Nuclear Instruments and Methods in Physics Research A 620 (2010) 563–577

Contents lists available at ScienceDirect

Nuclear Instruments and Methods in Physics Research A

journal homepage: www.elsevier.com/locate/nima

Review

Accelerators for hadrontherapy: From Lawrence cyclotrons to linacs ☆

U. Amaldi [1], R. Bonomi, S. Braccini *,[2], M. Crescenti [3], A. Degiovanni, M. Garlasché, A. Garonna, G. Magrin [4], C. Mellace [4], P. Pearce [4], G. Pittà [4], P. Puggioni [4], E. Rosso, S. Verdú Andrés [5], R. Wegner [6], M. Weiss [7], R. Zennaro [8]

TERA Foundation, Via Puccini 11, Novara, Italy

ARTICLE INFO

Article history:
Received 15 October 2009
Received in revised form
10 March 2010
Accepted 19 March 2010
Available online 10 April 2010

Keywords:
Medical accelerators
Linac
Cyclotron
Synchrotron
Cyclinac
Radiation oncology
Hadrontherapy
Particle therapy
Proton therapy
Carbon ion therapy
Dose delivery

ABSTRACT

Hadrontherapy with protons and carbon ions is a fast developing methodology in radiation oncology. The accelerators used and planned for this purpose are reviewed starting from the cyclotrons used in the thirties. As discussed in the first part of this paper, normal and superconducting cyclotrons are still employed, together with synchrotrons, for proton therapy while for carbon ion therapy synchrotrons have been till now the only option. The latest developments concern a superconducting cyclotron for carbon ion therapy, fast-cycling high frequency linacs and 'single room' proton therapy facilities. These issues are discussed in the second part of the paper by underlining the present challenges, in particular the treatment of moving organs.

Contents

☆ In memory of Mario Weiss who led the developments of cyclinacs from 1993 to 2003

* Corresponding author at: University of Bern, Albert Einstein Center for Fundamental Physics, Laboratory for High Energy Physics, Sidlerstrasse 5, CH-3012 Bern, Switzerland
E-mail address: Saverio.Braccini@cern.ch (S. Braccini).
[1] Also at University of Milano-Bicocca, Piazza della Scienza 3, I-20126 Milano, Italy.
[2] Now at University of Bern, Albert Einstein Center for Fundamental Physics, Laboratory for High Energy Physics, Sidlerstrasse 5, CH-3012 Bern, Switzerland.
[3] Now at European Patent Office, Patentlaan 2, NL-2288 EE Rijswijk, The Netherlands.
[4] Now at A.D.A.M. SA, rue de Lyon 62, CH-1211 Genève, Switzerland.
[5] Also at Instituto de Física Corpuscular (IFIC), Centro Mixto CSIC-UVEG, Edificio Investigación Paterna, Apartado 22085, 46071 Valencia, Spain.
[6] Also at CERN, CH-1211 Genève 23, Switzerland.
[7] Deceased.
[8] Now at Paul Scherrer Institut, CH-5232 Villigen PSI, Switzerland.

0168-9002/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.nima.2010.03.130

1. Introduction

'Hadrontherapy' ('hadronthérapie' in French, 'hadronentherapie' in German, 'adroterapia' in Italian) is a collective word that covers all forms of radiation therapy which use beams of particles made of quarks and thus experiencing the strong nuclear force: neutrons, protons, pions, antiprotons, helium (i.e. alpha particles), lithium, boron, carbon and oxygen ions are all hadrons. 'Hadron therapy', 'hadrotherapy', 'particle therapy', 'heavy ion therapy' and 'light ion therapy' are other terms, which are often used. In our opinion the single word 'hadrontherapy' has to be preferred to the more natural 'hadron therapy' because also radiotherapy was written as two separate words till it became a very important modality in cancer therapy.

Fast neutrons (i.e. neutrons having kinetic energies between a few MeV and a few tens of MeV) were the first hadrons used in radiotherapy soon after the invention of the cyclotron by Lawrence and Livingston [1]. The two first applications were the production of radioisotopes and later, the therapeutical use of fast neutron beams. It is interesting to remark that the first treatments with neutron beams were performed by Ernest Lawrence together with his brother John who was a medical doctor at Yale.

At the end of 1932 Ernest Lawrence, Stan Livingston and David Sloan managed to produce 4.8 MeV protons with the new 27 in. cyclotron. However, the planning of physics experiments had not paralleled the construction of the instruments and important nuclear discoveries were missed. Undeterred, Lawrence focused the cyclotron activity on the investigation and production of artificial isotopes, which were used as tracers. In 1935, he asked his brother John to join him in Berkeley and use the new powerful accelerator for medical purposes (Fig. 1).

Following a paper by Gordon Locher [2], who in 1936 underlined the therapeutic potentialities of both fast and slow neutrons, first experimental studies were performed by the Lawrence brothers [3] and, at the end of September 1938, the first patients were treated with neutrons on the 37 in. cyclotron. The neutrons were produced in the reaction of 8 MeV deuterons on a beryllium target [4]. This first study on 24 patients, based on single fractions, was considered a success and led to the construction of the dedicated 60-in. Crocker Medical Cyclotron.

Fig. 1. The Lawrence brothers at the console of the first cyclotron used for isotope production and radiation treatments with neutron beams.

Here, Robert Stone and his collaborators treated patients with fractionated doses using neutrons produced by 16 MeV deuterons on beryllium. The technique was primitive and the doses given to healthy tissues were too high, so that in 1948 the treatment was abandoned [5]. In 1965, neutron therapy was revived by Catterall [6] at Hammersmith Hospital in London. Good results were obtained for superficial adenocarcinomas so that by 1970 it became clear that, for certain tumours, local control could be achieved using neutron irradiation. Twenty-five years later, neutron therapy has been almost abandoned because the dose distribution is not better than the one that can be obtained with modern X-ray therapy techniques, while charged hadrons are much more suited to give 'conformal' doses. It has to be noted that neutron therapy is still practiced nowadays in some laboratories for the treatment of radio resistant tumours of the salivary glands.

The story of charged hadrons in radiation therapy started in 1945 when Ernest Lawrence asked his student 'Bob' Wilson to clarify the stopping process of protons in matter. Wilson did measurements at the Berkeley Cyclotron and, after some calculations, realized that the depth profiles have a significant increase in dose at the end of their range in matter, the so called 'Bragg peak', which had been measured 50 years before in the tracks of alpha particles by Bragg [7]. He understood that – due to the Bragg peak that can be 'spread' with modulator wheels – the dose can be concentrated on the tumour target sparing healthy tissues better than what can be done with X-rays and wrote the famous seminal paper [8], which is considered the first work on hadrontherapy. It is interesting to remark that in his paper Wilson discusses mainly protons but mentions also carbon ions.

In the elapsed 60 years, hadrontherapy has flourished. Turnkey proton therapy centres and 'dual' centres – featuring both proton and carbon ion beams – are offered at present by many commercial companies. The accelerators for proton therapy are 3–4 m diameter cyclotrons, both at room temperature and superconducting, and 6–8 m diameter synchrotrons while for carbon ion therapy only 20–25 m diameter synchrotrons are in use. Only recently a company has completed the design of a large superconducting cyclotron for carbon ions and the construction of the first prototype is starting. It has to be remarked that all the patients treated up to now have been irradiated with accelerated beams produced by circular machines. Accelerator technology for particle therapy is undergoing at present an important development phase to which both research centres and commercial companies strongly contribute [9–11].

Due to the continuous development of hadrontherapy, one can expect that in 10 years, of the about 20 000 patients treated every year with high energy photons (X-rays in the radiation oncologist parlance) for every 10 million inhabitants, about 2500 will undergo proton therapy. Also the therapy of radio resistant tumours with carbon ions is rapidly developing. Two carbon ion and proton 'dual' centres are running in Japan, in the Prefectures of Chiba and Hyogo, and two more centres are under construction. In Europe, one centre started treatments at the end of 2009 in Heidelberg and one is in the commissioning phase in Pavia. Here the centre proposed and designed by TERA [12] is built under the responsibility of the CNAO Foundation [13].

This paper is focused both on the conventional particle accelerators used in hadrontherapy (Sections 2 and 3) and on the future trends of this discipline (Section 4). The developments of accelerators for carbon ion therapy which took place in the last 15 years are discussed in Sections 5 and 6. The performances of different accelerators in treating moving tumours are compared in Section 7 while in Section 8 is devoted to recent developments directed towards the reduction of the investment and running costs of hadrontherapy facilities.

Before entering in the gist of the matter, two remarks are in order. Firstly, a hadrontherapy facility is much more than its accelerator, as it is also indicated by the fact that its cost is about of 20–30% of the overall cost of the whole high-tech part of a centre with 3–4 treatment rooms (50–80 M€). By choice, in this paper the accent is on accelerators and dose delivery systems.

Secondly, there is no space to discuss the developments of the last 20 years in the precision of the localization of solid tumours made possible by the clinical application of Computed Tomography (CT), Magnetic Resonance Imaging (MRI), scintigraphy (or SPECT, Single Photon Emission Computer Tomography) and Positron Emission Tomography (PET). Nevertheless, it must be underlined that the millimetre accuracy, which is made possible in delivering the dose with charged hadron beams, could not be exploited without these fundamental instruments.

2. Radiation therapy with X-rays, protons and carbon ions

More than 10,000 electron linear accelerators (linacs) are used worldwide by radiation oncologists to treat patients [14]. The absorbed dose due to a beam of photons has a roughly exponential absorption in matter after an initial increase. The maximum, for beams having a maximum energy of about 8 MeV, is reached at a depth of 2–3 cm of soft tissue. At a depth of 25 cm the dose is about one third of the maximum. Because of this non-optimal dose distribution, the unavoidable dose given to the healthy tissues represents the limiting factor to obtain the best local control of the pathology in conventional radiation therapy. In this connection, it has to be remarked that even a small increase of the maximum dose can be highly beneficial: for a typical tumour which is controlled with a 50% probability, a 10% increase of the dose usually improves this probability by 15–20%, so that the control rate increases from 50% to 65–70%.

To increase the dose to the tumour – and thus the 'tumour control rate' – it is essential to 'conform' the dose to the target. In order to selectively irradiate deep-seated tumours, radiotherapists use multiple beams from several directions, usually pointing to the geometrical centre of the target. This is achieved by using a mechanical structure containing the linac, which rotates around a horizontal axis passing through the isocentre ('isocentric gantry'). The most recent *Intensity Modulated Radiation-Therapy* (IMRT) makes use of up to 10–12 X-ray beams; the beams may be non-coplanar and their intensity is varied across the irradiation field by means of computer-controlled collimators ('multi-leaf collimators') [15].

The depth-dose curves of proton and light ion beams are completely different from those of photons (X-rays), because these charged particles have little scattering when penetrating in matter and give the highest dose near the end of their range in the famous 'Bragg peak', just before coming to rest. This is the main reason why protons and light nuclei are nowadays more and more used to obtain the highest local control of many types of tumours with minimal damage to the surrounding healthy tissues.

In order to reach depths of more than 25 cm in soft tissues – necessary to treat *deep-seated tumours* – proton and carbon ion beams must have an initial energy not lower than 200 and 4500 MeV (i.e. 375 MeV/u), respectively. For this reason sizeable particle accelerators are needed in hadrontherapy, which instead do not have to be special from the point of view of the output current since 1 and 0.1 nA are sufficient for treating patients with protons and carbon ions, respectively.

Protons and light ions are advantageous in IMPT (*Intensity Modulated Particle Therapy*) because of *three* physical properties. Firstly, as just said, they deposit their maximum energy density in the Bragg peak at the end of their range, where they can produce severe damage to the cells while sparing both traversed and deeper located healthy tissues. Secondly, they penetrate the patient practically without diffusion. Thirdly, being charged, they can easily be formed as narrowly focused 'pencil beams' of variable penetration depth, so that any part of a tumour can be accurately and rapidly irradiated. Thus a beam of protons, or light ions, allows highly conformal treatment of deep-seated tumours with millimetre accuracy, giving a minimal dose to the surrounding tissues.

One more property pertains only to carbon and other light ions: the fact of having a larger biological effectiveness with respect to X-rays and protons. The physical and radiobiological arguments of this can be summarized as follows. In a cell, a carbon ion leaves about 24 times more energy than a proton having the same range. This produces a dense column of ionization, especially near the Bragg peak region of the track, causing many 'Double Strand Breaks' and 'Multiple Damaged Sites', when crossing the DNA contained in the cell nucleus. In this way, the effects on the cell are *qualitatively* different from the ones produced by sparsely ionizing radiations, such as X-rays and protons. In fact, these radiations interact mainly *indirectly* with the DNA through the production of active radicals that, reaching the DNA, produce mostly repairable 'Single Strand Breaks'. For these reasons, high ionizing ions show their effectiveness against hypoxic and otherwise radioresistant tumours, i.e. tumours that need deposited doses of 2–3 times higher if they are to be controlled with either photons or protons.

Due to the much larger proportion of *direct* effects, light ions have at the Bragg peak – for many end-points and delivered doses – a *Radio Biological Effectiveness* (RBE) which is about three times larger than the one for X-rays and protons. In the slowing down of an ion in tissue this effect becomes important when the Linear Energy Transfer (LET) – the 'stopping power' in physicist parlance – becomes larger than ≈ 20 keV/μm. For carbon ions this happens in the last 4 cm of their range in water, while for helium this only happens in the last millimetre. Due to this relatively high 'threshold', protons behave along their full range – with the exclusion of the last tenth of a millimetre – practically as the electrons which are put in motion by the high-energy photons produced with medical linacs and have a LET in the range 0.2–0.5 keV/μm. For this reason, the extensive radiobiological and clinical experience with photon radiation therapy can be applied to proton therapy.

The presence or absence of oxygen within cells has a strong influence in the biological effects of radiation and hypoxic tissues are known to be less radiosensitive. This effect – which is expressed in terms of *Oxygen Enhancement Ratio* (OER) – is very much dependent on LET. For low LET radiation, such as X-rays or protons, hypoxia represents a serious limitation factor to the effectiveness of the treatment. For high LET this effect is very limited and carbon ions represent a powerful tool for the treatment of hypoxic radio resistant tumours [16].

The depth of the Bragg peak depends on the initial energy of the ions, while its width on the straggling and on the energy spread of the beam which, to make good use of the distal steep drop of the peak, has to be smaller than 0.4–0.5%. By varying the energy during the irradiation in a controlled way, one can superimpose many narrow Bragg peaks and obtain a *Spread-Out Bragg Peak* (SOBP). This can be achieved in *two* ways: the first one is based on the interposition, along the beam path, of absorbing materials of variable thickness; the second one is based on the modulation of the beam energy of the accelerator during the irradiation. This modulation can be obtained directly with the accelerator in the case of synchrotrons but not for cyclotrons,

Table 1
Facilities used in the past for hadrontherapy.

Centre	Start	Stop	Acc.*	Beam	Max. En. (MeV)	Total patients	Particle(s)
LBL, Berkeley (USA)	1954	1957	SC	Horiz.	230	30	p
GWI, Uppsala (Sweden)	1957	1976	C	Horiz.	185	73	p
HCL, Cambridge (USA)	1961	2002	C	Horiz.	160	9116	p
JINR, Dubna (Russia)	1967	1996	S	Horiz.	200	124	p
PMRC-1, Tsukuba (Japan)	1983	2000	S	Vert.	250	700	p
UCL, Louvain (Belgium) **	1991	1993	C	Horiz.	90	21	p
MPRI-1, Indiana (USA) **	1993	1999	C	Horiz.	200	34	p
Chiba (Japan) **	1979	2002	C	Horiz.	90	145	p
LBL, Berkeley (USA)	1957	1992	SC	Horiz.	225/amu	2054	He
LBL, Berkeley (USA)	1975	1992	S	Horiz.	400/amu	43	He, C, Ne, Si, Ar Ions
Total						10 243	Protons
						2054	He
						433	Ions

* C=cyclotron, S=synchrotron, SC=synchrocyclotron.
** Ocular tumours only.

which need movable absorbers and a beam transport line for 'cleaning' the beam, the so called Energy Selection System (ESS). With respect to beam energy variation, linacs represent an ideal solution, as discussed in the second part of this paper.

3. Cyclotrons and synchrotrons in hadrontherapy

The facilities that treated patients with protons and ions and are nowadays no more operative are listed in Table 1 [17]. All these facilities made use of existing accelerators built for fundamental research in nuclear and particle physics. The neutron therapy facilities as well as the negatively charged pion therapy ones in Los Alamos, TRIUMPH and PSI (SIN at that time) – which have been operative in the periods 1974–1982, 1979–1994 and 1980–1993, respectively – are not reported in the table. The clinical results had shown that neither neutrons nor pions are superior to protons and light ions either to obtain conformal dose volumes or in the treatment of radio resistant tumours. For these reasons, and for the complications on the healthy tissue surrounding the tumour, these therapeutical modalities are now considered obsolete.

In 1954, the first patient was treated at Berkeley with protons [18], followed by helium treatments in 1957 and neon ions in 1975. In these treatments – as in most of the following facilities – the beam was distributed over the target volume using 'passive' shaping systems, like scatterers, compensators and collimators that were adapted from the conventional photon therapy. In other words, ions were treated as photons without making use of their most important characteristic, the electric charge, which makes their beams easy to detect and, even more importantly, to control by means of magnetic fields.

The first treatments on humans consisted in irradiations to destroy the pituitary gland in patients with metastatic hormone-sensitive breast cancer. This treatment stopped the pituitary gland from making hormones that stimulated the cancer cells to grow. Between 1954 and 1974 at Berkeley about 1000 pituitary glands and pituitary tumours were treated with protons.

In 1957 the first tumour was irradiated with protons at the Uppsala cyclotron [19] but the facility that made the largest impact on the development of proton therapy is the Harvard Cyclotron [20]. The cyclotron was built after the war as a project led by Bob Wilson, but the staff of the Harvard Cyclotron Facility became interested in using protons for medical treatment only after proton therapy was started in the 1950s in both Berkeley and Uppsala. The Harvard Cyclotron subsequently began treatment of the pituitary gland and developed specialized techniques for treating other lesions such as arteriovenous malformations (AVMs). Overall, three groups of radiation oncologists worked for many decades together with Harvard physicists on three clinical studies: neurosurgery for intracranial lesions (3687 patients), eye tumours (2979 patients) and head–neck tumours (2449 patients). The main people who did work on malignant brain and eye tumours and malformations were R. Kjellberg, a surgeon of Massachusetts General Hospital in Boston, I. Constable and E. Gragoudas of the Massachusetts Eye and Ear Hospital. The successes obtained on large brain tumours are due to Herman Suit, Michael Goitein and colleagues of the Radiation Medicine Department of the Massachusetts General Hospital.

The results obtained, particularly for eye melanoma and for chordomas and chondosarcomas of the base of the skull, convinced many clinicians of the superiority of protons with respect to X-rays for tumours that are close to organs at risk (OARs). At the end of the century, these medical skills developed in Boston were soon transferred to the new hospital-based facility of the Massachusetts General Hospital, now called Francis H. Burr Proton Therapy Center, which opened in 2001.

As shown in Table 1, soon after the start-up of the Harvard facility, other nuclear physics laboratories in USSR, Japan and Switzerland set up horizontal proton beams for therapy. As already remarked, all the facilities listed in Table 1 were located in physics laboratories and the irradiation conditions were far from ideal. In many places and at many times it was felt and said that the field would not develop without dedicated facilities. It took almost 20 years to realise this fundamental step.

The first hospital-based centre was built at the Loma Linda University Medical Center in California and treated the first patient in 1990. The realization of this challenge was made possible thanks to the determination of John Slater who initiated a strong and fruitful collaboration with Fermilab which was founded and directed for many years by Bob Wilson and had direct experience in neutron therapy. The centre in Loma Linda is equipped with three rotating gantries, which are 10 m high, 100 tons structures supporting a set of bending magnets and quadrupoles which drive the beam out of the horizontal direction so that a laying patient can be treated with protons coming from any direction, according to the treatment planning elaborated by radiation oncologists and medical physicists.

As reported in Table 2, the hospital based proton therapy centre in Loma Linda is the facility which has irradiated the largest number of patients worldwide.

Table 2
Hospital based proton therapy facilities in operation at the end of 2008 [17].

Centre	Country	Acc.	Max. clinical energy (MeV)	Beam direction[a]	Start of treat.	Total treated patients	Date of total
ITEP, Moscow	Russia	S	250	H	1969	4024	Dec-07
St. Petersburg	Russia	SC	1000	H	1975	1327	Dec-07
PSI, Villigen[b]	Switzerland	C	72	H	1984	5076	Dec-08
Dubna[c]	Russia	SC	200	H	1999	489	Dec-08
Uppsala	Sweden	C	200	H	1989	929	Dec-08
Clatterbridge[b]	England	C	62	H	1989	1803	Dec-08
Loma Linda	USA	S	250	3G, H	1990	13,500	Dec-08
Nice[b]	France	C	65	H	1991	3690	Dec-08
Orsay[d]	France	SC	200	H	1991	4497	Dec-08
iThemba Labs	South Africa	C	200	H	1993	503	Dec-08
MPRI(2)	USA	C	200	H	2004	632	Dec-08
UCSF[b]	USA	C	60	H	1994	1113	Dec-08
TRIUMF, Vancouver [b]	Canada	C	72	H	1995	137	Dec-08
PSI, Villigen [e]	Switzerland	C	250	G	1996	426	Dec-08
HZB (HMI), Berlin[b]	Germany	C	72	H	1998	1227	Dec-08
NCC, Kashiwa	Japan	C	235	2G, H	1998	607	Dec-08
HIBMC, Hyogo	Japan	S	230	2G, H	2001	2033	Dec-08
PMRC(2), Tsukuba	Japan	S	250	2G, H	2001	1367	Dec-08
NPTC, MGH, Boston	USA	C	235	2G, H	2001	3515	Oct-08
INFN-LNS, Catania[b]	Italy	C	60	H	2002	151	Dec-07
Shizuoka	Japan	S	235	2G, H	2003	692	Dec-08
WERC,Tsuruga	Japan	S	200	H, V	2002	56	Dec-08
WPTC, Zibo	China	C	230	3G, H	2004	767	Dec-08
MD Anderson Cancer Centre, Houston, TX[f]	USA	S	250	3G, H	2006	1000	Dec-08
FPTI, Jacksonville, FL	USA	C	230	3G, H	2006	988	Dec-08
NCC, Ilsan	South Korea	C	230	2G, H	2007	330	Dec-08
RPTC, Munich [g]	Germany	C	250	4G, H	2009	Treatments started	Mar-09
TOTAL						50,879	

[a] Horizontal (H), vertical (V), gantry (G).
[b] Ocular tumours only.
[c] Degraded beam.
[d] 3676 ocular tumours.
[e] Degraded beam for 1996–2006; dedicated 250 MeV proton beam from 2007. Scanning beam only.
[f] With spread and scanning beams (since 2008).
[g] Scanning beam only.

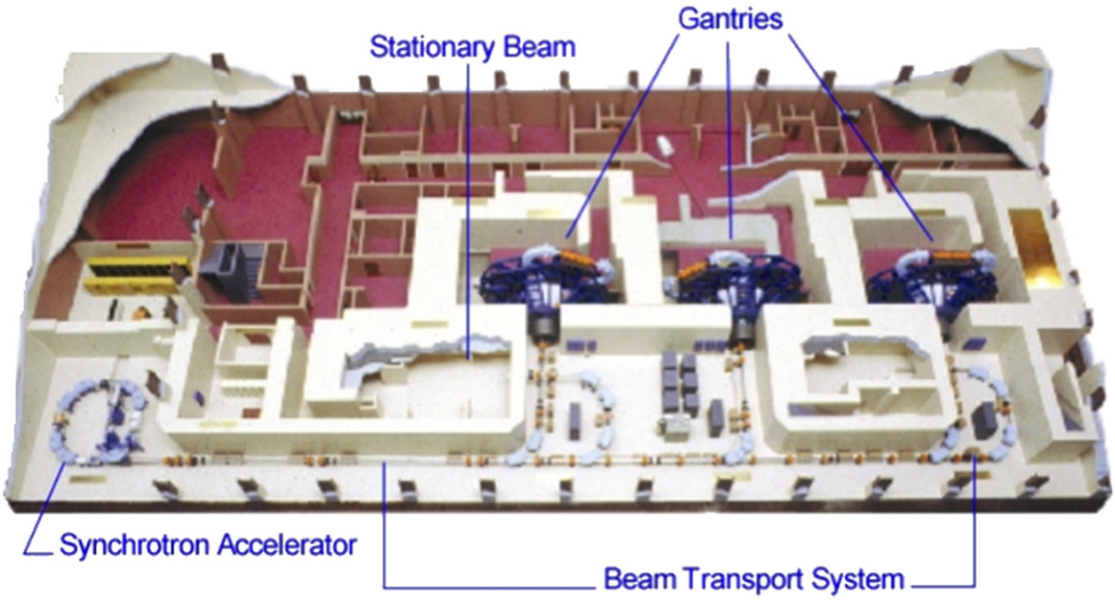

Fig. 2. The heart of the proton therapy facility of the Loma Linda University Medical Centre is a 7 m diameter synchrotron built by Fermilab. The protons are accelerated up to 250 MeV. Three gantry rooms and one room with horizontal beams are used.

A smooth conversion 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 built for physics studies at the High Energy Accelerator Research Organization (KEK). A total of 700 patients were treated at this facility from 1983 to 2000. In 2000, a new in-house facility, called

Fig. 3. Commercial accelerators for proton therapy: cyclotrons (by IBA and Varian/Accel) and synchrotrons (by Mitsubishi and Hitachi).

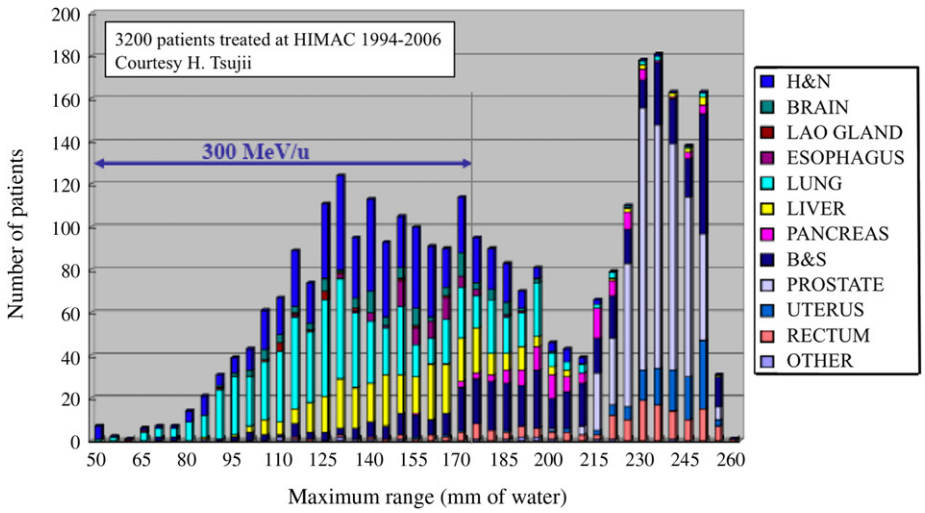

Fig. 4. On the vertical axis the number of patients is plotted while the horizontal axis represents the water equivalent depth of the maximum range used for each patient. The 3200 HIMAC patients had the tumours indicated in the inset.

Proton Medical Research Centre (PMRC), was constructed adjacent to the University Hospital, as reported in Table 2. PMRC features a proton synchrotron built by the company Hitachi and is equipped with two rotating gantries.

Table 2 includes seven centres accelerating proton beams to 60–70 MeV, which are used for the treatment of choroidal melanomas and other eye tumours and malformations. They are located in PSI, Clatterbridge, Nice, UCFS, Triumph, Berlin and Catania and feature a single horizontal beam.

The other centres of the table are hospital-based, in the sense that they feature an accelerator built for medical purposes, have more treatment rooms and possibly at least one rotating gantry. The companies, which have built the accelerators and the high-tech parts of these centres, are Optivus (USA), IBA (Belgium), Varian/Accel (USA/Germany), Hitachi (Japan) and Mitsubishi (Japan). The Fermilab/Optivus synchrotron is shown in Fig. 2. The accelerators designed and built by the other four companies are reproduced in Fig. 3.

As far as light ion therapy is concerned, in 1975 at Berkeley Cornelius Tobias and collaborators used silicon ions for two patients and then passed to neon ions, with which 433 patients were irradiated until the Bevalac stopped operation in 1992. Only towards the end of the program it was found that the neon charge ($Z=10$) is too large and undesirable effects were produced in the traversed and downstream healthy tissues [21].

At the end of this period the radiobiological experimental results were such that carbon ions ($Z=6$) were chosen as the optimal ion type. In fact, as mentioned above, in the entrance channel the LET is about 10 keV/μm and the effects are quite similar to the ones of X-rays and protons, while in the last centimetres in matter the LET is definitely larger than 20 keV/μm and this leads to the potential control of radioresistant tumours.

Table 3
Proposed new hadrontherapy facilities.

Location	Country	Particle	Max. energy (MeV) - Acc.	Beams [a]	Rooms	Foreseen start date
University of Pennsylvania	USA	p	230 cyclotron	4G, 1H	5	2009
PSI, Villigen	Switzerland	p	250 SC cyclotron	1G additional to 1G, 1 H	3	2009 (OPTIS2), 2010 (Gantry2)
WPE, Essen	Germany	p	230 cyclotron	3G, 1H	4	2009
HIT, Heidelberg	Germany	p, C	430/u synchrotron	1G for C ions, 2H	3	2009
CPO, Orsay	France	p	230 cyclotron	1G additional to 2H	3	2010
CNAO, Pavia	Italy	p, C	430/u synchrotron	2H, 1 H+V	3	2010
PTZ, Marburg	Germany	p, C	430/u synchrotron	3H, 1 OB	4	2010
NIPTRC, Chicago	USA	p	250 SC cyclotron	2G, 2H 1H (research)	4	2011
NRoCK, Kiel	Germany	p, C	430/u synchrotron	1H, 1V+OB, 1H+V	3	2012
Trento	Italy	p	230 cyclotron	1G, 1H	2	2012
Skandionkliniken, Uppsala	Sweden	p	250 SC cyclotron	2G, 1H	3	2013
Med-AUSTRON, Wiener Neustadt	Austria	p, C	400/u synchrotron	1G (p only), 1V, 1V+OB	3	2013
Shanghai	China	p, C	430/u synchrotron	1H, 1V+OB, 1H+V	3	?
iThemba Labs	South Africa	p	230 cyclotron	1G, 2H	3	?
RPTC, Koeln	Germany	p	250 SC cyclotron	4G, 1H	5	?
ETOILE, Lyon	France	p, C	?	?	?	?

[a] Horizontal (H), 90° vertical (V), 45° oblique (OB), rotating gantry (G).

In Japan, Y. Hirao and collaborators proposed the realization of the Heavy Ion Medical Accelerator in Chiba (HIMAC) to be built in the Chiba prefecture. In 1994 the facility treated the first patient with carbon ions at a maximum energy of 400 MeV/u, corresponding to a maximum range of 27 cm in water.

By the end of 2009, under the leadership of Hirohito Tsujii, about 5000 patients have been treated and many difficult and common tumours have been shown to be controllable [22]. The distribution of the range of carbon ion beams used at Chiba is shown in Fig. 4.

In 1993, Gerhard Kraft obtained the approval for the construction of a carbon ion facility at GSI (Darmstadt), later called the 'pilot project' [23]. Treatments started in 1997 and since then about 400 patients have been treated with carbon ion beams. There are four novel features of the GSI pilot project:

(i) the active 'raster' scanning system;
(ii) the fully automatic control of the GSI accelerator complex, that can be handled by an operator trained for standard X-ray equipment;
(iii) the sophisticated models and codes that take into account the RBE of different tissues in the treatment planning system;
(iv) the two gamma ray detectors placed above and below the patient to determine 'on-line' the exact location and shape of the irradiated volume by means of the detection of 511 keV back-to-back photon pairs from positron annihilation. This technique, named 'in-beam-PET' [24], is based on the fact that, when penetrating the body, some of the incident carbon ions fragment into β^+ radioactive nuclei, mainly ^{11}C.

Hadrontherapy is now expanding very rapidly and several hospital based facilities will be operational in the next years, as reported in Table 3. This list is necessarily incomplete due to the continuously increasing number of projects, which nowadays characterize this very active field of application of particle physics to medicine.

4. Future developments of hadrontherapy techniques

Present hadrontherapy techniques have to be improved to fully exploit the unique spatial and biological advantages of proton and ion beams. Even without major novelties, there is ample space for improvements. In particular, it has to be remarked that 'active' dose delivery systems – based on scanned pencil beams – have been used for less than 2% of the about 60,000 patients treated with protons or ions. All the other patients have been treated with wide beams shaped in the transverse dimensions and in energy by sophisticated sets of passive devices such as scatterers, absorbers and collimators [25]. More advanced approaches, still based on passive devices, have been developed in Japan: the 'layer stacking' technique [26] and the most recent 'cone type filter' method [27].

In spite of the fact that most new centres have the possibility of going from these 'passive' methods to 'active' systems, the implementation in the clinical practice has been quite slow. Since equipment for active scanning is nowadays commercially available, significant improvements in the quality of the dose distribution systems are foreseen in the near future.

Looking further ahead, it has to be noted that, for proton therapy, the challenge is greater than for carbon ions. In the last 10 years, the introduction of new X-ray delivery techniques has improved significantly the conformity of the dose distributions, with which proton treatments have to be naturally compared, since – within 10% – X-rays and protons have the *same* radiobiological effects. Indeed, more and more hospitals introduce *Intensity Modulated Radiation Therapy* (IMRT) which uses many crossed X-ray beams with optimized not uniform intensity distributions produced by computer controlled 'multi-leaf' collimators [15]. *Tomotherapy* [28] and *Rapid Arc* technologies [29] are novel developments now routinely used in many radiation therapy departments. Moreover, the recent development of *Image Guided Radiation Therapy* (IGRT) [30][31] allows the on-line localization of tumour targets, which move during irradiation due, for instance, to the inspiration–expiration cycle.

The irradiation of moving tumours is surely one of the main challenges hadrontherapy is facing. To effectively accomplish this task, important technological developments are needed in the fields of

1. systems to actively scan in three dimensions with a pencil beam tumours which are subject to movements;
2. devices which can detect the instantaneous position of the tumour target and produce signals to be used in a feedback loop connected with the systems of point 1;
3. instruments capable of continuously monitoring the distribution of the dose in the body of the patient;
4. in-beam PET devices allowing the range determination of the proton and ion beams at the end of an irradiation by detecting

the positrons emitted by the radioactive nuclei (particularly ^{11}C and ^{15}O) produced by the clinical beam during the irradiation;
5. radiobiological and clinical information to be used in the personalized computation of ion RBE for different patients;
6. rotating gantries for carbon ions which are less weighty and costly than the one built by GSI for the Heidelberg Ion Therapy centre (HIT).

Points 1–4 are relevant for both proton and carbon ion therapy, while points 5–6 specifically refer to carbon ions. In this paper, the authors decided to focus mainly on point 1. The relevant economical problem of reducing the cost of hadrontherapy treatment is discussed in the last Section.

At present moving targets are treated at HIMAC and in many other centres, with the much simpler 'respiratory gating' technique [32]. In this method, in order to limit the dose given to the healthy tissues, the tumour target is irradiated only during the expiratory phase of the breathing cycle. This method, although effective, only uses a partial fraction of the beam substantially increasing the treatment time and not exploiting at best the physical properties of proton and ion beams.

It has been said that active scanning of tumours with pencil beams has been systematically applied only at PSI ('spot' scanning with protons) [33] and at GSI ('raster' scanning with carbon ions) [34]. In both facilities the transverse position of the Bragg spot is adjusted by changing two perpendicular magnetic fields located many metres upstream of the patient. In parallel, the longitudinal position of the spot is varied by *mechanically* moving properly shaped absorbers and by 'cleaning' the beam of reduced energy with one or more downstream bending magnets. As mentioned in Section 2, such an Energy Selection System is compulsory in the case of cyclotrons (PSI) and synchrocyclotrons, since the output energy is fixed, but it is also used in the case of ions accelerated by a synchrotron (GSI) because the time needed to vary the synchrotron energy is of the order of 1 s, too long with respect to the breathing period. From this point of view the energy has to be changed in about 100 ms, i.e. with a repetition rate of about 10 Hz which can still be achieved with mechanical movements.

In 2010, the PSI new gantry (Gantry2) will be operational. Using the 250 MeV superconducting cyclotron built by Accel/Varian, deep-seated tumours will be 'painted' with a fast *spot scanning* or a *raster scanning* system which moves the proton spot at the speed of 1 cm/ms. With such a speed a 1 l volume can be painted about 10 times in 1 min.

In the case of a fast cycling machine, to achieve the same goal with the proton *spot scanning* technique (which requires about 5000 proton deliveries) the repetition rate has to be in the range 100–200 Hz. Such a high repetition rate allows *not only* the synchronization with the breathing movements *but also* the 'volumetric multipainting' of the tumour target, which reduces the statistical error in the delivered dose by a factor $n^{1/2}$ (where n is the number of repaintings) and allows to correct any accidental under-dosage or over-dosage in a following delivery to the same volumetric element (voxel). Note that, to make the best possible conformal therapy with carbon ions, higher repetition rates can be useful because the 'spot' diameter is smaller than in the proton case due to the reduced straggling and multiple scattering.

With a much longer time scale, the use of antiproton beams has been proposed and studies on the radiobiological effects of this kind of radiation have been carried out at CERN [35]. Due to their annihilation, antiprotons have a potential larger RBE but, the conformation of the dose with precision comparable to protons and carbon ions questionable. In fact, the energy of the produced fragments and the statistical fluctuations of the microscopic cellular dose may cause problems. Moreover, the tremendous effort needed to produce antiprotons with large and highly sophisticated equipment poses serious questions about a possible hospital based application.

The next two sections are devoted to novel *carbon ion* accelerators and to their use with active dose distribution systems.

5. New designs of carbon ion accelerators

In 1987, an initiative was launched to create a full-fledged European light ion therapy centre and the needed hadron beams were defined in a series of expert meetings. EULIMA, the *European Light Ion Medical Accelerator* project led by Pierre Mandrillon, was financed by the European Commission and involved many European laboratories and centres. Initially the project, by making use of the Berkeley experience, foresaw the use of O^{+8} ions, but, during the study, a worldwide consensus was reached that a better choice is C^{+6}. In the design the long-range possibility was also kept open to treat patient with radioactive beams.

The core of the project group was hosted by CERN. Two 400 MeV/u accelerators, a superconducting cyclotron and a synchrotron, have been studied together with an active dose spreading system and a rotating gantry. In Ref. [36], advantages and disadvantages of the superconducting cyclotron and synchrotron solutions are described. The cyclotron has an easy operation and produces a continuous beam suited for active beam scanning, but the energy is fixed and the degrader introduces an extra 1% momentum spread. However, the superconducting design is novel, the magnet is weighty and the access to the interior is difficult. The synchrotron requires costly injectors and sophisticated controls but the techniques are well known and the repair times are short. The conclusion was 'Based on these arguments, the EULIMA project management board has recommended the synchrotron option as the accelerator for EULIMA'. However, such a European therapy synchrotron was never built and national projects in Germany (HIT, Heidelberg) and Italy (CNAO, Pavia) had to be pushed ahead before European radiation oncologists could have available facilities similar to the Heavy Ion Medical Accelerator at Chiba and the Hyogo Ion Beam Medical Centre, both based on synchrotrons. HIT and CNAO are based on synchrotrons, as well as the MedAustron project, approved to be built in Wiener Neustadt (Austria), which acquired the CNAO design. The rest of this section is devoted to different accelerator schemes proposed in the last 5 years.

In 2004, the time was ripe for the design of a new 400 MeV/u superconducting cyclotron by IBA and the Joint Institute for Nuclear Research [37]. This cyclotron, operating in 4th harmonic, is based on the design of the 'old' 235 MeV IBA protontherapy cyclotron and will be used for radiotherapy with proton, helium or carbon ions. $^{12}C^{6+}$ and $^{4}He^{2+}$ ions will be accelerated to 400 MeV/u by two cavities located in two opposite valleys and extracted by an electrostatic deflector with a 80% efficiency. He^{2+} ions will be accelerated to the energy 260 MeV/u and extracted by stripping. The two extraction channels join outside the cyclotron. The main parameters of this accelerator are reported in Table 4.

As for all cyclotrons, the energy is fixed and a 18 m long Energy Selection System is needed to obtain the desired energy. This is by now a standard, even if bulky and radioactive, component of all the proton therapy centres based on cyclotrons, but it is a novelty for carbon ions. For this reason specific Monte Carlo calculations have been performed to check its performances.

In 2007, IBA decided to build the prototype of this machine close to GANIL (Caen) in the framework of the ARCHADE project. This will be a research facility aiming, among other activities, to gather physical and biological information for the development of

Table 4
Main parameters of the IBA 400 MeV/u superconducting cyclotron.

Total weight (tons)	700
Outer diameter (m)	6.06
Height (m)	2.76
Pole radius (m)	1.87
Valley depth (cm)	60
Bending limit (K)	1600
Hill field (T)	4.50
Valley field (T)	2.45
Radial dimension of the RF system (cm)	190
Vertical dimension of the RF system (cm)	117
RF frequency (MHz)	75
Injection energy in the spiral inflector (kV/Z)	25
Inflector gap (mm)	8
Inflector electric field (kV/cm)	20
Dee voltage in the centre (kV)	100
Dee voltage at extraction (kV)	200
Cyclotron power consumption (MW)	500

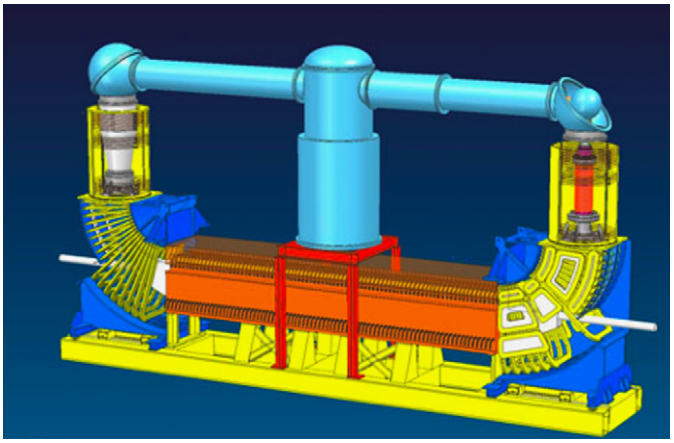

Fig. 5. Layout of the Novosibirsk electron cooler. The cooling section is 4.6 m long out of a total length of 7.8 m [39].

a biologically optimized ion treatment planning system to be pursued in collaboration with INFN, Dresden University, ARCHADE and the company CMS-Elekta.

In 2005, Grishakov et al. [38] proposed to perform electron cooling to a carbon ion beam circulating in a small aperture synchrotron. This lead to the design of an accelerator by the Budker Institute of Nuclear Physics (BINP) which foresees an injection tandem, based on a 1.25 MV high voltage terminal, followed by a booster ring which accelerates particles to 30 MeV/u. The booster can also accelerate protons to 250 MeV and be used for proton therapy. The carbon beam is then injected at 10 Hz into a 70 m long racetrack synchrotron, where 10 bunches are 'cooled' by an electron cooler, similar to the one shown in Fig. 5. In 300 ms the transverse emittances of the carbon beam are reduced by more than a factor 10. Then the particles are accelerated to a maximum energy of 430 MeV/u.

The electron cooler is also used to extract 'pellets' from the debunched beam with a flat momentum spread equal to $\Delta p/p = \pm 2.5 \times 10^{-3}$. Tests have been performed at the ion cooler-storage CSR constructed at the Institute of Modern Physics in Lanzhou [40].

In the last 10 years, Fixed Field Alternating Gradient accelerators (FFAGs) have been the focus of great interest because of their potentialities in the acceleration of the large currents needed for the future neutrino factories and for the practical realization of

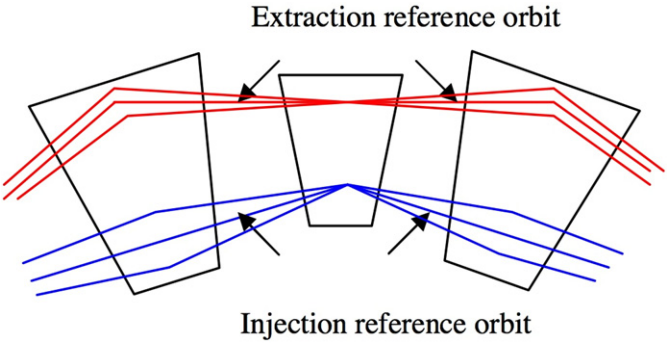

Fig. 6. $1^{1/2}$ cells of a non-scaling, linear-field FFAG which is tune-stabilized for medical therapy.

muon–muon colliders. Hadrontherapy requires nanoampere currents and *a priori* a FFAG does not seem to be the right instrument. Still many designs have been proposed because of another advantage with respect to cyclotrons and synchrotrons: the possibility, at least on paper, of producing a high repetition rate beam having a different energy at every cycle. As discussed at the beginning of the next section, this is an important feature in the treatment of moving organs and explains the interest in the therapy use of these accelerators.

Recently two papers have reviewed the many designs and uses of FFAGs [41,42] and the reader is referred to them for the details. Here it suffices to recall that FFAGs operate as synchrocyclotrons since the magnetic field is fixed and the radio-frequency system is modulated so that the output beam is pulsed. The magnet is subdivided in sectors, each one made of triplets having strong radial field gradients: the central magnet bends the circulating beam outwards while the two external ones bend it inwards. The sectors at the beginning were radial but more recently have taken a spiral shape. The sectors form a ring, so that the iron mass is reduced with respect to a synchrocyclotron. This system has the disadvantage that an injector is needed.

Since the first proposal, it took more than 40 years to see the first Proof of Principle (PoP) 1 MeV proton FFAG built in Japan [43]. The same group, led by Mori [44], has built in total five FFAGs; the largest one accelerates protons to 150 MeV, a suitable energy for cancer treatment. These machines are of the 'scaling' type, i.e. during the acceleration the wiggling orbit increases in average radius but maintains the same shape. 'Non-scaling' FFAGs require magnets which are smaller in the radial direction but have the inconvenience that, during acceleration, many resonances are necessarily crossed [45].

A facility proposed for carbon ions by Keil et al. [46] used three concentric FFAGs in a dense doublet lattice to accelerate protons to 250 MeV (rings 1 and 2) and Carbon to 400 MeV/u (rings 2 and 3). However, some technical problems were identified that make it difficult to realise in practice [47]. In order to solve these issues, tune stabilised lattices have been developed to mitigate the effects of resonance crossing and two solutions have been proposed. The first [48] uses a FODO doublet cell (Fig. 6) with wedge-shaped magnets for additional focussing to achieve reasonably flat tunes [49]. The proton and carbon rings are one inside the other and have 22 and 45 m circumferences, respectively [50], so that – to reach 400 MeV/u – more than 60 m of focussing and accelerating structures have to be built.

The second approach [51] uses a 12-cell triplet FDF lattice with a field expansion to octupole or decupole to achieve flat tunes. At the beginning of 2010, a proton tune-stabilized non-linear non-scaling FFAG – injected by a 30 MeV cyclotron and running at 1000 Hz – has been designed. The length of the proton medical

FFAG is 40 m long because it is made of 12 triplets with 1.7 m insertions where the RF cavities will be installed. The variable energy extraction is done in the vertical plane.

A 20 MeV electron non-scaling FFAG (EMMA) is under construction to test the non-scaling scheme in the easier relativistic regime in connection, in particular, with the development of muon storage rings [52]. While EMMA and the proton FFAG are well advanced, the design of the carbon ion FFAG is still under development, it will require a 7 MeV/u RFQ-linac injector and will be about 55 metres long—as a typical carbon ion synchrotron of the same energy.

For completeness we conclude this short review of FFAGs used in deep cancer therapy by quoting the French project RACCAM (*Research on ACCelerators and Applications in Medicine*) which aims at designing a cancer facility based on a scaling scheme producing 70–180 MeV protons [53].

6. High-frequency linacs for carbon ion therapy

In 1989, as described in a review recently written and indicated as ABP in the following [54], Lennox [55] and Lennox et al. [56] published the first design of a 24 m long 3 GHz proton linac for cancer therapy. The other initial proposals and the ongoing work, initiated in 1993 by the TERA Foundation and pursued since then, are described in detail in ABP.

The main reason for this long-standing activity is the effective treatment of organs, which move during the irradiation, mainly because of the respiration cycle. Three strategies can be used: (1) the dose delivery is synchronized with the patient expiration phase (*respiratory gating*); (2) the organ movement is detected by a suitable system and a set of feedback loops compensates with on-line adjustments of the transverse and longitudinal locations of the following delivered spots (*3D feedback*); (3) the tumour is painted many times in three dimensions so that each delivery gives a small contribution to the local dose and any possible delivery error can be corrected during the following 'visits' to the same voxel (*repainting*). An optimal delivery mechanism should be such as to allow the use of any combination of these three approaches, the most effective one being the combination of a 3D feedback with repainting.

The needed instruments are fast-cycling accelerators (with repetition rates in the range 100–1000 Hz) with a pulse-by-pulse energy adjustment. As discussed in the previous section, the novel FFAGs have, at least on paper, these characteristics as well as the well-known ion linacs.

In 1993, one of us (U.A.) introduced the 'cyclinac' concept, i.e. the combination of a high frequency proton linac (having the standard 3 GHz frequency) and a 30 MeV cyclotron injector that could be also used for other medical purposes—for instance the production of radioisotopes [57]. The main argument was that the fraction of a continuous beam transmitted by a linac is very small, of the order of 10^{-4} or less. Typically, this is the product of a 10^{-3} duty cycle and a 10% capture rate of the practically continuous cyclotron beam. In the case of hadrontherapy, such a small overall acceptance does not pose any problem because, as mentioned before, very small protons and carbon ion currents are required: 1 and 0.1 nA, respectively. These very small currents are easily obtained from a linac placed downstream of a commercial cyclotron, which can produce without problems 10^5 times larger currents.

The study of the TERA Foundation soon branched out in the two approaches described in the 'Green Book' published in 1996 [58]. Firstly, Mario Weiss and collaborators designed a 3 GHz Cell Coupled Linac adapting the classical Los Alamos design to the much higher frequency, as described in the Green Book, which lead to the construction and test of a full scale prototype, called LInac BOoster (LIBO) [59], which in about 1 metre accelerated protons from 62 to 74 MeV (Fig. 7). Secondly, an all-linac solution was studied by Luigi Picardi et al. [60]: protons are accelerated in a standard RFQ+DTL injector up to 7 MeV and then boosted by a patented 3 GHz SCDTL (Side Coupled Drift Tube Linac) to the 65 MeV needed to enter the last section, a LIBO-like CCL that accelerates protons to 210–230 MeV.

In the last few years various cyclinacs have been designed by TERA and are described in ABP. The first scheme is based on a commercial high-current proton cyclotron, which accelerates protons up to 30 MeV, followed by a linac of the LIBO type running at 3 GHz which boost them to 230 MeV. The second design (Fig. 8) is based on a superconducting cyclotron that accelerates carbon ions C^{+6} to 300 MeV/u. In both cases the hadron beam is maintained focused by a FODO structure of Permanent Magnet Quadrupoles (PMQs), which are integrated in gaps located between two successive 'tanks', made of 15–16 accelerating cells each.

The 300 MeV/u cyclotron, dubbed SCENT (*Superconducting Cyclotron for Exotic Nuclei and Therapy*), was designed by Calabretta et al. [61]. It accelerates H_2^{+1} hydrogen molecules – which are extracted as usual from the cyclotron in the form of single protons by stripping in a thin foil – and also carbon ions C^{+6}, extracted through the same magnetic channel by a deflector. The 250 MeV protons are used for proton therapy. The 3600 MeV carbon ions penetrate 17 cm of water while the output beam of the linac CABOTO (CArbon BOoster for Therapy in Oncology) has a 5160 MeV (430 MeV/u) maximum energy and reaches a depth of 32 cm.

The parameters of these two high-frequency linacs – for 230 MeV protons and 430 MeV/u carbon ions – are given in ABP together with a detailed description of how the three-dimensional multipainting 'spot scanning' technique can be applied by a fast-cycling accelerator to large deep-seated tumours. For these applications the rapid (1–2 ms) and continuous energy variation of the accelerated beam is obtained by

(i) switching off the output RF power of a number of klystrons and
(ii) adjusting the power of the last active klystron.

Fig. 7. Picture of the four 'tanks' of the LIBO prototype. Each tank is made of a number of basic units machined with high accuracy in copper and called 'half-cell-plates'. The cut-out shows the structure of the accelerating and coupling cells.

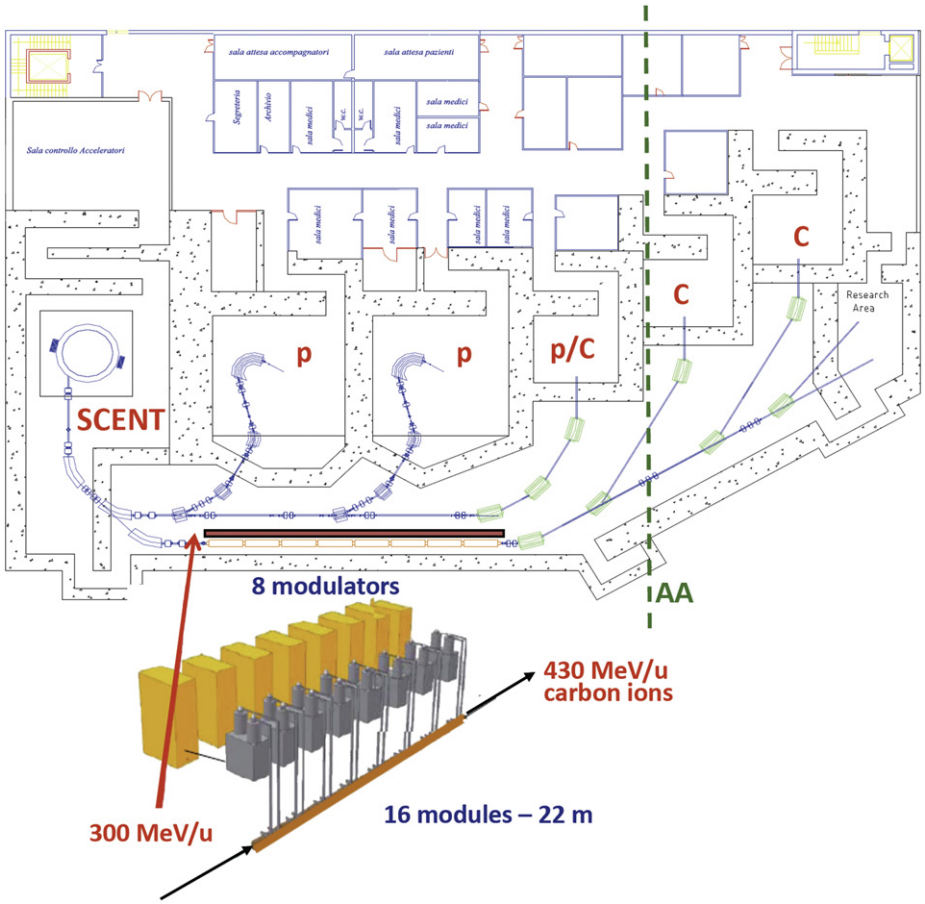

Fig. 8. The hadrontherapy centre designed by the Catania group is the one at the left of the AA line. The installation of the 8 units of CABOTO and the addition of the building at the right of the AA line will allow reaching with carbon ions a depth equivalent to 32 cm of water.

This is a unique possibility offered by the modularity of the linac but implies a delicate balance between the lengths of the tanks (i.e. the distances between successive PMQs forming the focussing FODO structure), the number of tanks powered by a single klystron and the peak power of the available klystrons [62]. The result of this optimization is that the proton and carbon ion linacs – providing 200 MV in 18 m and $2\times(430-300)=260$ MV in 22 m – need ten and sixteen 7.5 MW klystrons, respectively. It has to be remarked that the rapid and continuous energy variation in linacs is technically simpler than in FFAGs because of the linearity of the particle trajectories and the modularity of the structure.

Higher gradients, and thus shorter structures, are a natural line of development of the linac approach to hadrontherapy. But there are limits to what can be done. Once the geometry of the accelerating cells of a given RF frequency f has been optimized by maximizing their efficiency (i.e. their "shunt impedance"), the first limitation comes from the overall peak power P which is injected into the active length L of the linac—which typically is 35% shorter than the linac physical length because of the space needed for the bridge couplers and the focussing quadrupoles [62]. The active length L is inversely proportional to P [54] and thus to the number of klystrons of given peak power. But the power per unit length P/L cannot be increased at wish because of a second limitation: the maximum electric surface field E_{max} which, in the case of low velocities CCLs, is 4–5 times larger than the average accelerating field E_{acc}. In relativistic electron linacs this factor is definitely smaller, about 2–3. This limitation comes from electron field emission (FE) with the consequent breakdown phenomena that can locally damage the metal surface.

In the last 20 years, many data on breakdown phenomena have been collected, also in connection with the design of normal conducting electron–positron colliders running in the 10–30 GHz range. In particular, it is now known that (i) at 3 GHz the limit is larger than 150 MV/m [63]; (ii) for frequencies around 3 GHz, E_{max} is roughly proportional to $f^{1/2}$ and (iii) in the frequency range 12–30 GHz E_{max} is approximately constant [64].

Starting from this background knowledge, the TERA group has designed a 5.71 GHz linac which can accelerate $^{12}C^{6+}$ carbon ions and H_2^+ molecules from 120 to 400 MeV/u with $E_{max}=180$ MV/m [65]. A 'tank' of CABOTO (CArbon BOoster for Therapy in Oncology) is shown in Fig. 9.

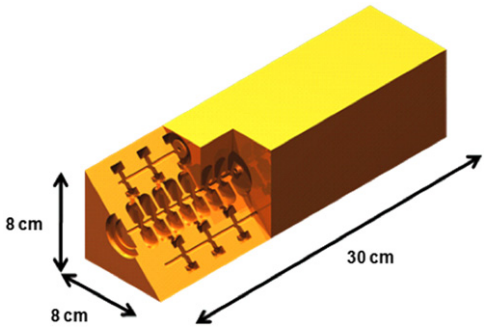

Fig. 9. CABOTO is made of 54 tanks similar to the one shown in this figure. The lengths are increasing to keep the 5.71 GHz field in synchronism with the accelerated particles.

Table 5
Parameters of the 5.71 GHz CABOTO (CArbon BOoster for Therapy in Oncology) which accelerates carbon ions and hydrogen molecules from 120 MeV/u to 400 MeV/u.

Total length of the linac [m]	25
Cells per tank/tanks per module	21–17/3
Number of accelerating modules/klystrons	18
Diameter of the beam hole [mm]	3.0
Number of permanent magnetic quadrupoles	54
Length and gradient of the PMQs [mm and T/m]	60/195
Synchronous phase Φ (degrees)	$-18^{\circ}/-16^{\circ}$
Peak power per module (with 15% losses) [MW]	9.5
Effective shunt impedance ZT^2 (inject.-extr.) [MΩ/m]	115–150
Axial electric field E_{acc} (inject.-extract.) [MV/m]	39-41
Maximum surface electric field E_{max} (inject.-extract.) [MV/m]	175–185
Number of klystrons (peak power = 12 MW)	18
Total peak RF power for all the klystrons [MW]	220
Repetition rate with three 100 Hz EBIS sources [Hz]	300
Duration of each carbon ions pulse [μs]	1.5
Max. number of C ions in 1.5 μs (for 2 Gy L^{-1} min^{-1})	$2\ 10^5$
Transverse emittances of the output beam (π mrad mm)	1.2
RF duty cycle (with 0.7 μs linac filling time)	0.066%
Linac plug power at 300 Hz+100 kW auxiliaries [kW]	500

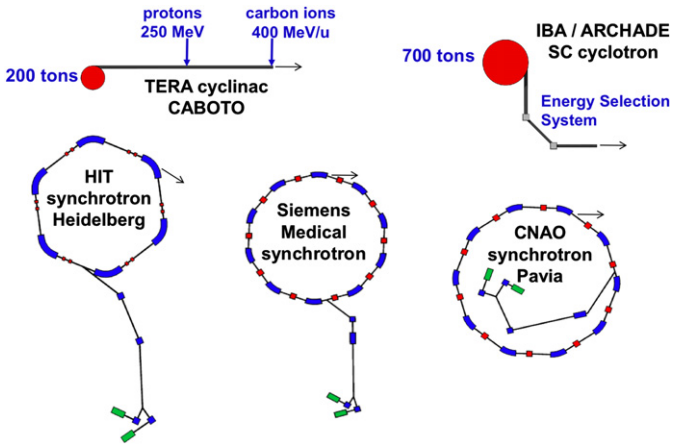

Fig. 10. Dimensional comparison of the cyclinac solution with the European carbon ion accelerators.

The C^{6+} beam is produced by three superconducting EBIS sources by DREEBIT GmbH (Dresden) which run at 100 Hz and produce up to 2×10^9 ions/pulse each [66]. The beam is then injected axially into a K480 isochronous cyclotron. Its superconducting magnet is about 4 m in diameter and has a total weight of 200 tons.

The main parameters of the linac are collected in Table 5.

The linac length is 25 m for a total peak voltage equal to $2\times(400-120)=560$ MV. In a less challenging design the maximum surface field E_{max} is decreased from 185 to 150 MV/m so that the length increases to 28 m, with the advantage that the number of klystrons is reduced to 16 and the plug power decreases to 450 kW.

In both designs the output energy can be varied continuously, as in the linacs discussed above, by switching off some klystrons and adjusting the power of the last active klystron.

When judging the length of a linac complex, the natural yardsticks are (i) the diameter of a synchrotron of equal energy (6–8 m for protons and 18–25 m for carbon ions), with its injector linac (15–20 m long) and (ii) the length of the *Energy Selection System* (ESS) needed for reducing the energy of the proton and carbon ion beams from the cyclotron energy, which is 15–20 m long. A comparison among the dimensions of different carbon ion accelerators is shown in Fig. 10.

Two remarks are in order: (i) the two cyclotron solutions are more compact (even if still large) with respect to the synchrotron ones, (ii) the IBA cyclotron is 4 times heavier than the CABOTO cyclotron. Moreover, the transverse emittances of the linac beam are about five times smaller than the ones of the other accelerators of Fig. 10. This entails smaller and lighter beam transport magnets.

7. Cyclotrons, synchrotrons, linacs: a comparison

As discussed above, all the hadrontherapy centres in operation or under construction are based on circular accelerators: cyclotrons and synchrotrons. For proton therapy both the solutions are in use while, due to the larger energy and magnetic rigidity, only synchrotrons are presently employed to accelerate carbon ions.

The beam produced by cyclotrons is characterized by a fixed energy – usually for protons in the 230–250 MeV energy range – and a time structure, made of pulses separated by about 10–20 ns, which has no relevance when organ motion is considered. An Energy Selection System (ESS) varies in 50–100 ms the beam energy through the movement of suitable wedge shaped absorbers. Due to the debris of nuclear interactions in the absorbers, the ESS area becomes radioactive – especially if a 60–70 MeV proton beam is needed for eye treatments. Because of nuclear fragmentation, this system is an even more critical issue in the case of carbon ion beams.

The beam produced by *conventional* synchrotrons is characterized by a dead time of 1–2 s, which is needed to decrease the magnetic field and to accelerate the particles to the desired energy. The energy can be adjusted cycle by cycle even if, in many cases, only a few energies are commissioned and used in combination with movable absorbers. It has to be remarked that the beam periodicity is similar to the one of the respiration cycle and this represents a disadvantage for the irradiation of moving organs with the 'respiratory gating' technique.

A first advantage of linacs is the smaller transverse emittance of the accelerated beams (typically $1–2\pi$ mm mrad), which entails smaller apertures of the beam line elements. Most importantly, linacs, as FFAGs, have the capability of varying in a couple of milliseconds both the energy and the intensity of each hadron bunch. In particular, in a cyclinac, the energy can be varied between the cyclotron output value and the maximum possible for the linac, a feature that will never be fully used because of the finite momentum acceptance of the beam transport channel. However, a $\pm1.5\%$ ($\pm2\%$) momentum acceptance is enough to obtain a very fast adjustment ΔR of the particle range: $\Delta R/R\approx\pm5\%$ ($\pm7\%$). This corresponds to a longitudinal fast adjustment of ±10 mm (±15 mm) for $R=200$ mm. This is more than enough to compensate for the possible variation of the particle path in the patient body due to organ movements. For shallow tumours ($R=50–70$ mm) a ±5 mm variation is not sufficient, but a larger span can be obtained by running at higher energies and placing a 10 cm water-equivalent slab very close to the patient.

The possibility of a fast variation of the range, offered by linacs and FFAGs, can be combined with the standard use of two transverse magnetic fields in an electronically controlled 3D feedback system. In the linac case, the system acts on the intensity of the two transverse magnetic fields, the power level of the last active accelerating module and on the intensity of the computer controlled particle source, so as to adjust the number of particles delivered in the next spot. This feature is optimal for the

Table 6
Properties of the beams of various accelerators.

Accelerator	The beam is always present?	The energy is electronically adjusted?	In how many ms the beam energy can be varied?
Cyclotrons	Yes	No	100
Synchrotrons	No	Yes	1000
Linacs and FFAGs	Yes	Yes	1–2

Table 7
Estimate of the number of X-ray and hadron treatment rooms.

Radiation treatment	Patients per year in 10^7 inhabitants	Av. number of sessions per patient	Sessions/d in 1 room (d=12 h)	Patients/y in 1 room (y=230 d)	Rooms per 10 million people	Relative ratio
Photons	20 000	30	48	370	54	8^2
Protons (12%)	2 400	24	36	345	7.0	8
C ions (3%)	600	12	36	690	0.87	1

implementation of the hold and shot (spot scanning) technique and of the multipainting strategy for treating moving organs.

Finally, in a linac there is neither the need for complex injection and extraction systems, typical of a synchrotron and of a FFAG, nor for the Energy Selection System, needed for a cyclotron. The absence of passive absorbers and mechanical devices is an advantage in terms of reliability, maintenance and radiation protection issues.

Table 6 summarizes the main properties of the beams accelerated by cyclotrons, synchrotrons and fast cycling accelerators (linacs and FFAGs) which are relevant for 3D hadrontherapy and for the treatment of moving organs in particular (4D hadrontherapy).

8. Future perspectives

If 200 MeV proton accelerators would be cheap and small as the 10 MeV electron linacs used in conventional radiotherapy, at least 90% of the patients would be treated with proton beams. The accelerators used today are instead large and expensive and, to make good use of them, existing facilities feature 3–5 treatment rooms. With this approach a proton treatment is today about 2.5 times more expensive than a X-ray Intensity Modulated Radiation Therapy even if, with further improvements in technology, the ratio could reduce to about 2.1 [67]. A negative aspect of this approach is that, with few large multi-room facilities per country, patients have to travel and stay away from home for about 1 month since these large centres are usually located far from the local hospital.

The accelerator costs typically about 20 and 40 M€ for protons and carbon ions, respectively, while the price of a commercial proton gantry is about 10 M€, so that the standard three proton gantries cost more than 50% of the overall cost of the high-tech part of a centre. Their huge dimensions reflect also in the cost of the building, which typically covers about 3000 m^2 and needs investments in the 20–40 M€ range, the largest figure being needed for 'dual' centres which treat patients with both carbon ions and protons. The building contains the treatment rooms but also the reception and visit areas, the common areas and the offices for the medical doctors, the nurses and the technical staff. The overall cost, which can be as high as 130–150 M€, hampers the development of hadrontherapy; sizeable cost reductions would foster a wider application of these techniques.

Two obvious approaches are based on the choice of treating patients *without* rotating gantries and on the developments of novel accelerators suited for installation in *single room facilities*.

The first choice is practically compulsory in the case of carbon ions, given the dimension of the ion gantry installed in HIT (Heidelberg). In fact – starting from HIMAC built at the end of the 1980s – all the other dual centres feature only horizontal, vertical and, sometimes, inclined ion beam lines. On the other hand, the five commercial companies selling proton-only facilities offer gantries because in such a way any irradiation angle can be used.

To get rid of *proton* gantries radiation oncologists should agree in irradiating with a horizontal beam on either seated or standing patients. This issue has been amply debated but, even if the savings would be considerable, the horizontal only approach has entered in the clinical practice only for eye therapy – performed in the centres listed in Table 2 with energies ≤ 70 MeV – or for head and neck tumours [10]. To this end new techniques should be introduced since cancers localized in the trunk easily change position and shape and thus the Computer Tomography images have to be taken while the patient is in the same posture he/she will have during irradiation. A vertical CT scan has been in operation at Berkeley in the 1980s and more advanced and commercial systems are becoming available [68]. Further developments concern the use of robotic systems, which allow keeping the patient comfortably in different postures [69]. At CPO in Orsay (France) such a system has been built and companies are now offering valid commercial solutions.

The second line of development concerns single room proton facilities. The logic can be best appreciated by browsing Table 7 [70,71], which has been constructed by using the results of the already mentioned epidemiological studies performed in Austria, France, Italy and Germany in the framework of the EU funded network ENLIGHT [72]. They can be summarized by saying that in the medium–long term about 12% (3%) of the patients treated with high-energy photons would be better cured with fewer secondary effects if they could be irradiated with proton (carbon ion) beams.

The table presents the number of treatment rooms needed in 5/10 years for a population of 10 million people living in a developed country. Two hypotheses have been made: (i) the number of sessions scales as 1:2:3 and (ii) a photon (hadron) session lasts 15 min (20 min). The estimated numbers of rooms turn out to be in the easy-to-remember proportions $1:8:8^2$.

Since a typical hadrontherapy centre has 3–4 rooms, the above figures imply that in the medium term a proton (carbon ion) centre would be needed every about 5 (40) million people. If the carbon centre is 'dual' and patients are also treated with protons, the second number decreases to about 30 millions.

For proton therapy this indicates the fading out of the multi-room 'paradigm' serving 5 million people (or more) and

containing one accelerator, 3–4 gantry rooms, offices, laboratories and patient reception areas. For the long term a more flexible and patient-friendly solution will be the one based on a single-room proton accelerator/gantry system, which is constructed on a relatively small area ($\leq 500\ m^2$) attached to an existing hospital building. Small (large) radiotherapy departments run 1–2 (5–6) electron linacs so that, typically, 8 conventional rooms are present in 3–4 hospitals covering a population of 1.5–2 millions. The single-room proton facility will be attached to one of these hospitals but serve also the others. Such a facility should cost no more than 15 M€, which is the order of the global investment needed for the 8 conventional rooms.

Already in 1993, Blosser [73] proposed a facility based on a 200 MeV rotating superconducting synchrocyclotron. Its modern version is the single-room facility now under development by Still River Systems Inc. in collaboration with MIT [74]. This machine is a very high field niobium–tin *superconducting synchrocyclotron* designed to fit in a single treatment room and rotate around the patient. The fixed energy output beam will be pulsed at 200 Hz. Of course, as in the case of cyclotrons, movable absorbers are needed to adjust the proton beam energy to scan the tumour longitudinally. The shielding of the patient from the neutrons produced in the close-by absorbers is a challenging problem. In 2009, the 15 tons synchrocyclotron has been constructed and in 2010 the company foresees the installation of the first two systems.

Another single-room facility is based on the slow cycling synchrotron by ProTom International [75], which is designed to treat the patients with a horizontal proton beam. The compact 5.5 m diameter, 330 MeV *proton synchrotron* has been developed in Russia for about 20 years by Balakin [76] of the Lebedev Physics Institute. Successful acceleration tests have been recently performed at the MIT-Bates Linear Accelerator Centre.

Two further projects, which should produce proton beams rotating around the patient, are under study.

The Lawrence Livermore National Laboratory (LLNL), in collaboration with Tomotherapy and CPAC, is developing the *Dielectric Wall Accelerator* (DWA) which accelerates protons in a non-conducting beam tube (the dielectric wall) energized by a pulsed power system. DWA is an induction accelerator. A classical induction accelerator [77] is made of modules, containing ferromagnetic cores, which – powered in sequence – accelerate large currents with gradients of the order of 1 MV/m. According to Caporaso et al. [78], the high-gradients (100 MV/m) and low currents needed for a medical DWA can be obtained with a coreless induction accelerator which applies the voltage on a High Gradient Insulator (HGI) made of alternating layers of conductors and insulators with periods of about 1 mm. Open problems of this scheme are the focusing of the accelerated protons and 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.

A *high-frequency proton linac* rotating around the patient – according to a scheme patented by TERA [71] – is a much better understood solution but it would take more space. To reduce the length of TULIP (TUrning Linac for Protontherapy) a 6 GHz radio-frequency has been chosen by designing a CCL with an average electric field of about 40 MV/m. High-gradient linac of frequencies larger than 3 GHz are pursued by TERA in collaboration with the RF group of the CERN electron–positron linear collider CLIC.

A rotating linac, can produce a proton beam cycling at hundreds of Hz, which is advantageous in spot scanning since it can apply the very powerful technique called Distal Edge Tracking (DET) [79]. Moreover, there is no intense neutron flux created close to the patient typical of fixed-energy cyclotrons and also of the Still River Systems synchrocyclotron, which however is in a much more advanced state of realization.

Even further in the future, the first proton single-room facility based on the illumination of a thin target with powerful (10^{18}–$10^{20}\ W/cm^2$) and short (30–50 fs) *laser pulses* is expected. Proton acceleration is a consequence of the acceleration of electrons that are violently accelerated in the laser field and draw behind them protons that are on the back surface of the target. The proton spectrum is continuous but the phenomenon has been studied experimentally and is reasonably well understood [80]. Computations show that using two properly shaped targets a 3% energy spread can be obtained [81]. While companies are reducing the size and cost of the needed high-power lasers, many projects aim at improving the quality of the beam and transforming a general concept into a medical device [82]. This will take many years since a single-room therapy facility requires much more than a proton beam of about 200 MeV [83].

Single-room facilities will certainly have a large role in the future of proton therapy. Instead, as far as carbon therapy is concerned the figures of Table 7 suggest that 'dual' *multi-room* centres will be the only ones to be built even in the long term. Certainly synchrotrons and superconducting (synchro) cyclotrons accelerating carbon ions – and possibly other light ions – will play an important role. But there will be newcomers, linacs and, possibly, FFAGs.

A final remark: whatever the accelerator and even if carbon ion single-room facilities are difficult to conceive, the psychological and economical burden for the patient and the health service can be minimized by using a carbon ion beam for a 4–5 session 'boost' to be delivered in 1 week before the conventional treatment, which can then be performed – together with the necessary follow-up – in the radiotherapy department close to the patient's home.

The cyclinacs for protons IDRA [84] and TULIP [71], for carbon ions CABOTO [85] and the CLUSTER accelerating structure [86] are covered by patents.

Acknowledgments

We are grateful to Sonia Allegretti, Alessandro Citterio, Ken Crandall, Marco Dominietto and Arianna Giuliacci for their contributions to the early development of cyclinacs and to Prof. Ken Peach for the important contribution he provided on FFAGs.

The financial support of the Monzino Foundation (Milano), the Price Foundation (Geneva), the Associazione per lo Sviluppo del Piemonte (Torino) and A.D.A.M. – Applications of Detectors and Accelerators to Medicine, Geneva – are gratefully acknowledged.

References

[1] E.O. Lawrence, M.S. Livingston, Phys. Rev. 40 (1932) 19.
[2] G.L. Locher, Am. J. Roentgenol. 36 (1936) 1.
[3] J.H. Lawrence, P.C. Aebersold, E.O. Lawrence, Proc. Natl. Acad. Sci. U.S.A. 22 (9) (1936) 543.
[4] R.S. Stone, J.H. Lawrence, P.C. Aebersold, Radiology 35 (1940) 322.
[5] R.S. Stone, Am. J. Roentgenol. 59 (1948) 771.
[6] M. Catterall, C.R. Rogers, H.R. Thomlinson, S.B. Field, Br. J. Radiol. 44 (1971) 603.
[7] W.H. Bragg, Philos. Mag. S 6 (8) (1904) 719.
[8] R.R. Wilson, Radiology 47 (1946) 487.
[9] J.B. Flanz, Nucl. Instr. and Meth. B (2007) 768.
[10] H.M. Kooy, T.F. Delaney, in: Proton and Charged Particle Radiotherapy, Lippincott Williams & Wilkins, 2007.
[11] S. Braccini, Scientific and Technological Development of Hadrontherapy, World Scientific, ISSN 2010-0868 and arXiv:1001.0860.
[12] TERA Foundation, ⟨www.tera.it⟩.
[13] CNAO Foundation, ⟨www.cnao.it⟩.
[14] W. Maciszewski, W. Scharf, Int. J. Radiat. Oncol. (2004).

[15] S. Webb, in: Intensity-modulated Radiation Therapy, Institute of Physics Publishing, Bristol and Philadelphia, 2001.
[16] H. Suit, T.F. Delaney, A. Trofimov, Physical and biological basis of proton and carbon ion radiation therapy and clinical outcome, Reviews of Accelerator Science and Technology, vol. II, World Scientific, 2009 1–15.
[17] Particle Therapy CoOperative Group (PTCOG), 〈www.ptcog.com〉 and 〈www.ptcog.web.psi.ch〉.
[18] C.A. Tobias, J.H. Lawrence, J.L. Born, R.K. McCombs, J.E. Roberts, H.O. Anger, B.V.A. Low-Beer, C.B. Huggins, Cancer Res. 18 (1958) 121.
[19] B. Larsson, Application of a 185 MeV proton beam to experimental cancer therapy and neurosurgery: a biophysical study, Ph.D. Thesis, University of Uppsala, 1962.
[20] R. Wilson, A. Brief, in: History of the Harvard University Cyclotrons, Harvard University Press, 2004.
[21] J.R. Castro, Heavy ion therapy: the BEVALAC epoch, in: U. Amaldi, B. Larsson (Eds.), Hadrontherapy in Oncology, Elsevier, 1994, pp. 208–216.
[22] H. Tsujii, et al., J. Radiat. Res. 48 (Suppl. A) (2007) 1.
[23] U. Amaldi, G. Kraft, J. Radiat. Res. 48 (Suppl. A) (2007) 27.
[24] W. Enghardt, et al., Nucl. Instr. and Meth. A 525 (2004) 284;
K. Parodi, et al., IEEE Trans. Nucl. Sci. NS-52 (2005) 778;
P. Crespo, Optimization of in-beam positron emission tomography for monitoring heavy ion tumor therapy, Ph.D. Thesis, Technische Universitaet Darmstadt, 2005;.
[25] A.M. Koelher, et al., Med. Phys. 4 (1977) 297.
[26] N. Kanematsu, et al., Med. Phys. 29 (2002) 2823.
[27] A. Ishizaki, et al., Med. Phys. 36 (2009) 2222–2227.
[28] T.R. Mackie, et al., Med. Phys. 20 (1993) 1709 〈www.tomotherapy.com〉.
[29] F. Lagerwaard, W. Verbakel, E. van der Hoorn, B. Slotman, S. Senan, Int. J. Radiat. Oncol. Biol. Phys. 72-1 (2008) S530.
[30] D.A. Jaffray, Semin. Radiat. Oncol. 15 (2005) 208.
[31] G. Baroni, M. Riboldi, M.F. Spadea, B. Tagaste, C. Garibaldi, R. Orecchia, A. Pedotti, J. Radiat. Res. 48 (2007) A61.
[32] S. Minohara, et al., Int. J. Radiat. Oncol. Biol. Phys. 47 (2000) 1097.
[33] E. Pedroni, R. Bacher, H. Blattmann, T. Böhringer, A. Coray, A. Lomax, S. Lin, G. Munkel, S. Scheib, U. Schneider, A. Tourosvsky, Med. Phys. 22 (1995) 37.
[34] T. Haberer, W. Becher, D. Schardt, G. Kraft, Nucl. Instr. and Meth. A 330 (1993) 296.
[35] H. Knudsen, et al., Nucl. Instr. and Meth. Phys. Res. B 266 (3) (2008) 530.
[36] P. Mandrillon, Feasibility studies of the EULIMA light ion medical accelerator, in: Proceedings of the Third European Particle Accelerator Conference, Berlin, 1992, pp. 179–181.
[37] Y. Jongen et al., Design studies of the compact superconducting cyclotron for hadron therapy, in: Proceedings of the EPAC06, pp. 1678–1680.
[38] B. Grishanov, V. Parkhomchuk, S. Rastigeev, Electron cooling for cold beam synchrotron for cancer therapy, Presented at the International Workshop on Beam Cooling and Related Topics, COOL 2005.
[39] E.B. Levichev et al., Carbon ion accelerator facility for cancer therapy, in: Proceedings of RuPAC 2006, Novosibirsk, pp. 363–365.
[40] V.V. Parkhomchuk et al., Electron cooling for the therapy accelerator complex, in: Proceedings of COOL 2009, Lanzhou, China, pp. 1–5.
[41] M.K. Craddock, K.R. Symon, Cyclotrons and fixed-field alternating-gradient accelerators, Reviews of Accelerator Science and Technology, vol. I, World Scientific, 2008 65–97.
[42] D. Trbojevic, FFAGs as accelerators and beam delivery devices for ion cancer therapy, Reviews of Accelerator Science and Technology, vol. II, World Scientific, 2009 229–251.
[43] M. Aiba et al., Development of a FFAG proton synchrotron, in: Proceedings EPAC'00, 2000, pp. 581–583.
[44] Y. Mori, Neutrino factory in Japan based on FFAG accelerators, in: Proceedings EPAC'02, 2002, pp. 278–280.
[45] F. Mills, in: Proceedings of the Fourth International Conference Physics Potential and Development of $\mu+\mu-$ colliders, San Francisco, 1997, 1998, pp. 693–696;
C. Johnstone, ibid., 696–698.
[46] E. Keil, A.M. Sessler, D. Trbojevic, Phys. Rev. Spec. Top. Accel Beams 10 (2007) 54701.
[47] E. Keil, Are non-scaling FFAG rings for hadron therapy competitive?, Presented at FFAG08, Manchester, 2008.
[48] C. Johnstone, S. Koscielniak, Tune-stabilized linear-field FFAG for carbon therapy, in: Proceedings of EPAC 2006, Edinburgh, 2006, pp. 2290–2292.
[49] C.J. Johnstone, Tune-stabilized, non-scaling fixed-field, alternating gradient accelerator, Patent Application US 2007/0273383 A1.
[50] C. Johnstone, Nonscaling FFAG variants for HEP and medical applications, Proceedings PAC09, Vancouver, 2009.
[51] K. Peach et al., Pamela overview: design goals and principles, Proceedings PAC09, Vancouver, 2009.
[52] T.R. Edgecock et al., EMMA—the world's first non-scaling FFAG, in: Proceedings of EPAC 2008, Genoa, 2008, pp. 3380–3382.
[53] F. Meot, RACCAM research project, Presented at the Workshop on Hadron Beam Therapy of Cancer, Erice, Italy, 2009.
[54] U. Amaldi, S. Braccini, P. Puggioni, High Frequency Linacs for Hadrontherapy, Reviews of Accelerator Science and Technology, vol. II, World Scientific, 2009 111–131.
[55] A.J. Lennox, F.R. Hendrickson, D.A. Swenson, R.A. Winje and D.E. Young, Proton linac for hospital-based fast neutron therapy and radioisotope production, Fermi National Accelerator Laboratory, TM-1622, 1989.
[56] A.J. Lennox, Nucl. Instr. and Meth. B 56/57 (1991) 1197.
[57] U. Amaldi, The Italian hadrontherapy project, in: U. Amaldi, B. Larsson (Eds.), Hadrontherapy in Oncology, Elsevier, 1994, p. 45.
[58] M. Weiss, et al., The RITA network and the design of compact proton accelerators, in: U. Amaldi, M. Grandolfo, L. Picardi (Eds.), INFN, 1996 Chapter 9.
[59] U. Amaldi, et al., Nucl. Instr. and Meth. A 521 (2004) 512.
[60] L. Picardiet al., Progetto del TOP Linac, ENEA-CR, Frascati 1997, RT/INN/97-17.
[61] L. Calabretta, G. Cuttone, M. Maggiore, M. Rea, D. Rifuggiato, Nulc. Instr. and Meth. A 562 (2006) 1009.
[62] A. Degiovanni, High Frequency Linac for Carbon Ions Hadrontherapy, Master Thesis, University of Milano, 2009.
[63] J.W. Wang and G.A. Loew, Field emission and RF breakdown in high-gradient room-temperature linac structures, SLAC PUB 7684, October 1997.
[64] W. Wuensch, High-gradient breakdown in normal conducting RF cavities, Proceedings of the EPAC02, 2002, pp. 134–138.
[65] U. Amaldi, R. Bonomi, A. Degiovanni, M. Garlasché, A. Garonna, R. Wegner and S. Verdú Andrés, A cyclotron–linac complex for carbon ion therapy, Presented at the Workshop of Physics for Health in Europe, CERN, February 2010.
[66] D.R.E.E.B.I.T. GmbH, Private Communication, February 2009.
[67] M. Goitein, M. Jermann, The relative costs of proton and X-ray radiation therapy, Clin. Oncol. 15 (2003) S37–S50.
[68] V. Bashkirov et al., Development of Proton Computed Tomography for Applications in Proton Therapy, Application of Accelerators in Research and Industry: Twentieth International Conference, AIP Conference Proceedings, vol. 1099, 2009 pp. 460–463.
[69] C.E. Allgower, A.N. Schreuder, J.B. Farr, A.E. Mascia, Int. J. Med. Robot. Comp. Assisted Surg. 3 (2007) 72 Ref. [10], pp. 62–64.
[70] U. Amaldi, Private Communication to Varian Medical System, November 2006.
[71] U. Amaldi, S. Braccini, G. Magrin, P. Pearce, R. Zennaro, Ion acceleration system for medical and/or other applications, Patent WO 2008/081480 A1.
[72] Carbon ion therapy, Radiotherapy Oncol. 73/2 (2004) 1.
[73] H. Blosser, Superconducting medical cyclotron, US Patent 4641104.
[74] 〈www.stillriversystems.com〉.
[75] 〈www.protominternational.com〉.
[76] V. Balakin, New equipment and new technology for the mass treatment of the oncological diseases by proton beam, Presented at PTCOG47, Jacksonville, USA, 2008.
[77] N. Christofilos, et al., Rev. Sci. Instr. 35 (1964) 886.
[78] G.J. Caporaso, Y.-J. Chen, S.E. Sampayan, The dielectric wall accelerator, Reviews of Accelerator Science and Technology, vol. II, World Scientific, 2009 253-263.
[79] U. Oelfke, T. Bortfeld, Technol. Cancer Res. Treat. 2–5 (2003) 401.
[80] J. Fuchs, et al., Nat. Phys. 2 (2005) 48.
[81] S.V. Bulanov, G.A. Mourou, T. Tajima, Rev. Mod. Phys. 78 (2006) 309.
[82] U. Amaldi, S. Braccini, Present and Future of Hadrontherapy, in: Plasmas, D. Batani et al.(Ed.), Superstrong Fields, American Institute of Physics, 2006, p. 248.
[83] U. Linz, J. Alonso, Phys. Rev. ST Accel. Beams 10 (2007) 094801.
[84] U. Amaldi, Proton accelerator complex for radio-isotopes and therapy, Patent US 7554275.
[85] U. Amaldi, M. Crescenti, R. Zennaro, Ion acceleration system for hadrontherapy, Patent US 7423278.
[86] U. Amaldi, M. Crescenti, R. Zennaro, Linac for ion beam acceleration, Patent US 6888326.