RELATIVISTIC ION BEAMS FOR TREATING HUMAN CANCER*

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Abstract

At EO Lawrence Berkeley National Laboratory, clinical trials were conducted (1975-1992) for treating human cancer using ion beams from the Bevalac and treated about 700 patients with helium-ion and about 300 patients with neon-ion beams [1]. Clinical trials (1997-2005) at GSI in Darmstadt, Germany used carbon-ion beams to treat about 250 patients. In 1994, NIRS in Chiba, Japan, commissioned its ion-beam therapy facility, HIMAC, which accelerates ions as heavy as argon nuclei to 800 MeV/μ. Following it, several carbon-ion therapy facilities have been, or will be soon, constructed in: Hyogo (2001) and Gunma (2010), Japan; Heidelberg (2009), Marburg (2010) and Keal (2012), Germany; Pavia (2010), Italy; Lyon (2013), France; Wiener Neustadt (2013), Austria; Shanghai and Lanzhou, China; and Minnesota and California, USA. Technical specifications of these facilities are: ion sources delivering all ion species from proton to carbon, accelerator energy of 430 MeV/n (30-cm range in tissue), beam intensity of about 10^9 pps (to deliver 1 Gy/min into 1-liter volume), repetition rate of about 0.5 Hz with long spill (for beam scanning), and treatment beam delivery and patient safety systems.

INTRODUCTION

In 1948, E.O. Lawrence completed construction of the 184-inch Synchrocyclotron at the University of California at Berkeley, making possible the acceleration of protons, deuterons and helium nuclei to energies of several hundred MeV per nucleon. Realizing the advantages of delivering a larger dose in the Bragg peak when placed inside deep-seated tumors, Robert Wilson published his seminal paper on the rationale of using accelerated protons and light ions for treatment of human cancer [2]. These particle beams promised higher cure rates with fewer complications, as they would deliver tumor-killing doses more precisely, therefore lowering doses to normal tissues adjacent to the treatment volume compared to those in conventional (photon) treatments. In 1954, Cornelius Tobias and John Lawrence performed the first therapeutic exposure of human patients to ion (deuteron and helium ion) beams [3]. Soon after, programs of proton radiation treatments had opened in proton accelerators, which were originally constructed for nuclear physics research, in: Uppsala, Sweden (1957), Cambridge, Massachusetts (1961), Dubna (1967), Moscow (1969) and St Petersburg (1975) in Russia. Chiba (1979) and Tsukuba (1983) in Japan; and Villigen, Switzerland (1984) [4]. The first hospital-based proton facility was commissioned at the Loma Linda University Medical Center in 1990; and many industry-built proton therapy facilities became operational in hospitals around the world.

In the 1950s, LBNL constructed the Bevatron, a 6-GeV synchrotron, which by the early 1970s accelerated ions with atomic numbers between 6 and 18, at energies that permitted the initiation of radiological physics and biological studies [5]. In the 1970s LBNL established the Bevalac accelerator complex, in which the SuperHILAC (Heavy Ion Linac) was used to inject heavier ion beams into the Bevatron for acceleration to energies up to 2.1 GeV per nucleon. The Bevalac, producing high intensities of protons and other light ions with sufficient energy to penetrate the human body, expanded the opportunity for medical studies for treatment of deep-seated diseases.

Ion beams combine superior physical and biological characteristics for effective cancer therapy. The superior physical characteristics are: higher "linear energy transfer" (LET, which stands for the radiation energy deposited per unit length in tissue. X-rays and proton beams are low-LET radiation, whereas carbon-ion beams are high-LET radiation) in Bragg peaks, smaller multiple scattering (narrower lateral penumbrae), and smaller energy straggling (steeper distal dose falloffs). And advantageous biological characteristics are: higher LET, elevated "relative biological effectiveness" (RBE) of high-LET radiation, and lower "oxygen enhancement ratio" (OER). Light-ion beams have demonstrated their superior tumor eradicating ability. Subsequent results of research at the 184-Inch Synchrocyclotron and the Bevalac in physics, biology and medicine of light-ion therapy were summarized in an LBNL report [6].

J.R. Castro, of UC San Francisco, and his team conducted clinical trials for treating human cancer using the spread-out Bragg peak of light ion beams at the 184-inch Synchrocyclotron and the Bevalac from 1975 to 1992, before the accelerators were closed [1]. Ions of interest ranged from ^{4}He to ^{28}Si; ^{20}Ne was most commonly used. The numbers of patients treated on NCOG/RTOG protocols in the NCI and DOE supported trials were ~700 patients with helium ion beams and ~300 patients with neon-ion beams. The patients treated with helium ions included primary skull-base tumors: chondrosarcomas, chordomas, meningiomas, etc. The patients treated during 1987-1992 showed increased local control, representing the influence not only of the superior physical characteristics of the ion beams, but also the improved immobilization, treatment planning and availability of MRI for target visualiztion. Using ^{20}Ne ions, they also treated, and obtained excellent 5-year local control of lesions arising from paranasal sinuses, nasopharynx or salivary glands, and extending into the skull base.

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CARBON IONS VS. PROTONS FOR CANCER TREATMENT

Carbon ions have distinct advantages relative to both photons and protons: Carbon ion beams deliver higher dose to tumors than photon or proton beams could, with less effects on surrounding normal tissues. Furthermore, they have an increased RBE in eradicating hitherto difficult-to-treat tumors, even using proton beams. These particular characteristics have been exploited in the clinic to obtain excellent cure rates in many different tumors.[‡] In these cancers, carbon-ion therapy produced a significant reduction of the tumors in all patients without any significant recurrences.

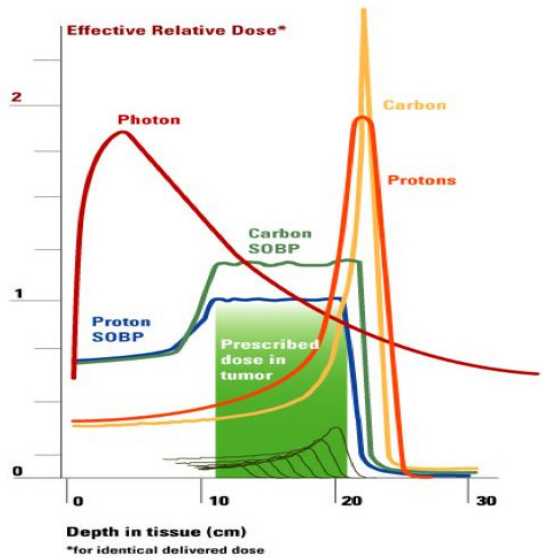

Figure 1: The particle beam is modulated to adjust the position of Bragg peak to form a Spread-Out Bragg Peak (SOBP). The relative doses of the SOBP of proton and carbon ion beams as a function of penetration depth in water are compared with that of a photon beam. The doses are normalized to the dose at the entrance to the body. For equal target dose, carbon beams exhibit the lowest entrance dose among the three beams.

The therapeutic advantage of light ions versus protons stems from three decisively superior characteristics: light-ion beams deliver higher cure rates of cancer, cause fewer complications, require fewer patient visits, and increase patient throughput of the facility. Specifically–

(i) Compared with proton beams, light-ion beams produce higher dose conformation to the tumor volume (Fig. 1). As the sparing of the surrounding healthy tissues from unwanted radiation is increased, higher therapeutic doses can be placed in the tumor, producing higher cure rates with fewer complications.

(ii) Many recurrences of tumors following radiation treatment come from the re-growth of hypoxic tumor cells (cells that have "outgrown" their blood supply and are thus oxygen starved). They are radioresistant to x-rays and protons. Light-ion beams, which have higher LET, are more efficient in killing anoxic tumor cells and significantly lower the chance of tumor recurrence.

(iii) Proton-beam treatments are usually delivered 4 or 5 times per week over 7-8 weeks (in 28-32 fractions). Safe and effective light-ion beam treatments are delivered in fewer fraction numbers, such as 8-12, or possibly less for some tumor sites, perhaps as low as 1-4 fractions. This allows higher patient throughput in an ion-beam facility, which lowers the cost of treatment and enhances patient comfort.

Therapy plans for carbon-ion beam and photon beam treatments are shown in Fig. 2, which demonstrates the superiority of single beam of carbon-ions over the most advanced photon treatment, IMRT (Intensity Modulated Radiation Therapy), which uses multiple beams.

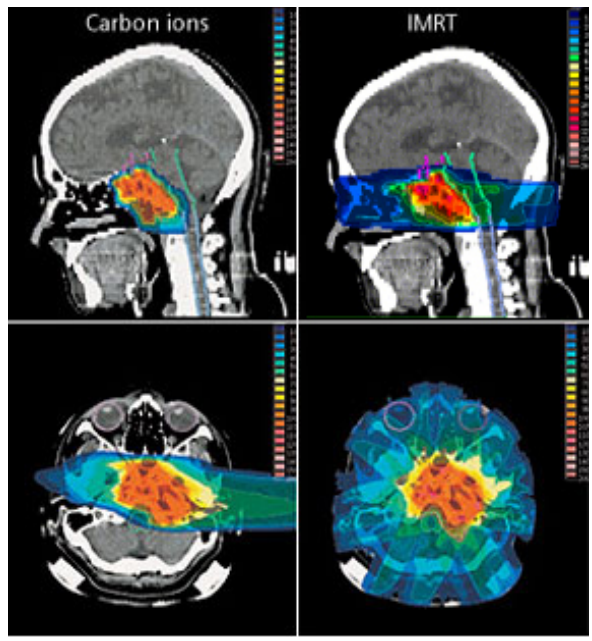

Figure 2: Left panels show a therapy plan for treating a head-and-neck tumor using one carbon ion beam. For comparison, right panels show a therapy plan for treating the same tumor using most advanced photon treatment, IMRT that employs multiple beams. (Based on a publication of Heidelberg University, Dept. Clinical Radiology and German Cancer Research Center.)

As high-dose 3D-conformal treatment has become the clearly accepted objective of radiation oncology, clinical trials using proton and ion-beams are concurrently and methodically pursued. Protons with relatively low values of LET have been demonstrated to be beneficial for high-dose local treatment of many of solid tumors, and have reached a high degree of general acceptance after more than six decades of treating over 60,000 patients by the end of 2009. However, some 15% to 20% of tumor types

[‡] Such as Stage-I non-small cell lung cancers, sacral chordomas, rectal cancers, liver cancers, as well as relatively radioresistant tumors such as chordomas and low-grade chondrosarcomas of the skull base, adenoid cystic carcinomas and malignant meningiomas. See Ref. [1].

have shown resistant to even the most high-dose low-LET irradiation. For these radio-resistant tumors, treatment with ions (e.g., carbon) offers great potential benefit. These high-LET particles offer the unique combination of excellent 3D-dose distribution and increased LET values, to eradicate tumor cells while reducing the effects of unwanted radiation in adjacent healthy tissues [7].

CLINICAL REQUIREMENTS OF AN ION-BEM THERAPY FACILITY

Table 1 shows a list of clinical requirements, which was prepared jointly by LBL/UCDavis-MGH in 1992 for the construction of proton therapy facilities [8]. The first proton facility built according to these clinical requirements by industry was the MGH's Francis H. Burr Proton Therapy Center; and many subsequently-built facilities followed the suit.

Table 1: Clinical Requirements of Proton Therapy Facility

Item	Clinical Requirements
Range in Patient	3.5 – 32 g/cm^2
Range Modulation	Steps of 0.5 g/ cm^2 over full depth 0.2 g/ cm^2 for ranges < 5 g/ cm^2
Range Adjustment	Steps of 0.1 g/ cm^2 0.05 g/ cm^2 for ranges < 5 g/ cm^2
Average Dose Rate	2 Gy/min for 25 x 25 cm^2 field at 32 g/cm^2 full modulation
Spill Structure	Scanning compatible
Field Size (cm^2)	Fixed: 40 x 40; Gantry: 26 x 20
Dose Compliance	±2.5% over treatment field
Effective SAD	Scattering: 3 m from the first scatterer Scan: 2.6 m from the center of magnet
Distal Dose Falloff (80–20%)	0.1 g/ cm^2 above range straggling
Lateral Penumbra (80–20%)	<2 mm over penumbra due to multiple scattering in patient
Dose Accuracy	±2%

Based on these clinical requirements, a report on technical performance specifications of *proton* therapy facilities was prepared at LBNL [8]. Table 2 shows a list of technical specifications for a *carbon-ion* therapy facility. It is developed by modifying for the physical differences between protons and carbon ions: mainly for higher energy loss by ions that increases the beam energy requirement, and higher LET that reduces the beam intensity requirement.

Table 2: Specifications of a Carbon-Ion Therapy Facility

Item	Specifications
Ion Species	Carbon - p, He, Li, Be, B,C and beyond (N, O, and Ne)
Energy	400 – 140 MeV/μ
Range/SOBP/Lateral-Size	250/40 - 150/220 mm
Max. Dose Rate	5 Gy RBE/min in 1 liter
Beam Intensity	1.2x 10^9 pps
Treatment Rooms	3: H&V, H, V / Gantry
Irradiation Method	Pixel Scanning / with Beam Gating / Motion Tracking

CURRENT STATUS OF ION-BEAM THERAPY FACILITIES

In 1994 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, commissioned its Heavy Ion Medical Accelerator in Chiba (HIMAC), which has two synchrotrons and produces ion beams from ^{4}He to ^{54}Xe up to a maximum energy of 800 MeV/μ (Fig. 3).

The HIMAC serves two treatment rooms, one with both a horizontal and a vertical beam, and the other with a vertical beam only. There are also a secondary (radio-active) beam room, a biology experimental room, and a physics experimental room, all equipped with horizontal and/or vertical (downward) beam lines. As of February 2010, a total of 5,189 patients have been treated. Clinical results have shown that carbon-ion treatments have the potential ability to provide sufficient dose to the tumor, together with acceptable morbidity in the surrounding normal tissues. Tumors that appear to respond favorably to carbon ions include locally advanced tumors as well as those with histologically non-squamous cell type of tumors, such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. By taking advantage of the unique properties of carbon ions, treatment with a large dose per fraction within a short treatment period has been successfully carried out for a variety of tumors [9].

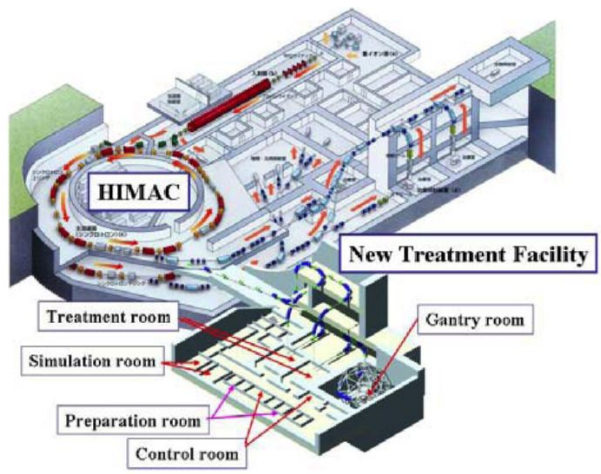

Figure 3: Schematic view of HIMAC. The lower part depicts the new treatment facility addition (2011). (K. Noda, NIRS)

In 2001, the Hyogo Ion Beam Medical Centre (HIBMC) was commissioned at Harima Science Garden City, Japan, as the first hospital-based facility in the world to provide both proton and carbon-ion beam therapy. The third carbon-ion therapy facility in Japan was commissioned at the Gunma University Heavy Ion Medical Center, and its first patient was treated in March 2010.

At the Heidelberg Ion Beam Therapy Centre (HIT), as shown in Fig. 4, two ion sources feed the synchrotron via a linear accelerator. It houses three treatment rooms: two with a horizontal beam and one with a rotating gantry,

which makes it possible to aim the beam at the patient from all directions. This system, which will be capable of treating tumors with both carbon ions and protons, was commissioned in 2009 [10]. A second carbon ion and proton beam therapy center in Germany is under construction at the Klinikum Geisse-Marburg in Marburg.

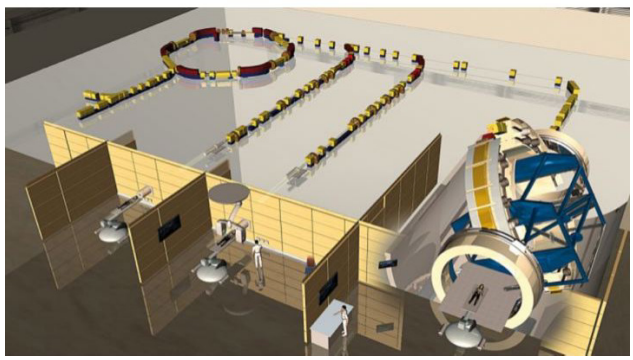

Figure: 4: Schematic view of HIT at Heidelberg, Germany.

The Centro Nazionale Adroterapia Oncologica (CNAO) will commission an ion-beam facility in Pavia, near Milan, in 2010. The facility will provide therapeutic beams of protons and carbon ions with maximum energy of 400 MeV/μ [11]. The basic design of the CNAO accelerator and beam lines are based on the results the Proton-Ion Medical Machine Study (PIMMS) hosted at CERN from 1996 to 1999 [12].

Table 3 lists technical characteristics of existing light ion facilities. There are several additional facilities under planning in Shanghai, China, Saga Prefecture (Tosu city) and Kanagawa Prefecture (Kanagawa Cancer Center, Yokohama city) in Japan, Aachen and Berlin in Germany, Catania, Italy, Lyon (Centre Etoile) and Caen (Asclepios) in France, and Minnesota and California, USA.

In contrast to the fact that every ion-beam facilities discussed here uses a synchrotron, Ion Beam Associate (IBA) of Belgium proposes to use a superconducting isochronous cyclotron, with an ECR source, 25 keV/Z axial injection, to accelerate He and C ions to 400 MeV/u and protons to 260 MeV [13].

Table 3: Physical Characteristics of Ion Beam Facilities, Existing and Under Construction

	HIMAC Chiba	**HIBMC Hyogo**	**HIT Heidelberg**	**CNAO Pavia**	**GUNMA Maebashi**	**Marburg**
Particles	p, C, O, Ar, Xe	p, He, C	p, He, C, O	p, He, C, O	C	p, C
Accelerator	2 Synchrotrons	Synchrotron	Synchrotron	Synchrotron	Synchrotron	Synchrotron
Ion Sources	PIG for low Z; ECR for high Z	2 ECR sources	2 ECR sources	2 ECR sources	ECR source	2 ECR sources
Injector	RFQ (8 to 800 keV/u) and Alvarez LINAC (0.8 to 6 MeV/μ) at 100 MHz	RFQ (1MeV/μ) and Alvarez LINAC (5 MeV/μ)	7 MeV/u linac injector	RFQ (8 to 400 keV/μ) and IH-DTL LINAC (to 7 MeV/μ)	RFQ and APFIH	
Particle Energy (MeV/μ)	C (420) Ar (800)	p & He(70- 230) C (70 - 320)	50 - 430	p: 250 C: 60 - 400	C only: 400	100-430
Beam Intensity, particles per spill (pps)		p: 7.3×10^{10} He: 1.8×10^{10} C: 1.2×10^{9}	p: 4×10^{10} He: 1×10^{10} C: 1×10^{9} O: 5×10^{8}	p: 2×10^{10} C: 4×10^{8}	C: 1.2×10^{9}	C: 3×10^{8}
Repetition Rate		p: 1 Hz He C: 0.5 Hz				
Spill Length (msec)		400		250 - 10,000		
Treatment Rooms	1 H, 1 V, and 1 H&V 1 gantry (planned)	p: 1 H and 2 gantry rooms C: 1 H&V and 1 45 degree	2 H and 1 gantry room	2 H and 1 H&V	H, V, H&V; no gantry	3 H and 1 45 degree
Beam Delivery Technique	Passive scattering		Intensity controlled 3D raster scan	Intensity controlled 3D raster scan	Passive, respiration gated	
Field Size (cm^2)		15 x 15	20 x 20	20 x 20	15 x 15	
# Pts Treated or Planned /Year	5189 (2010.2)	515 (2009.3)	> 1,000			1500-2000
First patient	1994	2001	2009	2010	2010	2010

CONCLUDING REMARKS

Each year in the United States, nearly one million patients are treated with radiation therapy, and at least 75 percent of these patients are treated with the intent to cure the cancer, rather than control the growth or relieve symptoms including pain [14]. Clinical experience suggests that at least 10% of these patients would benefit significantly from treatment with therapeutic beams of light ions, in place of conventional megavoltage x-ray treatment. This potential benefit arises from two important properties, which together are uniquely characteristic of accelerated light ions: (i) the ability to locally deliver high tumor-killing doses of radiation to tumor sites deep within the body, while sparing surrounding critical tissues from harmful radiation, and thereby increase the likelihood of cure with fewer complications [15], and (ii) the effectiveness of light-ion radiation in killing tumor cells that are resistant to conventional radiation, thereby reducing the incidence of local failures of treatment.

There are now five carbon-ion therapy facilities in the world, and more are under construction or in planning stages; however, most of them are in developed countries. For the welfare of mankind everywhere, it is hoped that ion-beam therapy facilities should become more universally available. To accomplish this objective, we need development of technologies in accelerating and delivering ion beams more effectively, safely and economically. The LBNL report, LBL33749 [8] is still a valid resource for proton radiotherapy and we extend it here to a carbon-capable machine. In that report, it is stated– and we emphasize for the future ion-beam therapy facility developers– that, "Operation in a clinical environment requires conservative and simple design that can be operated and maintained by a non-specialist staff to produce reliable and consistent performance, even with gradual subsystems degradation."

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