REVIEW OF HADRON THERAPY ACCELERATORS WORLDWIDE AND FUTURE TRENDS

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Abstract

Hadron beams have attractive growing interest for cancer treatment owing to their high dose localization around the Bragg peak. Heavier-ions such carbon-ion beams, in particular, can realize higher 3D dose localization, compared with a proton beam, owing to a highly biological effect around the Bragg peak and a low multiple scattering effect. Recently, therefore, hadron cancer radiotherapy has been successfully growing in the world, based on the development of the accelerator and beam-delivery technologies.

INTRODUCTION

The foundations of hadron radiotherapy (RT) were laid in 1930 with the invention of the cyclotron by Ernest Lawrence, and in 1946 Robert Wilson proposed the clinical application of the cyclotron advocating the use of protons and heavier ions in treating human cancer [1]. The fundamental physics features of the hadron beams are their capability of depositing only relatively lower doses as the beam enters the body en route to the target (plateau region), the release of the greatest amount of energy at the end of the beam range (Bragg peak), and the deposition of a very low dose in the tail region beyond the Bragg peak. Pioneering work in hadron RT was commenced in 1950's at LBL (Lawrence Berkeley Laboratory) [2] and then the proton RT has begun in 1957 at the University of Uppsala [3], and in 1961 at MGH (Massachusetts General Hospital), using the 160 MeV/u-cyclotron [4]. Basic techniques used in hadron RT were developed in these facilities. Early clinical trials of hadron RT were conducted using accelerators for physics research. In 1990, on the other hand, the first hospital-based proton RT facility was commissioned at LLUMC (the Loma Linda University Medical Center) [5], and the first hospital-based heavy-ion facility, HIMAC [6], was constructed at NIRS (National Institute of Radiological Sciences) and has been conducted since 1994. Now many hospital-based hadron RT facilities are available worldwide [7]. Ions utilized for hadron RT are currently protons and carbon-ions, even though proton, helium, carbon, and neon were used in clinical application historically. So far, more than 70,000 patients have been treated with charged particle beams around the world, with more than 87% of these treatments being delivered with proton RT and about 8% with carbon ions. Up to 2010, there are 30 operating proton therapy facilities, while carbon-ion RT is provided at five facilities. More than 20 hospital-based facilities are under construction or are planning to be constructed within the next 10 years. Such growing the hadron RT has been based on the development of both the beam-delivery and accelerator technologies. This report reviews the hadron RT facilities in the world and the related development of accelerator and beam-delivery technologies.

BEAM-DELIVERY METHOD

The hadron RT has required a 3D uniform field with several % of the uniformity on a tumour, while dosage in normal tissue as low as possible. For the purpose, the beam-delivery methods have been developed.

Passive Beam-delivery Method

There are mainly two passive beam-delivery methods [8] to form an irradiation field matched with a tumour shape: Beam-wobbling method and double-scattering method. In the beam-wobbling method, a pair of beam-wobbling magnets rotates the beam in a circular orbit at high frequency so as to generate a pseudo-stationary broad beam in conjunction with a scatterer. A ridge filter spreads out the Bragg peak (SOBP) so as to match it with a thickness of tumour. A range shifter system inserts variable-thickness energy absorbers to adjust the beam range. A multi-leaf collimator (MLC) and/or a customized patient collimator define the field aperture. A bolus compensates the beam ranges so that the beam end of range conforms with the distal part of the target volume in the field. The double-scattering method has utilized two scatterers, instead of the wobbling magnets, in order to spread the beam laterally. The beam-wobbling method has advantages over the double-scatterer method in minimizing the material that might shorten the beam range. The conventional methods, as mentioned above, were improved to increase the irradiation accuracy. NIRS developed the layer-stacking method [9-11] in order to significantly reduce undesirable dosage to the normal tissue in front of target due to the fixed SOBP in the conventional beam-wobbling method. This method is to conform a variable SOBP to a target volume by controlling dynamically the conventional beam-modifying devices. The target volume is longitudinally divided into slices, and the small SOBP with several mm in WEL, which is produced by a single ridge filter, is longitudinally scanned over the target volume in a stepwise manner. Changing an aperture of the MLC dynamically, on the other hand, a lateral dose distribution of each slice is conformed according to a cross-sectional shape of each slice.

Active Beam-delivery Method

Pencil-beam 3D scanning is an active beam-delivery method to paint the dose distribution with a small beam and narrow Bragg peak, which allows us to take full advantage of the hadron beam. The pencil beam is laterally scanned so as to form a lateral irradiation field with orthogonal scanning magnets, and is then longitudinally scanned by either a range shifter or by stepwise energy change by the accelerator. NIRS carried out the first treatment with the scanning method in the world, which was two dimensional scanning with using a proton beam from cyclotron [12]. Several hadron RT facilities [13-15] developed the pencil-beam 3D scanning for the conformal irradiation.

Scanning for fixed target

GSI (Gesellschaft fur Schwerionen forschung) had carried out a pilot study of hadron RT in Germany from 1997 to 2009 [15], and developed a sophisticated 3D scanning method with synchrotron, which does not turn on/off the beam when spot position moves to the next one. In this scheme, further, the beam energy for slice change can be directly changed cycle-by-cycle of synchrotron operation. The GSI's scanning system, in addition, can change the beam profile and positions dynamically by the feedback system.

Scanning for moving target

It is difficult for the single paint by scanning to deliver a uniform dose distribution for moving target, although a beam-tracking method has been developed. NIRS, therefore, has developed a 3D rescanning method for both the fixed and moving targets. Especially for the moving target, the phase-controlled rescanning (PCR) method was developed [16]. In the PCR method, rescanning completes the irradiation of one slice during a single gated period corresponding to the phase between the end of expiration and the beginning of inspiration, because the organs are most stable during this gated period. The PCR method requires mainly two technologies: (1) Intensity-modulation technique for a constant irradiation time on each slice having a different cross-section. (2) Fast 3D scanning technique for completing several-times rescanning within a tolerable time. Essential technologies in this method are a treatment planning taken account of the extra dose when an irradiation spot moves, an extended flattop-operation of the HIMAC synchrotron to reduce dead time in synchrotron operation and high speed scanning magnets. They bring about 100 times faster 3D scanning compared with the conventional one. PSI has also developed the rescanning technology with cyclotron through fast scanning technique including fast energy change with a wedge energy degrader [17].

ACCELERATOR SYSTEM

The accelerator performance required for hadron RT depends strongly on the beam-delivery method. Therefore, the accelerator physics and engineering field has paid their efforts to develop the accelerator technologies for hadron RT, as well as the medical physics field.

Respiratory-gated Irradiation

Damage to normal tissues around tumour was inevitable in treatment of a tumour moving along with respiration of a patient. Therefore, a respiratory-gated irradiation system with the passive method was developed. In this system, the beam can be delivered according to the gate signal produced when the target is in the design position. University of Tsukuba developed the first respiratory-gated irradiation in the world with using rapid cycling synchrotron (KEK 500MeV proton synchrotron) that could extract the beam every 50 ms [18]. NIRS, on the other hand, developed the respiratory-gated irradiation [19] in slow cycling synchrotron. An essential technology in this scheme is the RF-KO slow extraction method [20], which can switch the beam on/off within 1 ms respond to respiration. For the respiratory-gated irradiation, on the other hand, some of cyclotrons have applied turning arc-voltage of an ion source on/off.

Variable Energy Operation

Even in the passive beam-delivery system, quick energy change is useful for an efficient operation. In the pencil-beam 3D scanning, variable energy operation by accelerator itself has great advantages over the range shifter method: keeping the spot size small and suppressing secondary neutron production. Since the cyclotron cannot change the energy within tolerable time, an energy-degrader system has been employed, which can select the ions degraded energy with a momentum slit (ESS: Energy Selection System). The energy degrader system in PSI, in particular, can change the energy corresponding to one slice change within 80 ms [17]. The synchrotron can change the energy within tolerable time. GSI developed the variable energy operation in cycle-by-cycle. In this case, it takes a few second of the operation cycle to change the energy for one slice change in the scanning method. Hitachi also developed the similar variable energy operation of the synchrotron for proton RT. NIRS is under developing the variable energy operation within one operation cycle of the HIMAC synchrotron, and it will take less than 100 ms to change a slice [21].

Beam Control

Spill structure control

The RF-KO method, which developed for the respiratory gate irradiation, has originally a huge ripple of kHz order in time structure of the extracted beam due to the coherency in its extraction mechanism. However, the huge spill ripple has never disturbed the dose distribution in the beam-wobbling method, because the wobbling frequency of 50-60 Hz is much difference from the ripple one. In the pencil-beam 3D scanning method, however, the spill ripple disturbs a dose distribution. NIRS, thus, improved the RF-KO slow extraction method [22] in order to significantly suppress the spill ripple. Further, NIRS also developed the method to suppress a fluctuation of Hz order in the time structure by optimizing AM function of the RF-KO system [23]. A beam-spill control system has been developed [24], based on the improvement of the time structure in the spill as mentioned above. Owing to this control system, the HIMAC synchrotron has given a low spill ripple and high reproducibility of the spill structure, which results in the fast treatment planning for the fast 3D scanning in HIMAC.

Intensity modulation

A dynamically intensity modulation has been required for the efficient scanning method. The synchrotron utilized the RF-KO method can easily control the extracted intensity by using the AM function. A typical intensity modulation using the spill controller of the HIMAC synchrotron is shown in Fig. 1. The COMET cyclotron at PSI (Paul Scherrer Institute) carries out the intensity control by using a vertical deflector installed in the central region.

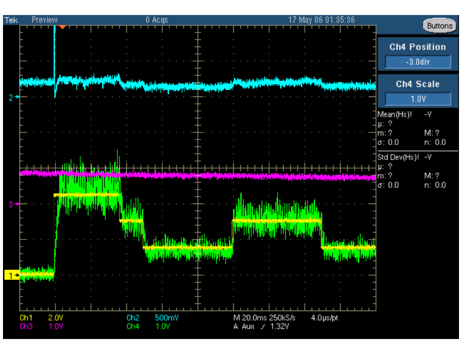

Figure 1. Time structure of extracted beam obtained by the spill control system. Spill time structure (green) can be modulated by request signal (yellow).

Control of beam profile and position

Tolerance of beam position at iso-center has been ±2.5 mm in the beam-wobbling method at HIMAC. In the pencil beam 3D scanning, on the other hand, the position error should be generally less than 1 mm. In order to deliver the beam with the desired profile and positions at a target, therefore, the HIMAC applied an accurate prediction method of the optical parameters at the extraction channel through an outgoing-separatrix estimated by a rod-monitor measurement [25]. Some of hadron RT facilities have employed a dynamically control of the beam profile and positions in the pencil-beam 3D scanning, based on the GSI development.

HADRON RT FACILITY IN THE WORLD

Carbon-ion RT Facility

In Asia, the operating carbon-ion RT facilities are HIMAC, HIBMC (Hyogo Ion Beam Medical Center), GHMC (Gunma University Heavy-ion Medical Center) and IMP (Institute of Modern Physics in China). HIMAC has treated more than 6,000 patients since 1994. HIBMC was constructed as a smaller version of HIMAC, and treated more than 600 patients per year using both proton and carbon-ion beams. On the basis of the design study and R&D works at NIRS, GHMC was constructed as a pilot facility for widespread-use of carbon-ion RT in Japan, and treatments has been successfully initiated since 2010. As shown in Fig. 2, further, NIRS constructed the new treatment research facility connected with the existing HIMAC accelerator complex and has successfully carried out treatments using the pencil-beam 3D rescanning, since May 2011. In Japan, Saga-HIMAT (Heavy-Ion Medical Accelerator in Tosu) project has constructed a carbon-ion RT facility and Kanagawa prefectural cancer center has been approved to construct the carbon-ion facility. They will apply both the broad-beam and pencil beam rescanning methods developed by NIRS.

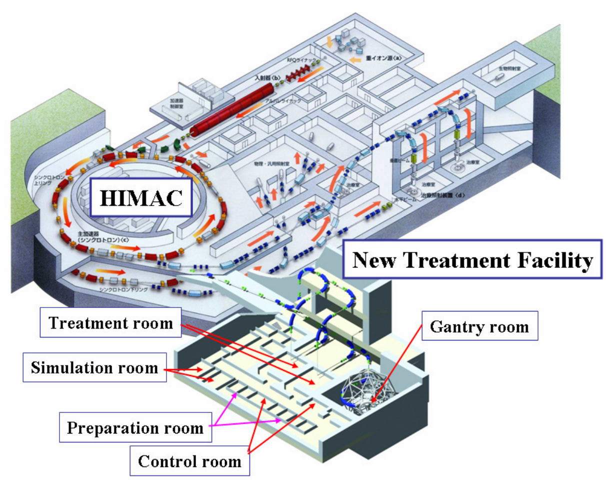

Figure 2. Layout of HIMAC and new treatment research facility. Treatments with the pencil-beam 3D rescanning have been successfully carried out at one fixed port room in the new treatment facility, since May 2011.

IMP in China has also carried out treatments for superficially-placed tumor using 100 Mev/u carbon-ions from cyclotron and those for deeply-seated tumor using 400 Mev/u carbon-ion from cooler synchrotron [26]. As a good result of its clinical study, the facility dedicated to carbon-ion RT has been constructed near IMP. Shanghai project has been also progressed, which has employed a similar machine with HIT facility. In Korea, the carbon-ion RT facility project, employing a superconducting cyclotron with 430 MeV/n, has been approved.

In Europe, on the basis of the GSI study, the HIT facility for both proton and carbon-ion RT was constructed at Heidelberg [27] in Germany, and the treatment has been successfully carried out since 2010. Fig. 3 shows the layout of the HIT facility. Similar machines are provided by Siemens to Marburg and Kiel projects. CNAO constructed a proton/carbon-ion RT facility in Pavia [28], and the beam commissioning has been carried out. Other projects are also going: The ETOILE project in France [29] has been progressed since 2006. The Med-Austron project [30] has designed a synchrotron based facility for both proton and carbon-ion RT, based on the modified PIMMS design. ARCHADE project [31] has designed superconducting carbon cyclotron, cooperating with IBA (Ion Beam Application). This cyclotron is designed to deliver 400 MeV/u carbon-ion and 250 MeV proton. INFL has also designed a superconducting cyclotron for both proton and carbon-ion RT [32]. Acceleration energy is 300 MeV/u for carbon-ion and 260 MeV for proton. In Italy, CABOTO (Carbon Booster for therapy in Oncology) [33] has been proposed, which the carbon-ions extracted from a cyclotron can be accelerated up to 435 MeV/u by 3 GHz linear accelerator with high repetition frequency of 400 Hz. Thus, this system will bring easily a variable energy operation.

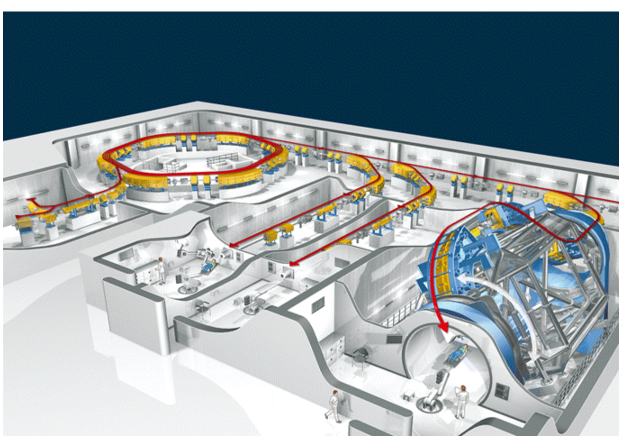

Figure 2. Layout of HIT facility. HIT facility consists of two ion sources, 7MeV/u injector, synchrotron with variable-energy operation and two horizontal fixed ports and one rotating gantry.

Proton RT Facility

LLUCM is the first accelerator facility dedicated to proton RT. Many proton RT facilities have been constructed and have been in service in the world. For example, MGH and PSI have employed an AVF cyclotron manufactured by IBA and a superconducting AVF cyclotron by Varian/ACCEL, respectively, and MDACC (MD Anderson Cancer Center) has employed a compact synchrotron manufactured by Hitachi. Among of them, we herein describe the cyclotron and synchrotron facilities in Japan.

NCCHE (National Cancer Center Hospital East in Japan) has carried out proton RT since 1998. The main accelerator is an AVF cyclotron manufactured by IBA and SHI (Sumitomo Heavy Industry). Since the cyclotron is operated at a fixed energy of 235MeV, the ESS is employed to change the energy. Two rotational gantries and one horizontal fixed port are installed in three different treatment rooms. The double-scattering method has been employed for one rotational gantry. In another rotating gantry system, the 3D scanning beam-delivery system has been installed instead of the beam-wobbling system.

PMRC (Proton Medical Research Center), University of Tsukuba, has carried out proton RT since 2001. The accelerator and beam-delivery systems were manufactured by Hitachi. The main accelerator is a compact synchrotron with a strong focusing function and with a circumference of 23 m. Output proton energy ranges from 70 to 250MeV. The rise and fall timing of the main magnet current can be triggered by external signals generated from the patient's respiration curve for an efficient respiratory gated irradiation. Two rotational gantries are routinely used for cancer treatment and one horizontal beam line for basic experiments. ON the basis of this synchrotron design, the accelerator system in MDACC proton RT facility was developed by Hitachi, which results in the variable energy operation cycle-by-cycle.

The accelerator system at SCC (Shizuoka Cancer Center), manufactured by Mitsubishi Electric Corporation, is also very compact and its diameter is 6 m. A weak-focusing synchrotron with edge focusing was chosen as the main accelerator in order to increase the proton intensity by suppressing the space-charge effect. The proton beam is delivered thorough the acceleration-driven extraction method. The beam-delivery system employs the beam-wobbling method. There are three treatment rooms, two equipped with rotating gantries and the third with a horizontal beam line.

DEVELOPMENT FOR FUTURE HADRON THERAPY

For future progress of hadron RT, the radiation therapy field has required the following development: 1) Adaptive cancer therapy, 2) Treatment with higher dose localization and 3) More compact and/or advanced machine.

1) Adaptive cancer therapy

For more precise treatment, we should precisely monitor a target movement for second order due to breathing and/or heartbeat and the shape and volume changes of target during several days and weak. The pencil-beam scanning is a powerful tool for a flexible treatment for the target change for several days, because it does not require a bolus and a customized collimator. Concerning the target movement, monitoring by X-ray has been proposed. However, this cannot easily three-dimensionally monitor the movement with high precision. If the precise 3D monitoring will be possible, a beam tracking with a pencil-beam 3D scanning will be a powerful method for a moving-target treatment.

2) Higher dose localization.

Higher dose localisation has been required to realize the shorter course treatment and/or the better treatment result by increasing dose on a target while decreasing on normal tissue. For the purpose, the multi-field optimization method, which utilizes the combining the pencil-beam 3D scanning with the rotating gantry, has been studied and developed. A biological adaptive therapy, furthermore, has proposed and studied. In this method, a higher dose is concentrated on more malignant part inside a tumor, while a lower dose on other part, because an organ with a low Oxygen concentration is much insensitive in radiation.

3) More compact and/or advanced machine

More compact and/or advanced machines have been required to reduce the construction running cost, which will result in boosting the hadron RT in the world. Therefore, various challenges are carried out in the accelerator and beam-physics fields. The laser ion acceleration has great advantages: Compactness owing to high acceleration gradient (~TeV/m) and very small volume size in 6D phase space [34]. Coherent acceleration of ions by laser is recently proposed, which utilises very thin target with nm-order thickness and high power laser. Its simulation study estimates to obtain 10^{12} protons/pulse with energy of 250 MeV and 10Hz under 10^{21} W/cm^2 of laser power, although this should be sufficiently confirmed by experiments. The Dielectric Wall Accelerator (DWA) [35], one of induction accelerators, has been studied, which employs a novel insulating beam tube to impress a longitudinal electric field on a bunch of charged particles. The DWA has a potential of high accelerating gradient on the order of 100 MV/m for accelerating pulses on the order of a nanosecond in duration. For proton RT, thus, the DWA, may be permitted to be installed on a rotating gantry. FFAG has been also developed, because of the simplicity of fixed magnetic fields rather than pulsed operation, potential for variable energy extraction and more simplicity of the cyclotron [36]. KEK designed and constructed the first ion-FFAG in the world, and its advanced one with proton 150 MeV is working at Kyoto University. Some institutes have developed FFAGs for hadron RT [37].

6. SUMMARY

More than 500,000 persons are diagnosed with cancer every year in Japan, and it is forecast that this number will continue to rise in the future. This trend is similar in the world. In such a situation, therefore, the hadron RT should be boosted up and will certainly play an important role in cancer therapy.

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