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ORIGINAL ARTICLE

DEGRO/DGK guideline for radiotherapy in patients with cardiac implantable electronic devices

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Abstract An increasing number of patients undergoing radiotherapy (RT) have cardiac implantable electronic devices [CIEDs, cardiac pacemakers (PMs) and implanted cardioverters/defibrillators (ICDs)]. Ionizing radiation can cause latent and permanent damage to CIEDs, which may result in loss of function in patients with asystole or ventricular fibrillation. Reviewing the current literature, the interdisciplinary German guideline (DEGRO/DGK) was developed reflecting patient risk according to type of CIED, cardiac condition, and estimated radiation dose to the CIED. Planning for RT should consider the CIED specifications as well as patient-related characteristics (pacing-dependent, previous ventricular tachycardia/fibrillation). Antitachyarrhythmia therapy should be suspended in patients with ICDs, who should be under electrocardiographic monitoring with an external defibrillator on stand-by. The beam energy should be limited to 6 (to 10) MV CIEDs should never be located in the beam, and the cumulative scatter radiation dose should be limited to 2 Gy. Personnel must be able to respond adequately in the case of a cardiac emergency and initiate basic life support, while an emergency team capable of advanced life support should be available within 5 min. CIEDs need to be interrogated 1, 3, and 6 months after the last RT due to the risk of latent damage.

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Leitlinie der DEGRO/DGK zur Strahlentherapie bei Patienten mit kardialen implantierten elektronischen Geräten

Zusammenfassung Strahlentherapie (RT) ist zunehmend häufig bei Patienten mit kardialen implantierten elektronischen Geräten (CIED; Herzschrittmacher [SM] und Kardioverter-Defibrillatoren [ICD]) indiziert. Durch ionisierende Strahlen können Schäden und Fehlfunktionen des CIED auftreten, die einen permanenten Funktionsverlust beim Gerät und eine Asystolie oder Kammerflimmern beim Patienten auslösen. Deshalb wurde vor dem Hintergrund der bisher verfügbaren Daten eine interdisziplinäre Leitlinie (DEGRO/DGK) erarbeitet, die sich an der zu erwartenden Strahlendosis am CIED sowie dem kardialen Risiko des Patienten orientiert. In die Planung zur Strahlentherapie sollten sowohl CIED-Spezifika als auch Charakteristika der kardialen Erkrankung (SM-Abhängigkeit, stattgehabte ventrikuläre Tachykardie/Kammerflimmern) einfließen. In implantierten ICDs sollte die antitachyarrhythmische Therapie zur RT pausiert werden. Diese Patienten sollten dann zwingend mittels Elektrokradioghramm überwacht werden und ein externer Defibrillator sollte unmittelbar verfügbar sein. Bei allen CIEDs sollte die Strahlenenergie auf 6(−10) MV limitiert werden. Der CIED sollte niemals im direkten Strahlengang liegen. Eine Gesamtstreustrahlendosis sollte 2 Gy nicht überschreiten. Das Personal sollte in der Lage sein, adäquat auf kardiale Notfälle nach „Basic-life-support"-Kriterien zu reagieren. Ein Reanimationsteam muss innerhalb von 5 min präsent sein. Nach der letzten RT sollten die CIED innerhalb von 1, 3 und 6 Monaten erneut abgefragt werden, da ein Risiko für verspätet auftretende CIED-Schäden besteht.

Schlüsselwörter Strahlentherapie · Herzschrittmacher · Implantierter Kardioverter/Defibrillator · Kardiale implantierte elektronische Geräte · Ionisierende Strahlung

In Germany, there is a rising coincidence of patients aged over 65 years undergoing radiotherapy for malignancies (approx. 480,000 newly diagnosed cases per year according to the Robert Koch Institute) and implantation of cardiac pacemakers (PMs) and cardioverter-defibrillators (ICDs, 150,000 newly implanted devices per year [63]). Radiotherapy (RT) is applied in up to 70% of cancer cases [35] and it can be assumed that the number of patients in need of both therapies is growing due to demographic changes.

In the field of cardiology and radiation oncology there is a significant lack of knowledge regarding the safe handling of cardiac implantable electronic devices (CIEDs) during RT. This has been substantiated by a recent poll among British radiation oncologists, which showed that most clinicians still use the 1994 American Association of Physicists in Medicine (AAPM) guidelines, which are outdated today (Table 1) [32]. This is most likely true for many other countries and accounts for the need to review the available evidence. The goal of the national guidelines of the German Society of Radiation Oncology (DEGRO) and the German Society of Cardiology (DGK) is to provide information on the safe handling of CIEDs during RT and to develop practical guidelines that minimize risk for patients during their cancer treatment.

Effects of ionizing radiation on CIEDs

PMs detect the ventricular electric activity and are inhibited if the intrinsic heart rate is sufficient. PMs will stimulate the heart if the heart rate drops below a preprogrammed threshold rate. ICDs are implanted for treatment of symptomatic ventricular tachycardia (VT) and to prevent sudden cardiac death due to ventricular fibrillation (VFib). ICD functions include PM activity, antitachycardia pacing, and defibrillation therapy. The use of complementary metal oxide semiconductors (CMOS) in modern CIEDs results in less energy consumption, higher dependability, and smaller devices. In comparison with bipolar transistors that were used in older models, these modern CMOS are more sensitive to damaging events caused by ionizing radiation that might lead to electron-hole pairs resulting in electric leakage and shortcuts [29, 55, 60]. These events may occur in any part of the CMOS and even in more than one position at a time. The

Table 1 Guidelines of the American Association of Physicists in Medicine [5, 35]

Radiation source	a) No use of betatrons
	b) Due to lack of data for other sources, recommendations are given only for betatrons, linear accelerators, and telecobalt sources. Other radiation sources/qualities should only be used after individual risk assessment
Execution of radiation treatment	a) PMs should not be located directly in the beam
	b) The expected dose at the PM should be estimated before first treatment
	c) PM dose > 2 Gy: PM interrogation before initiation of RT, once weekly. PM dose 2–10 Gy: early parameter changes might be indicative for imminent PM failure
Patient monitoring	a) Mandatory monitoring of the patient during first RT treatment

PM pacemaker, *RT* radiotherapy

Table 2 Potential errors in cardiac implantable electronic devices [5]

	Potential error	Cardiac pacemaker	ICD
Ionizing radiation	Altered stimulation (amplitude, frequency)	X	x
	Altered sensing (over-/under sensing)	X	x
	Inhibition of stimulation (pause, asystole)	X	x
	Change in operational mode (incl. asynchronous stimulation)	X	x
	Battery depletion (ERI-exchange indicator)	X	x
	Altered electrode sensing (impedance)	X	x
	Inhibition of antitachyarrhythmia therapy		x
	Altered (reduced) shock energy		x
	Prolonged detection and charging intervals		x
	Inadequate (shock) therapy		x
	Loss of telemetry or programming capabilities	x	x
	Reset in default setting (fallback mode)	x	x
	Loss of function	x	x
Electromagnetic interference	Altered sensing (over-/under sensing)	x	x
	Inhibition of stimulation (pause, asystole)	x	x
	Reed-switch interaction (asynchronous stimulation)	x	x
	Atrial-triggered fast ventricular pacing	x	x
	Inhibition of antitachyarrhythmia therapy		x
	Inadequate (shock) therapy		x
	Reset/reprogramming of device	x	x

ERI elective replacement indicator, *ICD* implantable cardioverter-defibrillator

resulting damage can be temporary or permanent. In CIEDs, radiation tolerance may be limited due to the complex design in a small space, limited battery capacity, thinner housing with less shielding, and the usage of random access memory (RAM). RAM holds patient-related data by small amounts of highly volatile increments in energy. RAM damage can therefore lead to complete loss of function in a CIED.

The most critical defects comprise altered sensing (loss or inaccurate sensing), altered stimulation (change in stimulation frequency or amplitude), change of antitachyarrhythmia therapy (ATA therapy) settings in ICDs, premature battery depletion, loss of telemetry, and complete loss of function ([29, 34, 55, 60], Table 2). Clinical consequences of CIED failures depend on the patient's characteristics: For example, loss of stimulation in a patient with sick sinus syndrome may not be harmful but will lead to life-threatening cardiac pump deficiency in a patient with grade III atrioventricular blockade. The prevalence of PM dependency is unknown and can be caused by a variety of etiologies [58]. In pacing-dependent patients, failure of the PM may result in ineffective or missing stimulation and therefore cause symptomatic bradycardia or asystole making reanimation or temporary stimulation necessary. By contrast, loss of stimulation control may lead to fast stimulation ("runaway pacemaker" or "runaway ICD") with loss of systolic blood pressure, cardiogenic shock, angina pectoris, and VT [45, 69]. Loss of sensing may lead to excessive and nonsynchronized ventricular stimulation occurring during the T wave. This can result in VFib with subsequent cardiac arrest and death. Additionally, loss of sensing can result in omission of ATA therapy in ICDs. It has been discussed that either electromagnetic interference or artificial sensing mimics high ventricular frequencies and results in inadequate shock therapy [53].

Data supporting evidenced-based guidelines

Table 3 shows all in vitro studies that have been published to date.

CIEDs were placed either directly in the beam or in close vicinity investigating scatter photon and secondary neutron radiation. In PMs, errors resulting in asystole >10 s or even complete loss of stimulation were found at ≤1 Gy [43]. Other findings included changes in stimulatory impedance as first sign of failure and latent decrease in battery life after 1 week [21]. Device failure was not predictable by a threshold dose [56]. Electrical potentials up to 1.2 mV were detected in leads. This can result in oversensing with inhibition of PM stimulation leading to bradycardia, asystole, or fast pacing [7, 66]. In ICDs, ventricular oversensing was recorded after 0.5 Gy, which may be misread by the ICD as VFib or VT and can therefore result in inadequate defibrillation [20]. Complete device failure occurred even at <1.5 Gy [20]. Errors happened only when the device itself but not the electrodes were within the beam [62].

Data from case series or case reports are presented in Table 4.

In three reported cases, PMs were directly located in the beam, which resulted in device failures [11, 61, 68]. One runaway PM occurred after 0.11 Gy. The PM was not in

Table 3 In vitro studies on cardiac implantable electronic devices (modified and extended from [5])

Author	Year	CIEDs	Type	Effects
Souliman [56]	1994	18 (15 × 1-chamber and 3 × 2-chamber system), various manufacturers	PM	Irreversible malfunction of all 2-chamber systems between 16.8 and 64.4 Gy; irreversible malfunction of eight 1-chamber systems between 25.2 and70 Gy
Wilm [66]	1994	20 (3 manufacturers)	PM	10 Gy: decrease of stimulatory amplitude; 40 Gy: first loss of function; 90–300 Gy: 19× loss of function (loss of entire stimulation capability)
Röthig [50]	1995	3 manufacturers (no information reg. number of devices)	PM	Failure of all tested systems at 40–90 Gy
Mouton [43]	2002	96 (different models and manufacturers)	PM	Decrease in stimulatory amplitude > 10 % (n = 63) between 2–130 Gy; intermittent loss of stimulation > 10 s (n = 39) between 0.15 and 90 Gy; irreversible loss of stimulation (n = 48) between 0.5 and 170 Gy
Hurkmans [21]	2005	19 (4 manufacturers)	PM	Irreversible failure of 14 systems between 20 and 130 Gy (loss of stimulation, battery depletion, loss of telemetry); first significant sign of malfunction (telemetry) at 10 Gy
Hurkmans [20]	2005	11 (4 manufacturers)	ICD	Irreversible failure of all systems between 1.5 and 120 Gy (shock delivery not possible, loss of stimulation, loss of sensing); first significant sign of malfunction (decrease in shock energy) at 0.5 Gy
Uiterwaal [62]	2006	11 (4 manufacturers)	ICD	Interference in all ICDs when directly irradiated (starting from 0.5 Gy); misinterpretation as ventricular fibrillation
Kapa [24]	2008	20 (3 manufacturers), incl. 8 CRT systems	ICD	No malfunction due to scatter radiation (4 Gy, 6 MV)
Hashii [14]	2012	10 ICDs (1 manufacturer, 2 models)	ICD	8 ICDs arranged around a water phantom; 2 ICDs in 140 cm distance: software failures in both locations, 8× more often with 18 MV compared with 10 MV; 14–20× more secondary neutrons with 18 MV compared with 10 MV; no difference in scatter radiation (18.8 mSv/10 MV vs. 20.23 mSv/18 MV)
Hashimoto [15]	2012	4 ICDs (1 manufacturer)	ICD	107 GyE proton radiation: only scatter radiation but still exposure to high rate of secondary neutrons; one ICD malfunction every 15 GyE (reset, reversible loss of function); no irreversible failures
Zaremba [67]	2014	10 PM (new), 2 ICD (explanted; 5 manufacturers)	PM/ ICD	Increasing fractional doses up to 150 Gy; all CIEDS were placed in a phantom in the beam; 6/18 MV photons: 14 malfunction in 5 PM with 18 MV; one malfunction in PM with 6 MV (HR 9,11 [95 % (CI): 1.04–79.69]; no failures in ICDs

All experiments were carried out with photon or electron radiation otherwise noted

Gy Gray, *GyE* Gray equivalent, *MV* megavolt, *mSv* milliSievert, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter-defibrillator, *PM* pacemaker

the beam and 18 MV photons were used, therefore secondary neutrons most likely contributed to the damage (personal communication; [69]). One PM reset happened during intensity-modulated RT (IMRT) for prostate cancer (15-MV photons) [54]. In several ICD failures, the devices were located out of the beam (scatter radiation < 0.5 Gy) and energies > 6–10 MV were applied (Gelblum, 15 MV; Lau, 23 MV; Thomas, 18 MV) [12, 31, 59]. Most reports describe ICD reset into a fallback or power-on-reset mode, with remaining basic diagnostic and therapeutic modalities. One runaway ICD is reported to have occurred during RT for lung cancer in the left hemithoracic region where the ICD was also located. In this case, reset of the ICD stimulatory frequency to 175/min induced polymorph VT of 230–370/min, which made resuscitation of the patient necessary [45].

Mechanisms leading to CIED failures

CIED failure caused by photon radiation occurred either when the device was directly irradiated or when the energy was > 6 MV (see Table 3). No proven threshold dose or linear relationship exists for radiation-induced damage to CIEDs [19]. However, risk for damage to the CIED is considered to increase with radiation dose. In this respect, it is necessary to understand that the amount of energy delivered to a CIED accumulates [30, 34, 55].

Energies > 6–10 MV cause excessive formation of secondary neutrons that harm the RAM or CMOS [10, 14, 15, 50, 65]. At 18 MV, PM defects occurred even at low radiation doses (15 cGy) [43]. On the other hand, irradiation of 20 ICDs with 6-MV photons up to 4 Gy did not result in any ionizing radiation-related effects [24]. In ICDs, placed either close to the central beam or 140 cm away, errors occurred in both locations about eight times more often at 18 MV than at 10 MV [14]. The neutron dose was 14–20 times higher with 18 MV than with 10 MV. No difference was observed in the photon scatter radiation dose (18.8 mSv/10 MV vs. 20.23 mSv/18 MV) [14]. Another study reported ICD failures with 18 MV while no failures were observed at 6 MV [8]. In CIEDS that were placed directly in the beam and irra-

Table 4 In vivo results with cardiac implantable electronic devices (CIEDs;modified and extended from [5])

Author	Year	*n*	Tumor entity or site	CIED	RT dose	Dose CIED/energy	Effects
Raitt [49]	1994	1	Thyroid cancer	PM	4.8 GyE neutrons	0.9 GyE	Uncontrollable increase in pacing frequency (runaway pacemaker, 180/min)
Tsekos [61]	2000	1	Neuroendocrine cancer right arm	PM	50.4/1.8 Gy	~50 Gy (PM in beam)/n.m.	Intermittent decrease in magnetic frequency
Nibhanupudy [46]	2001	1	Breast cancer	PM	<60/2 Gy	1.8 Gy/6 MV	No malfunction
Hoecht [17]	2002	3	Pelvic metastases	ICD	No information	<0.5 Gy/n.m.	Reset into fallback mode ($n=1$), identical malfunction after ICD replacement
Frantz [11]	2003	1	Breast cancer	PM	66/2 Gy	50 Gy (PM in beam)/n.m.	Loss of telemetry capabilities
John [22]	2004	1	Breast cancer	ICD	50/2.5 Gy	Lead in beam/n.m.	Battery depletion, shock impedance > 125 Ω (damaged ICD lead)
Thomas [59]	2004	1	Lung cancer	ICD	56/2 Gy	<0.5 Gy/18 MV	Reset into fallback mode
Mitra [42]	2006	1	Lung cancer	PM	40/2 Gy	0.73 Gy (TPS)/n.m.	No malfunction
Sepe [52]	2007	1	Laryngeal cancer	ICD	60/2 Gy	2.5 Gy/6 MV	No malfunction
Nemec [45]	2007	1	Lung cancer	ICD	<5.4/1.8 Gy	n.m./n.m.	Uncontrollable increase in pacing frequency (runaway ICD, 175/min); induction of polyform VT, necessitation of CPR
Munshi [44]	2008	1	Breast cancer	PM	50.4/1.8 Gy	4.3 Gy/10 MV	No malfunction
Kapa [24]	2008	8	Head and neck, lung, breast cancer	PM	30–70 Gy	n.m. (only scatter)/n.m.	No malfunction
Oshiro [48]	2008	8	Thorax, abdomen	PM	36.3–77 GyE protons	0 GyE to CIED/0–69 Gy leads	Reset into fallback mode ($n=1$), deviation from programmed stimulatory frequency ($n=1$)
Lau [31]	2008	1	Prostate cancer	ICD	4/2 Gy	0.004 Gy/23 MV	Reset into fallback mode
Zweng [69]	2009	1	Esophageal cancer	PM	30/3 Gy	0.11 Gy/18 MV	Deviation from programmed stimulatory mode (DDD ®AAI) and uncontrollable increase in stimulatory frequency (runaway pacemaker,185/min)
Gelblum [12]	2009	33	Head and neck, thorax, abdomen, pelvis, legs	ICD	6–86.4/1.8–2 Gy	0.01–2.9 Gy/15 MV	Reset into fallback mode ($n=2$, no ICD in beam)
Zaremba [68]	2010	1	Breast cancer	PM	48/2 Gy	2–37 Gy (PM partially in beam)/6 + 18 MV	Software warning: "invalid data detected," no malfunction detected
Ferrara [9]	2010	37	Head and neck, thorax, abdomen, pelvis	PM	8–79.2 Gy	<2 Gy ($n=32$), >2 Gy ($n=5$)	No malfunction
Wadasadawala [64]	2011	8	Head and neck, lung, breast cancer	PM	45–70/1.8–2 Gy	0.14–60 Gy (PM partially in beam)/6–15 MV	No malfunction
Dasgupta [6]	2011	1	Cardiac metastases (right atrium and left ventricle)	PM	37.5/2.5 Gy	0.26 Gy (leads in beam)/n.m.	Intermittent ventricular under sensing
Soejima [54]	2011	60	Head and neck, thorax, pelvis, breast cancer	PM	20–74 Gy	<2 Gy ($n=59$), >2 Gy ($n=1$)/15 MV	Reset into fallback mode ($n=1$), prostate cancer case
Menard [41]	2011	5	Breast cancer	ICD	32.5–66/2 Gy	<0.1–0.3 Gy/4–6 MV	No malfunction
Croshaw [5]	2011	8	Breast cancer	ICD	34/3.4 Gy HDR-BT/ 38.5/3.85 Gy EBRT	0.99–1.68 Gy/n.m.	No malfunction neither HDR-BT nor EBRT
Kirova [28]	2012	1	Sarcoma	PM	30/3 Gy	0.1 Gy/20 MV	No malfunction
Kesek [25]	2012	1	Lung cancer	PM	80 Gy/1.6 Gy b.i.d.	25 Gy mean/48 Gy max (PM partially in beam)/n.m.	No malfunction

Table 4 (continued)

Author	Year	*n*	Tumor entity or site	CIED	RT dose	Dose CIED/energy	Effects
Makkar [36]	2012	69	Head and neck, breast cancer, lung, abdomen, pelvis, limbs	ICD	BC 45/1.8, rectal cancer 50.4/1.8 Gy	4 + 123 cGy/16 MV	Reset into fallback mode ($n=2$, lung cancer/ rectal cancer)
Elders [8]	2012	15	Head and neck, lung, abdomen, pelvis, legs	ICD	16–70/2–8Gy	n.m./6–18 MV	Reset into fallback mode, invalid data retrieval, inappropriate tachycardia sensing ($n=5$)
Keshtgar [26]	2012	1	Breast cancer	PM	20 Gy IORT	8 cGy/50 kV	No malfunction
Gomez [13]	2013	5	Thorax	ICD/ PM	4–67,5 GyE protons	0.745 GyE protons; 655 mSv sec. neutrons	Reset into fallback mode
Gauter-Fleckenstein (in preparation)	2007–2011	5	Breast cancer, lung, prostate cancer	ICD/ PM	56–76/2–3Gy	9.57 cGy ($n=1$)/18–23 MV	Reset into fallback mode

All treatments were carried out with photon or electron radiation otherwise noted

Gy Gray, *GyE* Gray equivalent, *MV* megavolt, *kV* kilovolt, *mSv* milliSievert, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter-defibrillator, *PM* pacemaker, *AAI* atrial single-chamber pacemaker, *DDD* dual-chamber pacemaker, *n.m.* not mentioned, *TPS* treatment-planning system, *IORT* intraoperative radiotherapy, *HDR-BT* high-dose-rate brachytherapy, *EBRT* external beam radiotherapy

diated up to a dose of 150 Gy with fractional doses of 2 Gy, one error was observed at 6 MV while 14 defects were noted with 18 MV [67]. Case series report CIED failures at 10- and 18-MV photon RT for tumors that were not located near the CIED. CIED radiation doses ranged from 84.4 ± 99.7 cGy (PM) to 92.1 ± 72.6 cGy (ICD) [8, 12, 31, 36,54]. Other case reports describe safe RT at 6 MV [12, 36, 52]. At our department, we observed CIED failures in five patients who received RT with 18–23 MV for breast, lung, and prostate cancer. No further incidents were observed under intensive surveillance after limiting the energy to 6 MV in more than 100 observed cases.

Dose rate effects were evaluated systematically in a study of 96 PMs [43]. While dose rates of 0.2 Gy/min did not result in any ionizing radiation-related effect, dose rates of up to 1 Gy/min yielded two defects and dose rates of 8 Gy/min resulted in failures in 70 % of the tested PMs. Sensitive were especially electronic parts of the CIEDs relevant for sensing and therefore failure would haveresulted in CIED reset, asystole, or inadequate defibrillation therapy [39]. Regularly used dose rates in the isocenter are between 1 and 10 Gy/min. Resulting dose rates at the CIED are about ten times lower (< 1 Gy/min) if the CIED is not placed within the RT field.

Electron radiation is less dangerous due to lower production of secondary neutrons at the same energy level. At 15 MeV, electron radiation produces only 5 % and at 25 MeV only 20 % of the amount of secondary neutrons that photon radiation produces at the same nominal energy.

Brachytherapy also exerts little influence on CIEDs due to the applied energy levels (20–380 keV) and steep dose gradient [26, 27]. To date, no brachytherapy-related incident of radiation-induced damage to CIEDs has been reported [5, 26, 27].

Radiological imaging techniques employing ionizing radiation also use less energy (kV) and smaller radiation doses (0.01–0.4 Gy) in comparison with RT [3]. Nevertheless, radiologic imaging may result in CIED failure if the device is subjected directly to radiation [16, 39].

Electromagnetic fields, produced by linear accelerators (LINAC) when the beam is switched on [47, 38], are well shielded and therefore do not significantly contribute to CIED failures in clinical routine.

Of greater concern are particles that are used increasingly for different tumor entities [51]. In four ICDs, subjected to scatter proton radiation, formation of secondary neutrons resulted in a total of 29 software failures during ten RT sessions with a cumulative dose of 107 Gy [15]. Several case series on particle radiation report severe failures (reset of stimulatory frequency to a rate of 180/min, runaway pacemaker), reset into fallback mode, and reprogramming of device settings that occurred at high rates in CIEDs that were located out of the field [13, 48, 49]. Therefore, no assumption can be made for safe strategies regarding particle radiation.

German Guideline for CIEDs

It is not possible to discern between different models because manufacturers provide heterogeneous recommendations (Table 5). It becomes apparent from the available data that placement of the CIED in the beam, energies > 6–10 MV, high radiation dose rate close to the CIED, as well as par-

Table 5 Manufacturer recommendations (modified and extended from [5])

Recommendations	Biotronik [2]	Boston Scientific [4]	Medtronic [40]	St. Jude Med. [23]
Device relocation				
PM	Yes	Yes	Yes (≥3 cm)	Yes
ICD	Yes	Yes	Yes (≥3 cm)	Yes
Acceptable CIED dose	<10 MeV			
PM	<2 Gy	No safe dose	<5 Gy	20–30 Gy
ICD	<2 Gy	No safe dose	<5 Gy	n.m.
Shielding (lead) of CIED	Yes	Yes	Yes	Yes
Before treatment				
Assessment by cardiologist	Yes	Yes	n.m.	n.m.
Device interrogation	Yes	Yes	n.m.	Yes
Before RT session				
Device interrogation	Yes	Yes, e.g., programming asynchronous stimulation	n.m.	n.m.
ICD: deactivation of antitachycardia therapy	Yes (programming)	Yes (programming))	n.m.	Yes (programming or external magnet)
During RT session				
Patient monitoring	ECG, NIBP, SpO_2, CPR stand-by	According to individual patient's needs	n.m.	n.m.
After RT session				
Device interrogation	Yes, reprogramming if applicable	Yes, e.g., reprogramming if applicable	If accumulated RT dose >5 Gy	Yes, after first RT session; afterward weekly interrogation throughout RT
After last RT	Additional device interrogation (home monitoring if applicable)	Additional device interrogation	n.m.	PM: interrogation; if pathological findings then short-scheduled controls; ICD: induction testing

CPR cardiopulmonary reanimation, *ECG* electrocardiogram, *Gy* Gray, *ICD* implantable cardioverter-defibrillator, *n.m.* not mentioned, *MV* megavolt, *NIBP* noninvasive blood pressure monitoring, *PM* pacemaker, *SpO_2* pulse oximetry

Table 6 Differentiation into low-, intermediate-, and high-risk groups: risk for clinically relevant interaction in pacemaker patients in relation to pacemaker dependency and accumulated radiation dose to the CIED (parts or whole system)

	<2 Gy	2–10 Gy	>10 Gy
Non-pacemaker dependent	Low	Middle	High
Pacemaker dependent	Middle	High	High

Table 7 Differentiation into low-, intermediate-, and high-risk groups: risk for clinically relevant interaction in ICD patients in relation to likelihood of ventricular tachyarrhythmias and accumulated radiation dose to the CIED (parts or whole system)

	<2 Gy	2–10 Gy	>10 Gy
ICD without VT/VFib	Low	Middle	High
ICD with VT/VFib before/after Implantation	Middle	High	High

CIED cardiac implantable electronic devices, *ICD* implantable cardioverter-defibrillators, *VFib* ventricular fibrillation, *VT* ventricular tachycardia

ticle radiation may be positive predictors of CIED failure. In this respect, it is necessary to understand that CIED defects can occur with latency and may become manifest as total breakdown weeks or months after the end of RT [66]. This recommendation takes into account whether a patient is PM-dependent or has a history of previous VT as well as the cumulative dose at the CIED respecting the aforementioned precautions.

Risk assessment

For practical reasons, RT dose in relative distance to the CIED is graded (Table 6, 7). Risk for CIED failure with RT doses close to the CIED <2 Gy is considered low, between 2 and 10 Gy intermediate, and >10 Gy high. The relative dose close to the CIED may be derived from Fig. 1 (according to Hurkmans [19]). This graph does not take into account that modern three-dimensional conformal radiation fields result in much smaller doses to the contralateral side or behind the penumbra. Modern IMRT in particular results in extremely low scatter radiation to the normal tissue close to the tumor. Therefore, even RT of thoracic tumors close to the CIED may be possible if precautions are followed (see Fig. 2, VMAT plan of RT for thoracic vertebral metastases at Th2–Th9). The exact dose over the CIED should be calculated using the treatment planning system (TPS) if the CIED was depicted in the planning CT [57]. Nevertheless, it is necessary to bear in mind that most TPS on regular workstations truncate scatter dose calculations behind the penumbra due to limited calculation time. Measuring RT dose with thermoluminescent dosimetry or optically stimulated dosimetry (TLD/OSLD) above the CIED during the first fraction adds more information.

Patients at highest risk are PM-dependent and may experience a cardiac arrest due to severe bradycardia or asystole in case of device failure. Patients with ICD and a history of VT are also at high risk. These patients are endangered

Fig. 1 Delineation of the estimated radiation dose to a CIED implanted in typical left pectoral location depending on the target volume in the patient (according to Hurkmans et al. [19]). If a tumor is located in the *red* area, then the radiation dose to the CIED is likely to be > 10 Gy, in the *blue* area between 2 and 10 Gy, and in the *gray* area < 2 Gy. This figure does not take into account the fact that modern three-dimensional conformal or stereotactic radiation fields result in much smaller doses to the CIED

due to: (1) possible induction of VF resulting from fast pacing due to ICD failure; (2) imminent risk of VF during RT while the ATA therapy is deactivated; and (3) risk of sudden cardiac death in case the ATA therapy remains accidentally deactivated after RT or due to ICD failure that remains unrecognized after RT.

The risk assessment in the guideline presented here differs from other recent guidelines in the number or definition of risk categorizations [19, 57] and in the distinction between PM and ICD patients [19]. There is no clear evidence for discrete differentiation between 2 and 10 Gy that might serve as threshold radiation doses to distinguish between low and intermediate risk. Nevertheless, these RT doses have been used before in guidelines [38, 19]. Although ICDs are regarded to be more radiation-sensitive than PMs [8, 12, 14, 18, 36, 54, 55], this guideline proposes 2 Gy as a threshold dose for both ICD and PM due to lack of clear evidence from clinical studies.

Prerequisites for treatment of patients with CIEDs

All personnel treating CIED patients should be able to identify critical CIED complications immediately (asystole, VFib, cardiogenic shock) and initiate basic life support (BLS) [1]. This mandates regular training in BLS as well as CIED specific knowledge since the ATA therapy has to be deactivated in ICDs for RT. This is achieved either by reprogramming or magnet placement. Using a magnet may be safer because removal will immediately reactivate the ATA therapy in case of ventricular tachyarrhythmias. By contrast, external defibrillation can damage the ICD or leads [37]. Furthermore, ICDs with deactivated ATA therapy by reprogramming may accidentally stay in suspended ATA therapy mode and therefore leave the patient unnoticed at risk. A magnet still in place over the ICD is harder to overlook (Table 9). In this context, it is necessary to understand the difference between magnet functionality in ICDs and PMs: In a PM, a magnet will induce asynchronous stimulation while in an ICD it deactivates the ATA therapy and only reprogramming achieves asynchronous stimulation. Therefore, a magnet should be used only if the health-care provider has readily understood the underlying technical principles and if secure placement of the magnet over the CIED is ensured throughout the entire radiation treatment. Patients at high risk or with deactivated ATA therapy should be monitored more closely with an electrocardiogram (ECG) and pulse oxymetry. A defibrillator should be immediately available and competent personnel should be present. Contact via in-room camera and microphone needs to be maintained throughout every treatment session. One camera should always be directed toward the ECG monitor and camera quality should be sufficient to recognize a pathologic electric rhythm. An emergency protocol should be implemented and it should be ensured that a reanimation team is available in case of (suspected) emergency. Emergency equipment (monitoring ECG, blood pressure, blood oxygen saturation, external defibrillator, crash cart) should be available immediately in a cardiac emergency. In high-risk patients (Table 6 and 7), permanent presence of a team capable of advanced life support is warranted to avoid any delay in treatment and to assure the possibility of immediate defibrillation therapy [33]. A physician with qualification in CIED therapy should be available and present in case of CIED failure. Therefore, cooperation between the

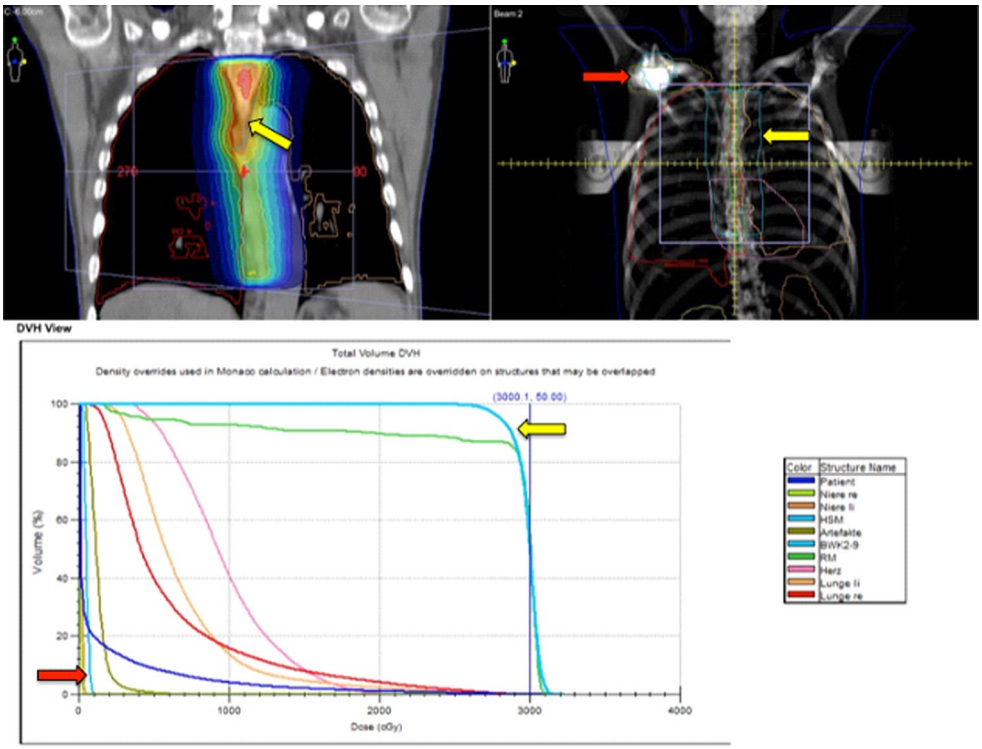

Fig. 2 VMAT (volumetric arc therapy) plan, a modern form of intensity-modulated radiotherapy for a patient suffering from hepatocellular carcinoma with vertebral metastasis in the thoracic vertebral bodies Th2–Th9. The patient had a right pectoral implanted pacemaker (PM) and was PM-dependent (heart frequency < 30/min). *Left upper* image shows the isodoses (*yellow arrow* indicating 100 % isodose for 30 Gy). *Right upper* images shows planning CT DICOM image with planning target volumes (PTV, *yellow arrow* indicating blue PTV Th1—Th10; *red arrow* indicating PM). *Lower image* shows dose–volume histograms (DVH, *yellow arrow* indicating DVH for Th1—Th0, mean dose 2,977.9 cGy; *red arrow* indicating DVH for PM, mean dose 43.8 cGy)

Table 8 Measures before radiation therapy

1. Identification of CIED-bearing patient, labeling in patient's chart, specification of CIED (manufacturer, model).
2. The patient should be made aware of the signs of syncope or dizziness as potential signs of latent CIED defects. In this case, patients should seek immediate advice with their treating cardiologist.
3. Documentation of RT-associated risks in consent form including risk of radiation-induced CIED failure und potential device replacement surgery.
4. If CIED is located in beam: seek contact with treating cardiologist; discussion of relocation is advised,
5. Presentation at cardiologist: indication for CIED, interrogation and documentation of all programmed parameters, pacemaker-dependency (VVI, 30/min), documented episodes of VT/VFib in RAM, percentage of mandatory cardiac stimulation, battery capacity.
6. RT planning: acquisition of CIED in planning CT if feasible, limitation of energy to 6 MV (10 MV) when photons are used, computation/recording of cumulative radiation dose to CIED, no direct placement of CIED in beam.
7. Classification into risk category (low, intermediate, high).

CIED cardiac implantable electronic devices, *RT* radiotherapy, *VFib* ventricular fibrillation, *VT* ventricular tachycardia, *VVI* asynchronous ventricular inhibited stimulation

Table 9 Measures during radiotherapy

1. Evaluation of radiation dose at CIED during first fraction and comparison with calculated CIED dose.
2. Pacemaker-dependent patients: consider asynchronous stimulation (VOO, DOO, AOO); either through reprogramming or magnet placement (only possible with pacemaker, 2 adhesive stripes necessary!).
3. ICDs: Deactivation of ATA therapy throughout each RT session; either through reprogramming or magnet placement (pacemaker stimulation is not affected, 2 adhesive stripes necessary!).
4. Continuous audiovisual contact. Continuous ECG and SpO_2 monitoring in patients with suspended ATA therapy and high-risk patients. Personnel should be able to recognize ventricular fibrillation or asystole and to act accordingly (to initiate BLS until arrival of emergency team).
5. Availability of cardiologist and programming device.
6. Emergency protocol: immediate notification/activation of a reanimation team, high-risk patients need continuous presence of cardiologist, anesthesiologist, emergency physician.
7. CIED interrogation after every RT session including reprogramming and reactivation of initial settings or antitachycardia therapy.

AOO asynchronous atrial stimulation, *ATA* antitachyarrhythmia therapy, *BLS* basic life support, *CIED* cardiac implantable electronic devices, *DOO* asynchronous atrial and ventricular stimulation, *ECG* electrocardiography, *RT* radiotherapy, SpO_2 pulse oximetry, *VFib* ventricular fibrillation, *VOO* asynchronous ventricular stimulation, *VT* ventricular tachycardia

Table 10 Measures after radiotherapy

1. Final interrogation (threshold levels, sensing and stimulation parameters, lead impedance, battery capacity), reprogramming of CIED.
2. Asynchronous stimulation not longer than necessary (competitive stimulation against the intrinsic heart rhythm may cause malignant ventricular arrhythmias; R-on-T phenomenon [15]).
3. Analysis of any CIED irregularities in connection to RT and forwarding of data to manufacturer; even clinically nonsignificant changes in parameter settings may precede CIED defects.
4. Exchange of CIEDs with significant defects even if the malfunction is temporary and full device recovery is observed.
5. Repetitive interrogation 1, 3, and 6 months after RT; telemetric surveillance if available.
6. Education of patient for clinical symptoms of CIED failure (irregular or slow cardiac rhythm, dizziness, syncope), emergency sounds emitted by CIED.

CIED cardiac implantable electronic devices, *RT* radiotherapy

Table 11 Requirements for facility and personnel

Low risk *CIED dose* *2 Gy without pacemaker dependency or history of prior ventricular fibrillation*	Intermediate risk *CIED dose 2–10 Gy without pacemaker dependency or history of prior ventricular fibrillation* *CIED dose* *2 Gy with pacemaker dependency or history of prior ventricular fibrillation*	High risk *CIED dose* *10 Gy* *CIED dose* *2 Gy with pacemaker dependency or history of prior ventricular fibrillation*
• Emergency protocol	• Interrogation of CIED before and after every RT session	• Surgical relocation or replanning of RT with the goal of reducing CIED dose
• Cooperation between radiation oncology and cardiology	• PM in asynchronous modes (VOO, AOO, DOO)	• If reduction of CIED dose is impossible then consider RT on individual basis
• Personnel qualified for specific procedures in respect to CIED patients	• Continuous ECG and SpO_2 monitoring	• Cardiologist or anesthesiologist present
	• External defibrillator and external pacemaker available, ECG, NIBP, SpO_2, programming device	• CIED interrogation immediately after RT session
	• Personnel trained to recognize and treat asystole or ventricular fibrillation according to BLS guidelines	• Transportation of an ICD patient with deactivated ATA therapy under surveillance to the cardiology outpatient clinic should remain an exception

AOO asynchronous atrial stimulation, *ATA* antitachyarrhythmia therapy, *BLS* basic life support, *CIED* cardiac implantable electronic devices, *DOO* asynchronous atrial and ventricular stimulation, *ECG* electrocardiography, *NIBP* noninvasive blood pressure monitoring, *PM* pacemaker, *RT* radiotherapy, *SpO_2* pulse oximetry, *VFib* ventricular fibrillation, *VOO* asynchronous ventricular stimulation, *VT* ventricular tachycardia

radiation oncology department and the cardiology department should be initiated early and all necessary steps for prevention as well as treatment of an emergency should be discussed and agreed on in an in-house standard operating procedure (SOP).

Specific considerations before initiation of RT are presented in Table 8.

Specific measures to be followed during radiotherapy are shown in Table 9.

The specific measures to be followed after RT are presented in Table 10.

Modifications that need to be made according to risk groups are listed in Table 11.

The feasibility and practicability of these guidelines are based on the structural conditions of the German healthcare system. International recommendations in regard to the presence of manufacturer-affiliated technicians who interrogate or reprogram CIEDs in an outpatient setting are not applicable in Germany.

Compliance with ethical guidelines

Conflict of interest M. Roser has received speaker's fees from the companies Medtronic, Biotronik, and St. Jude Medical. He has also received counseling fees from Biotronik. R. Schimpf has received speaker's fees from Medtronic and St. Jude Medical. B. Gauter-Fleckenstein, C.W. Israel, M. Dorenkamp, J. Dunst, V. Steil, J. Schäfer, U. Höller, and F. Wenz state that there are no conflicts of interest.

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