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The first Korean carbon-ion radiation therapy facility: current status of the Heavy-ion Therapy Center at the Yonsei Cancer Center

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Purpose: This report offers a detailed examination of the inception and current state of the Heavy-ion Therapy Center (HITC) at the Yonsei Cancer Center (YCC), setting it apart as the world's first center equipped with a fixed beam and two superconducting gantries for carbon-ion radiation therapy (CIRT).

Materials and Methods: Preparations for CIRT at YCC began in 2013; accordingly, this center has completed a decade of meticulous planning and culminating since the operational commencement of the HITC in April 2023.

Results: This report elaborates on the clinical preparation for adopting CIRT in Korea. It includes an extensive description of HITC's facility layout at YCC, which comprises the accelerator and treatment rooms. Furthermore, this report delineates the clinical workflow, criteria for CIRT application, and the rigorous quality assurance processes implemented at YCC. It highlights YCC's sophisticated radiation therapy infrastructure, collaborative initiatives, and the efficacious treatment of >200 prostate cancer cases utilizing CIRT.

Conclusion: This manuscript concludes by discussing the prospective influence of CIRT on the medical domain within Korea, spotlighting YCC's pioneering contribution and forecasting the widespread integration of this groundbreaking technology.

Keywords: Heavy ion radiotherapy, Carbon ion therapy, Radiation oncology, Particle accelerators, Clinical trials and research, Quality assurance

Introduction

A substantial shift has occurred in cancer treatment in recent years from traditional schematic approaches to advanced particle radiotherapy. This evolution in treatment methodology is recognized as a leap forward in radiation therapy techniques [1]. Particle therapy, utilizing protons and carbon ions, is distinguished by its ability to deposit energy in a highly localized manner.

This feature facilitates a dose distribution with minimized lateral diffusion in deep-seated tissues, presenting advantages over conventional X-ray therapy. Clinical trials have shown that carbon-ion radiation therapy (CIRT) improves outcomes such as overall survival and local control in various cancers, although more phase III trials are needed to fully establish its advantages over conventional therapies [1–7].

One of the major benefits of particle therapy lies in its unique biological properties, including a higher linear energy transfer (LET) and an enhanced relative biological effectiveness (RBE) compared with conventional X-ray therapy. These attributes contribute to superior cell-killing efficacy and the ability to target tumors that are resistant to radiation [8–12], paving new avenues in cancer treatment. Reflecting the unique advantages of particle therapy, several institutes have established dedicated centers for particle-based radiotherapy [13–20].

South Korea has emerged as a leader in adopting advanced radiation therapy techniques, as evidenced by the increase in the life expectancy of the South Korean population [21] and the growing number of patients undergoing radiotherapy for various cancers, including breast, lung, prostate, colorectal, and liver [22]. To enhance patient care through radiotherapy, the infrastructure and equipment for both X-ray and particle therapy have been substantially enhanced. Notably, the National Cancer Center (NCC) Korea [23] and Samsung Medical Center (SMC) [18] were pioneers in this field as they established the first (in 2007) and second (in 2015) proton therapy centers in the country, respectively. These centers have been instrumental in advancing particle radiation therapy in Korea. By the end of 2018, the NCC Korea and SMC have respectively treated 2,914 patients and 1,250 patients with proton therapy [23]. Moreover, both centers have contributed extensively to physical and biological research on proton therapy, yielding a range of publications [24–29].

The Yonsei Cancer Center (YCC) is recognized as a premier medical institution in South Korea, equipped with a comprehensive suite of advanced radiation therapy technologies. The Department of Radiation Oncology at YCC is equipped with seven linear accelerators (LINACs), five tomotherapy units, and one CyberKnife machine. Furthermore, YCC respectively offers high- and low-dose-rate brachytherapy, and eye plaque radiotherapy, addressing a broad spectrum of cancer treatment requirements. Located in the capital area, the department effectively treats more than 8,000 patients annually.

Preparations for CIRT at YCC began in 2013; accordingly, a decade of meticulous planning and culminating has elapsed since the operational commencement of the Heavy-Ion Therapy Center (HITC) in April 2023. Initial actions in 2013 involved a review of the introduction of particle therapy, including visits to the Hyogo Ion Beam Medical Center in Japan and the Heidelberg Ion-beam Therapy Center in Germany to analyze technological advancements and their practical applications. From 2013 to 2018, professionals conducted multiple visits to various particle therapy facilities in Japan, including the Saga Heavy Ion Medical Accelerator in Tosu, National Institute of Radiological Sciences (NIRS), and Heavy Ion Medical Accelerator in Chiba, which led to the final decision to adopt heavy-ion therapy, which was approved by the board of directors in April 2016. Subsequent negotiations led to a contract with Toshiba for CIRT equipment (model: CI-1000), the only available commercial model supporting a rotating gantry at that time, with construction of the HITC beginning in July 2018. Following a foundation phase and a construction period of approximately 26 months, the installation of the synchrotron commenced in April 2021, with the HITC becoming fully operational in October 2022. Following the approval from the Ministry of Food and Drug Safety (MFDS) for the CIRT system in April 2023, the first treatment was successfully administered to a prostate cancer patient on April 29, 2023. By the time this manuscript was compiled, approximately 200 prostate cancer patients had been treated at YCC HITC, with preparations ongoing for the operation of two superconducting gantries.

This report aims to provide an in-depth overview of the HITC facility at YCC, including design, software systems, and clinical preparations, to provide comprehensive insights into the establishment and operation of YCC HITC.

Materials and Methods

1. Facility design

Since the inauguration of the first heavy-ion therapy facility by NIRS in Japan in 1994, the HITC at YCC represents the fifteenth center of its kind to be launched globally. The discussions for setting up a particle therapy center at YCC commenced in February 2013. A substantial milestone was achieved in April 2016 with the board's approval. The project gained momentum in March 2018 following the finalization of a contract with the vendor for the installation of carbon-ion therapy equipment.

In the following sections, we will detail the specific design fea-

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tures of the therapy center and its equipment.

2. Building design

Located within the premises of YCC, the construction of the HITC facility began in July 2018 and concluded in September 2019 (construction period of 15 months). The main building's construction commenced in October 2019 and was completed in November 2021 (required 26 months to finalize). The facility covers a construction area measuring 61 m × 56 m (with a total area of 3,107 m^2) and features a comprehensive floor area of 33,343 m^2. This multistorey structure consists of eight levels above ground, reaching a height of 36.4 m, and four underground levels, extending to a depth of 28.45 m.

Fig. 1 presents a three-dimensional (3D) visual layout of our CIRT facility, illustrating the strategic placement of the accelerator, fixed beam port, and two rotational gantry rooms. In addition to the particle therapy facilities, the HITC is equipped with two computed tomography (CT) simulation rooms, a magnetic resonance imaging (MRI) simulation room, a dosimetry room, a server room, a power supply room, two respiratory training rooms, an accelerator control room, a multidisciplinary conference room, an international collaboration conference room, and a Toshiba office for equipment maintenance.

Fig. 2 illustrates the current and projected timelines of the treatment system at the HITC. The process from the onset of civil engineering work to the treatment of the first patient spanned approximately 5 years. Throughout this period, intensive weekly meetings were conducted among the HITC and the vendor (Toshiba Energy

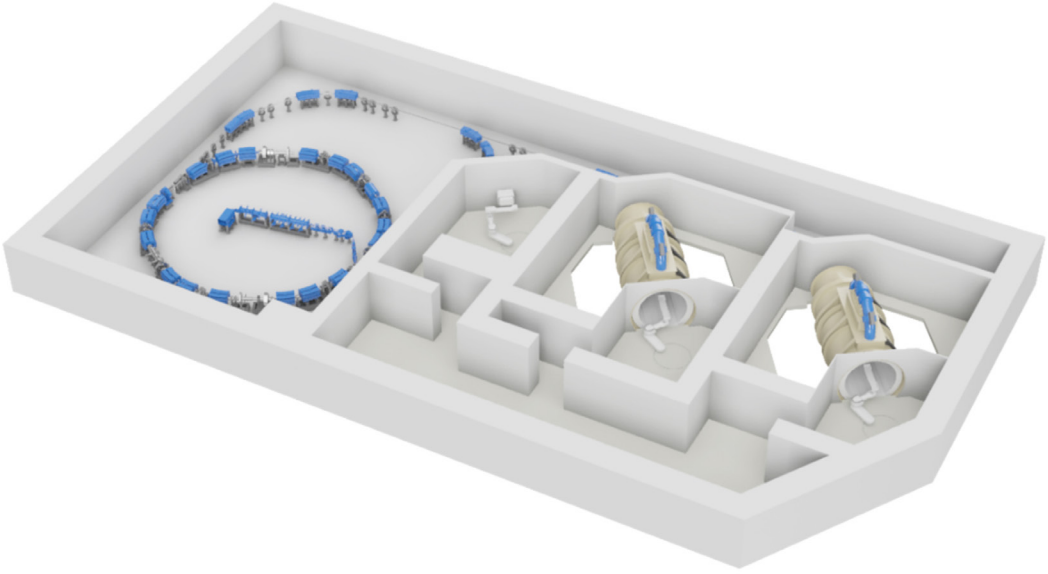

Fig. 1. Three-dimensional layout of the accelerator and three treatment rooms (i.e., fixed- and two gantry-type rooms) at the Yonsei Cancer Center (from left to right).

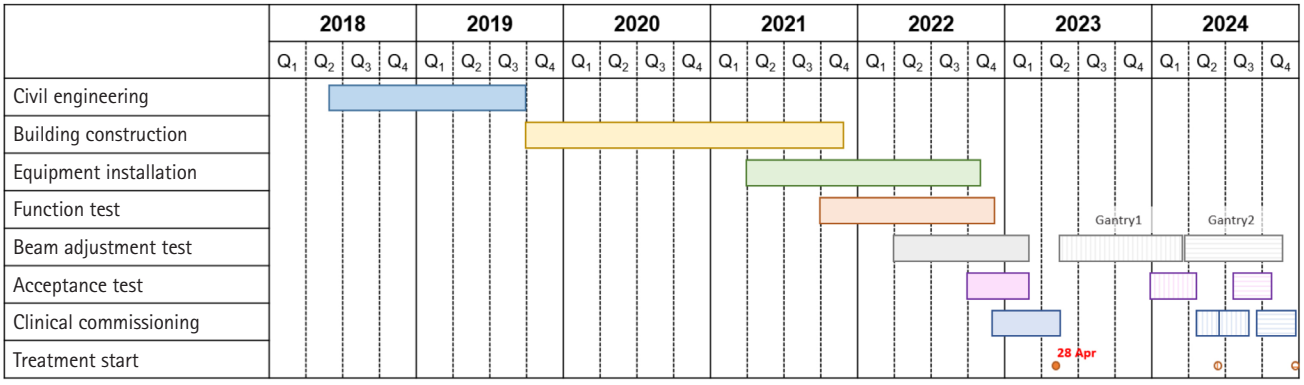

Fig. 2. Progress (solid) and expected (patterned) schedule of the carbon-ion treatment system at the Yonsei Cancer Center.

Table 1. Specifications of the heavy-ion therapy system at the Yonsei Cancer Center

Item	Specification
Particle type	Carbon ion ($^{12}C^{6+}$)
Treatment rooms type	Room 1: Fixed beam (horizontal only)
	Rooms 2 & 3: Rotating gantry
Beam delivery	Pencil beam scanning
Number of energy layer	600 levels with 0.5 mm beam range difference (from 55.6 to 430 MeV/u)
Energy switching time	< 200 ms
Range in water	0.5–30 cm
Irradiation field size	20 cm × 20 cm at isocenter
Maximum gantry speed	0.5 RPM
Beam broadening method	Ridge filters (1 mm as a default, 3 mm for gating treatment)
Dose rate	2 Gy/min for 1 L dose volume
Irradiation methods	Respiratory gated irradiation

RPM, revolutions per minute.

Systems & Solutions Corporation), and the administration of YCC. At the initial phase of installation, the schedule experienced delays due to the coronavirus 2019 pandemic. Consequently, to compensate for these delays, the consideration of the pursuit of parallel works—implementing three shifts per day—was adopted.

We calculated particle transport and activation using particle and heavy ion transport code system (PHITS) Monte Carlo code [30] and DCHAIN-SP [31] code for adequate radiation protection shielding. Dose distributions, flux, and nuclide yield were calculated using the PHITS code in a 3D numerical model. The 3D numerical model used for Monte Carlo calculations was created based on the 3D computer-aided design data of the entire facility. The DCHAIN-SP code estimated the time evolution of decaying nuclides using the Bateman equation and a decay data library [31]. Doses were calculated in μSv/week at locations of interest inside and outside the facility and assessed for compliance with legal standards. The estimated activation was compared with the legal activation limit. All shielding goals for clinical operations were met according to national guidelines.

3. Accelerator and Treatment rooms

The HITC at YCC is equipped with cutting-edge facilities specifically designed for the delivery of CIRT. Table 1 provides a detailed summary of HITC's specifications as installed at the YCC. The listed specifications for the HITC approximately match those of the equipment used at Yamagata University.

1) Accelerator room installed at the HITC at YCC

The accelerator room is compartmentalized into several sections, namely the carbon-ion source cage, injector, synchrotron, and high-energy beam transport (HEBT). The process begins with the generation of C^{4+} ions (carbon-ion particles) in the source cage. These ions are initially propelled through the injector, traversing the low-energy beam transport line at 10 keV/u. The particles are then accelerated from 0.6 MeV/u to 4 MeV/u via the radio frequency quadrupole LINAC and the drift tube LINAC. Subsequently, they are converted into C^{6+} ions in the middle-energy beam transport system section, immediately before their transfer from the injector to the synchrotron.

Table 2. Number of magnets installed in the synchrotron equipment

Magnet equipment	Quantity
Bending magnet	18
Steering magnet	12
Quadrupole magnet	14
Hexapole magnet	10
Bump magnet	6
Septum magnet	2

In the synchrotron, which has a circumference of approximately 63.3 m, the particles undergo full-fledged acceleration. The synchrotron employs various magnets and cavities along its length for the acceleration/deceleration of particles and for focusing/defocusing tasks. For details on the types and quantities of magnets utilized within the synchrotron at our facility, please refer to Table 2.

Our synchrotron can accelerate carbon ions to a maximum energy of 430 MeV/u, after which the particles are gradually decelerated to achieve the desired, user-specified energy level. This deceleration process can reach a minimum of 55.6 MeV/u, with the synchrotron offering up to 600 energy adjustment steps between these maximum and minimum energy levels. The synchrotron delivers a spill of 3×10^9 particles per cycle. Once accelerated, the particles are conveyed to the treatment rooms via HEBT.

The intensity of the extracted beam during this transportation varies from 3×10^7 to 1×10^9 pulses per second. The operational protocol ensures that when one treatment room is in use, the beam is not directed to other treatment rooms. The time required to switch the course and direct the beam to a different treatment room upon completion of delivery is ≤ 60 seconds. Any residual beam is safely absorbed by the beam's stopper, which is positioned before the exit of the treatment room.

To facilitate comprehensive monitoring, various monitors are strategically placed between the injector, accelerator, and HEBT sections. These monitors track electric signals related to the accelerator's status and the beam's position, shape, and dose. All pertinent signals can be monitored from the accelerator control room, ensuring precise control and safety during operations.

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2) Beam delivery system and treatment rooms

At our institution, a pioneering approach has been adopted with the installation of one fixed beam (horizontal beam only) and two rotating gantry beams, marking a global first. Fig. 3 depicts the layout of the accelerator room, treatment rooms equipped with fixed and rotational gantries, and the interior parts of a rotational gantry.

The beam delivery system for all treatment rooms in our carbon-ion therapy center employs raster scanning technology (active spot scanning technique) with active energy variation. This 3D irradiation method enables precise irradiation of the target tumor and improves the dose conformation. Moreover, spot sizes with a minimum sigma value of <2 mm feature a sharper lateral penumbra and steeper dose gradients, potentially resulting in reduced absorbed doses to organs at risk [32].

Our center has introduced two compact gantry systems incorporating superconducting magnets to facilitate precise adjustments of the carbon-ion beam angle. Each gantry measures 9 m in length, features a rotational radius of 6.3 m, and weighs 200 tons. These gantries are downsized by 2/3 relative to the models used at NIRS, mirroring those at Yamagata University Hospital. They permit rotations of $\pm 180°$, providing optimal beam direction for patient treatments and ensuring effective irradiation angles. Currently, acceptance tests are being conducted for our inaugural gantry equipment.

Each treatment room is furnished with a six-dimensional (6D) couch and a stereoscopic imaging system consisting of the UD150B-40 (Shimadzu Medical Systems, Kyoto, Japan) and the PaxScan 3030X (Varex Imaging, Salt Lake City, UT, USA), dedicated to patient setup and intratreatment motion tracking, respectively. Furthermore, a respiration-gated irradiation system, based on the respiratory gating system (AZ-733VI; Anzai Medical Co. Ltd, Tokyo, Japan), is implemented for gated irradiation in gantry rooms.

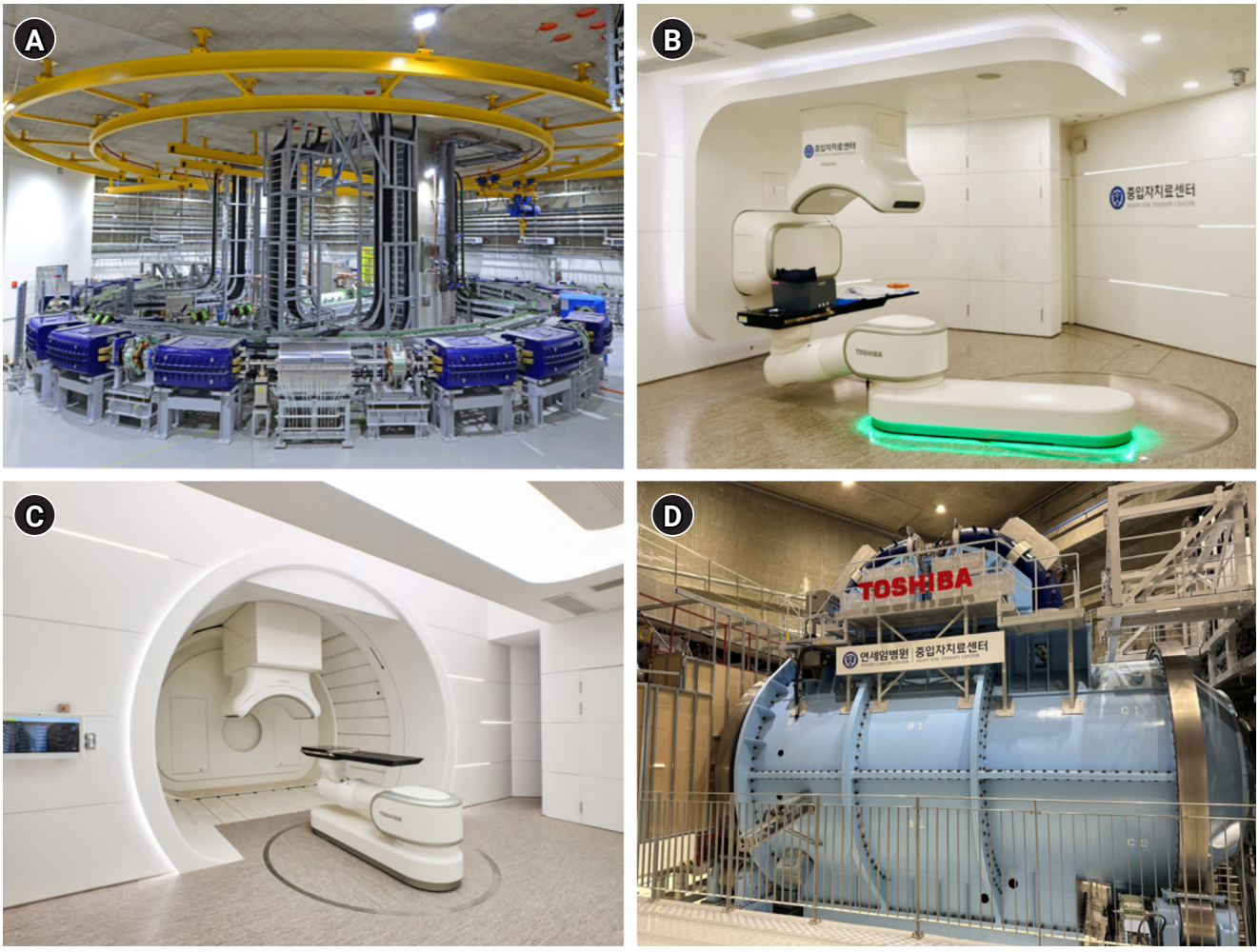

Fig. 3. (A) Synchrotron for carbon ion acceleration, (B) fixed treatment room, (C) gantry treatment room, and (D) inner parts of gantry with a superconducting magnet.

4. Clinical workflow software

Before the commencement of any treatment, the HITC at YCC implements a structured workflow to ensure the optimal execution of patient treatment and adherence to quality assurance (QA) standards. Treatments are scheduled 4 days per week (from Tuesday to Friday) following a daily QA routine. Every Monday is allocated for comprehensive QA sessions encompassing both machine QA (daily, monthly, and annual) and patient-specific QA (PSQA) to maintain the highest levels of accuracy and safety for forthcoming treatments. New patients are scheduled to initiate the first fractions of their treatments every Tuesday after the successful completion of PSQA. This treatment and QA schedule is based on the protocols established by NIRS.

For treatment planning, HITC has adopted the RayStation (RaySearch Laboratories, Stockholm, Sweden) as the treatment planning system (TPS), which is one of the commercial TPSs designed for carbon-ion dose calculations. RayStation employs a pencil beam dose calculation algorithm for CIRT based on the conversion curve from CT numbers to stopping power ratios (SPR). Our treatment planning for CIRT incorporates robust optimization to ensure that the planned dose achieves an optimal balance between therapeutic benefits and potential risks, considering both beam and setup uncertainties. In the realm of RBE calculations, YCC utilizes the modified microdosimetric kinetic model, developed in collaboration with vendors and quantum science and technology (QST); the parameters for RBE dose calculation are based on the linear quadratic model of survival curves for human salivary gland tumor cells. To validate the RBE model implemented in RayStation, we compared the RBE values calculated from our TPS with those calculated by QST under identical conditions, confirming that the differences were within the tolerance limits set by QST's external audit standards. Currently, the TPS does not support LET calculation and optimization; however, the vendor plans to introduce LET evaluation and optimization in the latest version of the TPS, coinciding with the full operational status of our facility.

The oncology information system (OIS) plays a crucial role in facilitating the seamless integration of patient data across various clinical, radiological, and administrative platforms [33,34]. Specifically, the Department of Radiation Oncology leverages the OIS to manage its clinical workflow effectively, promoting efficient communication among the radiation oncology team members, including radiation oncologists, medical physicists, medical dosimetrists, nurses, and radiation therapists. In addressing the complex needs associated with CIRT, which are substantial more intricate than conventional X-ray treatments, we integrated RayCare (RaySearch Laboratories) into our HITC system. RayCare encompasses RayPACS, a picture archiving and communication system (PACS), and RayTreat, a record and verify (R&V) system, offering optimal compatibility with the TPS used in the YCC HITC system.

To ensure effective implementation, a dedicated task force (TF) was established to bridge the OIS with our hospital information system (HIS). The connectivity between the HIS and OIS, utilizing their Health Level 7 (HL7) and scripting capabilities, provides significant advantages in minimizing potential errors from redundant inputs between the two systems. First of all, adopting the HL7 standard facilitates streamlined communication between these systems, utilizing a single user input. Key modules such as admission, discharge, and transfer (ADT), observation message (ORU), and schedule information (SIU) were integrated, with additional synchronization achieved through custom scripts in RayCare and internal application programming interfaces within the HIS, all tailored to the clinical workflow's direction of interaction. Fig. 4 presents an automated, streamlined workflow undergoing CIRT. The TF is currently focused on refining processes, with a particular emphasis on the enhancement of communications for the gantry-based treatment workflow.

RayTreat, employed at YCC HITC, is recognized as the first international R&V system to attain compatibility with Toshiba's CIRT equipment. To accomplish this landmark compatibility, a series of exhaustive steps were undertaken, encompassing a thorough factory validation, two on-site validations (each spanning approximately 2 weeks), and multiple online discussions between our team and the vendors. Full interoperability has not yet been achieved, especially with advanced features such as spatial registration objects. Efforts are ongoing to enhance compatibility based on the integration of the latest updates from both vendors.

As we approach the launch of HITC's second gantry, substantial improvements in compatibility are expected, highlighting our commitment to leveraging cutting-edge technology for optimal treatment outcomes.

Results

1. Global collaboration and educational activities

To enhance collaborative relationships and advance clinical research, YCC has established memorandums of understanding (MOU) with several leading institutions, including the QST, Kanagawa Cancer Center, Gunma University, and Yamagata University. These MOUs stand as a testament to our shared commitment to collaboration, knowledge exchange, and a unified vision in the field of radiation oncology.

On April 6, 2019, YCC hosted the inaugural symposium on heavy-ion therapy in Korea, named the Yonsei Cancer Center–QST·NIRS Joint Symposium. This event aimed at fostering a com-

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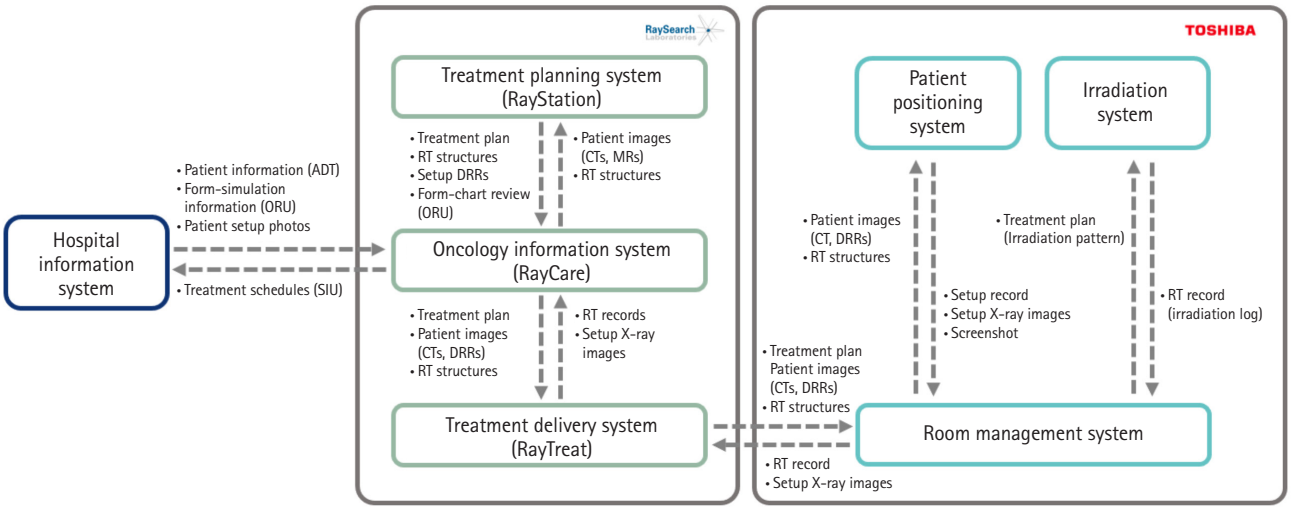

Fig. 4. Automated workflow of streamlines for carbon-ion radiotherapy system at the Yonsei Cancer Center. ADT, admit-discharge-transfer; RT, radiotherapy; CT, computed tomography; MR, magnetic resonance; DRR, digitally reconstructed radiograph; ORU, observation result; SIU, scheduling information unsolicited.

prehensive understanding of CIRT processes, culminating in a delegation of 27 individuals visiting the MOU institutes. Among these, 15 received training in fixed treatment techniques, while the remaining 12 engaged in specialized training for gantry-based treatments. To reinforce our collaborative endeavors, YCC and QST co-organized a joint symposium in 2019, marking a substantial milestone in our partnership. In addition to hosting both online and offline conferences, continuous efforts are undertaken to facilitate the ongoing exchange of academic insights about CIRT. On October 10, 2023, YCC held the Yonsei–Gunma Heavy-ion Therapy Collaborating Meeting, further emphasizing the importance of collaboration in advancing the field. We also actively participate in academic conferences, such as the International Training Course on Carbon Ion Radiotherapy (ITCCIR), Annual Particle Therapy Co-Operative Group (PTCOG) Conference, and International Symposium on Heavy-ion Therapy (ISIT) to stay abreast of the latest developments and research findings in CIRT. Additionally, we have organized various seminars with invited speakers to discuss advances and techniques in particle therapy and held internal particle therapy conferences where we share international research, case studies, and clinical data. We have also received training on equipment utilization and QA from Toshiba which has enhanced our operational expertise.

2. Clinical preparations

1) Establishment and operation of a specialized clinic for CIRT of the HITC at the YCC

Since December 2022, the YCC has been operating a dedicated reservation center for the HITC, laying the groundwork for CIRT triage. In this system, following specialized consultations with radiation oncologists, patients considered suitable for CIRT are directed toward further specialized consultations for this treatment. Conversely, those found ineligible for external radiation therapy are guided toward appropriate, timely interventions, and alternative treatments.

In April 2023, coinciding with the commencement of CIRT operations for prostate cancer patients, YCC expanded its specialized outpatient clinics for CIRT. Prostate cancer was chosen as the first cancer type for CIRT at our institution because it allows for relatively straightforward setup and planning, enabling efficient operation of the fixed-beam therapy room and high patient throughput. The establishment of the dedicated reservation center for the HITC facilitates direct scheduling of consultations within the department of radiation oncology. Additionally, referrals from the departments of urology and medical oncology are made for patients who (following their initial consultations) meet the criteria for CIRT. Four radiation oncologists, specializing in the treatment of prostate cancer, conduct these specialized consultations for CIRT, determining the appropriate treatment schedules. Furthermore, another radiation oncologist oversees the overall consultation for CIRT concerning other types of carcinoma.

Looking ahead, YCC has plans to initiate gantry treatment in 2024 and broaden the spectrum of cancer types treated beyond prostate cancer. Additionally, plans to expand outpatient clinics specializing in CIRT exist, by assigning radiation oncologists to oversee treatments for all specific cancer types. Currently, 12 radiation oncologists at YCC HITC are either engaged in or are planning to undertake CIRT.

2) First approval for the use of CIRT in Korea

The initiation of the first application of CIRT in South Korea necessitated a preliminary step related to the assessment of new medical technology. This evaluation is crucial for establishing the safety and efficacy of the CIRT technology and the CIRT machine as secure medical technologies. In Korea, the assessments of new medical technology encompass three processes that can be conducted simultaneously or sequentially: the acquisition of medical device approval by MFDS in Korea (which is equivalent to the U.S. Food and Drug Administration), the conduct of medical technology evaluations by the National Evidence-based Healthcare Collaborating Agency (NECA), and the reviews of existing technologies by the Health Insurance Review and Assessment Service (HIRA). Upon the approval of new medical technologies, subsequent steps include the determination of reimbursement and pricing by HIRA, following an announcement by the Ministry of Health and Welfare, before the formal introduction of the medical technology into clinical practice.

The process for obtaining approval from the MFDS for CI-1000 commenced in May 2022. Over approximately 11 months, practitioners engaged in dedicated efforts and discussions to prepare clinical data substantiating the safety and efficacy of CIRT. The MFDS comprehensively reviewed the results of several clinical studies, including a clinical trial of CIRT for prostate cancer conducted at the Kanagawa Cancer Center. The MFDS convened multiple Medical Device Evaluation Committee meetings (comprising experts in radiation oncology and nuclear medicine) to assess thoroughly the safety and efficacy of CI-1000. On March 21, 2023, CI-1000 was approved as the first domestically approved CIRT machine in South Korea. Following the approval from the MFDS, YCC is currently conducting a postmarket surveillance study targeting patients undergoing CIRT. This investigation, which began on April 28, 2023, and will continue until April 27, 2027, aims to survey 600 cases under the supervision of Principal Investigator Professor Hong-In Yoon. The objectives of the postmarket surveillance are twofold: (1) to assess the occurrence of unforeseen adverse events and efficacy not identified in previous clinical studies during prostate cancer treatment, and (2) to gather additional information on adverse events and efficacy that may occur in patients with solid cancers other than prostate cancer.

Since YCC applied for the medical technology review of CIRT in May 2022, NECA has assigned a subcommittee (which comprised seven experts in the field) to evaluate the safety and effectiveness of CIRT. The assessment included a systematic literature review, with safety assessed using procedure-related complications and adverse events as indicators, and the effectiveness evaluated based on local tumor control, recurrence, and patient survivals. A comprehensive literature review of 34 articles (two randomized control trials, 32 cohort studies) on CIRT was conducted, supplemented by an additional review of 32 preceding systematic literature reviews. Ultimately, on December 23, 2022, the NECA completed its deliberation on CIRT as a "new technology with safety and effectiveness." The committee's findings, along with the subcommittee's review results, were reported to the Minister of Health and Welfare on January 4, 2023, with the final announcement made on April 27, 2023.

3. Insurance coverage status of CIRT in Korea

The approval of CIRT as a new medical technology signifies its distinction from therapeutic procedures currently covered by existing health insurance items in South Korea. Health insurance reimbursement categories in South Korea accommodate treatment and planning procedures related to X-ray and proton therapy; however, CIRT has not yet been covered by insurance companies. Consequently, in the context of South Korean insurance policies, CIRT is presently offered as a service not eligible for reimbursement. The determination of its eligibility for insurance coverage will be subject to future evaluations. Currently, the treatment costs for CIRT at the YCC are determined according to several factors: (1) type of beam used, whether fixed beam or gantry, (2) total treatment dose, categorized into three stages based on the doses of 60 GyE and 70 GyE, (3) employment of a respiratory gating system, and (4) the application of a single field or multifield treatment plan.

4. Protocol for CIRT at the YCC

1) Prostate cancer

Patients with prostate cancer visiting HITC's specialized outpatient clinics undergo an examination by a radiation oncologist who determines their eligibility for CIRT and schedules their treatment. The eligibility criteria for CIRT include (1) the diagnosis of localized prostate cancer at the cT1c-T3N0M0 stage, (2) histological confirmation of adenocarcinoma of the prostate, and (3) the Eastern Cooperative Oncology Group performance status of 0 or 1. Several reports have been referenced regarding the eligibility and clinical utility of CIRT in prostate cancer [35–40].

The clinical target volume encompasses the prostate, contingent upon the risk classification, along with partial or entire seminal vesicles, or in some cases, excluding the seminal vesicles. Setup margins are specified as follows: 10 mm to the right and left, 5–7 mm anteriorly, 3 mm posteriorly, and 5 mm both superiorly and inferiorly. The prescribed dose is set at 51.6 GyE, delivered in 12 fractions, at a rate of 1 fraction per day, totaling 4 fractions per week. The treatment plan employs robust optimization, factoring 18 scenarios to accommodate isotropic uncertainty related to the patient setup margins and systematic uncertainties related to density vari-

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ations. Treatment is administered using opposing lateral fields with alternate daily treatments between the right and left beams (as scheduled).

Before treatment at the YCC, all patients, except those for whom it is contraindicated, undergo SpaceOAR hydrogel (Boston Scientific, Marlborough, MA, USA) insertion between the rectum and prostate and fiducial marker placement (SGM18-20-Cy183; SGM Co. Ltd., Seoul, Korea) within the prostate. The SpaceOAR hydrogel, a biodegradable medical device, is commonly utilized to reduce potential rectal toxicity during CIRT. Following this, personalized immobilization devices are crafted, and simulation CT and MRI scans are performed. Patients are instructed to maintain a specific bladder volume (approximately 150– 200 cm^3) during CT simulations in each CIRT session, ensuring consistent urine retention. Before each treatment session, the image-guided system verifies the position of fiducial markers and bladder volume. Upon confirmation that these are within the specified ranges, beam delivery commences. To enhance treatment precision and minimize side effects, a mid-treatment re-evaluation with an evaluation CT scan is conducted during the 12-fraction treatment period. This re-evaluation confirms the positions of the prostate and adjacent organs at risk (OARs), assesses any dose discrepancies, and implements adaptive plans if necessary. As of March 1, 2024, YCC has successfully treated 203 patients with CIRT for prostate cancer since the initiation of treatments on April 28, 2023.

2) Other solid cancers

YCC is poised to commence treatments using a gantry in early 2024, initially focusing on pancreatic, liver, and lung cancers. There are subsequent plans to methodically expand CIRT indications to encompass head and neck cancers (excluding squamous cell carcinoma), osteosarcoma, and various other cancers.

For pancreatic cancer, the contemplation of CIRT encompasses several scenarios: (1) preoperative CIRT in resectable pancreatic cancer, (2) sequential administration of chemotherapy followed by CIRT in borderline resectable pancreatic cancer, (3) definitive CIRT in locally advanced pancreatic cancer, and (4) salvage CIRT for cases of local recurrence following surgery or chemotherapy. Considering the radioresistance and location of pancreatic cancer, the application of CIRT is expected to improve the overall oncologic outcomes in locally advanced cases [41–44] and in resectable/borderline-resectable cases [45–49]. As one of the neoadjuvant strategies, preoperative CIRT can be effective in eliminating retroperitoneal microinvasion of malignant cells and reducing both tumor size as well as perivascular and lymphatic involvements.

In the realm of liver cancer, CIRT is primarily considered for tumors that are difficult to treat with conventional curative treatments. Favorable indications for CIRT include liver lesions that are less or equal to three, preserved liver function, and lesions located in peripheral or hilum regions. Additionally, cases exhibiting incomplete response or recurrence following transarterial chemoembolization (TACE) or transarterial radioembolization (TARE), as well as those with portal vein invasion, are deemed suitable for CIRT in the absence of lymph node or distant metastases. The exploration of CIRT in combination with immunotherapeutic agents (such as atezolizumab/bevacizumab) to augment immune responses and potentially enhance treatment outcomes, is also being considered.

Regarding lung cancer, CIRT is primarily being considered for peripheral stage I lung cancer, with the treatment strategy varying according to the tumor's location and size. Options include either a single fraction or four fractions. Plans are in place to extend gradually the indications for CIRT, potentially including central-type tumors or locally advanced tumors with careful consideration of dose constraints for adjacent OARs.

5. QA

QA has a crucial role in our clinical workflow. Mondays are designated exclusively for QA processes at our institute. This practice ensures the delivery of consistent and precise treatments from Tuesday to Friday each week.

Our QA procedures adhere to the guidelines of the vendor's recommendations and the American Association of Physicists in Medicine (AAPM) Task Group (TG) Report 224, a document primarily devised for proton QA. However, owing to fundamental differences between proton and carbon-ion therapy machines, such as variations in spot size, certain QA items, and their associated tolerances as outlined in the TG Report are not directly applicable to CIRT. Our QA measurement system is guided by the TRS398 standards and a prominent Japanese publication, "Standard Measurement Method 12." Although Toshiba is our principal equipment supplier for most QA tools, we have integrated a multilayer ion chamber (Giraffe, IBA Dosimetry, Schwarzenbruck, Germany) and various other devices from external sources to streamline the QA process. Efforts are currently underway to develop strategies that will further enhance the efficiency of our daily QA procedures.

PSQA is conducted with utmost importance, ensuring it is completed before any treatment. For PSQA, three pivotal regions—the proximal, distal, and center of the spread-out Bragg peak—are meticulously measured using a two-dimensional array detector (Octavius 1500 XDR; PTW, Freiburg, Germany). These dose distributions are then rigorously evaluated by comparison with the planned data. We are in the process of implementing a log-based QA system, which aims to achieve a comprehensive analysis of the overall 3D dose distribution, thereby enhancing our understanding and en-

suring the highest standards of treatment accuracy and safety.

Discussion and Conclusion

1. Current status of the YCC HITC

The YCC HITC commenced its operations with fixed-beam CIRT treatments by specifically targeting prostate cancer. Since its inception, we achieved a substantial milestone by successfully treating over 200 cases of prostate cancer using this innovative method. The forthcoming integration of our first gantry represents a major advancement in our treatment capabilities, enabling us to offer gating-based therapies for pancreatic, liver, and lung cancers. Following comprehensive commissioning from various angles, our goal is to broaden our treatment spectrum to encompass a more diverse array of conditions that could benefit from the precision and efficacy of CIRT. Our approach, used to select diseases for treatment, is rigorously aligned with the standards and guidelines set forth by the Japan Carbon-ion Radiation Oncology Study Group (JCROS), ensuring that our strategies are both scientifically grounded and clinically relevant.

2. TG guidelines for carbon-ion therapy

The lack of heavy-ion therapy centers in the United States has resulted in a notable gap in the AAPM guidelines pertaining to heavy-ion therapy (specifically carbon-ion therapy). Although the Japanese Society for Radiation Oncology provides comprehensive resources on this subject in Japan [50], their utility is limited because they are primarily written in Japanese. While existing guidelines, such as TG224 [51], provide a framework for the QA of proton therapy machines, the unique properties of carbon ions necessitate modifications to these standards when applied to carbon-ion therapy at the HITC of the YCC. For example, the acceptable variance in spot size for proton therapy is 10%; however, for carbon-ion beams that have spot sizes in the range of 2–4 mm, this tolerance must be adjusted to 20%. Additionally, guidelines such as TG185 [52], which addresses the clinical commissioning of intensity-modulated proton therapy, are only partially applicable to carbon therapy. The establishment of more heavy-ion radiotherapy centers in the United States could lead to the establishment of more comprehensive AAPM guidelines. These guidelines can be supported by existing publications such as TG016 [53], TG290 [54], and TG256 [55], which offer valuable perspectives on carbon therapy despite being primarily focused on proton therapy.

3. External audit

Our initiatives as pioneers in the field of carbon-ion therapy within Korea have introduced distinct challenges, especially as these pertain to the external audit processes applied to validate our beam delivery system and TPS, particularly concerning physical and biological dose calculations and the conversion of CT images to stopping power ratio (a.k.a. CT2SPR) curve. We are profoundly grateful for the invaluable support provided by QST during this critical audit phase. As interest in heavy particle therapy continues to grow within Korea, we anticipate that more organizations will venture into this domain. This expansion highlights the necessity for regular external audits conducted by national entities aimed at upholding the highest quality and safety standards in this innovative field of medical treatment.

4. Future directions for CIRT clinical and research endeavors

Notable advancements toward the fostering of international collaborations and conducting high-level research in CIRT at the YCC led to the inauguration of the Heavy Ion Therapy Research Institute on January 12, 2022. Under its auspices, we are at the forefront of initiating numerous clinical, biological, and translational research projects. These projects are dedicated to the delineation of the clinical advantages of CIRT and the expansion of its applications across various domains. Central to our research agenda is the execution of randomized trials designed to produce compelling evidence of CIRT's efficacy surpassing that of traditional photon therapy.

Our key initiatives include launching over three prospective studies in pancreatic cancer research to compare CIRT with conventional treatment modalities. These studies encompass randomized trials for resectable pancreatic cancer, comparing the outcomes of CIRT followed by surgery to those of surgery alone, and for borderline resectable pancreatic cancer, comparing CIRT combined with chemotherapy to the standard FOLFIRINOX regimen. Additionally, for liver cancer, we are preparing prospective studies to evaluate the efficacy and safety of CIRT following TACE or TARE, or in combination with atezolizumab/bevacizumab. Alongside these clinical trials, we are meticulously designing translational studies to optimize the therapeutic potential of CIRT. Moreover, we are actively planning and organizing facilities for upcoming biological research initiatives focused on exploring radiobiology concepts such as RBE, tumor immunity, and radiosensitivity.

Moreover, with the increasing establishment of CIRT centers within Korea in recent years, it is anticipated that the number of patients receiving CIRT will increase. Consequently, it is expected that the establishment of a Korean Carbon-ion Radiation Oncology Study Group, such as JCROS, will facilitate multi-institutional clinical research endeavors. This initiative is poised to elucidate the clinical benefits of CIRT and aid in the development of domestic CIRT guidelines for Korea.

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5. Conclusion

Korea's medical landscape is currently witnessing an increasing demand for advanced treatment modalities. The introduction of CIRT meets this critical need by offering superior therapeutic outcomes for various cancers. As the benefits of CIRT become increasingly recognized, hospitals across Korea are anticipated to consider its broader implementation. The YCC pioneered the first CIRT treatment in Korea facilitated through collaborations via MOUs. Since the initiation of the inaugural CIRT treatment for prostate cancer, our medical staff has been committed to extending CIRT services to patients with a diverse array of cancer types. Leveraging YCC's extensive resources and clinical expertise, we are dedicated to generating high-level evidence that substantiates the clinical advantages of CIRT. Our goal is to demonstrate the substantial impact of our efforts on enhancing survival rates and improving the quality of life for cancer patients. We are optimistic that these endeavors will not only contribute to the wider adoption of CIRT within Korea but also promote its recognition and implementation on a global scale.

Statement of Ethics

No ethics approval was required for the report and no human participants were included.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, MCH, SHC, CSH, HIY, LJL; Investigation and methodology, MCH, SHC; Project administration, YBK, IJL, KCK; Resources, WSK, JC, CWW, JWP; Supervision, HIY, IJL; Writing of the original draft, MCH, SHC, CSH; Writing of the review and editing, JC, JSK; Visualization, CK, SH, HL.

Data Availability Statement

Not applicable.

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