# ADVANCED ACCELERATOR TECHNOLOGY ASPECTS FOR HADRONTHERAPY

L. Falbo, CNAO, Pavia, Italy

*Abstract*

Nowadays cancer can be considered as one of the wide spread diseases all around the world. About 50% of the patients are successfully cured and in 40% of these cases radiotherapy is the applied treatment modality. Radiation beams are produced by particle accelerators and about 30% of the 17500 particle accelerators running in the world are devoted to radiotherapy.

Classical radiotherapy employs photons and electrons that damage the diseased cells but irradiate also the healthy ones. A better conformation of the dose to the tumour and an increasing sparing of the healthy tissues is obtained using hadrontherapy, a high-precision radiotherapy exploiting the depth-dose deposition characteristics of hadronic particles.

The first hadrontherapy treatments have been performed in particle physics research centers clinically adapted; nowadays there are dedicated facilities designed and built as hadrontherapy clinical centres. The realization of machines for hadrontherapy is more challenging than standard radiotherapy: while many hospitals have a device for classical radiotherapy, hadrontherapy needs a dedicated complex with the needed technology for the hadron acceleration.

This paper will give an overview on the existing hadrontherapy centres presenting the technology that is applied in the hadrontherapy world.

## HADRONTHERAPY RATIONALE

Cancer is one of the major world health problems: about 7 million people are known to die each year because of this disease. Cancer is the hysterical and irregular growth and propagation of a cluster of cells. Radiotherapy technique is based on the principle of using ionizing particles to damage the DNA of the cancer cells in order to first block their ability to regenerate and finally to cause their death.

As soon after their discovery in 1895, X-Rays have been used with medical purposes for the treatment of ill tissues. From these first completely empirical tests, radiotherapy has evolved a lot becoming an important tool in medicine and one of most exploited technique in the fight against cancer: about 40% of cancer patients are cured by radiotherapy, either alone (25%) or in combination with other techniques like surgery or chemotherapy. Nowadays among the 17500 accelerators running in the world, 50% are for medical use and more than 8000 are only for radiotherapy purposes.

Standard radiotherapy uses photons and electrons that deposit the maximum of their energy near the beam entrance and a significant part of energy also after the tumour target. As a consequence not only the tumour cells are damaged but also the healthy ones. Recently several techniques are employed to confine this problem: computer-aided optimization of the treatment plans (Intensity Modulated Radiation Therapy) allows to reach a better dose conformity irradiating from several directions and using collimators to transversally shaping the tumor. Anyway also considering the recent improvements, the depth dose deposition characteristics of the standard particles represent a great limitation and disadvantage in the radiotherapy field.

Hadrontherapy is the answer to this problem. Indeed it is based on the use of hadrons (the hadrons we are talking about are protons and heavy ions) whose Bragg curve is characterized by a narrow peak that occurs distant from beam entrance: this gives a good dose localization with low dose at the entrance and at the exit of tumour target. This effect is well shown in Fig. 1.

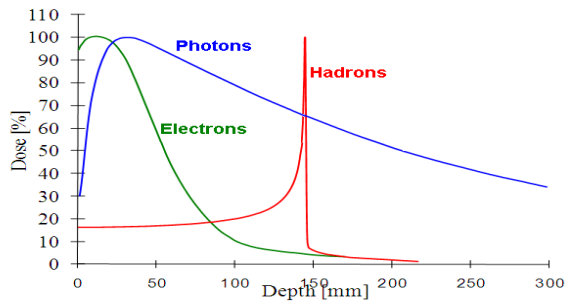


Figure 1: Bragg peaks in the case of photons, electrons and hadrons□

This allows to shape the radiation field not only transversally but also longitudinally using several Bragg peaks at different penetration depths that create the so called SOPB (Spread Out Bragg Peak). In other words hadrontherapy is a high precision kind of radiotherapy. The hadrons mostly exploited are protons and carbon ions. Some figures of merit that allow to understand the advantages of hadrontherapy are the Linear Energy Transfer [1] (LET, whose value along the particle path describes the Bragg curve), the Relative Biological Effectiveness (RBE) [2], i.e. the ratio between the photon and ions doses to produce the same biological effect, the Oxygen Enhancement Ratio (OER) [3], i.e. the dose to produce a biological effect in the absence of oxygen to the dose to produce the same effect in oxygen presence. For Cobalt gamma rays the maximum LET is about 10 keV/µm, for protons it is approximated 100 keV/µm while for heavier ions it may reach 1000 keV/µm presenting a high value in the Bragg peak region and a low one at the beam entrance. The proton RBE is about 1 while ions heavier than helium have a RBE greater than 3 at the Bragg peak and about 1 in the entry channel. The photon OER is about 3 while it decreases when LET is greater than 100 keV/µm approaching to unit at 300

keV/µm. Another aspect to be considered is the multiple scattering: for higher mass the scattering is less relevant giving improvement in the lateral and longitudinal dose distribution. However when increasing the mass there is an increasing of the nuclear fragmentation creating a tailing of the Bragg peak.

Theoretical studies taking into account all these aspects indicate that ions for Z>6 should not be a good clinical choice. When, during the '80s hadrontherapy had a revival in Europe and Japan, carbon ions were indicated as the best medical choice and often the only solution for radio-resistant tumors. Other species in the range $1<Z\leq6$ could be as or more interesting than carbon ions [4] and clinical experimentations at the existing hadrontherapy facilities could reveal interesting results.

## HADRONTHERAPY FACILITY DESIGN CRITERIA

The considerations reported above are of fundamental importance to define the design of a hadrontherapy centre. Indeed the main points that influence the characteristics of such a facility are the ion species to be accelerated and the technique to shape the radiation field. Three different accelerator types are possible: linear accelerators, cyclotrons, synchrotrons.

The penetration depth ranges between 30 mm and 300 mm. In case of protons and carbon ions, this corresponds to a range of energy respectively of 60 MeV-220 MeV and 120 MeV/u-425 MeV/u. In principle these energy ranges can be obtained with the three accelerators. However linacs are not very practical and feasible for high energies and then we will consider only cyclotrons and synchrotrons that are the main layouts in the hadrontherapy facilities. On the other hand synchrotrons can perform easily the acceleration of both proton and carbon ions. Indeed considering that the limitation is the magnetic rigidity, a synchrotron for carbon ions can accelerate all the species with $1\leq Z\leq6$; also Oxygen can be accelerated with such a layout but only up to a penetration range of 190 mm. Even if they are more flexible than cyclotrons, synchrotrons are technologically more complicated and then more costly: for example the synchrotron needs an injection energy of some MeV/u which requires an injector linac. The cyclotron appears to be more compact, especially in the case of a superconducting one. In the case of proton beams acceleration, a cyclotron has a diameter of about 4-5 m while a synchrotron reaches 7-11 m (a synchrotron designed for carbon ions has a diameter of about 20 m).

The maximum energy of carbon ions makes very challenging the realization of a dedicated cyclotron: up to now cyclotrons for 400 MeV/u carbon ions have not been realized yet but a centre has been recently proposed by IBA [5] consisting of a carbon cyclotron and a proton cyclotron. The advantage of more compact accelerators is partially reduced by the overall size of the facility that is occupied mainly by the beam lines and the treatment rooms with the gantries and the technical infrastructures. The current from the cyclotron is DC while in a synchrotron it is pulsed because of the need to ramp the magnets from the injection value to the extraction value first and then to a maximum value that allows avoiding non repeatability problems when changing energy due to the magnetic hysteresis. As a consequence, generally, currents from cyclotrons are much higher than the one from synchrotrons: in the case of protons cyclotron can deliver about 300 nA instead of some nA from synchrotrons.

There are essentially two techniques to shape beam distribution on the tumor target: passive and active beam delivery. The passive delivery consists essentially in putting before the patient several absorbers able to change beam characteristics. The passive technique consists of: a scatterer to enlarge the beam; a variable degrader and a ridge filter to increase energy spread creating a SOBP; a first collimator to select the central part of the beam; the so called bolus, a device with a "hole" that has the shape of the distal surface of the tumour; a final multileaf collimator that gives the beam the required transverse size. Fig. 2 shows schematically the absorbers used in the passive scanning.

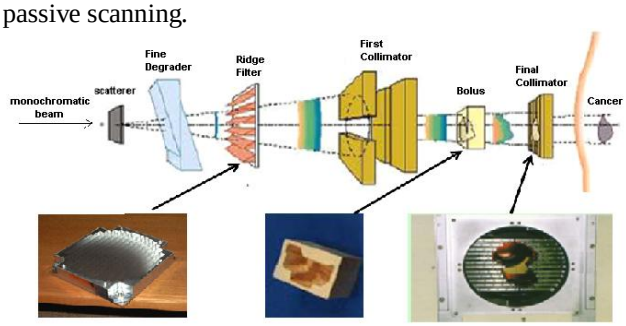


Figure 2: Scheme of a passive scanning.

Some variants to this scheme are the use of a rotating wheel range modulator as variable degrader and the wobbling method. The rotating wheel allows to change the thickness of material the beam passes through: in this way, making rotate the wheel, beams with different energies are obtained resulting in a SOBP. The wobbling method is based on the use of scanning magnets that cause the beam moves on a circle at high frequency before the scatterer so resulting in a flat beam to be adjusted transversally and longitudinally.

There are some evident disadvantages of the passive method. First the bolus and the multileaf collimator are strongly depending on the tumour and then they are specific for each patient. Second, as shown in Fig. 3, the bolus takes into account only the distal surface causing the proximal parts of the tumour are very badly irradiated. Third, the presence of lots of materials between the beam and the patient cause nuclear fragmentation that leads to dose tails after the Bragg peak. In particular in the case of heavy ions, passive scanning has other drawbacks. Indeed heavy ions cause nuclear fragmentation with the target; furthermore since they scatter less than protons thicker scatterers are needed to obtain a large treatment field: thicker scatterers imply larger energy and beam losses

requiring higher energies and currents from the accelerators.

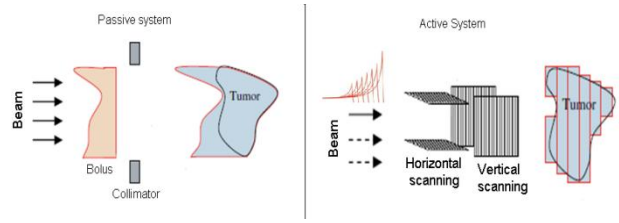


Figure 3: Dose uniformity in the case of passive and active system.

Active scanning was first used in Japan in 1980 [6] and then optimized and regularly used for treatments at PSI [7], GSI [8], HIT and CNAO [9].

In the active scanning method two magnets are used to move the beam in the two orthogonal directions. The tumour is virtually divided in slices in the longitudinal direction and each slices is thought as composed of small volumes called voxels (or spots). Each slice is irradiated fixing the beam energy and irradiating each voxel changing the currents of the scanning magnets. Furthermore for each voxel in a slice it can be taken into account the dose given during the irradiation of the previous slices.

Therefore with active scanning there is no specific hardware for each patient but, above all, the irradiated target is shaped very closely to the tumour target both in the transverse and in the longitudinal planes. The drawback of such beam delivery system is a greater difficulty in operation due to the management of the scanning magnets and of the beam position and also an increased sensitivity of the system to current ripples and changes. To obtain the precision in the dose shaping, the tumour must be known with the same precision that characterizes the active scanning. Problems occur in the cases in which tumour moves because of breathing and heart beating. In this case the passive scanning appears to be the easier solution; anyway considering the superiority of the active method, several studies are in progress worldwide in order to develop methods that allow to use the active scanning also with moving tumours: repainting, gating, beam tracking [10]. Repainting [11] consists in treating multiple (about 10) times the target with a reduced dose: in this way, amplitude, period and initial phase of the organ motion change randomly treatment by treatment and the irradiation uncertainty is statistically reduced. Gating [12] is a technique also used in case of passive scanning. It is based on the irradiation of the tumour only during a precise percentage (about 30%) of the organ motion: in this way a cyclotron treatment increases proportionally while in a synchrotron this disadvantage is mitigated by the cycle times needed to fill the ring. Finally beam tracking [13] is an adjustment of the parameters of the treatment plan in real-time using a 4D organ monitoring signal. A purely active scanning method, i.e. without absorbers, is possible only with a synchrotron because of the need of a variable extraction energy. Indeed the energy from a cyclotron is fixed and the active scanning is possible only after having changed the beam energy like in the passive methods with a wedge degrader (resulting in a maximum energy variation rate of about 15 MeV/sec).

All these considerations indicate that the best technological layout of a particle accelerator for hadrontherapy is a synchrotron designed for carbon ions equipped with active scanning.

## HADRONTHERAPY IN THE WORLD

The idea of hadrontherapy appeared in 1946 in a paper written by Robert Wilson [14] that proposed the medical use of protons produced by the new high energy accelerators. His idea was realized firstly when 30 patients were treated with protons at the Lawrence Berkely Laboratory (LBL) in 1954. In the next years other treatments have been performed in other research centers worldwide like Uppsala in 1957 and Harvard in 1963. Proton therapy experience followed in new facilities that became operative in Russia (Dubna in 1967, Moscow in 1969 and St. Petersburg in 1975), in Japan (Chiba in 1979, Tsukuba in 1983) and in Switzerland at the PSI center in 1985.

The world's first hospital-based dedicated proton facility started treatments in 1990 after 20 years from the feasibility study at Loma Linda. The LLUMC (Loma Linda University Medical Center) synchrotron has a diameter of 6 m with a 2 MeV injector placed on top of the ring. A beam of $2{\cdot}10^{10}$ particles per spill is extracted in the range 70-250 MeV with a half-integer resonant extraction scheme. The center is equipped with a fixed beam room with two beam lines (for eye and for head-and-neck treatments), three rotating gantries and a research room with three beam lines. To date over 15000 patients have been treated.

Nowadays 38 hadrontherapy facilities are in operation all around the world: Europe (11 centers distributed in Italy, France, Germany, England, Switzerland, Sweden, Poland, Russia), Asia (8 centers in Japan, 2 in China, 1 in South Corea), America (11 centers in USA and 1 in Canada), South Africa (1 centre). Fig. 4 shows in detail the locations of each facility. Most centers are proton facilities using cyclotron technology with passive beam delivery system. The hadrontherapy synchrotrons are only 14: in Japan HIMAC (Chiba), PATRO (Hyogo), PMRC (Tsukuba), WERC (Fukui), Shizuoka Cancer Center (Shizuoka), GHC (Gunma), STPTC (Koriyama-City), Medipolis Medical Research Institute (Ibusuki); in China, IMP (Lanzhou); in the USA besides LLUMC, M.D. Anderson Cancer Center (Houston); in Russia ITEP (Moscow) and St. Petersburg; in Europe HIT (Heidelberg, Germany) and CNAO (Pavia, Italy).

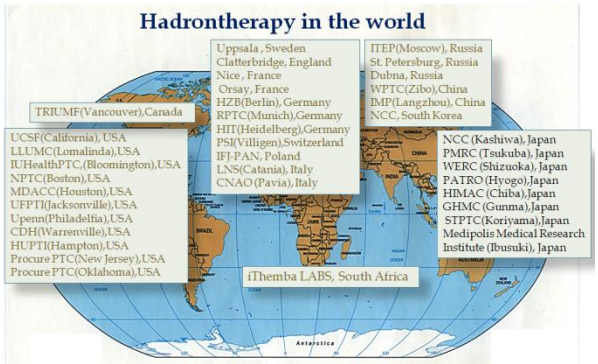


Figure 4: locations of the operative hadrontherapy facilities all around the world.

Other facilities are under construction or will start treatments in the next years in Europe, in Asia, in USA: 12 proton cyclotrons, 2 proton-carbon synchrotrons (Fudan University Shangai CC in China, MedAustron in Austria), 2 proton synchrotrons (McLaren PTC in USA, PMHPTC in Russia, CMHPTC in Slovak Rep.), 1 carbon synchrotron (HITFIL in China).

Presently carbon ions are produced in Asia at HIMAC, GHC, PATRO and IMP, in Europe at HIT and CNAO. Among these facilities, PATRO [15], HIT [16] and CNAO [17] produce both protons and carbon ions while HIMAC, GHC and IMP are dedicated facilities using only carbon ions. A particular mention is due to HIMAC centre [18] (see Fig. 5): operating since 1994, it is producing the most important clinical results with carbon ions (more than 6600 treated patients). It is equipped with two synchrotrons at the upper and lower floors that are much larger than the others (a 42 m diameter instead of the standard 20-22 m) because they were designed to deliver 800 MeV/u Si ions for clinical experimentation.

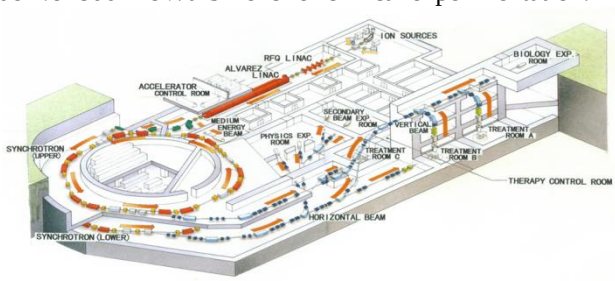


Figure 5: Himac layout.

Up to December 2011, the total number of treated patients with hadrons have been 75571, of which 7881 have been treated with carbon ions [19].

## LAYOUT OF A TYPICAL SYNCHROTRON

This section will show in detail some aspects of a synchrotron facility able to deliver proton and carbon ions. To give some typical orders of magnitude, datas of CNAO facility, shown in Fig. 6, will be given.

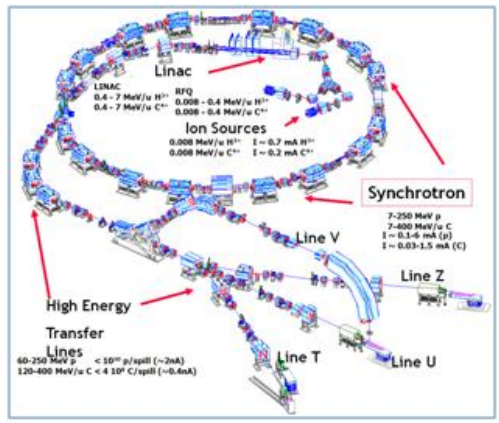


Figure 6: CNAO layout.

The scheme of such a facility is a low energy injector, a ring, several beam lines for the transfer of high energy beams in the treatment rooms. The injector can be placed outside the ring for easier maintenance, or inside the ring to save space. It is made up of two or three sources (depending on the number of species one wants to use with short switching times), a low energy transfer line (LEBT) to select and transport the ions produced by the sources, a linac and the transfer line (MEBT) to transport the preaccelerated beam to the synchrotron. Only few facilities have a PIG source or a EBIS source. PIG is based on the Penning vacuum gauges: a flux of electrons between an anode and a cathode ionizes a gas creating the beam. In the EBIS, ions are trapped inside a dense electron beam and is continuously bombarded by electrons and sequentially ionized. The most used source is the ECR one. It is based on the excitement of the electrons using radiofrequency fields at the electron cyclotron resonance frequency (10 GHz-18 GHz): the plasma electrons are confined by a magnetic trap (the so called minimum B-structure) realized by the superposition of a hexapole and axial structure. ECR source has the advantage to produce high intensity beams for a wide range of charge states.

The 14.5 GHz ECR sources [20] installed at CNAO can produce 250 μA of $C^{4+}$ beam with a normalized emittance of 0.56 π mm mrad and 1000 μA of $H^{3+}$ with an emittance of 0.67 π mm mrad with an energy of 8 keV/u. The RF, can be finely adjusted in frequency, has a power of about 8 W for protons and 180 W for carbon ions and is fed by 400 W TWTA power amplifiers.

The low energy linac is composed by an RFQ (Radio Frequency Quadrupole) and a IH (Interdigital H-type). The source current is DC but it enters in the RFQ pulsed thanks to a electrostatic chopper in the LEBT.

CNAO RFQ [21] is a four-rod type with 70 kV electrode voltage and delivers beams at 400 KeV/u; the IH [21] is a 5.3 MV/m, 3.77 m long, structure and accelerates beams up to 7 MeV/u; both tanks work at 217 MHz. MEBT contains elements to fit the transverse and longitudinal twiss parameters to the ring acceptance, in addition to stripping foils that change the charge status from the one produced by the sources. In CNAO stripping

foils allow to obtain $C^{6+}$ and $H^{+}$; quadrupoles match the transverse dimensions while a debuncher tank reduces the beam momentum spread.

In the needed energy range, proton magnetic rigidity varies in the range 1.16-2.31 Tm while the one of carbon ions goes from 3.18 Tm to 6.336 Tm. The use of normal conducting magnets giving at maximum 1.5 T implies that ring length is about 60-80 m (CNAO ring is 77.65 m). The acceleration is usually performed by a single cavity that must be a broadband resonator loaded with standard ferrites or with ferrite-like amorphous alloy (CNAO uses VITROVAC, a Fe-Co alloy). The use of such alloys have several advantages like reducing cavity dimensions and reducing (in some cases eliminating) the current for the cavity polarization [22]. The extraction from the ring is the most important and challenging aspect influencing ring design. Clinical requirements on dose uniformity is ±2-3%: this requirement with active scanning cannot be fulfilled with a single turn extraction. A single turn extraction means a beam shorter than 1 μsec requiring a passive system. As a consequence a slow extraction in the order of 1 s is mandatory. The slow extraction mechanism is realized by making unstable the particle betatron oscillations: the amplitude of their motion grows steadily until the particle "jumps" into the aperture of an electrostatic septum allowing the extraction. The lattice layout of the ring must be set so that the machine tune at the end of the extraction is near to an unstable value: to extract the beam, a mechanism must force the beam into the unstable region. Essentially three mechanisms are possible to make the beam passing from the stable to the unstable region. These are the amplitude selection, the amplitude-momentum selection, the RF knock out (RFKO). With the amplitude selection, used in the oldest facilities, the quadrupoles settings are changed before the extraction in order to vary the machine tune. In this case the beam that has small momentum spread and great betatron amplitude, acquires progressively the extraction tune.

The beam size, position and energy changes during the extraction because only one amplitude is extracted at a time. In the amplitude-momentum selection, the resonance region is fixed and beam moves towards the resonance. As a consequence momentum spread of the circulating beam is kept large and the extracted beam has fixed position, size and energy. At CNAO, beam is driven into the resonance by a betatron core: it is a toroidal magnet that creates a fem that accelerates the beam towards the instability.

Finally in the case of the RFKO method, the machine tune is fixed and the beam is excited by a transverse RF perturbation. Also in this case size, position and energy are stable. Furthermore with this method a rapid switch off of the dose irradiation is easy to be obtained. Fig. 7 graphically illustrates the three methods using the so called Steinbech diagram in which the resonance is represented in the phase space betatron amplitude-momentum spread.

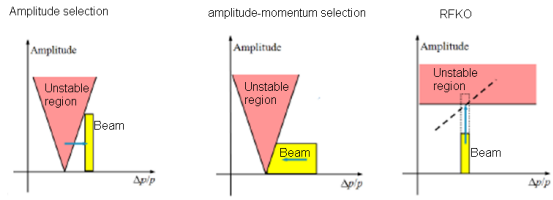


Figure 7: Steinbach diagrams of the three methods to put the beam in resonance.

At LLUMC the unstable tune was chosen to half-integer; nowadays the chosen resonance in all the facilities is obtained by a tune of N/3 and a sextupolar field that feeds the instability (the so called third integer resonance). Another important aspect of the extraction is the intensity quality of the spill. Considering the 2% dose homogeneity and that the time to irradiate a voxel is about 5 msec, beam has to be managed in a time structure of about 100 μsec: this means that the spill intensity spectrum must be controlled up to 10 kHz. This control is not easy with the amplitude selection because it requires a challenging control on the quadrupole ripple; on the contrary by the momentum selection and the RFKO technique spill structure can be well controlled. At CNAO spill ripple is greatly reduced by the use of the empty bucket technique, simply exploiting the RF cavity used for the acceleration; furthermore some improvements can be obtained by a rapid air core quadrupole in feedback on the spill intensity. Finally also the extraction lines are technologically challenging. First the number of lines must be high with rapid switching among the lines in order to maximize the number of patients. Second the beam quality needed at all the energies (stable position, possibility to have round beams with varying dimensions and so on) puts constraints on magnetic lattices and requires precise specifications on power supplies, magnets, control system, beam diagnostics controlling in real time the dose delivered to the patient (the so called nozzle), patient positioning. In particular the extraction lines must be equipped with a system able to guarantee a rapid switch off of the extracted beam (order of 100μsec considering the requirement on dose uniformity). Indeed a rapid switch off is not possible with a betatron core that is a highly inductive element and then slow; also in the case of the RFKO the time of a switch off is in the order of 1 msec. At CNAO this is obtained by four fast chopper magnets (100 μsec) (see Fig. 8) installed along the extraction line that create a bump on the beam orbit: if the bump is not performed beam orbit ends on a dump.

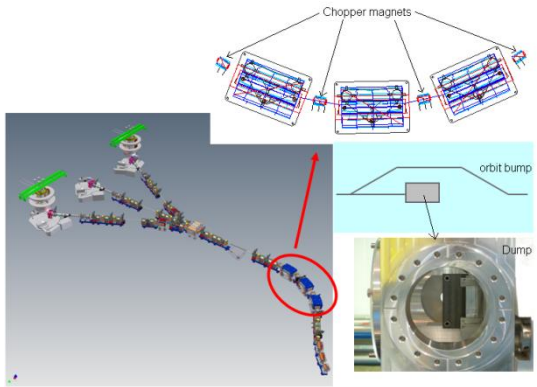


Figure 8: CNAO safety system for a fast beam switch off.

To improve the quality of the treatment, irradiation from different directions is mandatory. This is achieved either displacing the patient, or using several lines in the same room (e.g. horizontal and vertical) or installing rotating beam lines, the so called gantries. Nowadays gantries for protons are present in most facilities; on the contrary a gantry for carbon ions must have a higher weight and size: up to now only the Heidelberg facility is equipped with a carbon ions gantry (weight of 600 tons, diameter of 13 m against the standard dimensions for protons of 100 tons and 10 m) that is under commissioning [23].

## HADRONTHERAPY BUSINESS

Since the construction of the first hospital-based facility most technologic guidelines for the realization of a hadrontherapy centre have been delineated. This allowed some companies to produce projects for the commercialization of ion beam therapy centres with largely standard components. The main companies are IBA, Hitachi, Mitsubishi, Sumitomo, Varian, Still River. Considering the number of built facilities, IBA is the world's most important company. Its centres are based on a 230 MeV normal conducting cyclotron for protons with horizontal beam lines and rotating gantries with passive scanning. Varian, that bought ACCEL in 2007, builds facilities delivering protons in the range 70-250 MeV with an isochronous superconducting cyclotron to 6 treatment rooms. Hitachi has sold 70-250 MeV proton synchrotrons with performances that are similar to the LLUMC. Also Optivus company, that has followed maintenance and improvements of LLUMC, is marketing a proton system very similar to LLUMC.

Still River Systems is offering a miniaturized 250 MeV proton superconducting synchrocyclotron mounted directly on the gantry within the treatment room: installation of the first facility is underway in USA.

Sumitomo has commercialized a 230 MeV proton cyclotron with up to 5 rooms. It is also marketing carbon ions synchrotrons able to deliver $C^{6+}$ and $C^{4+}$ to three treatment rooms; even if it has installed injectors to PATRO and GHMC it has not yet sold a complete carbon synchrotron facility.

Mitsubishi markets a 70-250 MeV proton synchrotron for up to 6 treatment rooms; it also has sold two synchrotrons for both 70-250 MeV proton and 70-380 MeV/u carbon ions. The other commercial centre for both protons and carbons has been produced by Siemens. However in Summer 2011 Siemens announced its loss of commercial interest in the hadrontherapy field: as a consequence the nearly finished centre in Kiel will be dismantled selling components to other therapy centres, while the just finished Marburg centre will continue only research activities for about two years before its probable dismantling.

Even if there are a lot of firms, the hadrontherapy field is not limited to firms; the field is still technologically challenging then research centres still contribute to the design and the construction of facilities: e.g. CNAO, that started treatments in September 2011, was born from the PIMMS [24] performed at CERN and built by the help of a strong net of international collaborations with research centres: INFN (Italy), CERN, GSI (Germany), LPSC (France), NIRS (Japan), italian universities (Milan, Pavia, Turin).

Apart the R&D on technological aspects of the actual hadrontherapy facility layouts, lots of ideas are under developments to improve the performance of hadrontherapy centers, mainly in tumour tracking and tumour imaging sectors but also in accelerator technology field (like FFAG, LIBO, DWA and Laser acceleration).

FFAG [25] design foresees fixed-field combined-function bending magnets: a strong radial magnetic field gradient in the dipole component allows to keep the beam in a narrow ring like in a synchrotron but without ramping the magnets so having a DC beam with the possibility of fast energy changes.

LIBO (Linac Booster) [26] foresees a proton linac (1.5 m with 27 MV/m) booster from 30 to 250 MeV so it can be used in association with the standard cyclotron for radioisotopes; the application of this idea for carbon is under study.

DWA (dielectric wall-induction linac) [27] idea is based on the use of new dielectrics able to sustain greater voltage gradient (100 MV/m) in order to reach an acceleration of 250 MeV with a 3 m linac.

Finally the acceleration with high power lasers [28] is under study in order to meet the several clinical requirements.

## CONCLUSIONS

Since the birth of the idea, hadrontherapy field has developed a lot with a rapid growth in the last years in terms of treatments and operative facilities all around the world. The centers have passed from the status of research centres to the one of hospital dedicated facilities with firms that commercialize facility models. Carbon facilities are greater and more expensive than proton facilities but the clinical advantages of carbon with respect to protons push to the building of new synchrotrons able to deliver both species. Also R&D

remains an important aspect of this field both in the improvement of the present designs and in the search for new accelerator machine layouts.

## AKNOWLEDGEMENTS

A special acknowledgement is due to Marco Pullia, Erminia Bressi, Sandro Rossi and Caterina Biscari for the help in finding precious references and for useful discussions.

## REFERENCES

[1] R. E. Zirkle, *Radiation Biology*, 1, 315-350 (1954).
[2] International Commission On Radiation Units And Measurements, *The quality factor in radiation protection*, ICRU Report 40 (1986).
[3] L. H. Gray, *Am. J. Roentgenol.*, 85, 803-815 (1961).
[4] H. Eickhoff, U. Linz, *Reviews of Accelerator Science and Technology*, 1, 143-161 (2008).
[5] Y. Jongen, *"Design of a K=1600 SC cyclotron for Carbon therapy", ECPM* ,Nice (2006).
[6] T. Kanai et al., *Med. Phys.*, 7, 365-369 (1980).
[7] E. Pedroni et al., *Med. Phys.*, 22, 27-53 (1995).
[8] Th. Haberer et al., *Nucl. Instrum. Methods Phys. Res. A* 330, 296-305 (1993).
[9] M. Donetti et al., *Dose Delivery at CNAO, PTCOG51*, Seoul (2012).
[10] N. Saito et al., *Phys. Med. Biol.*, 54(16), 4849 (2009).
[11] M. H. Phillips et al., *Phys.Med. Biol.* 37, 223-233 (1992).
[12] H.D. Kubo et al., *Phys.Med. Biol.* 41, 83-91 (1996).
[13] S.O. Grozinger et al., *Radiat. Oncol.* 3, 34 (2005).
[14] R. Wilson, *Radiological use of fast protons, Radiology 47*,487-491, (1946).
[15] http://www.hibmc.shingu.hyogo.jp.
[16] Th. Haberer et al., *The Heidelberg Ion Therapy centre, Radiotherapy and Oncology,* Vol. 73, pp. S186-S190, (2004).
[17] S. Rossi, Eur. Phys. J. Plus, (2011) 126:78.
[18] Y. Hirao et al., *Nucl. Phys.*, A538, 541c, (1992).
[19] http://ptcog.web.psi.ch/ptcentres.html.
[20] G. Ciavola et al., *Commissioning of the ECR ion sources at CNAO facility, EPAC08* ,Genova (2008).
[21] B. Schlitt et al., *Linac Commissioning at the Italian hadrontherapy centre CNAO IPAC10*, Kyoto (2010).
[22] L. Falbo et al., *CNAO RF cavity: hardware description, IPAC11,* San Sebastian (2011).
[23] M. Galonska et al., *Commissioning of carbon beam gantry at HIT accelerator, WAO10,* Daejeon (2010).
[24] S. Rossi et al., *Proton-Ion Medical Machine Study (PIMMS)*, Part I and II, CERN/PS 1999-010 DI and CERN/PS 2000-007 DR, Geneva (2000).
[25] M. K. Craddock et al., *FFAG accelerators*, Erice (2009).
[26] U. Amaldi et al., *Fast-cycling accelerators for hadrontherapy, Nucl. Instrum. Methods A 521,512* (2004).
[27] G. J. Caporaso, *High Gradients induction Linacs for hadrontherapy*, Erice (2009).
[28] P. R. Bolton et al., *Toward laser-driven proton therapy of cancer at PMRC in Japan*, Erice (2010).