Safety verification of carbon-ion radiotherapy for patients with cardiac implantable electronic devices (CIEDs)

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ABSTRACT

According to guidelines, carbon-ion beam therapy is considered to carry a high safety risk for patients with cardiac implantable electronic devices (CIEDs), although the actual impacts remain unclear. In this study, we investigated the safety of carbon-ion beam therapy in patients with CIEDs. Patients with CIEDs who underwent carbon-ion therapy at Gunma University Heavy Ion Medical Center between June 2010 and December 2019 were identified and investigated for abnormalities in the operation of their CIEDs, such as oversensing and resetting during irradiation, and abnormalities in operation after treatment. In addition, the risk of irradiation from carbon-ion beam therapy was evaluated by model simulations. Twenty patients (22 sites) with CIEDs were identified, 19 with pacemakers and one with an implantable cardioverter-defibrillator (ICD). Treatments were completed without any problems, except for one case in which the treatment was discontinued because of worsening of the primary disease. Monte Carlo simulation indicated that the carbon beam irradiation produced neutrons at a constant and high level in the irradiation field. Nevertheless, with the distances between the CIEDs and the irradiation fields in the analyzed cases, the quantity of neutrons at the CIEDs was lower than that within the irradiation. Although carbon-ion beam therapy can be safely administered to patients with CIEDs, it is advisable to perform the therapy with sufficient preparation and backup devices because of the risks involved.

Keywords: pacemaker; cardiac implantable electronic devices (CIEDs); implantable cardioverter-defibrillator (ICD); carbon-ion; radiotherapy; Monte Carlo simulation

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) such as pacemakers and implantable cardioverter-defibrillators (ICDs) are medical devices used primarily for the treatment of arrhythmias. Implantation of CIEDs can reduce symptoms caused by arrhythmias, improve quality of life and prevent sudden death due to fatal arrhythmias. With aging, the number of arrhythmic diseases that require CIEDs, such as atrial fibrillation, atrioventricular block and sinus failure syndrome, tends to increase. Similarly, the incidence of cancer also tends to increase in the elderly. Although cancer treatment options such as surgery tend to be more limited in patients with implanted CIEDs, radiotherapy, being relatively minimally invasive, can be an option for such patients, either as a curative or palliative treatment.

Since guidelines were published by the American Association of Physicists in Medicine in 1994, the guidance for radiation therapy for patients with CIEDs has been regularly updated to take into account reports of clinical cases [1–6]. Ionizing radiation has been reported to affect the operation of devices by ionizing the material...
of semiconductor integrated circuits within the devices, creating unwanted currents inside circuits and destroying the crystal structure of the semiconductors [7].

Malfunctions of CIEDs are classified as software or hardware errors. Software errors include inappropriate pacing, resetting to a backup setting, temporary oversensing that occurs only during radiation, and inappropriate ICD activation. Hard errors include permanent malfunctions that require the replacement of the CIED [6–9]. In vitro experiments in which devices are placed inside and outside the irradiation field have been conducted, as have simulation studies using models. Soft errors resulting in a partial reset with loss of memory or program changes, transient signal disturbances intermittently resulting in oversensing, full resets, complete device failure and premature battery depletion or device failure have all been reported [6, 9–17].

Radiotherapy using high-energy ionizing radiation such as X-rays, protons and carbon-ions can cause the malfunction of CIEDs. In proton therapy, which is classified as being of high risk for developing malfunctions in Guidelines for Radiation Therapy for Patients with Implantable Cardiac Electrical Devices [18], there have been reports of pacemaker reset and battery depletion due to irradiation, with such malfunctions being reported in 20–30% of patients, highlighting the need for special attention [19–22].

Carbon-ion radiotherapy (CIRT) is also classified as high risk because of the production of secondary neutron radiation. However, there is only one report investigating the frequency of device malfunctions with the clinical settings used for heavy particle CIRT [22]. The aim of our study was therefore to investigate the safety of CIRT for cancer patients with CIEDs, and to simulate neutron doses in the environment of CIRT.

MATERIALS AND METHODS

Patients

This single-institution retrospective study was approved by the institutional review board of Gunma University Hospital (approval number: HS2019-252). Twenty consecutive patients who received carbon-ion beam therapy for malignant tumors at Gunma University Heavy Ion Medical Center between June 2010 and December 2019, and who had a CIED at the start of CIRT, were considered to be eligible.

Data collection

During CIRT, the patients’ CIEDs were monitored by biomonitors, including electrocardiogram and in-room video to detect any abnormalities. All patients were treated during hospitalization; therefore, we referred to their medical records during hospitalization and checked their CIED device check sheets before and after treatment sessions.

The medical records and device check records for patients whose CIEDs were followed at our hospital after they completed CIRT were also reviewed. For those patients whose CIEDs were followed at other hospitals, a letter survey was conducted to collect the relevant medical and device information.

In this study, CIED malfunctions were defined as both hard errors and soft errors, such as any reset, transient signal disturbances, oversensing, full reset, complete device failure and premature battery depletion or device failure.

Carbon-ion radiotherapy

Patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and immobilized using thermoplastic shells (Shellfitter; Kuraray, Osaka, Japan). For areas subject to respiratory movement, treatment plans were prepared with internal margins calculated from four-dimensional computed tomography (CT), and respiratory synchronous irradiation was performed. The clinical dose distribution was calculated on the basis of the physical dose and relative biological effectiveness, in line with previous studies [23]. Carbon-ion beams (290–400 MeV) were generated using a heavy particle accelerator at Gunma University Heavy Ion Medical Center (Gunma, Japan), and a passive scattering carbon-ion beam was used in all cases. XiO-N treatment planning software (Elekta/Mitsubishi Electric) was used to calculate the passive scattering carbon-ion dose distribution.

CIEDs were checked immediately before and after all sessions of CIRT. Each session took around 10 to 30 minutes, according to the target disease and location. During the session, pacemaker settings were not changed, and patients with ICDs were treated with defibrillation turned off. A defibrillator was also prepared next to the treatment room. Doctors, nurses, technicians and medical engineers were present during the sessions, to respond immediately if any abnormalities occurred.

Neutron dose simulation

To evaluate the neutron distributions and energy spectra generated by the carbon-ion beams, Monte Carlo simulation was performed using the ‘Particle and Heavy-Ion Transport Code System’ (PHITS) code [24]. In these simulations, a water phantom simulating a human body was irradiated with \( 1 \times 10^5 \) carbon-ions (Fig. 1A and B). The head of the human phantom was a sphere with a radius of 10 cm, and the body part was cuboid (10 × 21 × 120 cm) with two semicircular columns (radius = 10.5 cm). Simulations were performed with a passive beam and a collimator and a passive beam and no collimator (Fig. 1C). The energy distribution was configured to produce a 6 cm spread-out Bragg peak in the range of 220–290 MeV/u in an irradiation field of 10 cm square. No ridge filter or range shifter was used. The multi-leaf collimator (MLC) was shaped 10 cm square. The beam was irradiated at 20 cm distance, from the shoulder to the foot side. Neutron fluxes and energy spectra along the medial axis were calculated.

RESULTS

Patient characteristics

Twenty patients with CIEDs underwent CIRT during the period evaluated. Two patients received CIRT twice, and therefore data from a total of 22 courses of CIRT were collected. In one of these cases, the generator was replaced after the first irradiation. The patient characteristics are detailed in Table 1. The irradiated site was the head and neck in three cases, thorax in two, liver in five, prostate in nine and bone and soft tissue (right leg, sacrum and 12th thoracic vertebra) in three. One patient with a head and neck tumor could not complete CIRT because of disease progression. In this patient, data from six of the planned 16 sessions were available. The primary diseases requiring implantation of CIEDs were complete atrioventricular block in seven patients, sick sinus syndrome in nine, atrial fibrillation with bradycardia in two, dilated cardiomyopathy in one, left bundle branch block in one, atrioventricular block in one and sinus bradycardia in one.
Fig. 1. Simulation set-up. The green region represents the water phantom simulating the human body. The head part of the phantom was a sphere with a radius of 10 cm, and the body part was rectangular (10 × 21 × 120 cm) with two semicircular columns (radius = 10.5 cm) (B). The beam was irradiated at a 20 cm distance, from the shoulder to the foot side. The blue circles indicate the calculation points for the energy spectra of the neutron flux. The MLC was shaped 10 cm square (C).

Table 1. Patient characteristics

| Characteristic                  | Number |
|--------------------------------|--------|
| Total number of treatment courses | 22     |
| Gender                         |        |
| Male                           | 15     |
| Female                         | 7      |
| Age                            |        |
| Median                         | 72     |
| Range                          | 61-94  |
| Target disease site            |        |
| Head and neck                  | 3      |
| Thorax                         | 2      |
| Liver                          | 5      |
| Prostate                       | 9      |
| Bone and soft tissue           | 3      |
| Reason for CIED implantation   |        |
| Complete A-V block             | 7      |
| Sick Sinus Syndrome            | 9      |
| Atrial fibrillation with Bradycardia | 2    |
| DCM                            | 1      |
| Other                          | 3      |
| Pacemaker-dependent            |        |
| Yes                            | 13     |
| No                             | 9      |
| CIED generator exchange        |        |
| Yes                            | 7      |
| No                             | 13     |
| Follow-up period, months       |        |
| Median                         | 11.7   |
| Range                          | 0.5-73.5 |

Abbreviations: CIED = cardiac implantable electronic device; A-V block = atrio-ventricular block; DCM = dilated cardiomyopathy.

Table 2. Treatment details

| Prescribed radiation dose       | Number |
|---------------------------------|--------|
| 51.6 Gy(RBE) / 12 fr            | 5      |
| 52.8 Gy(RBE) / 4 fr             | 2      |
| 52.8 Gy(RBE) / 12 fr            | 1      |
| 57.6 Gy(RBE) / 16 fr            | 5      |
| 60.0 Gy(RBE) / 4 fr             | 2      |
| 60.0 Gy(RBE) / 12 fr            | 2      |
| 64.0 Gy(RBE) / 16 fr            | 2      |
| 67.2 Gy(RBE) / 16 fr            | 3      |

| Shortest distance from treatment field to CIED, cm | Number |
|---------------------------------------------------|--------|
| 0-10                                               | 1      |
| 10-20                                              | 4      |
| 20-30                                              | 6      |
| >30                                                | 11     |

| Planning technique                  |        |
|-------------------------------------|--------|
| Spread-Out Bragg Peak               | 22     |

Abbreviations: CIED = cardiac implantable electronic device; fr = fractions; RBE = relative biological effectiveness.

Thirteen of the patients were pacemaker-dependent. Before November 2014, replacement of CIEDs was strongly recommended, and in seven patients the generator was replaced shortly after the end of CIRT, regardless of the presence or absence of abnormalities.

Details of the CIRT are listed in Table 2. The irradiation dose was 51.6–67.2 Gy(RBE) in 4–16 fractions. The distance from the 95% isodose line to the CIEDs was 0–10 cm in one patient, 10–20 cm in four, 20–30 cm in six and >30 cm in 11.

Details of the CIEDs are provided in Table 3. Twenty-one devices were pacemakers and one was an ICD.

Malfunction of the CIEDs

No device malfunction was observed in any patients during the CIRT period or the follow-up period after CIRT. Premature battery loss was observed in three cases, and 29%, 31% and 51% of battery power decrease from the pre-treatment baseline. The distances between these CIEDs and the 95% isodose line were 16.9, 56.4 and 5.2 cm, respectively and the devices were two pacemakers and one ICD. Generator replacement was not necessary in any of the cases and was performed as usual for all patients.
Table 3. CIED characteristics

| Type of device      | Numbers |
|---------------------|---------|
| Pacemaker           | 20*     |
| Defibrillator       | 1       |
| Mode                |         |
| DDD                 | 13      |
| DDD/AAI             | 3       |
| VVI                 | 4       |
| DDD/CRTD            | 1       |
| Other               | 1       |
| Manufacture         |         |
| Medtronic           | 16      |
| Boston              | 3       |
| Sent-Jude Medical   | 3       |

Abbreviations: CIED = cardiac implantable electronic device; CRTD = cardiac resynchronization therapy-defibrillator.
*One of these underwent two sessions of CIRT.

**Neutron dose**

The flux distributions were evaluated by Monte Carlo simulation. Thermal, epi-thermal and fast neutron distributions along the medial line are shown in Fig. 2A. The calculated fluxes were almost constant within the irradiation field and decreased exponentially outside the field. MLC use increased the amount of neutrons generated outside the irradiation field. The distribution of each neutron beam is shown in Fig. 2B. Thermal, epi-thermal and fast neutron distributions are shown in Fig. 2B. Beam irradiation was from the left side and reached the patient through the MLC. Neutrons are generated in the MLC and in the patient’s body and spread to the surrounding area. Especially in the case of fast neutrons, a large number of neutrons were generated downstream of the beam path, confirming the forward scattering of the neutron’s generation direction. Nevertheless, at a distance of 10 to 20 cm from the irradiation field, the effect of forward scattering decreased. The neutron scattering decreased in the body axis direction at all energy bands.

**DISCUSSION**

In the present study, 20 patients with CIEDs received 22 courses of CIRT. No obvious operational abnormalities were observed during or after treatment, but premature battery failure was observed in three cases. The PHITS model was used to simulate the production of neutrons and predicted that the fluxes decreased exponentially outside of the irradiated field, as did the high-energy neutrons.

Neutrons are generated during irradiation and are considered to cause malfunctions in CIEDs. In particle beam therapy, the neutron distributions and the energy spectra depend on particle type, energy and beam delivery technique (passive versus scanning) [25]. Similar to our findings, Seidensaal et al. reported no obvious malfunctions in patients with CIEDs who underwent CIRT [22]. Their study used an active scanning beam technique, whereas our treatment used a passive scattering beam in which the beam was spread by placing scattering materials in the beam path. The secondary neutron dose from active scanning carbon-ion beams is lower than that from passive scattering carbon-ion beams [26]. However, in proton beam therapy, CIED malfunctions were reported in 0% of scanning treatments and in 20–28.6% of passive treatments [19–22]. Matsubara et al. reported that the risk of malfunctions in CIEDs from passive carbon-ion beams is about 20 times less than that from passive proton beams [9]. According to the literature, the risk of CIED malfunctions with carbon-ion therapy appears to be lower than that from proton therapy, which is consistent with the results of this study.

Premature battery depletion is mentioned in several papers. Hurkmans et al. reported that in an in vitro study, five out of 19 units exposed to 6 MV of X-ray irradiation showed a decrease in battery power after the end of treatment [13]. Nevertheless, Zecchin et al. reported that no battery depletion was observed with 15 MV X-ray exposure in an in vitro study. In MRI imaging, a temporary depletion in battery output was observed during scanning, but it returned to the normal level after about three months [6, 27]. Sinha et al. reported that a CIED manufacturer observed a case of premature pacemaker battery depletion and a case of hard reset in a defibrillator as a result of cold exposure [28]. The direct effects of irradiation and the mechanism causing battery depletion remain unclear, and this is the first report on battery drain caused by CIRT. In the cases examined in this study, the generator did not need to be replaced, but it was necessary to check the remaining battery capacity when checking the operation of the device.

The PHITS model simulations showed that neutrons of all energy bands are generated in the irradiation field, and these could possibly cause irreversible errors in CIEDs. Fast neutrons, which are particularly energetic in the irradiation field and are expected to have a strong impact on electronic circuits, semiconductors and the memory of CIEDs, are mostly generated in the irradiated field and the forward direction of the beam path. Nevertheless, fast neutrons exponentially decrease with distance from the irradiation field, and safety is therefore expected to increase with distance in the lateral direction.

On the basis of the results of our study, we emphasize the importance of avoiding direct irradiation of CIEDs. When CIEDs are outside of the irradiation field, the risk of CIED malfunctions is low. However, it is necessary to prepare for the possibility of signal abnormality due to memory corruption by having a backup system ready, checking the operation of the CIED before and after treatment, and careful monitoring during treatment. No obvious abnormality in CIED performance was observed during the long-term follow-up after CIRT. As for the soft errors caused by CIRT, long-term follow-up is not necessarily required because soft errors are likely to be corrected by the CIED’s correction program; however, the frequency of the CIED’s correction program may be unknown, and care should be taken during this period.

Our study has several limitations. First, the number of cases was small, especially with just a single ICD case, and a larger cohort is necessary to evaluate the incidence of malfunction precisely. Second, the distance from the irradiation field to the CIEDs was >30 cm in half of the cases, which may have resulted in underestimation of the malfunction rate. However, recent guidelines reported that proximity of the radiation treatment field to the device did not predict malfunction [29]. Third, the generator was replaced after the first irradiation in seven patients (35%) shortly after the end of CIRT.

In conclusion, CIRT for patients with CIEDs was found to be relatively safe, although neutron dose simulations showed that there
was a risk of CIED malfunction with CIRT. Several concerns should be raised during CIRT for patients with CIEDs, and it is necessary to be prepared for them when treating patients with CIEDs.

Careful attention must be paid when treating chest and head and neck regions where patients may have a CIED in close proximity to the irradiation field, and when treating patients with a high dependency on CIEDs.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest associated with the work described in this study.

PRESENTATION AT A CONFERENCE
Part of this study was presented in the 33rd Annual Meeting of the Japanese Society for Radiation Oncology.

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