10th Int. Particle Accelerator Conf. IPAC2019, Melbourne, Australia JACoW Publishing
ISBN: 978-3-95450-208-0 doi:10.18429/JACoW-IPAC2019-THXPLS1

REVIEW OF ION THERAPY MACHINE AND FUTURE PERSPECTIVE

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Abstract

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

INTRODUCTION

The foundations of ion radiotherapy (RT) were laid in 1931 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 the proton and heavier ions in treating human cancer [1]. The fundamental physics features of the ion 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 the ion RT was commenced in 1950's at Lawrence Berkeley Laboratory (LBL) [2] and then the proton RT has begun in 1957 at the University of Uppsala [3], and in 1961 at Massachusetts General Hospital (MGH), using the 160 MeV/u-cyclotron [4]. Basic techniques used in ion RT were developed in these facilities. Early clinical trials of the ion RT were conducted using accelerators for physics research. In 1990, on the other hand, the first hospital-based proton RT facility was commissioned at the Loma Linda University Medical Center (LLUMC) [5]. The first hospital-based heavy-ion facility, Heavy-Ion Medical Accelerator in Chiba (HIMAC) [6] as shown in Figure 1, has been successfully conducted by National Institute of Radiological Sciences (NIRS) since 1994. Ion species utilized for the cancer RT are currently protons and carbon-ions, even though proton, helium, carbon, and neon-ions were used in clinical application historically. According to the Ref. [7], so far, more than 200,000 patients have been treated with the ion RT around the world, with around 86% of these treatments being delivered with the proton RT and about 14% with the carbon-ion RT. Up to 2019, there are 80 operating the proton RT facilities, while carbon-ion RT is provided at 13 facilities. Such growing the ion RT has been brought by a result of accumulating numbers of protocols based on developments of both the beam-delivery and accelerator technologies. For further development, NIRS starts "Quantum Scalpel" project toward a healthy long-living society with zero-cancer-death. This report reviews the developments of the ion RT machines in the world and describes future perspective.

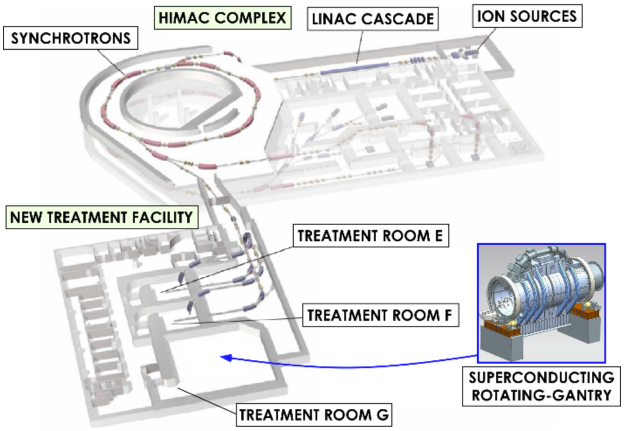

Figure 1: Layout of the HIMAC facility. The original HIMAC has been utilized for the carbon-ion RT since 1994. The new treatment research facility, as an annex, has been operated since 2011.

BEAM DELIVERY TECHNOLOGY

An ion beam extracted from an accelerator is delivered to a patient in a treatment room by a beam-delivery system. The beam-delivery system for the ion RT consists of beam modifying and monitoring devices to deliver a 3D uniform field on a tumour, while dosage in normal tissue as low as possible. The beam-delivery methods are categorised into the passive and active ones.

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 with 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 adjusts the beam range by inserting variable-thickness energy degrader. A multi-leaf collimator (MLC) and/or a customized patient collimator defines the field aperture. A bolus compensates the beam ranges so that the end of the beam 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.

In the conventional methods described above, a constant SOBP over the field area results in an undesirable dose to

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the normal tissue proximal to the target due to using the ridge filter. NIRS developed the layer-stacking method to suppress this undesirable dose [9-11]. 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 thin SOBP with several mm in water equivalent length (WEL), which is produced by a mini-ridge filter, is longitudinally scanned over the target volume in a stepwise manner. Changing an aperture of the MLC dynamically, in addition, a lateral dose distribution of each slice is conformed to a cross-sectional shape of each slice. Since 2005, HIMAC has routinely applied this method mainly for head & neck tumour treatments.

Active Beam-Delivery Method

A pencil-beam 3D scanning method paints the dose distribution with a small beam size and a narrow Bragg peak, which allows us to take full advantage of the ion RT. The pencil beam is laterally scanned so as to form a lateral irradiation field with orthogonal scanning magnets and is then longitudinally scanned by an energy degrader and/or by variable energy operation by an accelerator. Several ion RT facilities [12-14] developed the pencil-beam 3D scanning for the conformal irradiation.

Scanning for Fixed Target

Gesellschaft fur Schwerionen Forschung (GSI) had carried out a pilot study of the ion RT in Germany from 1997 to 2009 [14] 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 is directly changed by “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. On the basis of the developments by GSI, the Heidelberg Ion Therapy facility (HIT) [15] and Marburg Ion-Beam Therapy Center (MIT) [16] were constructed and has been successfully conducted.

Scanning for Moving Target

NIRS has developed a 3D rescanning method for treatments for both the fixed and moving tumours. Especially for the moving-tumour treatment, a phase-controlled rescanning (PCR) method was developed [17]. In this 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: Intensity-modulation technique for a constant irradiation time on each slice having a different cross-section [18] and 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. Paul Scherrer Institute (PSI) has also developed the rescanning technology with cyclotron [19].

ACCELERATOR TECHNOLOGY

The accelerator performance required for the ion RT depends strongly on the beam-delivery methods. Therefore, the accelerator physics and engineering field have paid their efforts to develop the accelerator technologies for the ion 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 both the passive and active methods 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 [20]. NIRS, on the other hand, developed the respiratory-gated irradiation [21] in slow cycling synchrotron. An essential technology in this scheme is the RF-KO slow extraction method [22], 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

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. Especially the 3D scanning with variable energy operation by accelerator itself has been very suitable for a paediatric cancer treatment. Since the cyclotron cannot change the energy within tolerable time, an energy degrader system has been employed. The energy degrader system in PSI, especially, can change the energy corresponding to one slice change within 80 ms [19]. 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, on the other hand, developed the variable energy operation within one operation cycle of the HIMAC synchrotron, which results in short slice-changing time with less than 100 ms [23]. The energy step is 200 in HIMAC.

Beam Control

The RF-KO method, which was developed for the respiratory gated 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 [24] 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 [25]. A beam-spill control system has been developed [18], 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 3D scanning in HIMAC. A dynamically intensity modulation was also developed for the efficient scanning method. The synchrotron utilized the RF-KO method can easily control the extracted intensity by using the AM function.

Rotating Gantry

A rotating gantry should be equipped in both the photon and ion RTs, because a treatment beam can be directed to a tumour from any of medically desirable directions, while a patient is kept in the best clinical position. The proton rotating gantry has been commercially available. However, it was very difficult to construct a rotating gantry for the carbon-ion RT, because the magnetic rigidity of a carbon-ion is higher by around three times than that for the proton RT under the same range. On the basis of the development by GSI, the HIT facility constructed the first heavy-ion rotating gantry in the world [15]. In order to realize compact-size, thus, NIRS developed an iso-centric carbon-ion rotating gantry with the superconducting technology [26]. This heavy-ion rotating gantry with the fast 3D scanning can delivered a carbon-ion beam with 430 MeV/u at maximum to an isocenter with irradiation angles of over ±180 degrees. An image figure is shown in Figure 1. The rotating gantry consists of ten combined-function superconducting magnets, a pair of the scanning magnets, and two pairs of beam profile-monitor and steering magnets, allowing a compact geometry - the length and the radius of the gantry are approximately 13 and 5.5 m, respectively. The weight is less than 300 ton.

In the 3D scanning with the rotating gantry, a beam-spot size, its shape and its ion distribution inside the spot delivered at the isocenter should be kept constant independently of the rotating angle. Therefore, NIRS proposed the compensation method of the asymmetric phase-space distribution for a slowly extracted beam from the synchrotron [27], which utilizes a multiple scattering through a thin foil set in a position having an optimized beta function along a transport line before the gantry entrance. Owing to this method, the rotation angle dependence of beam-spot size can be fairly eliminated. After the clinical test, the superconducting (SC) rotation gantry has been successfully utilized for routine treatment since 2018.

For further downsizing the rotating gantry, NIRS developed a compact 3D scanner, which can significantly shorten a SSD (Source-Surface Distance) from 9.0 m to 3.5 m, while keeping the field size of 24 cm ×24 cm. Features of the compact 3D-scanner are 1) changing gap of scanner along the beam direction, 2) X-Y combined type and 3) using high magnetic field. In a test of the compact 3D scanner, a good result was successfully obtained. This 3D scanner will be utilized for a rotating gantry Yamagata University project. Its weight will be around two-thirds of NIRS one.

QUANTUM SCALPEL PROJECT

The carbon-ion RT with HIMAC has brought promising results of cancer treatment: strong efficacy even for radio-resistive cancer treatment and short course treatment such as a single fractional treatment of lung cancer. It has been pointed out mainly two issues; 1) The carbon-ion RT has not been widespread use in the world due to both high construction and operation costs and 2) treatment results in some kinds of tumours are not satisfied. NIRS has progressed "Quantum Scalpel" project to overcome these issues. This project is developing an ultra-compact heavy-ions RT machine to reduce significantly both the construction and operation costs and to improve treatment results, especially in pancreas cancer, by a multi-ions irradiation method [28].

Ultra-compact Heavy-ion Machine

NIRS has studied a conceptual design of an ultra-compact heavy-ion machine with the superconducting and laser technologies. As shown in Figure 2, the size of the machine is very small;10 m ×20 m corresponding to two photon RT rooms, and this machine consists of a laser-acceleration injector with 4 MeV/u, a SC synchrotron ring with around 7 m in diameter and a SC rotating gantry. In a conceptual design, the SC synchrotron can accelerate ions with a charge-to-mass ratio of 1/2 from 56 to 430 MeV/u with an injection energy of 4 MeV/u.

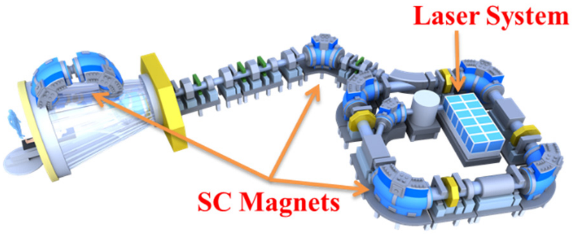

Figure 2: Layout of Quantum Scalpel. The size is 10 m × 20m corresponding to the size of two photon-RT rooms.

The dipole field of the main magnet of the synchrotron is designed to be 4 T at maximum over an effective area of ±55 mm (Horizontal) and ±17 mm (Vertical) with the field uniformity of $|\Delta B/B| < 1\times10^{-4}$. Further, the magnet has to provide the focusing quadrupole field with the maximum field gradient of 2 T/m over the same effective area. To obtain the above required magnetic fields, the super-conducting magnet is being designed to have a surface-winding

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coil structure, and both dipole and quadrupole superconducting coils are to be wounded on a mandrel so as to provide the required dipole and quadrupole fields. The field-change rate of around 1 T/s. The SC rotating gantry can be significantly downsized by a higher magnetic field of around 5 T and the compact 3D scanner.

Multi-ion Irradiation Method

In the HIMAC treatment with a carbon-ion beam, a biological-dose distribution, described as (Absorbed Dose: D) ×(Relative Biological Effectiveness: RBE), has been delivered to be uniform over a planning target volume (PTV), while the RBE and the oxygen enhancement ratio (OER) distributions have not yet been controlled. It is noted that the RBE increases with increasing the LET (< ~200 keV/µm) while the OER decreases with increasing the LET (~20 keV/µm < LET < ~200 keV/µm). When only carbon-ion beam is irradiated so as to deliver uniform D distribution on the PTV, both the D and LET distributions are shown in Figure 3. This irradiation scheme gives the higher RBE (higher LET) distribution around the boundary of PTV that is close to a normal tissue, because the Bragg-peak regions from various directions distributes around the PTV boundary. On the other hand, the lower RBE (lower LET) appears in the central region of the tumour. When a hypoxic state is in the central region of the tumour, a carbon-ion beam with the lower RBE might not be effective due to highly resistivity against radiation. In this case, the RBE close to normal tissue is higher than that of the central region of the PTV. Therefore, the clinical dose on the tumour cannot is sufficiently increased due to reducing significantly the dose on the normal tissue. In pancreas-cancer treatments for inoperable patients, it seems that the limited clinical dose on tumour causes the low five-years overall survival (OS) rate, in spite of the high two-years OS rate of around 60% with the carbon-ion RT.

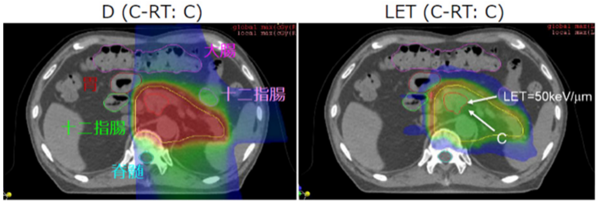

Figure 3: (a) Left: D distribution and (b) Right: LET one, when optimizing only carbon-ion irradiation to obtain uniform D distribution.

NIRS, therefore, has proposed a multi-ions irradiation method to control the RBE distribution over the PTV even when ion beams irradiate on the PTV from various directions. When both the D and LET distributions are optimized by using helium, carbon and oxygen-ions, they are shown in Figure 4 (a) and (b), respectively. Keeping the D distribution uniform as shown in Figure 4 (a), the LET distribution can be well controlled as shown in Figure 4 (b). The central region of the PTV is covered with the higher biological effect by oxygen-ion, the PTV boundary with the lower one with the helium-ion and the other region with middle one by carbon-ion. Combining a rotating gantry with 3D scanning, the multi-ions RT with the intensity modulated particle therapy (IMPT) [29] will bring much higher treatment efficacy.

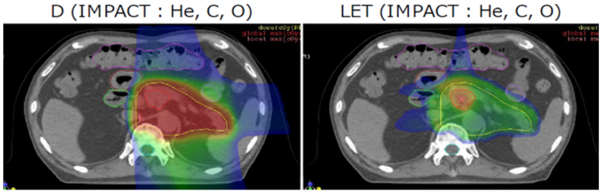

Figure 4: (a) Left: D distribution and (b) Right: LET one, when optimizing irradiations by helium-ion, carbon-ion and oxygen-ion.

NEW RBE CONTROLLED METHOD

Spatial distribution of energy deposited around ion tracks, namely 'track structure', strongly relates to the biological effectiveness of the ion beams [30, 31]. An external magnetic field may alter the track structure owing to deflections of secondary electrons, induced by the Lorentz force. Especially, a longitudinal magnetic field will more or less restrict the movements of the secondary electrons around the track center, and hence this would possibly result in the enhancement of cell-inactivation efficiency of the ion beams. For photons, it was pointed out such enhancement effects was negligibly small [32]. However, the microscopic energy distribution of ion beams is distinctly different from that of photons. Therefore, NIRS has carried out the biological experiments: various cells were exposed by carbon-ion beams under both longitudinal ($B_{//}$) and transverse ($B_{\perp}$) magnetic fields [33, 34].

In this study, human cancer and normal cell lines were exposed to low (12 keV/µm) and high LET (50 keV/µm) carbon-ion beams under $B_{//} = 0, 0.1, 0.2, 0.3$, or 0.6 T excited by a solenoid magnet. The effects of the magnetic fields on the RBE were evaluated by clonogenic cell survival. Doses that would result in a survival fraction of 10% (D_{10}) were determined for each cell line and magnetic field. Under the longitudinal magnetic field, for cancer cells exposed to the low/high-LET beams, D_{10} decreased from 5.2 /3.1 Gy at 0 T to 4.3/2.4 Gy at 0.1 T, while no further decrease in D_{10} was observed for the higher $B_{//}$. For normal cells, decreases in D_{10} of comparable magnitudes were observed by applying the magnetic fields. It is noted, on the other hand, that D_{10} is not significantly changed under the $B_{\perp}$.

Figure 5 (a) and (b), further, show survival rates for cancer cell and for normal cell with and without the $B_{//}$ of 0.6 T, respectively. As shown in Figure 5, D_{30} is decreased by around 30% with the $B_{\perp}$ of 0.6 T compared with that without the magnetic field. This means, surprisingly, that RBE is increased by 30% with the longitudinal magnetic field. In order to compare D_{30}s of various ion species with that with the longitudinal magnetic field, NIRS measured D_{30}s of cancer cell irradiated by helium, carbon, oxygen and neon-ion beams. The irradiation conditions are follows: the ions have the energies corresponding to the 15 cm WEL and cancer cells are irradiated by the low LET beams, because cells are emplaced at the beam entrance (entrance of Bragg curve). D_{30}s are shown in the Table 1. Considering the differences of D_{30}s in various ions from that in He-ion, it is found that the D_{30} change in carbon-ion irradiation under the longitudinal magnetic field of 0.6 T is equivalent to the D_{30} difference from helium-ion to oxygen-ion, which means the $B_{//}$ can enhance the RBE from helium-ion to oxygen-ion.

Table 1: D_{30}s and the Difference Between He-ion D_{30} and Other Ions D_{30}s

Ion Species	D_{30}	Difference
^{4}He	3.43 (Gy)	-
^{12}C	2.80 (Gy)	-18%
^{16}O	2.46 (Gy)	-28%
^{20}Ne	2.13 (Gy)	-38%

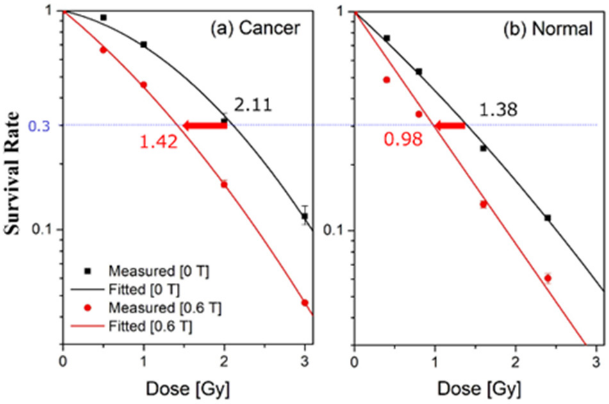

Figure 5: Variations of D_{30} with and without the longitudinal magnetic fields of 0.6 T. (a) Cancer and (b) Normal cells exposed by high LET (50 keV/μm) carbon-ion beam.

SUMMARY

Around 1,000,000 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, NIRS_QST starts the "Quantum Scalpel" project for a healthy long-living society with zero-cancer-death. For the purpose, NIRS has two strategies. The one is to control perfectly cancer including metastasis: The heavy-ions RT with controlling the RBE removes primary tumour, which keeps high quality of life and reserving immunity, and the targeted radioisotope therapy or the molecular target chemotherapy will be able to control metastatic and residual tumour. If necessary, the immunotherapy might support both. The another is to make the quantum scalpel widespread in the world though reducing significantly the construction and operation cost.

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