OPERATION AND PATIENT TREATMENTS AT CNAO FACILITY

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on behalf of the CNAO Collaboration.

Abstract

The CNAO (National Centre for Oncological Hadrontherapy) has been realized in Pavia. It is a clinical facility created and financed by the Italian Ministry of Health and conceived to supply hadrontherapy treatments to patients recruited all over the Country. A qualified network of clinical and research Institutes, the CNAO Collaboration, has been created to build and to run the centre. Three treatment rooms (equipped with three horizontal and one vertical beam lines) are installed. Beams of protons with kinetic energies up to 250 MeV and beams of carbon ions with maximum kinetic energy of 400 MeV/u are transported and delivered by active scanning systems. CNAO commissioning concerning the high technology started in 2009. First patient was treated with Proton beam in September 2011, the 22nd.

THE CNAO HISTORY

The hadrontherapy is a high precision kind of radiotherapy employing hadrons instead of the standard photons and electrons. Indeed Protons and Carbon ions have important advantages [1]:

- beams penetrate the patient without diffusion,
- they deposit their maximum energy at the end of their range. In this way the beam is able to produce severe damage to the diseased DNA while the traversed healthy tissue is preserved,
- due to the charge, the beams can be scanned and using variable penetration depths any part of the tumor can be accurately and rapidly irradiated,
- Carbon ions show an increased radiobiological effectiveness at the end of their range that allow the treatment of radioresistant tumours.

The CNAO idea was born in 1991, from a report by Ugo Amaldi and Giampiero Tosi titled "For a center of teletherapy with hadrons" [2].

In 1992 the TERA Foundation was created in order to build up a staff for the design of a hadrontherapy Centre.

Amaldi in 1995 convinced CERN to transform his idea in a general project for hadrontherapy in Europe: a synchrotron for carbon ions and protons, optimized for therapy. This study, called *Proton Ion Medical Machine Study* (PIMMS) [3], was completed in 2000 and evolved into the version CNAO realised in Pavia (in Table 1 are shown the main physical parameters of the project).

Table 1: CNAO Main Physical Parameters

physical parameters	**value**
Beam particle species	p, He^{2+}, Li^{3+}, Be^{4+}, B^{5+}, C^{6+}, O^{8+}
Energy range	60 – 250 MeV for protons 120 – 400 MeV/u for carbon ions
Energy step	0.02 MeV
Relative momentum $\Delta p/p_{max}$	1.7×10^{-5}
Beam size	4 to 10 mm FWHM
Beam size step	1 mm
Beam size accuracy	≤± 0.2 mm
Beam position step	0.1 mm
Beam position accuracy	≤± 0.05 mm
Field size	5 mm to 34 mm 2×2 cm^2 to 20×20 cm^2
Max. number of particles per spill at the patient	10^{10} for protons 4×10^8 for carbon ions
Min. number of particles per spill	10^8 for protons 4×10^6 for carbon ions
Nominal number of spills and treatment time	60 spills in 2-3 min

Figure 1: CNAO site.

The realisation of CNAO is based on a strong collaboration network, that links CNAO with the most important Institutions in Italy and abroad. The first important step for CNAO realization happens in 2000, when Umberto Veronesi, appointed Minister of Health, decided to finance the construction of CNAO. In Autumn 2001 the CNAO Foundation was created and Erminio Borloni was elected as President.

The years from 2002 to 2004 were essential to define the managerial structure of Foundation and to define the Institutions support.

From 2005 up to 2009 a great effort was done in order to realize the CNAO complex and to install the high technology components. In Fig. 1 we can see a photograph of the center at its site, after its completion.

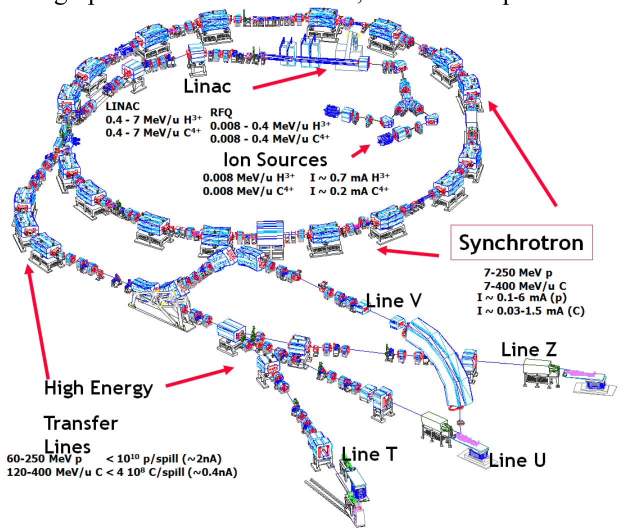

Figure 2: Layout of CNAO synchrotron and beam lines

In Fig. 2 a complete layout of the machine is presented and Fig. 3 shows a view of the synchrotron room.

CNAO beams are generated by two ECR sources, both producing the two particle species. The injection system of the synchrotron, placed inside the ring, is composed by an 8 KeV/u Low Energy Beam Transfer line (LEBT) , followed by an RFQ to accelerate the beams up to 400 keV/u, a LINAC to reach the synchrotron injection energy of 7 MeV/u [4], and a Medium Energy Beam Transfer line (MEBT) to transport the beam to the synchrotron. The synchrotron ring has a length of 77.65 m and after the acceleration delivers beam to four extraction lines (three horizontal lines named Z, U and T and one vertical line named V), in three treatment rooms. The extraction is realized via a resonant slow extraction mechanism; in particular the beam is accelerated to the resonant tune by a betatron core [5].

Proton beam was first commissioned in room Z (room on the left along the beam path) while room T was used for the first commissioning of the Carbon ions.

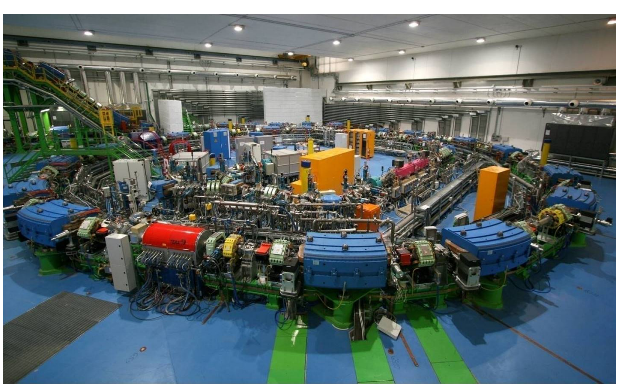

Figure 3: High technology installation view in the synchrotron room.

THE CNAO ACCELERATOR COMMISSIONING

High technology commissioning at CNAO was started in 2009. Installation of all the components finished in 2010 alternating periods of installations with periods of beam commissioning. In fact, in spring 2009 LINAC commissioning was performed and MEBT commissioning in autumn of the same year [6][7]. Synchrotron tests started in March 2010. First Proton beam acceleration was performed in September 2010 and after only some weeks first proton beam arrived at the end of the Z extraction line. During 2011 the machine started to work 7/7days 24/24 hours alternating the measurements for the beam parameters optimization to the beam clinical commissioning. In order to begin treatments as soon as possible, proton beam was first commissioned in a limited energy range (from 118 MeV/u up to 175 MeV/u that correspond to a longitudinal penetration in water, respectively of 100 mm and 200 mm) according to the medical requirements for the first patients.

First patient was treated in September 2011, 22th. From September to December 2011 the energy range of Proton beam was fully commissioned (from 60 MeV/u up to 250 MV/u) [8].

A typical machine cycle is shown in Fig. 4. DCCT signal (yellow line) shows the particle number in the different phases of the machine cycle, the blue line is the ramp of the synchrotron dipole field. The extraction length is 1.2 sec as shown by the pink line that represents the acceleration given by the Betatron core during the extraction. The whole cycle has a duration of about 4 sec.

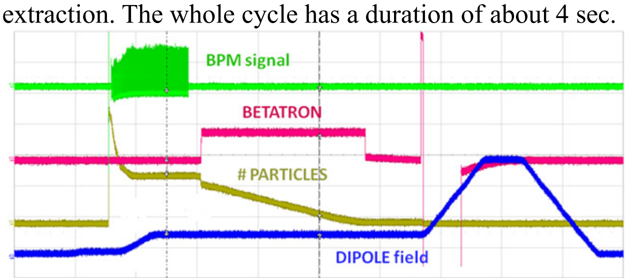

Figure 4: Machine cycle: a pick-up signal (green line), the Betatron ramp (pink line), the DCCT signal (yellow line) and synchrotron dipole field (blue line).

The commissioned energies allow to have steps in the longitudinal penetration of 2 mm; for each step the required precision is of 0.1 mm that corresponds, at 60 MeV/u, to an energy precision of 0.08 MeV and, at 250 MeV/u, to a precision of 0.03 MeV resulting in a maximum energy relative precision of 0.01%.

The current accelerated in the ring is about 7*10^9 particles and the transmission efficiency from synchrotron to treatment room is quite high at the different energies (60-70% including the losses at extraction). Particular care was dedicated to the time structure of the spill: the empty bucket channelling technique is used to reduce the ripple spill and optimize the uniformity of the dose delivered during the spill. In Fig. 5 the dose delivered during the spill is shown. It is measured with a sampling period of 10 µs: the ratio between the maximum dose delivered and its average value is about 6.

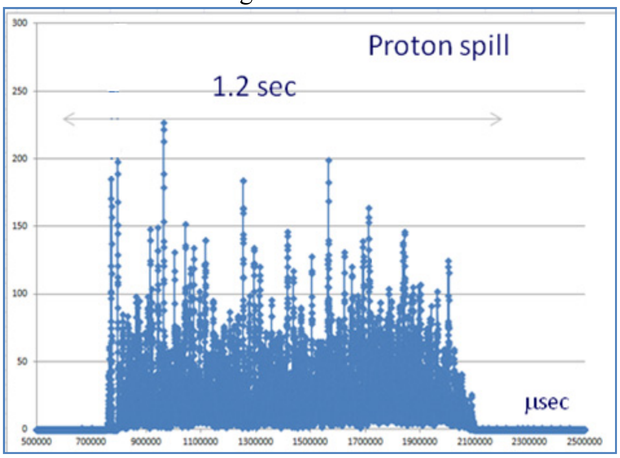

Figure 5: Time structure of a Proton beam spill.

HEBT optics has been set to have round beams at the exit of the extraction line with a FWHM of about 3 mm. The Commissioning of Carbon ions started in February 2012 [9] in T room. Due to the treatment planning of patients performed in Z room, carbon commissioning was scheduled during the afternoon and night hours. The full energy range of carbon has been commissioned (from 120 MeV/u to 400 MeV/u corresponding to the range 30 mm-270 mm). Also for carbon ions, a step of 2 mm in energy was commissioned with a maximum relative precision in energy of about 0.02%.

The carbon accelerated beam is composed of 1.5*10^8 particles and the transmission efficiency is comparable to the one of protons.

The first patient treatment with Carbon beam is foreseen in October 2012. Commissioning of the central room (horizontal and vertical line) will start in July 2012.

PATIENT POSITIONING AND VERIFICATION SYSTEM

Hadrontherapy needs a higher accuracy in patient positioning if compared to the conventional radiotherapy due to the enhanced sensitivity of the particle beam to the target misalignment. A dedicated solution is necessary in hadrontherapy centers in order to have a precise dose delivery.

Solution used at CNAO for patient set-up, immobility verification and dynamic tumour targeting relies on the integration of optical tracking and in-room imaging systems [9].

The CNAO Computer Aided Positioning System in Hadrontherapy (C.A.P.H.) includes 3 custom designed sub-systems combining ease of use with highest safety and accuracy:

- a robotic pantographic patient positioning system (PPS)
- an isocentric in-room imaging system, based on stereoscopic X-ray imaging (PVS)
- an infra-red (IR) optical tracking system (OTS)

The C.A.P.H. sub-systems integration allows one to perform fast and swift verification of patient set-up, to estimate and apply 6 degrees of freedom correction vectors for set-up error minimization and to implement target position estimation through in-out correlation models for time-resolved dose delivery techniques [10].

CLINICAL CHARACTERISATION OF PROTON BEAMS

The clinical commissioning of Proton beams has been a mandatory step before the clinical use of the machine to ensure safe and accurate treatments. This commissioning included physical and biological characterization performed with the CNAO active scanning. In particular Dose Delivery and treatment planning (TPS) systems, the determination of absorbed dose to water under reference conditions and the baseline for periodic quality control tests were commissioned during the clinical test period.

The available proton range, that is from 60 to 250 MeV, was verified using the dedicated dosimetry system called Peakfinder (PTW). The integral depth dose distribution is determined with very high resolution (10 micrometers) [11]. The instrument consists of a double, sealed and motorized water column assembly, with two large diameter ionization chambers (Bragg peak chambers, PTW, Germany).

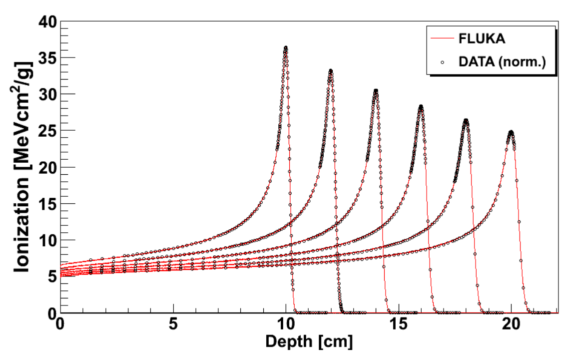

Figure 6: Proton Bragg peaks comparison between data and FLUKA simulations.

During the commissioning, all the beam energies were verified measuring the depth of the Bragg peak in water in the range from 30 mm to 320 mm. Fig. 6 shows some Bragg peaks measurements compared with the simulated ones, while in Fig. 7 the transverse dimensions of the beam at the isocenter at the different energies is compared with Monte Carlo simulations. As Fig. 7 shows, due to the scattering in air, proton beams suffer an increase of the transverse dimensions depending on the energy. The full-width at half maximum (FWHM) in both transverse planes at the isocenter were fixed at the nominal value of 10 mm at each energy.

Thanks to the use of intensity grids, four nominal beam intensities were chosen, obtaining from about 10^8 to 10^9 protons per spill.

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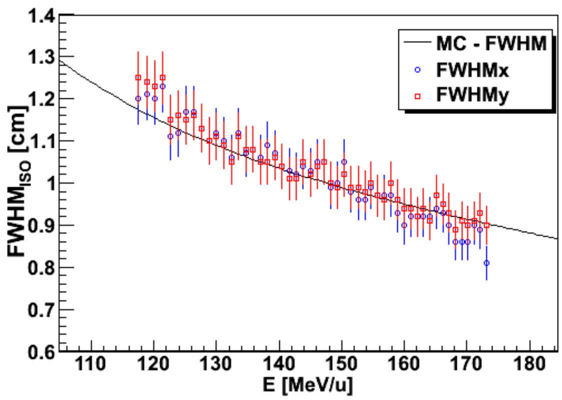

Figure 7: Beam dimensions in horizontal and vertical plane for a limited range of Proton beams.

Dose Delivery system [12] was commissioned during this phase. It consists of a double assembly of two large area ionization chambers, two orthogonal strip chambers and one pixel chamber.

Homogeneity of the proton beam was investigated and using a spread-out-Bragg-peak (SOBP) [13], the absorbed dose and the relative dose distribution was measured; it was found within the tolerance level (+/- 2.5%). In Fig. 8 a picture of the homogenous square realized to check dose homogeneity.

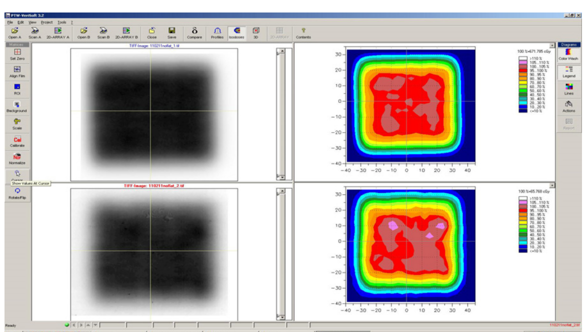

Figure 8: Homogenous square measured with a Proton beam.

RADIOBIOLOGICAL CHARACTERISATION OF PROTON BEAMS

For the radiobiological characterization of Proton beam the Relative Biological Effectiveness (RBE) concept was used. Many factors affect the RBE value; in the treatment with protons the "clinical RBE" is assumed to be about 1.1 along the Spread Out Bragg Peak (SOBP).

At CNAO, experiments in vitro were performed during May and June 2011 [14]. They consisted in studying Survival curves of three cell lines and the Biological depth-dose distribution of the SOBP beam using cell survival assay.

The three cell lines used for the beam characterization were:

- HSG (human salivary gland tumor), a reference cell line for preclinical activity used at various centers in Japan and Korea;
- T98G (human glioblastoma), radioresistant cell line widely used as a model in various radiobiological studies;
- V79 (Chinese hamster lung fibroblast), a reference cell line for radiobiological studies.

For these experiments, proton beams with an energy corresponding to a maximum range in water equal to 20 cm and a SOBP of 6 cm were selected. Three different depths along the SOBP have been selected for irradiation: one at the entrance of the SOBP plateau, one in the SOBP center and one in the SOBP distal end (see Fig. 9).

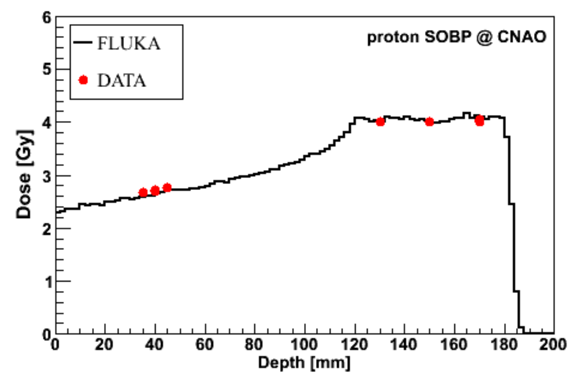

Figure 9: Position of measurements for radiobiological experiments with Proton beam.

EXPERIMENTATION ON PATIENTS

In September 2011, CNAO started patient treatments under two prospective phase II protocols approved by the Italian Health Ministry. Patients with chondrosarcoma or chordoma of the skull base or spine were eligible. In December 2011, four patients (one with skull-base chordoma, one with skull-base chondrosarcoma, two with sacral chordomas) completed treatments. Since January 13 new patients completed treatments and other are in waiting list: by July 2012 the number of patient treated at CNAO will be 17. The recruitment of new patients is in progress [15].

Immobilization was performed using rigid non-perforated thermoplastic-masks and customized head-rests or body-pillows. Non-contrast CT scans with immobilization devices in place and MRI scans in supine position were performed for treatment-planning. The patients were irradiated from two different directions (named PTV1 and PTV2). Each treatment has a duration of few minutes. For chordoma, the prescribed doses were 74CGE (CGE means cobalt-gray equivalent) and 54CGE to PTV1 and PTV2, respectively. For chondrosarcoma, the prescribed doses were 70CGE and 54CGE to PTV1 and PTV2, respectively. The treatment was delivered 5 days a week in 35-37 fractions. Weekly MRI incorporating diffusion-weighted-imaging was performed during the course of proton therapy. Patients were reviewed once weekly and acute toxicities were graded

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with the Common Terminology Criteria for Adverse Events (CTCAE).

All four 2011 patients completed the proton therapy without toxicities and without treatment interruption. Median dose delivered was 74CGE. The maximum toxicity recorded was skin desquamation (CTCAE Grade 2) in one patient.

Preliminary data demonstrates the clinical feasibility of scanned proton beams in Italy. Fig 10 shows the treatment plan for the first patient treated at CNAO.

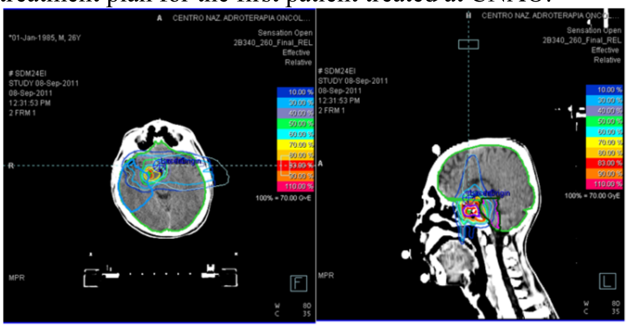

Figure 10: Treatment plan for the first patient with skull-base chondrosarcoma.

CHARACTERISATION OF CARBON BEAMS

As already mentioned, the acceleration, extraction and characterization of the carbon beams in the whole range of useful energies have been completed by April 2012.

Presently, the clinical and radiobiological commissioning of carbon beams are in progress following the same iter of the proton beams. The only but important difference are in vivo experiments for which the following radiobiological checks have been scheduled for the irradiation of 150 mice:

- Intestine crypt survival, which is a standard method in Japanese ion-therapy facilities;
- Grade II paresis after irradiation of the spinal cord to determine the radiation tolerance of the central nervous system.

For the in vitro and in vivo experiments, the required FWHM of the beam at the isocenter is 6 mm in the horizontal and vertical planes. Another focus will be commissioned in July (10 mm in both planes) to satisfy all the medical request for the patient treatments.

CONCLUSIONS

Medical activities with Proton beam at CNAO started in September 2011. Patients with chondrosarcoma and chordoma are presently under treatment. The first thirteen patients completed the treatment by April 2012, other eight patients have started treatment in May 2012.

High technology commissioning in all the treatment rooms will be completed in July 2012.

Carbon beams have been physically commissioned; clinical and radiobiological verifications are in progress. Medical activities with Carbon beam will start in October 2012.

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REFERENCES

[1] U. Amaldi and G. Tosi, Per un centro di teleterapia con adroni, TERA 91/1 GEN 1 (1991).
[2] G. Kraft, Tumour therapy with heavy charged particles, Prog. Part. Nucl. Phys., 45 (Suppl 2) (2000).
[3] L. Badano, 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).
[4] S. Rossi, Eur. Phys. J. Plus, (2011) 126:78.
[5] M. Pullia et al., Status report of CNAO Construction e Commissioning, IPAC11.
[6] E. Bressi et al., Status report on the Centro Nazionale di Adroterapia Oncologica (CNAO), PAC09, TU6PFP005 (2009).
[7] G. Bazzano, Status of the commissioning of the Centro Nazionale di Adroterapia Oncologica (CNAO), IPAC10, MOPEB005 (2010).
[8] E. Bressi et al., IPAC12.
[9] G. Baroni et al., Integration of Enhanced Optical Tracking Techniques and Imaging in IGRT, J. Radiat. Res. 48:A61-74 (2007).
[10] A. Esmaili et al., Targeting Accuracy in Real-time Tumor Tracking via External Surrogates: A Comparative Study, Technol. Cancer Res. Treat. 9(6): 551-562 (2010).
[11] C.P. Karger et al., Dosimetry for ion beam radiotherapy, Phys. Med. Biol. 55, R193-R234 (2010).
[12] M. Donetti et al., Dose Delivery system at CNAO, 51st PTCOG, Seoul, Korea.
[13] M. Donetti et al., Particle beam characteristics verification for patient treatment at CNAO, IPAC2011, San Sebastian, Spain.
[14] R. Cherubini, Attività preclinica al CNAO: caratterizzazione radiobiologica dei fasci di protoni, Internal workshop (November 7,2011).
[15] M.R. Fiore, Adroterapia: prospettive cliniche, LNF 4th Mini-Workshop series, 12th April 2012, Frascati (Rome-Italy).