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Proposal for Comprehensive Quality Control of Heavy-Ion Medical Accelerator

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Prior to the introduction of a medical apparatus based on heavy-ion medical accelerator in Korea, a study is needed on quality control in clinical operation for the safe and appropriate usage of the instrument. Data relevant for the study were obtained via information sharing sessions and visits by the Particle Therapy Co-Operative Group (PTCOG) and other related academic associations. Furthermore, investigative analysis of the European and Japanese performance evaluation guidelines for heavy ion, as well as research on relevant literature, were conducted. In addition, instrumental standards were analyzed through an investigation of the current usage status of the heavy-ion medical accelerator, and further analysis was conducted on the evaluation methods for the performance, safety, and significance of the instrument. Based on these analyses, regular quality control procedures for heavy-ion medical accelerators in hospitals and other institutes were extrapolated. It is hoped that the results of this study will facilitate hospitals that have introduced heavy-ion medical accelerators, or are considering the implementation of the instrument, in their understanding of the fundamental standards and capabilities of the treatment system, as well as in establishing and carrying out quality control procedures for clinical operations such that it will contribute to the safety of patients and the efficiency of medical practitioners.

Keywords: Heavy ion, Medical instrument, Quality control, Dose distribution, Dose limit

Introduction

Considering the vast differences in radioactive sources, acceleration methods, standards, and operating procedures between heavy-ion medical accelerators and the commonly used electron beam linear accelerators, there is a need to develop suitable checklists and procedures as the basis for indigenous safety and significance evaluation guidelines for heavy-ion medical accelerators by investigating the usage status of the machine abroad. As evident in Table 1, heavy-ion medical accelerators are being operated in 11 institutions across 5 countries: 1 each in Italy and Austria; 5 in Japan; and 2 in China and German. Additionally, 2 institutions from Korea, and 1 each from China, America, Australia, Russia, Taiwan, Japan, Malaysia, and Saudi Arabia are currently constructing or planning to introduce the accelerator. Domestically, the Korea Institute of Radiological & Medical Science (KIRAMS) has been conducting developmental research on a heavy-ion accelerator as a national project for several years in Gijang, and in recent years the Yonsei Cancer Center has pushed for its introduction. In this context, the aim of this study is to analyze some physical and technical properties of the heavy-ion medical accelerator to

Table 1. International/domestic trends in of heavy-ion medical accelerator usage (as of Dec 2014).

Classification	Nation	Facility	Region	Accelerator type	Remarks
Operational (11)	Japan	HIMAC	Chiba	Synchrotron	
		HIBMC	Hyogo	Synchrotron	
		GHMC	Gunma	Synchrotron	
		HIMAT	Saga	Synchrotron	
		i-Rock	Yokohama		
	Germany	HIT	Heidelberg	Synchrotron	
		MIT	Marburg	Synchrotron	
	China	IMP-CAS	Lanzhou	Synchrotron	
		SPHIC	Shanghai	Synchrotron	
	Italy	CNAO	Pavia	Synchrotron	
	Austria	MedAustron	Wiener	Synchrotron	
Under Construction (2)	China	HITFiL	Lanzhou	Synchrotron	2014
	Korea	KIRAMS	Busan	Synchrotron	2017
Construction Plan (6)	USA	Mayo	Rochester	Synchrotron	
	Saudi Arabia	KACST	Riyadh	Cyclotron	
	Malaysia	USM	Penang	Synchrotron	
	Taiwan	Chang Yung-Fa Foundation	Taipei	Synchrotron	
	Russia	ITEP	Moscow	Synchrotron	
	Australia	ANSTO	Clayton	Synchrotron	

deduce the fundamental capabilities and standards for its implementation based on "A Study on the Development of Safety and Performance Evaluation Techniques for Heavy-Ion Medical Accelerators" carried out in 2014 and 2015 as a commissioned research project from the Korea Food & Drug Administration. At the same time, this study aims to suggest an evaluation method for the key attributes, safety, and significance of the accelerator for regular quality control procedures. It is hoped that the results of this study will facilitate hospitals that have introduced heavy-ion medical accelerators, or are considering the implementation of the instrument, in their understanding of the fundamental standards and capabilities of the treatment system, as well as in establishing and carrying out quality control procedures for clinical operations such that it will contribute to the safety of patients and the efficiency of medical practitioners.

Current Usage Trends of Heavy-ion Medical Accelerator

Like hydrogen ions used in proton accelerators, the carbon ions that are often used in heavy-ion medical accelerators tend to exhibit a Bragg peak, meaning they show a drastic reduction in dose after peaking at the distal end of the beam, with little dose observed at the fore end of the beam, unlike an X-ray beam in which the dose peaks at the surface and subsequently decreases exponentially with increasing depth.[1,2] Such a property allows heavy-ion accelerators to focus a high dose of radiation on tumor cells in radiotherapy, while reducing radioactive exposures for other healthy organs. In particular, carbon ion exhibits a significantly more pronounced Bragg peak than a hydrogen ion owing to its relative mass, but the tail of the beam is relatively longer than that of a hydrogen ion beam.[3-5]

Most heavy-ion medical accelerators that are currently being operated both domestically and internationally use carbon ion as the radioactive source for treatment, and the energy output of the carbon ion beam is generally set between 400 MeV/u and 430 MeV/u, except for the Heavy Ion Medical Accelerator in Chiba (HIMAC, which produces 800 MeV/u of energy.[6] Unlike proton therapy, all heavy-ion medical accelerators utilize synchrotron accelerators and a combination of scattering (or passive beam) and scanning (or pencil beam) beam for irradiation.[6-10] However, it is understood that IBA, which has previously operated cyclotron accelerators, is working in tandem with Russia's JINR to install a heavy-ion accelerator based

on a superconducting magnetic cyclotron. Gantry-based accelerators, although commercialized and being used clinically, are not being operated as heavy-ion medical accelerators, implying that all accelerating mechanisms employ single or dual fixed-beam methods.[7,11-14)]

In terms of the heavy-ion source, except for HIMAC and the Hyogo Ion Beam Medical Center (HIBMC) in Hyogo, Japan, all facilities have adopted an Electron Cyclon Resonance (ECR) mechanism, including the Austrian heavy-ion accelerator that began operation in 2017.[15-19)] While HIMAC and HIBMC use radio frequency quadrupole magnets and Alveraz drift tube linear accelerators, it was found that most other heavy-ion medical accelerators constructed after these two facilities utilize radio frequency quadrupole magnets and interdigital H-mode drift tube linear accelerators. Table 2 illustrates the capabilities and specifications of heavy-ion medical accelerators currently in operation.

Treatment using heavy-ion medical accelerators began as an experimental method at HIMAC in Chiba, Japan, in 1979, and was officially introduced clinically in 1994. Judging by the constantly increasing trend in the number of patients since 2008, the role of heavy-ion medical accelerators in radiotherapy for cancer patients is expected to grow.[20-22)] HIMAC has compiled a record of patients treated using this technology from 1979 to 2010. With respect to the Quality of Life (QOL) of prostate cancer patients treated with radical operation, X-ray treatment, heavy-ion treatment, small-source radiation treatment, and endocrine therapy, HIMAC reported that radical local treatment methods, namely radiotherapy and operation, was effective in maintaining the utility value of QOL in the long term.[23,24)] Based on the records provided by HIMAC, the most common type of cancer treated with a heavy-ion medical accelerator was prostate cancer, which was the fourth most common type of cancer among Japanese males following stomach, colon, and lung cancers. Similarly, in Korea, while prostate cancer was a relatively less common type of cancer among patients, prostate cancer patients accounted for a considerable portion of those who received proton therapy as treatment.[24-27)]

Thus, it is expected, based on the cancer treatment trends in local proton therapy treatment centers, that the proportion of patients opting for heavy-ion medical accelerator treatment would be significant should it be introduced formally. Furthermore, noting that a radiotherapy for cancer in certain organs such as the lung and the liver may potentially result in undesirable side effects on other healthy organs exposed to low doses of radiation, it is possible to predict that the demand for heavy-ion medical accelerator treatment will increase for lung and liver cancer patients, as studies attesting to the ability of heavy-ion accelerators to focus radiation doses on the tumor target and reduce radioactive exposure to the peripheral organs increase in number.[28,29)]

Table 2. Capabilities of key heavy-ion medical accelerators currently operational.

Facility classification		HIMAC	GHMC	HIT	CNAO	KHIMA
Ion source		NIRS-10,18, PIG	NIRS-10 GHz	SUPERNANOGAN Pantechnik	SUPERNANOGAN Pantechnik	SUPERNANOGAN Pantechnik
inject layout	Vender	NIRS-OLD	NIRS-NEW	GSI+IAP Frankfurt	GSI	GSI
	Layout	RFQ+Alvarez DTL	RFQ+IH-APF DTL	RFQ+IH-KONUS DTL	RFQ+IH-KONUS DTL	RFQ+IH-KONUS DTL
	Energy (MeV/u)	0.8/6.0	0.6/4.0	0.3/7.0	0.4/7.0	0.4/7.0
Synchrotron Layout	RF	100 MHz	200 MHz	216 MHz	216.8 MHz	216.8 MHz
	Length	7.3/24 m	2.5/3.5 m	1.2/4.0 m	1.4/3.77 m	1.4/3.77 m
	Name	NIRS-OLD	NIRS-NEW	GSI+HIT	PIMSS/TERA	KHIMA
	Energy (MeV/u)	100~800	140~400	50~400	60~400	60~400
	Diameter (m)	41	21	21	25	27.5
	structure (cells)	12	6	2	2	2
	Extraction method	RF-KO-SE	RF-KO-SE	RF-KO-SE	Betatron Core	RF-KO-SE
	Spill time (s)	1	1.6	1~10	1~10	1~10

Key Capabilities of Heavy-Ion Medical Accelerators

Tables 3 and 4 show the required attributes for radiotherapy apparatuses based on heavy-ion medical accelerators, following the guidelines created in Europe and in Japan with respect to performance evaluation and the usage of heavy ions. The technical and physical properties of heavy-ion medical accelerators summarized in this report may be used as reference material by hospitals preparing for or hoping to introduce the apparatus, or by medical practitioners who plan to conduct acceptance trials or establish a regular quality control procedure for the accelerator. It is expected that the information can be adjusted to establish optimum medical procedures that best fit the needs of each hospital and facility.[30-32)]

Regular Quality Control

For the safe and effective clinical operation of heavy-ion medical accelerators, regular checks on key parameters of the equipment are necessary, as with general X-ray-based linear accelerator equipment. Maintenance may be carried out in a daily, monthly, or annual manner, which is to be conducted and managed by a team of medical practitioners within the hospital or the facility and medical radiology engineers. Listed below are the criteria for regular quality control procedures, arranged in the order of daily, weekly, monthly, half-yearly, and annual checks. The items suggested in this report may be used as a reference by medical practitioners when establishing quality control procedures, and it is recommended that each hospital make amendments to best fit their situation and needs.

Table 3. Key capabilities of radiation therapy equipments based on heavy-ion medical accelerator.

Performance evaluation criterion	Assessment reference standards	Unit	Reference conditions
Beam type	Carbon	u	
Beam range	3.0~27.0	g/cm^2	Chosen energy range 110~430 MeV/u
Bragg peak optimization	0.1~0.2	g/cm^2	Energy steps 250 steps
Beam optimizaion accuracy	≤±0.025	g/cm^2	Energy accuracy ≤±0.505~0.219 MeV/u
Beam adjustment region accuracy	0.1	g/cm^2	Energy adjustment range 2.03~0.878 MeV/u
Distal beam dose	<2	mm	Lateral dose between 80%~20%
Mean dose rate	<2	Gy/min	Min/Max number of beams 4×10^6~4×10^8
FWHM	4~10	mm	
Beam FWHM step	1	mm	
Beam FWHM accuracy	≤±0.2	mm	
Beam incidence axis height	120	cm	

Table 4. Physical properties of radiation therapy treatment equipment based on heavy-ion medical accelerator.

Performance evaluation criterion	Reference standard	Unit
Precision of Bragg peak position	±1	mm, %
Homogeneity incident surface (transverse profile)	5	%
Energy conformity	±1	mm
SOBP conformity and homogeneity	±5	%
Dose at standard volume	±3	%
Form accuracy of volume subjected to radiation	±2, ±5 (minimum)	mm, %
Precision of dose distribution in non-homogeneous phantom	24 data points; <5, single point: ±7	%
Precision of dose distribution in non-homogeneous phantom	24 data points; <5, single point: ±7	%
Determination of absorbed dose in water at standard conditions	≤±1	%

1. Daily quality control

1) Half width
2) Precision of beam location with respect to the isocenter
3) Precision of beam deflection
4) Check on round procedures in services room and signal panels
5) Check on emergency button in services room
6) Check on round procedures in the infirmary and signal panels
7) Check on intercom, lighting, and patient monitoring camera in the infirmary
8) Check on emergency button in the infirmary
9) Check on beam request signal
10) Check on treatment commencement signal
11) Security link on excess dose transferred per voxel
12) Laser alignment
13) Safety of dose transfer mechanism
14) Check on dose per unit volume
15) Precision of Bragg peak location

Steps 4)~12), which are designed to check if the safety mechanisms and their indicators are operating normally, are shown as either active or inactive depending on the conditions of the safety mechanisms and the indicators. Steps 1)~3) and 13)~15) are designed to determine the physical and dosimetric properties of the heavy-ion accelerator. In step 1), the half width is verified by measuring the FWHM of the pencil beam's transverse profile to determine if it corresponds with the standard value. Measurements are taken once each in the low-energy and high-energy regions to determine if the half width is within ±1 mm of precision, or 10% within the reference value.

Steps 2)~3) verify the precision of the zero reference and the change in deflection point when the pencil beam is deflected, in which the precision must fall within ±1 mm. 1) The category of the safety dose of the transfer mechanism is meant to check if the adjustment on the dose transfer mechanism can be maintained steadily. For reference, the CF(E) with respect to the Monitor Unit (MU), which corresponds to 1 cGy, must be within 3%. 2) Dose per unit volume, which is aimed at verifying the reproducibility of the dose at the center of SOBP by investigating the identical beam on the same phantom, must also fall within 3%. 3) The category of the precision of Bragg peak location verifies the precision of the location of the Bragg peak with respect to various values of energy, and must correspond within ±1 mm.

2. Weekly quality control

1) Uniformity of transverse profile (uniform scan, single energy mode)
2) Short-term stability of the dose transfer mechanism (uniform scan, single energy mode)

1) A check on the transverse profile is conducted by determining if $H = \left[\left(\frac{P_{max}-P_{min}}{P_{max}+P_{min}}\right) \times 100\%\right]$ measured at a region corresponding to 80% of the area of the incident surface is within 5%. A verification of the short-term stability of the dose transfer mechanism is carried out by repeatedly measuring the CF(E) of MU, which corresponds to 1 cGy per energy, 10 times, and determining if the difference is within 1%.

3. Monthly quality control

1) Half width
2) Precision of beam location with respect to the isocenter
3) Precision of beam deflection
4) Validation of scattering beam components
5) Distal beam dose
6) Bragg Peak modulation step
7) Beam strength modulation and accuracy
8) Mean dose rate
9) Dose per unit volume (Uniform scan, SOBP mode)
10) Linearity of dose transfer mechanism (Uniform scan, single energy mode)

Steps 1)~3) and 9) were explained in the daily quality control section. 4) A component check of the scattering beam is carried out by determining if key parts such as the range modulator, leaf filter, nozzle, and applicator are able to attain their original properties against time. Components may be checked by visual examination and the operability of parts. 5) For each energy value, based on the Bragg peak and SOBP beams, the distal beam dose can be checked by measuring the distance between the depth

at which the dose value becomes 80% that of the dose peak, and that at which the dose value is 20% of the peak, and afterward comparing the obtained value with the reference value. The difference between the calculated and reference values must be within 2 mm. 6) The precision of the change in the Bragg peak location that occurs owing to the Range Modulator Step must lie between 0.1~0.2 g/cm^2. 7) A tiny modulation is made to the beam energy using a beam range adjustor and scattering foil, and the calculated value must have a precision of ±0.025 g/cm^2 with respect to the predicted value. 8) The mean dose rate can be checked by determining if the dose measured per unit time using an ion chamber and phantom is sufficiently close to the reference value. 10) A check on the linearity of the dose transfer mechanism is similar to the verification method to determine the short-term stability of the dose transfer mechanism specified in the daily and weekly quality control sections. The deviation of CF(E) against the dose linearly increasing from 0.2 Gy to 2.0 Gy must be within 3% for three different values of energy.

4. Half-yearly quality control

1) Energy conformity
2) SOBP conformity and homogeneity (uniform scan, SOBP mode)
3) Beam Range Adjustment

1) Energy conformity aims to identify if the positional improvability of the Bragg peak in water is within 1 mm. 2) The SOBP conformity and homogeneity category is meant to determine the invariability and homogeneity of SBOP in the longitudinal dose profile, and is validated by taking the SOBP value, defined as the distance between the proximal 90% and the distal 90%, and determining if the value is within 5% of other SOBP values taken randomly. 3) The Beam Range Adjustment criterion serves to identify if the beam energy modulated by the range modulator and scattering foil falls within ±1 mm of the predicted value.

5. Annual quality control

1) Confirmation of the impossibility of radioactive contamination by the beam
2) Invariability of half width as a function of distance from air or water to the nozzle
3) Independence of dose against changes in beam strength and half width
4) Independence of dose against energy changes of the beam
5) Beam size accuracy
6) Drift of dose transfer (Uniform scan, single energy mode)

To ascertain that no radioactive contamination by the beam has taken place, a dosimetric system must be utilized regularly to identify the existence of additional peaks besides the Bragg peak. This is because heavy ions, unlike the usual X-ray treatment rays, may contaminate the treatment apparatuses and applicator substances if projected for a prolonged period. Should unexpected peaks be observed at other positions, an investigation must be carried out to identify its causes, and the problem must be rectified. For criterion 2), FWHM with respect to distance should be measured, and its value must fall within ±1 mm of the reference or predicted value. Although 3) and 4) were designed to project identical doses, beams with at least three different levels of beam strength (particles per second), different energies, and different half widths were projected to observe if the measured dose fell within 3% in order to identify that there is no correlation between the dose and beam energy, strength, or half width. 5) The beam size accuracy is a procedure designed to observe if the size of the heavy-ion beam is properly adjusted, and can be verified by calculating the difference between the predicted and the measured values of FWHMs of various sizes, which must be within 0.2 mm. 6) The criterion for the drift of dose transfer is designed to confirm the safety of the dose transferred, as described by the invariability of CF(E), during daily treatment periods. Particles present in 2 Gy of dose are measured prior to the start of treatment, and the same measurement is made after a day of treatment, after which the CF(E) values are compared to see if they are within 2% of each other.

Personnel Standards for Safe Operation of Heavy-Ion Medical Accelerators

A team responsible for the maintenance and the safe

operation of heavy-ion medical accelerators consists of a radiological oncology specialist, medical practitioner (quality control personnel), radiologic technician, nurse, and engineers. With regard to standards for necessary personnel, the number of radiological oncology specialists is determined by the annual incidence rate of cancer patients, while the number of nurses is determined by taking the number of new cancer patients and specialists into account, whereas two technicians are assigned per infirmary. Reports about the need for medical practitioners in departments of radiological oncology were reported in America, Europe, and Korea.[33-36] Based on such reports, one quality control person is required for a single piece of medical equipment, while main and assistant personnel are needed for the radiation therapy planning room, radiation therapy server room, patient quality control, and overall quality control.

For tailor-made treatment analysis and research for new patients, maintaining several professionals is crucial for safe radiotherapy treatment. In case of an unexpected problem within the team, an emergency measures team composed of at least two technicians should be formed, and a separate technical team for the management of the accelerator and beam adjustment according to the heavy-ion medical accelerator standards should be assembled. Fig. 1 illustrates the personnel chart for safe operation radiotherapy treatment system. The difference from the conventional X-ray based treatment method is the inclusion of additional technical team for the operation of heavy-ion medical accelerator in the organizational chart. As observable in the organizational chart in Fig. 1, the radiation safety manager is assigned as the chief of heavy-ion treatment center, who (a) bears the final responsibility pertaining to patient treatment, (b) establishes and authorizes quality control plans, (c) makes decision whether to administer heavy-ion treatment, (e) decides patient treatment and prescribes radiation therapy treatment. The role of a radiation oncology specialist, who prescribes radiation therapy, is to (a) bear final responsibility for patient treatment, (b) decide on treatment method, (c) prescribe treatment and confirm a treatment plan, (d) track and manage the outcome of patient treatment after radiation therapy. The responsibilities of a medical practitioner (quality control personnel) include (a) establishment of quality control plan for heavy-ion accelerator, (b) continual assessment of heavy-ion accelerator's quality control procedures, (c) execution of accelerator quality control, (d) correction of radiation detector required for quality control and (e) quality control of treatment plan and formation of computerized patient treatment plan. The duties of a nurse are (a) patient training on the general treatment process and management prior to and after heavy-ion treatment, (b) patient management and consulting room maintenance and (c) assistance on tracking patient treatment results upon completion of heavy-ion treatment, while those of a radiologic technician are (a) administration of treatment, (b) assistance in quality control of heavy-ion accelerator, (c) daily maintenance and reporting on quality control of the accelerator and (d) detection of fault within the accelerator. Finally, the roles of the technical team are (a) regular preventive treatment, (b) repair and maintenance, (c) providing technical advice to the operators of the accelerator and (d) operation of the heavy-ion medical accelerator.

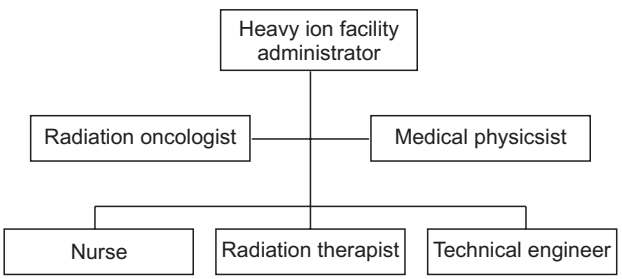

Fig. 1. Organizational chart for safe operation of radiation therapy system. Top-most box: Chief of heavy-ion medical treatment center, Second row – left: radiation oncology specialist, Second row – right: Medical practitioner (quality control personnel), Third row – left: Nurse, Third row – center: radiologic technician, Third row – right: Technician team (Engineers).

Discussion and Conclusion

Although it is difficult to opt for the introduction of heavy-ion medical treatment equipment due to the relatively expensive installation fee and cost of operation, preparations are being made for its installation in one of the facilities domestically, while a plan to construct

another one is under way as well.[32,37] As such, this study made an investigation into the current trends in the usage of heavy-ion accelerators, compiled 71 keywords relevant to the technology and suggested basic performance index, as well as some quality control criteria and reference values took potential future operation into consideration. However, it is hoped that the results suggested in this study, while recommended for use as a reference data for hospitals and other facilities planning to introduce heavy-ion accelerators, will be modified by the medical practitioner to formulate an optimum medical system that fits the needs of each facility or hospital. Also, it must be noted that this study does not explain about acceptance trial criteria, procedures and reference standard values, nor does it discuss any beam data criteria for treatment plan, procedures, acceptance trial and regular quality control of treatment plan that should be taken into consideration for choosing and efficient operation of a suitable radiation therapy treatment plan. Hence, a comprehensive guideline for radiation therapy treatment system based on heavy-ion medical accelerator technology must be completed after sufficient research on the acceptance trial and quality control of treatment plans for the medical equipment has been carried out. Also, for safe and efficient clinical operation of an enormous and complex system like a heavy-ion based medical equipment, sufficient number of medical practitioners must be secured, which would help to ameliorate the overall quality of patient treatment.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

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