Journal of Radiation Research, Vol. 62, No. 6, 2021, pp. 1006–1014
https://doi.org/10.1093/jrr/rrab088
Advance Access Publication: 20 September 2021

Study of feasible and safe condition for total body irradiation using cardiac implantable electronic devices

Hiroaki Matsubara[1,†*], Takatomo Ezura[2,‡], Yaichiro Hashimoto[1], Kumiko Karasawa[1], Teiji Nishio[1,§] and Masato Tsuneda[1,‖]

[1]Department of Radiation Oncology, Tokyo Women's Medical University, Tokyo 162-8666, Japan
[2]Department of Radiology, Tokyo Women's Medical University Hospital, Tokyo 162-8666, Japan
*Corresponding author. Email address: matubara@koto.kpu-m.ac.jp, mats.hiroaki@gmail.com (Hiroaki Matsubara)
[†]Present address: Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
[‡]Present address: Pharmaceuticals and Medical Devices Agency, Tokyo 100-0013, Japan
[§]Present address: Osaka University, Osaka 565-0871, Japan
[‖]Present address: Chiba University, Chiba 260-8677, Japan
(Received 23 June 2021; revised 9 August 2021; editorial decision 23 August 2021)

ABSTRACT

Cardiac implantable electronic devices (CIEDs) were believed to have a tolerance dose and that direct irradiation has to be avoided. Thus, no clinical guidelines have mentioned the feasibility of total body irradiation (TBI) with a CIED directly. The purpose of this work was to study a feasible and safe condition for TBI using a CIED. Eighteen CIEDs were directly irradiated by a 6-MV X-ray beam, where a non-neutron producible beam was employed for the removal of any neutron contribution to CIED malfunction. Irradiation up to 10 Gy in accumulated dose was conducted with a 100-cGy/min dose rate, followed by up to 20 Gy at 200 cGy/min. An irradiation test of whether inappropriate ventricular shock therapy was triggered or not was also performed by using a 6-MV beam of 5, 10, 20 and 40 cGy/min to two CIEDs. No malfunction was observed during irradiation up to 20 Gy at 100 and 200 cGy/min without activation of shock therapy. These results were compared with typical TBI, suggesting that a CIED in TBI will not encounter malfunction because the prescribed dose and the dose rate required for TBI are much safer than those used in this experiment. Several inappropriate shock therapies were, however, observed even at 10 cGy/min if activated. The present result suggested that TBI was feasible and safe if a non-neutron producible beam was employed at low dose-rate without activation of shock therapy, where it was not inconsistent with clinical and non-clinical data in the literature. The feasibility of TBI while using a CIED was discussed for the first time.

Keywords: cardiac implantable electronic devices (CIED); pacemaker (PM); implantable cardioverter defibrillator (ICD); cardiac resynchronization therapy (CRT); total body irradiation (TBI)

INTRODUCTION

Radiation-induced risk to cardiac implantable electronic devices (CIEDs) in radiotherapy has been discussed for a long time, where CIEDs denote implanted cardiac pacemakers (PMs), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices (CRTs). A guideline first published in 1994 by the American Association of Physicists in Medicine (AAPM) recommends that the accumulated dose to a PM should not exceed 2 Gy and that direct irradiation should be avoided [1]. Although a new guideline by the AAPM published in 2019 insists that the tolerance dose depends on the patient's risk [2], it still recommends that the dose should be kept at less than 2–5 Gy and direct irradiation should be avoided if possible. Such a dose tolerance and description is problematic for myeloablative total body irradiation (TBI) prior to hematopoietic stem cell transplantation [3, 4], as TBI is prescribed at around 10 Gy by direct irradiation to the whole body including the CIED if present in the patient [5, 6, 7]. Although several clinical guidelines for CIEDs in radiotherapy in addition to those by the AAPM have been

published [8, 9, 10, 11, 12, 13, 14, 15], there are no direct descriptions and discussions regarding the feasibility of TBI for those using a CIED.

There is only one clinical case of TBI while using a CIED [16], and it was reported that the irradiation using a 6-MV X-ray beam with a prescription dose of 8 Gy to an ICD was completed without malfunction. As for similar direct irradiation in clinical experiences, CIEDs were sometimes located in an irradiation field when breast treatment and lung stereotactic radiation were employed [17, 18, 19, 20, 21, 22, 23]. No malfunctions were reported from those clinical experiences. Some non-clinical experiments recently performed with direct irradiation using a flattening filter-free (FFF) beam, however, reported that high dose-rate irradiation affected CIEDs if it was beyond 800 cGy/min [24, 25, 26]. Such evidence may suggest that there is a safe low dose-rate for TBI with the presence of a CIED even by direct irradiation.

A recent study reported that neutrons were the main risk to CIEDs encountered in a clinical situation [27]. Then, another study reported that the number of malfunctions of CIEDs due to neutrons was proportional not to the photon dose but rather to the neutron dose [28]. Those findings indicate that malfunction by neutrons is randomly caused as long as neutrons are produced. Therefore, the usage of a non-neutron producible beam is essential for any study of the risk to CIEDs by the removal of contribution from neutrons.

The present article aims to study a feasible and safe condition for TBI for a patient with a CIED. Eighteen CIEDs were directly irradiated by a 6-MV X-ray beam with a slightly higher dose-rate up to a little larger accumulated photon dose than those typically employed in TBI. Here, a non-neutron producible beam was employed to rule out any contribution from neutrons to possible malfunction. The feasible and safe application of TBI during the use of a CIED has been directly discussed here for the first time.

DEFINITION AND SUMMARY OF MALFUNCTION

Definition of malfunction

Malfunction caused to a CIED during radiotherapy is defined in the present study as the following:

- Soft error. Switching to safety backup mode or something caused by a tiny upset in a memory owing to neutrons or charged nucleon incidence. Reprogramming is required for recovery.
- Transient effect. Incorrect action during irradiation, such as inhibiting and under-sensing. A device is automatically recovered when the beam is stopped.
- Failure. Loss of function such as lost telemetry capability, battery reduction including unexpected elective replacement indicator (ERI), or permanent silence. Replacement of the device is required because recovery is very difficult.

When an X-ray beam equal to or less than 6-MV is employed, neither secondary neutrons nor any charged nucleons are produced from a linac. Here, the energy stems from the neutron separation energy of tungsten [29], as an element of tungsten is included in every part of a linac. Thus, as long as a non-neutron producing X-ray beam is employed, a malfunction due to soft error can be ruled out.

Summary of risk factors

Risk factors for radiation-induced malfunction to CIEDs in radiotherapy using X-ray beams are summarized here.

Firstly, neutrons are one of the risk factors for malfunction, as numerically revealed in Matsubara *et al.* [28]. The malfunction process by neutrons can be understood as one of single-event effects through nuclear reaction of $^{10}B(n,\alpha)^{7}Li$ at a borophosphosilicate glass (BPSG) layer in a complementary metal-oxide-semiconductor (CMOS) field-effect transistor device, resulting in soft error [30]. Since neutrons are secondarily produced by a treatment X-ray beam and then scattered in the treatment room, malfunction caused by neutrons is possible even in the case of out-of-field irradiation. Thus, malfunctions reported by several clinical studies that occurred at low accumulated photon dose were able to be mainly explained by neutrons [31, 32, 33, 34, 35, 36].

Secondly, a high dose rate is thought to be a potential risk for malfunction [2]. Radiation by an X-ray beam turns into electrons when functioning as a dose. In other words, if a CIED receives a dose, its electrical circuit becomes excessively charged in a state of local high voltage. Since excess charges flow out to ground via a circuit to be discharged, pseudo signals in a circuit may be introduced. A local high voltage may lead baseline-shift to a circuit. These effects are considered to cause transient effects such as inhibiting and under-sensing during irradiation. Some malfunctions reported in non-clinical studies can be thought to have been caused by such high dose-rate effect [37, 38, 39, 46]. Recent experiments using FFF beams also clarified them [24, 25, 26].

Thirdly, a large accumulated photon dose is thought to be another potential risk for malfunction [2]. When X-ray beam radiation enters into a semiconductor or an insulator within it, pairs of electron-holes are produced, contributing to the dose. Since those pairs, particularly their holes, tend to accumulate, such accumulations cause a change of voltage properties in a semiconductor, possibly resulting in a change of bias voltage and then finally an insulation breakdown. Because such effects are considered to be connected to irreversible change, permanent function loss and failure may be caused, as reported in previous studies [32, 38, 39, 40, 41, 42, 43].

Direct irradiation itself by X-ray beams, however, is not thought to be an essential risk factor for malfunction. The physical difference between direct and indirect irradiation by X-ray beams is just the quality of the radiation (energy spectrum). Radiation quality (energy spectrum) is not taken into account among X-ray beams because dose is employed as a main parameter. That is why no one assumes that there is difference between 1 Gy by 6-MV and that by 10-MV, for example. As another example, no clinical guidelines specify X-ray beam energy when the prescription dose is described, suggesting that everyone assumes that 1 Gy by any kind of treatment X-ray beam is the same. Therefore, the difference between direct and indirect irradiation by X-ray beams can be described just by the dose rate. As long as the dose-rate is considered, distinguishing between direct and indirect irradiation is not essential. The above consideration is consistent with non-clinical studies reporting no malfunctions even by direct irradiation because neither a high dose-rate nor a large accumulated dose was applied under the usage of a non-neutron producible beam [44]. Clinical studies also did not report any malfunction even by direct irradiation [16, 17, 18, 19, 20, 21, 22, 23]. The above understanding is key for the study of safe conditions of TBI using a CIED. Here, it should be noted that direct irradiation in the case of charged nucleon beams (such as proton and carbon-ion therapies) still poses a risk for malfunction because they have the potential to directly

Table 1. Devices collected for the present study. Three devices were not used because they did not respond to a programmer

Device	Manufacturer		Model
S01	St. Jude	PM	Identity ADx XL DR 5386 DDDR
S02	St. Jude	PM	Zephyr XL DR 5826 DDDR
S03	St. Jude	CRT-D	Unity Quadra CD3251-40Q
S04	St. Jude	CRT-D	Unity Quadra CD3251-40Q(2)
S05	St. Jude	ICD	Ellipse DR CD2277-36Q
S06	St. Jude	PM	Anthem RF PM3212
S07	St. Jude	CRT-D	Unity Quadra CD3235-40Q
S08	St. Jude	CRT-D	Unity Assura CD3361–4
S09	St. Jude	CRT-D	Quadra Assura CD3367-40QC
M01	Medtronic	CRT-D	viva Quad XT CRT-D DTBA2Q1
M02	Medtronic	CRT-D	viva XT CRT-D DTBA2D1
M03	Medtronic	ICD	Evera MRI XT DR surescan DDMB2D4
M04	Medtronic	CRT-D	viva Quad XT CRT-D DTBA2QQ
M05	Medtronic	ICD	Evera XT DR DDBB2D1
M06	Medtronic	CRT-D	viva XT CRT-D DTBA2D1(2)
M07	Medtronic	PM	Adapta ADDR01 (Not used)
M08	Medtronic	PM	Adapa L ADDRL1 (Not used)
M09	Medtronic	PM	Advisa DR A5DR01
M10	Medtronic	PM	Advisa DR A5DR01(2)
M11	Medtronic	PM	Advisa DR MRI surescan A3DR01 (Not used)
M12	Medtronic	CRT-D	Protecta XT CRT-D D354TRG

cause single event effects resulting in soft error and to directly cause accumulation effects in a semiconductor, resulting in an insulation breakdown.

MATERIALS AND METHODS

Models and setup

Twenty-one CIEDs were collected as summarized in Table 1. They were explanted from patients during replacement. None of them experienced receiving radiation. Because three of them did not respond to a programmer, 18 devices were employed in the irradiation test described in Sec. 3.2. The devices were from two manufactures, St.-Jude (now Abbott Medical) and Medtronic.

The devices were set to AAI mode with 60 bpm of pulse frequency. The other setting parameters were as follows: output voltage 6 V with time width of 1.0 ms; sensing sensitivity was 0.2–0.3 mV, with the highest sensitivity of 0.15 mV avoided by Medtronic devices, as will be discussed later. Ventricular shock therapy was disabled and enabled in the irradiation test (Sec. 3.2) and in the shock therapy test (Sec. 3.3), respectively.

Irradiation was performed with a Varian TrueBeam linac at Tokyo Women's Medical University. The experimental setup is schematically shown in Fig. 1. An X-ray beam of 6-MV was employed as a non-neutron producible beam. The phantom on top of a couch consisted of water-equivalent slabs with a thickness of 17 cm in total to provide full backscatter conditions. The field size at the surface of the phantom and the source-surface distance (SSD) to the surface of the phantom were fixed at 10×10 cm^2 and 100 cm, respectively. Two CIEDs were placed simultaneously within the irradiation field in order to save experimental time. Since a typical density of a CIED is about 2 g/cm^3, for simplicity, a CIED placed on top of the phantom surface was assumed to receive a dose of 100 cGy when 100 MU was delivered. Output signals from a CIED were divided into two via an IS-1 type lead connector (bipolar). One signal was recorded by data recorder (MCR-4 V; T&G Corporation) in a step of 50 ms, and the other was used for online monitoring in a console room using an oscilloscope with a Bayonet Neill-Concelman (BNC) connector coaxial cable. Output signals displayed on the oscilloscope were distorted owing to the long BNC cable distance of 10 m between the treatment room and the console room. Pulse height according to the recorder was not stable because the pulse voltage was too low for accurate detection owing to an inner resistor or some measurement problem the authors failed to notice. Instability of pulse height was seen even in the case of no radiation. Signals registered by the recorder coincided with those operated by a programmer. Therefore, the present study aimed to determine whether pacing pulses are normally put out or abnormally inhibited, but its aim was not to consider changes of pulse height during irradiation.

Irradiation test

An irradiation test was carried out to determine whether a pacing pulse from a CIED was inappropriately inhibited or not due to irradiation. Eighteen CIEDs were tested. The CIEDs were directly irradiated at a dose rate of 100 cGy/min from 0 to 10 Gy in an accumulated photon dose, and then were irradiated at 200 cGy/min from 10 to 20 Gy. Device interrogation was performed when the dose rate was changed, in addition to before and after the irradiation. Ventricular shock therapy was disabled.

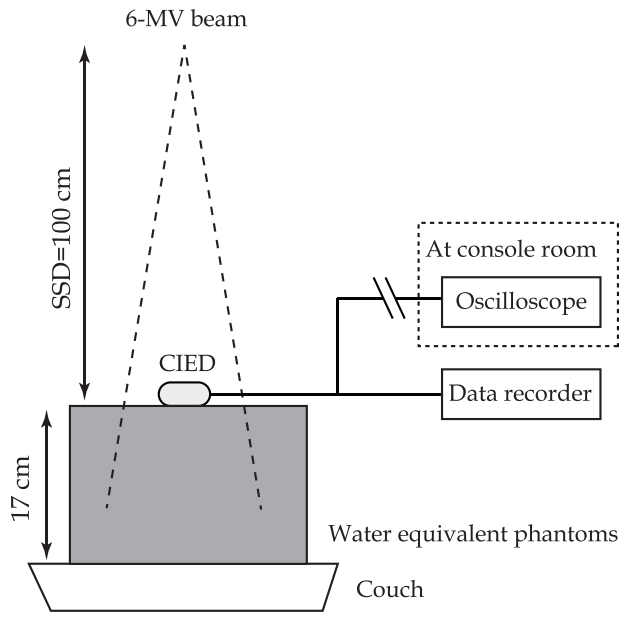

Fig. 1. Schematic figure of experimental setup.

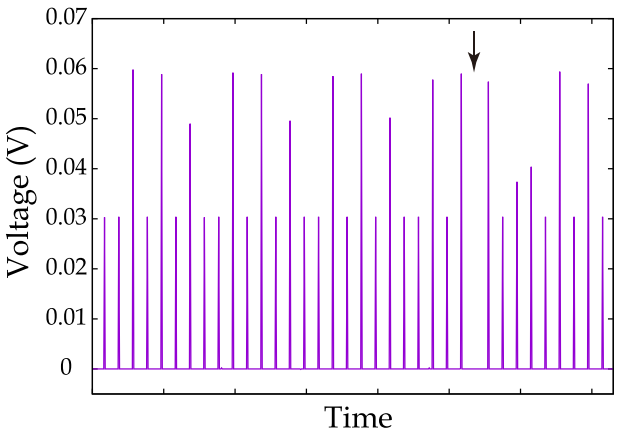

Fig. 2. Typical screenshot of inhibition signal taken by the recorder during irradiation in the case of M12. Unstable pulse height is due to measurement problem, as mentioned in Sec. 3.1. The arrow indicates the timing of inhibition.

Shock therapy test

Ventricular shock therapy test was performed to study whether it was inappropriately triggered or whether it was not due to irradiation. Only two CIEDs, M03 and M04 in Table 1, were studied. The CIEDs were directly irradiated for 10 minutes at dose rates of 5, 10, 20 and 40 cGy/min, meaning that they were irradiated for a total of 40 minutes in total. Because this experiment was performed after the irradiation test, the final accumulated photon dose to devices M03 and M04 became 27.5 Gy. Device interrogation was performed before and after irradiation.

RESULTS

Result of irradiation test

No transient effects such as inhibited signal were observed in any of the devices. Soft errors and failures were also not shown in the device interrogation. Although an inhibited event was sometimes observed at a frequency of once every few minutes during the irradiation, such random incident of single pulse inhibition does not bring any hazard to a patient because another pulse comes after 2 seconds in this case, as shown in Fig. 2. This random inhibition was not seen at all when no radiation was given. After the irradiation, all devices responded normally to the device interrogation.

Here, we note that the threshold setting of the sensing sensitivity was crucial to the transient effect. When the highest sensitivity of 0.15 mV was set on a Medtronic device, most pulses were inhibited during irradiation at 100 cGy/min. Then, setting the second highest sensitivity of 0.30 mV on the device, no inhibition was observed except for random events, as mentioned above. As the highest sensitivity setting for devices of St.-Jude Medical was 0.20 mV, however, those CIEDs did not show any inhibition of pulses during irradiation. Although the present study did not clarify whether it is related to the threshold level or to manufactured dependence, it can be said that the most sensitive setting to the sensing threshold should be avoided for the safe use of CIEDs during radiation.

Fig. 3 graphically demonstrates the result of the irradiation test, which is shown in two-dimensional relation between the accumulated dose and dose rate. Because the non-neutron producible beam was employed, these two factors were assumed to describe the risk. For comparison, in one clinical experience, no malfunction was encountered in TBI using a CIED by Hristova *et al.* [16], and the typical beam condition employed in TBI are also included in the figure [5, 6, 7]. Because the dose rate was not reported in Hristova *et al.* [16], the error bar was made to cover the commonly used range for this dose rate. It should be noted that the dose rate in TBI is intentionally suppressed to 10–30 cGy/min so as not to cause adverse effects such as pneumonitis, nausea, or vomiting [45]. The present experimental result exhibited no malfunctions even at much higher dose rates of 100 and 200 cGy/min and beyond, with a typical prescription dose of around 10 Gy. Therefore, the feasible and safe use of TBI for a patient with a CIED can be recommended.

Result of shock therapy test

Inappropriate shock during the irradiation was often observed, as numerically summarized in Table 2 and as visually shown in Fig. 4, where error bars originated from statistical uncertainty based on Poisson distribution. Inappropriate shock was observed several times at a low dose-rate of 10 cGy/min. After irradiation, the devices normally responded to the device interrogation. Although inappropriate shock was not observed at a dose rate of 5 cGy/min, it is hard to insist that this represents the threshold border between risk and safety because of the limited number of studies. At least, however, it can be said that shock therapy should be deactivated for safety reasons during any radiotherapy, since it can be triggered by a low photon dose-rate, i.e. even by out-of-field irradiation. Thus, it is obvious that its deactivation is indispensable for TBI using a CIED.

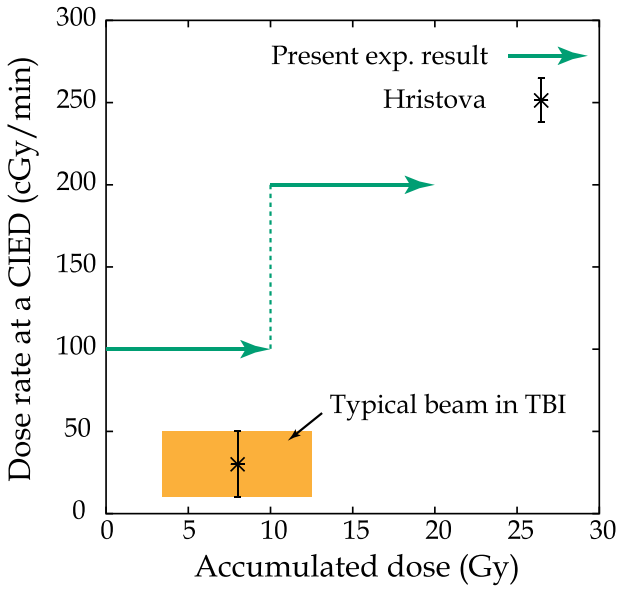

Fig. 3. Graphical expression of the result by irradiation test shown in two-dimensional correlation between accumulated dose and dose rate. No malfunctions were observed in the experiment. One clinical experience (Hristova *et al.* [16]) is also plotted in the figure. Orange region denotes a typical beam employed in TBI.

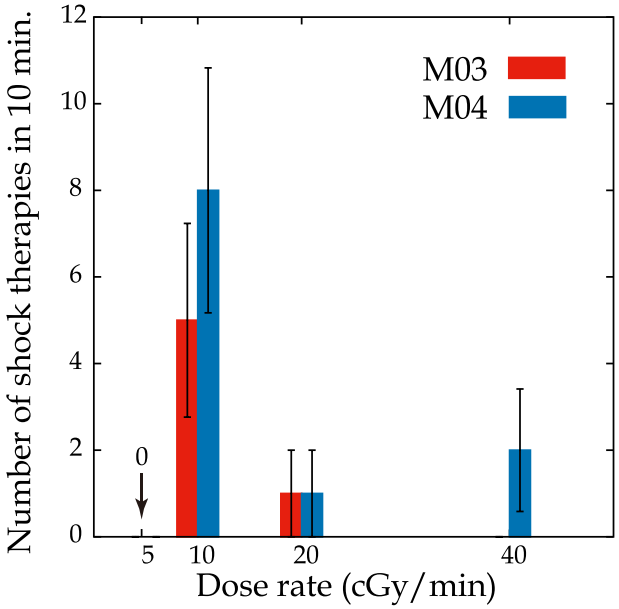

Fig. 4. Visualized results of shock therapy test. Error bars originated from statistical uncertainty based on Poisson distribution.

Table 2. Numerical results of shock therapy test. Number of shock therapies triggered during 10 minutes of irradiation are summarized

Dose rate (cGy/min)	M03	M04
5	0	0
10	5	8
20	1	1
40	0	2

DISCUSSION

Comparison with clinical experiences

Table 3 summarizes the received dose of a CIED in terms of clinical experiences, where only the result of TBI was extracted in the case of Hristova *et al.* [16]. No malfunctions were reported by the references, although neutron producible beams were often employed. Because details of the dose rates were not available, those clinical experiences were not plotted in Fig. 3. However, those clinical experiences suggest that direct irradiation to a CIED with a prescription dose of 10 Gy, corresponding to TBI, is feasible and safe.

Comparison with non-clinical experiments

Table 4 summarizes the non-clinical experiments of irradiation of CIEDs with non-neutron producible beams. The data collected from Table 4 were plotted in two-dimensional correlation between accumulated dose and dose rate with the addition of the result of the present study, as shown in Fig. 5. Here, only the data taken by irradiation with a simple beam were gathered because it is hard to calculate the actual dose rate in a complex beam using like a Volumetric Modulated Arc Therapy (VMAT) plan. The number by a symbol denotes the number of overlapped data. From the literature, results of 263 devices were extracted in Table 4: 34 devices became failures, 15 devices exhibited transient effect and 214 devices had no malfunctions. Although the two-dimensional plot (Fig. 5) does not provide a clear border line between safety and malfunctions, the area of no malfunctions observed in the present study is consistent with previous studies. The above consistency, again, suggests that TBI for a CIED can be feasible and safe.

Age and generation of CIED

As one of the possibilities, the age and generation of CIED may have to be considered for the non-clinical experiments taken from the literature. One reason to insist this is that the present study did not observe any obvious noise by oscilloscope at baseline due to irradiation, although continuous noise during irradiation was clearly seen in Fig. 1 of Hurkmans *et al.* [38] published in 2005. Since recent studies also did not report any noise during irradiation [25, 26, 44], it may be said that recent CIEDs are stronger in terms of noise and failure than older ones. Since a CIED used for more than 10 years is usually replaced with a new one owing to battery problems, it may be suggested that only the CIED model currently being used has to be taken into account. Therefore, Fig. 6 was updated from Fig. 5 by removing the data published before 2010 and removing the data of the old models in Mollerus *et al.* [41], to the study of CIEDs being currently active. If removal of the data from the consideration of age and generation of CIED is reasonable, the result shown in Fig. 6 suggests that no failure

Table 3. Summary of received dose by a CIED in clinical experiments. No malfunctions were reported from those references, although neutron-producible beams were often employed. Details of dose rate were not available

Year	Author	Mean dose (Gy)	Max. dose (Gy)	Min. dose (Gy)	Beam
2011	Wadasadawala *et al.* [17]	0.1–20.6	0.1–60.0	0.1–2.0	Cobalt, 6/15-MV
2012	Kesek *et al.* [18]	25	48	9	NA
2014	Ahmed *et al.* [19]	29.3	52.4	13.5	6/15-MV
2015	Scobioala *et al.* [20]	5.6	15.6	NA	6/15-MV
2017	Martínez-Sande *et al.* [21]	NA	30	NA	6/15-MV
2017	Hristova *et al.* [16]	8	8	8	6-MV
2020	Mielczarek *et al.* [22]	NN	NA	NA	10-MV
2020	Schernthaner *et al.* [23]	29	47	8.7	6-MV

NA: Not available.

Table 4. Summary of non-clinical experiments. Only results using non-neutron producible beams in a simple treatment plan were extracted from literatures. The mark # means number

Year	Author	# of devices	
2005	Hurkmans *et al.* [38]	19	Fourteen devices became failures, and five were non-malfunctions.
2005	Hurkmans *et al.* [39]	11	All devices became failures.
2006	Uiterwaal *et al.* [46]	11	All devices encountered transient effect at 400 cGy/min.
2008	Kapa *et al.* [47]	20	No malfunctions at 16 cGy/min.
2013	Zaremba *et al.* [48]	5	No malfunctions at 600 cGy/min.
2014	Zaremba *et al.* [40]	6	One device became failure at 150 Gy, and five were non- malfunctions.
2014	Mollerus *et al.* [41]	8	Four devices encountered transient effect, and four were non-malfunctions.
2016	Augustynek *et al.* [49]	2	No malfunctions at 800 cGy/min.
2018	Zecchin *et al.* [44]	19	No malfunctions at 85 cGy/min.
2020	Nakamura *et al.* [25]	4	Three devices encountered transient effect at 400 cGy/min, and one at 1000 cGy/min.
2020	Aslian *et al.* [26]	4	No malfunctions below 1000 cGy/min in dose rate.
2021	Falco *et al.* [50]	140	No malfunctions at 600 cGy/min.
2021	Baehr *et al.* [42]	14	Four devices became failures, and ten were non-malfunctions. Results by brachytherapy were excluded due to unknown dose rate.

is expected within 50 Gy in accumulated dose or 400 cGy/min in dose rate for any CIEDs currently implanted in patients.

Gap between clinical and non-clinical situations

The gap of CIED malfunction between clinical situation and non-clinical experiment is discussed here. It should be noted that malfunction of a CIED triggered by the radiation incidence is just a physical process as explained in Sec. 2.2, relates to neither biological effect nor clinical response. The above indicates that malfunction itself by irradiation does not change whether a CIED is implanted in a patient or it is placed on a phantom in a non-clinical experiment, except for one parameter that will be discussed below. Thus, since it can be expected that knowledge of no malfunction obtained in non-clinical experiments is clinically applicable, the present study suggests that TBI for a patient with a CIED is feasible and safe.

One parameter that differs between a clinical situation and a non-clinical experiment is the temperature of a CIED. The difference between room temperature (20°C, 293 K) and body temperature (37°C, 310 K) is just 6% in absolute temperature. Such a minor physical difference is assumed not to drastically change the property of the electrical circuit and not to affect a malfunction in a CIED, as discussed in Hurkmans *et al.* and Adamec *et al.* [38, 51]. Thus, it can be concluded that there is little gap between a clinical situation and a non-clinical experiment for the study of CIED malfunctions.

It is true that there may be large gaps among patients after malfunctions encountered in clinical situations. Even though a similar malfunction may occur, clinical intervention could differ depending on the patient. However, the above is beyond the scope of the present study, because our focus herein is on whether malfunctions occur or not.

CONCLUSION

The feasibility and safety of TBI for a CIED were suggested by the present study as well as the data in the literature. Here, usage of a non-neutron producible beam, avoiding the highest sensitivity to the sensing threshold, and deactivation of ventricular shock therapy were required for safety. It is expected that the present study will contribute

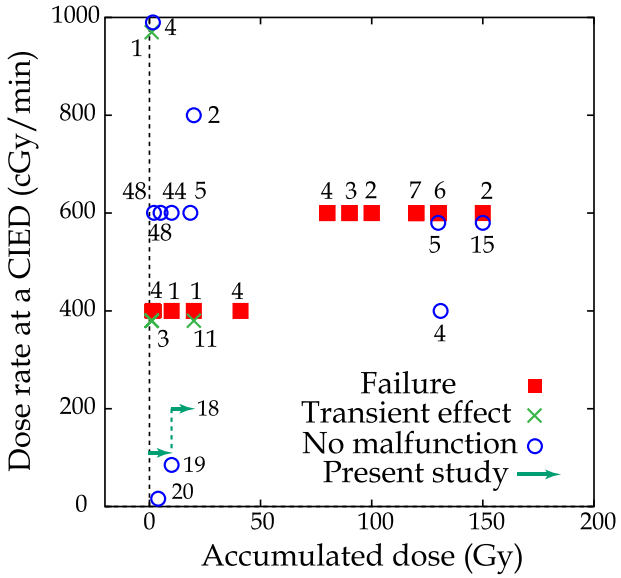

Fig. 5. Two-dimensional correlation of non-clinical experimental results between accumulated dose and dose rate. The data were taken from the literature summarized in Table 4. The results of the present study are also shown by an arrow. The numbers by symbols denote the numbers of overlapping data.

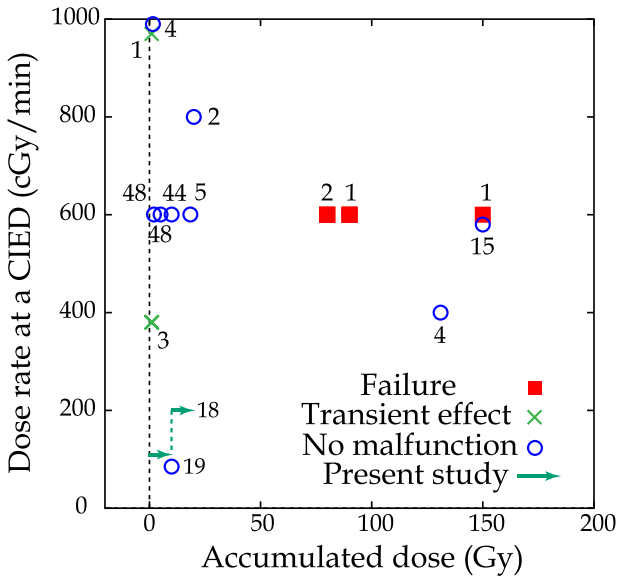

Fig. 6. Two-dimensional correlation of non-clinical experimental results limited to CIEDs being currently active. The data published before 2010 and the data of the old models in Mollerus *et al.* [41] were removed from Fig. 5.

to the safe and curative treatment of a patient with a CIED under radiotherapy.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP18K15647.

REFERENCES

1. Marbach JR, Sontag MR, Van Dyk J et al. 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.
2. Miften M, Mihailidis D, Kry SF et al. Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: A Report of the AAPM TG-203. *Med Phys* 2019;46:e757–88.
3. Hartman AR, Williams SF, Dillon JJ. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation: a meta-analysis. *Bone Marrow Transplant* 1998;22:439–43.
4. Gupta T, Kannan S, Dantkale V et al. Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther* 2011;4:17–29.
5. Giebel S, Miszczyk L, Slosarek K et al. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Cancer* 2014;120:2760–5.
6. Studinski RCN, Fraser DJ, Samant RS et al. Current practice in total-body irradiation: results of a Canada-wide survey. *Curr Oncol* 2017;24:181–6.
7. Ishibashi N, Soejima T, Kawaguchi H et al. National survey of myeloablative total body irradiation prior to hematopoietic stem cell transplantation in Japan: survey of the Japanese Radiation Oncology Study Group (JROSG). *J Radiat Res* 2018;59:477–83.
8. Hurkmans CW, Knegjens JL, Oei BS et al. Management of radiation oncology patients with a pacemaker or ICD: a new comprehensive practical guideline in the Netherlands. Dutch Society of Radiotherapy and Oncology (NVRO). Radiot. *Oncologia* 2012;7:198.
9. Gauter-Fleckenstein B, Israel CW, Dorenkamp M et al. DEGRO/DGK guideline for radiotherapy in patients with cardiac implantable electronic devices. *Strahlenther Onkol* 2015;191:393–404.
10. Salerno F, Gomellini S, Caruso C et al. Management of radiation therapy patients with cardiac defibrillator or pacemaker. *Radiol Med* 2016;121:515–20.
11. Tajstra M, Gadula-Gacek E, Buchta P et al. Effect of therapeutic ionizing radiation on implantable electronic devices: systematic review and practical guidance. *J Cardiovasc Electrophysiol* 2016;27:1247–125.

12. Indik JH, Gimbel JR, Abe H et al. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. *Heart Rhythm* 2017;14:e97–e153.
13. Zecchin M, Severgnini M, Fiorentino A et al. Management of patients with cardiac implantable electronic devices (CIED) undergoing radiotherapy: a consensus document from Associazione Italiana Aritmologia e Cardiostimolazione (AIAC), Associazione Italiana Radioterapia Oncologica (AIRO), Associazione Italiana Fisica Medica (AIFM). *Int J Cardiol* 2018;225: 175–83.
14. Tajstra M, Blamek S, Niedziela JT et al. Patients with cardiac implantable electronic devices undergoing radiotherapy in Poland. Expert opinion of the Heart Rhythm Section of the Polish Cardiac Society and the Polish Society of Radiation Oncology. *Kardiol Pol* 2019;77:1106–16.
15. Ohno T, Soejima T, Sekiguchi Y et al. JASTRO/JCS Guidelines for radiotherapy in patients with cardiac implantable electronic devices. *J Radiat Res* 2021;62:172–84. https://doi.org/10.1093/jrr/rraa102.
16. Hristova Y, Köhn J, Preus S et al. A clinical example of extreme dose exposure for an implanted cardioverter-defibrillator: beyond the DEGRO guidelines. *Strahlenther Onkol* 2017;193: 756–60.
17. Wadasadawala T, Pandey A, Agarwal JP et al. Radiation therapy with implanted cardiac pacemaker devices: a clinical and dosimetric analysis of patients and proposed precautions. *Clin Oncol* 2011;23:79–85.
18. Kesek M, Nyholm T, Asklund T. Radiotherapy and pacemaker: 80 Gy to target close to the device may be feasible. *Europace* 2012;14:1595.
19. Ahmed I, Zou W, Jabbour SK. High dose radiotherapy to automated implantable cardioverter-defibrillator: a case report and review of the literature. *Case Rep Oncol Med* 2014;2014: 989857.
20. Scobioala S, Ernst I, Moustakis C et al. A case of radiotherapy for an advanced bronchial carcinoma patient with implanted cardiac rhythm machines as well as heart assist device. *Radiat Oncol* 2015;10:78.
21. Martínez-Sande JL, García-Seara J, Rodríguez-Mañero M. Radiotherapy in a leadless pacemaker. *Europace* 2018;20:81.
22. Mielczarek S, Syska P, Lewandowski M et al. A pacemaker-dependent patient undergoing high-dose stereotactic radiotherapy with the device located in the radiation area. *Kardiol Pol* 2020;78:607–8.
23. Schernthaner C, Kopp M, Dagn K et al. Safe application of extensive radiotherapy to a cardiac resynchronization device. *ESC Heart Fail* 2020 Oct 11;7:4293–6.
24. Gauter-Fleckenstein B, Nguyen J, Jahnke L et al. Interaction between CIEDs and modern radiotherapy techniques: Flattening filter free-VMAT, dose-rate effects, scatter radiation, and neutron-generating energies. *Radiother Oncol* 2020;153:196–202; and Gauter-Fleckenstein B, Nguyen J, Jahnke L *et al.* Corrigendum to "Interaction between CIEDs and modern radiotherapy techniques: flattening filter free-VMAT, dose-rate effects, scatter radiation, and neutron-generating energies" [*Radiother Oncol* 2020;**152**;196–202]. *Radiother Oncol* 2021;**154**;291.
25. Nakamura K, Aoyama T, Kaneda N et al. Effect of X-ray dose rates higher than 8 Gy/min on the functioning of cardiac implantable electronic devices. *J Radiat Res* 2020;61:419–25.
26. Aslian H, Kron T, Watts T et al. The effect of stereotactic body radiotherapy (SBRT) using flattening filter-free beams on cardiac implantable electronic devices (CIEDs) in clinical situations. *J Appl Clin Med Phys* 2020;21:121–31.
27. Grant JD, Jensen GL, Tang C et al. Radiotherapy-induced malfunction in contemporary cardiovascular implantable electronic devices. *JAMA Oncol* 2015;1:624–32.
28. Matsubara H, Ezura T, Hashimoto Y et al. Prediction of radiation-induced malfunction for cardiac implantable electronic devices (CIEDs). *Med Phys* 2020;47:1489–98; and Matsubara H. CIEDs (cardiac implantable electronic devices) error due to neutrons from X-ray therapy equipment. *Impact* 2021;**2021**:31–3.
29. Firestone RB. *Table of Isotopes*, 8th edn. New York: John Wiley & Sons, 1996.
30. Baumann RC, Smith EB. Neutron-induced boron fission as a major source of soft errors in deep submicron SRAM devices. *2000 IEEE International Reliability Physics Symposium Proceedings. 38th Annual (Cat. No.00CH37059)*. 2000, pp. 152–157. doi: 10.1109/RELPHY.2000.843906.
31. Raitt MH, Stelzer KJ, Laramore GE et al. Runaway pacemaker during high-energy neutron radiation therapy. *Chest* 1994;106:955–7.
32. Hoecht S, Rosenthal P, Sancar D et al. Implantable cardiac defibrillators may be damaged by radiation therapy. *J Clin Oncol* 2002;20:2212–3.
33. Lau DH, Wilson L, Stiles MK et al. Defibrillator reset by radiotherapy. *Int J Cardiol* 2008;130:e37–8.
34. Zweng A, Schuster R, Hawlicek R et al. Life-threatening pacemaker dysfunction associated with therapeutic radiation: a case report. *Angiology* 2009;60:509–12.
35. Makkar A, Prisciandaro J, Agarwal S et al. Effect of radiation therapy on permanent pacemaker and implantable cardioverter-defibrillator function. *Heart Rhythm* 2012;9:1964–8.
36. Elders J, Kunze-Busch M, Smeenk RJ et al. High incidence of implantable cardioverter defibrillator malfunctions during radiation therapy: neutrons as a probable cause of soft errors. *Europace* 2013;15:60–5.
37. Mouton J, Haug R, Bridier A et al. Influence of high-energy photon beam irradiation on pacemaker operation. *Phys Med Biol* 2002;47:2879–93.
38. Hurkmans CW, Scheepers E, Springorum BG et al. Influence of radiotherapy on the latest generation of pacemakers. *Radiother Oncol* 2005;76:93–8.
39. Hurkmans CW, Scheepers E, Springorum BG et al. Influence of radiotherapy on the latest generation of implantable cardioverter defibrillators. *Int J Radiat Oncol Biol Phys* 2005;63: 282–9.
40. Zaremba T, Jakobsen AR, Thogersen AM et al. The effect of radiotherapy beam energy on modern cardiac devices: an in vitro study. *Europace* 2014;16:612–6.

41. Mollerus M, Naslund L, Lipinski M et al. Radiation tolerance of contemporary implantable cardioverter-defibrillators. *J Interv Card Electrophysiol* 2014;39:171–5.
42. Baehr A, Conrads L, Oertel M et al. Impact of different radiation techniques and doses on cardiac implantable electronic devices. *Z Med Phys* 2021;31 S0939-3889(20)30132-X.:327–35. https://doi.org/10.1016/j.zemedi.2020.12.003 Epub ahead of print.
43. Nakamura K, Aoyama T, Kaneda N et al. Implantable cardiac pacemaker failure by cumulative dose effects of flattening filter free beams. *J Radiat Res* 2021;62:735–9. https://doi.org/10.1093/jrr/rrab041 Epub ahead of print.
44. Zecchin M, Artico J, Morea G et al. Radiotherapy and risk of implantable cardioverter-defibrillator malfunctions: experimental data from direct exposure at increasing doses. *J Cardiovasc Med* 2018;19:155–60.
45. Hill-Kayser CE, Plastaras JP, Tochner Z et al. TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions. *Bone Marrow Transplant* 2011;46:475–84.
46. Uiterwaal GJ, Springorum BGF, Scheepers E et al. Interference detection in implantable defibrillators induced by therapeutic radiation therapy. *Neth Heart J Phys* 2006;14:330–4.
47. Kapa S, Fong L, Blackwell CR et al. Effects of scatter radiation on ICD and CRT function. *Pacing Clin Electrophysiol* 2008;31:727–32.
48. Zaremba T, Jakobsen AR, Thogersen AM et al. Effects of high-dose radiotherapy on implantable cardioverter defibrillators: an in vivo porcine study. *Pacing Clin Electrophysiol* 2013;36:1558–63.
49. Augustynek M, Korpas D, Penhaker M et al. Monitoring of CRT-D devices during radiation therapy in vitro. *Biomed Eng Online* 2016;15:29.
50. Falco MD, Genovesi D, Caravatta L et al. A randomized in vitro evaluation of transient and permanent cardiac implantable electronic device malfunctions following direct exposure up to 10 Gy. *Strahlenther Onkol* 2021;197:198–208.
51. Adamec R, Haefliger JM, Killisch JP et al. Damaging effect of therapeutic radiation on programmable pacemakers. *Pacing Clin Electrophysiol* 1982;5:146–50.