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The National Centre for Oncological Hadron therapy (CNAO): Present Status and Future Perspectives

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Some elementary particles used for experiments of fundamental physics have properties useful to the treatments of patients affected by oncological pathologies. They are protons and carbon ions, collectively named hadrons, hence the term hadron therapy. Hadrons, in particular carbon ions, are more precise on the target than conventional X-rays and possess radiobiological characteristics suited to treat radioresistant or inoperable tumors. Italy is at the forefront of these techniques, and in Pavia a clinical facility called CNAO (Italian acronym that stands for National Centre for Oncological Hadron therapy) has treated so far more than 2800 patients with very good results. The CNAO was created by the Health Ministry and was realized by the CNAO Foundation in collaboration with the Italian Institute of Nuclear Physics (INFN), CERN, GSI and other institutions in Italy and abroad. The facility in Pavia delivers beams of hadrons in three treatment rooms with four fixed beam ports: three horizontal and one vertical. A new room, with an horizontal beamline and multiple isocenters, was completed and will be fully devoted to research applications. The CNAO has also launched a development programe to add a new single room for proton therapy with a gantry and a dedicated accelerator. Attention is also devoted to the most interesting aspects of research and development in the hadron therapy domain, like the creation of a new BNCT (Boron Neutron Capture Therapy) facility and the design of a novel gantry for carbon ions.

Keywords: Hadron therapy, Tumor, Synchrotron, Protons and Carbon ions
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I. INTRODUCTION

The National Centre for Oncological Hadron therapy (CNAO) has been created in Pavia; the Centre in operation has as its main purpose the treatment of oncological patients by using nuclear particles. The CNAO is equipped with a complex particle accelerator, called a synchrotron, the only one in Italy capable of extracting protons and carbon ions from atom, which are the most powerful particles effective in destroying the DNA in cancer cells while preserving the surrounding healthy tissues. The Italian Ministry of Health has recently included hadron therapy in the Essential Levels of Care, recognizing its scientific effectiveness. Every day more than 50 patients are treated at CNAO, and in fall 2019, more than 2800 oncological patients from all over Italy benefited from hadron therapy.

II. HADRON THERAPY: THE RATIONAL AND THE CLINICAL INDICATIONS

Hadron therapy is an advanced radiation therapy technique that employs beams composed of the nuclei of hydrogen atoms, protons, and the nuclei of carbon atoms. The term hadron therapy derives from the therapeutic use of hadrons, a collective name that defines the particles constituted by quarks, as the nuclei in question are. In fact the Greek word "adros" means "strong", to indicate the type of force that holds the quarks together in carbon nucleus and in protons in an indissoluble way.

The idea of using these particles for the treatment of tumors dates back over seventy years to the time, when the American scientist Bob Wilson [1] understood the potential of particle beams thanks to their physical characteristics. Because they are "heavy" particles compared to the electrons that surround the nuclei, they tend to move in a straight line when they enter the tissues of the human body and, therefore, travel over a defined and determined distance. Along their paths, the particles interact with the atoms of the tissue, progressively transferring their energy to the matter and finally stopping in a few millimetres distance, where they release most of their destructive power, the so-called Bragg peak. Thanks to the Bragg peak, the hadron beam is suitable for hitting with precision solid targets within the human body and, thus, conforming the damage (in the radiation oncologists jargon the dose, *i.e.*, the energy released per unit mass of tissue) with millimetric precision. This ballis-

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tic precision is particularly useful for hitting tumor targets nearby critical organs and for achieving significant savings in healthy tissues, therapy reducing the risk of secondary cancers related to the effects of radiation.

Hadrons are charged particles, nuclei of atoms from which electrons have been torn: the charge of the proton is unitary and positive, the charge of the carbon nucleus is positive and equal to 6 times the proton charge. In turn, the mass of the carbon nucleus is about 12 times the proton mass and the result is that the "tendency" to maintain the straight line mentioned above is even more pronounced than for the proton. Thanks to this feature, a greater precision in the conformation of the dose to the tumor volume is achievable with carbon ion beams than with protons.

In the case of carbon ions, an additional effect linked to the mass, twelve times greater than the proton one, has to be taken into consideration. In fact, while proton beams with an energy of 250 MeV are required to penetrate deeply into water or tissue equivalent material (MeV means Millions of Electron Volts and is a unit of energy measurement on an atomic scale), in the case of carbon ions, over 5100 MeV are necessary to reach the same penetration. At the same depth reached, considering a carbon ion beam, the energy deposited per unit length of track is, therefore, on average twenty times higher. In other words, the damage density produced over typical distances of cellular DNA, *i.e.*, in a few billionths of a meter (nanometers), is much higher in the case of carbon ions than it is in the case of protons. This phenomenon causes the generation of multiple and clustered damage sites that cannot be remedied by cellular repair mechanisms and, therefore, lead to irreversible processes of death of the affected cells. This increased therapeutic efficacy of carbon ions makes them suitable for the treatment of so-called radio-resistant tumors, *i.e.*, tumors not responding to conventional radiotherapy (X-rays) or to protons.

The state of the art of hadron therapy in the world is experiencing a strong expansion, with 78 running proton therapy centers, as reported by the PTCOG, (Particle Therapy co-operative Group) website [2], and 13 centers exploiting carbon-ion beams. Proton centers are located mainly in the USA (34), in Europe (20) and in Japan (13). Carbon-ion centers can be found in Japan (6), Europe (4) and China (3); 6 of these produce both carbon ions and protons and potentially other ionic species; therefore, they are called multi-particle centers, among them, the CNAO of Pavia in Italy should be mentioned. At present, over 220,000 patients have been treated, 190,000 of which with protons and 28,000 with carbon ions. Every year 22,000 new patients are added to the proton therapy cohort and 4,500 to the carbon-ion therapy cohent. The number of centers under construction or in the planning phase is such that in the next five years, the number of running centers is going to double. Finally, it is important to point out that the technological standard of proton therapy includes rooms equipped

Fig. 1. Layout of the synchrotron with the corresponding four extraction beam lines.

with rotating beam lines (gantry) and a total number of over 190 treatment rooms while in the case of carbon ions over the twenty existing treatment rooms in the world, only 2 are equipped with rotating beam lines. This limitation is linked to the size, consumption and costs of gantry for carbon ions, which are currently prohibitive by hospital standards; furthermore, these devices are still being investigated in several research and development projects.

Evaluating which patients can benefit from the use of hadrons, keeping in mind that conventional radiotherapy is already today capable of giving effective answers to almost half of patients suffering from cancer, is important. All the more reason, given the higher costs of facilities producing hadrons with respect to those providing conventional radiotherapy, identifying the pathologies that the National Health Service must address with these innovative therapies is important. This task has been carried out several times by national and international radiation oncologists communities, with the support of scientific societies, such as the Italian Association of Radiation Oncologists (AIRO). The image in Fig. 1 reports the results of these investigations and the evaluation of the number of patients expected per year for each category, as can be seen from an analysis of Italian Cancer Registries.

Every year in Italy over 150 thousand patients are subjected to conventional radiotherapy treatments; therefore, the pathologies indicated in the Fig. 1 are relatively rare. Hence, hospital networks, together with selection and referral mechanisms for elective patients for hadron therapy, need to be built in order to refer those patients to the CNAO.

In fall 2019, the number of patients treated at CNAO exceeded 2800 (Fig. 2). After a first phase, which served to obtain the CE marking of the CNAO medical device, in 2014, hadron therapy became one of the recognized clinical services reimbursed by the National Health Service.

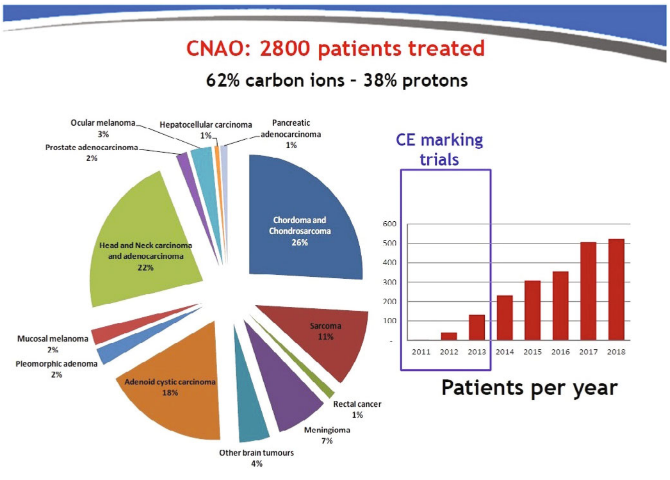

Fig. 2. Typology and number of patients treated per year at the CNAO.

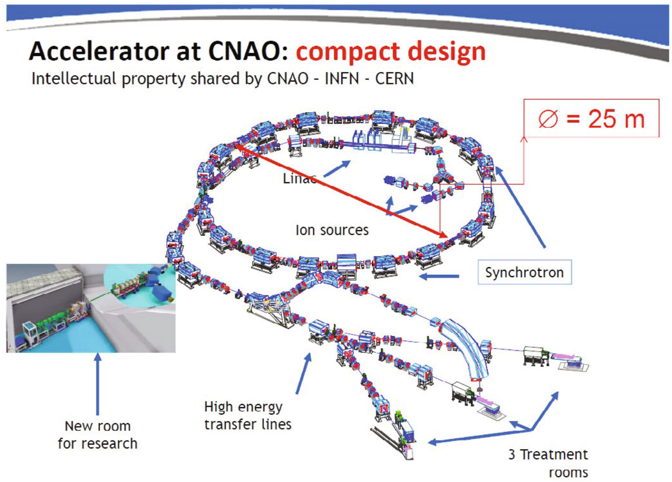

Fig. 3. Layout of the synchrotron with the corresponding four extraction beam lines.

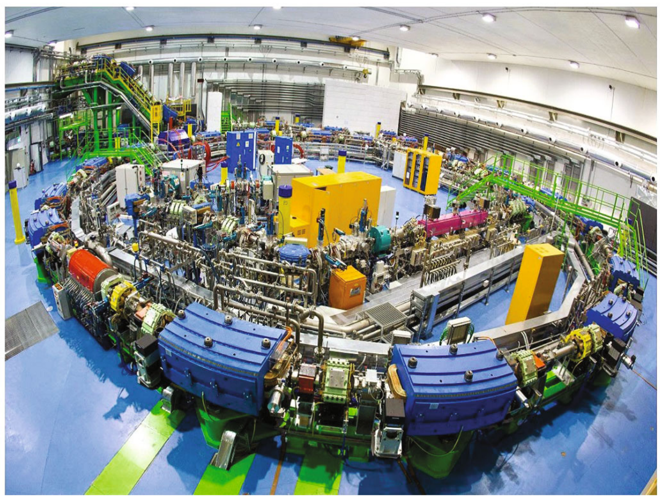

Fig. 4. View of the synchrotron with corresponding extraction beam lines.

In 2017, hadron therapy was included in the Essential Levels of Care (LEA), even though without the approval of a national fee, which, in fact, still affects the authorization procedures for patients coming from outside the Lombardy region. As a result of these events, the number of patients treated per year, which was growing, began to level off in the last two years. In this aspect, the difficulty of creating a network that efficiently gathers elective hadron therapy patients has a negative impact; furthermore, as indicated above, those patients are mostly affected by relatively rare pathologies. The image in Fig. 2 also shows the incidence of different pathologies, which are, in most cases, radio-resistant tumors for which carbon ions are used.

III. CNAO: THE TECHNOLOGY OF FUNDAMENTAL PHYSICS SERVING PATIENTS

The heart of the CNAO consists of a synchrotron for the production and acceleration of proton and carbon ion beams (Figs. 3 and 4). The design of the machine stems from a collaboration among the CNAO Foundation, INFN and CERN in Geneva while several Institutes have contributed to the realization phase: in particular, the TERA Foundation, to which the original idea and final design is due, the Universities of Milan and of Pavia, the Polytechnic of Milan and others [4,5]. The accelerator layout is rather compact: the ion sources and the linear accelerator (linac) are located inside the ring that constitutes the synchrotron. The extracted beams are then sent along four beam lines, three horizontal and one vertical, which serve three treatment rooms.

The electric charge of the hadrons allows physicists to use magnetic fields to bend their trajectorier. In this way, the beams can be addressed to designated points in the transverse directions with respect to the direction of motion of the particles: up or down, to the right or to the left, depending on orientation, polarity and intensity of the employed magnetic fields. By appropriately combining the energy of the particles (the regulator of the depth reached by the Bragg peak) and the intensity of the magnetic field (responsible for the transversal deflection with respect to the direction of propagation), we can precisely and selectively hit a small volume of tissue. A volume of about the size of a cubic centimeter, placed anywhere within a volume 20 centimeters high, 20 centimeters wide and 30 centimeters deep, around the initial direction of the particle beam should be considered. The damage distribution system described above is the one used in all new-generation hadron therapy centers and allows hadron ballistic precision to be optimally used.

About 600 companies participated in the construction of the synchrotron. The project group of the CNAO Foundation was in charge of the coordination: they drew up the specifications, followed the implementation and took charge of the integration and commissioning of the numerous systems. The real challenge in the realization of the synchrotron was the need to make the various systems work in an integrated manner, whether they were industrial products or medical devices, or unique and prototype devices. The process must guarantee the safety of patients and operators, the efficiency and maximum availability of the beams to treatments, the reliability so that the planned activities are carried out with the necessary punctuality, and a simplified maintainability suitable for a hospital environment. The performance of the CNAO medical device, collected from 2011 (the year of the first treated patient), to the end of 2018, certifies a system efficiency higher than 92% and an overall reliability higher than 97%; such performances allowed the achievement of the CE marking and the fulfilment of the highest operating standards.

IV. SUCCESSFUL WORLDWIDE RESEARCH

The CNAO is also a research center. The characteristics of the particle beams and the potential of the accelerator complex make the CNAO a suitable tool for research activities in various sectors, from clinics to radiobiology, from the development of detectors to dosimetry and the study of materials. Over the course of 2018, more than 200 hours of beam time were devoted to the activities of external research groups, both national and foreign groups. In collaboration with the Italian National Institute of Nuclear Physics, the construction of a new experimental line that would brings a research beam line to a dedicated room was completed. In the first six months of 2019, the beams were certified and the operation of the experimental room was definitively set up.

V. CNAO EXPANSION PROJECT

Italian law 145, dated December30, 2018, provided the CNAO with new financial resources to "allow the continuation of research activities, assistance and treatment of cancer patients, through the provision of an innovative life-saving therapy called hadron therapy". The first objective of the investment plan concerns the addition of a proton therapy room equipped with an accelerator and a rotating beam line (gantry). Recent technological evolution has made available interesting, compact and economically competitive solutions in terms of rotating proton beams. The rotating gantries allow the beam to be moved around the patient, and not vice versa, on the one hand reducing the positioning time and on the other widening the therapeutic solutions. (For example, a gantry that is going to be implemented in the CNAO will be dedicated to paediatric treatments for the irradiation of moving organs and for extended pathologies that require a wide treatment field.) With this implementation, the CNAO will provide a complete therapeutic service.

Secondly, the investment plan foresees the addition of a third ion source, which will allow both the actual current intensity to be increased so as to reduce treatment time, and other ion species to be made available. The new source will initially be used in the experimental room for research activities. One of the objectives will be to validate hadrons different from protons and carbon ions in clinical practice and to have increasingly precise ions suitable for personalized treatment. Finally, the investment plan will be completed with the preparation of areas and tools at the service of research activities. The laboratory foresees new premises for a total area of about 250 square meters and the availability of various types of equipment for users (including laminar flow cabinets, incubators, microscopes, centrifuges, work benches, *etc.*).

Finally, two medium, and long-term research and development projects, which will represent an effective and excellent way of implementing and maintaining CNAOs role in cancer treatments, should be mentioned the first project concerns BNCT (boron neutron capture therapy) [6,7]. This is a clinical research project that aims to extend innovative radiotherapy techniques to tumors that today cannot be treated, such as infiltrating diseases or metastases. A collaboration with INFN, the US Company TLS and the Chinese Company Neuboron is already active in this domain. The University of Pavia itself has shown interesting and intends to participate in, this initiative. The introduction of BNCT requires a properly structured multidisciplinary research phase with distributed skills (medical doctors, radiobiologists, medical physicists ...), necessarily involving qualified Institutes. The second deals with the future realization and installation of a carbon-ion rotating gantry. At present the technology does not seem to be mature enough to proceed with the choice of a solution, but would be worth while investing in the exploration for an innovative, cheap and small-sized technical solutions. In this respect, activating synergies with organizations such as INFN and CERN and involving industries interested in developing a new gantry for carbon ions are important.

VI. CONCLUSIONS

The CNAO represents a center of excellence as a result of the initiative and the support of the Italian Ministry of Health and the Lombardy Region. It is a state-of-the-art facility at the service of clinical research for the benefit of patients suffering from difficult pathologies and without any valid alternatives to treatment. In addition to the clinical activity, which has already led to the treatment of more than 2800 patients, the contributions given by hadron beams to research activities in various sectors, often aimed at translating research into clinical settings, are fundamental. The CNAO also manages research and development projects that will assure the excellence of the center even in the coming years and will greatly expand its ability to respond to difficult and aggressive diseases.

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