Review article

Radiotherapy in patients with cardiac implantable electronic devices – clinical experience

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Received:
4.03.2017.
Accepted:
21.03.2017.

DOI: 10.24292/01.OR.300617.2

ABSTRACT

The number of patients with cardiac implantable electronic devices (CIEDs) constantly increases and due to growing incidence of cancer, many of them will require an anticancer treatment. At least a half of patients treated for malignant neoplasms, apart from other treatment methods, require radiotherapy. Although papers presenting the results of in vitro studies provide clues on the susceptibility of CIEDs to ionizing radiation, the research methods used often stand out from typical clinical situations. Direct irradiation of the devices is avoided and the doses delivered to pulse generators are far below those seen in the in vitro studies. In this review the most important clinical observations made during irradiation of patients with CIEDs are summarized and practical directions for physicians and physicists involved in radiation treatment planning and delivery are given.

Key words: radiotherapy, cardiac implantable electronic device, pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy

INTRODUCTION

Systematically growing population of patients with cardiac implantable electronic devices (CIEDs) and increasing incidence and prevalence of cancer make the patients with CIEDs more and more commonly seen recipients of anticancer treatment and at least a half of them is expected to require radiotherapy [1, 2].

Although the susceptibility of the cardiac implantable electronic devices to ionizing radiation is systematically tested since many years, the conclusions from the in vitro studies are not obvious. First, the technology systematically changes and the CIEDs gain new functionalities and programming options. New models are introduced which makes prior assessments unreliable and difficult to apply to new and untested devices. New generations of pacemakers (PMs) and implantable cardioverters-defibrillators (ICDs) emerge on the market, including those with novel conception of heart stimulation, like subcutaneous devices which do not require intravenous leads or leadless intracardiac pacing systems [3, 4]. Additionally, new devices used for different than before purposes are becoming popular. Cardiac resynchronization therapy devices (CRT) with or without the ICD function (CRT-D, and CRT-P, respectively) have already a well-established position in the armamentarium of treatment methods used in congestive heart failure [5]. Although the role of CRT devices is not questioned in contemporary cardiology, little is known about their susceptibility to radiation and it is hard to define what way they should be treated like. Due to their predominantly stimulating function, potentially similar precautions to those used in case of PMs could be applied. When they have also an ICD function, a question can be raised if patients with CRT-D should be treated in a similar way to patients with ICDs, or rather specific treatment algorithms should be elaborated.

Moreover, apart from the dynamic changes in the construction of the CIEDs, also recent advances in the radiotherapy technique contribute to the fact that the results of studies on cardiac implantable electronic devices in patients subject to radiotherapy rapidly become obsolete. Relatively new dynamic techniques, like volumetric modulated arc therapy (VMAT), tomotherapy or respiratory gating quickly became a standard in the clinic because of the advancements in dose distribution and sparing critical organs from high doses of radiation they offer. At the same time, utilization of such techniques is inevitably associated with increased volumes of low and very low doses delivered in large volumes of the patient's body which can translate into larger dose deposited in the cardiac devices [6].

The susceptibility of CIEDs to ionizing radiation is confirmed in several clinical studies. Until recent years, most of the reports on device malfunctions were found in case reports or small case series. The dose delivered to the CIEDs associated with device malfunction varies widely and a number of potential predictive factors for failure were proposed, of which, radiation energy, prescribed dose and location of the irradiated target volume play the major role [7–9].

CONSIDERATIONS ON THE RESULTS OF IN VITRO STUDIES

Many in vitro studies indicate that radiotherapy can negatively influence the operation of the CIEDs. There are, however, some examples of studies potentially indicating that the current dose limits for CIEDs are too restrictive because the currently used devices can withstand more dose than models used previously [10]. Closer look at the methods used to prove this assumption reveals that the study setup does not resemble the clinical conditions seen during typical radiotherapy sessions. The commonly used guidelines preclude direct irradiation of the devices [11–14]. Moreover, the planned dose during radiotherapy in case of conventional treatment is delivered in several fractions which results with a 5–8 weeks long treatment. It is widely accepted that the damaging effects of even low radiation doses are accumulative and the probability of occurrence of a malfunction is also a function of the length of the treatment, apart from the dose deposited in the generator and energy of the radiation used [8]. Thus, to reliable test the CIEDs in clinical-like conditions it is advisable to prepare and execute the treatment plan in the same way it is carried-out in the clinic. It makes such an in vitro study more complicated and time- and resource-consuming but the results should be more reliable and more easily applicable in appropriate clinical conditions.

CLINICAL EXPERIENCE WITH RADIOTHERAPY IN PATIENTS WITH CIEDs

In vivo data published in recent years indicate that the problem of CIED malfunction in patients subject to radiation therapy can involve as many as 7% of the patients with implanted devices irradiated for various types of cancer [7, 8]. Interestingly, one of the predictors of CIED malfunction was the body region which was irradiated, with higher risk in patients irradiated for abdominal and pelvic tumors. As in these patients more often high energy, neutron-producing radiation is used, this observation would not be surprising, but when the analysis was limited only to cases in which neutron-producing radiation was used, the location

of the target volume remained a significant predictive factor for CIED malfunction [7]. The authors described 249 radiation therapy courses in 215 patients. The cumulative dose to CIEDs varied between 0.002 and 3.2 Gy. In 3 patients it was not estimated. In patients irradiated with electrons only, no device upsets were recorded [7]. Bagur et al. also described a relatively large cohort (230) of irradiated patients with CIEDs. Although detailed information on the cardiac devices and comorbidities was provided, neither information on radiation energy nor on dose to the pulse generator were recorded. In no case, however, the device was exposed to direct radiation [8]. In 9% (21 patients) device relocation prior to radiotherapy was performed to minimize the risk of radiation exposure. Interestingly, device failure was observed more often in patients after relocation of the generator. Also shorter device age was associated with higher probability of malfunction. The multivariate analysis showed, however, that the only independent factor associated with CIED malfunction was the total dose prescribed to the tumor [8]. Due to the lack of details concerning radiotherapy, a possible association between CIED malfunction and energy of the ionizing radiation was not tested.

Although both Bagur et al. and Grand et al. noticed the same number of device malfunctions during radiotherapy, there are also reports indicating that the risk of malfunction can be lower, especially if a systematic policy of risk assessment and patient management is introduced. Brambatti et al. analyzed a group of 261 patients with CIEDs receiving radiotherapy in their center [15]. Of that number, only in 4 devices malfunctions were recorded. In one patient a device power-on reset occurred, the remaining 3 experienced ventricular pacing at maximum sensor rate which was, however, well tolerated [15]. Notably, in all but 3 patients the estimated dose to the CIED was below 2 Gy, in one the measured dose was 3 Gy. In 9 patients CIED relocation was made.

On the other hand, in patients irradiated solely with neutron-producing radiation, the percentage of malfunctions can be even higher than the 7% estimated for the whole population of irradiated patients with CIEDs. Elders et al. reported on 15 patients with ICDs subjected to 17 courses of radiotherapy [9]. In this relatively small group, in 5 patients (29% of radiation therapy courses) malfunctions were registered. In additional one patient a late data error was encountered during interrogation which in total adds up to 35% of the 17 radiotherapy courses analyzed. All of the patients were irradiated with 10–18 MV photons. Similar observations were made in the already mentioned series described by Grant et al. If only neutron-producing radiation was considered, CIED malfunctions occurred in 15 of 71 radiotherapy courses in which 15–18 MV photons were used, which constitutes 20% of the subgroup irradiated with high-energy photon radiation. In 13 of 15 single event upsets in this group, the dose delivered to the generator was below 2 Gy [7].

According to data published in the largest clinical series, device malfunctions are detected more often in ICD devices than in PMs. Due to a very non-uniform way of malfunction definition and reporting, it is challenging to compare the results of various authors but one of the most common failure is device reset to backup mode (tab. 1). Some authors indicate that the most common failure is ventricular pacing at the maximum sensor rate while others did not report such kind of dysfunction at all [7, 15]. The critical failures, requiring acute replacement of the generator are rare. In general, most of the detected malfunctions were correctable by reprogramming. It should be noted, however, that it is not a rule and 2 unrecoverable resets requiring replacement of the compromised device, although uncommon, were also described (tab. 1) [7].

TABLE 1.
Frequency and types of CIED malfunctions due to exposure to ionizing radiation reported in clinical studies [7–9, 15–18].

	Device type	
	PM	ICD
Common failures	• parameter reset/ backup mode • pacing at maximum sensor rate	• data loss • parameter reset/ backup mode
Uncommon failures	• signal interference	• unrecoverable reset • signal interference

ICD – implantable cardioverter-defibrillator; PM – pacemaker.

A potentially lethal event of inappropriate pacing resulting with triggering ventricular tachyarrhythmia (VT) was described by Nemec et al. The device was a one-chamber ICD placed for primary prophylaxis of sudden cardiac death. During irradiation for lung cancer (left upper lobe), the patient collapsed and required on-site cardiopulmonary resuscitation resulting with reappearance of the sinus rhythm. The device was interrogated but no malfunction was detected. The manufacturer also examined the device and suggested that inappropriate pacing which, as a result, triggered VT could be a result of change of the content of random access memory caused by ionizing radiation [19].

The reported CIED malfunction rate during radiotherapy oscillates in wide range and in most cases the detected failures are

not associated with clinical manifestation of the device dysfunction. For that reason it is reasonable to compare the reported failure rates during radiotherapy with failure rates in general population of CIED recipients. Theoretically, the increased surveillance during radiotherapy could potentially allow for detection of malfunctions that would have occurred independently of radiation exposure. The failure rate of CIEDs is not exactly known. The available data are scarce and refer mainly to manufacturer advisories which not necessarily are equivalent to a malfunction. Some advisories do not require generator replacement but only reprogramming or close follow-up, depending on which class of advisory is announced.

In the paper published by Maisel et al., the annual PM replacement rate was 4.6, and ICD – 20.7 per 1000 implants, respectively. The ICD replacement rate dropped from 38.6 to 7.9 per 1000 implants between 1993 and 1998 but later increased markedly, to reach maximum equal to 36.4 in 2001. The PM replacement rate decreased significantly from 9.0 in 1993 to as low as 1.4 in 2002 [20]. The increasing ICD replacement rate, even in the peak year 2001, and the number of explanted devices (3.86% per annum) was definitively lower than the number of malfunctions during radiotherapy reported in clinical studies. As mentioned previously, the observed malfunctions or single upset events during radiotherapy oscillate at the level of 7% of the irradiated patients (or even 20% and higher in case of neutron-producing radiation) in the period of irradiation, which is usually between 1 and 7 weeks, depending on the type (radiosurgery, hypofractionated or conventionally fractionated radiotherapy) and intention (palliative or curative) of the treatment. Both the number of observed events and strong association with the treatment-related parameters preclude incidental detection of randomly occurring malfunctions, independent of the exposure to ionizing radiation. This observation is true even taking into account the fact that in case of CRT-D devices, the number of electronic failures and other malfunctions is significantly higher than in ICDs without rate-responsive or resynchronization pacing [21].

A number of national guidelines, reviews and recommendations concerning radiotherapy in patients with CIEDs were published to date [11–14, 22–24]. Although the standards of treatment proposed in these papers are similar, still many discrepancies can be seen, especially concerning the schedule and need for monitoring and systematic interrogation of the devices during treatment. Moreover, recommendations concerning patients with CRT devices are rare and the amount of in vitro and clinical data being the groundwork for formulation of specific guidelines is still very limited. There is also no agreement on handling the CIEDs after radiotherapy. Some authors suggest that a CIED irradiated with doses greater than 5 Gy during the whole treatment course should be replaced after completion of the therapy [25]. However, there is a risk of manifestation of a damage even after a treatment with cumulative dose deposited in the generator being below this limit, as described by Elders et al. in a patient treated with 18 MV photons. The device reset trend data error was recorded 9 months after the treatment but the causative role of radiotherapy could not be proven [9].

Following the practice in other centers, as well as recommendations formulated by the Polish Society of Radiation Oncology and other national scientific societies, with special respect to the latest DEGRO/DGK guidelines, an internal procedure of the management of patients with CIEDs subjected to radiotherapy in the author's center was introduced. The safety measures taken are briefly summarized in table 2 and in full detail are available in the referenced papers [11, 26].

TABLE 2.
Safety measures taken according to risk group.

Risk group	Safety measures
Low risk	• device check before and after radiotherapy course • ECG monitoring by radiation therapist if indicated by cardiologist
Intermediate risk	• reprogramming into asynchronous mode • ECG monitoring during irradiation • interrogation before and after each fraction in patients with ICD-capability devices (cardiologist present)
High risk	• analysis of the possibility of treatment technique change to reduce dose to the CIED • reconsideration of device relocation after analysis of the radiation treatment plan • reprogramming the device into asynchronous mode • continuous ECG monitoring during irradiation with the presence of cardiologist • interrogation before and immediately after each fraction

CIED – cardiac implantable electronic device; ECG – electrocardiogram; ICD – implantable cardioverter-defibrillator.

In all cases the patients are seen by a cardiologist before treatment initiation to verify the type and operation mode of the device, determine the risk group and the way of further management.

CONCLUSIONS

In spite of systematically emerging new data on performance of CIEDs during irradiation in clinical conditions and research

on susceptibility of newly introduced devices to ionizing radiation in vitro, there are still many controversies regarding proper handling of patients with implantable cardiac devices during radiotherapy. There is a need for commonly accepted and systematically updated guidelines, preferably endorsed by international scientific societies. All radiotherapy facilities should at least introduce their own procedures concerning radiation treatment planning, delivery and monitoring of patients with CIEDs. The patients should be aware of the possibility of unpredictable behavior of their device during and after radiotherapy. An informed consent should be taken before initiation of radiotherapy and the information provided should include the risk of acute or elective replacement of the device. Many questions are open, no reliable recommendations or procedures are given concerning patients with CIEDs after completion of radiotherapy. Devices with hardware malfunction should be replaced but handling the ones with minor software errors detected or even intact but irradiated with borderline dose is not clear. Interdisciplinary co-operation of cardiologist, electrophysiologist, radiation oncologist and manufacturers is crucial because of a wide spectrum of potential and unpredictable software and hardware problems. Creation of a registry of patients with cardiac implantable electronic devices who underwent radiotherapy would definitely provide invaluable data on their short- and long-term outcome. Apart from avoiding direct irradiation, the main guideline for physicians and physicists involved in radiation treatment planning should be avoidance of neutron-producing radiation, as most up-to-date clinical studies indicate that application of this kind of ionizing radiation is the most important predictive factor for cardiac implantable electronic devices malfunction.

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Conflict of interests:
None.
Financial support:
None.
Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.