REVIEW ON CYCLOTRONS FOR CANCER THERAPY

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Abstract

The science and technology of proton and carbon therapy was initially developed in national and university laboratories. The first hospital based proton therapy facility was built at Loma Linda University with the help from Fermilab. After this initial phase, and starting with the tender for the proton therapy system at MGH, many proton and carbon beam facilities have been ordered from industry and built. Industrially made proton and carbon therapy facilities represent today the vast majority of the installed base.

INTRODUCTION: THE HISTORY OF PROTON THERAPY SYSTEMS

Robert Wilson was the first to point out the possibilities offered by the Bragg peak in the field of the radiotherapy of cancer in a paper published in 1946 (1).

A few years later, tests were conducted at Lawrence Berkeley Laboratory to verify Bob Wilson's predictions, and in 1954 protons started to be used on patients in Berkeley.

Similarly, proton treatments were started in Uppsala in Sweden in 1957.

Harvard cyclotron Laboratory (HCL) had a 160 MeV synchrocyclotron. In 1961, Dr. Ray Kjellberg started to use the proton beams at HCL to do radio-surgery of brain malformations. Then, in 1972, Dr. Herman Suit, from Massachusetts General Hospital (MGH), helped by Michael Goitein, started to apply the proton beams of HCL to do fractionated radiotherapy of cancer. A lot of what is today considered as standard proton therapy technology was developed between 1970 and 1990 by Herman Suit, Michael Goitein, and a team of talented physicists at HCL: Andy Koehler, Bernie Gottschalk, and later Miles Wagner, Skip Rosenthal and Ken Gall.

But as successful as HCL was in proton therapy, it quickly became clear that a proton therapy facility located directly within the hospital campus was a much better option. In 1983, the institutions doing or planning to do proton therapy got together to form an informal group named the Proton Therapy Cooperative Group or PTCoG.

One of the first tasks of the PTCoG was to reach a consensus on a set of desirable specifications for an in hospital proton therapy facility. These specifications are still today the bible of those who plan to design a proton therapy system.

Unexpectedly, the first group which succeeded to raise the funds needed to build the first hospital based PT facility was not MGH or Berkeley, but the team led by Dr. James (Jim) Slater at Loma Linda University Medical Center (LLUMC) in California. Jim Slater was a friend of Herman Suit, and they had worked together as interns at MDACC. LLUMC requested the help of the Fermi National Laboratory to design and build the required proton accelerator. The accelerator was designed and built by a group of experienced accelerator physicists from Fermilab and, not surprisingly, the accelerator technology selected by this group was a small, compact synchrotron. The gantry design and construction was subcontracted to SAIC. A private company initially named today Optivus, was established in Loma Linda, CA by Jim Slater to maintain and develop the system at LLUMC. The company is led by Jon Slater, the son of James Slater. Optivus is trying to sell a PT system that essentially is based on the design of the LLUMC system. Although Optivus is probably the oldest company in the PT field, it is the only one that has not designed nor built a PT system. Some members of the company, however, were associated with the development and testing of the LLUMC PT system, first at Fermilab and then at the Loma Linda site.

In the mid-1970s at the Catholic University of Louvain (UCL) in Louvain-la-Neuve, Belgium, Professor Andre Wambersie and Yves Jongen developed a close collaboration to build a fast neutron therapy facility, which was used to treat a large number of patients. In 1986, Jongen left UCL to start the Belgium-based company Ion Beam Applications s.a. (IBA). Wambersie met Jongen in 1989 and suggested that IBA start the design of a cyclotron-based proton therapy facility. The following year, IBA presented the initial design of its PT system based on an isochronous cyclotron and compact, scanning-only, gantries at the Particle Therapy Co-Operative Group (PTCOG) XII meeting in Loma Linda.

In 1991, IBA and Sumitomo Heavy Industries (SHI) in Japan signed a 10-year collaboration agreement to jointly develop a PT system based on the IBA concept. Though this collaboration ended in 2001, it explains why the PT systems developed by IBA and SHI share many common features.

The first official tender to acquire a commercially built PT facility was launched by the Massachusetts General Hospital (MGH) in 1992. Several companies responded, but the competition finally narrowed to three groups: Maxwell-Brobeck, in association with Varian, offered a synchrotron-based system; Siemens offered two versions: one based on a synchrotron and another based on a superconducting isochronous cyclotron (the isochronous cyclotron was designed by Pierre Mandrillon from CERN and CAL, Nice); and IBA, in association with General Atomics, offered a system based on a resistive isochronous cyclotron. The tender process took a long time, but finally the contract was awarded to the IBA-GA team in April 1994.

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The development of the MGH PT facility was very challenging. The specifications were new and demanding and the budget available to MGH was only $20 million for a two-gantry facility. At the time of the contract, an experienced observer drily commented: "Unfortunately, this tender will probably mean the death of three good accelerator companies. Perhaps the two companies who did not win the contract, but certainly the company who got it."

He was partly right, and came close to being entirely right. Shortly after the MGH contract was signed, the Brobeck division of Maxwell was disbanded and the special project group of Siemens was sold to its management. The group restarted business under the name of ACCEL Instruments and later returned to proton therapy.

IBA also met serious problems in the development of the MGH PT system. Although the new cyclotron, the beam lines and the isocentric gantries were developed and delivered in time and within budget, IBA had badly underestimated the effort and the methodology needed to develop the complex software needed to control a PT facility. The project was seriously delayed and the first patient finally was treated at the Northeast Proton Therapy Center in Boston in November 2001. IBA's financial loss on the MGH project was huge and might have killed the company if IBA had not had other, more profitable, activities.

In 1995, the National Cancer Center in Japan launched a tender for the construction of a PT center in Kashiwa. The contract was signed the following year with SHI, who built the system in close collaboration with IBA. Knowing the difficulties IBA had with developing software for MGH's PT system, SHI selected a simpler and more pragmatic approach in the design of the control system, which proved robust and effective but limited in its functionalities. As a result, NCC Kashiwa's PT center treated its first patient in November 1998, three years ahead of MGH.

After 2000, the commercial activity and the number of competitors in the field of proton therapy began to increase dramatically. From 1994 to 2010, 37 proton therapy facilities, representing a total of 96 treatment rooms were contracted to industrial companies (fig. 1). In Japan, the government funded the construction of several PT facilities. Hitachi and Mitsubishi Electric introduced synchrotron-based PT facilities. In Germany, ACCEL Instruments teamed up with Pr. Henry Blosser to propose a PT system based on a 250 MeV superconducting isochronous cyclotron.

Over the last five years, radically new concepts have appeared on the PT market. The company Still River Systems (SRS) was founded in Boston by a group of medical physicists who had shared the proton therapy experience of HCL and MGH. They started the company to develop and commercialize a single-room PT system based on a very high magnetic field superconducting synchrocyclotron mounted on a gantry that rotates around the patient. PROTOM International Inc., based in Flower Mound, TX was founded to commercialize a very simple and inexpensive synchrotron developed in Russia by Professor V. Balakin. At the Lawrence Livermore National Laboratory, the concept of the Dielectric Wall Accelerator was developed by Georg Caporaso and his team and will be commercialized by Compact Particle Acceleration Corporation, a spin-out of Tomotherapy Inc.

Finally, several research institutions in the world work actively on the acceleration of protons by laser beams.

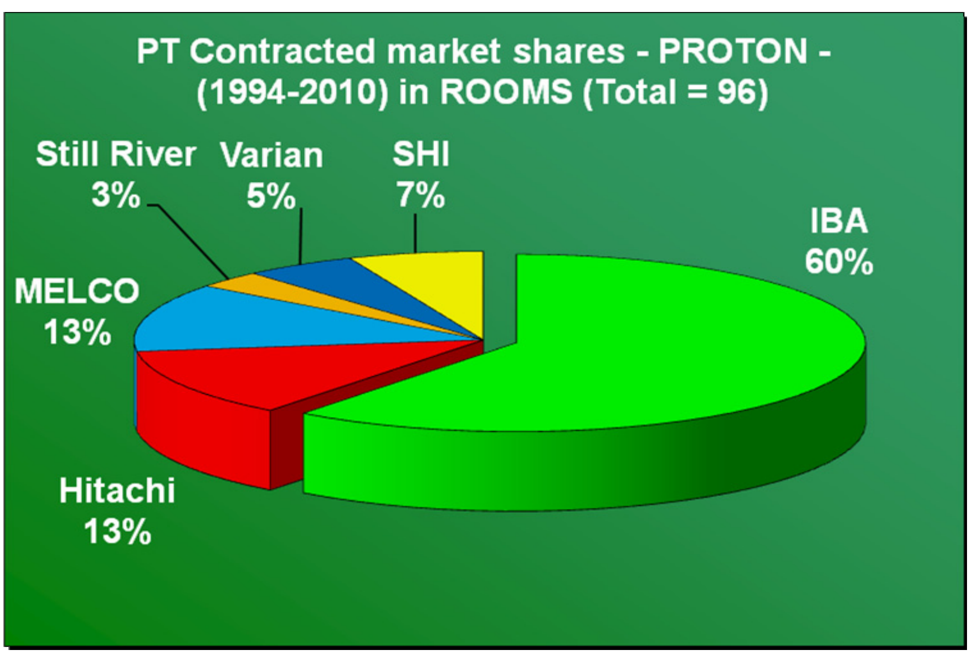

Figure 1: Commercial Proton Therapy Systems Sales - market shares - (1994-2010) in ROOMS

COMMERCIAL PROTON BEAM THERAPY SYSTEMS

The IBA Proteus® 235 Proton Therapy System

IBA's Proteus 235 is without doubt the system which enjoyed the largest commercial success so far. The cyclotron uses a fixed field resistive magnet, a fixed frequency RF system, and accelerates protons to a fixed energy of 230 MeV . The cyclotron's magnet (Fig. 2) is 4.34 meters in diameter, 2.1 meters high, weighs 220 tons, and the coils power is 175 kW. The RF system uses 2 30° dees located in opposite valleys and connected at the center. The dees operate at 106 MHz, on the 4th harmonic of the protons' orbital frequency. The beam extraction is made by an ESD located in one of the valleys without RF cavities. The beam extracted at 230 MeV is then adjusted to the energy required for the treatment by the use of a variable energy degrader made of graphite, followed by a magnetic analyzer to select the required energy width. The system formed by the degrader and the magnetic analyzer is named the Energy Selection System or ESS

Figure 2. IBA 230 MeV resistive cyclotron for proton therapy

Figure 3. Gantry Treatment Room of the IBA Proteus Proton Therapy System

The energy of the beam extracted from the cyclotron is 230 MeV and is fixed. The beam extracted from the cyclotron is then focused into a small spot into a variable energy degrader made of graphite, followed by a magnetic analyzer. This energy selection system allows precise tuning of the continuous proton beam, from 60 MeV to 230 MeV, in under a second.

Most often, proton therapy is delivered in rooms equipped with isocentric gantries. The IBA isocentric gantry has 370 degrees of rotation with 0.4 mm radius precision, and a gantry rolling floor. Each gantry room includes a patient positioning system featuring a robot-controlled patient couch. The robot allows three orthogonal linear motions, rotation around the vertical axis, and ±3 degrees of pitch and rolling of the patient couch. 17 of the 35 commercial PT systems sold to date were designed and built by IBA. The 9 systems named in bold are already treating patients. The others are under construction or installation.

- **The Francis H. Burr Proton Therapy Center** at Massachusetts General Hospital, Boston, MA
- **Midwest Proton Radiotherapy Institute**, Bloomington, IN (Gantries only on an existing cyclotron)
- **Wanjie Proton Therapy Center**, Zibo, China
- **University of Florida Proton Therapy Institute**, Jacksonville, FL
- **National Cancer Center**, Ilsan, Korea
- **Roberts Proton Therapy Center**, University of Pennsylvania Health System, Philadelphia, PA
- **Procure Proton Therapy Center**, Oklahoma City, OK
- **Centre de Protonthérapie de I'Institut Curie**, Orsay, France
- Westdeutsches Protontherapiezentrum, Essen, Germany
- **Hampton University Proton Therapy Institute**, Hampton, VA
- Central DuPage Hospital (a Procure Center), Warrenville, IL
- ATreP Proton Therapy Center , Trento, Italy
- PTC Prag, University Hospital Bulovka, Czech Republic
- Somerset Procure Proton Therapy Center, Somerset, NJ
- Seattle Procure Proton Therapy Center, Seattle, WA
- Krakow proton therapy center (Krakow, Poland)

Sumitomo Proton Therapy System

The proton therapy system proposed by Sumitomo Heavy Industries (SHI) of Japan is very similar to the system proposed by IBA because initially the two companies shared a common development. However, since 2001, the two systems have undergone separate developments.

SHI has only one system currently treating patients, built in collaboration with IBA, but it was the first commercial system to do so. Its proton therapy facility at the National Cancer Center East, in Kashiwa, Japan has been treating patients since 1998. The company reports that firm contracts have been signed for three systems, one in Taiwan, one in the United States and a compact system in Japan. Although construction of the Taiwan system is underway, installation has not yet begun.

Hitachi PROBEAT Proton Therapy System

Hitachi proposes a proton therapy system based on a synchrotron, which has been sold to four institutions. The first one, at the Proton Medical Research Center (PMRC) at the University of Tsukuba in Japan, began treating patients in 2001. The second, at the University of Texas M.D. Anderson Cancer Center in Houston, went into operation in 2006. These systems are based on a slow-cycle synchrotron that provides 70-250 MeV protons. Hitachi proton therapy systems have also been sold to the Wakasaka Wan Energy Research Center in the Fukui prefecture in Japan, and more recently at the Nagoya City proton Center, in Aichi prefecture, Japan.

Mitsubishi Proton Beam Treatment System

Mitsubishi Electric is marketing a PT system powered by a synchrotron that delivers 70 – 250 MeV protons to up to six treatment rooms.

Two of the PT systems are now in clinical use, one at the Shizuoka Cancer Center and the other at the Southern Tohoku Proton Therapy Cancer Center in Fukushima, Japan. Two additional systems are under construction at the Fukui Prefecture Proton Therapy Center and at the Medipolis Medical Research Institute, in Kagoshima, Japan

Varian Proton Therapy System

Varian's proton therapy system is based on a isochronous superconducting cyclotron, providing 250 MeV. Unlike the IBA and SHI isochronous cyclotrons, the ACCEL-Varian cyclotron is equipped with 4 RF cavities to maximize the energy gain per turn and the extraction efficiency. Here again, a graphite variable energy degrader is used to adjust the proton energy between 70 and 250 MeV. The 3-meter diameter, 1.6 meter-high cyclotron weighs 90 Tons

In 2007, Varian bought ACCEL, who designed and was in the process of building the PT system at the Rinecker Proton Therapy Center in Munich, Germany. Varian took over the project, which began treating patients in March 2009. So far, no other sales have been officially confirmed by Varian, but several cyclotrons are under construction.

Still River Systems Monarch 250 TM Proton Therapy System

Still River Systems (SRS) has developed a very original concept for a single room proton therapy system. The SRS system uses a very high field synchrocyclotron mounted on a gantry and rotating around the patient (Fig. 6). The very high field synchrocyclotron, initially developed by Tim Antaya at MIT has a central field of 9 T and uses coils made of Nb-Sn superconductor. To support the large mechanical forces encountered in this magnet, the coils are placed inside a stainless steel bobbin and are conduction cooled at 4°K by cryocoolers. The SRS magnet does not use liquid helium: a dry cryostat is indeed very desirable for a gantry-mounted magnet.

The beam of the SRS cyclotron is extracted at 250 MeV, in the direction of the patient. Range shifting is done at the exit of the cyclotron.

The Monarch 250 system includes a gantry that rotates 190 degrees and a treatment couch that turns 270 degrees so all clinically required beam orientations can be achieved.

The development of the very high field cyclotron magnet took quite longer than expected, but finally the prototype of the Monarch 250 has produced its first extracted beam in June of this year, and should be delivered to the first customer end of 2010 or early 2011.

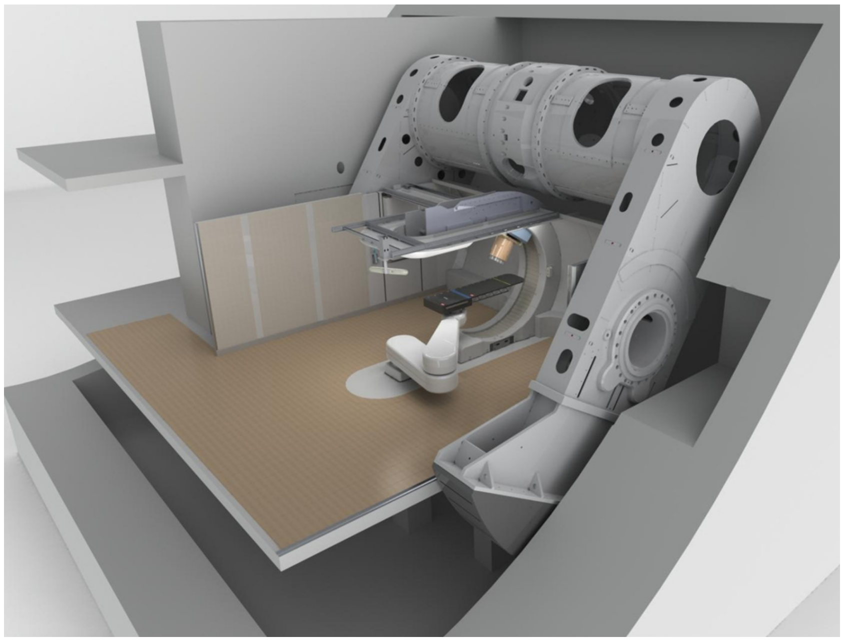

Figure 6. Still River Systems Monarch 250 Proton Therapy System

COMMERCIAL CARBON BEAM THERAPY SYSTEMS

Synchrotron Based Carbon Therapy Systems

The development of carbon beam therapy started in national laboratories. The first treatments of patients with heavier ions were made at the LBNL, at the Bevalac facility in Berkeley in the 1980's. After LBNL, heavy ion therapy was developed in Chiba (Japan) at the National Institute for Radiological Sciences (NIRS), on the HIMAC accelerator system. It can be said that the bases of modern hadron therapy were really developed at NIRS. Among other findings, NIRS demonstrated that carbon ions were probably the ions offering the best compromise in the conflicting demands of hadron therapy of cancer.

After NIRS, the scientists at GSI in Darmstadt started to study the radiobiology of carbon ions, and soon after started to build at GSI a facility for the clinical research of the potential advantages of carbon beam therapy.

The work at GSI brought a lot of new knowledge and understanding in the field of the interaction between carbon beams and living tissues. The group of Pr. Gerhard Kraft at GSI developed the now famous "local effect model" which is today the standard reference in calculating the relative biological efficiency of hadron beams. In the field of technology, the group at GSI was also the first to develop an efficient, fast and safe method to deliver the carbon beam to the patient by spot scanning.

There were limits to the possibility to do clinical research into a facility intended for basic physics research like GSI. So the GSI team, under the leadership of Thomas Haberer, started to develop the design of a more compact, hospital based, carbon therapy facility. This system is based on a large (27 m diameter) carbon synchrotron, able to accelerate carbon ions to 4.8 GeV, or 400 MeV/u. The 4+ carbon ions are produced in an ECR ions source, pre-accelerated by a RFQ, then by a DTL, and injected into the synchrotron after stripping to the 8+ charge state.

The prototype of this facility was built by GSI in collaboration with Siemens in Heidelberg, at the German Cancer Research Center (DKFZ), and started treating patients in 2009.

Siemens Medical Systems acquired the rights of the GSI design, and sold similar carbon therapy facilities in Marburg and in Kiel (Germany) and in Shanghai (China)

In a similar way, NIRS developed the design of a compact, hospital based carbon therapy facility based on a synchrotron. The prototype of this facility is installed in Gunma University (Japan) and started treating patients this year. The Gunma design is now proposed industrially by Japanese industries such as SHI, MELCO or Hitachi.

IBA's C-400 Hadron Therapy System

IBA has designed a compact superconducting isochronous cyclotron for carbon therapy in collaboration with scientists from Dubna, Russia.

The C-400 can accelerate Q/M = 0.5 ions such as hydrogen (as H2+ molecule), helium, lithium-6, boron-10, carbon-12, nitrogen-14, oxygen-16, and neon-20 ions. All ion species will be accelerated to 400 MeV/u except for hydrogen, which will be accelerated in the form of H2+ to achieve the desired Q/M, then split and extracted at 260 MeV/u. Live ion sources for hydrogen, helium, and carbon will be located under the cyclotron, allowing to switch very rapidly from one ion to another. This cyclotron is described more extensively in another paper of this conference presented by Nikolay Morozov (2)

Figure 7. The IBA C-400 cyclotron

CONCLUSIONS

Proton therapy and carbon beam therapy were initially developed in national or university laboratories. The initial experiments were conducted at LBNL. At Harvard, the HCL played a key role in the development of proton therapy technology. In carbon beam therapy, the role of NIRS in Japan was also essential.

After the contract of the MGH facility awarded to IBA in 1994, more than 40 proton and carbon therapy facilities have been ordered from industry. Half of these are built and treat patients. The other half is under construction or being installed.

In 1991, after the development of the first hospital based proton therapy facility at LLUMC, the synchrotron was generally considered the choice accelerator technology for proton therapy.

Then in 1992, IBA came with an efficient cyclotron design. Other manufacturers followed, and the cyclotron technology was finally selected in 75% of the proton therapy facilities built since that time.

Today, in carbon beam therapy, the synchrotron technology has been selected for every facility. But IBA has introduced the design of a compact, superconducting cyclotron for carbon beam therapy. It is possible that, in the future, cyclotrons will be preferred in carbon beam therapy as they are today in proton therapy.

BIBLIOGRAPHY

[1] Robert Wilson "The radiological use of fast protons" (Radiology 1946-47 487-91)

[2] Nikolay Morozov "IBA-JINR 400 MeV/u superconducting cyclotron for hadron therapy" (this conference, paper FRM1CIO03")