The effect of radiotherapy beam energy on modern cardiac devices: an in vitro study

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Aims
Radiotherapy (RT) for malignancies can harm pacemakers (PMs) and implantable cardioverter-defibrillators (ICDs). There is some evidence that, besides cumulative dose, the damaging radiation effects increase with beam energy. The aim of this study was to determine whether modern PMs and ICDs are more sensitive to high-energy than to low-energy photon beams.

Methods and results
Two groups of unused PMs and explanted ICDs (five PMs and one ICD in each) were subjected to irradiations in a phantom with 6 and 18 megavolt (MV) photons, respectively. The devices were exposed to radiation at doses of 2 gray (Gy) daily to simulate two clinical scenarios with the PM/ICD in the RT field. A cumulative dose of 150 Gy was given to each device, corresponding to approximately twice the therapeutic dose. In the 6 MV group, one episode of PM malfunction was detected after reaching 150 Gy. In the 18 MV group, a total of 14 episodes of malfunction were detected starting at 30 Gy in all five PMs. No episodes appeared in the ICD, at the respective treatment groups. This corresponded to a hazard ratio of 9.11 [\( \approx \) 95% confidence interval (CI): 1.04–79.69] by Cox regression analysis between the two groups. In a repeated measures logistic regression model comparing the incidence rate of malfunctions, the odds ratio was 18.29 (\( \approx \) 95% CI: 1.52–219.41).

Conclusion
Photon beam energy plays a considerable role in inducing implantable cardiac device malfunctions. Low-energy RT may be safer in PM/ICD patients despite relatively high radiation dose to the device.

Keywords
Pacemaker • ICD • Radiotherapy • Ionizing radiation • Device malfunction

Introduction
The number of individuals with pacemakers (PMs) and implantable cardioverter-defibrillators (ICDs) increases. With age being a risk factor, there is a growing probability that some of these patients will develop malignancies and have indication for radiotherapy (RT) treatment.1,2

Pacemakers from the 1960s and the beginning of the 1970s were based on discrete bipolar transistors and were found highly resistant to ionizing radiation.3–5 In comparison, modern PMs and ICDs rely on complementary metal oxide semiconductors circuitry which has the advantages of greater reliability and lower power consumption.6 However, these devices have been reported to be more susceptible to ionizing radiation.7

Official guidelines for managing PM patients undergoing RT were published by the American Association of Physicists in Medicine back in 1994.8 This document gives no recommendations for RT in ICD patients. Furthermore, the recommendations by PM/ICD manufacturers vary regarding tolerable dose of ionizing radiation and follow-up.9

Radiation doses in RT are typically measured in grays (1 Gy = 1 Joule of absorbed energy of ionizing radiation per 1 kg of matter). Cumulative doses of curative RT for solid tumours range usually from 50 to 80 Gy.10–12 A typical radiation dose for breast cancer is about 50 Gy, while in case of lung cancer, cumulative doses of at least 60 Gy are usually administered.13,14 Lower doses of 20–40 Gy may be applied in the treatment of lymphomas.15,16 Commonly, so-called fractionation is used, i.e. the total dose is being delivered in smaller

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What’s new?

- Risk of modern electronic cardiac device malfunction during radiotherapy (RT) correlates with photon beam energy.
- During irradiations with low-energy photons, no pacemakers (PM)/implantable cardioverter-defibrillator (ICD) malfunctions occurred at therapeutic doses of radiation.
- In selected patients, removal of a PM/ICD may be unnecessary before the RT, provided low-energy photon beams are used.

fractions. Usually, 1.8–2 Gy is being given daily for 5 days of a week followed by a 2-day break. This serves two main purposes. First, normal cells are allowed to recover between fractions. Secondly, the survived tumour cells may have entered a more radiation-sensitive phase of the cell cycle before a subsequent fraction.

Photon (gamma ray) beams generated in a linear accelerator are typically applied in RT. Along with the cumulative dose, a parameter known as beam energy is being used. It determines the depth of maximum dose and the penetration properties of the beam. The energy of the photons used in the RT is measured in megavolts (MV) and may commonly range from 6 to 20 MV. The beam energy is being chosen individually at the planning stage of the RT, primarily based on the depth of the tumour.

Reimplantation of a cardiac device or usage of a temporary PM is currently advocated before RT if maximal dose to PM exceeds 2–10 Gy, while removal of the ICD is recommended at even lower radiation doses to the device.6,8,9,18,19 These dose levels are considerably lower than the cumulative target doses used in cancer treatment. On the other hand, every additional surgical intervention to the PM/ICD exposes the patient to a substantial hazard of infectious and surgical complications20–22 and probably augments healthcare costs.

Besides cumulative radiation dose, an increasing number of authors recommend limiting photon beam energy while treating patients with PM/ICD.11,23

During irradiations with photons of ≥10 MV, so-called secondary neutrons are being generated. These neutrons interact adversely with the electronics.19,23,24

The purpose of this in vitro study was to compare the effect of high-energy and low-energy photon beams on modern PMs and ICDs. The experiment was based on a realistic clinical scenario of a PM/ICD patient undergoing RT. The radiation fractions mimicked the actual RT doses used in the treatment of breast cancer, with five weekly doses of 2 Gy.13

Irradiations

Every device was irradiated repeatedly with 2 Gy for 5 days followed by a 2-day break. The photon beams were generated by a Clinac iX linear accelerator (Varian Medical Systems, Inc.) and delivered with a dose rate of 600 monitor units/min.

During irradiations, the devices were placed in a custom manufactured polymethyl methacrylate phantom (Figure 1) placed between adequate build-up material of solid water boards. This permitted locating the PMs/ICDs at the depth of dose maximum for each photon energy. The distance from the head of the linear accelerator to the surface of the phantom including build-up material was 100 cm. The irradiation field was 10 × 10 cm² for the PMs and 15 × 15 cm² for the ICDs. Radiotherapy treatment planning software (Eclipse v. 10.0, Varian Medical Systems, Inc.) was used to plan the irradiations.

After reaching a cumulative dose of 70 Gy, the doses per fraction in the 6 MV group were increased. They consisted of 10, 10, 20, and 40 Gy and were delivered during the same day. In the 18 MV group, single doses were increased after reaching 50 Gy to 10, 10, 20, 20, and 30 Gy. After reaching 80 Gy in this group, the intervals between the irradiations were prolonged to a median of 55 days (inter-quartile range 28–75). The irradiations were chosen not to be performed during the same day to avoid exposing the investigators to the increased in-room level of induced radioactivity due to secondary neutrons. The intervals

Methods

Devices

Ten unused PMs and two explanted fully functional ICDs were used in the study. The devices came from five different manufacturers: Biotronik SE & Co. KG; Boston Scientific Corporation; Medtronic, Inc.; Sorin S.p.A.; and St Jude Medical, Inc.

The following devices were irradiated with 6 MV photons: Biotronik Evia DR-T, Boston Scientific Altrua 60, Medtronic Adapta L, Sorin Esprit DR, St Jude Medical Zephyr XL DR, and Medtronic Secura VR.

The remaining devices (Biotronik Evia DR-T, Boston Scientific Altrua 60, Medtronic Adapta, Sorin Esprit DR, St Jude Medical Zephyr XL SR, and Medtronic Maximo II DR) were irradiated with 18 MV photons. The PMs were programmed with standard settings, e.g. DDDR 60–130 b.p.m., output 3.5 V/0.4 ms on both channels. Regarding the ICDs, antitachycardia pacing and shock therapies were inactivated. Ventricular tachycardia (VT) monitor zones were programmed active, e.g. VT zone from 167 b.p.m. and ventricular fibrillation zone from 214 b.p.m. All lead connector ports were closed with pin plugs.

Figure 1 Polymethyl methacrylate phantom used during the in vitro irradiations. The phantom was cut to fit all generator models. Room temperature water was added to fill the cut.
between irradiations were also prolonged due to logistic constraints at our institution.

In both the 6- and the 18 MV group, cumulative radiation doses of 150 Gy per device were delivered, thus exceeding approximately twice the clinically used target doses.

Interrogations
The PMs and ICDs were interrogated after every radiation dose either on the same or on the following day, using manufacturer-specific standard telemetry equipment. The presence or absence of the following events was recorded:

- Noise during the RT sessions;
- Spontaneous change in programmed device parameters without reset to backup mode;
- Reset to backup mode or other error; recoverable using the programmer;
- Error, not recoverable using the programmer;
- Clinically significant reduction in battery capacity;
- Inappropriate antitachycardia pacing or delivery of shock therapy in the ICDs in spite of deactivation of these functions;
- Loss of telemetry.

When all irradiations were completed, the devices were interrogated at least twice during a period of at least 2 months.

Statistical analysis
The cumulative dose until first potentially clinically hazardous failure was recorded for every device. An equivalent of survival analysis was then performed. The cumulative dose of ionizing radiation was used as a substitute for timescale.

The data were interval censored as the exact radiation dose at malfunction was unknown. To accommodate for this, the events were placed either at the starting point of the interval, at the mid-point, or at the end-point of the interval. Using a Cox proportional hazard regression model, the mid-points were compared. In the same manner, start-point events in the 6 MV group were compared with endpoint events in the 18 MV group, and vice versa. Owing to the low number of events, P values do not have any practical interpretation, and confidence intervals (CIs) may not have 95% coverage. Hence, we refrain from reporting P values, and emphasize that caution should be taken when interpreting CIs.

The incidence rate of all potentially hazardous malfunctions was compared between the two groups with regard to the cumulative dose. To accommodate for the correlation within PMs, a population averaged repeated measures logistic regression model was applied to detect potential differences between the groups. This requires a balanced design between the groups. The dose per fraction was not the same for the two groups; hence, a balanced design was achieved by collapsing non-overlapping intervals.

All statistical analyses were performed using Stata version 12.1 (StataCorp).

Results
Detected PM and ICD malfunctions are summarized in Table 1. In the 6 MV group, no malfunctions were detected in Biotronik, Boston Scientific, St Jude Medical, or Sorin PMs. The Medtronic PM suddenly lost telemetry capability after reaching a cumulative dose of 150 Gy. Telemetry capabilities were neither present 6 nor 29 days later. However, the device was able to communicate at a supplementary interrogation 269 days after the last irradiation. The PM reported an electrical reset 81 days after last RT.

At interrogations, all the devices from Medtronic reported multiple ventricular high-rate episodes (VHRs). These episodes usually lasted a few seconds and were not related in time to RT.

In the 18 MV group, the Medtronic ICD lost its preprogrammed patient data after reaching 44 Gy. No other malfunctions in this device were recorded, except for the above-mentioned susceptibility to report artefacts as VHRs. All the PMs in the 18 MV group exhibited some degree of potentially hazardous failure. The most common abnormal behaviour was electrical reset, which is a fallback to backup or ‘safe’ mode. The PMs could be reprogrammed to the initial settings by using automatic algorithms in the programmers. However, the St Jude Medical PM could not be reprogrammed from the fallback mode after 150 Gy using the programmer. In the Medtronic PM, battery depletion was present after reaching 150 Gy. All the devices in the 18 MV group preserved their telemetry capabilities.

No inappropriate antitachycardia pacing or shock therapy was reported by the ICDs.

The Cox regression comparing the assumption of events occurring at the mid-point in both groups showed a hazard ratio (HR) of 9.11 (≏95% CI: 1.04–79.69). Comparison of events occurring at the start-point of intervals in the 6 MV group to endpoint in the 18 MV group yielded the same HR and CI, as events occurred in the same order. Assuming events occur at the endpoint in the 6 MV group and at the start-point in the 18 MV group, the Cox regression showed a HR of 11.32 (≏95% CI: 1.24–103.55).

The incidence rates of all episodes of potentially hazardous malfunctions in the two groups with regard to the cumulative dose were compared by repeated measures logistic regression. The 18 MV group showed an increased risk of malfunction with an odds ratio of 18.29 (≏95% CI: 1.52–219.41).

### Table 1 Recorded PM and ICD malfunctions during the irradiations

<table>
<thead>
<tr>
<th>Device</th>
<th>Malfunctions in the 6 MV group</th>
<th>Malfunctions in the 18 MV group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotronik PM</td>
<td>None</td>
<td>Reset after 100, 120, and 150 Gy</td>
</tr>
<tr>
<td>Boston Scientific PM</td>
<td>None</td>
<td>Reset after 30 Gy</td>
</tr>
<tr>
<td>Medtronic PM</td>
<td>No telemetry after 150 Gy</td>
<td>RRT/ERI detected after 150 Gy</td>
</tr>
<tr>
<td>Sorin PM</td>
<td>None</td>
<td>Reset after 80, 120, and 150 Gy</td>
</tr>
<tr>
<td>St Jude Medical PM</td>
<td>None</td>
<td>Error after 150 Gy</td>
</tr>
<tr>
<td>Medtronic ICD</td>
<td>None</td>
<td>None, except for loss of patient data after 44 Gy</td>
</tr>
</tbody>
</table>

A cumulative dose of 150 Gy was reached in all devices.

PM, pacemaker; ICD, implantable cardiover-defibrillator; MV, megavolt; Gy, gray; RRT, recommended replacement time; ERI, elective replacement indicator.
Discussion

Our study showed that the RT with high-energy photon beams has significantly more damaging effects on modern implantable cardiac devices than the RT using low-energy beams. A worst-case clinical scenario with a PM/ICD located in the radiation field was simulated in the study. The devices were exposed to cumulative doses of ionizing radiation $\sim 15$ times higher than what is currently considered safe for the devices. Also, the dose of 150 Gy is approximately two times higher than the clinically used cumulative doses.11,23

During irradiations with photons of $> 10$ MV energy, secondary neutrons are produced in parts of the accelerator. This process takes place when the photons interact with the components in the accelerator head.25 The magnitude of neutron contamination increases proportionally with photon beam energy.26 It is known that scattered neutrons can have negative effects on electronics.26,27

Within an electronic device such as a PM or an ICD, the most sensitive part of the circuit is the random access memory, as this contains information only by small amounts of electric charge. The microprocessor of a PM/ICD is equipped with an error detection algorithm that regularly performs a checksum of the software. If an error is detected, a correction algorithm is executed. Following such a correction, the software may reset.28 A reset to a backup mode may thus be regarded as a safety measure. In such a case, the error presumably occurred at the software level and was corrected by the microprocessor. However, such an event can have adverse clinical effects, as the device loses the preprogrammed settings. In case of an ICD, this could potentially lead to inappropriate or withheld antidysrhythmia therapy.

Hashii et al.24 compared the effects of different beam energies on four ICDs from one manufacturer in vitro. An accelerated course of RT was imitated with the ICDs outside the RT field. Interrogating the devices every 10–50 Gy, the authors found that scattered radiation with 18 MV photons led to a greater number of software errors, compared with 10 MV. Dosimetry showed that during high-energy beaming, more neutrons are generated. The authors expressed their concern regarding the risk of ICD malfunction during high-energy photon irradiations even with devices located at a distance from the RT field.

Patient cases of PM/ICD malfunction during treatment with high-energy irradiation with devices outside the RT field have previously been published as well. Thomas et al.29 reported on a patient, who experienced an RT-induced electrical reset of a single-chamber ICD. The reset had occurred during an RT session with 18 MV photons for bronchial carcinoma with the ICD kept outside the radiation field. No symptoms or other possibly radiation-induced device dysfunctions were recorded. The authors speculated on the adverse effects of electromagnetic interference from the linear accelerator as a possible cause of the reset.

Lau et al.30 reported a similar case of a single-chamber ICD resetting twice during the RT sessions with 23 MV photons to the pelvic area. Real-time interrogation of the same device during an RT treatment showed no malfunctions such as over-sense or triggering. All the parameters of the ICD remained normal. The radiation dose to the device was $< 3\%$ of that recommended as safe by the manufacturer. The authors thus suggested that the cumulative dose cannot be used as a stand-alone parameter.

Gelblum and Amols31 reported data on 34 ICD patients undergoing RT at their institution. In two patients, the ICDs had reverted to nominal settings during a course of RT with 15 MV photons. In both cases, the irradiations were delivered to the pelvic area. The remaining patients in the series were treated with 6 MV photons. Among these, no ICD malfunctions were recorded, although some devices were exposed to cumulative doses of $> 2$ Gy. As an explanation for these differences, the authors proposed the effect of neutrons.

Soejima et al.31 performed a prospective survey of PM/ICD patients undergoing RT in Japan from 2006 to 2008. The study included 60 patients with PMs and 2 with ICDs. Device reset occurred in one PM patient who was treated with 15 MV photons for prostate cancer. Neutron contamination was pointed out as the probable reason for the malfunction. Moreover, in six patients, absorbed doses to the cardiac devices exceeded 2 Gy without any malfunctions. The authors recognized that device failure can occur even outside the RT field.

Finally, the effect of secondary neutrons on ICD malfunction was clearly suspected by Eiders et al.23 The authors reported on 15 ICD patients who underwent 17 RT treatments. In 29% of these treatments, ICD malfunctions were recorded. All of them occurred in patients treated with photons of $> 10$ MV energy. Interestingly, the malfunctions occurred despite the fact that the ICDs were located outside the RT field. In the same paper, an increase in measured neutron dose with increasing photon beam energies was reported. Careful monitoring of ICD patients undergoing high-energy RT was advocated.

The effects of ionizing radiation on electronic devices seem to be able to manifest by two different pathways, as highlighted by Bradley and Normand.28 One pathway is proportional to the cumulative dose of ionizing radiation. It is mostly explained by ionizing radiation creating so-called electron/hole pairs in silicon dioxide. SiO$_2$ functions as an insulator in integrated circuit (IC). The holes, being more immobile than electrons, tend to be trapped at Si and SiO$_2$ interfaces inside the IC. This, in turn, can lead to a change in the parameters of the circuit. For example, a transistor in the IC can remain turned on, although no voltage at its gate is applied.22

The other pathway is more unpredictable and can manifest as IC errors occurring regardless of cumulative radiation dose. In the physics community, these phenomena are called single-event effects. They in turn can be destructive (‘hard errors’) or non-destructive (‘soft errors’), the latter being much more common.28

In the present study, we demonstrate the correlation between photon beam energy and incidence of malfunctions in modern implantable cardiac devices from five major manufacturers. Potentially hazardous malfunctions were included in the statistical analysis. A loss of programmed patient data also occurred in the ICD exposed to 18 MV photons. Note that a loss of battery capacity was observed in Medtronic PM in the 18 MV group. In our opinion, this malfunction could be induced by the effect of total absorbed dose. This estimation can be supported by the fact that ionizing radiation can lead to the formation of false connections between adjacent components, resulting in current leaks within the circuit.6,31

Summing up, RT with low-energy photons may be safe in selected patients despite cumulative radiation doses of 70–80 Gy to the device.34 In some breast or lung cancer patients, a PM/ICD may
possibly be left in the RT field if the patient has a stable underlying rhythm and beam energy is kept < 10 MV. If such an approach is considered, close monitoring of the patient and regular checks of the device should be ascertained. Still, larger-scale studies would be needed to support this conclusion.35

**Limitations**

The study sample consisted of 12 devices, limited to 2 or 4 from each manufacturer. This limits the statistical power of our analyses. The unbalanced design of the study limited our ability to compare the incidence rate of all events. When collapsing non-overlapping intervals to achieve a balanced design, some information will be lost. No direct telemetry or monitoring of device output was performed during the irradiations. Minor software errors, eventually not reported at interrogations by the clinical programmer, could have been missed. Measurements of neutron doses were not performed in this study.

**Conclusions**

The recommendation to limit photon beam energy during the RT of the PM/ICD patients is supported by the findings of this study. The examined devices withheld cumulative doses of ionizing radiation higher than currently suggested as a safe margin. In the low-energy radiation setting, the devices tolerated doses higher than those used clinically. In the absence of updated international guidelines, close cooperation between oncologists and cardiologists in managing PM/ICD carriers undergoing RT is recommended. In low-energy RT, the relocation of a PM/ICD may be avoided in carefully selected patients.

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**References**


