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Approach to cardio-oncologic patients with special focus on patients with cardiac implantable electronic devices planned for radiotherapy: results of the European Heart Rhythm Association survey

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The aim of this European Heart Rhythm Association (EHRA) survey was to evaluate clinical practice regarding cardio-oncologic patients, with special focus on patients with cardiac implantable electronic devices (CIEDs) planned for anticancer radiotherapy (RT), among members of the EHRA electrophysiology research network. Of the 36 responding centres, 89% managed patients who were diagnosed or treated oncologically, and this diagnosis affected 1–5% of cardiovascular patients in majority of centres (57%). The main side effects of anticancer therapy in patients treated by cardiologists were thromboembolic complications and left ventricular dysfunction (both reported as 'frequent' by 43% of the centres). The main agents associated with complications were anthracyclines, RT, and monoclonal antibodies. Echocardiography was the most common method of screening for cardiovascular complications (93%), and 10% of the centres did not routinely screen for treatment-induced cardiotoxicity. Opinions on the safe radiation dose, methods of device shielding, and risk calculation prior to RT in CIED patients differed among centres. Precaution measures in high-risk CIED patients were very heterogeneous among centres. Our survey has shown that the awareness of cardiac consequences of anticancer therapy is high, despite relatively low proportion of patients treated oncologically among all cardiovascular patients. There is a consensus of which screening methods should be used for cardiotoxicity of anticancer treatment, but the apprehension of screening necessity is low. Methods of risk assessment and safety measures in CIED patients undergoing RT are very heterogeneous among the European centres, underscoring the need for standardization of the approach to cardio-oncologic patients.

Keywords Arrhythmias • Cancer • Cardiac implantable electronic devices • Cardio-oncology • Cardiac toxicity • Device programming • EHRA survey • EP Wire • Radiotherapy

Introduction

Substantial progress in the field of oncology in the recent years has significantly improved prognosis of patients with cancer.[1,2] However, better survival of these patients has uncovered significant side effects of anticancer therapy. More efficient, but often also more aggressive treatment of oncologic disease, inevitably expose patients to an increased risk of complications.[3] Moreover, the majority of complications associated with cancer treatment affect the cardiovascular system. Accordingly, heart disease is the leading cause of mortality and

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morbidity in cancer survivors and cardio-oncologic patients have emerged recently as a new entity.[4] These patients pose new challenges, such as potential damage of cardiac implantable electronic devices (CIED) associated with radiotherapy (RT). Presently, no uniform policy has been established regarding the approach to cardio-oncologic patients, and many issues remain unresolved.

The aim of this European Heart Rhythm Association (EHRA) survey was to evaluate clinical practice regarding the management of cardio-oncologic patients, with special focus on patients with CIED planned for anticancer RT.

Methods and results

Participating centres

The survey was based on an electronic questionnaire sent out via Internet to the centres—members of the EHRA electrophysiology (EP) Research Network. Of the 36 responding centres from 12 countries, 69% were university hospitals, 11% were private hospitals, and 19% were hospitals of another type. During the last year, CIEDs were not implanted in 3% of centres, 39% centres implanted 300–499 devices, 30% implanted 500–1000 devices, and 11% implanted >1000 devices. In 50% of the centres, implantable cardioverter–defibrillators (ICDs) constituted 11–25% of newly implanted devices, and in 11%, they made up >50% of new CIED implantations.

Expertise in the management of cardio-oncologic patient and side effects of anticancer treatment

Among the 36 responding centres, 89% have managed patients who were diagnosed or treated oncologically, or in whom side effects of anticancer therapy involved the cardiovascular system, while 11% of the centres never had any contact with cardio-oncologic patients. In 57% of the centres, between 1% and 5% of their cardiac patients were diagnosed with a neoplasm, 37% reported 6–10% of such patients, and in 7% of centres cardio-oncologic patients constituted >10% of cardiac patients.

Thromboembolic complications and left ventricular dysfunction emerged as the two most common complications of oncologic treatment requiring cardiologic care; 43% of the centres reported both complications as relatively frequent (>10% of cases). Biventricular dysfunction or isolated right ventricular dysfunction was only reported as an infrequent complication of anticancer treatment by 87% and 80% of the centres, respectively. Other complications included atrial fibrillation (37% of centres), pericardial effusion or cardiac tamponade (30%), arterial hypertension (23%), and premature coronary artery disease (perceived as a relatively common complication by 20% of the centres). Cardiac arrest, peripheral vascular disease, and ventricular tachycardia/fibrillation were less common complications in oncologic patients—they were reported as 'never occurring due to anticancer therapy' by 69%, 53%, and 50% of the responding centres, respectively.

The anticancer treatment modalities most commonly perceived as associated with cardiovascular complications included anthracyclines (doxorubicin, idarubicin, and mitoxanthone), RT, and monoclonal antibodies (trastuzumab and bevacizumab). Their use was reported to be relatively frequently (in >10% of cases) associated with complications by 64%, 55%, and 21% of the respondents, respectively (*Figure 1*). In contrast, 61% and 57% of the centres reported no complications associated with the use of proteasome inhibitors (bortezomib and carfilzomib) or androgen deprivation agent (bicalutamide), respectively. Of note, 11 centres (55% of 20 centres answering this question) reported lack of experience with anticancer drugs.

Screening for complications of anticancer treatment

Echocardiography was the most commonly used method of screening for cardiovascular complications of anticancer treatment used in 93% of the responding centres. Less commonly used methods included regular clinical follow-up (83%), regular electrocardiography (ECG) monitoring (70%), assessment of cardiac biomarkers [troponins, brain natriuretic peptide (BNP), N-terminal-proBNP at 50% of centres], and Holter ECG monitoring (33%). Both stress testing and coronary angiography were used in 17% of centres, while cardiac magnetic resonance was used in 13% of centres. Of note, 10% of the centres did not routinely screen cardio-oncologic patients for treatment-induced toxicity.

Risk assessment in patients with cardiac implantable electronic devices planned for radiotherapy

When assessment of a patient with CIED before thoracic RT for cancer was planned, general cardiologists were routinely involved in 72% of centres, oncologist in 71%, and cardiologist implanting or checking up CIED in 64% (*Figure 2*). Routine participation of RT specialist was less frequent (61% of centres), but all centres (100%) reported occasional participation of another consultant, including anaesthesiologist or psychologist (94% each).

When calculating the radiation-associated risk in CIED patients, pacemaker dependency was the most commonly considered risk indicator (taken into account by 83% of respondents), followed by patients' co-morbidities and the distance between CIED and radiation beam (each considered important by 69% of centres) or primary vs. secondary indications for ICD (66%).

Radiotherapy-associated risk was considered high mainly in pacemaker-dependant patients, irrespectively of the radiation dose (as stated by 48% of the respondents) or only in pacing-dependant subjects who will receive a cumulative dose ranging between 2 Gy and 10 Gy (33%) or >10 Gy (30%). Less often (26% of the centres), the high-risk patients were defined as those receiving radiation dose of >10Gy, regardless of pacemaker dependency. Remarkably, 7% of the centres did not know criteria for high risk.

Patients with ICD were considered a high-risk group for radiation-associated complications if they had ICD implanted for secondary prophylaxis of sudden cardiac death, irrespective of the dose (41% of centres) or if dose was 2–10 Gy (33%) or >10 Gy (33%) in secondary prevention patients.

Types of radiotherapy-induced device malfunctions and safety measures

The reported proportion of all CIED patients undergoing RT, in whom device or lead damage occurred after radiation ranged

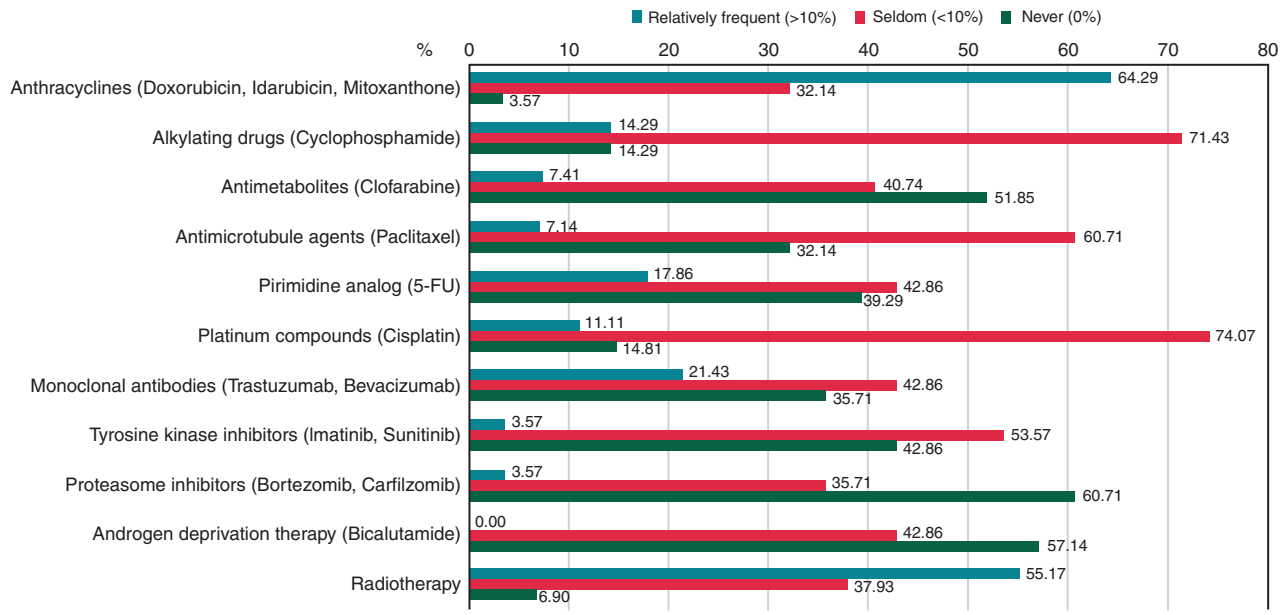

Figure 1 Reported frequency of side effects associated with the use of particular anticancer agents. 5-FU, 5-fluorouracil.

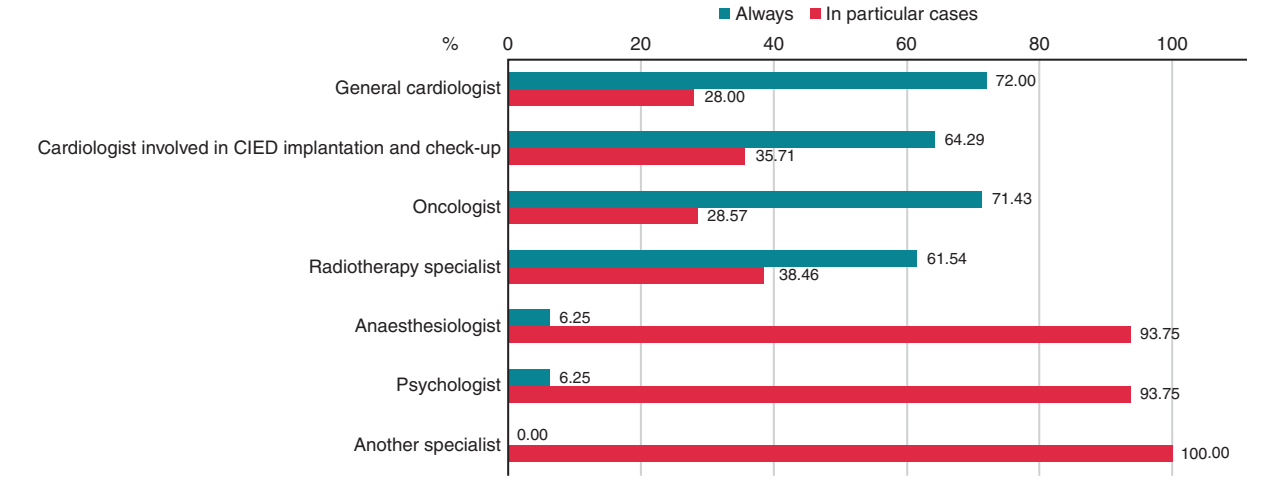

Figure 2 Specialists involved in cardiovascular assessment of CIED patient planned for thoracic radiotherapy for cancer. CIED, cardiac implantable electronic device.

between 0% and 5%. No occurrence of RT-associated CIED dysfunction was reported by 37% of the respondents, 30% reported device dysfunction in 2% of irradiated patients, and 11% of the centres found CIED dysfunction in 5% of patients. Relatively frequent types of CIED dysfunction (>10% of patients) attributable to RT included change of pacing stimulus amplitude, decrease in ICD shock energy, and CIED reset to fallback mode or power-on-reset mode (each reported by 8% of the centres) (*Table 1*). Less often occurring (<10% of patients) device dysfunction included under-sensing or loss of sensing or premature battery depletion (each reported by 38% of the respondents). The majority (88%) reported prolonged arrhythmia detection/capacitator charging of ICD as 'never occurring' after radiotherapy.

Considering the upper limit of cumulative dose that can be safely received by CIED in patients undergoing RT, 14% of the respondents

Table 1 Abnormalities in cardiac implantable electronic devices function after radiation therapy

	Relatively frequent (>10%)	Seldom (<10%)	Never
Under-sensing/loss of sensing	0	10 (38.5)	16 (61.5)
Over-sensing	1 (3.8)	9 (34.6)	16 (61.5)
Lower pacing rate/loss of pacing	1 (3.7)	9 (33.3)	17 (62.9)
Higher pacing rate—runaway pacing syndrome	0	5 (19.2)	21 (80.8)
Change of stimulus amplitude	2 (7.7)	8 (30.8)	16 (61.5)
Change of arrhythmia detection settings	0	4 (15.4)	22 (84.6)
Change of arrhythmia therapy settings	1 (3.8)	3 (11.5)	22 (84.6)
Premature battery depletion	1 (3.8)	10 (38.5)	15 (57.7)
Lead damage (impedance/sensing/pacing threshold out of range)	2 (7.41)	7 (25.9)	18 (66.7)
Inadequate low-energy ICD antiarrhythmic therapy	1 (3.8)	5 (19.2)	20 (76.9)
Inadequate high-energy ICD antiarrhythmic therapy	1 (3.8)	5 (19.2)	20 (76.9)
Prolonged arrhythmia detection/capacitator charging	0	3 (11.5)	23 (88.5)
Decrease in ICD shock energy delivered	2 (7.7)	3 (11.5)	21 (8.8)
CIED reset to fallback mode or power-on reset	2 (7.7)	6 (23.1)	18 (69.2)
Telemetry malfunction	1 (4)	6 (24)	18 (72)
Complete loss of function	2 (7.4)	6 (22.2)	19 (73.9)
Other dysfunction	1 (4.3)	5 (21.7)	17 (73.9)

Numbers (percentage) of centres that responded are presented.
CIED, cardiac implantable electronic device; ICD, implantable cardioverter-defibrillator.

declared the limit of 2 Gy, whereas for a smaller proportion of centres (10%), the limit depended on the CIED manufacturer, CIED type (ICD, resynchronization pacemaker, or 'standard' pacemaker), or was influenced by patients' characteristics (each reported by 10% of the centres). Of note, 7% of centres accepted as safe a dose of up to 5Gy, another 7% adopted no safety limit and treated all CIED patients undergoing RT the same way, and 38% of the respondents did not know which limit should be used.

According to 45% of the respondents, both the device can and the electrodes should be protected against direct irradiation during RT, and 38% of the centres replied that only the can should be protected; 37% always deactivated ICD therapies prior to RT, while smaller proportions of centres would refrain from deactivating ICD in patients with normal continuous ECG recording (22%) or normal intracardiac electrograms (22%) during first RT session.

The most common safety precautions undertaken in high-risk CIED patients before RT for cancer included optional surgical relocation of the device and continuous ECG monitoring during every RT session, each reported as necessary by 59% of the centres (*Table 2*). Less often safety measures included the possibility to have a cardiologist or CIED specialist present within 10 min during RT session (52%), on-site CIED interrogation and reprogramming before and after every RT (52%) or reconsidering RT need or modification of RT plan aiming at radiation reduction (41%). Only 19% of the respondents considered the 'emergency protocol ready and resuscitation team at hand' an important point, and none of the centres required the anaesthesiologist presence during RT. Most commonly undertaken safety precautions in low-risk CIED patients before RT included device interrogation only after the last radiation session (carried on by 48% of the centres), followed by cardiologist or CIED specialist available within 10 min (37%), optional surgical CIED relocation (33%), and continuous ECG monitoring during every RT fraction (30%) (*Table 2*). In patients requiring ICD explantation before curative RT, 33% of centres used in-hospital continuous ECG monitoring, another equipped the majority (22%), or selected patients (18%) with a life vest. Of note, 26% centres did not protect patients against sudden cardiac death after ICD removal.

Discussion

This EHRA survey provides a contemporary overview of approach to cardio-oncologic patients across Europe, with special emphasis on CIED patients planned for anticancer RT. A relatively low response rate (36 centres participated) is the main limitation.

The main findings of this survey were: (i) a growing awareness of possible adverse cardiovascular effects of anticancer therapy (9 of the 10 participating centres have already coped with cardio-oncology patients); (ii) thromboembolic complications and left ventricular dysfunction were the most frequently encountered side effects after anticancer treatment requiring cardiological treatment, while anthracyclines, RT and monoclonal antibodies were most commonly associated with adverse effects; (iii) a general agreement to use echocardiography to screen for cardiotoxic effects of anticancer therapy, but relatively low awareness of screening necessity (10% of centres did not routinely screen cardio-oncologic patients); (iv) a great heterogeneity among centres in the risk assessment, including risk calculation prior to RT in CIED patients; (v) relatively low occurrence of RT-induced device dysfunction (reported as 0–5%), but with potentially serious consequences (change in stimulus amplitude,

Table 2 Safety precautions undertaken in high-risk and low-risk patients with cardiac implantable electronic devices before or during radiotherapy

	Undertaken in high-risk CIED patients	Undertaken in low-risk CIED patients
Reconsideration of the need for RT or modification of the RT plan—radiation reduction	11 (40.7)	6 (22.2)
Other therapeutic options taken into consideration (chemotherapy)	9 (33.3)	4 (14.8)
Surgical CIED relocation considered	16 (59.3)	9 (33.3)
Crash card with external defibrillator available	7 (25.9)	5 (18.5)
External cardiac pacing available	8 (29.6)	3 (11.1)
Presence of cardiologist with programmer during RT	6 (22.2)	1 (3.7)
Cardiologist/CIED specialist available within 10 min	14 (51.8)	10 (37)
Presence of anaesthesiologist during RT	0	0
Emergency protocol ready and resuscitation team at hand	5 (18.5)	2 (7.4)
Continuous audiovisual patient monitoring during RT	8 (29.6)	4 (14.8)
Continuous ECG monitoring during every RT fraction	16 (59.)	8 (29.6)
Continuous SpO_2 monitoring during every RT fraction	6 (22.2)	3 (11.1)
Transport of the patient under medical surveillance to cardiology centre to check-up, deactivate/activate CIED before and after every RT session	7 (25.9)	4 (14.8)
On-site interrogation/programming of CIED before and after every RT	14 (51.8)	3 (11.1)
CIED interrogation only after the last RT session	4 (14.8)	13 (48.1)

Numbers (percentage) of centres that responded are presented.
CIED, cardiac implantable electronic device; RT, radiotherapy; SpO_2, peripheral oxygen saturation.

decrease in ICD shock energy, or device reset); and (vi) a great inter-centre heterogeneity in safety measures undertaken in high-risk CIED patients prior to RT.

Despite the projected exponential increase in the number of cardio-oncologic patients in the near future, no uniform policy has been settled so far regarding the approach to patient with cancer and cardiovascular disease. A recent position paper systematized some aspects, mainly related to cardiac toxicity of oncologic drugs.[5] Several documents addressing the problem of CIED patients have been issued by individual European National Cardiology Societies (often in cooperation with other health care organizations), but these contributions are mostly limited to specific countries.[6–9]

Our data have shown that the spectrum and frequency of cardiovascular side effects of anticancer therapy encountered by responding sites were comparable to other reports, with dominant left ventricular dysfunction and thromboembolic events, followed by atrial fibrillation and pericardial effusion.[5,10–13] However, anticancer therapies most commonly associated with high complication rates in this survey were not necessarily identified as such dangerous in previous reports.[10–12] Importantly, 55% of the respondents have felt that their knowledge on the effects of anticancer drugs is insufficient, underscoring the need for further educational activities among cardiologists and continuous collaboration with oncologists.

Most participating centres used echocardiography to screen for cardiovascular side effects of anticancer treatment, as recommended by recent guidelines.[5] The utilization of other imaging techniques, such as cardiac magnetic resonance (used by 13% of centres) or nuclear imaging (used by 0%), was surprisingly low. Remarkably, 10% of the responding centres used no routine screening for cardiovascular side effects in their patients treated for cancer, despite clear European Society of Cardiology recommendations for routine cardiac assessment, including the left ventricular function, after completion of treatment with potentially cardiotoxic agents.[5]

Data from this survey indicate a great variability in assessing the risk in CIED patients planned for RT between various centres. Indeed, no exact threshold dose or linear relationship has been identified yet for radiation risk in CIED patients. However, available data suggest low risk of CIED failure if total RT dose close to device equals <2 Gy.[14,15] The acceptable dose may depend on CIED type (with ICD probably being more fragile than pacemaker, and possibly able to receive safely only 0.5–1Gy), device manufacturer, and radiation energy (energies >6–10 MV are always associated with higher risk). The acceptable dose may differ with the different radiation source (proton and neutron beams being more dangerous that photon energy) or the distance from CIED to the irradiated area.[16,17] Also, it may depend on the patient itself (pacing-dependent and secondary prevention ICD patients being at higher risk). Finally, the calculated safe dose has to be always compared with the 'real' dose received by CIED after first fraction.[6,8,9]

The safety measures undertaken in high-risk CIED patients prior to RT differed significantly among the participating centres. Safety precautions ranged from aggressive, highly invasive approach such as surgical relocation of CIED (considered by 59% of the respondents), through CIED interrogation and reprogramming before and after every RT (52%), to very liberal strategies such as CIED interrogation only after last RT session (15%). Remarkably, only 19% of the responders considered the 'emergency protocol ready and resuscitation team at hand' important, and none of the centres required an anaesthesiologist presence during RT in high-risk patients. Emergency protocol, reanimation team, and the anaesthesiologist

presence are recommended for high-risk patients in all documents endorsed by national societies.[6,8,9] These discrepancies between common clinical practice and recommendations underscore the urgent need for further research and development of international guidelines on management of these patients

Conclusions

Our survey has shown that awareness of possible adverse cardiovascular effects of anticancer therapy was relatively high among European centres. While echocardiography is widely used for screening for cardiotoxicity of anticancer treatments, more sophisticated imaging modalities are underused and the understanding of screening necessity is suboptimal. Pronounced heterogeneity in the risk assessment and safety measures in CIED patients undergoing RT among the European centres underscores the need for further research and the standardization of the approach to cardio-oncologic patients.

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