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PRESENT STATUS AND FUTURE PROSPECT OF HEAVY ION RADIOTHERAPY

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Abstract

Heavy Ion Radiotherapy (HI-RT) is one of important applications of an electron cyclotron resonance ion source (ECRIS). At present, ten facilities are under operation and eight are under commissioning or construction. All of them utilize ECRISs for the production of carbon ions, mainly. Heavy ion radiotherapy has been approved to cover by the National Health Insurance in Japan since 2016. In April 2018, fees for treatment in Japan were revised to 1,600,000 Yen for 'prostate tumor' and 2,375,000 Yen for 'bone and soft tissue tumor' and 'head and neck tumor', respectively. The expectation of widespread use has accelerated sharply. There is no failure that disturbs daily treatment due to ECRISs in facilities. The ECRISs have effectively contributed to the stable operation of the present facilities. On the other hand, the cost reduction for a facility has been urged too. Laser ion acceleration has a potential to take over the role of ECRIS in the future. However ECRIS still has a scope of research and development to improve clinical dose distribution for intractable radioresistance tumors at present.

INTRODUCTION

In order to treat a deep-seated tumor with the good localized dose distributions, carbon ion was predicted as one of good candidates for heavy-ion radiotherapy by Rovert R. Willson even in 1946[1]. Based on physics, lighter ion species cause larger multiple scattering in the deep side, and heavier ion species give unexpected dose over the end-point due to projectile fragmentation. In addition, the biological dose distribution depends on the depth and thickness of a tumor. In the case of ten and several cm depth and several cm thickness, the linear energy transfer of neon ions is too high than that of carbon ions shown by Lawrence Berkeley Laboratory, University of California in 1980's[2]. Although heavier ions shows other biological advantages like oxygen enhancement ratio, the National Institute of Radiological Sciences (NIRS) chose carbon ions for the clinical trial at the Heavy-Ion Medical Accelerator in Chiba (HIMAC) [3] in 1994. Figure 1 shows biological depth-dose distributions of the Spread-Out Bragg Peak in the case of a depth of 16 cm and a thickness of 6 cm with different ion species. By HIMAC's success, the existing and almost all the planned heavy-ion radiotherapy (HI-RT) facilities require a carbon beam at present.

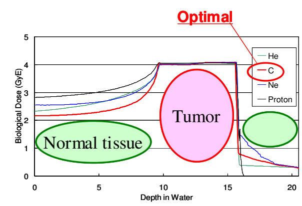

Figure 1: Biological depth-dose distributions of a 6cm Spread-Out Bragg Peak with a depth of 16cm.

The requirement of carbon-beam intensity strongly depends on the facility design, i.e. the volume and shape of the target, the efficiency of the irradiation method, the transmission of the accelerator complex and so on. In order to obtain the biological dose rate of 5 GyE/min. (it's roughly equals to a physical dose of 2 Gy/min.), a few 10^8 particles per second are required at a typical present facility. Long-term stability and reproducibility are important for daily treatment. On the other hand, the short-term stability of the ion sources is not so sensitive. Because the existing facilities consist of a synchrotron and any injector and the fine structure of the beam pulse will almost disappear during the acceleration in the synchrotron. Moreover easy operation and maintenance are also important to reduce the operation cost. An ion source should satisfy these requirements. An electron cyclotron resonance ion source (ECRIS) was expected to realize these requirements. The details and the history of the development of ECRISs have been described in Ref. [4]. As a result, ECRISs have been adopted at all existing carbon-ion radiotherapy (C-RT) facilities.

STATUS OF CARBON-ION RADIOTHERAPY

Clinical results

Clinical data of HIMAC have been accumulated under prescribed clinical protocols since 1994. All the clinical protocols and their results have been reported routinely through an authorities' committee. Since 2016, other Japanese C-RT facilities have gathered their data into a unified clinical database at the National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology (QST-NIRS, the former NIRS). At present, the total number of patients in Japan exceeded 20,000. The summaries for various diseases have clearly demonstrated the advantages of C-RT. There are three remarkable advantages of C-RT: lower toxicity, better local control and survival ratio, and shorter treatment period, the so-called Hypo-Fractionation.

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Regarding toxicities, from systematic phase-I/II dose-escalation studies for many kinds of diseases, the safe doses have been determined and irradiation techniques have been improved with the observation of no further severe side effects than have been already observed. The dose fractionations have also been determined as optimal in the same dose-escalation studies. Clinical results are evaluated by two measured clinical statistics, i.e. local control and survival ratios. Good local control ratios have been achieved for some intractable tumors, such as inoperable bone and soft tissue tumors, postoperative pelvic recurrence of rectal cancer, and so on. In these diseases, even if the case is operable, HI-RT gave a large benefit to prevent a great reduction of the organ function due to the resection and to keep the survival ratio comparable to that obtained by the resection. In addition, the benefit of HI-RT over other modalities has been demonstrated in terms of a significant reduction in overall treatment time with acceptable toxicities. Peripheral-type non-small-cell lung cancer has also been very effectively treated by low-LET RT, but usually low-LET RT must divide the dose into 20-30 fractions and a few months are needed for the treatment period. In the case of HI-RT, the number of fractions and treatment period were carefully reduced step by step from 18 fractions over 6 weeks to one single fraction, thus one-day treatment has been realized. The respiratory-gated irradiation method[5,6] for target organs with respiratory movement and multi-port irradiation from 3- or 4-field directions were utilized for all patients to reduce toxicities. For hepatocellular carcinoma, 2 fractions over 2 days have been adopted without severe side effects. Some recent clinical results have been described in Ref. [7-12].

Spread of Treatment

Under the Japanese health insurance system, a new medical technology should verify its effectiveness and safety with adequate evidence during its clinical trial. A goal of the technology is the approval to be covered by the Health Insurance. However, there is an Intermediate phase between the clinical trial and the Health Insurance, the so-called “advanced medicine.” In this phase, an equitable share and medical economy are carefully discussed. A hospital can ask a fee to patients. In 2003, the Japanese Ministry of Health, Labour and Welfare (MHLW) approved carbon ion radiotherapy as the “advanced medicine”. The Japanese government is promoting development of new downsizing technologies under “The 3rd Comprehensive 10-year Strategy for Cancer Control (2004 - 2013)”. NIRS designed a hospital-specified carbon ion radiotherapy facility and developed prototypes of various components. The feature of the design is an exhaustive optimization for treatment by carbon beams. This realized a cost-effective and sure facility’s design. The successful results of developed prototypes also certified manufacturing companies of the minimum business risks. Based on these results, MEXT funded the project of the Gunma University Heavy Ion Medical Center (GHMC) as a demonstration facility. GHMC has been successfully operated since March 2010[13]. The facility was approved as a commercial medical device by MHLW. At present, ten facilities are in operation and eight are under commissioning or construction worldwide shown in Table 1. Seven of eighteen are located in Japan as the result of the strategy.

Table 1: Carbon-Ion Radiotherapy Facilities Worldwide.

Institute / Hospital (Abbreviation)	**Location**	**Start year**
National Institute of Radiological Sciences (HIMAC)	Chiba (Japan)	1994
Hyogo Ion Beam Medical Center (HIBMC)	Tatsuno (Japan)	2002
Institute of Modern Physics (IMP)	Lanzhou (China)	2009
Hidelberg Ion Therapy Center (HIT)	Heidelberg (Germany)	2009
Gunma-University Heavy-Ion Medical Center (GHMC)	Maebashi (Japan)	2010
Centro Nazionale Adroterapia Oncologica (CNAO)	Pavia (Italy)	2012
Kyushu International Heavy-Ion Treatment Center (Saga HIMAT)	Tosu (Japan)	2013
Shanghai Proton and Heavy Ion Center (SPHIC)	Shanghai (China)	2014
Marburg Ion Therapy Center (MIT)	Marburg (Germany)	2015
Kanagawa Cancer Center (i-ROCK)	Yokohama (Japan)	2015
MedAustron	Wiener Neustadt (Austria)	-
Heavy Ion Therapy Facility in Wuwei (HITFiW)	Wuwei (China)	-
Osaka Heavy Ion Therapy Center (Osaka HIMAK)	Osaka (Japan)	-
Heavy Ion Therapy Facility in Lanzhou (HITFiL)	Lanzhou (China)	-
Yamagata University	Yamagata (Japan)	-
Korea Heavy Ion Medical Accelerator (KHIMA)	Busan (Korea)	-
Yonsei University	Seoul (Korea)	-
Taipei Veterans General Hospital	Taipei (Taiwan)	-

The most recent remarkable epoch of C-RT in Japan is that some of diseases have been approved to cover by the National Health Insurance since 2016. In 2016, ‘bone and soft tissue tumor’ has been approved. The Japanese National Health Insurance system is revised every two years. In April 2018, ‘prostate tumor’ and ‘head and neck tumor’

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have been added too. The medical expenses in Japan are also revised every two years. The technical fees for C-RT are 1,600,000 Japanese Yen (JPY) for a common cancer, 'prostate tumor,' and 2,375,000 JPY for rare cancers, 'bone and soft tissue tumor' and 'head and neck tumor', respectively. The 70 % of the fee is covered by the government. So that a patient should pay 480,000 JPY and 712,500 JPY, respectively. The fee for an aged patient is reduced less. In addition, the Japanese Government put limitations on a medical expense per month. A patient is also able to receive a support to an excess of the fee. The expectation of widespread use has accelerated sharply. The cost reduction for a facility has been urged. On the other hand, many diseases like 'lung tumor', 'pancreas tumor' and so on are still in the 'advanced medicine' phase. The fee of such diseases is 3,140,000 JPY and patients should pay all of it by themselves. The extension of diseases covered by the National Health Insurance has been urged too.

Contribution From ECRISs

The existed ECRISs have been successfully operated in heavy-ion radiotherapy facilities. GHMC, Saga HIMAT, i-ROCK, Osaka HIMAK, Yamagata, Seoul, and Taipei have been dedicated only for C-RT. These facilities have only one ECRIS due to the reduction of the initial construction cost and the maintenance expense. This means that a failure of the ECRIS causes a fatal trouble for treatment. A copy of a compact magnet ECRIS, Kei2[14], is installed in each facility[15]. Although small leak currents and discharges were observed in some facilities[16], these have been almost improved. There was no failure that disturbed daily treatment due to ECRISs in all facilities in 2017. In addition, the maintenance of the ECRISs become simple year by year. Some facilities put a longer interval for the maintenance than one year. The ECRISs have effectively contributed to the stable operation of the present C-RT facilities.

FUTURE PROSPECT OF HEAVY ION RADIOTHERAPY AND AN ECRIS

Downsizing of A Facility

From the point of view of cost reduction, it seems that a present facility is still too large for a hospital. The size of facility is roughly 3000 m^2 and its initial construction cost will be ten billion JPY. At present the ECR ion source mainly supplies C^{4+} ions. Increasing the charge state can help to reduce the cost of injector. The research and development for the higher charge-state production have been continued. However it is not expected to give a drastic cost reduction.

There is a limitation in the present acceleration principle with electrodes, therefore an innovation to change the existed accelerator structure has been considered. Laser ion acceleration is expected to overcome this limitation. It appears to be closer to realization than it was 10 years ago. QST has started a new 'Quantum Scalpel project' to develop the combination of a laser ion injector and a superconducting synchrotron for HI-RT. Its goal is to realize a facility with a size of 20 x 10 m[17]. It seems ECRISs will not have a place in the future.

Scope of ECRIS Development

On the other hand, laser ion acceleration is not easy technology and is still far from the practical use. A ECRIS should face current issues for the present HI-RT. One example of such issues is the production of multiple ion species. As mentioned in the Introduction section, the reason why NIRS chose carbon ions for treatment was the advantage of carbon ions for the better biological dose distribution shown in Fig. 1. However, this distribution depends on a depth and thickness of a tumor. For exam-ple, lighter ions like Li or Be show the better distribution for a deeper and thinner tumor. In addition, the biological effectiveness is varied on the area of the tumor in vivo due to various mechanisms like the oxygen enhancement effect[2]. In order to obtain the maximum effect on a tumor and the minimum effect on normal tissues, various figures of merits for ion species shown in Fig. 2 should be considered. As a conclusion, it's impossible to obtain the best clinical dose distribution with carbon ion only. Therefore the multiple ion-species irradiation has been planed recently. It is specifically a combination of the carbon irradiation, the irradiation to a radioresistant part located near the central part of tumor with a heavier ion which has a large biological effectiveness, and the irradia-tion to the environs of a critical organ with a lighter ion which reduce a toxicity[18].

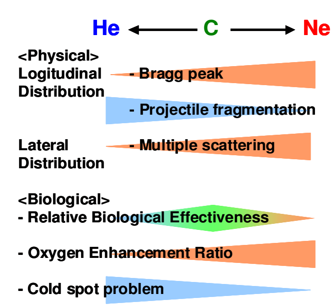

Figure 2: Various figures of merits for ion species.

This irradiation technique should be utilized with the respiratory-gated pencil-beam scanning technique. An injector system for a synchrotron should provide different ion beams sequentially. Although the scheme of the injector system has not been fixed yet, it is expected that one ECRIS produces all necessary ions with different acceleration voltages, instead of a set of multiple ion sources for each ions. This is a new challenge in the ECRIS's field.

SUMMARY

HI-RT has verified its effectiveness and safety and has reached to the National Health Insurance phase. The treatment fees have decreased to affordable price. The ECRISs have effectively contributed to the stable operation of facilities. ECRIS will be taken over its place by

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another technology in the future. However, ECRIS still has a scope of the present research and development to produce various ion species in order to improve clinical dose distribution for intractable radioresistant tumors.

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