



Review paper

History of hadron therapy accelerators

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ABSTRACT

In the last 60 years, hadron therapy has made great advances passing from a stage of pure research to a well-established treatment modality for solid tumours. In this paper the history of hadron therapy accelerators is reviewed, starting from the first cyclotrons used in the thirties for neutron therapy and passing to more modern and flexible machines used nowadays. The technical developments have been accompanied by clinical studies that allowed the selection of the tumours which are more sensitive to this type of radiotherapy. This paper aims at giving a review of the origin and the present status of hadron therapy accelerators, describing the technological basis and the continuous development of this application to medicine of instruments developed for fundamental science. At the end the present challenges are reviewed.

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Introduction

Hadron therapy (often written as “hadron therapy” and also known as “particle therapy” or “ion beam therapy”) is a specific type of oncological radiotherapy, which makes use of fast hadrons (non-elementary particles made of quarks and antiquarks) to obtain better dose depositions when compared with the ones of X-rays used in conventional radiotherapy.

Today only two types of hadrons are used to treat solid tumours – protons and fully stripped carbon ions – but other hadrons, such as neutrons, charged pions, antiprotons, helium ions (i.e. alpha particles) and other light ions nuclei (like lithium, oxygen, up to silicon ions) have been either used or planned to be used for the treatment of tumour patients. Protons are nowadays an important tool in clinical practice due to the about fifty hospital-based centres in operation and to the continuously increasing number of facilities proposed worldwide. Very promising results have been obtained with carbon ion beams, especially in the treatment of specific radioresistant tumours, but clinical trials are still needed to define the tumours types to be treated and to optimize the protocols.

Hadron therapy is a multi-disciplinary field in which physics, biology, medicine and engineering meet. The continuous technological improvements of medical particle accelerators are the result of the development of research accelerators used in nuclear and high-energy physics. Moreover rotating gantries, which deliver the clinical beam to the patient from different angles, have been developed for both protons and carbon ions.

In this paper a review of the origin and present status of hadron therapy accelerators is presented by describing the technological basis and the continuous improvements in an historical perspective. In this context it's important to underline that a modern hadron therapy facility is not only made of its accelerator. Indeed, the cost of the accelerator can be estimated to be 20–30% of the overall cost of the high-technology part of a multi-room centre, the rest being the cost of the building, of the beam lines and of the equipment of 3–4 treatment rooms, of the diagnostic tools and of the control and treatment planning systems.

Even if these subjects are not addressed in this paper, it is worth mentioning that the history of hadron therapy accelerators has moved on together with the development of precise and highly selective imaging technique such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Furthermore, the improvement of the computational tools has allowed the development of more robust and flexible treatment planning systems.

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X-rays developments and first treatments with hadron beams

Robert “Bob” Wilson is the father of hadron therapy for his 1946 seminal paper [1] in which, after realizing that depth-dose profiles of protons in matter have significant increase at the end of their range – the so-called “Bragg peak” – he proposed to make use of this property for treating deep seated tumours. Nevertheless, this important observation would not have developed into a very effective and not invasive way of treating some type of solid tumours if three important discoveries and inventions had not been made in the fifty years preceding Wilson's work.

The first one was the discovery of the X-rays by Wilhelm Conrad Roentgen, who, at the end of 1895, detected for the first time the effect of a new type of radiation on a fluorescent sheet while he was doing a series of experiments on electrons, accelerated in a glass tube by a potential difference of about 20 kV. His discovery was published at the end of December 1895 [2]. On 13th January 1896, Röntgen demonstrated the properties of X-rays (as he called this new kind of rays, “for the sake of brevity”) to Kaiser Wilhelm II.

With the discovery of X-rays, Röntgen originated a series of extraordinary developments not only in fundamental physics, but also in medical diagnosis and cancer treatment. Only three weeks later, in Liverpool, the physicians Robert Jones and the physicist Oliver Lodge used an X-ray radiograph to image a bullet embedded in a boy's hand [3]. In parallel to diagnostic applications, X-rays were also used in tumour therapy. At the end of January 1896 in Chicago, Emil Grubbe irradiated (without success) the breast of a woman [4]. The irradiation of a patient with a stomach cancer by Victor Despeignes in Lyon is documented in an article of July 1896 [5]. One year later the Viennese doctor Leopold Freund used X-rays to successfully cure a skin tumour in a five-year-old girl [6].

By the beginning of the twentieth century all laboratories and many hospitals had electron tubes similar to Röntgen's one (Fig. 1). They were the precursors of accelerators for radiotherapy and X-ray imaging.

The second fundamental contribution to tumour cure with radiations was the invention of the electron linac, which arose from the association of three friends: the American physicist William Webster Hansen and the two brothers of Irish origin, Russell and Sigurd Varian. In 1937 the three of them – working in a basement in the Stanford physics department, with \$100 funding from the university – succeeded in constructing their first working “klystron”, a device that can produce megawatt microwave impulses. After the war Bill Hansen built an electron linear accelerator to bombard nuclei and study them. Hansen chose a frequency of 3 GHz and produced microwaves both with a klystron and with a generator known as “magnetron” in which, applying the same principle of the klystron but adding a strong magnetic field, the electron beam followed a circular orbit. His first linac was 90 cm long and in 1947 accelerated electrons to 1.7 MeV. In 1948 the three friends founded Varian Associates, a company to manufacture klystrons and linear accelerators.

Today Varian Medical Systems is still the leading company producing radiotherapy equipment and, in particular, therapeutic

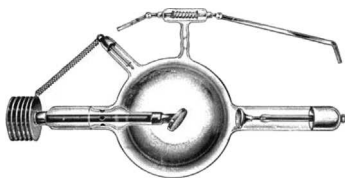


Figure 1. At the beginning of the twentieth century Crookes' tubes like this one were the standard sources of X-rays (taken from Ref. [7]).

electron linacs. In 2012 Varian had a 50% share of the total market distributing more than 1000 linacs. Overall there are more than 20,000 electron linacs at present that, in the advanced world, irradiate (with the X-rays produced by 4–10 MeV electrons hitting high density and high Z materials) about 2000 patients every 1 million inhabitants.

The third event, that opened the way to hadron therapy, was in 1929 the invention of the cyclotron by Ernest Orlando Lawrence. On April the 1st 1929 in Berkeley, Lawrence had the idea of adding a magnetic field to the linear accelerator recently proposed by Wideröe [8]. The first cyclotron had a diameter of 4 inches (about 10 cm), and was able to accelerate protons up to 80 keV. In few years many cyclotrons were built at Berkeley and in 1932 Lawrence and collaborators were able to produce a 4.8 MeV proton beam with their 27-inch cyclotron (Fig. 2) [9].

The invention of the cyclotron was a milestone not only in the development of nuclear physics but also for its use in medicine. In 1935 Lawrence asked his brother John, who was a medical doctor, to join him in Berkeley and use the new 27-inch cyclotron accelerator for medical purposes. Although the principal activity of the laboratory was nuclear research, Lawrence was indeed very interested in medical applications and several cyclotron-produced radionuclides were soon used in studies of physiology, both in animals and humans. The foundations of the three important applications of radioisotopes still relevant today – radiotracing in biology, diagnosis in medicine, and brachytherapy – were laid down at that time.

The first hadrons used in radiotherapy, soon after the construction of the first cyclotron by Lawrence and Livingstone, were fast neutrons. In 1936 the first experimental studies were published by the Lawrence brothers [10] and, at the end of September 1938, the first patients were treated with neutrons, produced with the more powerful 37-inch cyclotron which accelerated deuterons up to 8 MeV.

The fast neutrons, used for therapy, were produced by bombarding a beryllium target. In the traversed tissues the neutrons transfer their energy mainly to highly ionizing protons, which have a value of the “Linear Energy Transfer” (LET) that is much larger than the one of the electrons put in motion by MeV photons produced by linacs. This is a favourable feature when treating “radio-resistant” tumours, i.e. tumours tissues that are less sensitive to X-rays than the surrounding normal tissues. However neutron beams have an unfavourable depth-dose distribution and are difficult to collimate; these are the reasons for which they are no longer used

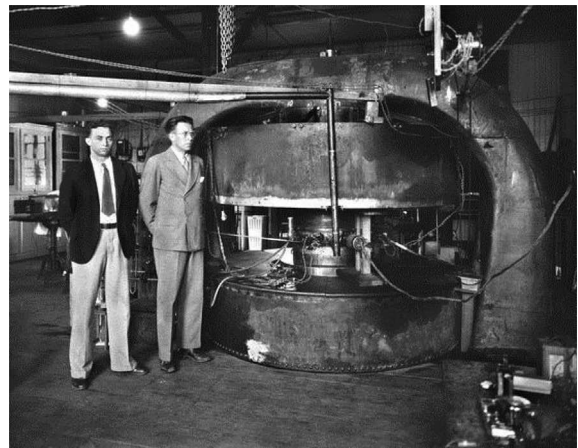


Figure 2. E. O. Lawrence (right) and M.S. Livingstone (left) standing beside the 27-inch cyclotron (Berkeley Lab).

in the treatment of radioresistant tumours and have been substituted by beams of carbon ions and other light ions as discussed in section *Accelerators for carbon ions*.

Another technique, which makes use of either thermal or epithermal neutrons, is Boron Neutron Capture Therapy (BNCT) [11]. This form of hadron therapy is based on the fact that, utilizing particular pharmaceuticals that bind to boron compounds, boron may accumulate in certain tumours (particularly brain tumours). The atoms of boron capture the neutrons used for the irradiation and give rise to alpha and lithium ions. These are very high LET hadrons; moreover their tracks are a fraction of millimetre long, so that they do not leave the tumour and can control the development of the cancerous tissues in which the boron is fixed. However, also in this case the results obtained – on limited cohorts of patients – are not satisfactory and many programs have been discontinued due to the absence of solid clinical evidence.

In 1954 in Berkeley, beams of protons – rather than neutrons – were used for the first time by Cornelius Tobias and John Lawrence to irradiate the pituitary gland [12]. Thus sixty years ago the radiotherapy technique now known as “proton therapy” was born; today the number of treated patients increases by 10% per year.

Although the accelerating principle is still the same, since then the technology of cyclotrons has greatly advanced. The first area of progress is related to the shape of the iron poles producing the vertical magnetic field, which bends the accelerated particles along a spiral trajectory. The two oppositely facing poles are no longer flat, but are made of “hills” and “valleys”, as shown in Fig. 3a. In such an “Azimuthal Varying Field” cyclotron the outward spiralling bunches of particles cross the boundary between a high-field region and a low-field region many times and are subject to alternating focussing and defocussing forces. As in all strong focussing accelerators [13], such an alternation causes an overall focussing effect on the particle bunches that thus remain transversely compact. For energies lower than 10 MeV, the pole faces are typically flat. At higher energies relativistic effects become important and the poles have more complicated shapes, as shown in Fig. 3b.

A second development is related to the maximum proton current. In the first cyclotrons the particle bunches were extracted with an electrostatic deflector and this process typically had an 80% efficiency, so that 20% of the current was lost and activated the deflector and the magnet. In the 1970s the acceleration of negative ions H^- – made of one proton and two electrons – was introduced. The extraction of the beam is simplified since it can be achieved using a thin stripping foil conveniently positioned on the beam trajectory. In the foil the two electrons of each negative ion are stripped leaving a positively charged proton that deviates in the opposite direction under the influence of the magnetic field and is

extracted without the need of a deflector. The result is a clean extraction with efficiency very close to 100%, which implies a drastically reduced activation of the cyclotron components – simplifying maintenance, regular inspections, and decommissioning – and allowing larger extracted currents.

A remarkable characteristic of these cyclotrons is the possibility of obtaining simultaneous multiple beams by partial extraction using more stripping foils. This is the case in the so-called “baby cyclotrons”, stable and reliable machines used for the production of radiopharmaceuticals, used in particular in Positron Emission Tomography. Such cyclotrons can run continuously – in hospitals and radiopharmaceutical companies – with proton beam currents of 100–500 μA , and require limited supervision and maintenance.

Contrary to the cyclotrons, in which the magnetic field is constant in time and therefore the radius of the beam trajectory is increasing with the beam energy, synchrotrons are machines having a fixed radius: the magnetic field increases during the acceleration cycle and the beam follows the same circular trajectory. The radio frequency of the accelerating cavity also increases to follow the revolution frequency of the beam. Such machines were developed mainly for fundamental research in high-energy physics, to overcome the energy limitation of the cyclotrons. The invention of the synchrotron is based on the principle of phase stability, which was proposed in 1944/45 independently by Vladimir Veksler in USSR and Edwin McMillan (a former student of Lawrence) in Berkeley.

From physics laboratories to clinical centres

From the 50's both cyclotrons and synchrotrons – built for fundamental research – have been used for hadron therapy treatments and radiobiology. Certainly the facility that made the largest impact on the development of proton therapy was the 160 MeV Harvard cyclotron, shown in Fig. 4 [14]. This was the cyclotron at which Bob Wilson was working in 1946 and was undoubtedly the best place to start proton therapy.

In 1961 Raymond Kjellberg, a young neurosurgeon at Massachusetts General Hospital (MGH) in Boston, became the first to use the Harvard beam to treat a malignant brain tumour. By the mid-1970s at the Harvard Cyclotron Laboratory the physicists Andy Koehler, Bernard Gottschalk and their colleagues – working with radiation oncologists guided by Herman Suit – had developed methods to treat large brain tumours, while Michael Goitein had written very sophisticated codes for quantifying the related treatment plans. Overall three groups of radiation oncologists worked for many decades with Harvard physicists on three clinical studies: neurosurgery for intracranial lesions (3687 patients), eye tumours

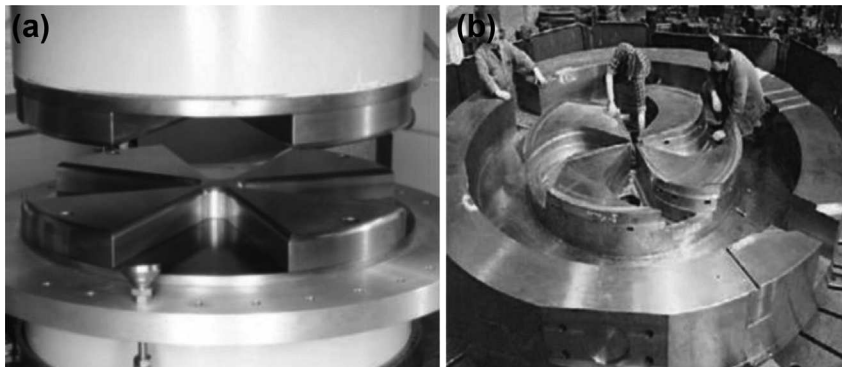


Figure 3. (a) By introducing hills and valleys an overall focussing effect is obtained (source: Rutgers cyclotron). (b) The spiralling is used to improve the focussing effects (courtesy of IBA).



Figure 4. N. Ramsey (right) and L. Davenport (left) in front of the brand new 160 MeV Harvard cyclotron in 1949.

(2979 patients) and head-neck tumours (2449 patients). The results obtained convinced many radiation oncologists of the superiority of protons with respect to X-rays to treat tumours that are close to organs at risk.

From the fifties to the mid-eighties particle radiotherapy was based exclusively on accelerator facilities developed for nuclear physics research, with easy-to-build horizontal beam lines used for proton therapy (Table 1). Significant numbers of patients were treated at the Harvard Cyclotron Laboratory and also, even if with smaller numbers, at the Gustav Werner Institute in Uppsala, the Institute of Theoretical and Experimental Physics (ITEP) in Moscow, the Joint Institute of Nuclear Research in Dubna, the Leningrad Institute of Nuclear Physics in Gatchina, the National Institute of Radiological Sciences (NIRS) in Chiba, the University of Tsukuba and the Paul Scherrer Institute (PSI) in Villigen, that started a program devoted in particular to paediatric tumours.

It was frequently stated that the field would not develop without dedicated facilities. However this step took almost thirty years, a much longer time compared to X-ray therapy. The reasons are easy to explain. For X-ray therapy of deep tumours, it is enough to accelerate electrons up to 10 MeV; instead protons must be taken to at least 200 MeV, an energy that is twenty times larger. Moreover, the proton mass ($938 \text{ MeV}/c^2$) is about two thousand times larger than that of the electron; medical proton accelerators – cyclotrons or synchrotrons – are therefore much larger and more expensive than the electron linacs producing X-rays. For these reasons, until the beginning of the nineties accelerators built for nuclear and particle physics experiments were used for proton therapy; a fraction of the machine time was dedicated to the treatment of a few patients, the rest to research activities.

Going back to Boston, when in 2002 the Harvard cyclotron was closed, almost 10,000 patients had been irradiated and foundations

laid for the subsequent development of the field. In particular, the expertise developed was soon transferred to the new 230 MeV hospital-based facility of the Massachusetts General Hospital (MGH), which was built by the Belgian company Ion Beam Applications (IBA) and opened in 2001.

A new era in particle therapy started with the construction and installation of dedicated accelerators in hospital-based clinical centres. The first was the MC60, a 62.5 MeV proton cyclotron, delivered by Scanditronix, which has been operating at the Clatterbridge Oncology Centre (UK) since 1989. The cyclotron has been used for fast neutron radiotherapy and is still used for the treatment of ocular tumours [15]. In the same period, other six centres (mostly located in physics laboratories, differently from the case of Clatterbridge) accelerating proton beams to 60–70 MeV started treatment of eye melanomas and other eye tumours and malformations. They were located in PSI, Nice, University California San Francisco, Triumph, Berlin and Catania and feature a single horizontal beam.

The next major step was the installation at Loma Linda University (LLUMC, California, USA) of a dedicated 7-m-diameter 250 MeV synchrotron built by Fermilab (Fig. 5). This was the first hospital-based facility using a synchrotron, and it has been a pioneer also because of the three 10 m diameter rotating gantries that allow adjusting the angle of the beam penetrating into the patient's body [16]. The first patient was irradiated in 1990 and, in the same year, USA Medicare approved the insurance coverage of this new cancer treatment.

A smooth transition from a physics laboratory to a hospital facility took place in Japan. The University of Tsukuba started proton clinical studies in 1983 using a synchrotron constructed for physics at the High Energy Accelerator Research Organization (KEK). A total of 700 patients were treated from 1983 to 2000. In 2000, a new in-house facility, called the Proton Medical Research Centre (PMRC), was constructed adjacent to the University Hospital. Built by the Hitachi Company, it was equipped with a 250 MeV synchrotron.

Another major advancement in particle therapy was the application of scanning beams, which allows “painting” the tumour target with the Bragg peak. The Bragg peak produces – at the end of the range of the hadrons in tissue – a “spot” in which a large dose is delivered. This technique results in a significant improvement of the conformity of the dose distribution to the target volume and is thus expected to improve the sparing of close-by organs at risk. The first scanning systems were developed in the research facilities at PSI (Villigen, Switzerland) for protons [17] and GSI (Darmstadt, Germany) for carbon ions [18] and have been used to treat patients since 1996 and 1997, respectively. More recently scanning beams have started to be used on a routine base in several clinical facilities, such as at the Rinecker Proton Therapy Center in Munich and at the University of Florida Proton Therapy Institute in Jacksonville (Florida).

Table 1

The pioneers of proton therapy; these facilities are now no longer in operation except for PSI and the centres in Moscow and St. Petersburg.

Facility	Country	Years of operation
Lawrence Berkeley Laboratory	USA	1954–1957
Uppsala	Sweden	1957–1976
Harvard Cyclotron Laboratory	USA	1961–2002
Dubna	Russia	1967–1996
Moscow	Russia	1969–now
St. Petersburg	Russia	1975–now
Chiba	Japan	1979–2002
Tsukuba University	Japan	1983–2000
Paul Scherrer Institute (PSI)	Switzerland	1984–now

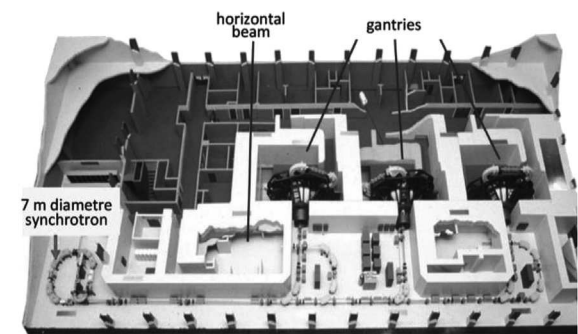


Figure 5. The LLUMC synchrotron was built by Fermilab.

To fully exploit the accelerator, every hospital-based centre has from 3 to 5 treatment rooms so that, while a patient is irradiated for 3–5 min in one room, in others precise alignment measurements are taken to prepare other patients. Because each patient needs 20–30 sessions, one four-room centre can treat up to 1200–1300 patients a year. The size of the facility and the optimization of the workflow are still debated and many studies have addressed this problem [19,20].

Figure 6 shows a typical commercial centre featuring three gantries, each one with a diameter of about 10 m and a weight of almost a hundred tons.

At present about forty-five proton therapy centres are in operation or under construction throughout the world. The list of the centres in operation with the statistics of the number of treated patients is updated every year by the Particle Therapy Co-Operative Group (PTCOG) and can be found in Ref. [21]. About ten companies offer turnkey hadron therapy centres, organised around a cyclotron (either at room temperature or superconducting), a synchrotron or a linac. Among them are A.D.A.M. (Switzerland), Hitachi (Japan), IBA (Belgium), Mevion (USA), Mitsubishi (Japan), Optivus (USA), ProTom (USA), Sumitomo (Japan) and Varian (USA).

Accelerators for carbon ions

A beam of carbon ions is by its nature a very different radiation compared to X-rays and protons. Firstly a fully stripped carbon ion – i.e. a nucleus of carbon made of six protons and six neutrons – produces a sharper Bragg peak than the one produced by protons so that the “spot” due to a mono-energetic carbon ion beam has a FWHM of 3–4 mm instead than 10 mm. This implies that with carbon ions one can deliver a dose that is *macroscopically* more conformal to the tumour target than the doses due to protons and X-rays.

Secondly, to reach a 28 cm depth a carbon ion must have initially about 4800 MeV (400 MeV/nucleon) instead than the 210 MeV of a proton. This is due to the fact that carbon ions, with an electric charge six times larger than protons, slow down more rapidly. In this process they leave more energy per unit length than a proton in the ratio of the energy needed to reach the same depth: $4800/210 \sim 23$. This is the average ratio of the LET of the two beams and is also the ratio between the numbers of ionizations left in the nucleus of each traversed cell. The consequence is that, even if a beam of carbon ions deposits the *same* dose in a tumour tissue, at the molecular level the biological effects are *different* from those of protons (and of X-rays) because they have a larger “Radio-Biological Efficiency” (RBE). Carbon ions at the end of their range can have, in

some types of cell, *three times* higher RBE than protons. This makes them more effective in killing radioresistant cells than protons and X-rays, similarly to what happens with fast neutron beams but with the advantage that the macroscopic distribution of the dose can be made very conformal to the tumour target because of the small dimensions of the spot [22]. Thus, the high LET difference makes carbon ions capable of treating radioresistant and hypoxic tumours which represent about 5% of the 2000 tumours irradiated each year with X-rays, in a population of one million inhabitants.

The road to the treatment of tumours with carbon ions finds its root in Wilson's paper of 1946, where he commented “... For a given range, the straggling and the angular spread of alpha particles will be one-half as much as for protons. Heavier nuclei, such as very energetic carbon atoms, may *eventually become therapeutically practical*...”. Thirty years later, at Lawrence Berkeley Laboratory, the group of radiobiologists led by Cornelius Tobias started to develop ion beam hadron therapy, initially experimenting with cell cultures and animals [23]. In 1975 patients were treated for the first time at the Bevalac accelerator with argon ions, which are made up of 18 protons and 18 neutrons and seemed good candidates against hypoxic and radioresistant tumours. But problems arose owing to non-tolerable side effects in the normal tissues. After a few irradiations of some 20 patients, Tobias and collaborators used lighter ions, in particular neon ions – which are made of 10 protons and 10 neutrons – for 433 patients, until the Department of Energy decided to close the Bevalac in 1993. The results obtained led to the conclusion that neon ions had too high an electric charge and damaged the healthy tissues through which the beam passed. In contrast, carbon ions, having only six protons, were considered more adapted to the treatment of radioresistant tumours, as well as for the preservation of healthy tissues.

At the same time, in Japan, Yasuo Hirao and collaborators proposed the realization of the Heavy Ion Medical Accelerator in Chiba (HIMAC) to be built in the Chiba prefecture (Fig. 7). In 1994 the facility treated the first patient with carbon ions at a maximum energy of 4800 MeV. By the end of 2014, under the leadership of Hirohito Tsujii, about 9000 patients have been treated and many difficult and common tumours have been shown to be controllable [24]. Recently a second building has been added, which contains three rooms with fixed beams and a carbon ion superconducting gantry.

In 1993, Gerhard Kraft obtained the approval for the construction of a carbon ion facility at GSI (Darmstadt), later called the “pilot project” [25]. Treatments started in 1997 and about 400 patients have been treated with carbon ion beams under the direction of the radiation oncologist Jürgen Debus.

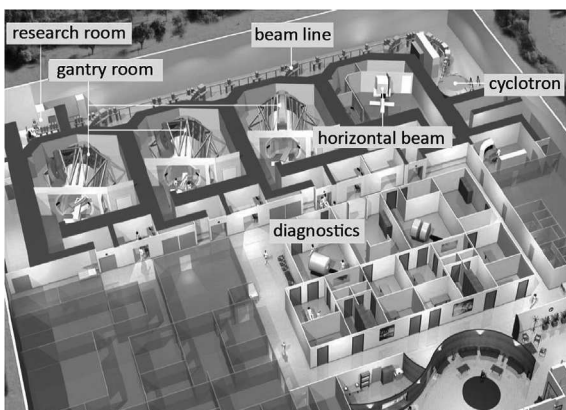


Figure 6. Layout of a commercial centre based on a 230 MeV cyclotron. The Energy Selection System is visible on the left upper part of figure (courtesy of IBA).

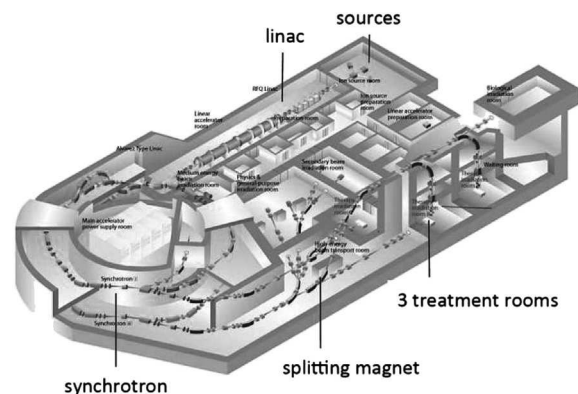


Figure 7. HIMAC features two large synchrotrons, injected by an Alvarez linac, and three treatment rooms for a total of two horizontal and two vertical beams.

In 2009 the pilot project was closed and the brand new Heidelberg Ion-beam Therapy (HIT) Centre was opened (Fig. 8), where all the medical and technical competence accumulated in Darmstadt has been applied. The HIT was a joint endeavour of the GSI and the Siemens Medical company. HIT, with its 25 m long rotating gantry [26] that can be used both for protons and carbon ions, has been the first hadron therapy centre able to compare clinical results obtained with protons and carbon ions with beams coming from the optimal directions.

After HIT, CNAO (Centro Nazionale di Adroterapia Oncologica) in Pavia was the second institution in the world to offer – outside Japan – radiotherapy treatment with carbon ions. The CNAO design is based on a study carried out at CERN between 1996 and 2000, the so-called PIMMS (Proton-Ion Medical Machine Study). The TERA Foundation contributed, together with the Austrian MedAustron group, the group Oncology 2000 (Czech Republic) and many CERN scientists and engineers, under the leadership of Phil Bryant. The outcome of PIMMS [27] was conceived as a toolkit from which any European user could select and adapt the parts best suited to their own goals.

The PIMMS design was then modified by TERA into the PIMMS-TERA design eventually adopted for the CNAO centre [28]. The modifications consisted mainly in a reduction of the total footprint, obtained by moving the proton and carbon ion sources inside the ring and by using a single injection linac and a fan-out magnet with short magnetic lines to transport the beams from the synchrotron to the three treatment rooms. No gantry was built but space was kept free – to the left of Fig. 9 – for the later installation of two carbon ion gantries, as large as the one of HIT (Fig. 8).

The MedAustron design is also based on the PIMMS-TERA synchrotron. The lines are similar to the ones described in the PIMMS reports [27]. In this case there are three rooms with fixed beams and also a proton gantry [29]. Beams have been extracted in fall 2014 and the first patient treatment is expected before the end of 2015.

In the framework of ENLIGHT, the European Network for Light Ion Therapy [30] coordinated by Manjit Dosanjh, HIT and CNAO have joined forces to develop common protocols and compare the effects of proton and carbon ion treatments on a number of tumours. With HIT and CNAO – recently joined by the centres in Marburg (Germany) built by Siemens Medical and MedAustron – Europe is well placed to perform coordinated therapy comparisons on many patients, so to define those tumours that are the optimal targets of this unique approach to the radiotherapy of radio-resistant tumours. Japan remains at the forefront of ion therapy with about 10,000 patients, while in 2013 – twenty years after the closure of the Berkeley Bevalac – the National Cancer Institute and the Department of Energy in the USA have decided to launch a study for an American carbon ion and proton centre.



Figure 8. The Heidelberg Ion-Beam Therapy Centre features two horizontal beams and a carbon ion gantry, the first one ever built (HIT Photo Gallery).

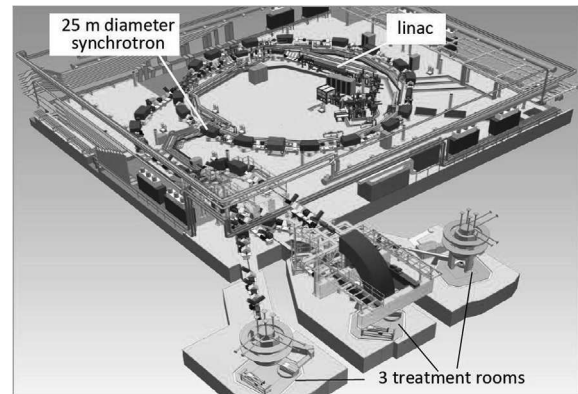


Figure 9. The CNAO synchrotron serves, with very short magnetic transport lines, three treatment rooms; the central one features a horizontal and a vertical line.

Recent trends in accelerators and gantries

In 2014 only cyclotrons or synchrotron are used clinically for hadron-therapy treatments, but in the last years novel ideas and approaches have been proposed and studied to improve the beam quality and/or reducing the overall size and cost [31]. Recent developments include: i) fast extraction synchrotrons with fast varying energy, ii) novel commercial solutions for proton therapy single room facilities, iii) new accelerating schemes (FFAG and linacs) and other accelerating techniques (DWA, laser driven accelerators), iv) proton and carbon ion gantries with novel superconducting solutions.

New synchrotrons

For a synchrotron, typically one has to wait 1–2 s until the next spill reaches a different beam energy. Ideas for rapid cycling synchrotrons are based on fast extraction schemes, as opposite to slow extraction scheme adopted by the existing medical synchrotrons. The beam is fully extracted in one turn and at a repetition rate as high as 30 Hz, allowing energy variation in the energy range from 70 to 250 MeV [32]. Small beams are obtained by strong focussing optics. With a high repetition rate (spills with variable energy at 30 Hz) and strong focussing, a high dose rate of 20 Gy per litre per minute can be obtained. The design exists also for a dual machine for both protons and carbon ions up to 400 MeV/u, which consists of a racetrack lattice of 60 m, with two parallel zero dispersion straight sections and an injector which is placed inside the ring, as in CNAO (Fig. 9) [33]. The design of this “ion Rapidly Cycling Medical Synchrotron” (iRCMS) has been adopted by Best Medical International (USA), with a collaboration agreement signed with Brookhaven National Laboratory at the beginning of 2012.

Fast changes of the energy of a conventional synchrotron have been studied at HIMAC [34] and carbon-ion beams with various energies have been used for scanned particle therapy at NIRS [35]. By carefully changing the magnets current and simultaneously decelerating the beam during the slow extraction process, the energy of the extracted beam can be varied within a spill (Fig. 10). Energy variation times of about 10–20 ms have been achieved. This makes such synchrotrons more suitable for rapid scanning techniques than the ones of traditional designs.

Single room facilities

Several commercial companies are proposing proton therapy facilities consisting of a single accelerator and beam delivery

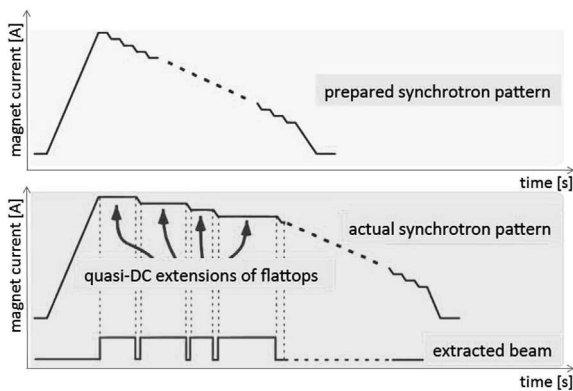


Figure 10. Scheme of synchrotron operation with stepwise flat-top extraction. Starting from a prepared pattern (top), each flat-top can be extended, and the beam can be extracted from the synchrotron during any of these flattops (adapted from Ref. [36]).

system. From an economical and decision-making perspective, the investment cost of a single room facility is obviously much lower than that of a multi-room facility, even if the cost per room is larger. From the technical point of view, the required technological solutions are very interesting and challenging.

Compact synchrotron designs have been proposed in the 90's. The design of a compact synchrotron has been studied by ENEA, BINP and TERA [37,38]. The maximum energy of 200 MeV protons is achieved in a ring of 2.2 m diameter, equipped with 4 T dipoles. The ring is injected with 12 MeV negative hydrogen ions, which enter the ring after stripping. The magnets should be pulsed with 3.5 ms, 180 kA pulses at 1 Hz. The same technology is also proposed for a compact gantry design.

Another 200 MeV compact synchrotron (3.6 m diameter) has been designed and developed at KEK [39]. It features a simple lattice design with 4 FODO cells and 4 bending magnets with peak magnetic field of 3 T. Particular care has been put into the design of the power supplies which should provide field currents as large as 200 kA for a single turn coil [40]. Injection is proposed by stripping 2 MeV H^- ions with a carbon foil.

The company PROTOM (Protvino, Russia) proposes a commercial small synchrotron, 6 m in diameter, with a very low energy injector (1 MeV). The optics is simplified by the low energy beam injection and by the fact that no sextupole magnets are used, differently from traditional synchrotrons. The synchrotron energy can be varied up to 330 MeV and the machine is small enough to fit into one room. The first prototype installed at MIT Bates Linear Accelerator Center in 2009 has now been delivered to McLaren Proton Therapy Center in Flint, Michigan. Other three installations are being constructed in Protvino and Pushino (Russia) and in Ruzomberok (SK) [41].

The first proposal of a single room system consisting of a small 250 MeV cyclotron mounted on a rotating gantry dates back to the 1989 by Henry Blosser [42]. For this purpose, the use of superconducting (SC) magnets is needed in order to reduce the machine radius. However the high risk of quenching during the rotation makes the coil design challenging. The first SC-cyclotron of 250 MeV has been based on a NSCL design and has been built by ACCEL (now Varian Medical), in collaboration with PSI [43]. With a magnetic field strength of 3.8 T, the outer diameter is 3.2 m, to be compared to the typical 5 m needed with normal conducting magnets. The weight (90 tons) is also significantly lower than the one of normal conducting cyclotrons [44].

More compact machines can be built by increasing the magnetic field (up to 9 T) and designing a synchrocyclotron, in which the difficulties related to the high field and small orbit separations at

extraction can be overcome. Both Mevion Medical Systems [45] and IBA [46] sell now single room facilities based on high field SC synchrocyclotrons. Mevion Medical Systems (once Still River Systems) has built a 9 T SC synchrocyclotron mounted on a gantry delivering a 250 MeV beam, without energy selection system (Fig. 11). The proton energy is adapted with range shifters and modulator wheels and the beam is spread by means of a passive scattering system. An upgrade of this single room facility foresees the use of a spot scanning system.

IBA proposes a single room facility consisting of a static small synchrocyclotron, in which the proton bunches perform 40,000 turns, followed by an energy selection system mounted on a gantry which can be equipped with a scanning nozzle (Fig. 12).

New accelerator concepts

FFAG accelerators

The Fixed Field Alternating Gradient (FFAG) accelerator combines the concept of the synchrocyclotron – in which the magnetic field is fixed and the RF frequency varies in time at a typical repetition rate of up to 1 kHz – with the use of separated sector magnets. The sector magnets are designed to include strong, alternating gradients, which provide the beam focussing [47,48]. The major advantage of FFAGs is the very large acceptance of beam energy and emittance, and its capacity to achieve higher beam intensities than synchrocyclotrons. Even if a priori high currents are not required in hadron therapy, FFAG are still attractive with respect to cyclotrons and synchrotrons because of the possibility of actively varying the energy at high repetition rate, by simply switching off the RF when the required energy is achieved.

Several designs of both scaling and non-scaling FFAGs have therefore been proposed for hadron therapy in the last decade [49,50]. On the other hand, the proposed FFAGs have a typical diameter of about 15 m and can weigh up to 200 tons, the sector magnets are not easy to build and the RF structures needs to be compact and with high voltage gain. Finally, proton FFAGs need an external injector of about 10 MeV, which can be a cyclotron or even another FFAG.

Keil et al. have proposed a difficult to build facility also for carbon ions [51], which features three concentric FFAGs in a dense doublet lattice to accelerate protons to 250 MeV (first two rings) and carbon ions up to 400 MeV/u (rings 2 and 3). Extensive reviews of the subject can be found in Refs. [52,53].

Linear accelerators

The use of high frequency linacs for protons has first been proposed in 1991 [54,55]. These designs were based on an “all linac” approach. Another approach, based on the combination of a high intensity cyclotron with a high frequency linac – thus called “cyclinac” – was proposed in 1994 [56].



Figure 11. Mevion S250 is based on a large field superconducting synchrocyclotron mounted on a gantry that can rotate by $\pm 110^\circ$ (Courtesy of Mevion Medical Systems).

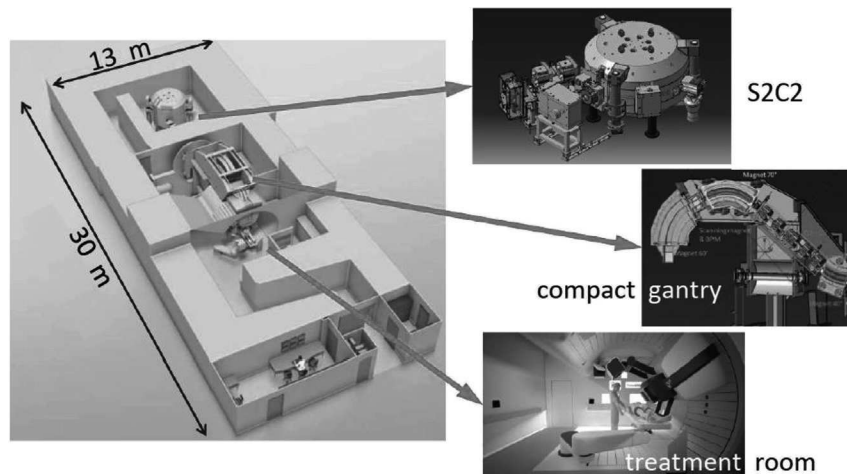


Figure 12. The 7.5 m diameter gantry of ProteusONE (IBA) rotates by $\pm 120^\circ$ around the patient (courtesy of IBA).

Very low proton (carbon ions) currents – of the order of 1 nA (0.1 nA) – are enough to deliver the typical dose of 2 Gy per litre in 1 min. For this reason high-frequency (typically 3 GHz) linacs, with small beam apertures (5–8 mm) and low duty cycles (about 0.1%), have been developed as hadron therapy machines. The main advantage of linacs, pulsing at 200–400 Hz, is that the output energy can be *continuously* varied on a pulse to pulse basis (i.e. every 2.5–5 ms) and the tumour target can be covered about ten times in 2–3 min by applying the so-called “spot scanning technique with multi-painting”. Furthermore, in a linac, there are neither complex injection or extraction systems (typical of synchrotrons and FFAGs) nor the Energy Selection System (ESS), needed to vary the beam energy of a cyclotron. The absence of passive absorbers and mechanical devices is an advantage in terms of reliability, maintenance and radiation protection. On the other hand, a large number of modular accelerating units (typically 10), powered by independently controlled modulator-klystron systems, is needed to obtain the desired final beam energy variation, by adjusting the amplitude and/or phase of the klystron RF pulses.

At the end of the 90's TERA Foundation built the first high-frequency proton linac in collaboration with CERN and the INFN Sections of Milano and Naples [57]. This proof of principle prototype called LIBO (Linac BOoster) was based on a 3 GHz Cell Coupled Linac design and was made of 4 “tanks”, in which the average accelerating field was 16 MV/m so that protons would be accelerated in about 1 m from 62 to 74 MeV. The computed values of the acceleration and the transmission have been checked experimentally in a “cyclinac” formed by the INFN superconducting cyclotron in Catania and LIBO [58].

Following this first demonstration, several designs and construction projects have been launched. Firstly, G. Picardi et al. are constructing IMPLART in the Frascati ENEA laboratories [59], where in 2014 protons have been accelerated to 11.7 MeV. Secondly, as a follow-up of the development described in Ref. [60] a 150 MeV proton “all linac” is being built by ITEL and INFN in South Italy [61]. The rationale and the basics of hadron therapy linacs are described in Ref. [62].

From the commercial point of view, at present the CERN spin-off company A.D.A.M. is building a Linac for Image Guided Hadron Therapy (LIGHT) based on a novel 750 MHz RFQ (built by CERN) followed by a Side Coupled Drift Tube Linac (SCDTL) and a CCL very similar to LIBO (Fig. 13). At the end of 2016, after the proton acceleration tests made on CERN premises, LIGHT will be moved to a hospital.

In collaboration with CERN, TERA is building prototypes of the novel travelling wave linac structure, which will reach the 50 MV/m needed for the compact single room facility of Fig. 14. As for all linacs the patient will be treated with the 200 Hz spot scanning multi-painting technique. The same applies to the carbon ion (and proton) linac of CABOTO (Carbon Booster for Therapy in Oncology) – also been studied in collaboration with CERN [63].

Dielectric wall accelerators

The Dielectric Wall Accelerator (DWA) is a new compact accelerator for tumour therapy. Protons are accelerated in a tube made of a stack of High Gradient Insulator (HGI) disks, alternated with conducting elements (with a period of 1 mm). High voltage switching units (Blumlein generators) are connected to each conducting sheet and are activated by a laser pulse of 3–4 ns. Such a scheme is shown in Fig. 15.

The high gradient insulators in principle are capable to stand electric fields as large as 100 MV/m [64]. When the Blumleins are activated via photoconductive switches, an electric field is induced on the inner side of the insulator (the so called “dielectric wall”). With such high gradients, the size of a low current DWA for proton therapy applications would be of 2–2.5 m [65].

Open problems of this scheme are the focussing of the accelerated protons, the repetition rate of the pulsed laser and the very short pulses which put severe constraints on the ion source that should provide accurately the large amount of protons per pulse needed. Finally the practical feasibility of a 100 MV/m gradient, which would allow having the DWA rotating around the patient in a small single-room facility, is still under study. The Lawrence

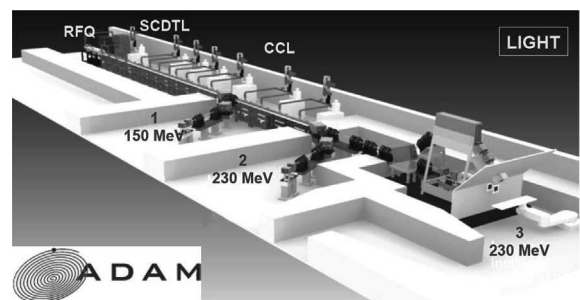


Figure 13. The magnets of the beam lines are fast and can follow the fast adjustments of the beam energy of LIGHT.

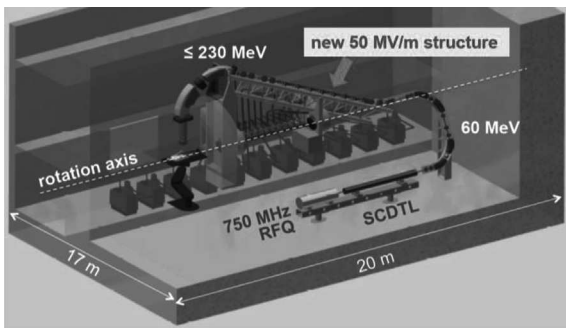


Figure 14. In TULIP (TURNing LInac for Proton therapy) the high-gradient linac rotates around the patient couch by $\pm 110^\circ$.

Livermore National Laboratory (LLNL), in collaboration with Tomotherapy and CPAC (USA), has designed and is building a DWA for proton therapy. A first prototype, including an RFQ injection system with a pulsed kicker that selects the desired proton bunches, and a linear accelerator incorporating the HGI with stacked Blumleins and switches connected to capacitor plates is now under test. The module has achieved accelerating gradients in the order of 20 MeV/m [66]. More recently higher fields have been obtained (up to 35 MV/m), still far from the expected 100 MV/m.

Laser driven accelerators

Another very attractive solution for a compact accelerator for proton therapy is given by the use of powerful and short laser pulses to irradiate thin target foils, generating a plasma field [67]. Electrons in this plasma emerge from the rear surface of the target inducing strong electrostatic fields (of the order of GV/m), which then pull out the protons from the rear surface of the target. This scheme, known as TNSA (Target Normal Sheet Acceleration) method [68], has been proved to work, generating proton energies up to 20 MeV with laser pulses of 320 fs and intensity of 6×10^{19} W/cm² [69]. Recently, proton energies as high as 160 MeV have been obtained at LLNL (USA) [70].

Radiation Pressure Acceleration (RPA) is another method of laser driven acceleration. In this case the thin target foil is illuminated by a much larger intensity laser pulse and the whole foil is accelerated by the radiation pressure of the laser pulse incident on it [71].

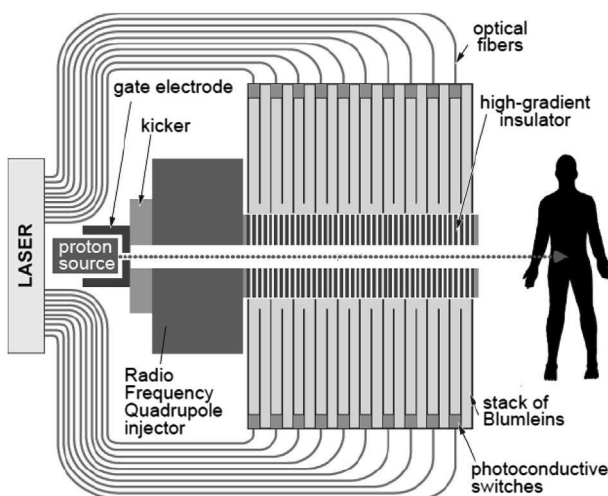


Figure 15. Scheme of a compact Dielectric Wall Accelerator for proton therapy. A virtual travelling wave is obtained by switching consecutive switches with a laser pulse of few ns.

Laser driven systems are very attractive because of their compactness, but also because optic components for laser light transport lines are typically small, light and easy to align compared to heavy magnets used for beam transport. Gantries based on optical lenses are the ultimate goal for a compact and light accelerator. Though, many issues need still to be solved before this type of accelerator becomes practical [72]. First of all, the energy spectrum of the produced beam is almost continuous. The use of properly shaped targets would allow to reduce significantly the energy spread of the beam and to obtain 200 MeV proton beams with affordable laser intensities [73]. Another possible solution obtained with Monte Carlo simulations is to shape the target in such a way to transmit energy spectra producing spread out Bragg peaks within one laser shot. The sensitivity to the initial conditions of the proton beam is in this case a critical issue. Furthermore the reduction of size and increase in repetition rate of the laser system is also challenging.

Proton and carbon ion gantries

A carbon ion gantry needs more powerful and weightier magnets than a proton gantry because of the three times bigger beam rigidity of 5000 MeV carbon ions than the one of 200 MeV protons. Therefore the HIT gantry, the first gantry for carbon ions, is 25 m long and weighs 600 tons, while a typical proton gantry is 5–10 m long and four times lighter. Novel interesting developments are taking place in this field, mostly based on superconducting magnets technology.

Some major challenges such as rotatable cryogenic systems and rapid field scanning have to be solved for superconducting magnets to be used for hadron therapy gantries.

At HIMAC (Japan) the design of a light superconducting gantry for beams of 430 MeV/u carbon ions has been completed. The gantry measures 13 m in length and 5.5 m in radius and is composed of 10 superconducting magnets with a field of about 3 T, one pair of scanning magnets, and two pairs of beam profile-monitor and steering magnets, mounted on a cylindrical supporting structure. Beam focussing is obtained by combined function magnets [74].

A superconducting magnet design proposed already in 2008 for an ion gantry is the CEA design, firstly developed for the ETOILE project in Lyon [75] and then continued in collaboration with IBA. The use of two 45° conventional dipole and one final 90° superconducting dipole is foreseen. The final dipole, with twelve planar coils, is designed for a magnetic field of 3.2 T, corresponding to a bending radius of 2 m for a beam of 410 MeV/u carbon ions. The total size of the gantry is 13.5 m length and 4 m radius.

At Lawrence Berkley National Lab, a novel design of a curved superconducting dipole for carbon cancer therapy accelerator has been proposed by Robin et al. [76]. The proposal concerns a combined function 90° dipole magnet working at 3.5 T. The main innovation consists in the two layers curved coils, placed around two opposite wound and skewed solenoid fields [77]. A laminated mandrel design has been prototyped, allowing for increased manufacturing techniques and reduction of eddy currents produced during field changes. Future tests on the magnet performance and field quality are foreseen [78].

FFAG-type beam optics, based on very strong alternating gradients, could be of interest for beam transport systems in a gantry [79]. The large momentum acceptance (on paper up to 30%) of the optics would allow to keep the magnetic fields settings constant even when the beam energy is changed, therefore enabling a much faster energy modulation.

Finally, it is worth mentioning another study conducted in the framework of the ULICE (Union of Light Ion Centres in Europe)

project, a European network aiming at improving the access to hadron-therapy facilities for particle therapy research. In this study a review of gantries for carbon ions is presented and, by taking into account the global cost for several possible solutions, a “Riesenrad gantry” consisting in a 90° normal conducting magnet and an eccentrically positioned patient cabin is proposed [80].

Conclusions

Sixty years after the first treatments performed in Berkley, more than 110,000 patients have been treated with protons and 11,000 with carbon ions. More than 95% of these patients have been treated with “passive” spreading systems, i.e. by using a wide hadron beam covering the whole transverse dimensions of the tumour. The “active” methods (spot scanning and raster scanning) are entering in the clinics, with their improved dose distributions. Only very recently moving tumours (because of the inspiration cycle, for instance) have been irradiated with a technique, already in use for X-rays, which can be called “Image Guided Particle Therapy”. The advantages of hadron beams will be fully exploited only when this technique will become common practice.

Despite of the fact that the numbers of treated patients are increasing, they are still very small compared to all the cases that would benefit from proton or carbon ion therapy, and that are nowadays treated with conventional X-ray therapy. While carbon ions are indicated for particular types of tumours (the so called radioresistant tumours) representing up to 5% of the total number of patients treated with X-rays, protons would be indicated in more than 12–15% of the cases, that is in about 240–300 cases every year per 1 million inhabitants.

More than 45 centres dedicated to delivering therapeutic beams of protons and carbon ions are currently in operation. Some of them are still hosted in physics laboratories, but all the new centres are dedicated clinical facilities, often well integrated with close-by hospitals. The costs, together with the size of hadron therapy accelerators and beam transport lines, compared to linacs for conventional X-ray therapy, represent still an obstacle to a further spread of hadron therapy. Many commercial companies are now offering complete turn-key proton-therapy centres with multiple treatment rooms. Recently the first commercial single room facilities have also been installed and started operation, allowing a reduction of the initial investment from the typical 120–150 million euros (with three gantry rooms) to about 25–30 million euros (for a single room). Taking into account both the expenses, as well as the number of patients treated each year, in Europe the cost of a complete proton therapy course varies between 20,000 and 25,000 Euros, corresponding to 2–2.5 times the cost of IMRT and less than one half of the cost of many chemotherapies.

In terms of size, hadron therapy centres are much bigger than conventional radiotherapy machines. In fact accelerating proton beams to the energy of 230 MeV needed for treatments or carbon ions up to 400 MeV/u in small spaces is still a technological challenge. The accelerators used for proton therapy are mainly cyclotrons, while for carbon ion therapy only synchrotrons have been used up to now. Such machines have been proved to be reliable and efficient, but more compact and more adapted designs have been investigated. In particular high frequency RF linacs are now commercially available for proton therapy and in the future possibly also for carbon ions. FFAG have also been prototyped. Further in the future laser accelerators, potentially smaller than cyclotrons, synchrotrons or linacs, would allow to reduce the dimensions of hadron therapy facilities; but certainly time is needed to bring such a technology to a mature stage [72].

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