Malfunction of cardiac devices after radiotherapy without direct exposure to ionizing radiation: mechanisms and experimental data

Massimo Zecchin[1]*, Gaetano Morea[1], Mara Severgnini[2], Elisabetta Sergi[3], Anna Baratto Roldan[3], Elisabetta Bianco[1], Silvia Magnani[1], Antonio De Luca[1], Anna Zorzin Fantasia[1], Luca Salvatore[1], Vittorino Milan[4], Gianrossano Giannini[3], and Gianfranco Sinagra[1]

[1]Cardiovascular Department, University and Hospital, Trieste, Italy; [2]Department of Medical Physics, University and Hospital, Trieste, Italy; [3]Department of Physics, University, Trieste, Italy; and [4]Radiotherapy Department, University and Hospital, Trieste, Italy

Accepted after revision 29 June 2015

Aims Malfunctions of cardiac implantable electronical devices (CIED) have been described after high-energy radiation therapy even in the absence of direct exposure to ionizing radiation, due to diffusion of neutrons (n) causing soft errors in inner circuits. The purpose of the study was to analyse the effect of scattered radiation on different types and models of CIED and the possible sources of malfunctions.

Methods and results Fifty-nine explanted CIED were placed on an anthropomorphous phantom of tissue-equivalent material, and a high-energy photon (15 MV) radiotherapy course (total dose = 70 Gy) for prostate treatment was performed. All devices were interrogated before and after radiation. Radiation dose, the electromagnetic field, and neutron fluence at the CIED site were measured. Thirty-four pacemakers (PM) and 25 implantable cardioverter-defibrillators (ICD) were analysed. No malfunctions were detected before radiation. After radiation a software malfunction was evident in 13 (52%) ICD and 6 (18%) PM; no significant electromagnetic field or photon radiations were detected in the thoracic region. Neutron capture was demonstrated by the presence of the $^{198}Au(^{197}Au + n)$ or $^{192}Ir(^{191}Ir + n)$ isotope activation; it was significantly greater in ICD than in PM and non-significantly greater in damaged devices. A greater effect in St Jude PM (2/2 damaged), Boston (9/11), and St Jude ICD (3/6) and in older ICD models was observed; the year of production was not relevant in PM.

Conclusion High-energy radiation can cause different malfunctions on CIED, particularly ICD, even without direct exposure to ionizing radiation due to scattered radiation of neutrons produced by the linear accelerator.

Keywords CIED malfunction • Radiotherapy • Soft errors • Scattered radiation • Implantable cardioverter-defibrillator • Pacemaker

Introduction

Radiotherapy is a widely used treatment for several malignancies and its rate increased of nearly 200% in the last decade in pacemaker (PM) and implantable cardioverter-defibrillator (ICD) patients.[1] As ionizing radiation can lead to cardiac implantable electronical devices (CIED) malfunctions, every effort is usually made to focus the beam away from the device, according to the document published in 1994 by the American Association of Physicists in Medicine.[2] Nevertheless, a damage is possible even if the target of the therapy is far from the thorax, especially if directed to deep structures (as prostate, bladder, and gut), and X-ray production is achieved by the emission of high-energy electrons from the linear accelerators (LINACs).[3,4] At photon beam energies >10 MV, neutrons are produced by a reaction in the head of the LINAC; these neutrons can be captured in CIED mainly by boron and lithium

* Corresponding author. Tel: +39 040 399 4828; fax: +39 040 399 4878, *E-mail address*: massimo.zecchin@alice.it, massimo.zecchin@aots.sanita.fvg.it

What's new?

- During radiotherapy, the risk of CIED malfunctions is frequently under-estimated in the absence of direct exposure to ionizing radiation; nevertheless, to reach deep structures, X-ray production can be achieved by the emission of high-energy electrons from the linear accelerators, with the production of scattered neutrons causing soft errors in inner circuits.
- At devices interrogation, performed after a simulation of radiotherapy treatment for prostatic cancer on an anthropomorphous phantom of tissue-equivalent material, permanent malfunctions were frequently observed.
- Malfunctions were more frequent in ICDs than in PMs and in older ICD (but not PM) compared with more recent models; different effects were observed among manufacturers.
- No significant electromagnetic field or photon radiations were detected in the thoracic region during radiotherapy.
- Neutron capture was demonstrated by the presence of the $^{198}Au(^{197}Au + n)$ or $^{192}Ir(^{191}Ir + n)$ isotope activation in the devices; it was significantly greater in ICD than in PM and non-significantly greater in damaged devices.

contained in memories and battery (*Figure 1*) and this can be source of PM and ICD malfunctions due to soft errors.[5] In a population study,[1] a low risk of damages was detected, but a beam energy $\geq$15 MV, often used for the treatment of sub-diaphragmatic tumours, was the greatest predictor of malfunctions, particularly electrical reset. Very recently, German guidelines developed by the German Society of Radiation Oncology (DEGRO) and the German Society of Cardiology[6] and a detailed review of the literature by Zaremba *et al.* were published.[7] However, the incidence, precise mechanism, and the variety of effects on different devices are still unknown.

The aim of our experimental study was to assess the risk and the mechanism of malfunctions in several CIED (both PM and ICD) placed on a neutron tissue-equivalent anthropomorphous phantom exposed to high-energy radiation, simulating a course of treatment for prostate cancer.

Methods

All CIEDs explanted for any reason (except malfunction of generator) from 1 July 2013 to 31 August 2014 and never previously exposed to radiations were analysed.

To simulate a radiotherapy course for prostatic cancer, a 15 MV X-ray radiotherapy treatment with a dose of 70 Gy was performed by a LINAC Varian Clinac 2100C (15 MeV).

For the purpose of the study, two anthropomorphous phantoms designed for neutron dosimetry by a group of researchers of the National Institute for Nuclear Physics according to the indications of the International Commission on Radiological Protection[8] were used. Before 24 June 2014, a phantom made up of seven sheets of plexiglass and a central sheet of polyethylene (with a hydrogen composition similar to the human tissue and therefore equivalent with regard to neutron absorption), weighing ~37 kg (Jimmy) was used; afterwards, another phantom (Ryan), all made of polyethylene and assembled by employing

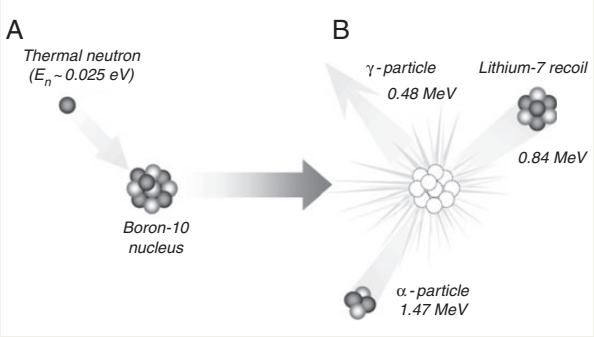

Figure 1 Effect of thermal neutrons (*A*) interaction with Boron producing (*B*) ionizing particles (α).

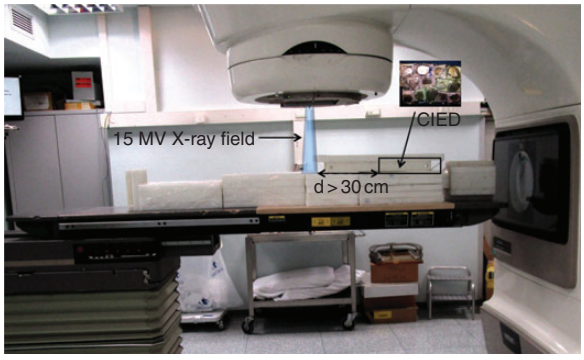

Figure 2 One of the two antropomorphous phantoms (Ryan) designed for neutron dosimetry according to the indications of the International Commission on Radiological Protection,[8] the minimum distance between cardiac implantable electronical devices (CIED), positioned under a polyethylene layer of 3 cm (simulating for neutrons the adipose tissue and skin) and the radiation field (30 cm) is pointed out.

the size of the average man (71 kg), was used, as Jimmy was no longer available. All devices were positioned, in several sessions, on the phantom, in a site equivalent to the pectoral region, under a polyethylene layer of 3 cm simulating for neutrons the adipose tissue and skin (*Figure 2*).

Radiation dose and neutron uptake at the CIED site were measured. To quantitatively evaluate the radiation gamma-dose absorbed by the CIED, a dosimetric film GAFCHROMIC-EBT2 was used. Neutron dose was measured with bubble dosimeters for both thermal and fast neutrons and with CR-39 track detectors.

The radiation emitted by the devices before and after radiotherapy was used to assess whether their activation could be associated with the capture of thermal neutrons. For this purpose, we used a High Purity Germanium detector for gamma spectrometry as already indicated by Koivunoro *et al.*[9]

The presence of any significant electromagnetic field was evaluated by a specific ElectroMagnetic (EM)-field measuring device (PMM 8035A with a EP300 probe).

After radiation, all devices were interrogated again.

All the test results were affected by a statistical error of ~10%.

Data were presented as mean and standard deviation or count and percentages, as appropriate. Comparison between groups was made by using the ANOVA test for continuous parameters and χ^2 for discrete variables.

Results

Fifty-nine devices from several manufacturers (34 PM: 10 Boston Scientific/Guidant/Intermedics, 9 Medtronic/Vitatron, 10 Biotronik, 3 Sorin, and 2 St Jude Medical; 25 ICDs: 11 Boston Scientific/Guidant, 7 Medtronic, and 7 St Jude Medical) were analysed (*Table 1*). Most devices ($n = 43$, 73%) were explanted because of nearly depleted battery although still working. Some devices were explanted because of lead malfunction/infection ($n = 6$, 10%), system upgrading ($n = 2$, 3.5%), or death ($n = 2$, 3.5%). In six patients (10%), the reason of explant was not available.

The interval between market release and the analysis was 12 ± 3 and 9 ± 2 years for PM and ICD, respectively. Medtronic models were the oldest (15.1 ± 0.3) PM, while Boston (9.5 ± 1.4 years) and St Jude (9.9 ± 1.5 years) were the oldest ICD.

At baseline interrogation, performed just before irradiation, all CIED were working and no malfunctions were detected.

After radiation delivery, battery depletion was excluded because battery voltage and impedance values were unchanged.

A software malfunction was evident in 13 (52%) ICD and 6 (18%) PM. Different kinds of soft errors were detected, or at least different responses to the interrogation were given by the programmer (*Table 2*): an electrical reset was present in two PM and one ICD, backup to VVI mode in two PM (all the St Jude models), a 'failure of the pulse generator' in seven ICD (in all cases Renewal 3 or 4, Boston Scientific); one PM and three ICD were impossible to interrogate, in one ICD the programming was found to be changed and in one ICD the response to magnet was deactivated.

Among PM, some malfunctions were present in 1 of 9 Medtronic, in 3 of 10 Boston, and in both the St Jude devices. No malfunctions were evident among Biotronik (0/10) and Sorin (0/3) devices (*Figure 3A*).

Among ICD, malfunctions were more frequently detected in Boston (9/11) and St Jude (3/6) devices, while failures were less frequent among Medtronic ICDs (1/8) (*Figure 3B*).

The interval between the year of production and irradiation was not statistically different in damaged and not damaged PM (10.3 ± 5.0 and 12.6 ± 2.4, respectively; $P = \text{NS}$) while, among ICD, malfunctioning models were older in comparison with those not damaged (9.8 ± 1.3 vs. 7.4 ± 2.0; $P = 0.001$).

The dosimetric film GAFCHROMIC-EBT2 positioned at the thoracic region for the detection of photonic radiation measured an average dose under 0.2 Gy.

Table 1 Cardiac devices evaluated

Manufacturer	Model	N	Year of production
Pacemakers			
Boston Scientific ($n = 10$)	Insignia I Ultra DR 1290	3	2003
	Altrua 60 S606	1	2008
	Intelis II 1499	2	1999
	Insignia I Ultra DR 1290	1	2003
	Altrua 60 S601	2	2008
	Insignia I Ultra DR 1291	1	2003
Medtronic ($n = 9$)	Geo1 SSI VSC 01/9.1	3	1999
	Kappa KDR703	5	1999
	Sigma SS 303	1	1998
Biotronik ($n = 10$)	Axios D	10	2001
Sorin ($n = 3$)	Rhapsody D2410 (T3)	3	2003
St Jude Medical ($n = 2$)	Verity AD × XL SR 5156	1	2003
	Sustain XLDC PM 2134	1	2011
Defibrillators			
Boston Scientific ($n = 11$)	Cognis 100D P107	1	2008
	Contak Renewal 3F H215	2	2005
	Contak Renewal4 H190	2	2003
	Contak Renewal4 H195	1	2003
	Vitality 2 DR T 165	2	2004
	Contak Renewal4RF H230	3	2005
Medtronic ($n = 8$)	Concerto C174 AWK	2	2006
	Maximo II DR D284DRG	2	2008
	Maximo II CRT-D D284TRK	1	2008
	InSync III Marquis 7279	1	2003
	Protecta CRT-D D364 TRG	1	2010
	Maximo-VR	1	2008
St Jude Medical ($n = 6$)	Atlas + VR V-193 Merlin PCS	3	2004
	Epic VR V-197 Merlin PCS	1	2002
	Atlas II + HF V-367 Merlin PCS	2	2006

Table 2 Damaged devices

Manufacturer	Model	*n*	Type of malfunction
Pacemakers			
Medtronic	Sigma SS 303	1	Electrical Reset
Boston Scientific	Intelis II 1499	1	Interrogation Impossible
	Insignia I Ultra DR 1291	1	Electrical Reset
	Altrua 60 S601	1	Electrical Reset
St Jude Medical	Verity AD × XL SR 5156	1	Backup in VVI mode
	Sustain XLDC PM 2134	1	Backup in VVI mode
Defibrillators			
St Jude Medical	Epic VR V-197 Merlin PCS	1	Magnet deactivation
	Atlas II + HF V-367 Merlin PCS	1	Interrogation impossible
	Atlas II + HF V-367 Merlin PCS	1	Change of programmation
Boston Scientific	Contak Renewal4 H190	2	Failure of the pulse generator
	Vitality 2 DR T 165	2	Failure of the pulse generator
	Contak Renewal4RF H230	1	Interrogation impossible
	Contak Renewal4RF H230	2	Failure of the pulse generator
	Contak Renewal 3F H215	1	Failure of the pulse generator
	Contak Renewal4 H195	1	Interrogation impossible
Medtronic	InSync III Marquis 7279	1	Electrical Reset

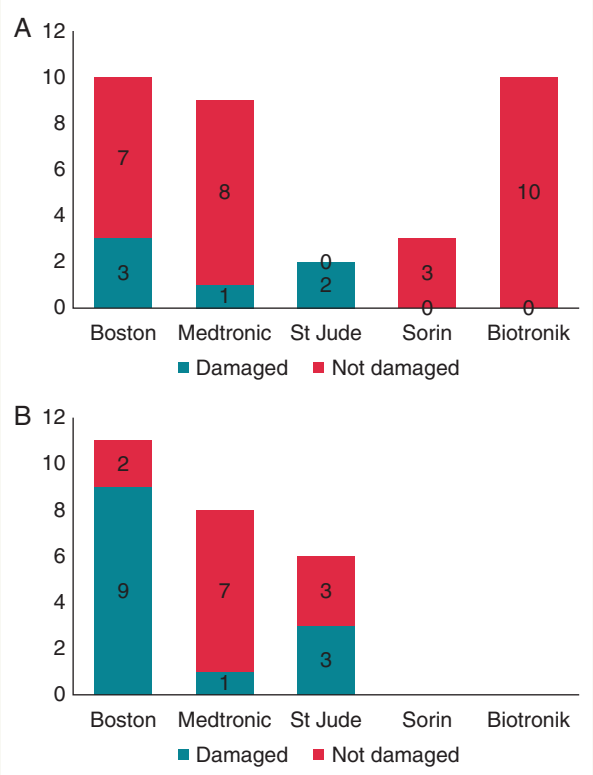

Figure 3 Number of damaged and not damaged PM (*A*) and ICD (*B*) according to different manufacturers.

No electromagnetic field was detected with the specific EM-field measuring devices.

The measured neutron dose in the CIED region was 19 ± 4 mSv. Neutron capture was demonstrated by the presence of the isotope $^{198}Au(^{197}Au + n)$ or $^{192}Ir(^{191}Ir + n)$ γ lines from the devices. The activation of elements was slightly greater in ICD than in PM ($7.5 \pm 5.5 \times 10^2$ vs. $6.6 \pm 5.0 \times 10^2$ Bq), in damaged vs. not damaged PM ($7.4 \pm 4.8 \times 10^2$ and $6.4 \pm 5.2 \times 10^2$ Bq, respectively), and ICD ($8.3 \pm 5.4 \times 10^2$ and $6.4 \pm 5.5 \times 10^2$ Bq, respectively), although the differences were not statistically significant.

Data about neutron dosage were comparable using the two phantoms.

Discussion

In radiotherapy, the most commonly used types of radiation are photons, electrons or (less frequently) protons, generated and delivered by a LINAC. Even if not predictable by a threshold value, CIED malfunctions due to ionizing radiations can occur in the presence of a radiation dose exceeding 2 Gy at the CIED site.[6] In order to protect the CIED from electromagnetic interferences, several measures have been suggested: magnet position, device reprogramming, or even CIED relocation in the presence of direct exposure to the radiation beam in high-risk patients, such as those who are PM dependent. A lead cover can be inadequate as it should be too thick to be considered in clinical practice.[7]

Permanent CIED malfunctions may be due either to the destruction of the electrical components, often by direct irradiation, or to negative effects on the random access memory (RAM) by secondary radiations, scattering or electromagnetic interferences. In addition, photons in megavolt range (commonly 6–20 MV) are used to increase the depth of the maximal delivered radiation for more deeply located neoplasms. When photons energy exceeds >10 MV, or in the presence of Proton Beam Therapy,[10] neutrons are produced; these neutrons can be source of PM and ICD malfunctions due to soft errors.[5] The effect of a temporary exposure to radiation can vary from the inability to communicate with the programmer to

deactivation of shock therapy or inappropriate shocks, reset, loss of diagnostics, limitations in programmability, or damage to the device components. However, effects due to direct radiation are different from those due to scattering radiation or secondary radiation,[11] which may locally induce ionization. The ionization leaves the local electric circuits intact but gives rise to error data; this type of interaction is called soft error. Soft errors, in semiconductor devices, are due to three types of radiations: (i) radiation α, (ii) high-energy neutrons resulting from cosmic radiation, and/or (iii) the interaction between thermal neutrons and the ^{10}B content in the devices,[12] producing ionizing particles (α) according to this reaction: $n + {}^{10}B \rightarrow \alpha + {}^{7}Li$.

The first guidelines for the management of patients with CIED undergoing radiotherapy were published in 1989 as a Newsletter from the American Society for Therapeutic Radiology and Oncology.[13] More formal recommendations were published in 1994 by the American Association of Physicists in Medicine[2] but they did not include patients with ICD.

The maximum tolerated doses are rather variable; typically a maximum photon dose of 2 Gy for PM (and possibly 1 Gy for ICD) is suggested, but other types of radiations are not mentioned and, in particular, the interaction between the devices and the neutrons is not entirely clear if not almost unknown among cardiologists.

Some reports suggest that in clinical practice malfunctions can happen even in the absence of direct exposure to beams of ionizing radiation, as in patients undergoing radiation treatments for prostate or rectal cancer.[14] This has been ascribed to the diffusion of neutrons produced by the LINAC when high energy is delivered, causing the soft errors in the circuits.[12] According to Elders *et al.*,[3] in 5 of 17 radiation treatments (29%) there were 6 ICDs malfunctions (35%), all observed at 10 and 18 MeV beam energies; a direct comparison of these doses showed that the risk is higher using 18 MeV than 10 MeV.[15] According to another *in vitro* experience by Zaremba *et al.* mimicking the treatment of breast cancer with high-energy (18 MV) and low-energy (6 MV) photon beams, in all PM from the 18 MV group some malfunctions were detected, while only one ICD was analysed, not showing any damage. In the 6 MV group, malfunctions were less frequent, observed only when a very high-radiation dose (150 Gy), not used in clinical practice, was achieved.[16] On the other hand, *in vivo* data on large population studies[1,4] and other smaller experiences showed that the risk of malfunction in clinical practice is much lower if high energies are avoided: for example, none of the 13 CIEDs were damaged after radiation according to Kapa *et al.*[11]; however, in that study only 5 ICDs were analysed, the total dose was <70 Gy in all patients and most treatments were directed to relatively superficial structures, therefore lower beam energies were required. Very recently, Dutch[17] and German (DEGRO) guidelines[6] were published, suggesting, whenever possible, to avoid high-energy photons (>10 MV). However, high-energy radiation can be necessary for the treatment of deep structures as prostate or other pelvic organs, while the treatment of thoracic neoplasms (breast or lung), despite closer to the CIED, usually needs lower energies, not producing neutrons, and can be associated with a lower risk of soft errors. In our simulation, radiation directed to deep pelvic organs (as the prostate), required a high energy (15 MV), and therefore produced neutrons, explaining the high proportion of soft errors in our experience.

Neutron dose we measured at the CIED site was different from that observed in the study by Gomez *et al.*,[10] who found a 20% risk of CIED reset after a proton beam therapy of the thorax but a comparison between these data is difficult, as methods of measurements were different and an estimation, rather than a direct measure, was calculated in the study by Gomez *et al.*[10] In our radiated CIED, neutron uptake was proved, however, by the presence of the isotope ^{198}Au or ^{192}Ir, not detectable in nature without an interaction with neutrons.

Photonic radiations were excluded as a cause of possible malfunction of our devices. In fact, the dosimetric film placed in the thoracic region was not impressed, meaning that the operating dose was $\leq$15 cGy and therefore much lower than the maximum tolerated dose suggested of 2 Gy for PM and ICD[6] and even to the lower dose potentially harmful ever described in the literature.[18] The presence of a significant electromagnetic field was excluded, too.

Although a systematic comparison of X-ray effects on PMs vs. ICD has not been performed yet, the 2003 recommendations by Guidant (former name of Boston Scientific) suggested that ICD may be up to 10 times more sensitive to radiation damage than PM since operation instructions are stored in the RAM, more sensitive to scatter radiation.[19] Our observations supported this hypothesis.

In our work, for the first time, the behaviour of many different models from different manufacturers was assessed. Considering the relatively small dimension of the sample considered, a chance effect could not be excluded. However, some models seemed to be particularly susceptible to soft errors and to some specific malfunctions (for example failure of the pulse generator in most Renewal models by Boston Scientific). For the purpose of our analysis, we considered only explanted devices, mainly produced in the last decade. We do not know if our observation can be applied also to more recent devices, as among ICDs, but not PMs, malfunctioning models were significantly older than those not damaged, confirming previous published data.[15]

The reason for this different behaviour among different CIED and models is not clear. A more complex electronic circuit or a greater amount of materials (i.e. ^{10}B or ^{6}Li) producing ionizing particles interacting with neutrons can be found in ICD than in PM and, possibly, in some models in comparison with others. However, if these considerations can be related to the different risk of malfunction is far to be proved and is still speculative. As far as we know, a direct correlation between neutron uptake and CIED malfunctions was never evaluated before. A clear association was not even proved in our study, but we observed a greater neutron uptake in ICD than in PM and a non-significantly higher uptake in damaged vs. non-damaged devices.

The use of conventional X-ray shielding during radiotherapy does not protect the pulse generator from the effects of scattered neutrons. Therefore, the development of special neutron absorbing and reducing shields could be desirable.

In the next future, with the spread of modern radiotherapy techniques as Intensity-Modulated Radiation Therapy and Volumetric Modulated Arc Therapy, the risk of neutron contamination will be significantly reduced or eliminated.

Limitations of the study

The limited number of CIED evaluated cannot allow definitive conclusions, in particular about the different effect on different models of CIED.

Our data suggest a higher risk of malfunctions than what detected in clinical practice.[1,4,11] However, also other *in vitro* studies showed a high rate of malfunctions.[3,6,7,15–17] These discrepancies may have several explanations:

- a possible different time dependent, and not only dose dependent, effect of radiations cannot not be excluded; despite all efforts to reproduce clinical conditions were made, in our simulation the whole dose (70 Gy) was administered in a single session, a condition not practicable in the real patient.
- Despite mimicking biologic tissue, matter composition of phantoms can have different effects on radiations; our phantoms were built to mimick neutron absorption, but the heterogeneity of biologic tissues is difficult to reply.
- The effect of other device components, as leads, cannot be evaluated during *in vitro* studies.
- During *in vitro* studies, the worst possible situations are usually tested: in our laboratory all devices were radiated with high energies (>15 MV) and were placed in the thoracic region from 30 to 60 cm far from isocentre of the radiation beam.
- During *in vivo* studies, the limited number of patients with comparable CIED and therapy regimens can lead to some inaccuracies and in large population studies an underestimation of malfunctions can be possible, as a comprehensive evaluation of all devices both before and after radiotherapy can be difficult to achieve.[1]

According to our measurements, the presence of significant electromagnetic fields (range 0.15–300 V/m) was excluded, but these data should be considered just indicative, as low frequencies (<100 KHz) were not explored with our instruments. However, significant electromagnetic interferences due to LINACs were never described during radiotherapy[1] and low frequencies in particular, although being a possible source of interference, are very unlikely to cause permanent malfunctions.[20] As an experimental model, other possible malfunctions (modifications of pacing thresholds, inappropriate sensing or shock delivery) could not be excluded, although rarely associated with soft errors. In order to evaluate and estimate all possible malfunctions of the interface CIED patient, a study with the devices connected to a cardiac simulator could be desirable, but this was not the aim of our analysis.

Conclusions

High-energy radiation can determine CIED malfunctions even in the absence of direct exposure to the radiation beam, because of the diffusion of neutrons produced by the LINAC, causing soft errors in the circuits. In our experimental model, we simulated a complete radiotherapy treatment for prostatic cancer on an anthropomorphic phantom designed for neutron dosimetry. Despite the absence of significant photonic radiation and electromagnetic field in the thoracic zone, some malfunctions were detected in 52% of ICD and 13% of PM. The effect was more evident in some ICD and PM models than others; the year of production did not seem to be correlated with the risk of PM damages, while damaged ICD were older than those without malfunctions; finally a slightly, although non-significantly, greater neutron uptake in ICD than in PM and in damaged vs. not damaged PM was observed.

Conflict of interest: none declared.

References

1. Zaremba T, Jakobsen AR, Søgaard M, Thøgersen AM, Johansen MB, Madsen LB *et al.* Risk of device malfunction in cancer patients with implantable cardiac device undergoing radiotherapy: a population-based cohort study. *Pacing Clin Electrophysiol* 2015;**38**:343–56.
2. Marbach JR, Sontag MR, Van Dyk J, Wolbarst AB. Management of radiation oncology patients with implanted cardiac pacemakers: report of AAPM Task Group No. 34. American Association of Physicists in Medicine. *Med Phys* 1994;**21**:85–90.
3. Elders J, Kunze-Busch M, Smeenk RJ, Smeets JL. High incidence of implantable cardioverter defibrillator malfunctions during radiation therapy: neutrons as a probable cause of soft errors. *Europace* 2013;**15**:60–5.
4. Soejima T, Yoden E, Nishimura Y, Ono S, Yoshida A, Fukuda H *et al.* Radiation therapy in patients with implanted cardiac pacemakers and implantable cardioverter defibrillators: ?a prospective survey in Japan. *J Radiat Res* 2011;**52**:516–21.
5. Gelblum DY, Amols H. Implanted cardiac defibrillator care in radiation oncology patient population. *Int J Radiat Oncol Biol Phys* 2009;**73**:1525–31.
6. Gauter-Fleckenstein B, Israel CW, Dorenkamp M, Dunst J, Roser M, Schimpf R *et al.* DEGRO/DGK guideline for radiotherapy in patients with cardiac implantable electronic devices. *Strahlenther Onkol* 2015;**191**:393–404.
7. Zaremba T, Jakobsen AR, Søgaard M, Thøgersen AM, Riahi S. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a literature review. *Europace*, doi:10.1093/europace/euv135.
8. International Commission on Radiation Units and Measurements. Measurement of Absorbed Dose in a Phantom Irradiated by a Single Beam of X or Gamma Rays. ICRU Report 23. Bethesda, MD: International Commission on Radiation Units and Measurements, 1973.
9. Koivunoro H, Seren T, Hyvonen H, Kotiluoto P, Iivonen P, Auterinen I *et al.* Epithermal neutron beam interference with cardiac pacemakers. *Appl Radiat Isot* 2011;**69**:1904–6.
10. Gomez DR, Poenisch F, Pinnix CC, Sheu T, Chang JY, Memon N *et al.*Malfunctions of implantable cardiac devices in patients receiving proton beam therapy: incidence and predictors. *Int J Radiat Oncol Biol Phys* 2013;**87**:570–5.
11. Kapa S, Fong L, Blackwell CR, Herman MG, Schomberg PJ, Hayes DL. Effects of scatter radiation on ICD and CRT function. *PACE* 2008;**31**:727–32.
12. Baumann RC. Soft errors in advanced semiconductor devices: Part I. The three radiation sources. *IEEE Transactions on Device and Materials Reliability 1.1*, 2001. pp. 17–22.
13. Marbach JR. Recommended precautions in the management of radiation oncology patients with implanted pacemakers. *ASTRO Newsl* 1989;**VIII**:7–8.
14. Makkar A, Prisciandaro J, Agarwal S, Lusk M, Horwood L, Moran J *et al.* Effect of radiation therapy on permanent pacemaker and implantable cardioverter-defibrillator function. *Heart Rhythm* 2012;**9**:1964–8.
15. Hashii H, Hashimoto T, Okawa A, Shida K, Isobe T, Hanmura M *et al.* Comparison of the effects of high-energy beam photon radiation (10 and 18 MV) on two types of implantable cardioverter-defibrillators. *Int J Radiation Oncol Biol Phys* 2013;**85**:840–5.
16. Zaremba T, Jakobsen AR, Thøgersen AM, Oddershede L, Riahi S. The effect of radiotherapy beam energy on modern cardiac devices: an in vitro study. *Europace* 2014;**16**:612–6.
17. Hurkmans CW, Knegjens JL, Oei BS, Maas AJ, Uiterwaal GJ, van der Borden AJ *et al.* Management of radiation oncology patients with a pacemaker or ICD: a new comprehensive practical guideline in The Netherlands. *Radiat Oncol* 2012;**7**:198.
18. Mouton J, Haug R, Bridier A, Dodinot B, Eschwege F. Influence of high-energy photon beam irradiation on pacemaker operation. *Phys Med Biol* 2002;**47**:2879–93.
19. Guidant Corporation Cardiac Rhythm Management Technical Services. Impact of therapeutic radiation and Guidant ICD/CRTD/CRT-P/Pacing systems. St Paul, MN: Guidant Corporation, 2004, Revision; pp. 1–6.
20. Tiikkaja M, Aro AL, Alanko T, Lindholm H, Sistonen H, Hartikainen JE *et al.* Electromagnetic interference with cardiac pacemakers and implantable cardioverter-defibrillators from low-frequency electromagnetic fields in vivo. *Europace* 2013;**15**:388–94.