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RADIOTHERAPY IN PATIENTS WITH PACEMAKERS AND IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

BY
TOMAS ZAREMBA

DISSERTATION SUBMITTED 2015
Radiotherapy in Patients with Pacemakers and Implantable Cardioverter Defibrillators

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The Faculty of Medicine, Aalborg University, Denmark has approved this PhD dissertation for public defense. The public lecture and defense will take place May 29, 2015 at 13.00 in the Auditorium in the House of Research, Aalborg University Hospital.
Preface

This journey began in 2009 during my cardiology training at Aalborg University Hospital. I was fortunate enough to be approached by Anna Margrethe Thøgersen who proposed me to write a case report on a patient with a pacemaker functioning normally despite exposure to a relatively high radiation dose. At that time, it appeared that there were a rather limited number of studies present on the effects of ionizing radiation on heart rhythm devices. During the initial stage of working on the case report, cooperation with Sam Riahi and Annette Ross Jakobsen was established as well. This lead to our next work, where we conducted a survey of Danish radiotherapy and cardiology departments aiming to elucidate practical treatment of patients with a pacemaker or an implantable cardioverter defibrillator undergoing radiotherapy. Afterwards, we resolved to keep working in the field, as the number of pacemaker patients undergoing radiotherapy appeared to be increasing, and there still seemed to be numerous aspects to be explored.

Enrolled as a PhD student in September 2012, I had the great privilege to have Sam Riahi as my main academic advisor. He guided and supported me through the whole project with great enthusiasm. Sam’s inspiring commitment and his ability to show the way by seeing solutions in every challenge made this endeavor an exciting experience. I am grateful to Sam for introducing me to Mette Søgaard, who as my academic advisor played a key role in the epidemiological aspects of the study and made invaluable contributions during the writing process. I would also like to acknowledge and thank Anna Margrethe Thøgersen for sharing her great ideas and for being a great academic advisor always ready to discuss both small details and large questions of the project. Her practical electrophysiology skills were essential during our experiments.

Very special thanks go to Annette Ross Jakobsen who has been a fantastic colleague and partner, and who used tremendous amounts of her time and efforts during the experiments and data collection. Being the only physicist in our group, she played a pivotal role in guiding me through the technological aspects of radiotherapy. I owe also many thanks to Benedict Kjærgaard and his great team from the Biomedical Research Laboratory, Aalborg University Hospital, for their commitment, immense practical help during the in vivo study, and for making complex things possible and fun.

Furthermore, I thank all colleagues at cardiology and radiotherapy departments in Western Denmark for their enthusiasm and help during the data collection. It has been a great pleasure to work with you during this project. I am especially indebted to Peter Skogholt, Oncology Department, Vejle Hospital, for assisting with extraction of archived radiotherapy data.

In particular I would like to thank Søren Pihlkræ Hjortsøj, the head of the Department of Cardiology, Aalborg University Hospital, for supporting me during the study and for allocating time for the project when it was most needed. I am also grateful to professor Erik Berg Schmidt for his assistance and practical guidance during the PhD study and to Lars Oddershede, Martin Berg Johansen, and Søren Lundbye-Christensen for their statistical support. I thank Lærke Bruun Madsen for her help during data collection in the epidemiology study. I also owe a big thank to Hanne Madsen for revising the manuscripts. Great thanks go as well to the rest of my colleagues at the Department of Cardiology, Aalborg University Hospital; amongst them, I thank fellow PhD student Jacob Moesgaard Larsen for the encouragement and helpful insights.

I am grateful to the manufacturers for donating pacemakers and implantable cardioverter defibrillators for the project: Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical.

Last, but definitely not the least, I would like to thank my charming wife Sandra and our two great sons Gustas and Ignas. Only your love and tremendous support have made it all possible.

Tomas Zaremba
February 2015
List of Papers

This thesis was based on the following papers:


Introduction

Since the first implantation of a pacemaker (PM) in humans by Senning and Elmqvist in 1958, implantable electronic devices have evolved into the mainstay of the treatment of cardiac rhythm disturbances.\(^1\)\(^-\)\(^3\) Initially used for management of bradyarrhythmias, these devices have during the last decades been increasingly used for treatment of tachyarrhythmias as well.\(^4\) An implantable PM consists of an impulse generator which is typically placed subcutaneously in the pectoral region and is connected to endocardium via one or two transvenous leads. Powered by a lithium battery, modern PMs rely on complementary metal oxide semiconductor (CMOS) technology, permitting incorporation of up to millions of transistors which in turn enable the usage of sophisticated programmable algorithms in the management of cardiac rhythm disturbances.\(^5\) Besides single and dual chamber PMs, cardiac resynchronization therapy PMs (CRT-P) are implanted in selected patients suffering from systolic dysfunction.\(^6\)\(^,\)\(^7\) In addition, due to treatment modalities such as antitachycardia pacing (ATP) and shock therapy, implantable cardioverter defibrillators (ICDs) were proven effective in preventing sudden cardiac death in patients at risk of life threatening ventricular arrhythmias.\(^8\)\(^,\)\(^9\) In some devices, both defibrillator and resynchronization functions are used concurrently [cardiac resynchronization therapy defibrillators (CRT-D)].\(^6\)

With more than 700,000 new PMs and more than 200,000 new ICDs implanted worldwide each year, the rate of PM/ICD implantations is increasing both on a global scale and in Europe.\(^10\)\(^,\)\(^11\) In Denmark, 4,725 PMs were implanted in 2013, of which 3,543 (75.0%) were first implants.\(^11\) The corresponding numbers for ICDs were 1,285 and 890 (69.3%), respectively. In addition, 1,001 cardiac resynchronization therapy (CRT) units were implanted in Denmark in 2013.\(^11\)

As the functionality of modern PMs/ICDs to a high extent relies on sensing the intrinsic electrical signals of the heart, these devices may be susceptible to extraneous signals.\(^12\) In order to mitigate these effects, the manufacturers have introduced protective measures such as shielding in hermetic metal cases, signal filtering, interference rejection circuits, modern alternatives to reed switches, and use of bipolar leads.\(^12\)\(^,\)\(^13\) However, hazardous factors may still be present in the medical environment: e.g. electrosurgery, direct current external defibrillation, magnetic resonance imaging (MRI), neurostimulation, radiofrequency catheter ablation, lithotripsy, diagnostic radiation, and cancer radiotherapy (RT).\(^14\) As interference from these factors may lead to malfunction of the cardiac rhythm devices, the ability to predict and reduce these negative effects plays a central role for safe treatment of PM/ICD patients in these circumstances.

This project focuses on external beam RT for cancer in PM/ICD patients. Based on three research papers, the present work emphasizes the epidemiological, clinical, and safety aspects in the management of patients with PM/ICD undergoing RT.
Background

Due to the ageing and growth of the world population, the burden of cancer is increasing. The number of new cancer cases is expected to increase worldwide from 12.7 million in 2008 to 21.4 million by 2030, with lung cancer being the most frequently diagnosed cancer type in males and breast cancer in females. Likewise, the incidence of cardiovascular diseases is increasing. Being responsible for 31% of deaths worldwide, cardiovascular diseases are projected to maintain this leading position by 2030. As a result of the age being a risk factor for both cardiovascular diseases and cancer, there is a growing probability that some of PM/ICD patients will develop malignancies and receive RT treatment.

Among cancer treatment options, RT has become an established therapy method in oncology, in both curative and palliative intent, with at least 50% of all cancer patients requiring RT during the course of their illness. RT uses high energy radiation to kill or damage cancer cells and stop them from growing and multiplying. Radiation doses used in cancer therapy are measured in grays (1 Gy = 1 joule of absorbed energy of ionizing radiation per 1 kg of matter). Commonly, RT is given as a course of several treatments over days or weeks with daily fractions of typically 1.8-2 Gy. This serves two main purposes. Firstly, normal cells are allowed to recover between fractions. Secondly, the survived tumor cells may have entered a more radiation-sensitive phase of the cell cycle before a subsequent fraction. Cumulative doses of curative RT for solid tumors generally range from 50 to 80 Gy. A typical radiation dose for breast cancer is about 50 Gy, while cumulative doses of at least 60 Gy are administered for lung cancer. Lower doses of 20-40 Gy may be applied in treatment of lymphomas, whereas RT for bone metastases usually consists of 8-30 Gy in 1-10 fractions.

At present, the most commonly used types of radiation in RT are photons or electrons, which are generated and delivered by a RT machine called linear accelerator (LINAC). Along with other characteristics, the radiation beams are often described by their depth dose curves (Figure 1). By increasing the beam energy of the LINAC, the depth of the maximal delivered radiation dose also increases. Hence, photons in megavolt (MV) range (commonly 6-20 MV) are used for more deeply located tumors, whereas electrons due to their sharp decline with increasing depth and hence finite range are typically used for superficially located tumors. Kilovolt (kV) photons are also often used for superficial lesions such as skin cancer.

RT is normally delivered according to an individually designed treatment plan based on image data derived from modalities such as computed tomography (CT), MRI, positron emission tomography, and ultrasound. When creating this treatment plan, beam energy is chosen according to depth of the tumor, also taking other parameters such as the number of RT fields and their angles into account.

Besides injuring the tissues, ionizing radiation may cause damage to the circuits in electronic implants. In the early years of treatment with PMs, RT did not pose any considerable threat, as the devices from the 1960s and the beginning of the 1970s were based on discrete bipolar transistors and were found to be highly resistant to ionizing radiation. In comparison, modern PMs and ICDs rely on CMOS circuitry which has the advantages of greater reliability and lower power consumption. However, these devices have been reported to be more susceptible to malfunctions at exposure to ionizing radiation.

Official guidelines for managing PM patients undergoing RT were published by The American Association of Physicists in Medicine Task Group No. 34 (AAPM TG-34) in 1994 and give no recommendations for RT in ICD patients. Furthermore, the recommendations by PM/ICD manufacturers vary regarding both tolerable dose of ionizing radiation and follow-up. Reimplantation of a cardiac device or use of a temporary PM is currently advocated before RT if the maximal dose to the PM exceeds 2-10 Gy, while removal of the ICD is recommended at even lower radiation doses to the device. While these dose levels are lower than the cumulative target doses used in cancer treatment, every additional surgical intervention to the PM/ICD exposes the patient to a substantial hazard of infectious and surgical complications and likely augments healthcare costs. Importantly, while some devices are able to resist radiation doses considerably higher than recommended as safe, other PMs/ICDs may malfunction despite exposure to only scattered radiation from RT to an anatomically remote area.

Besides external beam RT, RT is in some cases delivered as short range brachytherapy. While the literature on the effects of this treatment modality on PMs/ICDs is limited, no device malfunctions during brachytherapy have been reported so far. Meanwhile, although there seems to be no solid evidence that kV photons should harm modern PMs/ICDs, a few prior case reports have described PM malfunctions during diagnostic (kV) radiation, e.g. in relation to CT.

Figure 1: Depth doses for different radiation types and energies.

\( \text{kV} = \text{kilovolt}; \text{MeV} = \text{megaelectronvolt}; \text{MV} = \text{megavolt} \).
Aims and hypotheses

Aims

Study I
- To assess the influence of high-energy (18 MV) photon beams on modern PMs and ICDs compared to low-energy (6 MV) photon beams.

Study II
- To evaluate the effects of cumulative radiation dose and beam energy on ICDs in vivo.
- To determine the feasibility of a porcine model to study the effects of ionizing radiation on ICDs.

Study III
- To quantify the annual rates of RT in patients with PM/ICD.
- To elucidate safety measures used in clinical practice during RT in PM/ICD patients.
- To quantify the frequency of PM/ICD malfunctions during RT.
- To identify the predictors of PM/ICD malfunctions during RT.

Hypotheses
- Modern PMs/ICDs can resist higher doses of ionizing radiation than generally anticipated (Study I and II).
- Animal models are feasible for studying the effects of RT on ICDs in vivo (Study II).
- The rate of RT in PM/ICD patients in the general population is increasing (Study III).
- The use of safety measures varies during RT in PM/ICD patients in clinical practice (Study III).
- PM/ICD malfunctions can be predicted based on parameters of RT and/or type of the device (Study I and III).
Materials and methods

Study I

The purpose of the study was to evaluate the effects of high-energy photon beams on modern PMs/ICDs compared to the effects of low-energy photon beams in a realistic clinical scenario mimicking the actual RT doses used in treatment of a breast cancer.

Devices

Ten unused PMs and two explanted fully functional ICDs were exposed to either 6 MV or 18 MV photons (Table 1).

Table 1: Devices irradiated in vitro in Study I.

<table>
<thead>
<tr>
<th>Device type</th>
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<tr>
<td>DDD</td>
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<td>DDD</td>
<td>St. Jude Medical Zephyr XL DR</td>
<td>AAI/VVI</td>
<td>St. Jude Medical Zephy XL SR</td>
</tr>
<tr>
<td>VVI-ICD</td>
<td>Medtronic Secura VR</td>
<td>DDD-ICD</td>
<td>Medtronic Maximo II DR</td>
</tr>
</tbody>
</table>

AAI = single chamber atrial pacemaker; DDD = dual chamber pacemaker; DDD-ICD = dual chamber implantable cardioverter defibrillator; MV = megavolt; VVI = single chamber pacemaker with ventricular lead; VVI-ICD = single chamber implantable cardioverter defibrillator.

The PMs were programmed with standard settings, e.g. DDDR 60-130 beats per minute (bpm), 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 bpm and ventricular fibrillation (VF) zone from 214 bpm. All lead connector ports were closed with pin plugs.

Irradiations

Each device was irradiated repeatedly with 2 Gy daily for five days followed by a two-day break. The photon beams were generated by a Clinac iX LINAC (Varian Medical Systems, Inc., Palo Alto, CA, USA) 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 2) 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, as the depth where maximum dose is delivered correlates with beam energy and field size. The distance from the radiation source to the surface of the phantom including build-up material was 100 cm. The irradiation field was 10 cm x 10 cm for the PMs and 15 cm x 15 cm for the ICDs. RT treatment planning software (Eclipse v. 10.0, Varian Medical Systems, Inc., Palo Alto, CA, USA) 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, 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 (IQR) 28-75]. The irradiations were chosen not to be performed during the same day in order to avoid exposing the investigators to the increased in-room level of induced radioactivity due to secondary neutrons. The intervals 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.

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. Presence or absence of the following events was recorded:

- Noise during RT sessions;
- Spontaneous change in programmed device parameters without reset to backup mode;
Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators

- 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 two months.

**Study II**

The study was performed as a porcine in vivo experiment of accelerated RT delivered to implanted modern ICDs simulating a worst case scenario of a device irradiated directly in the RT field.

**Implantation procedures**

Five pigs (1 Göttingen minipig and 4 Danish Landrace pigs), all weighing around 40 kg, were implanted with ICD systems in our Biomedical Research Laboratory. The reason for switching from one pig race to another was purely logistic.

Prior to the implantation procedures, the animals were pre-anesthetized with intramuscular injection of Zoletil. Zoletil is a veterinarian medicine consisting of a mixture of two dissociative anesthetics (Ketamine 6.25 mg/ml and Tiletamine 6.25 mg/ml), a benzodiazepine (Zolazepam 6.25 mg/ml), a synthetic opioid (Butorphanol 1.25 mg/ml), and Xylazin (6.25 mg/ml).

The animals were intubated and ventilated with Sevofluran 1% using a Dameca Dream anesthesia machine (Dameca, Rodovre, Denmark). Volume-controlled respiration was used. During surgery, the anesthesia was maintained with intravenous infusion of Fentanyl 50 µg/ml at 10 ml/h rate and infusion of Midazolam 5 mg/ml at 10 ml/h rate. The blood pressure was monitored invasively via femoral artery cannulation. If needed, single doses of intravenous Ketamine 50-100 mg (50 mg/ml) as an anesthetic, potassium chloride 10 mmol to correct hypokalemia, and Lidocaine 100 mg (10 mg/ml) for ventricular arrhythmias were administered during the anesthesia. Antibiotic prophylaxis consisted of a single dose of periprocedural intramuscular Gentamycin 80 mg (40 mg/ml) and intramuscular Benzylpenicillin 5 millions IU, the latter continued q.d. for 3 days.

The following ICD generators from five different manufacturers were implanted:

- Biotronik Lumax 540 DR-T, unused;
- Boston Scientific Energen ICD F141, unused;
- Medtronic Maximo II CRT-D D284TRK, unused;
- Sorin Paradym SonR CRT-D 8770, explanted;
- St. Jude Medical Uniﬁy CD3235-40, unused.

The Medtronic ICD was implanted in a Göttingen minipig, while the remaining devices were implanted in Danish Landrace pigs.

Intravenous access for placement of the leads was acquired by Seldinger technique through a puncture of the brachiocephalic vein. Medtronic Capsurefix Novus 5076 52 cm active fixation leads (Medtronic Inc., Minneapolis, MN, USA) were used as right atrium leads. St. Jude Medical Durata 7120, 65 cm active fixation leads (St. Jude Medical, Inc., St. Paul, MN, USA) were implanted in the right ventricular septum in all animals. In the Sorin ICD, left-sided Medtronic Ability Plus 4296, 88 cm (Medtronic, Inc., Minneapolis, MN, USA) lead was implanted to a branch in the coronary sinus as well. Due to price constraints, the left ventricle connector ports in the Medtronic and St. Jude Medical ICDs were left unused and were closed with pinplugs. The positions of the leads in the heart were verified by fluoroscopy. The generators were ﬁxed and placed in a subcutaneous pocket after making an incision on the left side of the cranial part of the sternum. Shock therapy was not tested at the implantations.

In the postoperative period, all animals were housed in the laboratory and observed for signs of infection and failure to thrive. Intramuscular injections of Ketoprofen 300 mg (150 mg/ml) t.i.d. for 3 days were used as a pain killer.

**Irradiations**

After an average observation time of 9 days (range 4-18), the animals were anesthetized with intramuscular injections of Zoletil and transported to one of the treatment rooms in our Radiotherapy Department. The initial dose of Zoletil was 4-5 ml, supplemented with 2 ml as needed during the study. During the transportation and the irradiations, the pigs were intubated and ventilated with Sevofluran 1% by a portable anesthesia machine Siemens SV 900 (Siemens AG, Munich, Germany).

The animals were positioned in a supine position supported by a vac lock bag (Par Scientiﬁc A/S, Odense, Denmark) on the accelerator couch. A Varian Clinac IX LINAC (Varian Medical Systems, Inc., Palo Alto, CA, USA) was used (Figure 3). During the study, the heart rhythm was monitored with an ECG monitor visible in the operator room.

The ICDs were interrogated, and all antitachycardia therapies were programmed OFF, while detection was left ON. Two or three zones were programmed, e.g. a VT zone between 150 bpm and 200 bpm, a fast VT zone between 200 bpm and 250 bpm, and a VF zone above 250 bpm.

RT with 6 MV photons and field dimensions of 15 cm x 15 cm, with the ICD generator in the center, was planned with a source-to-surface distance of 100 cm. The area above the ICD generator was covered with 5 mm Superflap build-up material (Mick Radio Nuclear Instruments Inc., Mt. Vernon, NY, USA) in order to achieve the adequate dose to the ICD. The gantry was rotated to ensure a perpendicular direction of the beam toward the ICD generator.

Incremental doses of 6 MV photons to the ICD generators were delivered: 0.5 Gy, 1.0 Gy, 2.0 Gy, 5.0 Gy, and 10.0 Gy, with a total radiation dose of 18.5 Gy. Photon energy was then increased to a maximum of 18 MV. The area over the ICD generators was covered with additional 10 mm of Superflap build-up material to a total of 15 mm in order to achieve the adequate dose for the ICDs. Irradia-

tion with correspondingly increasing identical doses to the ICDs was performed, thus reaching a cumulative dose of 37.0 Gy in all cases.
Interrogations
The ICDs were interrogated after every dose step. Programmed parameters were assessed, and battery status, lead impedance, sense, and capture threshold were measured. After the irradiations, the shock function of the ICDs was tested. Before this, all pigs were treated with extra anesthetics and with Rocuronium, a muscle relaxant. The shock function of the ICDs was tested with both single- and dual-coil setting. VF was induced by T-wave shock or 50 Hz pacing.

Upon completion of the shock testing, a new control of the devices was performed. Afterwards, the animals were killed with an overdose of intravenous Pentobarbital 6 g (300 mg/ml), and the ICDs were removed. All ICDs were also interrogated 2, 4, and 17-18 days later. Time period from the irradiations to last additional interrogation ranged from 75 to 402 days.

Study III
Study population
The Danish National Patient Registry (DNPR) contains information on all inpatient hospitalizations at Danish non-psychiatric hospitals since 1977 and on all emergency room and hospital outpatient specialist clinic visits since 1995. Each hospital visit is recorded by physicians with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th edition (ICD-8) until the end of 1993, and ICD-10 thereafter. The DNPR also includes codes for performed procedures: Danish Hospital Sector Classification System (used since 2000); Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (used in 1996-2000); and procedure codes used historically before NOMESCO.

We used the DNPR to identify all patients in Western Denmark with at least one PM/ICD-related procedure or diagnosis code registered from January 1, 1977 to December 31, 2012 (all codes are provided in Appendix A) who also had a code for RT (planning of RT or external RT) recorded between January 1, 2003 and December 31, 2012. Patients with RT performed prior to insertion of their PM/ICD were excluded.

Radiotherapy data
Data on RT treatments were collected from RT-planning systems at Aalborg University Hospital, Aarhus University Hospital, Herning Regional Hospital, and Vejle Hospital. In cases of incomplete data in the planning systems, the medical files were reviewed. If needed, data from the DNPR were subsequently used to identify the start and/or end dates and the number of fractions of RT course.

Data included information on the hospital where RT was delivered, start date, end date, anatomical region irradiated, cumulative tumor dose, number of fractions, fraction dose (maximal applied during the RT course), beam type, and beam energy (maximal applied during the RT course). The anatomical regions were classified as: head and neck, thorax, esophagus, abdomen and pelvis, spine (thoracic and lumbar), upper extremity, and lower extremity. In case two anatomical regions were treated simultaneously, the one closest to the PM/ICD generator was recorded. If both photons and electrons were applied, the treatment was classified as photon RT.

PM/ICD data
Data on PMs/ICDs were collected from implanting cardiology departments at the following hospitals in Western Denmark: Aalborg University Hospital, Aarhus University Hospital, Esbjerg Hospital, Haderslev Hospital, Herning Regional Hospital, Kolding Hospital, Vejle Hospital, and Viborg Regional Hospital. The data included information on device class (PM, CRT-P, ICD, or CRT-D), device type [single chamber atrial PM (AAI), single chamber PM with ventricular lead (VVI), single chamber pacemaker with ventricular lead and dual chamber sensing (VDD), dual chamber pacemaker (DDD), CRT-P, single chamber ICD (VVI-ICD), dual chamber ICD (DDD-ICD), or CRT-D], generator manufacturer, model, hospital of implantation, and follow-up.

Safety measures
For each RT course we collected information on potential safety measures: evaluations at the PM/ICD clinic including visits before,
during, and after RT. Scheduling of supplementary visits up to three months after RT was recorded as well. Other recorded safety measures were reprogramming of the device before RT, application of a magnet to the ICD during RT, use of a temporary PM, and surgical relocation of the generator.

Complications related to application of a temporary PM or relocation of the device occurring during a six-month period were also recorded. The following complications were defined as major: lead-related re-intervention, local infection requiring re-intervention, device-related systemic infection/endocarditis, pneumohotax requiring drainage, cardiac perforation (without or with intervention), pocket revision because of pain, generator-lead interface problem with re-intervention, haematoma requiring re-intervention, deep venous thrombosis, Twiddler’s syndrome, wound revision, stroke, acute myocardial infarction (AMI), procedure-related death. Minor complications included haematoma without re-intervention, resulting in a prolonged hospital stay, hospital re-admission, or additional out-patient visit, wound infection treated with antibiotics, conservatively treated pneumothorax, and lead dislodgement without re-intervention, as suggested by Kirkfeldt et al. 59

Outcome
Information on PM/ICD malfunctions potentially attributable to RT was obtained through reviews of cardiology records, including PM/ICD follow-up charts. Remote monitoring controls were included if documented in the patient file. The follow-up period ended at first PM/ICD evaluation after completion of RT course or on December 31, 2013, whichever came first.

PM/ICD malfunctions were categorized as:
- Electrical reset to backup mode or other minor software error;
- Electrical reset or other software error requiring reprogramming of the device by the manufacturer;
- Unexpected decrease in battery capacity without reaching elective replacement indicator (ERI);
- Unexpected ERI;
- Loss of telemetry;
- Change in one or several lead parameters eventually resulting in supplementary visits or lead replacement (only the changes suspected at the subsequent device control to have occurred due to RT and not explained by other variables, such as changes in antiarrhythmic drugs, were recorded);
- Noise oversense without symptomatic pacing inhibition, ATP, or shock therapy;
- Oversense with symptomatic pacing inhibition, ATP, or shock therapy.

Statistical analyses

Study I
Using the cumulative dose of ionizing radiation as a substitute for time scale, an equivalent of survival analysis was performed until first potentially clinically hazardous failure for every device.

The data were interval censored as the exact radiation dose at the exact time malfunction occurred 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.

Kaplan-Meier curves were plotted to illustrate this approach. 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 to end-point events in the 18-MV group, and conversely. Due 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 of the cumulative dose. To accommodate for correlation within pacemakers a population averaged repeated measures logistic regression model was applied to detect potential differences between groups. 60 This requires a balanced design between groups. The dose per fraction were not the same for the two groups, hence a balanced design was achieved by collapsing non-overlapping intervals.

Study II
In this descriptive explorative study, continuous variables were expressed as absolute values or means. Changes in PM/ICD battery voltages were analyzed by linear regression.

Study III
Continuous variables were reported as medians and IQRs. Categorical variables were expressed as counts and percentages. Continuous variables were compared by Wilcoxon rank sum test. The annual rate of RT in PM/ICD patients was calculated by using the total Western Denmark population (obtained from Statistics Denmark).

The device malfunctions and safety measures were compared at RT treatment course (consisting of one or more fractions) level. Only RT courses with a later device control were included in the analysis of the malfunctions.

Odds ratios (ORs) with 95% CIs of PM/ICD malfunctions were computed using logistic regression. Independent variables in the model were type of device (ICD vs. PM), anatomical region irradiated (below vs. above the diaphragm), cumulative radiation dose to the tumor (10 Gy increments), fraction dose (1 Gy increments), and beam energy (215 MV vs. .15 MV). The cut-off value of 15 MV for beam energy was chosen entirely based on sensitivity and specificity, since this value gave a high sensitivity to detect device malfunctions (79%) and a higher specificity (61%) than other values with equally high sensitivity. Adjusted ORs were adjusted for beam energy.

As some patients received more than one RT course, the RT courses were not completely independent. To accommodate for this dependence, the method of generalized estimating equations was used in a generalized linear model. 61

Statistical analyses were performed using Stata versions IC 11.2 and 13.1 (StataCorp LP, College Station, TX, USA).

Ethics
Prior to the experiments in Study II, a written permission to conduct the study was obtained from the Danish Animal Experiments Inspectorate (permission number 2011/561-59). Study III was approved by the Danish Health and Medicines Authority (record number 3-3013-300/1) and the Danish Data Protection Agency.
allowing the researchers to access registry data and to review medical records of the study patients.
Results

Study I

Detected PM and ICD malfunctions are summarized in Table 2. 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. The 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 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 artifacts as VHRs. All PMs in the 18-MV group exhibited some degree of potentially hazardous failure. The most common abnormal behavior was electrical reset, which is a fallback to backup or “safe” mode. The PMs could be reprogrammed to initial settings by using automatic algorithms in the programmers except the St. Jude Medical PM (after 150 Gy). In the Medtronic PM, battery depletion was present after reaching 150 Gy. All devices in the 18-MV group preserved their telemetry capabilities. No inappropriate ATP or shock therapy was reported by the ICDs.

Figure 4 shows the radiation dose given before first malfunction. The Cox-regression analysis comparing the assumption of events occurring at the mid-point in both groups showed a hazard ratio (HR) of 9.11 (approximate 95% CI: 1.04-79.69). Comparison of events occurring at the start-point of intervals in the 6-MV group to end-point in the 18-MV group yielded the same HR and CI, as events occurred in the same order. Assuming that events occur at the end-point in 6-MV and at the start-point in the 18-MV yielded a HR of 11.32 (approximate 95% CI: 1.24-103.55).

Table 2: Recorded pacemaker and ICD malfunctions during the irradiations. A cumulative dose of 150 Gy was reached in all devices.

<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>Reset after 32, 42, 80, 100, and 120 Gy</td>
</tr>
<tr>
<td>Medtronic ICD</td>
<td>None</td>
<td>Error after 150 Gy</td>
</tr>
</tbody>
</table>

ERI = elective replacement indicator; Gy = gray; ICD = implantable cardioverter defibrillator; MV = megavolt; PM = pacemaker; RRT = recommended replacement time.

Figure 4: Kaplan-Meier graph of dose to first malfunction.

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

Study II

The animals tolerated the implantation procedures, transportations, and irradiations well. No significant hemodynamic disturbances or infectious complications were present.

During all irradiations, the animals maintained sinus rhythm without any arrhythmias on the monitor. Programmed settings in all the ICDs remained stable between the fractions. During the irradiations, the devices reported no stored arrhythmias, noise, or oversense events. No reset, other unexpected behavior, or malfunction in the ICDs was observed during the irradiations. The ICDs detected VF correctly and delivered therapy as programmed in all tests. Defibrillator threshold in dual coil and active can configuration ranged from 10.4 to 41 J, and from 10 to 41 J in single coil and active can.

In the Medtronic ICD, a temporary decrease in battery voltage by 0.16 V or 5.2% was observed starting at a cumulative dose of 18.5 Gy. This decline was statistically significant by linear regression analysis, with 0.018 V between interrogations (p=0.028). Battery voltage at interrogations 2, 4, and 18 days after the irradiations was 2.97 V, 2.98 V, and 3.06 V, respectively, thus returned to the initial value.

In the Sorin ICD, the magnet rate had decreased from 91 to 85 bpm at interrogation 2 days after the irradiations. The ICDs detected VF correctly and delivered therapy as programmed in all tests. Defibrillator threshold in dual coil and active can configuration ranged from 10.4 to 41 J, and from 10 to 41 J in single coil and active can.

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In the Sorin ICD, the magnet rate had decreased from 91 to 85 bpm at interrogation 2 days after the irradiations. The ICDs detected VF correctly and delivered therapy as programmed in all tests. Defibrillator threshold in dual coil and active can configuration ranged from 10.4 to 41 J, and from 10 to 41 J in single coil and active can.

Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators

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to a safe program: pace mode VVI 70 bpm, output 7.5 V / 1.5 ms, VF zone from 150 bpm (400 ms), maximum energy shock of 40 J. The ICD could not be reprogrammed using a clinical interface in the programmer, and a firmware update of the ICD had to be performed by the manufacturer. Afterwards, no malfunction was detected at controls up to 75 days from the irradiations.

Compared with data at the day 2 control, the Boston Scientific ICD showed an increase in power consumption and a decrease in remaining battery charge at the interrogation 4 days after the irradiations. The power consumption increased from 31 to 40 µW, and the remaining battery charge decreased from 1.70 to 1.67 Ah. The parameters were at 31 µW and 1.67 V at the day 17 interrogation and remained stable.

During the study, all lead parameters, including impedance, sense, and capture threshold, remained stable.

**Study III**

**Descriptive characteristics**

Among 690 PM/ICD patients recorded in the DNPR, we included 560 (81.2%) patients with 678 separate RT courses in the study (Figure 5). Among the 130 excluded patients, 79 (60.8%) only had a temporary PM before RT, while the remaining 51 (39.2%) were excluded due to not receiving RT, not having a PM/ICD at all, PM/ICD not being implanted until RT, only having a loop recorder, or RT being started after 2012.

The annual rate of RT courses in PM/ICD patients increased by 199% from 1.45 to 4.33 per 100,000 person-years from 2003 to 2012 (Figure 6).

The median age at start of RT (first RT in case of several RT courses) was 75.6 years (IQR 69.3-81.7 years), with predominance of males (68.4%). Most patients had only one device during the study period. Six patients (1.1%) had two devices (Table 3).

Bradycardia PMs constituted the majority of the devices [462 (82.5%)] of which dual chamber models were dominant [331 (59.1%) of 560 devices]. There were 25 (4.5%) CRT-Ps. Defibrillators, including ICDs [54 (9.6%)] and CRT-Ds [19 (3.4%)], represented 73 (13.0%) of the devices.

Among the 678 separate RT courses, complete data on both the device and RT were available in 658 (97.1%), of which 453 (68.8%) had at least one subsequent PM/ICD control. One-year mortality among patients with complete data on last RT course, but no device control afterwards, (n=185) was 93.5% compared with 28.2% among those who had a device control (n=358). In the RT courses with subsequent control, patients tended to be younger and were more often treated with kV photons or electrons, while tumor dose, beam energy, proportion of ICDs, as well as frequency of RT to thorax were higher compared with RT courses without control.

The most common anatomical region was thorax (36.0%) followed by head and neck (27.2%), and abdomen and pelvis (27.1%). The remaining 9.7% regions were spine, extremities, and esophagus. Median time from device implantation to start of RT was 2.7 years (IQR 1.0-5.0).

The PMs/ICDs were manufactured by 13 companies, with Medtronic most frequently represented [227 (40.1%) of 556 devices with known manufacturer], followed by St. Jude Medical [175 (30.9%)] (Appendix B).

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**Figure 5: Flowchart of the study population in Study III.**

**Figure 6: Annual rates of radiotherapy courses in patients with pacemakers or implantable cardioverter defibrillators in Western Denmark, 2003-2012.**
Electrons

Supplementary within 3 months

Under the diaphragm

During RT*

kV photons

≥15 MV

≥15 MV

<15 MV

Table 3: Baseline characteristics of 560 patients with pacemaker or implantable cardioverter defibrillator receiving radiotherapy, 2003-2012.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years†</td>
<td>75.6 (69.3-81.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>383 (68.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>177 (31.6)</td>
</tr>
<tr>
<td>Number of RT courses per patient†</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>470 (83.9)</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>73 (13.0)</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>13 (2.3)</td>
</tr>
<tr>
<td>4, n (%)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>5, n (%)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>10, n (%)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Age of the device at RT, years†</td>
<td>2.6 (0.9-4.8)</td>
</tr>
<tr>
<td>Device class†</td>
<td></td>
</tr>
<tr>
<td>Single chamber PM, n (%)</td>
<td>130 (23.2)</td>
</tr>
<tr>
<td>Dual chamber PM, n (%)</td>
<td>331 (59.1)</td>
</tr>
<tr>
<td>PM, unspecified, n (%)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>CRT-P, n (%)</td>
<td>25 (4.3)</td>
</tr>
<tr>
<td>ICD (single and dual chamber), n (%)</td>
<td>54 (9.6)</td>
</tr>
<tr>
<td>CRT-D, n (%)</td>
<td>19 (3.4)</td>
</tr>
</tbody>
</table>

CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; PM = pacemaker; RT = radiotherapy. Values are shown as median (interquartile range). †During first RT course with the first device in case of several RT courses and/or several devices in the patient.

Safety measures

Precautionary device relocation from the RT field was performed in 24 (3.5%) of 678 RT courses. In these cases, the same generator was reused in two (83.3%) patients. At least one lead was extracted in eight (33.3%), and at least one new lead was implanted in 20 (83.3%) procedures. Among RT courses to thorax with complete data (n=237), in cases where the device was relocated, both the cumulative radiation dose and the beam energy were higher compared with RT courses without PM/ICD relocation (46.5 Gy [IQR 22.5-48 Gy] and 20 Gy [IQR 10-30 Gy], respectively, p=0.0001, and 15 MV [IQR 9-18 MV] and 6 MV [IQR 6-15 MV], respectively, p=0.0011). One of the patients suffered a major complication after device relocation (AMI). In terms of minor complications, the same patient had a displacement of the atrial lead without intervention. Another patient experienced a hematoma in the pacemaker pocket resulting in additional clinic visits. No backup temporary PM was used for any of the RTs.

Data on scheduling visits at PM clinics specifically due to upcoming RT was available for 655 RT courses in 549 patients. In 101 (15.4%) of these RT courses, the patient was seen both before and upon completion of the RT course, while 47 (7.2%) patients were only controlled before RT and 82 (12.5%) only had a control after completion. Thus, device controls due to RT before and after the RT course were performed in 148 (22.6%) and 183 (27.9%) RT courses, respectively. Among 533 RT courses consisting of more than one fraction, device control was performed at least once during the RT course in 76 (14.3%) of RT courses. A supplementary control within three months after RT was performed in 26 (4.0%) RT courses. The proportion of RT courses leading to device controls was highest among RT courses with photons in MV range, followed by electrons and kV photons (Figure 7). The median time from last RT fraction to first device control was 31 days (IQR 2-145 days) in 453 RT courses with a subsequent control. In 205 (31.2%) RT courses the device was never controlled after the RT (Figure 5).

The proportion of RT courses leading to a subsequent device evaluation was higher when the tumor was located above the diaphragm and in cases where higher beam energy was used (Figure 8). Hence, at <15 MV, the patients were scheduled for a device evaluation after 26.2% of RT courses given above the diaphragm and in 12.9% of those under the diaphragm (24.2% in total at <15 MV). At ≥15 MV, the proportions were 42.0% and 29.1%, respectively (34.4% in total at ≥15 MV).

Figure 7: Proportions of radiotherapy courses with device controls scheduled due to radiotherapy, classified by beam type.

Application of a magnet to the ICD during irradiations after cardiologists recommendation was used in 8 (10.8%) of 74 treatments with implanted ICD in treatments with available data on safety measures. Reprogramming of the device prior to RT was only documented in nine PMs and one ICD (1.5% of 655 RT courses), and it mainly consisted of increasing pacing output and/or reprogramming to fixed-mode pacing. In the ICD, the antitachycardia therapies were inactivated during the RT sessions.

Device malfunctions

Among 453 RT courses with complete data on devices and RT and a device control after RT, 14 (3.1%) device malfunctions occurred (Table 4).
Predictors of device malfunctions

Crude logistic regression analysis showed that PM/ICD malfunctions were associated with beam energy ≥15 MV (OR 5.73, 95% CI 1.58-20.76) and location of the tumor below the diaphragm (OR 4.31, 95% CI 1.42-13.12) (Table 5).

The median cumulative radiation dose in RT courses associated with device malfunctions was 46.5 Gy (IQR 20-70 Gy), and the median beam energy was 16.5 MV (IQR 15-18 MV) compared with 30 Gy (IQR 20-52 Gy) and 8 MV (IQR 6-15 MV) in treatments without malfunctions. No PM/ICD malfunctions were observed during electron RT or photon RT in kV range.

Seven (50%) malfunctions occurred during RT for tumors located in abdomen or pelvis while 4 (28.6%) involved RT of the thorax (Appendix C). The most frequent malfunction was electrical reset or transient minor software errors, occurring in 11 (78.6%) of affected devices. In these cases, the device could be reprogrammed by the staff in the clinic, whereas in 2 (14.3%) cases, assistance from the manufacturer was necessary in order to update the software of the device. In one PM, the only deviation was an increase in atrial pacing threshold from 1.25V to 2.75V. Importantly, no malfunctions required device explantation or lead revision. In terms of other adverse clinical consequences from the malfunctions, one patient experienced diaphragmatic pacing after the reset of a single-chamber PM which ceased after reprogramming of the device.
adjustment for beam energy, the latter remained the only signifi-
cant predictor of device malfunction.

Interestingly, no significant correlation was detected between
device malfunctions and cumulative radiation dose to the tumor
(adjusted OR 1.13, 95% CI 0.89-1.44) or fraction dose (adjusted OR
0.92, 95% CI 0.71-1.18). Although insignificant, device malfunctions
were more frequent in ICDs (6.8%) compared with PMs (2.5%),
adjusted OR 2.93, 95% CI 0.87-9.86.
Prevalence of patients with PM/ICD undergoing RT

To date, no large-scale studies on the size of the population of PM/ICD patients undergoing RT have been performed. In 1991, Rodriguez et al. estimated, based on clinical experience, that 0.4-0.5% patients undergoing RT had a PM/ICD. In 2000, Tsekos et al. reported that they saw at least 10 PM patients per year at their RT department at a university hospital. In 2004, Solan et al. also stated that any busy RT department would see several PM/ICD patients per year. More recently, Gossman et al. estimated, based on survey data, that the median proportion of RT patients requiring a change in the RT approach due to PM/ICD was 0.8%, and expected the total proportion of RT patients having a PM/ICD to be higher. In the present study, the annual rate of RT courses in Western Denmark reached 4.33 per 100,000 person-years in 2012. Our findings also demonstrate a sharp increase in the annual rate by 199% during the ten-year period from 2003 to 2012.

Probability and consequences of device malfunction

Since the publication of the AAPM TG-34 guidelines, numerous in vitro experiments on the effects of RT on both PMs and ICDs have been reported (Table 6 and Table 7).

Variations exist in the reported rates of device malfunctions. Differences are also present in terms of radiation doses at these episodes. Hurkmans et al. irradiated 19 PMs with 6 MV photons to a dose of up to 120-130 Gy. Points of first malfunctions varied from 10 to 120 Gy, while five devices were irradiated with full dose without any adverse effects. In the largest in vitro study so far, Mouton et al. analyzed the effects of direct irradiation with 18 MV photons on 96 PMs, reaching doses up to 200 Gy per device. The authors classified the observed malfunctions, with three of the classes being potentially lethal: amplitude change of >10%, pauses in electrical signal of >10s, and permanent silence. These malfunctions were observed at doses starting from 2 Gy, 0.15 Gy, and 0.5 Gy, with mean doses at their occurrence of 56 Gy, 17.4 Gy, and 71 Gy, respectively. The majority (70%) of malfunctions were observed at a dose rate of 8 Gy/min, with no malfunctions occurring at or below the dose rate of 0.2 Gy/min, thus suggesting that dose rate is a potential risk factor in inducing PM/ICD malfunctions.

In terms of in vitro studies on ICDs, Hurkmans et al. exposed 11 ICDs to 6 MV photons, reaching a dose of 120 Gy. Failures were observed in all devices with doses at first malfunction varying from 0.5 Gy to 120 Gy. Of note, sensing interference was observed in all these devices, potentially leading to shock therapy in case of a clinical situation. At the same time, exposing 20 ICDs (including 8 CRT-Ds) to 4 Gy of scattered radiation from a 6 MV photon beam, Kapa et al. reported no device malfunctions. Hashii et al. 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. In addition, 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.

Along with in vitro experiments, a number of case reports and case series have been published as well (Table 8 and Table 9). In terms of malfunction rate, the proportion of 3.1% in Study III is in line with a retrospective study by Gossman et al., who reported device malfunctions in four (3.6%) out of 112 RT courses in PM/ICD patients. With a median time from RT to the first device control of 31 days in 453 devices, the follow-up period in Study III corresponds to 14043 device-days, suggesting approximately 1 malfunction per 1000 device-days. Hence, this rate seems to be higher than the rate of spontaneous minor software errors of approximately 1 event per 13000 device-days, as observed by Bradley and Normand in ICDs. The rate of device malfunctions in Study III might even have been higher, since 24 devices were relocated before the RT. The proportion of device malfunctions is comparable with the findings by Makkar et al. who observed two partial resets of ICDs, exposed to 1.23 Gy and 0.04 Gy, respectively, (2.9% of all devices) among 69 patients [50 (72.5%) PMs, 19 ICDs]. The remaining intact devices received doses ranging from 0.9 to 5.057 Gy with 6-16 MV photons with or without electrons. In a study of 62 patients [60 (96.8%) PMs, 2 ICDs], Soejima et al. observed one PM (1.6% of all devices) that reset during RT for prostate cancer with 15 MV photons. The remaining 61 devices were exposed to radiation doses reaching as high as 20.7 Gy (>2 Gy in six cases), thus indicating that PMs/ICDs may develop malfunctions outside the RT beam and the occurrence of malfunctions may not be related to radiation dose.

Regarding proton beam RT, Oshiro et al. observed malfunctions in two (25%) out of eight PM patients with devices located outside the RT field. In a study of 42 patients (28 PMs, 14 ICDs) undergoing proton RT with varying doses to the device, Gomez et al. observed five resets during thoracic RT in four (9.5%) patients and an expected ERI in one patient. Hence, these limited clinical data suggest that probability of PM/ICD malfunction during proton RT might be higher compared with photon RT. However, with only five devices described in an in vitro setting of proton RT, probably no direct firm conclusions can be drawn to support this statement. Clinical data on neutron beam RT in PM/ICD patients are even scarcer. To the best of our knowledge, there has only been published one case report on uncontrollable pacing occurring during neutron RT to thyroid. Although limited to 16 PMs, in vitro data suggest that PMs/ICDs might be even more sensitive to neutron RT compared with other beam types.
Table 6: Studies examining the effects of radiotherapy on pacemakers in vitro, published in English since 1994.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>n</th>
<th>Beam type</th>
<th>Beam energy, MV</th>
<th>Maximal generator dose, Gy</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Souliman†</td>
<td>77</td>
<td>Photons</td>
<td>8</td>
<td>70</td>
<td>Complete failure at 16.8-70 Gy in 11 PMs. No effects from EMI alone.</td>
</tr>
<tr>
<td>1999</td>
<td>Mouton‡</td>
<td>42</td>
<td>Photons (n=19); Co-60 (n=23)</td>
<td>4 (LINAC); 1.17-1.33 (Co-60 source)</td>
<td>140</td>
<td>No malfunction at therapeutic doses (n=15); frequency modifications (n=9) starting at 2 Gy; deprogramming and modification in battery characteristics (n=11) starting at 4 Gy; destruction of the PM (n=7) at 44-77 Gy.</td>
</tr>
<tr>
<td>2002</td>
<td>Mouton§</td>
<td>96</td>
<td>Photons</td>
<td>18</td>
<td>200</td>
<td>Amplitude change &gt;10%: 38 PMs at 2-130 Gy; silence &gt;10 s: 35 PMs at 0.15-74 Gy; permanent silence: 12 PMs at 0.5-170 Gy.</td>
</tr>
<tr>
<td>2005</td>
<td>Hurkmans‖</td>
<td>19</td>
<td>Photons</td>
<td>6</td>
<td>120; 130 (n=2)</td>
<td>5 PMs: no malfunction; 7 PMs: no output at 80-130 Gy; 5 PMs: ERI at 120-130 Gy; 2 PMs: no communication at 20-130 Gy; 8 PMs: inhibition during direct irradiations.</td>
</tr>
<tr>
<td>2008</td>
<td>Oshiro¶</td>
<td>1</td>
<td>Protons</td>
<td>250</td>
<td>NA (35 Gy to the lead)</td>
<td>No malfunctions.</td>
</tr>
<tr>
<td>2011</td>
<td>Koivunoro∥</td>
<td>2</td>
<td>Epithermal neutrons</td>
<td>0.414 eV &lt; E &lt; 9.12 keV</td>
<td>1.2; 2.0</td>
<td>Reset due to memory changes in microprocessor; many severe bit flips and loss of telemetry. Both PMs got activated.</td>
</tr>
<tr>
<td>2012</td>
<td>Trigano¶</td>
<td>14</td>
<td>Neutrons</td>
<td>3.5-50 (peak around 20)</td>
<td>NA</td>
<td>Electrical reset in 6 cases.</td>
</tr>
<tr>
<td>2014</td>
<td>Zaremba¶ (Study I)</td>
<td>10</td>
<td>Photons</td>
<td>6; 18</td>
<td>150</td>
<td>6 MV group: one episode of malfunction at 150 Gy; 18 MV group: 14 episodes of malfunction starting at 30 Gy.</td>
</tr>
</tbody>
</table>

Co = cobalt; E = energy; EMI = electromagnetic interference; ERI = elective replacement indicator; eV = electronvolt; Gy = gray; LINAC = linear accelerator; MV = megavolt; PM = pacemaker.

Table 7: Studies examining the effects of radiotherapy on implantable cardioverter defibrillators in vitro, published in English since 1994.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>n</th>
<th>Beam type</th>
<th>Beam energy</th>
<th>Dose, Gy</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Hoecht∥∥</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>Scatter; &gt;50</td>
<td>No effects from EMI; scatter radiation: 1 fallback; direct exposure: malfunctions at &gt;50 Gy, unspecified.</td>
</tr>
<tr>
<td>2005</td>
<td>Hurkmans∥∥</td>
<td>11</td>
<td>Photons</td>
<td>6</td>
<td>120</td>
<td>Sensing interference in all ICDs, which would have resulted in shock in 4 ICDs. Failure of all devices at 0.5-120 Gy. Complete loss of function at 0.5-1.5 Gy in 4 ICDs.</td>
</tr>
<tr>
<td>2008</td>
<td>Kapa∥∥</td>
<td>20 (8 of them CRT-D)</td>
<td>Photons</td>
<td>6</td>
<td>4</td>
<td>No malfunctions.</td>
</tr>
<tr>
<td>2012</td>
<td>Hashimoto∥∥</td>
<td>4</td>
<td>Protons</td>
<td>200</td>
<td>Scatter</td>
<td>1 power-on reset per approximately 50 Gy, 1 soft error per approximately 15 Gy. No permanent malfunctions.</td>
</tr>
<tr>
<td>2013</td>
<td>Hashi∥∥</td>
<td>10</td>
<td>Photons</td>
<td>10; 18</td>
<td>Scatter</td>
<td>More soft errors during irradiation with 18 MV photons compared with 10 MV photons. No hard errors or permanent malfunctions.</td>
</tr>
<tr>
<td>2014</td>
<td>Mollerus∥∥</td>
<td>8</td>
<td>Photons</td>
<td>6</td>
<td>131.11</td>
<td>4 contemporary devices remained functional after 131.11 Gy despite minor memory faults in 3 of them; 4 legacy devices failed to deliver shock therapy after 41.11 Gy and had changes in lead impedance.</td>
</tr>
<tr>
<td>2014</td>
<td>Zaremba∥∥ (Study I)</td>
<td>2</td>
<td>Photons</td>
<td>6; 18</td>
<td>150</td>
<td>6 MV: no malfunctions; 18 MV: no malfunctions, except loss of patient data after 44 Gy.</td>
</tr>
</tbody>
</table>

CRT-D = cardiac resynchronization therapy defibrillator; EMI = electromagnetic interference; Gy = gray; ICD = implantable cardioverter defibrillator; MV = megavolt.
Concerning severity and clinical consequences of RT-induced PM/ICD malfunctions, removal of the device due to malfunction has been described in five published cases (two PMs, three ICDs) over the last two decades.\(^\text{74,80,82,84}\) Of note, the generators were located outside the direct RT field in all of these patients, and no lethal malfunctions have been reported. In a number of other published PM/ICD malfunction cases, the devices were either successfully reprogrammed, or the effects were transient, permitting completion of the RT.\(^\text{47,51,63,71,77,85}\) Similarly, no patients in Study III required device explantation, and the majority of the observed malfunctions were resets or transient software errors. In Study I, ERI was first recorded after 150 Gy in two devices, i.e. at supratherapeutic doses. In Study II, one episode of reset was observed, after which the device could be reprogrammed. Meanwhile, despite the fact that a PM/ICD after undergoing a reset is capable of delivering a basic treatment to the patient, it may be inappropriate for the patient to have the device functioning in this mode for a longer period due to deprivation of atrioventricular synchrony, rate-adaptive pacing, or biventricular pacing.\(^\text{85-88}\) In addition, one of the patients in Study III experienced diaphragmatic pacing. Regarding PM-dependent patients, while permanent or temporary loss of pacing during RT has been described in vitro experiments,\(^\text{65-67,77}\) this phenomenon to date has not been reported in a clinical setting. Concerns have been raised regarding noise oversense during RT, potentially leading to inappropriate shock therapies in ICD patients, as demonstrated in vitro by Hurkmans et al.\(^\text{67}\) So far, inappropriate tachycardia sensing without shock therapy has only been reported in one ICD patient undergoing RT to femur in a series (n=15) by Elders et al.\(^\text{51}\)

Although RT may affect the function of the generator of PM/ICD, the PM/ICD leads are considered to be resistant to these effects.\(^\text{41}\) Only one case report presented a course of RT where malfunction of an ICD shock lead was suspected due to direct irradiation, leading to device reimplantation.\(^\text{82}\) In Study III, an increase in pacing threshold was observed in two patients (0.4% of RT courses with subsequent device control), still none of the episodes required intervention.

### Table 8: Studies examining the effects of radiotherapy on pacemakers in vivo, published in English since 1994.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Devices, n</th>
<th>Tumor</th>
<th>Beam type</th>
<th>Beam energy</th>
<th>Tumor dose, Gy</th>
<th>Device dose, Gy</th>
<th>Outcome</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Raitt**</td>
<td>1</td>
<td>Thyroid</td>
<td>Neutrons</td>
<td>NA</td>
<td>4.8</td>
<td>0.9</td>
<td>Uncontrollable ventricular pacing at 180 bpm. Corruption of the programming code of the microprocessor.</td>
<td>Replacement of the device.</td>
</tr>
<tr>
<td>2000</td>
<td>Tsekos**</td>
<td>1</td>
<td>Right lower arm and axilla</td>
<td>NA</td>
<td>NA</td>
<td>50.4</td>
<td>50.4 (in the field)</td>
<td>Decrease in magnet rate, returning to normal 4 months later.</td>
<td>None</td>
</tr>
<tr>
<td>2001</td>
<td>Nibhanupudy**</td>
<td>1</td>
<td>Left breast and supraclavicular field</td>
<td>Photons</td>
<td>6</td>
<td>50.4</td>
<td>1.82</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2006</td>
<td>Ampil**</td>
<td>3</td>
<td>Lung</td>
<td>Photons</td>
<td>20-60</td>
<td>NA</td>
<td>No malfunctions.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Mitra**</td>
<td>1</td>
<td>Right lung and mediastinum</td>
<td>Photons</td>
<td>NA</td>
<td>40</td>
<td>1.66</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>Kapa**</td>
<td>8 (1 of them CRT-P)</td>
<td>Head and neck; thorax</td>
<td>Photons</td>
<td>6</td>
<td>30-69.96</td>
<td>NA (outside field)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>Oshiro**</td>
<td>8</td>
<td>Liver; lung (n=1)</td>
<td>Protons</td>
<td>155-250</td>
<td>36.3-77</td>
<td>NA (outside field)</td>
<td>Reverting to &quot;safety backup program&quot; after 46 Gy (n=1); 2 episodes (after 23 and 26 Gy) of changing in pacing frequency (n=1).</td>
<td>Both devices successfully reprogrammed.</td>
</tr>
<tr>
<td>2008</td>
<td>Zweng**</td>
<td>1</td>
<td>Esophagus</td>
<td>Photons</td>
<td>NA</td>
<td>30</td>
<td>0.11</td>
<td>Runaway PM. Change from DDD to AAI with a fixed rate of 185 bpm. Corruption of the software.</td>
<td>Circulatory collapse. Replacement of the device.</td>
</tr>
<tr>
<td>2010</td>
<td>Ferrara**</td>
<td>37</td>
<td>Various</td>
<td>Photons and electrons (95.6%); Co-60 (4.4%)</td>
<td>6; 18 (59%)</td>
<td>8-79.2</td>
<td>&gt;2 (n=5); &lt;2 (n=32)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>Croshaw**</td>
<td>3</td>
<td>Breast</td>
<td>Photons</td>
<td>38.5</td>
<td>0.23-0.73</td>
<td>No malfunctions.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Dasgupta**</td>
<td>1</td>
<td>Heart</td>
<td>Photons</td>
<td>37.5</td>
<td>0.37</td>
<td>Transient ventricular undersensing.</td>
<td>Devise successfully reprogrammed.</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Devices, n</td>
<td>Tumor</td>
<td>Beam type</td>
<td>Beam energy</td>
<td>Tumor dose, Gy</td>
<td>Device dose, Gy</td>
<td>Outcome</td>
<td>Clinical consequences</td>
</tr>
<tr>
<td>------</td>
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<td>-------------</td>
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<td>-----------------------</td>
</tr>
<tr>
<td>2011</td>
<td>Soejima\textsuperscript{43}</td>
<td>60</td>
<td>Various</td>
<td>NA</td>
<td>NA</td>
<td>20-74 \textsuperscript{43} (range in the whole study)</td>
<td>20.69 in 1 patient, otherwise not exceeding 4.78</td>
<td>1 CRT-P was found initialized at 46 Gy and 56 Gy (treated with 74 Gy 15 MV photons for prostate cancer).</td>
<td>Device successfully reprogrammed.</td>
</tr>
<tr>
<td>2011</td>
<td>Wadasadawala\textsuperscript{44}</td>
<td>8</td>
<td>Head and neck; breast; lung</td>
<td>Co-60 (n=3); photons (n=5)</td>
<td>Photons: 6 (n=3); 15 (n=2)</td>
<td>45-70</td>
<td>0.14-60 (including PM leads)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2012</td>
<td>Kesek\textsuperscript{45}</td>
<td>1</td>
<td>Lung</td>
<td>Photons</td>
<td>6</td>
<td>80</td>
<td>48</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2012</td>
<td>Kirova\textsuperscript{46}</td>
<td>1</td>
<td>Thoracic spine</td>
<td>Photons</td>
<td>20</td>
<td>30</td>
<td>0.3 (leads irradiated directly)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2012</td>
<td>Makkar\textsuperscript{47}</td>
<td>50</td>
<td>Various</td>
<td>Photons; photons and electrons</td>
<td>Photons: 6 (n=26); 16 (n=24). Both with or without electrons (6-16 MeV)</td>
<td>NA</td>
<td>0.844 +/- 0.997</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2013</td>
<td>Gomez\textsuperscript{48}</td>
<td>28</td>
<td>Various</td>
<td>Protons</td>
<td>NA</td>
<td>46.8-87.5</td>
<td>0.13-21 \textsuperscript{49} (range in the whole study)</td>
<td>Reset in 2 PMs, both treated to thorax, tumor doses at the episodes 4 Gy and 16.2 Gy, respectively. Distance from device to RT field 3 cm and 0.9 cm, respectively.</td>
<td>Both devices successfully reprogrammed.</td>
</tr>
<tr>
<td>2014</td>
<td>Ampiil\textsuperscript{50}</td>
<td>2</td>
<td>Head and neck</td>
<td>Photons</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2014</td>
<td>Gossman\textsuperscript{51}</td>
<td>67 (out of 107 devices)</td>
<td>Various</td>
<td>Presumably photons</td>
<td>Various</td>
<td>NA</td>
<td>&lt;2 in 85%, &gt;2 in 15%, not exceeding 6.5 (the whole study)</td>
<td>Failure at 0.3 Gy (n=1); increase in sensor rate during RT (n=1); irregular heartbeat leading to reprogramming (n=1); twinging in the chest wall resulting in respiratory arrest (n=1) (the whole study).</td>
<td>Not specified in more detail</td>
</tr>
<tr>
<td>2015</td>
<td>Zaremba\textsuperscript{52} (Study III)</td>
<td>487 (25 CRT-P)</td>
<td>Various (thorax 36% in the whole study)</td>
<td>MV photons, kV photons, electrons</td>
<td>9 (IQR 6-15) in all interrogated devices in the study</td>
<td>Various</td>
<td>NA</td>
<td>Reset or deprogramming (n=9); increase in atrial pacing threshold form 1.25 to 2.75 V (n=1) out of 394 interrogated PMs.</td>
<td>Devices successfully reprogrammed. No device replacements.</td>
</tr>
</tbody>
</table>

AAI = atrial pacing and sensing; bpm = beats per minute; Co = cobalt; CRT-P = cardiac resynchronization therapy pacemaker; DDD = dual chamber pacing and sensing; Gy = gray; IQR = interquartile range; kV = kilovolt; MeV = megaelectronvolt; MV = megavolt; PM = pacemaker.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Devices, n</th>
<th>Tumor</th>
<th>Beam type</th>
<th>Maximal beam energy</th>
<th>Tumor dose, Gy</th>
<th>Device dose, Gy</th>
<th>Outcome</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Hoecht$^{30}$</td>
<td>4 (3 patients)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 ICDs of the same model in the same patient fell into fall back mode at &lt;0.5 Gy to the ICD (RT to pelvis).</td>
<td>The device was replaced due to the first episode.</td>
</tr>
<tr>
<td>2004</td>
<td>John$^{31}$</td>
<td>1</td>
<td>Left breast</td>
<td>NA</td>
<td>NA</td>
<td>50</td>
<td>Leads: 50, partial exposure of the generator</td>
<td>Shock coil failure due to structural damage during RT was suspected (shock impedance &gt;125 ohms).</td>
<td>A new system was implanted.</td>
</tr>
<tr>
<td>2004</td>
<td>Thomas$^{32}$</td>
<td>1</td>
<td>Right lung</td>
<td>Photons</td>
<td>18</td>
<td>56</td>
<td>NA (outside field)</td>
<td>Electrical reset.</td>
<td>Unspecified (asymptomatic).</td>
</tr>
<tr>
<td>2007</td>
<td>Nemec$^{33}$</td>
<td>1</td>
<td>Left lung</td>
<td>NA</td>
<td>NA</td>
<td>59.4</td>
<td>NA (outside field)</td>
<td>Rapid pacing triggering polymorphic VT during the 3rd fraction of 1.8 Gy.</td>
<td>Collapse requiring resuscitation. Device removal afterwards.</td>
</tr>
<tr>
<td>2007</td>
<td>Sepe$^{34}$</td>
<td>1</td>
<td>Larynx</td>
<td>Photons</td>
<td>6</td>
<td>60</td>
<td>2.5</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>Kapa$^{35}$</td>
<td>5</td>
<td>Various</td>
<td>Photons</td>
<td>6</td>
<td>18-56</td>
<td>NA (outside field)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>Lau$^{36}$</td>
<td>1</td>
<td>Prostate</td>
<td>Photons</td>
<td>23</td>
<td>74</td>
<td>0.004</td>
<td>Resets during 2nd and 9th fractions of 2 Gy.</td>
<td>RT completed without other events. Normal ICD parameters afterwards.</td>
</tr>
<tr>
<td>2009</td>
<td>Gelblum$^{37}$</td>
<td>1+33</td>
<td>Various</td>
<td>Photons; electrons (n=1); photons and electrons (n=1)</td>
<td>6 (photons); 6 MeV (electrons); 6 MV and 9 MeV (photons and electrons); 15 (photons, n=2)</td>
<td>6-86.4</td>
<td>0.01-2.99</td>
<td>Reset in 2 patients treated with 15 MV photons, outside RT field.</td>
<td>Devices successfully reprogrammed.</td>
</tr>
<tr>
<td>2010</td>
<td>Ferrara$^{38}$</td>
<td>8</td>
<td>Various</td>
<td>Photons and electrons (95.6%); Co-60 (4.4%)</td>
<td>6; 18 (59%)</td>
<td>8-79.2</td>
<td>&gt;1 (n=2), &lt;1 (n=6)</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>Croshaw$^{39}$</td>
<td>2</td>
<td>Breast</td>
<td>Photons</td>
<td>6</td>
<td>38.5</td>
<td>1.01, 1.68</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>Soejima$^{40}$</td>
<td>2</td>
<td>Various</td>
<td>NA</td>
<td>NA</td>
<td>20-74 (range in the whole study)</td>
<td>NA</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2012</td>
<td>Makkar$^{41}$</td>
<td>19</td>
<td>Various</td>
<td>Photons; photons and electrons</td>
<td>6; 16. Both with or without electrons (6-16 MeV)</td>
<td>NA</td>
<td>0.921+-0.726</td>
<td>Partial resets in 2 devices after 1.23 Gy and 0.04 Gy 16 MV photons to the ICD, respectively.</td>
<td>RT completed successfully in both cases.</td>
</tr>
<tr>
<td>2013</td>
<td>Dell'Oca$^{42}$</td>
<td>1</td>
<td>Mediastinum</td>
<td>Photons</td>
<td>6</td>
<td>64</td>
<td>&lt;5</td>
<td>No malfunctions.</td>
<td>-</td>
</tr>
<tr>
<td>2013</td>
<td>Elders$^{43}$</td>
<td>15 (17 RT courses)</td>
<td>Various</td>
<td>Photons; photons and electrons (n=1)</td>
<td>6-18</td>
<td>16-70</td>
<td>&lt;1</td>
<td>6 malfunctions in 5 RT courses at 10 and 18 MV: invalid data retrieval (n=2), reset (n=1), inappropriate tachycardia sensing (n=1), reset and trend data error 9 months after the reset (n=1).</td>
<td>RT completed successfully in all patients.</td>
</tr>
<tr>
<td>2013</td>
<td>Gomez$^{44}$</td>
<td>14</td>
<td>Various</td>
<td>Protons</td>
<td>NA</td>
<td>46.8-87.5 (range in the whole study)</td>
<td>0.13-21</td>
<td>Reset after 40 Gy to the tumor (n=1); resets after 32.5 Gy and 47.5 Gy to the tumor (n=1).</td>
<td>Both devices successfully reprogrammed.</td>
</tr>
</tbody>
</table>
Predictors of device malfunction

The PM/ICD malfunctions seem to occur unpredictably as far as radiation dose is concerned both in vivo\textsuperscript{45-47,51,85,97} and in vitro\textsuperscript{55-57}. Besides the effects of radiation dose, RT beam energy has emerged as an important subject in several studies.\textsuperscript{48,51,69} We have clearly demonstrated this in Study I where a nine times higher risk of malfunction was observed in devices exposed to 18 MV photons compared with 6 MV. This was also proven to be the case in Study III, as beam energy ≥15 MV was the strongest predictor of PM/ICD malfunctions.

In Study III, there was also a trend of increased risk of malfunction in Devices compared to PMs, which is in line with previous reports that ICDs might be more sensitive to ionizing radiation than PMs.\textsuperscript{39,101} Unexpectedly, we observed that device malfunctions were associated with location of the RT fields below the diaphragm. This might be because beam energies used below the diaphragm were higher than those used above. Moreover, after adjustment for beam energy, the anatomical location was not significant associated with malfunction.

The correlation between damaging effects of RT on PMs/ICDs and dose rate was suggested by Mouton et al.\textsuperscript{66} Although not addressed directly in later studies, this concern was discussed by Hurkmans et al., who underlined that the dose rate to a PM/ICD located outside a direct beam with a dose rate of 1–10 Gy/min at isocenter is expected to be <1 Gy/min, hence not posing a considerable threat.\textsuperscript{41} In addition, the effects of dose rate on the device seem to be transient and reversible.\textsuperscript{62} The results of Study II appear in line with these considerations, as no ICD dysfunction was observed during the irradiation procedures.

Contemporary PMs/ICDs are relatively well protected against the effects of electromagnetic interference (EMI).\textsuperscript{13} Besides ionizing radiation, LINACs include several potential sources of EMI, such as couch drive motors, x-ray transformers, waveguides, power supplies, klystrons, or magnetrons,\textsuperscript{13} potentially leading to pacing inhibition, fixed rate pacing, or reprogramming.\textsuperscript{46} However, these effects are usually transient and are observed when the machine is turned on or off.\textsuperscript{102} In addition, modern LINACs are sufficiently shielded, and EMI typically does not pose any threats to the function of PMs/ICDs.\textsuperscript{41,103} This is supported by the findings of this project, especially Study III, where no events of symptomatic inhibition or rapid pacing were observed during RT.

It is unclear whether the different PM/ICD brands differ in risk of RT-induced malfunctions. The spectrum of the PM/ICD manufacturers represented in this project was relatively broad, and some were represented by few devices. Therefore, we were unable to draw any conclusions on this aspect.

Possible mechanisms

According to the literature, the manifestations of PM/ICD malfunctions can in broad terms be divided into three groups: 1) transient effects due to interference, occurring during the irradiation only; 2) reverting to backup settings (reset), recoverable after reprogramming the device; and 3) permanent damage to the device.\textsuperscript{77} Hashii et al. grouped PM/ICD errors during RT into hard errors and soft errors, with hard errors representing damage to the hardware of the device, while soft errors consist of software alterations.\textsuperscript{66} The latter group can be divided into severe reset requiring reprogramming of the device, moderate reset not requiring correction by the programmer, and minor error not detectable at interrogation and only recorded in the data log of the device.

The majority of all observed malfunctions in Studies I–III were electrical resets requiring reprogramming. Electrical reset, power-on-reset or fallback to back-up mode, is a relatively well known phenomenon in PM/ICD technology.\textsuperscript{76,86} It is a rather adequate behavior of the device, indicating that an error has been detected.\textsuperscript{88,104} In such case, the device switches from a software-
controlled mode to a basic hardware-driven condition. The purpose of this reversal is to ascertain basic pacing and an effective shock therapy in case of ICD. Electrical reset seems to pose no harm to the device itself, as the errors occur at software level without physical damage to the components, and the device can then usually be reprogrammed at interrogation. As demonstrated in Study II and Study III, in some of these cases, assistance by a manufacturer technician might be necessary. Production of high energy photons in a LINAC is accompanied by a generation of secondary neutrons which have a notoriously high capability of ionizing components of CMOS devices and inducing errors and resets. This underpins our findings of PMs/ICDs failing at high beam energies. Moreover, neutron production during electron RT is 5% and 20% of that during photon RT at 15 MV and 25 MV nominal energies, respectively. Thus, these aspects are in line with the fact that no device malfunctions were observed during electron or kV photon RT in Study III.

In contrast to soft errors, hard errors consist of structural damage to the device. There have been only few published cases describing other device damages than electrical resets in relation to RT. In Study III, an increase in pacing threshold occurred in 2 (0.4%) out of 453. Both patients were treated with 6 MV photons to the thorax and abdomen/pelvis, respectively. Still, as the negative effect of RT on the devices cannot be ruled out, a control group without exposure to RT would probably be needed to draw any reliable conclusions on this aspect. No deviations in lead parameters were observed in Study II. Hard errors seem to be observed more often in vitro where the devices typically are exposed to supratherapeutic doses of radiation. Hence, every device does have a threshold in radiation dose ultimately damaging the circuit. On the contrary, soft errors appear to be more stochastic and less predictable.

Safety measures

One of the dilemmas in treating PM/ICD patients undergoing RT arises when a decision has to be made whether to surgically remove the device from the vicinity of the RT field in order to avoid malfunction of the PM/ICD. Although the removal permits reduction of the radiation dose to the device, every surgical intervention to the PM/ICD exposes the patient to the risk of complications and is associated with increased healthcare costs. In terms of device relocation prior to RT in practice, it has not been performed in the majority of the published patient series.

In other series, the rate of device relocation varies between 7 and 31% of RT courses, which is higher than 3.5% observed in Study III. However, this comparison may be limited due to small sample sizes in the previous studies. The rate of relocation-related complications in Study III was in line with general practice.

It is generally recommended to estimate the radiation dose to the PM/ICD in a patient scheduled for RT. While the devices in Studies I and II received the entire administered radiation dose, the device doses were in most cases not available in Study III due to the retrospective design of the study. PM/ICD dose calculations are reported in most prospective studies, but only in less than a half of the retrospective case series. Some authors recommend to supplement the estimated values from treatment simulation with in vivo dosimetry, while others suggest that dose estimation only has to be accurate enough to determine in which of the three risk categories of device malfunction the patient will fall, especially as in most cases the dose to the device will be low (<2 Gy). In most larger prospective case series, the patients were evaluated in the PM/ICD clinic according to a predefined protocol, including controls before, during, and after RT. However, as demonstrated in Study III, only about a third of these patients are referred systematically to cardiologists in routine clinical practice.

Inactivation of antitachycardia therapies either by reprogramming or application of a magnet to ICDs is recommended before RT in several publications. The purpose of magnet (≥90 gauss) application to ICDs is to prevent inappropriate shocks in case of oversense from EMI, while bradycardia pacing mode is generally unaffected, contrary to PMs which switch to asynchronous pacing mode under application of a magnet. Although this precaution is supported by some in vitro data indicating oversense in ICDs during RT, to the best of our knowledge, there have been no published data of inappropriate shocks during RT in ICD patients. In Study III, application of a magnet was documented in 10.8% of RT courses with ICDs, and no inappropriate shocks were described in relation to RT in the patients with ICDs. Gossman et al. reported that in 3.6% of cases a magnet was applied during RT, not specifying device types in these patients.

Current safety recommendations

Several sets of practical recommendations on safe RT in PM/ICD patients have been issued since the publication of AAPM TG-34 guidelines (Table 10). After identifying that the patient scheduled for RT has a PM/ICD, it is usually recommended to estimate the cumulative radiation dose to the device, where it is essential to take the maximal dose to any part of the generator into account. Also, all shielding of the device should originate from the LINAC rather than additional shielding with lead. Although it has previously been recommended to shield the device with a lead alloy during RT in order to keep the dose as low as possible, this proportion was higher (42.0%) when ≥15 MV photon beams were given above the diaphragm. In addition, some authors recommend keeping the PM/ICD at least 3-5 cm from the RT field. The Heart Rhythm Society/American Society of Anesthesiologists Expert Consensus Statement mentions that usage of high-energy photon beams might lead to device malfunctions. Similar, recent multidisciplinary Dutch guidelines warn of using >10 MV photon beams in PM/ICD patients due to high risk of device malfunctions. On the other hand, the radiation dose still seems to be underscored as the main factor in some recently published review articles, leaving out the significance of beam energy.
In low risk patients, it is suggested that audiovisual assessment of the patient during RT fractions should be sufficient, and that the completed RT course should be followed by a device check, whereas ICDs should be interrogated weekly. Medium and high-risk patients should only be treated at institutions where trained staff with cardiology expertise and access to external pacing are available. Weekly and daily device controls are suggested in medium and high-risk patients, respectively. Heart rhythm monitoring during every RT fraction is advocated, especially in high risk patients. 

There seems to be no solid evidence on late device malfunctions in case a PM/ICD has exhibited normal function during and immediately after the RT; however, performing additional checks during a period of up to six months after RT has been recommended.

In terms of safety measures in ICD patients, most authors recommend to inactivate all antitachycardia functions of the ICDs at least during the first RT fractions, either by reprogramming the device or by application of a magnet to the ICD. However, this rate was relatively low in Study III (application of a magnet in 10.8%). In addition, heart rhythm monitoring is recommended as soon as antitachycardia therapies are switched off. Provided there is no oversense recorded at interrogations, the therapies might be considered to be reactivated during the remaining fractions. Taking the radiation dose and PM-dependency into account, surgical relocation of the device might be considered in high risk patients, e.g. in case of ipsilateral breast or lung tumor in a PM-dependent patient. Usage of a backup temporary PM during RT has been advocated, although not used in Study III and seldom described in the literature.

So far, no universal PM/ICD manufacturer-specific guidelines on safe RT have been published, besides a couple of references to recommendations from the major manufacturers. One of the reasons is the fact that not all technical data are available in the public domain, and also, the devices are continuously improved. According to Medtronic, their devices should be able to tolerate cumulative doses of 1-5 Gy depending on the model (Table 11). Boston Scientific and St. Jude Medical cannot rule out that their devices might fail even at scatter radiation, permitting no dose limit to be regarded as safe. In addition, Biotronik and Medtronic highlight the importance of beam energy due to the damaging effects of secondary neutrons with a recommendation to limit photon energy to 10 MV. Despite some variations, all major manufacturers caution against the PM/ICD being located in the RT field.
Table 10: Brief overview of recommendations on safe radiotherapy in patients with pacemakers and implantable cardioverter defibrillators published during the last decade.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Sundar 2005&lt;sup&gt;a&lt;/sup&gt; (PM only)</th>
<th>Tondato 2009&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Hudson 2010&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Hurkmans 2012&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Langer 2012&lt;sup&gt;e&lt;/sup&gt; (ICD only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of device dose estimation</td>
<td>RT planning calculations or dosimetry</td>
<td>Not specified</td>
<td>RT planning calculations and dosimetry</td>
<td>RT planning calculations; dosimetry can be considered</td>
<td>RT planning calculations and dosimetry</td>
</tr>
<tr>
<td>Maximal PM dose</td>
<td>Low risk if not PM-dependent and &lt;2 Gy; medium risk if PM-dependent and &lt;2 Gy; high risk if PM-dependent and &gt;2 Gy or if the PM in the RT field</td>
<td>2 Gy</td>
<td>&lt;2 Gy (never &gt;5 Gy)</td>
<td>Low risk if not PM-dependent and &lt;2 Gy; medium risk if PM-dependent and &lt;2 Gy or if 2-10 Gy; high-risk if &gt;10 Gy</td>
<td>-</td>
</tr>
<tr>
<td>Maximal ICD dose</td>
<td>-</td>
<td>2 Gy</td>
<td>&lt;1 Gy</td>
<td>Low risk if not PM-dependent and &lt;2 Gy; medium risk if PM-dependent and &lt;2 Gy or if 2-10 Gy; high-risk if &gt;10 Gy</td>
<td>As recommended by the ICD producer</td>
</tr>
<tr>
<td>Limit beam energy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>≤10 MV</td>
<td>No</td>
</tr>
<tr>
<td>Device checks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before the RT course</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes if not evaluated within the past 3 months</td>
<td>Yes</td>
</tr>
<tr>
<td>During the RT course</td>
<td>Weekly in high-risk patients</td>
<td>Routinely during RT (after every fraction in PM-dependent patients)</td>
<td>After every fraction (at least weekly in non-PM dependent patients)</td>
<td>Low risk: weekly in case of ICD Medium risk: weekly High risk: within 24 hours after each fraction</td>
<td>Yes (not specified in detail)</td>
</tr>
<tr>
<td>After the RT course</td>
<td>Yes</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Yes, including controls at 1, 3, and 6 months after the completed RT</td>
<td>Yes</td>
</tr>
<tr>
<td>Inactivation of antitachycardia therapies</td>
<td>-</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lead shielding of the device</td>
<td>Yes (if near the RT field)</td>
<td>Can be considered</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Heart rhythm monitoring during RT</td>
<td>In high-risk patients</td>
<td>Should be available in high-risk patients</td>
<td>In PM-dependent and ICD patients</td>
<td>In high-risk patients</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Gy = gray; ICD = implantable cardioverter defibrillator; MV = megavolt; PM = pacemaker; RT = radiotherapy.

Table 11: Summary of recommendations from the major PM/ICD manufacturers regarding safe radiotherapy in PM/ICD patients.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Biotronik&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Boston Scientific&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Medtronic&lt;sup&gt;c&lt;/sup&gt;</th>
<th>St. Jude Medical&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal PM dose</td>
<td>2 Gy</td>
<td>No safe dose (2 Gy as a reference)</td>
<td>5 Gy</td>
<td>No safe dose</td>
</tr>
<tr>
<td>Maximal ICD dose</td>
<td>2 Gy</td>
<td>No safe dose (2 Gy as a reference)</td>
<td>1-5 Gy depending on the model</td>
<td>No safe dose</td>
</tr>
<tr>
<td>Maximal beam energy</td>
<td>&lt;10 MV</td>
<td>Not stated</td>
<td>≤10 MV</td>
<td>Not stated</td>
</tr>
<tr>
<td>Device checks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before the RT course</td>
<td>Yes</td>
<td>Specific to each patient</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>During the RT course</td>
<td>Not stated</td>
<td>Specific to each patient</td>
<td>Yes (after each fraction if the recommended safe dose is exceeded)</td>
<td>Yes (a detailed evaluation once or twice during the RT course in PM-dependent patients)</td>
</tr>
<tr>
<td>After the RT course</td>
<td>Yes, including a supplementary follow-up shortly after the RT</td>
<td>Yes, including subsequent close monitoring of the device function</td>
<td>Yes (intensified follow-up schedule)</td>
<td>Yes</td>
</tr>
<tr>
<td>Inactivation of antitachycardia therapies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lead shielding of the device</td>
<td>Yes</td>
<td>All available shielding options, including both internal shielding within the LINAC and external shielding of the patient</td>
<td>No (ineffective against neutrons)</td>
<td>Not stated (reduction in the device dose is recommended)</td>
</tr>
<tr>
<td>Heart rhythm monitoring during RT</td>
<td>Yes</td>
<td>As determined most appropriate by the physician team</td>
<td>Not stated</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Gy = gray; ICD = implantable cardioverter defibrillator; LINAC = linear accelerator; MV = megavolt; PM = pacemaker; RT = radiotherapy.
Main findings
The overall aim of this study was to enlighten epidemiological aspects of PM/ICD patients undergoing RT and to evaluate the rate of malfunctions in modern cardiac rhythm devices. We also sought to elucidate the risk factors of these malfunctions in order to be able to tailor safety measures according to the risk. A short summary of the main findings is presented in the following:

Study I
- Risk of malfunction of modern electronic cardiac rhythm devices during RT correlates with photon beam energy.
- During irradiations with low-energy photons, no PM/ICD malfunctions occurred at therapeutic doses of radiation.

Study II
- The porcine model is feasible for investigating RT effects on implanted cardiac rhythm devices.
- No oversense was recorded during direct irradiations of modern ICDs in vivo.
- The devices were fully functional despite radiation doses considerably higher than the often recommended safe limit of 1 Gy.

Study III
- The rate of PM/ICD patients undergoing RT in Western Denmark increased from 1.45 to 4.33 per 100,000 person-years from 2003 to 2012.
- Discrepancies were shown between current recommendations and safety measures used in clinical practice, especially in terms of device evaluations after the RT.
- PM/ICD malfunctions were observed in 3.1% RT courses and consisted predominantly of resets.
- Beam energy seems to be the most important risk factor of PM/ICD malfunction during RT.
- Radiation dose plays a lower role in inducing PM/ICD malfunctions than previously anticipated.
- No PM/ICD malfunctions were observed during RT with electrons or kilovolt photons.

Strengths and limitations

Study I was the first study to compare head to head two photon beam energies as a predictor of malfunctions in directly irradiated modern PMs/ICDs. The study sample consisted of 12 devices, limited to 2 or 4 from each manufacturer. This limits the statistical power of the 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, possibly not reported at interrogations by the clinical programmer, could have been missed. Measurements of neutron doses were not performed in this study.

In Study II, an animal model was applied for the first time in the field of RT and PMs/ICDs, bringing the experimental setup close to a clinical setting. However, the study size is limited. Also, the animals had to be euthanized immediately after the study, as a radiation dose of 37 Gy delivered during 1 day would be expected to result in a severe radiation injury. In this study, the radiation fractions were delivered faster than in the clinical situation. The reason for this was that a prolonged in vivo experiment lasting several weeks with daily irradiations and general anesthesia would be poorly tolerated by the animals.

To our knowledge, Study III is the largest study on RT in PM/ICD patients published to date. The population-based design allowed us to include all PM/ICD patients receiving RT in Western Denmark over a period of 10 years. In this study, the proportion of RT patients having a PM/ICD was not examined. Neither the radiation dose to the device nor the distance from the RT field to the PM/ICD were generally available in the medical records. Therefore, the anatomical location of the RT was used as a surrogate marker in the statistical model. Due to high mortality among the patients, approximately one third of devices were never controlled after RT. Being outside the scope of the study, the causes of death were not analyzed. Thus, we may have underestimated both the occurrence and degree of severity of RT-induced device malfunctions. On the other hand, as beam energy and proportion of ICDs were lower in RT courses without control, we find it unlikely that we underestimated the occurrence to a major extent. In this study, we can neither rule out transient asymptomatic effects of radiation on the devices that were not detectable at subsequent PM/ICD controls. The subject of RT in PM/ICD patients was approached from a clinical and epidemiological perspective, and no dosimetric measurements were performed. Neither were we able to assess in technical detail the changes of the CMOS in the devices that exhibited malfunctions during the irradiations. Finally, the studied beam types were limited to photons and electrons.

Future perspectives
Reduction in neutron contamination during high-energy photon beaming and circuit hardening against errors might be among the possible approaches to prevent software-based PM/ICD malfunctions. We could also suggest manufacturers to consider a built-in “safe-RT” approach in the devices. This could be a hardware-based pacing mode running on especially radiation-resistant components of the circuit. It could be activated prior to RT, similarly to MRI-dedicated mode in some models. This could possibly avoid erratic and unexpected switching of the device to fall-back settings.

In our opinion, further studies on RT and PMs/ICDs should also include close imitations of real clinical scenarios, and the animal model seems to allow experiments that can serve as an interim step between in vitro and clinical studies. Furthermore, as device malfunctions during RT are relatively rare, large study populations may be needed, and therefore, a web-based registry of PM/ICD patients undergoing RT could be an option.40,118

In the waiting time for an update on international guidelines on safe RT in this patient group, the following suggestions could be advocated by the authors (Figure 9):

1) device relocation before RT is usually unnecessary as PM/ICD malfunctions only weakly correlate with radiation dose;
2) inactivation of antitachycardia therapies during RT as well as heart rhythm monitoring might be redundant;
3) patients undergoing RT with electrons or kV photons normally do not need supplementary device evaluations in PM/ICD clinic;
4) as the malfunctions mainly consist of resets, some safety measures such as repeated visits at PM/ICD clinic might
be abandoned in selected cases in favor of the comfort of the patient;

5) photon beam energy should be limited to ≤10 MV when possible.

Figure 9: Flowchart of suggested safety measures during radiotherapy in patients with pacemakers and implantable cardioverter defibrillators.

- If available, remote monitoring with daily evaluations could be considered instead of controls in the clinic.
- In case the last evaluation is more than three months old.
- Device evaluations after every fraction in case of a reset.

CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ICD = implantable cardioverter defibrillator; MV = megavolt; RT = radiotherapy.
Conclusions

The focus of this project is RT in cancer patients with implanted PM/ICD. With previous data in the field mainly originating from in vitro experiments and smaller-scale patient series, the current work approaches the subject from experimental, clinical, and epidemiological standpoints. In accordance with theoretical expectations, we highlight a substantial increase in the size of this patient group over the last decade. At times difficult to predict, PM/ICD malfunctions occur at a rate that is sufficient to pose a clinical challenge in tailoring optimal safety measures during RT in PM/ICD patients, and we also demonstrate that variations exist in applying these measures in clinic. We show that device malfunctions occurring in relation to RT mainly consist of software impairments eventually leading to a reset of the PM/ICD, wiping out the individually tailored parameters of the device. No fatal events or device replacements due to the malfunctions were observed in Study III, suggesting that the clinical consequences of these malfunctions tend to be relatively mild.

We found that radiation dose plays a smaller role in inducing PM/ICD malfunctions than generally anticipated. As one of the explanations for this, we confirm the previous observations that beam energy is the essential factor in inducing the damaging effects on PMs/ICDs. In line with this finding, a considerable number of device malfunctions occurred during RT to remote anatomical areas, such as abdomen and pelvis, where photon beams of higher energy are typically used. In addition, we observed no device malfunctions during RT with kV photons or electrons. The animal model in Study II proved to be feasible in investigating the effects of RT on heart rhythm devices and permitted us to bring the experiments close to a clinical setting where we demonstrate that modern devices might tolerate relatively high radiation doses. Based on all three studies, RT may be delivered safely in carefully selected patients without the need to remove the PM/ICD from the vicinity of the RT field. On the other hand, devices can still malfunction even at exposure to only minimal radiation doses during high-energy photon RT.
Summary

Background and objectives
The number of individuals with pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) increases. Approximately 6,000 of these devices were implanted in Denmark in 2013. Due to the ageing of the world population and with age being a risk factor for both cardiovascular diseases and cancer, there is a concern that increasing numbers of PM/ICD patients will develop malignancies and receive radiotherapy (RT) treatment. Modern PMs/ICDs have been shown to be susceptible to malfunctions during RT, possibly posing a threat to the safety of the patient. These malfunction events may be difficult to predict as they seem to only weakly correlate with radiation dose. Some malfunctions have been reported during only scatter radiation, while other devices appear to be able to resist high doses of direct irradiation. Little is also known about the size of this patient group, and in what proportion of RT courses PMs/ICDs eventually fail. Data on safety measures applied while treating PM/ICD patients with RT are scarce as well.

Following hypotheses were addressed by this thesis:
- Modern PMs/ICDs can resist higher doses of ionizing radiation than generally anticipated (Study I and II).
- Animal models are feasible for studying the effects of RT on ICDs in vivo (Study II).
- The rate of RT in PM/ICD patients in the general population is increasing (Study III).
- The usage of safety measures varies during RT in PM/ICD patients in clinical practice (Study III).
- PM/ICD malfunctions can be predicted based on parameters of RT and/or type of the device (Study I and III).

Methods
In Study I, 12 modern devices (10 PMs, 2 ICDs) from five different manufacturers were irradiated in vitro with either 6 megavolt (MV) photons or 18 MV photons. Reaching cumulative radiation doses to the device of 150 grays (Gy), the function of the devices was assessed regularly during the experiment. The malfunction rate was then compared between the 6 MV and 18 MV groups.

In Study II, five pigs were implanted with a functional ICD (one from each major manufacturer), and a clinical scenario with an ICD located in the radiation field was simulated. Every device was irradiated with increasing doses of 6 MV and 18 MV photons with a cumulative device dose of 37 Gy. The functionality of the ICDs was controlled during and after the irradiations.

In Study III, after conducting a search at the Danish National Patient Registry, an observational study of 560 patients undergoing 678 RT courses during 2003-2012 in Western Denmark was performed. Medical records of both PM and ICD patients undergoing all types of external beam RT were reviewed in order to identify applied safety measures and recorded device malfunctions.

Results
In the in vitro study (Study I), the devices failed earlier and at a higher rate during irradiations with 18 MV photons compared with irradiations with 6 MV photons. The first malfunction during exposure to 6 MV photons occurred at radiation doses considerably higher than used during cancer RT. The animal model (Study II) was feasible for investigating RT effects on implanted cardiac devices. All devices were fully functional during the in vivo irradiations, although one recoverable malfunction was observed in one of the ICDs. The rate of RT courses in PM/ICD patients increased 3-fold from 2003 to 2012 (Study III). Applied safety measures during RT in this patient group varies, with only at most a third of patients being seen at PM/ICD clinics due to the RT. PM/ICD malfunctions were observed in 3.1% of RT courses with beam energy being the strongest predictor for malfunction. There was a trend of device malfunctions to be more frequent in ICDs compared with PMs, while radiation dose was not associated with device malfunctions.

Conclusion
With an increasing number of PM/ICD patients undergoing RT, there is a considerable risk that these electronic devices may malfunction during exposure to ionizing radiation. As the beam energy emerges as the most important predictor of PM/ICD malfunctions, the radiation dose plays a smaller role in inducing these effects than might be expected. The majority of PM/ICD malfunctions are transient and do not harm the overall function of the device. Variations exist in applying safety measures in these patients, and a tailored approach should be taken based primarily on the risk of PM/ICD malfunction during RT.
Dansk resumé

Baggrund og formål
Antallet patienter med pacemakere (PM) og implanterbare kardioverterdefibrillatorer (ICD) er stigende. Alene i 2013 blev der indopereret omkring 6.000 af disse elektroniske apparater i Danmark. Da både risikoen for hjertesygdomme og cancer stiger med alderen og på grund af den stigende levealder, må det forventes at andelen af patienter med PM/ICD, som udvikler cancer med efterfølgende behov for stråleterapi, vil stige over tid. Moderne PM/ICD kan imidlertid beskadiges af de ioniserende stråler, som anvendes under denne behandling, hvilket potentielt kan bringe patienten i fare. Disse svigt af PM/ICD kan dog være vanskelige at forudsige, idet de ikke synes at hænge sammen med stråledosis. Nogle apparater påvirkes efter blot at have været udsat for spredt stråling, mens andre ikke viser tegn på svigt selv efter høj stråledosis. Desuden ved man kun lidt om, hvor stort et problem disse svigt reelt udgør, og om, hvilke sikkerhedsforanstaltninger, der bliver anvendt hos PM/ICD patienter under stråleterapi.

Formål med denne thesis var at teste følgende hypotesser:
- Moderne PM/ICD kan tåle højere stråledosis end hidtil antaget (Studie I og II).
- Dyremodel kan anvendes til at undersøge virkningen af stråleterapi på ICD in vivo (Studie II).
- Antallet af stråleterapi behandlinger hos PM/ICD patienter i Danmark er stigende (Studie III).
- Der er forskelle i anvendelse af sikkerhedsforanstaltninger under stråleterapi hos PM/ICD patienter (Studie III).
- Risikoen for PM/ICD svigt under stråleterapi kan forudsiges med baggrund i parametre af stråleterapien og/eller typen af PM/ICD (Studie I og III).

Metode
I Studie I blev 12 moderne PM/ICD (10 PM, 2 ICD) fra fem forskellige producenter bestrålet in vitro med enten 6 megavolt (MV) fotoner eller 18 MV fotoner. Funktionen af PM/ICD blev kontrolleret under strålingerne. Samtlige devices modtog en kumuleret stråledosis på 150 gray (Gy), hvorefter antallet af svigt blev sammenlignet mellem 6 MV og 18 MV grupperne.


Resultater

Konklusion
Set i lyset af stigende antal PM/ICD patienter, som gennemgår stråleterapi for cancer, findes der en risiko for, at disse apparater svigter under strålebehandling. Mens stråleenergi spiller en afgørende rolle i forekomst af svigt af PM/ICD, synes stråledosis at have mindre betydning end tidtil antaget. Hovedparten af de svigt, der opstår, er forbigående og medfører som regel ingen varig beskadigelse af PM/ICD. Der findes forskelle i praktisk håndtering af disse patienter, og behandlingen bør tilpasses ud fra forventede risiko for PM/ICD svigt under stråleterapi.
## Appendices

### Appendix A

Diagnosis and procedure codes used during the search in the Danish National Patient Registry in Study III

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>SKS</th>
<th>NOMESCO Classification of Surgical Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of cardiac pacemaker, excluding loop recorder</td>
<td>Z95.0, excluding Z95.0L</td>
<td>Implantation or replacement of permanent transvenous cardiac pacemaker: FPE</td>
</tr>
<tr>
<td>Pacemaker- or ICD-related intervention, excluding application of loop recorder</td>
<td>BFC, excluding BFCAS</td>
<td>Implantation or replacement of permanent epicardial pacemaker: FPF</td>
</tr>
</tbody>
</table>

**ICD-10**

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>SKS</th>
<th>NOMESCO Classification of Surgical Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation of permanent cardioverter-defibrillator</td>
<td>FPG</td>
<td></td>
</tr>
<tr>
<td>Removal of permanent cardiac pacemaker or cardioverter-defibrillator</td>
<td>FPH</td>
<td></td>
</tr>
<tr>
<td>Revision of pacemaker pulse generator or electrode</td>
<td>FPJ</td>
<td></td>
</tr>
<tr>
<td>Other operations for arrhythmias and disturbances of impulse propagation</td>
<td>FPW</td>
<td></td>
</tr>
<tr>
<td>Temporary use of transvenous or epicardial pacemaker</td>
<td>TFP00</td>
<td></td>
</tr>
</tbody>
</table>

**Codes used historically before NOMESCO Classification of Surgical Procedures**

<table>
<thead>
<tr>
<th>Codes used historically before NOMESCO Classification of Surgical Procedures</th>
<th>SKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation of pacemaker</td>
<td>30930</td>
</tr>
<tr>
<td>Transvenous implantation of cardiac electrode</td>
<td>32100</td>
</tr>
<tr>
<td>Surgical implantation of cardiac electrode</td>
<td>32105</td>
</tr>
<tr>
<td>Transvenous implantation of atrial electrode</td>
<td>32110</td>
</tr>
<tr>
<td>Surgical implantation of atrial electrode</td>
<td>32115</td>
</tr>
<tr>
<td>Implantation of generator (accelerator cordis)</td>
<td>32120</td>
</tr>
<tr>
<td>Replacement of generator</td>
<td>32121</td>
</tr>
<tr>
<td>Implantatio convertatoris cordis (defibrillator)</td>
<td>32122</td>
</tr>
<tr>
<td>Replacement of transvenous electrode</td>
<td>32130</td>
</tr>
<tr>
<td>Revision of electrode</td>
<td>32131</td>
</tr>
<tr>
<td>Implantation, revision, and removal of defibrillator</td>
<td>32159</td>
</tr>
<tr>
<td>Other pacemaker/defibrillator operation</td>
<td>32199</td>
</tr>
<tr>
<td>External pacemaker</td>
<td>32490</td>
</tr>
<tr>
<td>Implantationes electrodum</td>
<td>32600</td>
</tr>
<tr>
<td>Implantatio acceleratoris cordis</td>
<td>32610</td>
</tr>
<tr>
<td>Acceleratio cordis endocardialis (venous electrode)</td>
<td>32620</td>
</tr>
<tr>
<td>Implantationes electrodum in myocardium</td>
<td>32640</td>
</tr>
<tr>
<td>Excisio corporis alieni cordis (pacemaker, electrode etc.)</td>
<td>32660</td>
</tr>
<tr>
<td>Replacement of pacemaker</td>
<td>32680</td>
</tr>
<tr>
<td>SKS</td>
<td>Planning of radiotherapy</td>
</tr>
<tr>
<td></td>
<td>External radiotherapy</td>
</tr>
</tbody>
</table>

ICD = implantable cardioverter defibrillator; ICD-10 = International Classification of Diseases, 10th edition; NOMESCO = Nordic Medico-Statistical Committee; SKS = Danish Hospital Sector Classification System.
Appendix B

Characteristics of radiotherapy (RT) courses in Study III resulting in device malfunction versus courses without malfunction by device manufacturer, including courses with complete data on both the device and the RT (n=658)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>All RT courses (n=658)</th>
<th>PM/ICD controlled after RT [n=453 (68.8%)]</th>
<th>No PM/ICD malfunction [n=439 (96.9%)]</th>
<th>PM/ICD malfunction [n=14 (3.1%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotronik, n (%)</td>
<td>15</td>
<td>12 (80.0)</td>
<td>11 (91.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Boston Scientific, n (%)</td>
<td>11</td>
<td>8 (72.7)</td>
<td>8 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CPI, n (%)</td>
<td>1</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ela, n (%)</td>
<td>29</td>
<td>18 (62.1)</td>
<td>16 (88.9)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Guidant, n (%)</td>
<td>47</td>
<td>31 (66.0)</td>
<td>31 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Medtronic, n (%)</td>
<td>267</td>
<td>191 (71.5)</td>
<td>188 (98.4)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Pacesetter, n (%)</td>
<td>48</td>
<td>32 (66.7)</td>
<td>32 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Siemens, n (%)</td>
<td>4</td>
<td>2 (50.0)</td>
<td>2 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sorin, n (%)</td>
<td>1</td>
<td>0 (0.0)</td>
<td>0 (-)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>St. Jude Medical, n (%)</td>
<td>199</td>
<td>134 (67.3)</td>
<td>126 (94.0)</td>
<td>8 (6.0)</td>
</tr>
<tr>
<td>Teletronics, n (%)</td>
<td>1</td>
<td>0 (0.0)</td>
<td>0 (-)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Ventritex, n (%)</td>
<td>1</td>
<td>1 (100.0)</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vitatron, n (%)</td>
<td>34</td>
<td>23 (67.6)</td>
<td>23 (100.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

ICD = implantable cardioverter defibrillator; PM = pacemaker; RT = radiotherapy. *Percentages are row percentages to allow for comparison of RT courses without and with malfunctions.
Appendix C

Recorded device malfunctions during radiotherapy in Study III

<table>
<thead>
<tr>
<th>Device type</th>
<th>Manufacturer</th>
<th>Model</th>
<th>Anatomic area irradiated</th>
<th>Cumulative tumor dose / number of fractions</th>
<th>Beam type</th>
<th>Maximal beam energy, MV</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAI</td>
<td>St. Jude Medical</td>
<td>Victory SR 5610</td>
<td>Thorax</td>
<td>48 Gy/24</td>
<td>Photons and electrons (6 MeV)</td>
<td>18</td>
<td>Reset (and diaphragmatic pacing) after 10 Gy to the tumor. Device was relocated before RT.</td>
</tr>
<tr>
<td>DDD</td>
<td>Ela</td>
<td>Symphony DR 2550</td>
<td>Abdomen and pelvis</td>
<td>70 Gy/35</td>
<td>Photons</td>
<td>15</td>
<td>Spontaneous reprogramming to unipolar pacing, output 3.5 V/0.35 ms at both leads, basic rate 60 bpm. Dose at the event uncertain.</td>
</tr>
<tr>
<td>DDD</td>
<td>Ela</td>
<td>Symphony DR 2550</td>
<td>Head and neck</td>
<td>20 Gy/4</td>
<td>Photons</td>
<td>6</td>
<td>Program error preventing readout of historical data at a control 14 days after RT, otherwise normal function.</td>
</tr>
<tr>
<td>DDD</td>
<td>Medtronic</td>
<td>Adapta ADDR01</td>
<td>Thorax</td>
<td>30 Gy/10</td>
<td>Photons</td>
<td>6</td>
<td>Permanent increase in atrial pacing threshold from 1.25 V (before RT) to 2.75 V (after RT), other lead parameters unchanged.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Affinity DR 5330R</td>
<td>Thorax</td>
<td>48 Gy/24</td>
<td>Photons</td>
<td>18</td>
<td>Intermittent warnings about invalid data since 14 Gy to the tumor, otherwise normal function.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Identity ADx XL DR 5386</td>
<td>Thorax</td>
<td>20 Gy/4</td>
<td>Photons</td>
<td>18</td>
<td>Reset requiring reprogramming by the manufacturer after 20 Gy to the tumor.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Victory XL DR 5816</td>
<td>Spine</td>
<td>8 Gy/1</td>
<td>Photons</td>
<td>18</td>
<td>Reset.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Victory XL DR 5816</td>
<td>Abdomen and pelvis</td>
<td>78 Gy/39</td>
<td>Photons</td>
<td>15</td>
<td>Reset after 68 Gy to the tumor.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Zephyr XL DR 5826</td>
<td>Lower extremity</td>
<td>8 Gy/1</td>
<td>Photons</td>
<td>15</td>
<td>Reset; battery parameters not available (&quot;Data not read&quot;); Fast Path summary: “Diagnostics cleared because they were invalid”.</td>
</tr>
<tr>
<td>DDD</td>
<td>St. Jude Medical</td>
<td>Zephyr XL DR 5826</td>
<td>Abdomen and pelvis</td>
<td>45 Gy/25</td>
<td>Photons</td>
<td>15</td>
<td>Reset, dose at the event uncertain.</td>
</tr>
<tr>
<td>VVI-ICD</td>
<td>Biotronik</td>
<td>Lumax 540 VR-T</td>
<td>Abdomen and pelvis</td>
<td>78 Gy/39</td>
<td>Photons</td>
<td>6</td>
<td>Reset and permanent increase in pacing threshold to 4.4 V after 4 Gy to the tumor, other lead parameters unchanged</td>
</tr>
<tr>
<td>DDD-ICD</td>
<td>St. Jude Medical</td>
<td>Atlas + DR V-243</td>
<td>Abdomen and pelvis</td>
<td>60 Gy/30</td>
<td>Photons</td>
<td>18</td>
<td>Reset requiring reprogramming by the manufacturer after 40 Gy.</td>
</tr>
<tr>
<td>CRT-D</td>
<td>Medtronic</td>
<td>InSyncMaximo7304</td>
<td>Abdomen and pelvis</td>
<td>78 Gy/39</td>
<td>Photons</td>
<td>18</td>
<td>Reset after 78 Gy to tumor.</td>
</tr>
<tr>
<td>CRT-D</td>
<td>Medtronic</td>
<td>InSync III Marquis 7279</td>
<td>Abdomen and pelvis</td>
<td>25 Gy/5</td>
<td>Photons</td>
<td>18</td>
<td>Reset during the period of RT, dose at the event uncertain.</td>
</tr>
</tbody>
</table>

AAI = single chamber atrial pacemaker; bpm = beats per minute; CRT-D = cardiac resynchronization therapy implantable cardioverter defibrillator; DDD = dual chamber pacemaker; DDD-ICD = dual chamber implantable cardioverter defibrillator; Gy = gray; MeV = megaelectronvolt; ms = miliseconds; MV = megavolt; V = volt; VVI-ICD = single chamber implantable cardioverter defibrillator.
Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators


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45. Kesek M, Nyholm T, Asklund T. Radiotherapy and pacemaker: 80 gy to target close to the device may be feasible. Europace 2012; 14:1595.
Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators


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 (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 (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

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Effects of High-Dose Radiotherapy on Implantable Cardioverter Defibrillators: An In Vivo Porcine Study

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Introduction: Although the effects of radiotherapy (RT) on implantable cardioverter defibrillators (ICDs) have been studied in vitro, and some information has been gathered from case reports and series, no in vivo experiments have previously been performed.

Methods: In vivo effects of photon RT applied directly to five modern ICD generators from different manufacturers implanted in pigs were studied. The devices were interrogated between and after increasing doses of ionizing radiation. Afterwards, the shock function was tested.

Results: All ICDs withstood fractionated irradiations with a cumulative dose of 18.5 gray (Gy) of 6 megaray (MV) photons and 18.5 Gy of 18 MV photons and were still fully functional. Especially, no oversense was recorded. Induced ventricular fibrillation was detected and treated properly by shock therapy in all cases. However, one of the ICDs converted to back-up mode later the same night.

Conclusion: The animal model is feasible for investigating RT effects on implanted cardiac devices. During irradiations with 37 Gy, one recoverable malfunction was present in the tested devices. Additional animal studies could provide supplementary evidence for treating ICD patients, including recommendations for reprogramming of the ICD during RT and avoidance of relocating the device. (PACE 2013; 36:1558–1563)

radiotherapy, implantable cardioverter defibrillator, animal model, in vivo experimentation
Risk of Device Malfunction in Cancer Patients with Implantable Cardiac Device Undergoing Radiotherapy: A Population-Based Cohort Study

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**Background:** Pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) may develop malfunction during external beam radiotherapy (RT). We aimed to describe clinical practice in PM/ICD patients undergoing RT and to assess the rate and predictors of device malfunctions.

**Methods:** We reviewed medical records of all PM/ICD patients undergoing RT at four centers in Western Denmark during 2003–2012. Logistic regression was applied to identify predictors of PM/ICD malfunctions.

**Results:** Five hundred sixty patients were included. The annual rate of RT courses in PM/ICD patients increased by 199% from 1.45 treatments per 100,000 person-years in 2003 to 4.33 in 2012. Safety measures included supplementary evaluations of PM/ICD (38.3%), reprogramming (1.5%), relocation of the device (3.5%), and application of a magnet to the ICD during RT (10.8%). At device evaluations after the RT (n = 453), malfunctions were detected in 10 (2.5%) PMs and four (6.8%) ICDs. Electrical resets constituted 11 (78.6%) of the malfunctions, and no failures were life-threatening or warranted PM/ICD removal. Factors associated with device malfunctions in logistic regression analysis were beam energy ≥15 MV (odds ratio [OR] 5.73; 95% confidence interval [CI], 1.58–20.76) and location of tumor below the diaphragm (OR 4.31; 95% CI, 1.42–13.12). However, the effect of tumor location declined (OR 2.27; 95% CI, 0.65–7.95) after adjustment for beam energy.

**Conclusions:** Although the rate of RT in PM/ICD patients is increasing, the damaging effects of RT on the devices seem to be usually transient. Our data suggest that high beam energy plays the pivotal role in inducing impairments in these devices. (PACE 2015; 38:343–356)

**Keywords:** pacemaker, implantable cardioverter defibrillator, radiotherapy, ionizing radiation, device malfunctions, beam energy

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Conflicts of Interest: None.

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