IOP Conf. Series: Journal of Physics: Conf. Series **860** (2017) 012027 doi:10.1088/1742-6596/860/1/012027

Overview summary of clinical heavier-ion progress in Japan

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Abstract. Swift ion beams such as carbon has unique characteristics suitable for treating deep-seated tumours. In Japan, carbon-ion radiotherapy was started in 1994 at Heavy Ion Medical Accelerator in Chiba (HIMAC) at National Institute of Radiological Sciences and more than 10,000 patients have been treated by Aug. 2016. Clinical outcomes show superior efficacy of carbon ions even against radioresistant tumour while keeping the quality of life at high level, and also the usefulness of hypofractionated irradiation down to the completion of the course of lung-cancer treatment in 1 day. During the decades, the improvement of hardware and software technology such as 3D scanning technique, superconducting rotating gantry or biology model have been carried out aiming at further optimized ion-beam radiotherapy as well as reducing the cost of the facility. The developed technology has been transferred to the following facilities. As of 2016, 5 carbon ion radiotherapy facilities are in operation in Japan.

1. Introduction

Elevating energy loss of ion beams traveling in a matter toward its range end, known as Bragg curve, is attractive characteristics when thinking about delivering dose locally to deep-seated tumour in a patient's body while sparing surrounding normal tissues. The characteristics gets more significant on heavier ions. In case of carbon ions for example, the straggling of the beam is reduced to be about 1/3 of proton beam at certain depth. This realizes more localized dose delivery specific to tumour. In addition to that, for ions in proximity to carbon, their RBE (relative biological effectiveness) gradually increases as the energy loss increases, *i.e.,* from entrance to the Bragg peak. This increase in RBE tends to enhance the peak-to-plateau ratio of the Bragg curve from biological viewpoint. Here, it should be noted that this peak-to-plateau ratio gets rather diminished in reversal for further heavier ions because of increasing frequency of projectile fragmentation and overkill effect. Therefore radiotherapy with certain ion species such as carbon (hereafter ion-beam RT or C-ion RT) is considered advantageous for therapeutic application as a method to achieve both high clinical effect on tumour and low toxicity on normal tissues at the same time.

However, in order to deliver carbon ions to 30 cm depth in water for example, it is necessary to accelerate the carbon ions up to about 400 MeV/n which is more than 70 % of the light speed. That is why though the original idea of the ion-beam RT was proposed by R. Wilson in 1940s, it was necessary to wait for the development of powerful accelerator to make it possible. The first ion-beam RT was accomplished by Lawrence Berkeley Laboratory (LBL) [1] with Bevatron synchrotron accelerator dedicated for physics study. When the pioneering clinical trials at the LBL came to the end in 1993, Japan and Germany ran with the ball respectively. In Japan, world's first accelerator dedicated to ion-beam RT, HIMAC (Heavy Ion Medical Accelerator in Chiba) [2], was established at the National Institute of Radiological Sciences (NIRS) in 1994. Soon after, German first experimental

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ion-beam RT facility was built at the Gesellschaft für Schwerionenforschung mbH (GSI) in Darmstadt and started clinical trials in 1997 [3]. As of 2016, 10 ion-beam facilities have been in operation in the world mainly in Asia and Europe. This paper introduces the progress of C-ion RT in Japan.

2. Outline of the HIMAC project

The project of HIMAC was started in 1984 under "Comprehensive 10-years Strategy for Cancer Control" lead by Government of Japan. The HIMAC project was aimed at establishing the optimum ion-beam RT modality. Figure 1 shows the bird's eye view of the HIMAC facility. The main synchrotron ring is doubled and can be operated independently. HIMAC has 3 treatment rooms (room A, B and C) in the building. Rooms A and C are equipped with one vertical or horizontal port, respectively while room B has both ports. In addition, experimental rooms for physics and biology are prepared and open for fundamental research with ion beams. HIMAC supplies only carbon ion beams to treatment rooms for therapeutic purpose in daytime, and various ion beams ranging from H to Xe up to 800 MeV/n for the experimental research in night time.

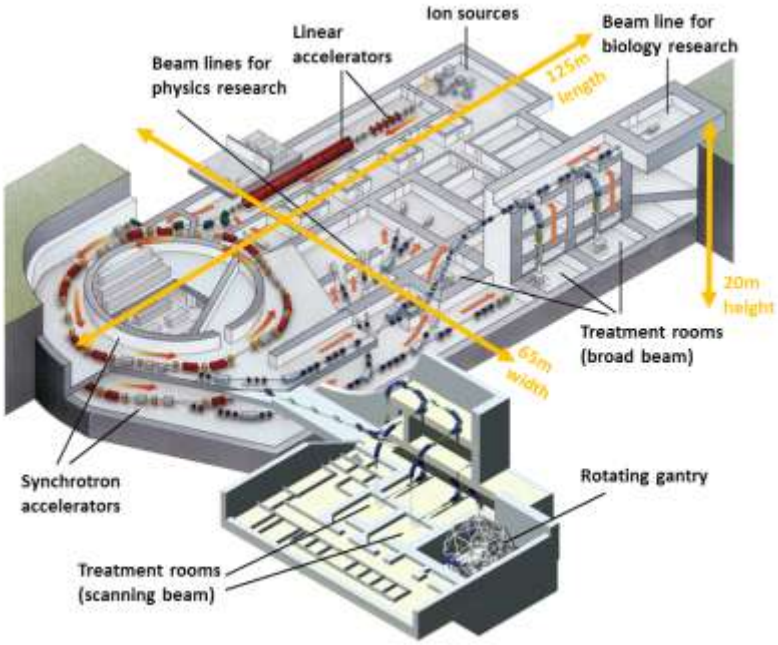


Figure 1. Bird's eye view of HIMAC facility.

Clinical trials of the C-ion RT was initiated in June of 1994. Figure 2 shows the annual accrual and patient distribution statistics treated at HIMAC as of March 2016. The first majority of patients treated so far is those suffered from prostate cancer, followed by those with solid tumours occurred at various sites. The annual number of treated patients gradually increases. In these days about 1,000 patients are treated annually and the total number exceeds 10,000 by August 2016. Most of clinical trials have been promoted to clinical practice by the approval by Government of Japan as the "advanced medical technology" in 2003. Under this category, 3.14 M JPY is charged per treatment. Since 2016, C-ion RT for inoperable bone and soft tissue sarcoma has been covered by Japanese national health insurance.

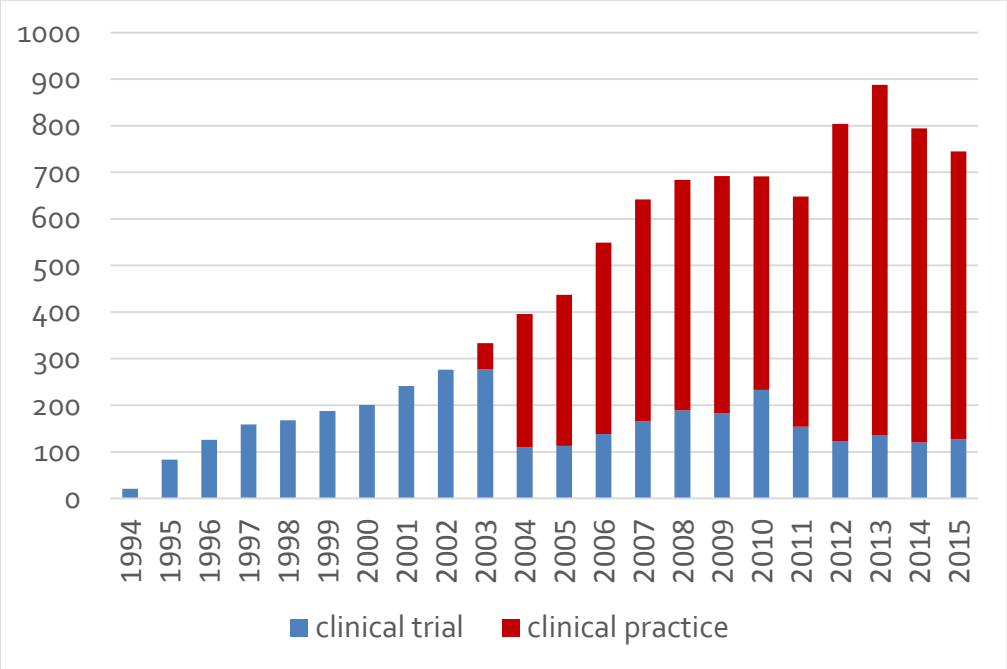


Figure 2. Annual accrual of patients treated at HIMAC in 1994 to 2015 (in fiscal year).

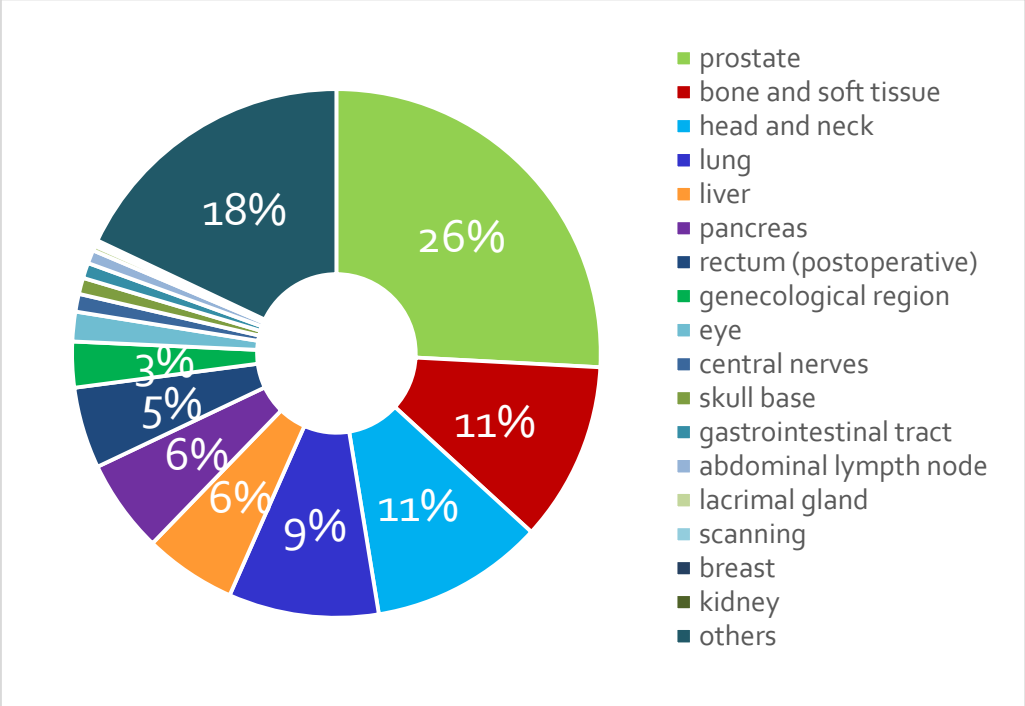


Figure 3. Distribution of patients treated at HIMAC by Feb. 2016.

One of the theme on clinical trials at HIMAC is to exploit the possibility of hypofractionation. In general, fractionated irradiation is preferred in radiotherapy as a method to spare normal tissue surrounding tumour by enhancing the difference in repair capacity between tumours and normal tissues. The reduction of the number of fractionation, hypofractionation, could be therefore regarded potentially hazardous. However, if hypofractionation can be performed in safe, it is beneficious for patient's reducing the burden. In case of C-ion RT, due to previously mentioned superior peak-to-

plateau ratio, dose deposited to normal tissue can be kept under tolerable limit even in hypofractionation scheme.

In each fraction schedule, dose escalation study was carried out in order to find the optimum dose level to prescribe by carefully observing the normal tissue response. In case of the most frequently-treated prostate cancer [4] for example, the number of fractionation was gradually reduced from 20 in 5 weeks at the beginning to 12 in 3 weeks. The ultimate is the non-small cell lung cancer treatment. The treatment with carbon ions was carried out in 18 fractions in 6 weeks at the beginning but now completed by successive 4 portal irradiations given within one hour [5]. Throughout these clinical experiences [6], it was confirmed that normal tissue response is tolerable in most cases and QOL (quality of life) after the treatment has been kept at high level even under hypofractionated irradiation.

3. Improvement of C-ion RT

While carrying out the C-ion RT routinely, HIMAC has been kept on updating as a research facility. A part of the hardware and software progress is introduced below.

3.1. Scanning beam delivery

The therapeutic ports of HIMAC was originally configured as a broad-beam irradiation method [7] to deliver the carbon-ion beam to entire tumour volume. In this method, a pencil-like beam extracted from the accelerator is at first circulated by a pair of dipole wobbler magnets. Then this ring-like beam passes through a thin metal foil as a scatterer inserted downstream of the wobbler magnets. Due to the scattering there, at the isocenter located about 10 m downstream from the scatterer, beam size is broadened up to 200 mm in diameter with uniformity better than 95 %. Regarding the axial direction, this dish-like beam is spread out up to 150 mm in water so that the spread out Bragg peak (SOBP) covers the maximum target thickness by passing through a ridge filter made of tapered aluminium blades lined in parallel. The resultant laterally and axially broadened beam is finally shaped by a patient collimator made of brass or a multileaf collimator made of iron, and a compensator made of polyethylene manufactured to match the beam to the cross section and distal plane of the individual target, respectively. The irradiation field shaped by the broad-beam method is characterized by the steadiness in time and space which is favourable especially treating tumours moving with respiration [8]. In case of lung or liver cancer treatment, the respiration phase is detected by a LED light attached to the patient, and the beam is delivered only at the expiration phase.

On the other hand, the rigid characteristic of the broad-beam method is disadvantageous from the viewpoint of flexibility. A few days of the leading time necessary for manufacturing the collimator or compensator makes it difficult to adapt to the change in tumour shape. In addition, due to the constant SOBP width irrespective to the difference in tumour thickness point by point, some portion of normal tissues inevitably receives full dose.

In order to overcome the problems, the development of the 3D scanning method [9] was started in 2007. In the method, the pencil-like beam extracted from the accelerator is directly delivered to appropriate position in the target. A pair of scanning magnets is used to control the lateral position while the axial stopping point is adjusted by the accelerator by changing the beam energy dynamically within one extraction phase from 430 MeV/n down to 56 MeV/n in 250 steps.

In general, it is regarded difficult to apply the scanning method for the irradiation to the moving target because the interplay between the scanning with narrow beam and target motion can spoil the dose uniformity easily. The 3D scanning technique developed at HIMAC tries to overcome this problem by a combination of gating and rescan feature [10]. The gating technique for scanning irradiation [11] has been updated from those used in the broad-beam irradiation. During the irradiation, the position of the target is frequently monitored on X-ray transmission image. The scanning irradiation takes place selectively when the target comes within a planned area in the expiration phase where the respiration motion is minimized. The small movement within the expiration phase is statistically smeared out by swiftly repeating the scanning irradiation for several times. In order to make the rescan possible, the scan speed reaches to 100 mm / 1 ms to the irradiation field size of 220 mm square.

The scanning irradiation ports have been installed to a vertical and horizontal port of newly built room E and F in an annex building in 2011. After pilot study successfully completed for 11 patients with stationary tumour, the scanning irradiation has been carried out even for moving tumour together with the broad-beam ports.

3.2. Rotating gantry

Currently all the irradiation ports in existing treatment rooms at HIMAC is fixed to either vertical or horizontal direction. Due to the limitation, sometimes a patient is tilted up to 20 degrees by a couch to deliver the beam from necessary direction. This can be a cause of uncomfortableness for the patient. Moreover, because positioning of the patient takes place for each portal irradiation, it is inevitable to position the patient again for multi-portal irradiation. The geometrical difference due to the deformation of the patient's organ by the repositioning makes it difficult to perform the intensity-modulated ion-beam RT, which is analogous to the intensity-modulated radiotherapy (IMRT) technique in X-ray RT and demands high precision and accuracy on the geometry of the target under current fixed port configuration. From the viewpoint, a rotating gantry for C-ion RT is under development at HIMAC [12]. The rotating gantry configuration is essential for the IMRT machine and getting popular even for proton therapy, however, challenging for C-ion RT due to the large Bρ value necessary for magnets to bend the therapeutic carbon-ion beam in a relativistic energy range. HIT (Heidelberg Ion Therapy Centre) [13] in Germany has realized the world's first rotating gantry applicable for C-ion RT. The huge construction has about 600 t of rotating weight with 20 m in diameter. The size of the gantry at HIMAC is reduced to be comparable to proton gantry, *i.e.*, 200 t in weight and 11 m in diameter by making use of compact superconducting magnets. Some of the magnets are designed as a hybrid of dipole and quadrupole in one magnet in order to further save the geometrical space. The 3D scanning technology is integrated to the rotating gantry. The gantry is under commissioning, and will be enrolled in C-ion RT by the end of 2016.

3.3. Biological model

It is requisite to estimate the changing RBE value of carbon ions quantitatively and precisely to conduct the C-ion RT effectively and safely. LET (linear energy transfer) has been widely used as an index of the radiation quality of the beam in estimating the RBE of radiation. In initiating the C-ion RT at HIMAC, the RBE value of human salivary gland (HSG) cells were chosen as the reference biological endpoint. The RBE value at 10 % clonogenic survival level of the HSG cells was experimentally studied by changing the LET of the carbon ions step by step. The derived dose-survival relationship at each LET was fitted with commonly-used LQ model $S=\exp(-\alpha D-\beta D^2)$ where S and D is the survival probability and the absorbed dose, respectively and α and β are the fitting parameters as a representative of the radiosensitivity for the beam. The derived α and β were tabulated as a function of LET and looked up in designing the ridge filter to form the SOBP beam [7].

This original approach was practically useful for estimating the RBE of therapeutic carbon-ion beams: in case of non-small cell lung cancer treatment for example, the clinical RBE values estimated by the model and verified with the clinical observation were both about 2.4 [14]. However, the model was not suitable for causal understanding between the incident radiation quality and observed radiosensitivity. From the viewpoint, the original model was updated to Microdosimetric Kinetic Model (MKM) [15] when starting the scanning irradiation at HIMAC. MKM was originally developed by Hawkins [16] as an update of microdosimetric dual radiation action theory [17]. The model starts with an energy imparted to a micrometre scale "domain". The number of lesions produced in the domain is associated with the energy deposition there, and the cell survival probability is given from Poisson statistics when none of the domains in a cell nucleus develop any single lesion. The final cell survival probability also shows the LQ dependency on the macroscopic absorbed dose while the parameter α can be interpreted with the microdosimetric energy information. MKM is tuned to harmonize with the original model [18] and now routinely utilized in a treatment planning system for both broad-beam and scanning irradiation [19].

4. Spreading of C-ion RT in Japan

Soon after HIMAC, Hyogo Ion Beam Medical Centre (HIBMC) [20] project was started. HIBMC offers both proton and C-ion RT in one machine first in the world since 2003 and 2004, respectively. In addition to the fixed vertical and horizontal ports, HIBMC has one 45 degree oblique port and two rotating gantries for proton beam in 4 treatment rooms in total.

Upon the superior clinical outcome of C-ion RT through the clinical trials and successive clinical practices at HIMAC, development of hospital-based compact C-ion RT machine by optimizing related technology developed at HIMAC was funded in the third decade of the cancer control strategy started in 2004 to spread this modality. In this framework, the GHMC (Gunma University Heavy Ion Medical Centre) project [21] was started in 2006. The accelerator ring was optimized solely for carbon ion beam up to 400 MeV/n, and matured broad-beam technique was adopted there. Together with additional optimizations and improvements, this compact model became about 1/3 of HIMAC in size and cost (33 G JPY to 12 G JPY). GHMC has been carried out C-ion RT since 2010. SAGA HIMAT (Saga Heavy Ion Medical Accelerator in Tosu) [22] also adopted the similar design and has started the clinical operation in 2013.

The newly developed techniques have been transferred to the successive facilities. i-ROCK [23], C-ion RT facility at Kanagawa Cancer Centre has started the C-ion RT in the end of 2015 with the respiratory gating 3D scanning technique. Ion-beam RT facility in Osaka is under construction for the open in 2018. The facility will be equipped with the scanning technique applicable for respiratory motion. The latest C-ion RT facility project at Yamagata University will open in 2019 with the superconducting rotating gantry with 3D scanning technique.

In order to accelerate the spreading further, study for further reduction of the facility cost has been in progress [24]. At the same time, cost-effectiveness analysis on C-ion RT has been in progress. The number of studies is still limited, however, the result is promising that C-ion RT can be superior to conventional modalities in the cost effectiveness, too [25].

5.Conclusion

C-ion RT has been carried out since 1994 in Japan. In more than two decades of experience, C-ion RT has been proven to be advantageous especially in treating radioresistant tumours such as bone and soft-tissue sarcoma, as well as in safely completing the course of the therapy even in short period as hypofractionation regime [26]. The high QOL and high clinical effectiveness of the C-ion RT will be advantageous in terms of cost effectiveness and contribute to sustainable development of the society. At the same time, research and development has been continuously carried out in order to further improve the ion-beam RT and further reduce the facility cost.

Acknowledgments

The Author wishes to acknowledge all the members at NIRS HIMAC.

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