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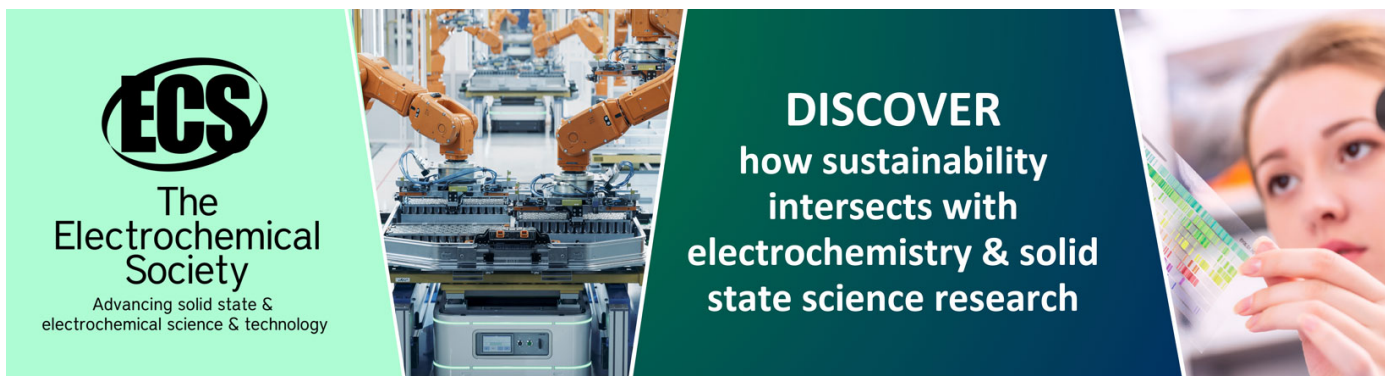
## Overview of Carbon-ion Radiotherapy

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# Overview of Carbon-ion Radiotherapy

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**Abstract.** The outcome of radiotherapy depends on potential efficiency of accelerators and their related accessories. In charged particle therapy before the 1990s, accelerators that were primarily installed for physics research had been shared, which however had limited flexibility for clinical use. Therapy-dedicated facility was first constructed at Loma Linda University for PBT in 1990 and at NIRS for CIRT in 1993. Currently, there are more than 56 facilities for PBT, 6 for CIRT, and 6 for PBT/CIRT, and even more facilities are under construction or active planning. CIRT has beneficial property for cancer therapy because, as compared with photon therapy, it offers superior dose distributions by exhibiting a Bragg peak in the body and, as compared with PBT, it has higher radiobiological effectiveness. The number of potential candidates for charged particle therapy is estimated to range from 0.018% to 0.035% of all irradiated cancer patients. In CIRT at NIRS, Japan, more than 9,000 patients have been treated with promising results in non-SCC tumors and photon-resistant types of tumors at various sites. It is of note that in CIRT a significant reduction in overall treatment time and fractions has been successfully achieved.

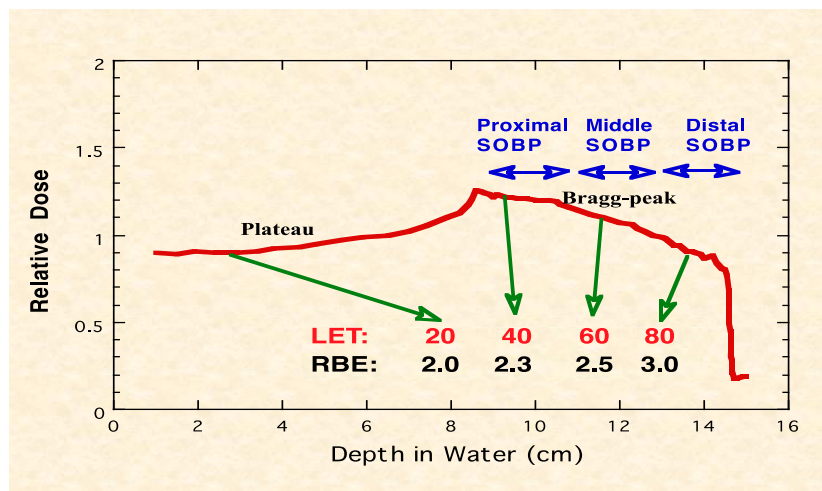
## 1. Introduction

The primary principle of radiotherapy lies on precise dose localization in the target volume with minimal damage to the surrounding normal tissues. This is particularly so when we notice the historical fact that the photon energy reaching the order of MV contributed significantly to improvement of treatment outcomes. In the 1950s, high-energy accelerators were developed and applied to clinical use, which marked the beginning of modern radiotherapy. In the late 20<sup>th</sup> century, high-tech radiotherapy such as IMRT and SBRT was developed and charged particle therapy such as proton beam therapy (PBT) and carbon-ion radiotherapy (CIRT) became popular in the world [1, 2].

## 2. Characteristics of carbon-ion beams

Among several types of ion beam therapy, CIRT has gained a strong interest because they exhibit Bragg peak in the body, enabling delivery of sufficient dose within a target volume and less dose to the surrounding normal tissues. In addition, carbon-ions being heavier than protons provide a higher radiobiological effectiveness (RBE), which increases with depth to reach the maximum at the end of beam's range [3]. This property is extremely advantageous from the therapeutic point of view, as the RBE of carbon ion beams also increases as they advance deeper to the tumor-lying region. The RBE ranges from 2.3 to 3.0 along the SOBP for skin reactions (Fig. 1).





**Figure 1.** LET and RBE of carbon-ion beams (290MeV, SOBP=60mm).

### 3. History of particle beam therapy

Historically, the world-first clinical application of particle beams was fast neutron radiotherapy, which started on September 28, 1938 at the Lawrence Berkeley National Laboratory (LBNL), USA. In the late 1970s, this therapy reached its peak in Europe, USA and Japan, and its effectiveness was reported in non-squamous cell tumors and bone/soft-tissue sarcomas. Despite the favourable local control in these tumors, however, fast neutron therapy caused severe late reactions, which eventually led all institutions abandon the therapy. Pi mesons can be generated by collision of high-energy protons or electrons with nucleons in the target. When delivering these elemental particles to the body, they are captured by the medium nucleus at the end of flight path, releasing short-range ions (star production), a mixture of low- to high-LET components. Pi meson radiotherapy was highly expected for its clinical effectiveness and three institutions in the USA, Canada and Switzerland conducted this therapy in the 1980s. However, the clinical outcome was not satisfactory and the clinical research was eventually discontinued. The last institution closed in 1994.

The LBNL pioneered the medical application of proton beams in 1954. Since then, PBT has been increasingly popular in the world. The success of PBT primarily lies on its superior dose distribution so that the definitive dose can be safely delivered with limited toxicities. The same team at LBNL then embarked on helium ions in 1957 and neon ions in 1975 [4]. The Berkeley however terminated all radiotherapy programs in 1992. As if the baton was passed across the Pacific, the NIRS started CIRT in 1994, followed by GSI in 1997 and thereafter by other facilities.

### 4. Facilities for charged particle therapy

As with the end of 2015, there 56 facilities for PBT and 12 facilities for CIRT including 6 facilities for CIRT alone and 6 facilities for both CIRT and PBT [2]. In addition, 4 new facilities are constructing carbon therapy centers (Japan 2, China 1, Korea 1).

CIRT was initiated in 1994 at NIRS using the world-first accelerator complex (HIMAC: Heavy Ion Medical Accelerator in Chiba) dedicated to cancer therapy. Following HIMAC, Gesellschaft für Schwerionenforschung (GSI) in Germany started CIRT in 1997, which was succeeded in 2009 by the proton/carbon center, the Heidelberg Ion-Beam Therapy Center (HIT). Marburg University also started proton/carbon therapy in 2015. Hyogo Ion Beam Medical Center (HIBMC) in Japan was the first proton/carbon center established in 2001. The Institute of Modern Physics (IMP), China, started clinical trials in 2006. The IMP constructed a carbon center in Wuwei and is also constructing a new center near the yellow river. Based on technological development at NIRS, a downsized carbon facilities were realized at Gunma University Heavy Ion Medical Center (GHMC), SAGA Heavy Ion Medical Accelerator in Tosu (SAGA HIMAT) and Kanagawa Cancer Center (iROCK). Each of them started CIRT in 2010, 2013 and 2015, respectively. At the National Centre of Oncological Hadrontherapy

(CNAO), Italy, the accelerator complex was completed for proton/carbon treatment in 2011. In the summer of 2014, Shanghai Proton Heavy Ion Center (SPHIC), China, started clinical application of proton/carbon beams. MedAustron in Austria will start clinical study in 2016. Two institutions are under construction for CIRT in Yamagata and Osaka in Japan.

Regarding the status of charged particle therapy in the United States, there are around 23 facilities for PBT but none for CIRT. However, the NCI recently issued two calls for P20 exploratory grant applications for Planning for a National Center for Particle Beam Radiation Therapy Research. In this framework, the NCI awards will support planning for establishment of a Center for charged particle therapy as a national research resource, as well as the DOE awards will address development of improved hardware that could shrink the size, increase the maneuverability, and considerably reduce the steep costs of charged particle therapy equipments. In the spring of 2015, the NCI awarded University of Texas Southwestern Medical Center (UTSW) in Dallas and Particle Therapy Research Group of UCSF in San Francisco a planning grant to develop research proposal for the center. They have decided to establish a heavy ion therapy center and started collaboration with NIRS, CNAO and HIT. The UTSW has already started a UTSW Master Plan for a PBT/CIRT center to be built in their campus. UCSF organized the North American Particle Therapy Alliance (NAPTA) to start the feasibility study for charged particle therapy including CIRT.

### 5. Potential indications for charged particle radiotherapy

In treatment of histologically radio-resistant and locally advanced tumors, treatment outcome has been improved with high-LET radiations like carbon ions. In CIRT the very sharp lateral fall-off is particularly beneficial, as critical organs next to the tumor are effectively spared from excessive radiation dose. According to PTCOG statistics, a total of 154,097 patients were treated with charged particle therapy in the world from 1954 to December 2015, of which 131,134(85.1%) were treated with protons and 193,76(12.6%) with carbon ions. The selection of patients for CIRT is primarily based on the following 4 clinical criteria: 1) loco-regional tumor growth, 2) tumor with no or low tendency to metastasize, 3) tumor that is highly resistant to conventional radiotherapy, and 4) either cure rates are low or side effects with standard therapy are unacceptably high.

**Table 1. How many patients need particle beam therapy?**

Author	Country	Population (a)	Annual number of patients treated with RT (b)	Patients eligible for charge particle therapy per year		
				% of pats in RT pats (c)	No. pats bxc/100 (d)	% d/ax100
Bengt (2005)	Sweden	9,593,000	16,000	14~15%	2,200~2,500	0.024%
Orecchia (1998)	Italy	59,830,000	-	-	11,000	0.018%
Baron (2004)	France	66,030,000	158,620	14.5%	23,000	0.035%
Mayer (2004)	Austria	8,474,000	15,132	13.5%	2,043	0.024%
Mella (2013)	Norway	5,100,000	16,000~19,000	7~8%	1,100~1,500	0.025%
Tsujii (2016)	Japan	127,300,000	201,000	14.9%	30,000	0.024%

There have been several studies investigating the potential number of cancer patients that could benefit from charged particle therapy. Using domestic and overseas cancer statistics for incidence and trend of treatment, we have made a strict estimation regarding the number of potential candidates for charged particle therapy, which ranged from 13% to 15% of all irradiated cancer patients. In Japan, the total number of the patients treated with radiotherapy was 201,000 in 2009, of which approximately 30,000 patients or 14.9% was estimated to benefit from charged particle therapy. The absolute number of the

patients suitable for charged particle therapy should vary according to the total number of cancer patients and is estimated to range from 0.018% to 0.035% of the population in each country (Table 1).

## 6. Clinical results of carbon-ion radiotherapy

Since 1994, CIRT has been conducted at the National Institute of Radiological Sciences (NIRS; Chiba, Japan), where more than 9,000 patients with various types of tumors have been treated. In other CIRT facilities in the world, the number of the patients has rapidly increased totalling more than 15,000 patients. Latest experiences on CIRT has indicated improved results in: non-SCC type of head and neck cancer; bone/soft tissue sarcoma arising from the skull base, head-and-neck, spine and pelvis; locally advanced large tumors at various sites; intermediate to high-risk prostate cancer; pelvic recurrence of rectal cancer; and locally advanced unresectable pancreatic cancer (LAUPC) [5]. Among them, the results of CIRT for LAUPC were promising and caused worldwide interest in conducting a comparative study on this tumor. Accordingly, even a randomized Phase 3 trial on “Carbon Ion versus Photon Therapy for Pancreatic Cancer” has been proposed [6].

Experiments with fast neutron beams as well as carbon-ion beams have demonstrated that increasing the dose per fraction tended to lower the RBE for both tumor and normal tissues, but the RBE for the tumor did not decrease as rapidly as the RBE for normal tissues [7]. Accordingly, in CIRT at NIRS a significant reduction in overall treatment time and fractions has been obtained with minor toxicities, such as single-fraction RT for early-stage lung cancer, single or two-fraction RT for liver cancer and 12-fraction RT for prostate cancer. Also for other tumors, 16 or even smaller fractions have been sufficient. This means that CIRT can be performed more efficiently than PBT, permitting treatment for a larger number of patients than is possible with PBT over the same period of time. Further reducing the number of fractions would increase cost-utility and patient throughput, thereby facilitating the use of CIRT for more patients and in more centers.

## 7. References

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