycardia). Meta-regression showed that the prevalence of device malfunction was associated with device type, particularly CRT-D ($p = .0012$), but not with the sample size ($p = .2031$) or year of publication ($p = .1417$); after the meta-regression, the unaccounted heterogeneity (I^2 residual) was 30%. Among subgroups, we found the highest heterogeneity in the PM/CRT-P group ($I^2 = 45\%$), followed by CRT-D ($I^2 = 8\%$), and ICD ($I^2 = 0\%$). Sensitivity analysis showed a low influence of single studies on pooled prevalence or heterogeneity (Figure S1). Visual inspection of the funnel plots and Egger's test did not show a significant publication bias (Figure S2).

3.3.2 | Analysis of risk factors for RT-associated device malfunctions

The association of RT using neutron-producing energy and CIEDs malfunctions was evaluated in 13 studies including 1350 patients.[17,19,21,22,26,27,29,32,34,36,39–41] The meta-analysis showed that the use of neutron-producing energies was associated with a risk ratio of 9.98 (95% CI: 5.09–19.60) for device malfunctions when compared to non-neutron-producing energies (Figure 3, Panel A). Low heterogeneity was observed among studies ($I^2 = 4\%$).

In 25 studies (3018 patients), it was possible to compare PM/CRT-P versus ICD/CRT-D.[13,16,19–21,23–26,28–43] The meta-analysis showed a risk ratio of 2.07 (95% CI: 1.40–3.06) for malfunctions in ICD/CRT-D patients when compared to PM/CRT-P patients (Figure 3, Panel B), with low heterogeneity ($I^2 = 1\%$). Subgroup analysis confirmed the statistical significance of both associations in retrospective and prospective studies.

TABLE 1 Main characteristics of the included studies and baseline population characteristics

Author, year	Study design	Study period	Patients	Mean age	Females%	Cancer site	Devices *n*	Malfunctions
Hoecht, 2002	Prospective	NR	8	NR	NR	Pelvic	ICD 8	2
Kapa, 2008	Retrospective	2002–2007	13	NR	NR	Lung, Skin, Lymphoma, Pancreas, Thyroid	PM 8 ICD 5	0
Oshiro, 2008	Prospective	2001–2008	8	79	12.5	Liver, Lung	PM 8	2
Gelblum, 2008	Prospective	2005–2007	33	NR	NR	Head and neck, Thorax, Abdomen, Pelvis, Legs	ICD 33	2
Ferrara, 2010	Prospective	1999–2007	45	71.3	18	Head and neck, Thorax, Abdomen, Pelvis	PM 37 ICD 8	0
Wadasadawala, 2010	Prospective	2005–2009	8	67	37.5	Head and neck, Lung, Breast	PM 8	0
Menard, 2010	Prospective	2008–2010	7	68	100	Breast	PM 7	0
Soejima, 2011	Prospective	2006–2008	62	76	27	Lung, Prostate, Oesophageal, Breast, Head and Neck	PM 60 ICD 2	1
Croshaw, 2011	Retrospective	2007–2010	8	79	NR	Breast	PM 5 ICD 3	0
Makkar, 2012	Prospective	2005–2011	69	74.1	27	Head and Neck, Breast, Abdomen, Thorax, Extremities, Oesophagus	PM 50 ICD 19	2
Elders, 2013	Prospective	NR	15	72	13	Head and neck, lung, Abdomen, Pelvis, Legs	ICD 8 CRT-D 7	4
Gomez, 2013	Retrospective	2009–2012	42	NR	NR	Thorax, Prostate, Liver, Skull	PM 28 ICD 14	5
Brambatti, 2015	Prospective	2008–2012	261	78	30	Lung, Skin, Breast, Oesophagus, Others	PM 206 CRT-P 1 ICD 51 CRT-D 3	4
Zaremba, 2015	Retrospective	2003–2012	453	74.7	NR	Head and Neck, Thorax, Abdomen, Pelvis - Oesophagus - Other	PM 370 CRT-P 24 ICD 48 CRT-D 11	14
Grant, 2015	Retrospective	2005–2014	215	73	29	Abdomen, Brain, Chest, Head and Neck, Pelvis	PM 123 ICD 92	16
Hudson, 2017	Retrospective	2008–2012	25	NR	NR	Lung, Rectum, Prostate, Bladder	ICD 25	2
Bagur, 2017	Retrospective	2007–2013	230	78	30	Lung, Skin, Prostate, Lymphoma, Brain	PM 199 ICD 21 CRT-D 10	17
Riva, 2018	Retrospective	2010–2016	63	74.1	11.1	Lung, Prostate, Bladder, Breast, Lymphoma, Uterin	PM 52 ICD 7 CRT-D 4	2
Bravo-Jaimes, 2018	Retrospective	2000–2015	109	79.3	35	Thorax, Abdomen, Pelvis, Other	PM 60 ICD 35 CRT-D 14	6

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Study period	Patients	Mean age	Females%	Cancer site	Devices *n*	Malfunctions
Yeung, 2019	Retrospective	2007–2018	189	78	29.1	Head and Neck, Abdomen, Pelvis, Thorax	PM 159 ICD 29	4
Brouillard, 2019	Retrospective	2007–2013	230	77.6	30.4	Head and Neck, Abdomen, Pelvis, Thorax, Brain	PM 199 ICD 21 CRT-D 10	18
Steger, 2019	Prospective	2014–2018	51	75	23.5	Head and Neck, Abdomen, Pelvis, Thorax, Brain	PM 41 CRT-P 1 ICD 7 CRT-D 2	3
Malavasi, 2019	Retrospective	2004–2018	127	77.8	33	Thorax, Abdomen, Pelvis	PM 99 ICD 14 CRT-D 13 NR 1	3
Seidensaal, 2019	Retrospective	2001–2013	31	72	39	Head and Neck, Thorax, Abdomen, Pelvis, Bone	PM 28 ICD 3	0
Sharifzadehgan, 2020	Retrospective	2006–2017	90	78	27	Head and Neck, Abdomen, Pelvis, Thorax	PM 82 ICD 8	5
Niedziela, 2020	Prospective	2016–2018	157	73	33	Brain, Thorax, Abdomen, Pelvis, Head and Neck	PM 113 ICD 36 CRT-D 8	1
López-Honrubia, 2020	Retrospective	2006–2017	56	78.2	23.2	Head and Neck, Abdomen, Pelvis, Thorax, Brain	PM 49 ICD 7	6
Levis, 2020	Retrospective	2007–2019	34	78	14.7	Lung	PM 24 ICD 6 CRT-D 4	0
Gauter-Fleckenstein, 2020	Prospective	2007–2011	200	73	NR	Head and neck, Thorax, Abdomen, Pelvis, Extremities	PM 108 ICD 92	8
Hamza, 2021	Retrospective	2000–2018	193	76	35	Head and Neck, Abdomen, Pelvis, Thorax, Brain	PM 125 ICD 68	2
Okano, 2021	Retrospective	2010–2019	22	72	31.8	Thorax, Abdomen, Prostate, Liver, Bones	PM 21 ICD 1	0
Hashimoto, 2021	Retrospective	2012–2019	69	81	21.8	Pelvic	PM 64 ICD 4 CRT-D 1	6

Note: References[11–42].

Abbreviations: CRT-D, cardiac resynchronization therapy and defibrillator; CRT-P, cardiac resynchronization therapy and pacing; ICD, implantable cardioverter defibrillator; NR, not reported; PM, pacemakers.

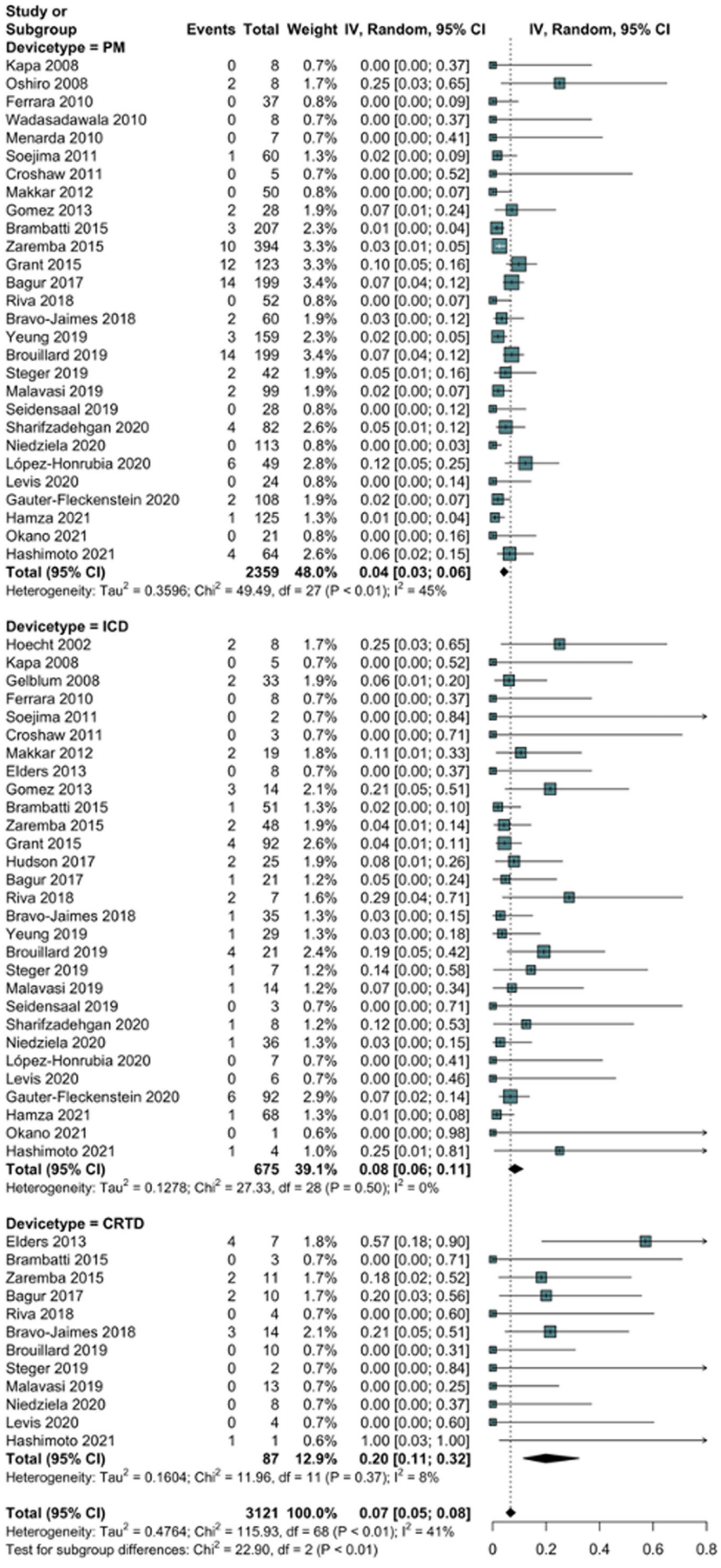

FIGURE 2 Forest plot showing the pooled prevalence of radiation therapy-induced malfunctions in patients with pacemaker, implantable cardioverter defibrillator, and cardiac resynchronization therapy and defibrillator. CRT-D, cardiac resynchronization therapy and defibrillator; ICD, implantable cardioverter defibrillator, PM, pacemaker.

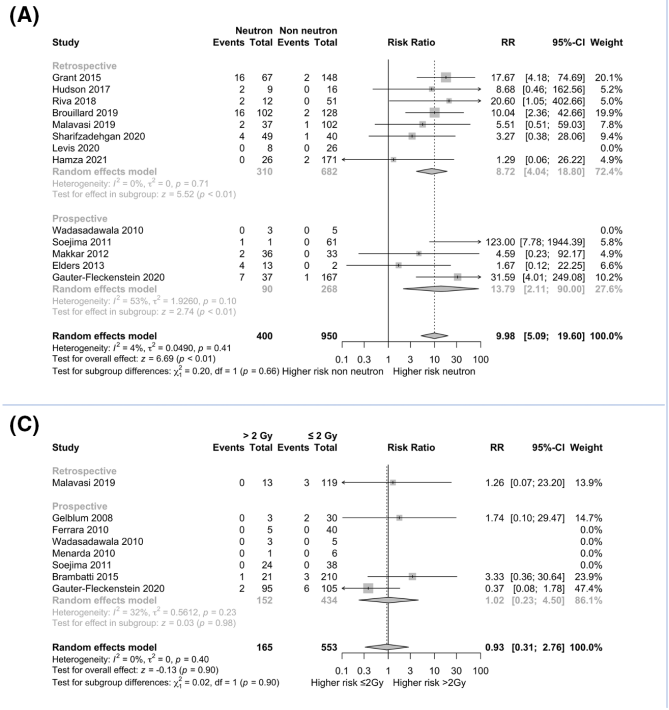

FIGURE 3 Forest plots showing the meta-analysis of risk factors for cardiac implantable electronic device malfunctions associated with radiation therapy. Panel (A) comparison of neutron-producing energies versus non-neutron-producing energies. Panel (B) comparison of PM/ CRT-P versus ICD/ CRT-D. Panel (C) comparison of maximal radiation dose at device >2 Gy versus ≤2 Gy. CI, confidence interval; CRT-D, cardiac resynchronization therapy and defibrillator; CRT-P, cardiac resynchronization therapy and pacing; Dmax, maximal radiation dose at device; Gy, greygray; ICD, implantable cardioverter defibrillator; PM, pacemakers; RR, risk ratio.

TABLE 2 Meta-analysis of risk factors for cardiac implantable electronic devices malfunctions associated with radiation therapy

	Studies (*n*)	Patients (*n*)	Malfunctions (*n*)	Risk ratio (95% CI)	*p*	I^2% (95% CI)	Egger's test *p*
Neutron-producing vs. non-neutron-producing energy	13	1350	65	9.98 (5.09–19.60)	<.0001	4 (0–61.7)	.472
PM/ CRT-P vs. ICD/ CRT-D	25	3018	123	2.07 (1.40–3.06)	.0003	1 (0–49.4)	.074
Dmax ≤2Gy vs. Dmax >2Gy	8	718	17	0.93 (0.31–2.76)	.8983	0 (0–84.7)	.282

Abbreviations: CRT-D, cardiac resynchronization therapy and defibrillator; CRT-P, cardiac resynchronization therapy and pacing; Dmax, maximal radiation dose at device; Gy, grey; ICD, implantable cardioverter defibrillator; PM, pacemakers.

The association between the maximal radiation dose at CIED (Dmax) and malfunctions was explored in eight studies for a total of 718 patients.[15–19,24,34,40] No association was found between Dmax >2 Gy and CIEDs malfunctions as compared to Dmax ≤2 Gy (risk ratio 0.93; 95% CI: 0.31–2.76) (Figure 3, Panel C), with no heterogeneity (I^2 =0%). At subgroup analysis, such an association was neither observed in retrospective nor in prospective studies. Table 2 summarizes the results of the aforementioned pairwise comparisons. Sensitivity analysis are shown in Figures S3–S5. No significant publication bias was detected (Figures S6–S8) Analysing the 5 Gy cut-off, no differences in the proportion of malfunctions were found nor any difference was found in a pairwise comparison (Figures S9 and S10). Some differences were found when taking into consideration the 10 Gy threshold, where the proportion of malfunctions became significantly different (5%, 95% CI: 2–9 in the group ≤10Gy vs. 37%, 95% CI: 8–79 in >10 Gy; p = .02, I^2 =72%), with a risk ratio in the >10 Gy vs. ≤10 Gy group of 13.91 (95% CI: 3.3–58.5; p = .0003; I^2 =41%) (Figures S11 and S12). These results should be taken with caution because in the >5 Gy and >10 Gy groups few patients were actually treated, and the number of malfunctions was small (1/70 in >5 Gy and 5/32 in >10 Gy group).

Specific details on the type of malfunctions, follow-up time, need for relocation, actions needed to sort the malfunctions out and RT energies/doses at cancer/CIED are reported in Tables S2 and S3, respectively.

4 | DISCUSSION

To the best of our knowledge, this is the first meta-analysis investigating the prevalence of RT-related CIEDs malfunctions and its risk factors. The main findings of the present paper are the following: (i) the pooled prevalence of RT-related CIEDs malfunctions is variable, ranging from around 4% to 20%; (ii) the use of neutron-producing energies is associated with a higher risk of CIED malfunctions as compared to non-neutron-producing energies; similarly, (iii) ICD/CRT-D showed a higher risk of malfunctions as compared to PM/CRT-P. On the contrary, (iv) a higher radiation dose, that is, Dmax >2 Gy did not confer a significantly higher risk of CIED malfunctions.

Our study shows that the prevalence of RT-associated CIEDs malfunctions is variable, and this suggests the need for risk stratification on the basis of factors related to the patient, the type of CIED, and the RT procedure. However, it is noteworthy that according to literature only three reported CIED malfunctions were classified as potentially life-threatening, thus highlighting the overall safety profile of RT even in this subset of patients.[38] Our analysis showed a pooled proportion of malfunction probably higher than what reported in a European Heart Rhythm Association survey[44] where approximately 1/3 of the 36 respondent centres reported no malfunction, 1/3 reported malfunction in 2% of the irradiated patients and 11% malfunction in 5%. This could depend on radiation and risk stratification protocols, volume of the centres or other not specified factors. Moreover, the type of feedback that can be obtained through a survey may be quite different from what measured in dedicated studies, either prospective or retrospective.

The use of neutron-producing energies was the strongest predictor of CIEDs malfunctions. This finding is substantiated by experimental data showing that at high beam energies (≥10 MeV), secondary neutrons are produced in the head of the linear accelerator.

We found that the prevalence of malfunctions increased in parallel with the complexity of implanted devices (4.1%, 8.2%, 19.8% for PM/CRT-P, ICD and CRT-D, respectively) and ICD/ CRT-D had a nearly double risk of malfunctions as compared to PM/CRT-P. This association has not yet been fully understood, but it can be speculated that more complex devices (e.g., ICD and CRT-D) contain more complex integrated circuits producing ionizing particles, potentially interacting with secondary neutrons.[45] Nowadays, the circuitry of CIEDs is based on complementary metal-oxide semiconductor (CMOS) technology. It is known that such technology is sensitive to radiation beams employed in RT and secondary neutrons can interact with the CMOS materials.[3,46,47] It has been hypothesized that ICD may be more sensitive to radiation damage due to the larger amount of software and hardware technology inside the device, with higher probability of software errors.[45] The year of study's publication was not associated with malfunctions prevalence, suggesting that modern therapies are as risky as older ones.

With regard to RT doses, we found that a Dmax >2 Gy was not associated with higher risk of device malfunctions. The cut-off value of 2 Gy was chosen according with current guidelines,[3,48] but our sub-analysis failed to reach statistical significance (RR 0.93, 95% CI: 0.31–2.76). In a recent in vitro study,[49] 19 explanted ICDs were irradiated with a 6-MV photon beam reaching an increasing cumulative dose at ICD sites of 0.5, 1, 2, 3, 5 and 10 Gy. After radiation, the authors showed no CIED malfunctions or electromagnetic interferences. These data were confirmed by another even more recent study where, again with 6-MV flattened and flattening-filter-free beams, CIED malfunctions were not related to total dose but seemed to be correlated with instantaneous local dose rate.[50] About the value of 2 Gy as a limit of the energy delivered to the CIED, an aforementioned European Heart Rhythm Association survey[44] reports that only 14% of centres involved in management of patients with CIED undergoing RT considered 2 Gy as risky limit, while 7% of respondent centres considered safe a limit of 5 Gy and another 7% did not take into account safety limits. It is noteworthy that, according to our meta-analysis, the type of CIED and the use of neutron-producing beam energies appear to be actually more important than these safety levels of RT dose. Taken together, these findings highlight that the radiation dose at CIED should not be considered as the most crucial variable during the risk stratification process for CIED patients undergoing RT unless higher doses (>10 Gy) are used. However, in this latest subset of patients, our assessment of the risk could actually be imprecise (with regard to the actual risk), since the values of doses in patients without malfunction were often omitted, resulting in wide confidence intervals and moderate heterogeneity. Nevertheless, overall low exposure is usually delivered at a low dose rate, therefore doses should always be as low as achievable without compromising therapy goals.

In any case, the use of neutron-producing energies should be avoided whenever possible as this dramatically reduces the risk of CIED malfunctions, especially when ICD and CRT-D devices are involved. This should be possible in most patients, as energies >6MV are hardly needed when advanced techniques such as static intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT) are used. The synergy and close collaboration between cardiologists

and radiation oncologists is essential to provide the best management for CIEDs patients undergoing RT.[3,51] Additional risk factors have been hypothesized such as distance between the radiation beam and CIED or subdiaphragmatic site of the cancer,[25] but either inconclusive (RT-beam and CIED distance) or not confirmed results were found. Further research in this field is needed to identify additional predictors of RT-related CIEDs malfunctions, which can be used to create personalized pathways for patient care, with a potentially positive impact not only on clinical outcomes, but also on resource allocation.[52,53] In this perspective, remote monitoring of CIEDs may represent a valuable tool to regularly check the devices' status during the whole duration of the RT course. Remote monitoring has a well-established role in the early detection of CIED technical issues[54] and, integrated with in-office visits, may be useful for a more effective and less expensive patient management.

4.1 | Limitations

The present study has several limitations that need to be acknowledged. The studies included in the meta-analysis were observational and approximately 60% were retrospective, thus data presented do not imply causality, rather they report associations. Nevertheless, for the comparisons associated with a high degree of malfunction, we found a very low heterogeneity and then we think that the signal detected by our analysis is hardly doubtful. Moreover, it is not likely that prospective controlled randomized trials will be performed in this field in the near future. It was not possible to meta-analyse some variables potentially associated with device malfunction such as different Dmax cut-offs, cancer location and distance between radiation beam and the device. Moreover, in all the papers analysed, the time-to-malfunction or follow-up period were not sufficiently detailed to allow a punctual analysis. However, the time-to-event was comparatively reported in Table S2. In most studies, a standardized patient management protocol was not provided, and may have differed between studies. Finally, given the chance that some data were underreported or missed from the literature search, a certain degree of publication bias cannot be ruled out.

5 | CONCLUSIONS

In a systematic review of the current literature, RT-related CIED malfunction had a prevalence ranging from around 4% to 20%. The use of neutron-producing energies and more complex devices (ICD/CRT-D) were associated with higher risk of device malfunction, while the radiation dose at CIED did not significantly impact on the risk of CIED malfunctions unless higher doses (>10 Gy) were used in the RT. Further research is needed to further improve patient risk stratification.

AUTHOR CONTRIBUTIONS

VLM involved in conceptualization, formal analysis, data curation, writing—review and editing. JFI involved in conceptualization, methodology, writing—original draft, and writing—review and editing. AT involved in data curation and investigation. GFR involved in methodology, formal analysis, review and editing. MV, MZ, EM, and GDM involved in investigation, writing—review and editing. FL and GB involved in investigation, writing—review and editing, supervision. TLF involved in writing—review and editing, supervision.

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CONFLICT OF INTEREST

GB: small speaker fee from Medtronic, Boston, Boehringer Ingelheim and Bayer. No fees are received personally. TL small speaker fees from Philips, Janssen and Incyte not related with the current work. The other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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