pISSN 1598-2998, eISSN 2005-9256

https://doi.org/10.4143/crt.2021.706

Cancer Res Treat. 2021;53(3):635-640

Special Article

Technological Advances in Charged-Particle Therapy

Jong Min Park[1,2,3,4], **Jung-in Kim**[1,2,3], **Hong-Gyun Wu**[1,2,3,4]

[1]Department of Radiation Oncology, Seoul National University Hospital, Seoul, [2]Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, [3]Cancer Research Institute, Seoul National University College of Medicine, Seoul, [4]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea

Charted-particle therapy (CPT) benefits cancer patients by localizing doses in the tumor volume while minimizing the doses delivered to normal tissue through its unique physical and biological characteristics. The world's first CPT applied on humans was proton beam therapy (PBT), which was performed in the mid-1950s. Among heavy ions, carbon ions showed the most favorable biological characteristics for the treatment of cancer patients. Carbon ions show coincidence between the Bragg peak and maximum value of relative biological effectiveness. In addition, they show low oxygen enhancement ratios. Therefore, carbon-ion radiotherapy (CIRT) has become mainstream in the treatment of cancer patients using heavy ions. CIRT was first performed in 1977 at the Lawrence Berkeley Laboratory. The CPT technology has advanced in the intervening decades, enabling the use of rotating gantry, beam delivery with fast pencil-beam scanning, image-guided particle therapy, and intensity-modulated particle therapy. As a result, as of 2019, a total of 222,425 and 34,138 patients with cancer had been treated globally with PBT and CIRT, respectively. For more effective and efficient CPT, many groups are currently conducting further studies worldwide. This review summarizes recent technological advances that facilitate clinical use of CPT.

Key words Charged-particle therapy, Carbon-ion radiotherapy, Proton beam therapy

Introduction

Charged-particle therapy (CPT) is advantageous for treating cancer patients compared to photon-based radiotherapy using X-rays by virtue of the charged particles' unique physical and biological properties, which are superior to those of X-rays in terms of cancer treatment [1]. The aforementioned properties of CPT result in more damage to tumor cells, enhancing the local control (LC) rate while causing less damage to normal tissue, which induces lower treatment-related complications compared to X-ray–based radiotherapy [1]. Nevertheless, the clinical adoption of CPT has been slower than that of X-ray–based radiotherapy owing to technical difficulties as well as the large facility-establishment cost [2]. With technological advances, the technical difficulties in the clinical use of particle beams have been overcome, and the cost-effectiveness of CPT has also been improved [3,4]. Therefore, the numbers of particle-therapy facilities and patients treated with CPT have increased rapidly recently [5]. The numbers of patients treated with protons and carbon ions between 2010 and 2014 were 51,098 and 10,154, respectively. However, between 2015 and 2019, these numbers reached 104,230 and 18,402, respectively, indicating respective increases of 200% and 180%. Here, we describe the technological advancements that led to this growth.

History of CPT

In 1904, Sir William Henry Bragg, a British physicist, reported a phenomenon in which a charged particle deposits much of its energy at the end of its range, resulting in a peak in the depth–dose plot along the beam direction in a medium, which is called the Bragg peak [6]. Robert R. Wilson recognized the clinical significance of the Bragg peak for the treatment of cancer, as favorable dose distributions could be generated using the Bragg peaks by localizing doses within the tumor volume to control tumors while minimizing doses to normal tissues [7]. He published a paper proposing the clinical use of protons and heavy ions for cancer treatment in 1946 [7]. He also suggested a method to cover the entire volume of tumors by stacking multiple pristine Bragg peaks called spread-out Bragg peaks (SOBP) [7]. Prior to Wilson's proposal, Lawrence developed a cyclotron at the University of California Lawrence Berkeley Laboratory (LBL) in 1930 [4]. He suggested that Cornelius A. Tobias and John H. Lawrence validate Wilson's proposal by using the 184-inch cyclotron [4]. They performed an animal study and obtained favorable results in 1954. Based on those results, in the mid-1950s, Tobias, Lawrence, and others treated a cancer patient with proton beams for the first time using the 184-inch cyclotron at the LBL [8]. In the late 1950s, Larsson and Leksel devel-

---

Correspondence: Hong-Gyun Wu
Department of Radiation Oncology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: 82-2-2072-3177 Fax: 82-2-742-2073 E-mail: wuhg@snu.ac.kr

Received June 14, 2021 **Accepted** June 14, 2021 **Published Online** June 21, 2021

oped radiosurgical techniques with proton beams to treat brain tumors at the Gustaf Werner Institute in Uppsala, Sweden [9]. They were the first to generate SOBP by range modulation along the beam direction and to use beam scanning to cover the tumor volumes in the lateral direction. Since the 1960s, there has been much activity in proton beam therapy (PBT) worldwide, especially in Russia, Europe, South Africa, and Japan [4]. The first hospital-based PBT was initiated in 1990 at the Loma Linda University Medical Center (LLUMC) with a synchrotron capable of accelerating protons up to 250 MeV and three isocentric gantries [10]. During the design of the LLUMC accelerator, the Proton Therapy Co-Operative Group, which is an international non-profit organization consisting of scientists in the field of PBT, was founded in 1985 [4]. Its name was later changed to the Particle Therapy Co-Operative Group as it was involved not only PBT but also heavy-ion therapy [4]. Many PBT facilities have been established, and there are currently 97 PBT facilities in operation worldwide [11]. Until 2019, 222,425 patients were treated with PBT worldwide [5].

For heavy-ion radiotherapy, the LBL group started a heavy-ion therapy program with the BEVELAC accelerator in 1975 [12]. The LBL group provided beam-delivery technologies and software, while the University of California at San Francisco provided medical expertise [4]. At the LBL, the first helium-ion radiotherapy, carbon-ion radiotherapy (CIRT), neon-ion radiotherapy, argon-ion radiotherapy, and silicon-ion radiotherapy were carried out in 1975, 1977, 1977, 1979, and 1982, respectively [13,14]. The LBL heavy-ion radiotherapy program was terminated in 1992 [15]. In 1994, the first dedicated medical facility for heavy-ion radiotherapy in the world was established in Japan, which was the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS), which is now called the National Institute for Quantum and Radiological Science and Technology (QST/NIRS) [3,16]. Before adopting heavy-ion radiotherapy, the NIRS performed CPT with fast neutrons and protons starting from 1975 [3,16]. Based on extensive studies to optimize the ion species for heavy-ion radiotherapy, the NIRS chose the carbon, which showed optimal relative biological effectiveness (RBE) and optimal oxygen enhancement ratio (OER) [1-3,16]. For effective radiotherapy, high RBE and low OER are typically preferred [17]. Heavier ions have higher linear energy transfers (LETs) across the Bragg peak than lighter ions [18]. However, for very large particles, such as argon, the increase in LET occurs in the plateau region of the beam path and not only at the Bragg peak, which results in excessive normal-tissue damage [19]. Therefore, neither very small and nor very large particles are optimal for heavy-ion radiotherapy [19]. Carbon ions show a favorable peak-to-plateau ratio showing the maximum RBE at the Bragg peak region [19]. Accordingly, the carbon ions have optimal RBE as well as OER, which improves the LC while minimizing the risk of normal tissue complications. Therefore, the NIRS has chosen carbon ions for heavy-ion radiotherapy [17]. In addition, the NIRS had been engaged in treating cancer patients with neutrons for about 20 years, which have a similar LET to that of carbon ions [17]. The NIRS could take advantage of the clinical experience of neutron therapy for CIRT. In this respect, carbon ions were chosen for patient treatment at the NIRS and have treated patients with carbon ions since 1994 [17]. After the HIMAC, the Hyogo Ion Beam Medical Center (HIBMC) started CIRT as well as PBT in Japan in 2002 [17]. In 2003, CIRT was approved as an advanced medical technology by the Japanese government; therefore, carbon ion facilities in Japan have received reimbursement for CIRT since 2003 [3]. In 2010, the NIRS collaborated with Gunma University to develop a compact synchrotron with a diameter approximately half that of the synchrotron of the HIMAC (approximately 20 m vs. approximately 40 m) [3]. By doing so, a compact CIRT facility could be constructed, with a size of approximately one-third of the HIMAC (building sizes of approximately 45×60 m^2 vs. approximately 65×120 m^2) [3]. By reducing the building size, the cost of establishing a CIRT facility could be reduced significantly. In 2013, the SAGA Heavy Ion Medical Accelerator in Tosu (SAGA-HIMAT) started CIRT, and in 2015, the Kanagawa Cancer Center started CIRT in Japan [17]. The most recent CIRT facility in operation in Japan is the Osaka Heavy-ion therapy Center, which started patient treatment in 2018. In Europe, the Gesellshaft fur Schwerionenforschung (GSI) in Germany started CIRT in 1997 and had treated 440 patients as of 2005 [20]. In contrast to the NIRS, the GSI developed and adopted the pencil-beam scanning technique, not the passive beam irradiation with SOBP for beam delivery [20]. In 2009, the clinical service with carbon-ion beams provided by the GSI was succeeded by the Heidelberg Ion-Beam Therapy Center (HIT), which is the first hospital-based particle-therapy facility in the world treating patients with proton and carbon-ion beams with the pencil-beam scanning technique [21]. In 2012, the Centro Nazionale Adrontherapia Oncologica (CNAO) in Italy started patient treatment with carbon-ion beams [17]. In 2015, the Marburg Particle Therapy Center in Germany initiated CIRT [11]. In Austria, MedAustron, which is the most recent CIRT facility in Europe, started patient treatment in 2019 [11]. In China, the Institute of Modern Physics started clinical trials for CIRT in 2006 [17]. Subsequently, the Shanghai Proton and Heavy Ion Center started CIRT in 2014 [17]. The Heavy Ion Cancer Treatment Center in Wuwei, which started patient treatment in 2019, is the most recent CIRT facility in operation in China [11]. In 2019, 34,138 patients were treated with

CIRT worldwide [5]. A total of 12 carbon ion facilities are currently in operation worldwide [11].

Technical Developments in Carbon-Ion Beam Irradiation Techniques

1. Layer-stacking method

Until 2011, the NIRS HIMAC used the SOBP-based passive-beam irradiation carbon-ion beam-delivery technique [3]. The passive beam irradiation increases neutron contamination, irradiation proximal to the target volume, and integral doses, which are clinically undesirable [22]. Therefore, to reduce the normal-tissue irradiation proximal to the target volume, the layer-stacking method, which delivers thin Bragg peaks (generally 1 cm) layer by layer from the distal to the proximal direction of the tumor volume, was introduced in Japan [23]. The lateral shapes of the irradiation fields were defined by the multi-leaf collimator (MLC) to conform to the tumor shape in the beam's-eye view at a specific depth. The depths of the thin Bragg peaks (i.e., layers) were determined using the range shifter. By doing so, normal-tissue irradiation proximal to the tumor can be reduced significantly [23].

2. Pencil-beam scanning technique

The pencil-beam scanning technique paints doses over the tumors continuously with narrow Bragg peaks using magnets [24]. In 1997, the world's first pencil-beam scanning-beam delivery technique, raster scanning, was presented at the GSI [24]. Transverse scanning was performed using two scanning magnets. The depths were modulated by utilizing the range shifters. In 2009, the HIT, which was a successor to the GSI, also adopted the pencil-beam scanning technique for patient treatment [21]. The NIRS and CNAO started applying pencil-beam scanning beam delivery in 2011 and 2012, respectively [3,17]. In 2014, depth modulation was achieved by a multiple-energy operation with extended flattops of the synchrotron without the range shifters at the NIRS, which enabled the maintenance of a small lateral beam size and a reduction in neutron contamination [25]. Although the pencil-beam scanning technique has various advantages over the passive irradiation technique, it is vulnerable to tumor movement due to patient respiration because a combination of the dynamic beam delivery of the pencil-beam scanning technique and the moving target could result in dose-delivery errors owing to the interplay effect [26]. In other words, in extreme cases, no doses would be deposited in some regions in the target volume, or doses as large as twice the prescription dose would be deposited in some regions in the target volume. Moreover, unintended normal-tissue irradiation with high doses may occur. This problem was solved at the NIRS using extremely fast scanning of the beam with a scanning speed of up to 100 mm/msec [26]. Compared to the pencil-beam scanning motion, the respiratory motion of the target volume is quite slow; therefore, the target volume can be regarded as static. In addition, to smear out the dose-delivery errors via single scanning, a rescanning technique that scans the target volumes four or eight times was proposed [26]. The NIRS began using respiratory-gated phase-controlled rescanning irradiation for moving targets in 2015 [26].

Rotating Gantry for CPT

The rotating gantry enables beam delivery at various angles; therefore, the optimal beam paths can be selected for each patient considering the target volume locations as well as organ at risk locations, resulting in favorable dose distributions [27]. If patient treatment is performed without the rotating gantry, that is, with fixed beam ports, the patient should be tilted on the couch by approximately 20° to secure more beam paths [27]. In this case, the patient's body is deformed by gravity despite rigorous immobilization [3]. To generate a treatment plan, the body images of the patient deformed by tilting needs to be matched to the patient's reference body images using a deformable image-registration algorithm [3]. This increases uncertainties in dose calculation, which is undesirable [27]. If a rotating gantry is used, deformable image registration is not required. In addition, when tilting a patient, to reduce the patient-setup error, the patient needs to be rigorously immobilized as mentioned above, which increases the staff workload, patient discomfort, and setup time [3]. A rotating gantry can eliminate these problems. Moreover, it enables intensity-modulated particle therapy, which can generate favorable dose distributions [27]. Therefore, CPT with a rotating gantry is more effective and efficient than that with fixed beam ports. For PBT, the first rotating gantry was installed at the LLUMC in 1990 [10]. For heavy-ion radiotherapy, the world's first rotating gantry was installed at the HIT in 2012 [21]. The prototype of the rotating gantry was tested at the GSI, and the rotating gantry system, which was produced by MT Mechatronics (MT Mechatronics, Mainz, Germany), was huge, with a length and weight of approximately 25 m and 600 tons, respectively [28]. To reduce the size and weight of the rotating gantry for heavy-ion radiotherapy, the NIRS utilizes superconducting magnet technology [3]. The world's first superconducting rotating gantry for heavy-ion radiotherapy was installed at the HIMAC by NIRS in 2017 [19]. With the use of superconducting magnets, the length and weight of this rotating gantry were brought down to approximately 13 m and 300 tons, respectively [3]. The first patient was treated with this rotating gantry using superconducting magnets in 2017. One year later, the first patient with moving targets was treated with the system at the HIMAC. Recently, the design of the scanning magnets was improved and a more compact rotating gantry than that at the HIMAC was commercialized and installed at the Yamagata University Hospital. The volume of the new rotating gantry was only 60% of that at HIMAC. This state-of-the-art superconducting rotating gantry will be installed at the Yonsei University Hospital and CIRT Center of Seoul National University Hospital in the Republic of Korea.

Image-Guided Particle Therapy

In the 1970s, the first image-guided particle therapy was enabled by the Massachusetts General Hospital and the LBL group, who developed the two-dimensional X-ray image guidance technique [29]. This image-guidance technique was introduced before X-ray–based radiotherapy. Because imaging with particle beams is extremely difficult and requires extremely high-energy particle beams to be transmitted to the patient body, two-dimensional X-ray imaging was used for CPT [29].

Image guidance with volumetric imaging for CPT lagged behind that of X-ray–based radiotherapy with linacs [29]. This is attributed to the small number of particle-therapy facilities compared to that of X-ray–based radiotherapy facilities and the heterogeneity in the design of the CPT machines, which made it difficult to develop commercial volumetric imaging systems. In this respect, the first gantry-mounted kV cone beam computed tomography (CBCT) became commercially available for PBT in 2014 [29]. For heavy-ion radiotherapy, instead of the gantry-mounted CBCT, the NIRS proposed a horizontal computed tomography (CT) system for rooms in the late 1990s [30]. Subsequently, heavy-ion radiotherapy facilities adopted in-room CTs sliding on rails for volumetric image guidance [31]. Generally, in-room CT scanners are located several meters away from the beam ports to avoid disturbing the treatment workflow, as well as to minimize the hardware damage by neutrons from the particle beams [29]. When imaging is done, the CT scanner slides on the rail to the imaging position. The robotic couch is located at the imaging position, and volumetric images are acquired. After image acquisition, the robotic couch is located at the treatment position, and treatment beams are delivered to the patient.

In 2015, the NIRS developed marker-less respiratory-gated heavy-ion radiotherapy with X-ray fluoroscopy [32]. During beam irradiation, the position of the moving target volume was identified in real-time using X-ray fluoroscopy. When the center of mass of the target volume was located at a predefined position during patient respiration, the treatment beam was on. The first patient treated with this technique at the NIRS was a patient with lung cancer. Currently, the NIRS is working on image guidance utilizing artificial intelligence technology [3]. With deep neural network-based real-time image processing, the NIRS is trying to deliver prescription doses accurately and precisely to targets moving due to patient respiration.

Future of CPT

1. Ultra-high-dose-rate (FLASH) CPT

FLASH radiotherapy is a new radiotherapy technique that delivers a prescription dose at ultra-high dose rates exceeding 40 Gy/sec, which could result in improved sparing of normal tissue while maintaining damage to tumor cells [33]. Although the mechanism of the FLASH effect is unknown, the possibility of FLASH radiotherapy showing significant improvement in the tumor-control probability over the normal tissue-complication probability was recently demonstrated in preclinical animal studies with electron beams [34]. For PBT, an *in vitro* study showed that FLASH irradiation could improve late adverse biological effects [35]. Currently, FLASH radiotherapy is not yet clinically available and remains in the research stage. Several recent studies proposed a technical strategy for clinical PBT machines to be used for FLASH radiotherapy [36].

2. Multi-ion irradiation: biological optimization

By mixed-beam irradiation of multiple ions, a high LET could be painted onto radioresistant regions in the target volumes while lowering the LET to normal tissue [37]. This can enhance tumor control more effectively and minimize local relapse. This treatment technique has not been applied clinically to patients yet and is in the research stage. The NIRS is currently developing a multi-ion irradiation technique with several candidate ions, such as helium, carbon, and oxygen ions [3].

3. Extremely compact particle-therapy system

By applying the superconducting magnet technology not only to the rotating gantry but also to the synchrotron, NIRS/QST is developing the SUPERconducting Magnet INstalled Ion Medical Accelerator in Chiba (Super MINIMAC or Quantum Scalpel) which is an extremely compact particle-therapy system with dimensions of 10 m×20 m [3]. This next-generation heavy-ion radiotherapy system is expected to reduce both the site size and cost of establishing a heavy-ion radiotherapy facility. This extremely compact particle-therapy system is expected to lower the barrier to heavy-ion radiotherapy.

Conclusion

The clinical use of charged particles for the treatment of cancer patients was first proposed by Wilson in 1946. Since then, 222,425 and 34,138 patients were treated with PBT and CIRT, respectively, as of 2019. With its unique physical and biological properties, CPT has been proven effective in the treatment of cancer patients by active clinical investigations. Recent technological advances have focused on the directions in which CPT can improve clinical efficacy and efficiency. The installation cost, which has been considered a major obstacle to the spread of CPT, continues to decrease. With these efforts, it is expected that more patients will benefit from CPT, and the evidence for its clinical usefulness will become more substantial in the near future.

Author Contributions

Conceived and designed the analysis: Wu HG.
Collected the data: Park JM, Kim Ji, Wu HG.
Contributed data or analysis tools: Wu HG.
Performed the analysis: Park JM, Kim Ji.
Wrote the paper: Park JM.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) with a grant funded by the Korean government (MSIT) (No. 2019R1F1A1040583) and the Radiation Technology R&D program through the National Research Foundation of Korea, funded by the Ministry of Science and ICT (2019M2A2B4095126).

References

1. Schulz-Ertner D, Jakel O, Schlegel W. Radiation therapy with charged particles. Semin Radiat Oncol. 2006;16:249-59.
2. Jiang GL. Particle therapy for cancers: a new weapon in radiation therapy. Front Med. 2012;6:165-72.
3. Mohamad O, Makishima H, Kamada T. Evolution of carbon ion radiotherapy at the National Institute of Radiological Sciences in Japan. Cancers (Basel). 2018;10:66.
4. Smith AR. Proton therapy. Phys Med Biol. 2006;51:R491-504.
5. Particle Therapy Co-Operative Group. Facilities in operation [Internet]. Villigen: Paul Scherrer Institute; c2020 [cited 2020 Dec 15]. Available from: https://www.ptcog.ch/index.php/facilities-in-operation.
6. Bragg WH, Kleeman R. On the ionization curves of radium. Philos Mag. 1904;8:726-38.
7. Wilson RR. Radiological use of fast protons. Radiology. 1946;47:487-91.
8. Lawrence JH, Tobias CA, Born JL, Mc CR, Roberts JE, Anger HO, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Res. 1958;18:121-34.
9. Larsson B, Leksell L, Rexed B, Sourander P, Mair W, Andersson B. The high-energy proton beam as a neurosurgical tool. Nature. 1958;182:1222-3.
10. Slater JM, Archambeau JO, Miller DW, Notarus MI, Preston W, Slater JD. The proton treatment center at Loma Linda University Medical Center: rationale for and description of its development. Int J Radiat Oncol Biol Phys. 1992;22:383-9.
11. Particle Therapy Co-Operative Group. Patient statistics [Internet]. Villigen: Paul Scherrer Institute; c2020 [cited 2020 Dec 15]. Available from: https://www.ptcog.ch/index.php/patient-statistics.
12. Castro JR. Results of heavy ion radiotherapy. Radiat Environ Biophys. 1995;34:45-8.
13. Raju MR. Particle radiotherapy: historical developments and current status. Radiat Res. 1996;145:391-407.
14. Brahme A. Recent advances in light ion radiation therapy. Int J Radiat Oncol Biol Phys. 2004;58:603-16.
15. Halperin EC. Particle therapy and treatment of cancer. Lancet Oncol. 2006;7:676-85.
16. Kamada T, Tsujii H, Blakely EA, Debus J, De Neve W, Durante M, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. Lancet Oncol. 2015;16:e93-100.
17. Tsujii H, Kamada T. A review of update clinical results of carbon ion radiotherapy. Jpn J Clin Oncol. 2012;42:670-85.
18. Kramer M, Weyrather WK, Scholz M. The increased biological effectiveness of heavy charged particles: from radiobiology to treatment planning. Technol Cancer Res Treat. 2003;2:427-36.
19. Ando K, Kase Y. Biological characteristics of carbon-ion therapy. Int J Radiat Biol. 2009;85:715-28.
20. Kraft G. Radiotherapy with heavy ions: radiobiology, clinical indications and experience at GSI, Darmstadt. Tumori. 1998;84:200-4.
21. Combs SE, Jakel O, Haberer T, Debus J. Particle therapy at the Heidelberg Ion Therapy Center (HIT): integrated research-driven university-hospital-based radiation oncology service in Heidelberg, Germany. Radiother Oncol. 2010;95:41-4.
22. Tessa CL, Berger T, Kaderka R, Schardt D, Burmeister S,

Labrenz J, et al. Characterization of the secondary neutron field produced during treatment of an anthropomorphic phantom with x-rays, protons and carbon ions. Phys Med Biol. 2014;59:2111-25.

23. Kanematsu N, Endo M, Futami Y, Kanai T, Asakura H, Oka H, et al. Treatment planning for the layer-stacking irradiation system for three-dimensional conformal heavy-ion radiotherapy. Med Phys. 2002;29:2823-9.
24. Haberer T, Becher W, Schardt D, Kraft G. Magnetic scanning system for heavy ion therapy. Nucl Instrum Methods Phys Res A. 1993;330:296-305.
25. Iwata Y, Kadowaki T, Uchiyama H, Fujimoto T, Takada E, Shirai T, et al. Multiple-energy operation with extended flattops at HIMAC. Nucl Instrum Methods Phys Res A. 2010;624:33-8.
26. Furukawa T, Inaniwa T, Sato S, Shirai T, Mori S, Takeshita E, et al. Moving target irradiation with fast rescanning and gating in particle therapy. Med Phys. 2010;37:4874-9.
27. Bhattacharyya T, Koto M, Ikawa H, Hayashi K, Hagiwara Y, Makishima H, et al. First prospective feasibility study of carbon-ion radiotherapy using compact superconducting rotating gantry. Br J Radiol. 2019;92:20190370.
28. Haberer T, Debus J, Eickhoff H, Jakel O, Schulz-Ertner D, Weber U. The Heidelberg ion therapy center. Radiother Oncol. 2004;73 Suppl 2:S186-90.
29. Landry G, Hua CH. Current state and future applications of radiological image guidance for particle therapy. Med Phys. 2018;45:e1086-95.
30. Kamada T, Tsujii H, Mizoe JE, Matsuoka Y, Tsuji H, Osaka Y, et al. A horizontal CT system dedicated to heavy-ion beam treatment. Radiother Oncol. 1999;50:235-7.
31. Oliver JA, Zeidan OA, Meeks SL, Shah AP, Pukala J, Kelly P, et al. The Mobius AIRO mobile CT for image-guided proton therapy: characterization & commissioning. J Appl Clin Med Phys. 2017;18:130-6.
32. Mori S, Sakata Y, Hirai R, Furuichi W, Shimabukuro K, Kohno R, et al. Commissioning of a fluoroscopic-based real-time markerless tumor tracking system in a superconducting rotating gantry for carbon-ion pencil beam scanning treatment. Med Phys. 2019;46:1561-74.
33. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014;6:245ra93.
34. Patriarca A, Fouillade C, Auger M, Martin F, Pouzoulet F, Nauraye C, et al. Experimental set-up for FLASH proton irradiation of small animals using a clinical system. Int J Radiat Oncol Biol Phys. 2018;102:619-26.

35 Buonanno M, Grilj V, Brenner DJ. Biological effects in normal cells exposed to FLASH dose rate protons. Radiother Oncol. 2019;139:51-5.

36. Jolly S, Owen H, Schippers M, Welsch C. Technical challenges for FLASH proton therapy. Phys Med. 2020;78:71-82.
37. Kim JI, Park JM, Wu HG. Carbon ion therapy: a review of an advanced technology. Prog Med Phys. 2020;31:71-80.