Heavy Ion Radiotherapy: Yesterday, Today and Tomorrow*

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Abstract
At EO Lawrence Berkeley National Laboratory (LBNL), clinical trials were conducted (1975-1992) for treating human cancer using heavy ion beams, in which about 700 patients were treated with helium-ion and about 300 patients with neon-ion beams. Clinical trials at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany used carbon-ion beams to treat about 250 patients (1997-2005). In 1993 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, commissioned its first-in-the-world medically-dedicated Heavy Ion Medical Accelerator in Chiba (HIMAC), which accelerates heavy ions to an energy of 800 MeV/µ (million electron volts per nucleon). By 2010 more than 5000 patients have been treated using carbon-ion beams at HIMAC. Following its successful clinical operation, several carbon-ion therapy facilities have been, or will be soon, constructed in: Hyogo (commissioned in 2001) and Gunma (2010), Japan; Heidelberg (2009), Marburg (2010) and Kiel (2012), Germany; Pavia (2010), Italy; Lyon (2015), France; Wiener Neustadt (2015), Austria; Shanghai (2015) and Lanzhou, China; and Busan (2016), Korea. Very active clinical research and technology development projects are carried out at these institutions to enhance beam delivery accuracy, such as beam scanning that compensates for organ movements, which will further improve the clinical efficacy of the ion-beam therapy in the future.

Introduction
In 1895, Wilhelm Conrad Röntgen produced X-rays, which are short-wave electromagnetic radiations that readily penetrate human body. Soon it was recognized that the energy that does not pass through the body would be deposited within it and it is this energy that causes the biological effects of radiation in tissue, such as killing cancer cells. Within two months of their discovery, X-rays were used both in Europe and North America not just to take pictures of the internal organs of living people but also to treat a wide variety of diseases, including malignant tumors [1]. As we know now, an X-ray beam is made up of energetic photons, which loses its intensity while penetrating human body. Therefore, in treating deep-seated tumors, photon-beams are bound to deposit higher dose upstream of the target volume, and also significant dose in its downstream regions (see the photon curve in Fig. 1). Nevertheless, photon beams are the most widely used cancer treatment modality today. Modern day radiation treatments of cancer employ linear accelerators (linacs) that accelerate electrons to tens of MeV before they bombard target materials to produce high-energy photon beams. The beam delivery method, called Intensity Modulated Radiation Therapy (IMRT), delivers photon beams aiming the target from many different directions, thereby dilutes unwanted doses outside the treatment volume. These photon beam treatments are often called “conventional” radiotherapy to distinguish them from the new proton and heavier ion-beam treatments that are discussed below.

![Fig. 1: The relative dose of a photon beam as a function of penetrating depth in water is shown as a reference radiation. The Bragg peaks of proton and carbon-ion beams are also shown. To cover the extended target volume, the energy of particle beam is modulated to adjust the depth of Bragg peak to form a Spread-Out Bragg Peak (SOBP). The relative depth doses of the SOBP of proton and carbon ion beams 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.](image-url)

In 1948, Prof. Ernest Orlando Lawrence completed construction of the 184-inch Synchrocyclotron at the University of California (UC) Berkeley, making it possible to accelerate protons, deuterons and helium nuclei to energies of several hundred MeV/µ. Note that protons and heavier ions are much more massive than electrons, and consequently it requires much bigger accelerators to accelerate them to acquire enough kinetic energy to reach deep-seated tumors in human body. For example, a proton is 1836 times more massive than an electron. Energetic ion beam deposits much of its energy at the end of the range, resulting in what is called Bragg peak (Fig. 1), so named after the Australian physicist Sir William Henry Bragg who discovered the phenomenon [2]. Realizing the advantages of delivering a larger dose in the Bragg peak when placed inside deep-seated tumors, Prof. Robert Wilson at Harvard University published his seminal paper on the rationale of using accelerated protons and heavier ions for treatment of human cancer [3]. Compared to conventional photon treatments, these particle beams promised higher cure rates with fewer
complications, as they would deliver tumor-killing doses more precisely, while lowering unwanted doses to normal tissues adjacent to the treatment volume. In 1952, Professors Cornelius A. Tobias and John H. Lawrence at UC Berkeley performed the first therapeutic exposure of human patients to ion (deuteron and helium ion) beams [4].

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) [5]. The first hospital-based proton facility was commissioned at the Loma Linda University Medical Center in California in 1990 [6]; and now about 30 industry-built proton therapy facilities became operational around the world.

Heavier Ions for Cancer Treatment

Early Clinical Trials Using Heavy Ions

In the 1950s, LBNL constructed the Bevatron, a 6 giga-electron-volts (GeV) synchrotron, which by the early 1970s accelerated ions with atomic numbers between 6 and 18, to energies that permitted the initiation of radiological physics and biological studies [7]. 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, by producing high intensities of protons and other heavier ions with sufficient energy to penetrate the human body, expanded the opportunity for medical studies for treatment of deep-seated cancers [8].

Ion beams combine superior physical and biological characteristics for effective cancer therapy. In penetrating human body, compared with proton beams, ion beams scatter less and exhibit smaller energy straggling resulting in steeper distal falloffs. These mean that the widths of fuzzy boundaries of radiation fields (called penumbrae) are much narrower for ion beams when compared with those for photon or proton beams. As ion beams could more accurately delineate target volumes sitting adjacent to critical organs than photon or proton beams could, higher ion-beam dose may be delivered into the target volumes. Clinical expectation is higher tumor control with a lower normal tissue complication probability.

In penetrating human body, heavier ion beams show 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 radiations that produce mostly single-strand breaks in irradiated DNA molecules inside the cells. Single-strand breaks are often repaired, resulting in recurrence of tumors. Whereas heavier ion beams, with high-LET radiation in Bragg peaks, produce double-strand breaks in DNA molecules. Double-strand breaks cannot be repaired and therefore the outcome results in lower recurrence of tumors (Fig. 2). Heavier ion beams have clinically demonstrated their superior tumor eradicating ability with lower complication and recurrence probability.

From 1975 to 1992, Prof. Joseph R. Castro and his team from UC San Francisco conducted clinical trials for treating human cancer using the spread-out Bragg peak of helium ion beams at the 184-inch Synchrocyclotron and heavier ion beams at the Bevalac [9]. Ions of interest ranged from $^4$He to $^{30}$Si; whereas, $^{28}$Ne was the most commonly used ions. The numbers of patients treated under US national protocols (NCOG/RTOG) 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. Using $^{28}$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.

Carbon Ions vs. Protons

The therapeutic advantage of carbon ions versus protons stems from three decisively superior characteristics of the former:

(i) Compared with proton beams, carbon-ion beams produce higher dose conformation to the tumor volume (Fig. 3). Sparing of the surrounding healthy tissues from unwanted radiation is increased, therefore 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. Carbon 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 28-40 fractions). Safe and effective carbon-ion beam
treatments are delivered in fewer fraction numbers, such as 8-12; and possibly even fewer for some tumor sites, perhaps as low as 1-4 fractions [10]. This allows higher patient throughput in an ion-beam facility, which lowers the cost of treatments and enhances patient comfort.

**Fig. 3:** 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 Univ., Dept. Clinical Radiology and German Cancer Research Center.)

Therapy plans for carbon-ion beam and photon beam treatments are shown in Fig. 3, which demonstrates the superiority of single beam of carbon-ions over the most advanced Intensity Modulated Radiation Therapy (IMRT) using multiple photon beams.

As high-dose 3D-conformal treatment has become the clearly accepted objective of radiation oncology, clinical trials using proton and carbon-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 70,000 patients by the end of 2010. However, some 15% to 20% of tumor types have shown resistant to even the most high-dose low-LET irradiation. For these radio-resistant tumors, treatment with carbon ions 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 [10].

**Current Status of Ion-Beam Therapy Facilities**

In 1994 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, under the leadership of Prof. Yasuo Hirao, commissioned the Heavy Ion Medical Accelerator in Chiba (HIMAC), which has two synchrotrons and produces ion beams from $^3$He to $^{129}$Xe up to a maximum energy of 800 MeV/μ (Fig. 4) [11].

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 (radioactive) 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, Prof. Hirohiko Tsuji and his staff have treated a total of 5,189 patients. 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, Prof. Tsuji successfully carried out treatments with a large dose per fraction within a short treatment period for a variety of tumors [10]. At GSI, Darmstadt, Germany, Prof. Dr. Jürgen Debus and his group of Heidelberg University conducted clinical trials using carbon-ion beams [12]. A comparison of clinical results from photon and carbon-ion radiotherapy for selected tumor sites is shown in Table 1. This list clearly demonstrates the superior clinical efficacy of carbon ion beams over photon beam treatments. The clinical results are based on the Table compiled by Prof. Gelhard Kraft [13], which is updated by Yamada et al. [14].
In 2001, the Hyogo Ion Beam Medical Centre (HIBMC) was commissioned at Harima Science Garden City, Japan, which provided for the first time both proton and carbon-ion beams for clinical use in one facility. The third carbon-ion therapy facility in Japan was commissioned at the Gunma University Heavy Ion Medical Center (GHMC), where its first patient was treated in March 2010.

<table>
<thead>
<tr>
<th>Indication</th>
<th>End point</th>
<th>Photons</th>
<th>Carbon Ion</th>
</tr>
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<tbody>
<tr>
<td>Chordomas</td>
<td>Local control rate</td>
<td>30-50%</td>
<td>NIRS-HIMAC</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>Local control rate</td>
<td>33%</td>
<td>GSI</td>
</tr>
<tr>
<td>Nasopharynx carcinoma</td>
<td>5 year survival</td>
<td>40-50%</td>
<td>100% (5y)</td>
</tr>
<tr>
<td>Glio-blastoma</td>
<td>Av. survival time</td>
<td>12 months</td>
<td>61%</td>
</tr>
<tr>
<td>Choroid melanoma</td>
<td>Local control rate</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Paranasal sinus tumors</td>
<td>Local control rate</td>
<td>21%</td>
<td>70% 5y</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>5 year survival</td>
<td>57%</td>
<td>72% (5y LC 81%)</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Av. survival time</td>
<td>6.5 months</td>
<td>21 months</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>5 year survival</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Recurrent Rectal cancer</td>
<td>5 year survival</td>
<td>0-16%</td>
<td>45%</td>
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<td>Salivary gland tumors</td>
<td>Local control rate</td>
<td>24-28%</td>
<td>81% (5y)</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>5 year survival</td>
<td>31-75%</td>
<td>52-83%</td>
</tr>
</tbody>
</table>

Table 1: Comparison of clinical results of photon and carbon-ion treatments of selected tumor sites.

In contrast to the fact that almost all 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 helium and carbon ions to 400 MeV/µ and protons to 260 MeV [17].
Very active clinical research and technology development projects are carried out at various carbon-ion therapy centers to enhance beam delivery accuracy. New beam delivery techniques will use beam scanning to conform the Bragg peak dose to irregularly shaped treatment volumes. When such dynamic beam delivery methods are used, one must compensate for organ movements during the beam delivery with beam scanning. Various techniques considered include: (i) beam gating that delivers radiation only during the selected physiological phases, such as in respiration-gated beam delivery, or (ii) beam tracking the organ movements. Improved beam delivery will further improve the clinical efficacy of the ion-beam therapy in the future. HIMAC is completing its expansion to be completed in the spring of 2011 (Fig. 4), where a beam scanning will be implemented for treatment delivery [18].

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 [19]. Clinical experience suggests that at least 10% of these patients would benefit significantly from treatment with therapeutic beams of carbon ions, in place of conventional megavoltage X-ray or proton treatments. It follows that one may perform parallel epidemiological analyses for the Japanese population, and arrive at similar conclusions.

This potential benefit of carbon-ion beam therapy arises from two important properties, which together are uniquely characteristic of accelerated carbon 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 [20], and (ii) the effectiveness of carbon-ion radiation in killing tumor cells that are resistant to photon or proton-beam radiation, thereby reducing the incidence of local failures of treatment.

There are now five carbon-ion therapy facilities operating 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 future ion-beam therapy facility developers should remember that operation of a complex facility in a clinical environment requires conservative and simple designs that can be operated and maintained by a non-specialist staff to produce reliable and consistent performance, even with gradual subsystems degradation with the usage of the facility.

Acknowledgment

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References

[1] First therapeutic attempt using X-rays to treat a local relapse of breast carcinoma by Emil Grubbe in Chicago (1895), first use of X-Rays for stomach cancer by Victor Despeignes in Lyon, France (1896), and irradiation of a skin tumor in a 4-year-old by Léopold Freund in Vienna, Austria (1896). See, for example: http://radonc.ucsd.edu/patientinformation/history.asp


