Proceedings Article

History of hadrontherapy in the world and Italian developments

U. AMALDI

University of Milano Bicocca and TERA Foundation

SUMMARY: *The first part of the paper is devoted to a historical review of the developments of the teletherapy techniques which make use of hadron beams and are collectively called "hadrontherapy". Leaving aside pions and antiprotons, the hadrons considered are neutrons, protons and light ions. The story recounted here has its origins in Berkeley in the thirties, around the first cyclotrons built by Ernest Lawrence and collaborators, and stops at the beginning of the nineties. In fact these are the years when protontherapy started to be recognized as a valid therapeutic tool for some tumours, especially because of the results obtained with the Harvard 160 MeV proton cyclotron. The Italian developments in the field of hadrontherapy are described in the second part, which begins in 1991, more or less where the first part stops. Two connected subjects are treated. Firstly, we discuss the conception, the production of many projects made by the TERA Foundation and the long approval process which brought to the "Centro Nazionale di Adroterapia Oncologica", now being built in Pave by the CNAO Foundation in collaboration with the Italian Institute of Nuclear Physics (INFN). Secondly, attention is paid to the project CATANA for the treatment of eye melanomas and malformations, which is the first Italian hadrontherapy centre and has been running since 2002 in Laboratori Nazionali del Sud (LNS) of INFN.*

KEY WORDS: *Hadrontherapy, Particle therapy, Protontherapy.*

Storia dell'adroterapia nel mondo e sviluppi italiani

RIASSUNTO: *La prima parte di questo lavoro descrive gli sviluppi delle tecniche di teleterapia dei tumori che fanno uso di fasci di adroni e ricadono sotto il nome collettivo di "adroterapia". Lasciando da parte pioni e antiprotoni, si ripercorre la storia delle applicazioni dei fasci di neutroni, protoni e ioni leggeri. La storia qui raccontata inizia negli anni trenta a Berkeley, intorno ai primi ciclotroni costruiti da Ernest Lawrence e collaboratori, e finisce all'inizio degli anni novanta. Infatti fu in quegli anni che la protonterapia cominciò a essere riconosciuta come una valida metodologia terapeutica di alcuni tumori, essenzialmente per merito dei risultati ottenuti a Harvard con il ciclotrone da 160 MeV. Gli sviluppi italiani sono descritti nella seconda parte, che inizia nel 1991, più o meno dove finisce la prima. Sono trattati due argomenti tra loro connessi. Innanzitutto si descrive la concezione, i molti progetti completati dalla Fondazione TERA e il lungo processo di approvazione del "Centro Nazionale di Adroterapia Oncologica", che è attualmente in costruzione a Pavia da parte della Fondazione CNAO in collaborazione con l'INFN. È poi discusso il progetto CATANA, il primo centro italiano di adroterapia, che e dedicato al trattamento dei tumori e delle malformazioni dell'occhio ed è in funzione dal 2002 presso i Laboratori Nazionali del Sud dell'INFN a Catania.*

PAROLE CHIAVE: *Adroterapia, Terapia con particelle, Protonterapia.*

Correspondence: Prof. Ugo Amaldi, TERA Group, CERN, 1211 Genova 23, tel. +41-227677565, fax +41-227679740, e-mail: ugo.amaldi@cern.ch, www.tera.it
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□ INTRODUCTION

'Hadrontherapy' ('hadronthérapie' in French, 'hadronentherapie' in German, 'adroterapia' in Italian) is a collective word covering all forms of radiation therapy which use beams of particles made of quarks: neutrons, protons, pions, antiprotons, helium ions (i.e. alfas), lithium ions, boron ions, carbon ions, oxygen ions etc. 'Hadron therapy','particle therapy', 'heavy ion therapy' and 'light ion therapy' are other terms, which I like less but are often used. In particular in English I prefer the single word 'hadrontherapy' to the more natural 'hadron therapy', because radiotherapy was written as two separate words as well till it became a very important modality in cancer teletherapy.
Due to their higher penetration depth, low energy neutrons were the first hadrons used in radiotherapy. Neutrons act via their scattering and recoil-ions - these are in biological tissues mostly low energy protons - and produce a greater Relative Biological Effectiveness (RBE) than high energy photons. In the clinical trials neutrons produced a greater tumour control rate especially of radio-resistant tumours. But because of the poor depth-dose distribution, the biologically high-effective dose was also large in the normal tissue outside the target volume, causing severe side effects. Therefore in the last years and in most countries neutron therapies have been terminated.
The next big hopes were negative-pion beams producing an additional boost of dose at the end of the pion range. Here the negative pions are captured by the target nuclei and release additional energy. Although the dose improvement at the end of the range could be confirmed by physics measurements, the clinical trials could not find an improved cure rate and the pion trials were terminated worldwide after the treatment of some 800 patients[10]. Today the proposed use of antiprotons[19] represents in many aspects a revival of the basic ideas of pion treatment, but, considering also cost and complication, its advantages with respect to the multiply charged ions discussed in this report are by far not obvious. For these reasons pions and antiprotons are not further discussed in this paper devoted to a review of the historical developments of the other types of hadrontherapy. The last sections are devoted to the birth and development of hadrontherapy in Italy.

□ CONVENTIONAL TELETHERAPY

The roots of teletherapy and brachytherapy date back to the discoveries of X-rays and radium made by Roengten and the Curies in the years 1885-1887. As far as X-ray teletherapy is concerned, around 1950 'megavoltage' tubes were built and 'cobalt bombs' entered clinical practice. The surprise was that, due to the longer electron ranges, these 'high-energy' radiations spared the skin much better than 'orthovoltage' X rays.
After a short season when X rays of energy larger than 5 MeV were produced with medical 'betatrons', electron linacs, running at the present standard 3 GHz frequency, became the instrument of choice. (Note that radiation oncologists call 'X rays' what physicists call 'gammas' or 'high energy photons'.) The first electron linac was built in the 50s at Stanford by Bill Hansen and collaborators for research purposes[23] and was powered by a klystron produced by Varian. Soon thereafter, this new tool superseded all other electron/photon sources and still now Varian is the market leader in the field of conventional teletherapy.
Today about 10,000 linacs are installed in hospitals all over the world and in the West there is one linac every 200,000-250,000 inhabitants. About 50% of all the tumour patients are irradiated, so that radiotherapy is used every year to treat about 20,000 patients on a western population of 10 million inhabitants. This enormous development has been possible because of the advancements made in computer-assisted treatment systems and in imaging technologies, such as CT imaging, MRIs, and PET scans. The progress has been generalized and steady. The most modern irradiation techniques are Intensity Modulated Radiation Therapy (IMRT), which uses 6-9 noncoplanar and non-uniform X-ray fields, and Image Guided Radiation Therapy (IGRT), a technique capable of following tumour target which moves, mainly because of patient respiration. More recently, helical tomotherapy has become a powerful new tool in the hand of radiation oncologists.

□ LAWRENCE CYCLOTRONS AND THERAPY WITH FAST NEUTRONS

Hadrontherapy initiated in 1930 with the invention of the cyclotron by Ernest Lawrence. In 1935 he asked his brother John (Figure 1), who was a medical doctor at Yale, to join him in Berkeley and use the new powerful accelerator for medical purposes[14]. The two applications were the production of radioisotopes and, later, the therapeutical use of fast neutron beams.

At the end of 1932 Lawrence, Stan Livingston and David Sloan managed to produce 4.8 MeV protons with the new 27-inch cyclotron. However the planning of physics experiments had not paralleled the construction of the instruments to perform them and in the following two years important discoveries were missed because the Laboratory lacked the proper detectors. Eventually in 1934, after the discoveries of alfa-induced and neutron-induced radio-activities by the Joliots in Paris and the Fermi group in Rome, Lawrence focused the cyclotron on the investigation and production of artificial isotopes by neutron, proton, deuteron, and alpha-particle beams. One of the reasons for this development is that Georg von Hevesy had shown that radioactive tracers in the body could give unique information about metabolism and other physiological processes[28]. The program was carried out with funds supplied by the Rockefeller Foundation and the Macy Foundation and brought to the introduction in the medical practice of sodium-24, phosphorus-32, cobalt-60, technetium-99 and iodine-131. In 1940 Martin Kamen and Samuel Ruben discovered carbon-14.

As far as therapy is concerned, let us recall that neutrons were discovered by Sir James Chadwick in 1932. Shortly thereafter Ernest and John Lawrence were experimenting with the effects of fast neutrons on biological systems. Following a paper by Gordon Locher[20], who in 1936 underlined the therapeutic potentialities of both fast and slow neutrons, at the end of September 1938, the first patients were treated with neutrons on the 37 inch cyclotron. The neutrons were produced in the reaction of 8 MeV deuterons on a beryllium target. This first study on 24 patients, which used single fractions, was considered a success and led to the construction of the dedicated 60-inch Crocker Medical Cyclotron. Here Robert Stone (Figure 2) and his collaborators treated patients with fractionated doses using neutrons produced by 16 MeV deuterons on beryllium till 1943, when the cyclotron was expropriated for the atomic bomb programme. The technique was primitive and the doses given to healthy tissues too high, so that in 1948 Stone evaluated the effects on 226 patients and concluded: "Neutron therapy as administered by us has resulted in such bad late sequels in proportion to the few good results that it should not be continued."[25].

Neutrontherapy was revived by 1965 by Mary Catterall at Hammersmith Hospital in London when it was understood that the radio biological effectiveness varies when fractionated treatments are given[13].

Figure 1. Ernest Lawrence at the control of the 27-inch cyclotron together with his brother John.

Good results were obtained for superficial adenocarcinomas, so that by 1969 it became clear that, for certain tumours local control could be achieved using neutron irradiation.

From 1968 until 1978, radiation oncologists from the Chicago area worked with Robert Rathbun (Bob) Wilson, Fermilab Director, to build the 'Neutron Therapy Facility' at Fermilab. One significant finding which came out of the trials was that only neutron beams produced by protons with energies greater than about 60 MeV could produce tumour control

Figure 2. John Lawrence watches by Robert Stone while aligning a patient in the neutron beam produced by the 60-inch cyclotron.

Figure 3. The neutron therapy gantry of the National Acceleration Center (Faure, South Africa) uses the p+Be reaction with 66 MeV protons.

with no worse side effects than low Linear Energy Transfer (LET) radiation for deep-seated tumours[22]. For this reason, facilities which had performed clinical trials using relatively low energy beams either stopped treating patients or upgraded their system. To produce neutrons the p+Be reaction is preferred since the same machine can accelerate protons to twice the energy of deuterons and thus provide more penetrating beams. Although some fixed beam arrangements are still used, isocentric facilities (as the one shown in Figure 3) are desirable.

As mentioned above, high-LET radiations are most effective for treating large, slow growing or radiation resistant tumours such as those of the salivary gland, paranasal sinus, head and neck, prostate, bone and breast, soft tissue sarcoma, uterine sarcoma and melanoma. A handful of facilities are still treating patients, so that more than 20,000 patients have been treated with neutrons.

Figure 4. Hymer Friendell (*left*), Bob Wilson (*centre*) and Percy Bridgeman (*right*).

☐ THE BEGINNINGS OF THERAPY WITH CHARGED HADRONS

In 1945 Robert Rathbun ‘Bob’ Wilson - who was a Lawrence student and much later became the Fermilab founder and director - was hired as an associate professor at Harvard and designed a new 160 MeV cyclotron which, after many years of exploitation for nuclear physics experiments, was first used in 1961 to irradiate patients. But already in 1946 Wilson, shown in Figure 4, had proposed the use of proton beams in radiation oncology[30]. In fact he had measured at the Berkeley cyclotron depth profiles with a significant increase in dose at the end of particle range, the so called Bragg peak, which had been observed fifty years before in the tracks of alpha particles by W. Bragg. Due to the Bragg peak - which 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.

It is interesting to remark that in his paper Wilson mainly discusses protons but mentions also alfa particles and carbon ions. He wrote “The intense specific ionization of alpha particles [...] will probably make them the most desirable therapeutically when such large alpha particle energies are attained. For a given range, the straggling and the angular spread of alpha particles will be one-half as much as for protons. Heavier nuclei, such as very energetic carbon atoms, may eventually become therapeutically practical.”

Two years later, researchers at the Lawrence Berkeley Laboratory (LBL) conducted extensive studies on protons and confirmed the predictions made by Wilson. In 1954, the first patient was treated at Berkeley with protons, followed by helium treatment 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 characteristics, the electric charge, which makes their beams easy to detect and, even more important, to control by means of magnetic fields. This was also due to the fact that, at these early times, the computer

power available was too poor for a control system of the active beam scanning techniques of today.
The first treatments on humans consisted of irradiation to destroy the pituitary gland in patients with a metastatic breast cancer that was hormone sensitive. This treatment stopped the pituitary from making hormones that stimulated the cancer cells to grow. The pituitary was a natural site for the first treatments because the glands location was easily identified on standard X-ray films, well localized, and surrounded by sensitive normal structures. Between 1954 and 1974 at Berkeley, under the leadership of Cornelius Tobias (Figure 5), about 1,000 pituitary glands and pituitary tumours were treated with protons.
In 1957 the first tumour was irradiated with protons at the Uppsala cyclotron by Börje Larsson (Figure 6), who obtained his PhD in 1962 by discussing the subject: “Application of a 185 MeV Proton Beam to Experimental Cancer Therapy and Neurosurgery: a Biophysical Study”.
At this point it is worth recalling that the energies for reaching deep-seated tumours (more than 25 cm of water equivalent) are of the order of 200 MeV for protons and 4800 MeV for carbon ions, so that on average in every cell a carbon ion leaves 24 times more energy than a proton having the same range. These energetic protons can be obtained either with cyclotrons (normal or superconducting) or with synchrotrons having a diameter of about 7 metres. To date, only synchrotrons are used to produce carbon ions of about 400 MeV per nucleon (400 MeV/u). In fact their magnetic rigidity of about 6 Tm is about three times larger than the one of 200 MeV protons, so that about 20 metre diameter synchrotrons are needed when fields in the range 1.5-2 tesla are used.

□ THE HARVARD CYCLOTRON

The facility that made the largest impact on the development of protontherapy is the Harvard cyclotron. Its story is long and very interesting[a].
Harvard built the first such machine in 1937, but the federal government drafted it during World War II. It was taken apart and shipped to Los Alamos in 1943, for service in designing the first atomic bombs. The move had to be made in secrecy, so Hymer Friendell

Figure 5. Cornelius Tobias (1918-2000)[26].

Figure 6. Börje Larsson (1931-1998).

(Figure 4) - a radiation therapist - arrived at Harvard to request its movement for what he said were medical purposes. Percy Bridgeman, who won a Nobel Prize in Physics in 1946, told the government agents they could not have the machine if they were going to use it for medical purposes. But, he added, “if you are going to use it for what I think you’re going to use it for, you are welcome to it”. As mentioned above, while designing the machine that should substitute the removed one, Bob Wilson thought of using it for medical purposes.
The new cyclotron was ready in 1949, as shown in Figure 7.
However the staff of the Harvard Cyclotron Facility

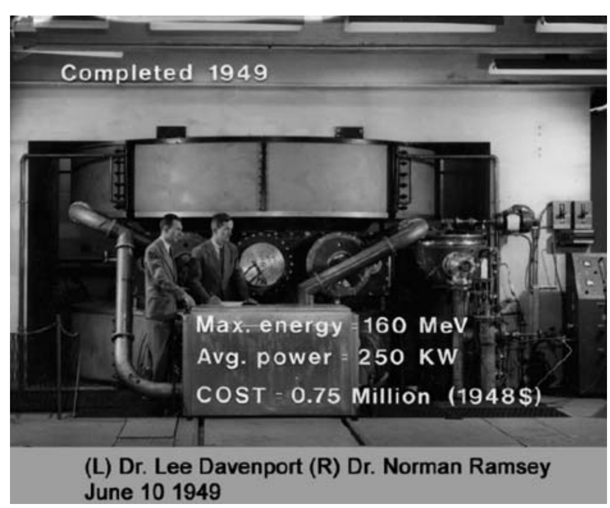

Figure 7. A famous picture of the just completed Harvard cyclotron. In 1989 Norman Ramsey was awarded the Nobel Prize together with Hans Dehmelt and Wolfgang Paul.

[a] In writing this section I have used some excerpts from the book of Richard: “A brief history of the Harvard University Cyclotron”, Harvard University Press, 2003[29].

Figure 8. Raymond (Ray) Kjellberg fastens his stereotactic device to a patient.

became interested in using protons for medical treatments only after protontherapy was started in the 1950s at both LBL and Uppsala.

In 1961, Raymond Kjellberg (Figure 8), a young neurosurgeon at Massachusetts General Hospital in Boston, became the first to use the Harvard beam to treat a malignant brain tumor.

The cyclotron facility reached its low point in 1967-68 so that Andreas Koehler (Figure 9), a first class experimental physicist, was for a period the only employee, at part-time even if he worked more than full time.

In spite of the fact that the cyclotron had to be closed, by the mid-1970s Koehler, Bernard Gottschalk and their colleagues - working with radiation oncologists and medical physicists of other institutions - had developed methods to treat larger brain tumors and various eye tumors. These included choroidal melanomas that, before proton therapy, had been treated by removing the eye. These medical successes impressed the National Institutes of Health enough to provide funds that rescued the machine.

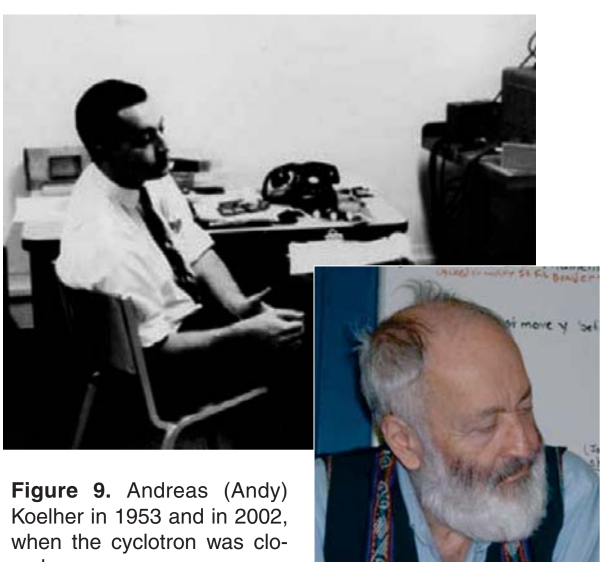

Figure 9. Andreas (Andy) Koelher in 1953 and in 2002, when the cyclotron was closed.

The early work was limited due to the inability to perform 3-D imaging and reliance on facilities primarily dedicated to physics research. With the development of the CT scanner, improved target definition allowed for the treatment of almost any site in the body. (It is interesting to note that Allan Cormack, who shared the Nobel Prize for the CT development, did his PhD work at the Harvard cyclotron.) The subsequent development of MRI, SPECT, and PET scanning has further improved target definition and allows even further benefits from protontherapy.

Overall three groups of radiation oncologists worked for many decades with Harvard physicists on three clinical studies: neurosurgery for intercranial lesions (3,687 patients), eye tumours (2,979 patients) and head-neck tumours (2,449 patients). The main people who did work on eye tumours and malformations were Ian Constable and Evangelos Gragoudas of the Massachusetts Eye and Ear Hospital. The successes on large brain tumours are due to Herman Suit (Figure 10), Michael Goitein and colleagues of the Radiation Medicine Department of Massachusetts General Hospital. Among the many contributions of Goitein to this new field in medical physics, the development of the first accurate treatment planning systems has to be underlined[15,16].

The results obtained (particularly for eye melanoma and for chordomas and chondosarcomas of the base of the skull) convinced many radiation oncologists of the superiority of protons with respect to X rays for tumours that are close to organs at risk. By 2002, when the cyclotron was definitely stopped, more than 9,000 patients had been irradiated and the bases were laid down for the following rapid development of the field. In particular, the competences 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.

☐ FROM HARVARD TO LOMA LINDA

Soon after the start-up of the Harvard facility other nuclear physics laboratories in USSR and Japan set up horizontal proton beams for therapy. As shown in

Table 1, in 1984 the Paul Scherrer Institute (Switzerland) did the same.
All the facilities listed in Table 1 were located in physics laboratories and the irradiation conditions were far from ideal. In many places and many times it was felt and said that the hadrontherapy field could not develop without dedicated facilities. However, this step took almost twenty years.
Not by chance the first hospital-based centre was built at the Loma Linda University Center (California), because of the determination of James Slater (Figure 11) who initiated the collaboration with Fermilab. This is the largest American particle physics laboratory which, as already said, was founded and directed for many years by Bob Wilson. With the help of congressman Jerry Lewis, Loma Linda University obtained federal support for its $80 million proton therapy facility. In 1986, Loma Linda University and Fermilab signed an agreement, and Fermilab took on the task of building the $25 million proton accelerator for the facility. Fermilab could build from experience in operating its own Neutron Therapy Facility. The first patient was treated in Loma Linda in 1990 and, in the same year, Medicare approved the coverage of this new modality for treating cancer.
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 constructed 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 Proton Medical Research Center (PMRC), was constructed adjacent to the University Hospital. PMRC is equipped with a synchrotron and two rotating gantries. Clinical treatment was started in September 2001 at this new facility and by March 2007, 1,046 patients were treated. The tumour types of the total 1,746 patients treated so far is shown in Figure 12.
To conclude this section it is worth recalling that in USA protontherapy was further expanded during the 1990s with the Proton Radiation Oncology Group (PROG) which sponsors the development of clinical trials involving proton therapy. In the world, the Proton Therapy Cooperative Group (PTCOG) was also created during the 1980s for scientists to exchange ideas on the development of hadrontherapy.
Over 50,000 patients have by now been treated with proton beams worldwide and numerous facilities are currently under construction or in the planning

Figure 10. Herman Suit (*right*) and J.E. Munzenreider visiting the cyclotron when it was closed in 2002.

Figure 11. James Slater (*left*) at the inauguration of the Loma Linda Centre.

Facility	Country	Year
Lawrence Berkeley Laboratory	USA	1954
Uppsala	Sweden	1957
Harvard Cyclotron Laboratory	USA	1961
Dubna	Russia	1964
Moscow	Russia	1969
St. Petersburg	Russia	1975
Chiba	Japan	1979
Tsukuba	Japan	1983
Paul Scherrer Institute	Switzerland	1984

Table 1. The pioneers of protontherapy.

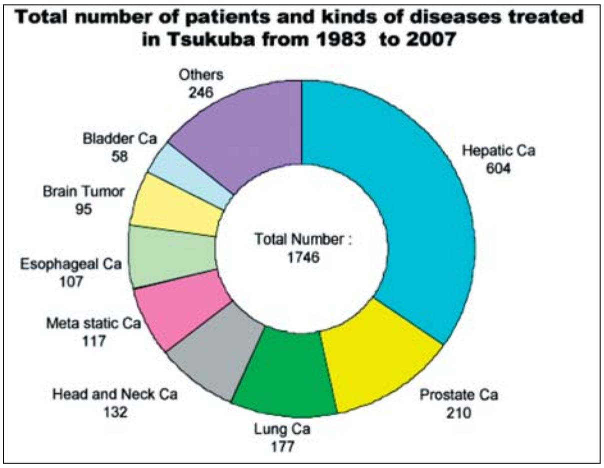

Figure12. Total number of patients and type of disease treated in Tsukuba from 1983 to 2007.

stages. Five companies offer turn-key facilities and it makes no doubt that protontherapy is booming.

□ THE BEGINNINGS OF LIGHT ION THERAPY

Ions heavier than protons, such as helium and later on argon, first came into use at Berkeley in 1957 and 1975, respectively. At the old 184-inch cyclotron 2,800 patients received treatments to the pituitary gland with helium beams, the lateral spread and range straggling being much smaller than in the proton case. The basis of these treatments was the already mentioned concept of a reduction of other tumours when the pituitary gland would be inactivated. In these treatments a general RBE of 1.6 was used as multiplication factor of the absorbed dose. Concerning the primary goals, the inactivation of the pituitary, the precision of the helium therapy and the RBE were correct and this type of therapy can be regarded as a first step towards light ion radiosurgery. About twenty years later argon beams were tried at the Bevalac (Figure 13) in order to increase the effectiveness against hypoxic and otherwise radioresistant tumours, i.e. tumours that need deposited doses 2-3 times higher if they are to be controlled with either photons or protons. But problems arose owing to non-tolerable side effects in the normal tissues. After a few irradiations of some 20 patients, Cornelius Tobias and collaborators used lighter ions, first silicon ions for two patients and then neon, for 433 patients until the Bevalac stopped operation in 1993. Only towards the end of the program was found that the neon charge (Z = 10) is too large and undesirable effects were produced in the traversed and downstream healthy tissues[12].

The larger effects that ions have with respect to the ones produced by cobalt-60 gammas is quantified by the already mentioned 'RBE'. RBE depends upon the cell type, the radiation used and the chosen end-point. For a given cell type and end-point, RBE varies with the energy loss (or LET) of the ionizing particles. The experimental results are such that only at the beginning of the 90s carbon ions (Z = 6) were chosen as the optimal ion type. In fact in the entrance channel the LET is smaller than 10 keV/μm and the effects are similar to the ones of X rays and protons, while in the last centimeters in matter the LET is definitely larger than 20 keV/μm and multiple close-by double strand breaks are produced, together with clustered damages, which are not repaired by the cell. Thus light ions produce a radiation field which is qualitatively different from the ones due to either photons or protons and

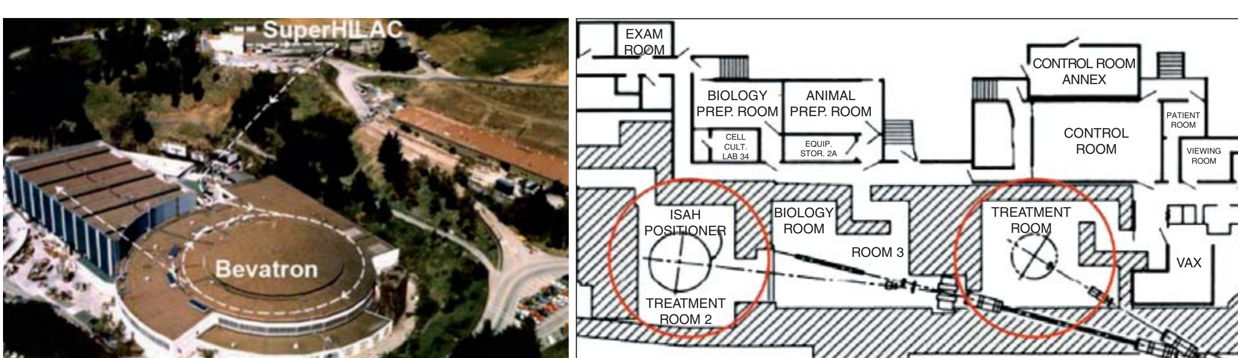

Figure 13. The Bevalac was a complex formed of a linear accelerator (SuperHILAC) and a synchrotron (Bevatron) connected by a long beam transport line. The treatment rooms were in the building at the left of the picture.

also succeed in controlling radioresistant tumours.

The carbon choice was made in Japan by Yasuo Hirao (Figure 14) and collaborators, who proposed and built HIMAC in the Chiba Prefecture (Heavy Ion Medical Accelerator in Chiba)[18].

In 1994 the facility treated the first patient with a carbon ion beam of energy smaller than 400 MeV/u, corresponding to a maximum range of 27 cm in water. By the end of 2007, under the leadership of Hirohito Tsujii (Figure 15), 4,000 patients have been treated and it has been shown that many difficult and common tumours (e.g. lung and liver) can be controlled. The most recent results and the techniques used are described in a supplement of Journal of Radiation Research[27].

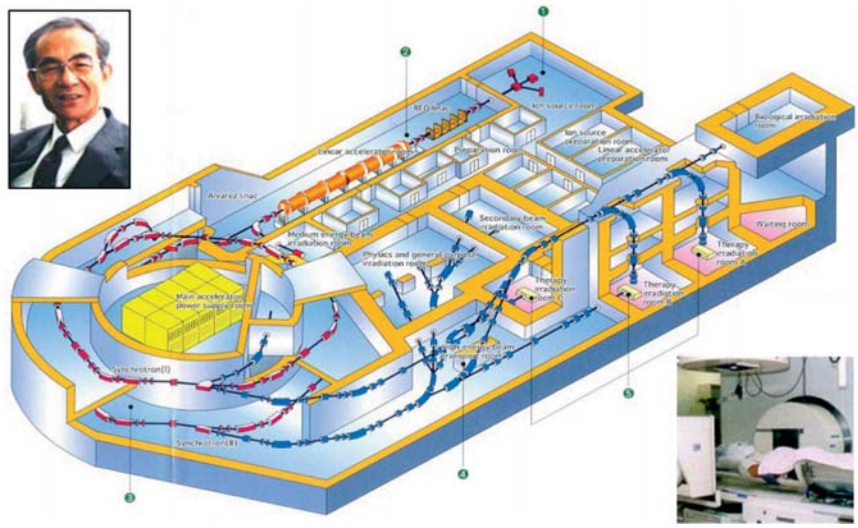

Figure 14. HIMAC features two large synchrotrons, injected by a Alvarez linac, and three treatment rooms for a total of two horizontal and two vertical beams.

The distribution of the range used at Chiba is shown in Figure 16.

In 1987 in Europe an important initiative was launched to create a full-fledged European light ion therapy centre. The needed hadron beams were defined in a series of expert meetings. EULIMA, the European Light Ion Medical Accelerator project, financed by the European Commission, was led by Pierre Mandrillon and involved many European laboratories and centres. Initially the project, by making use of the Berkeley experience, foresaw the use of oxygen ions, but during the study a worldwide consensus was reached that a better choice is carbon. 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. A paper describes the two 400 MeV/u accelerators, a superconducting cyclotron and a synchrotron, which have been studied together with the active dose spreading system and a rotating gantry[21]. In this report the advantages and disadvantages of the superconducting

Figure 15. Hirohiko Tsujii.

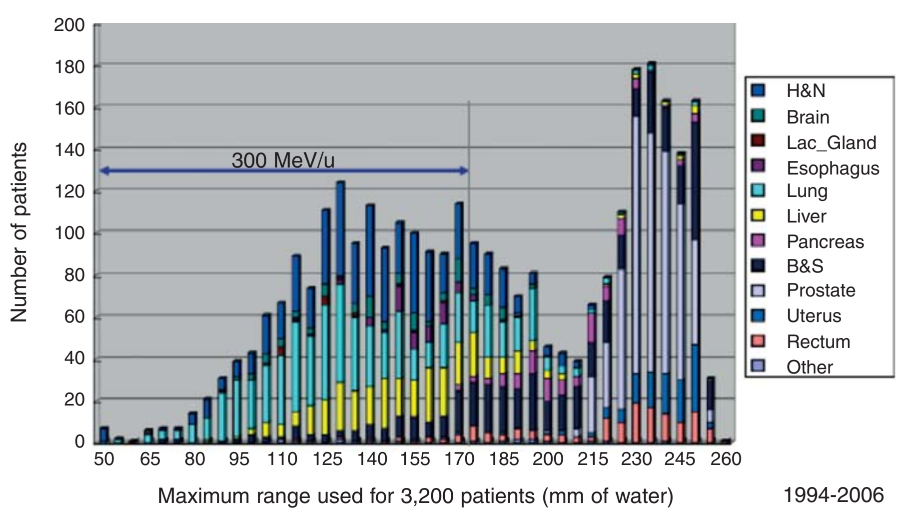

Figure 16. The distribution of the maximum range used at HIMAC (Chiba, Japan) for the 3,200 patients treated between 1994 and 2006 is characterized by two peaks. The arrow indicates the patients that could be treated with the superconducting 300 MeV/u cyclotron designed by Calabretta et al.[11] and proposed for the Cannizzaro Hospital in Catania (*Courtesy of H. Tsujii*).

cyclotron and synchrotron solution are listed and compared. 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 a 1% momentum spread. However, the superconducting design is novel, the magnet is weighty and 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. Overall, based on these arguments, the EULIMA project management board has recommended the synchrotron option as the accelerator for EULIMA".

Unfortunately such a European therapy synchrotron was never built and national projects in Germany and Italy had to be pushed through before Europe radiation oncologists could have available facilities similar to the Heavy Ion Medical Accelerator at Chiba and the Hyogo Ion Beam Medical Center.

Looking back to the development of both proton and light ion therapy, one can say that in the years 1992-1994 the pace changed. Before this time the facilities were physics-centered, not many patients could be treated and this only with horizontal beams. Instead, in the years 1994-2004 ten commercial turn-key proton centres were ordered and three new hospital-based 'dual' facilities - for carbon ions and protons - have either started treating patients (Hyogo Ion Beam Medical Center) or entered the construction phase (Heidelberg Ionenstrahl Therapy: HIT and Centro Nazionale di Adroterapia: CNAO in Pave).

The pace changed also because, and this has to be underscored, most of the needed technologies and procedures were already established or, at least, understood. The main events marking these years of change are worth listing:

- 1992 - Loma Linda and Tsukuba complete the commissioning of their proton beams;
- 1993 - The carbon 'pilot project' is launched by G. Kraft at GSI (Darmstadt);
- 1993 - MGH orders to IBA (Belgium) the first commercial proton facility;
- 1994 - The first patient is treated with carbon beam at HIMAC.

Thus the "First International Symposium on Hadrontherapy" organized in 1993 by Börje Larsson and myself in Como was very timely. Its proceedings[4] contain reports from all the main actors and - in spite of the 15 years that have elapsed - are still a book that in the field of hadrontherapy can be used as reference[17].

☐ THE START OF HADRONTHERAPY IN ITALY

From this point on the presentation becomes more detailed and more personal.

In 1991 I decided to leave basic research and pass to the medical application of radiations. At the time I had been senior scientist at CERN for twenty years and I was spokesman of the DELPHI collaboration, which had been active at the Large Electron Positron collider LEP since more than ten years. I knew the field of radiation physics because at the beginning of my activity I had been working for ten years at the Physics Laboratory of ISS, the Italian National Health Institute sited in Rome. I had also taught medical physics to postgraduate schools and written a treaty[3] used by almost every Italian senior radiation oncologist or medical physicist.

The idea was to launch a construction project in an academic environment. Thus in 1990 I applied for a full chair in medical physics. In 1991 I got an appointment in Florence; one year later I moved on a part-time basis to Milano University.

In May 1991 with Giampiero Tosi, well known medical physicist of the European Institute of Oncology (IEO), we wrote a report proposing to design, promote and realize a National Particle Therapy Centre, possibly featuring beams of light ions[7]. Shortly afterwards I introduced the word "adroterapia" (and its natural translation in the other languages) to indicate this kind of teleradiotherapy. (As a side remark, this term implies the expression "systemic hadrontherapy" for the endoradiotherapy which uses alfa decaying isotopose and is now called "alfa-immunotherapy").

In September 1991, we proposed to INFN (the Italian Institute of Nuclear Physics) the first Italian research and development (R&D) project in the field of hadrontherapy. A request for funds was submitted to the 5th National Scientific Committee of INFN (devoted to technological multidisciplinary research) which soon financed the "ATER experiment", a collaboration of the Milan Section of INFN and of CERN with the purpose of designing a centre based on a synchrotron optimized for medical treatment of cancer with light ion beams. For this project, about 80,000 Euro were allocated in 1992 and 100,000 Euro in 1993.

During the next five years (1994-1998) the ATER experiment - coordinated by me - became a large collaboration involving many groups located in nine INFN Sections (Genoa, Ferrara, Florence, Milan, Naples, Padua, Pave, Rome and Turin) and in the Legnaro

INFN National Laboratories. The groups of the "ATER Collaboration" worked mainly in radiobiology of hadron beams, detector developments and software applications for hadrontherapy. Only about 20% of the received grants was spent on the design of the first and the second light ion centres, which are discussed below.
The main funds for the design of the first two dual centres for carbon ions and protons, and the totality of the investments for the third and fourth design, were obtained from foundations and private citizens by the TERA Foundation (TErapia con Radiazioni Adroniche, Italian acronym that stands for "therapy with hadronic radiations"). We created this Foundation in 1992 with the purpose of forming and employing physicists and engineers fully devoted to the design and, later, the construction of hadrontherapy centres in Italy and in Europe so to bring therapeutical advantages to european cancer patients. TERA was created because, since the beginning of the ATER experiment in 1992, INFN made clear that no full time personnel paid by the institute could be seconded to this activity. In 1994 TERA was recognized by the Italian Ministry of Health. Today in the board, which I chair, sit two radiation oncologists (Roberto Orecchia, Vicepresident, and Jacques Bernier) one healthcare economist (Elio Borgonovi) and the Secretary General Gaudenzio Vanolo.

☐ THE PROTONTHERAPY PROJECT CATANA OF THE LABORATORI NAZIONALI DEL SUD

At the end of 1995, following the experiences made in the framework of TERA and ATER, scientists from the INFN Laboratory (Laboratori Nazionali del Sud: LNS) decided, under the leadership of Giacomo Cuttone, to create, in collaboration with Catania University, a protontherapy facility based on the super-conducting cyclotron already operating in the laboratories. The energy chosen was 62 MeV so to irradiate ocular and iris melanomas. The collaborating institutes were INFN-LNS, the Physics Department of the Catania University, the Sicilian Center for Nuclear Physics and the Ophthalmology Institute and the Radiology Institute of the Catania University. This collaboration, gave life to the CATANA project whose aim was the realisation of the first Italian proton therapy facility.
CATANA, that is the acronym of "Centro di AdroTerapia ed Applicazioni Avanzate", officially started

Figure 17. The CATANA set-up to treat eye tumours and malformations (www.lns.infn.it/CATANA).

in 1996. In 1999 funds were requested to the University and Research Ministry (MIUR). These funds allowed the CATANA Collaboration to start the first studies in the field of proton relative and absolute dosimetry and to design the proton transport beam line. Other MIUR grants were also attributed for the training of physicist and medical physicists.
The first Italian prototype of a patient-position chair was designed and developed (Figure 17). The chair, having six degrees of freedom, is fully computer-controlled and still today represents an advanced system for patient positioning.
In 2000 a dosimetric inter-comparison between LNS and two European protontherapy centers (Paul Scherrer Institute: PSI, Switzerland, and Clatterbridge Center for Oncology: CCO, UK) was successfully carried out. The inter-comparison demonstrated the capacity of the dosimetry system, developed at LNS, to measure the dose with an error smaller than the 3%.
As CATANA was representing the first Italian proton therapy centre, the double approval of the Health Ministry and the Ethic Panel was necessary. Once the approval was obtained, in March 2002 the first Italian patient, affected by ocular melanoma, was treated.
At present the LNS accelerator committee assigns to proton treatments five beam period per years. In normal conditions this allows to irradiate about 40 patients per year. Up to know, 160 patients have been treated. Most of them (85%) were affected by uveal melanoma but other pathologies were treated, like conjunctival melanoma (6%), non-Hodgkin lymphoma and metastases. The results are very promising: by following 103 patients an eye-retention rate of 93% and a disease specific survival of 97% have been recorded.

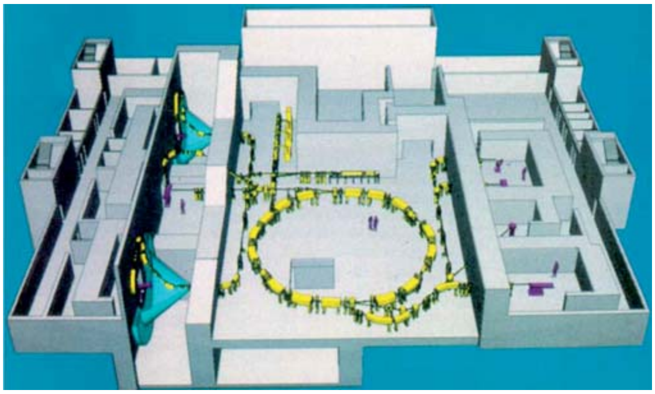

Figure 18. The CNAO project for the town of Novara was based on a synchrotron accelerating both carbon ions and protons, injected in the ring by two linacs.

□ STEPS TOWARDS THE CONSTRUCTION OF THE NATIONAL CENTRE FOR ONCOLOGICAL HADRONTHERAPY

For more than ten years, the main goal of TERA has been the creation of the Italian National Centre for Oncological Hadrontherapy based on an ion synchrotron optimised for medical purposes and capable of accelerating particles up to 400 MeV/u. In the years 1992-1999 TERA made two attempts to obtain from the Italian Health Ministry a partial financing to build CNAO firstly in Novara (the town where the Foundation has its legal seat) and later in Milan.

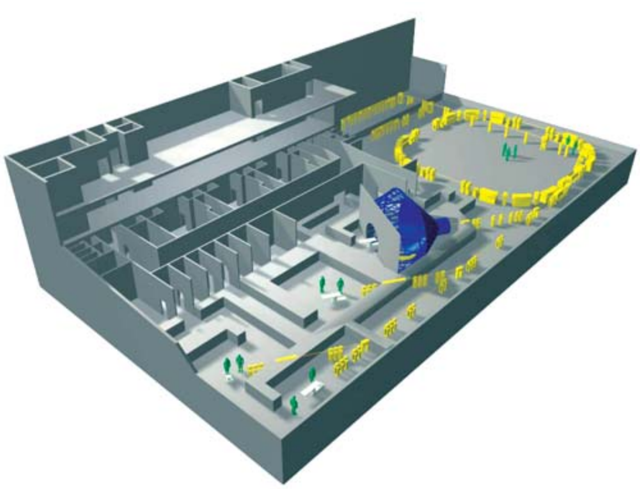

Figure 19. The project prepared in 1997 by TERA for Mirasole was based on a synchrotron similar to the Low Energy Accelerator Ring (LEAR) built at CERN and featured two linear injectors, one for protons and the other one for carbon ions.

For the Novara hospital (Ospedale Maggiore della Carità) TERA produced a design of the synchrotron and of the clinical beam lines. This project, described in the "Blue Book"(6), is shown in Figure 18.

Before financing its construction, the Health Ministry required the opinion of the Commissione Oncologica Nazionale (National Oncological Commission). At the end of 1995 the positive report of an ad-hoc Committee - chaired by the world wide known surgeon and oncologist Umberto Veronesi - was approved by this Commission. In spite of this, the project had to be abandoned for lack of further political support.

To get out of this difficult situation, in 1996 a Steering Committee was set up with five large hospitals of Milan and Pave for the construction of the National Centre CNAO in the vicinity of the Mirasole Abbey, which is located south of Milan not far from Pave. The medical partners of TERA were large hospitals of National relevance (Istituti di Ricovero e Cura a Carattere Scientifico: IRCCS): Ospedale Maggiore, the University Hospital of Milan, Policlinico San Matteo, the University Hospital of Pave, Istituto Nazionale dei Tumori (INT), the largest public oncological Italian Centre, seated in Milan, European Institute of Oncology (IEO), private oncological centre seated in Milan, and Istituto Neurologico C. Besta, the national neurological hospital, also seated in Milan.

For Mirasole TERA designed a new and more performing synchrotron, which is similar to the LEAR machine built at CERN. The full project, shown in Figure 19, is described in the "Red Book" published in 1997(5).

At the end of 1996 the six partners drafted the by-laws of the Mirasole Foundation, which had to have as founders the five hospitals and TERA. Funds were requested to the Health Ministry and to private foundations. Compagnia di San Paolo (Turin) granted 8 MEuro and Fondazione Cariplo (Milan) promised 16 MEuro, if the Health Ministry would have given the same sum. The Lombardy Region expressed its interest in contributing. In 1997 the Health Minister wrote to the Education and Research Minister to obtain 8 million Euro, but the needed discussion among the two Ministries was never initiated. The difficulties materialized in 1998 when the Health Minister froze the creation of the Mirasole Foundation.

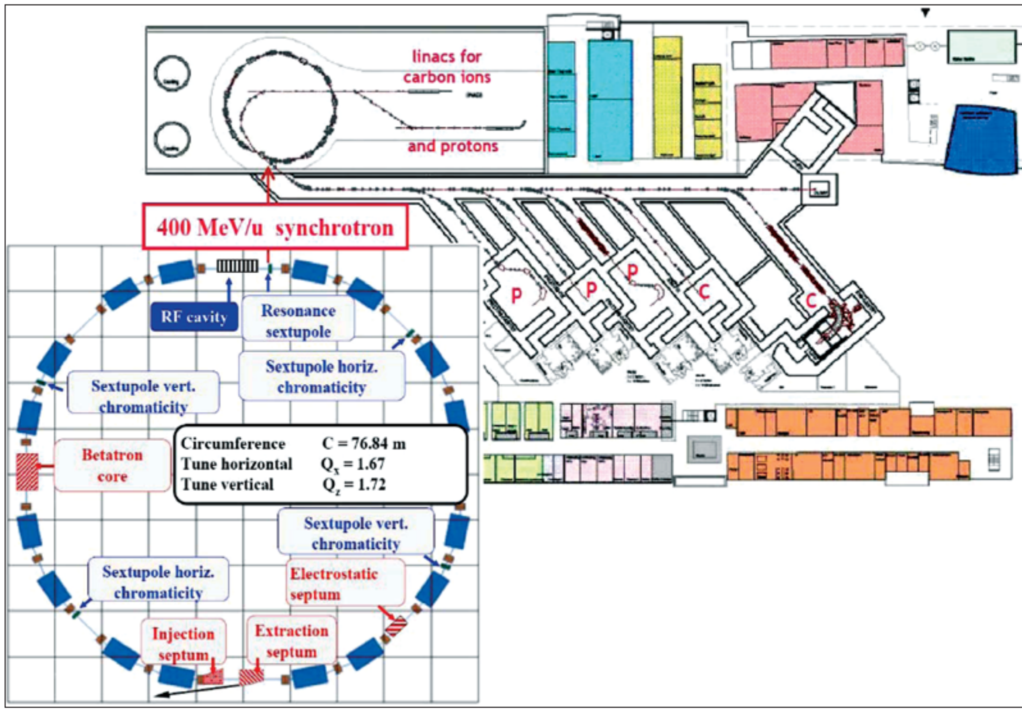

Figure 20. The PIMMS layout included two different proton gantries and a carbon ion gantry of the "mobile cabin" type.

The partial INFN financing of the two design projects of Figures 18 and 19 was terminated in 1998, while the ATER collaboration - under the leadership of Giancarlo Gialanella - continued to work on the other subjects listed above till the end of 2002. In the difficult years, which started in 1998 and ended in 2001, the design of the national centre and the 'political' action to get it approved were carried on by TERA alone.

□ PIMMS AND THE APPROVAL OF CNAO

To focus the best available competences on the design of a top-level facility, at the end of 1995 I proposed to the CERN management, with the help of Mainard Regler of the Med-Austron project, to initiate the "Proton Ion Medical Machine Study" (PIMMS) centred on the design of a synchrotron and a system of beam lines optimized for the treatment of deep seated tumours with collimated beams of carbon ions, protons and other light ions. The PIMMS project was approved by the CERN management and Philip Bryant - a CERN senior staff member - was chosen as the project leader. From 1996 to 2000 the study was carried out at CERN with the part-time participation of many members of the PS (Proton Synchrotron) Division.
Essential contributions to PIMMS have been given by the Med-Austron project (Austria), Oncology 2000 (Czech Republic) and TERA (Italy), which have invested 10, 3 and 25 man-years respectively. Sandro Rossi was leading the TERA group. Giorgio Brianti - who had been for about ten years CERN Technical Director - was chosen by TERA as the Chairman of the Project Advisory Committee. GSI (Darmstadt) contributed with expert's advice and participation in regular meetings of the Project Advisory Committee. This design study was closed at the end of 2000 with the publication of two long reports[8,9].
The PIMMS layout and its synchrotron are shown in Figure 20.
PIMMS mandate was to design a light ion hadrontherapy centre made of a combination of systems, optimized for the medical application, without any financial and/or space limitation. The output could later be used by any interested group as a tool kit for designing its centre. Thus during the years 1998-2003 TERA used many parts of PIMMS and modified others in order to reduce space and costs. This was achieved in two phases.
In the first phase - while acting to obtain the Government approval for the construction on the Mirasole site - TERA prepared, on the basis of the ongoing PIMMS activity, a third detailed project[2]. The layout of the third version of CNAO, completed before the closing of PIMMS, is shown in Figure 21.

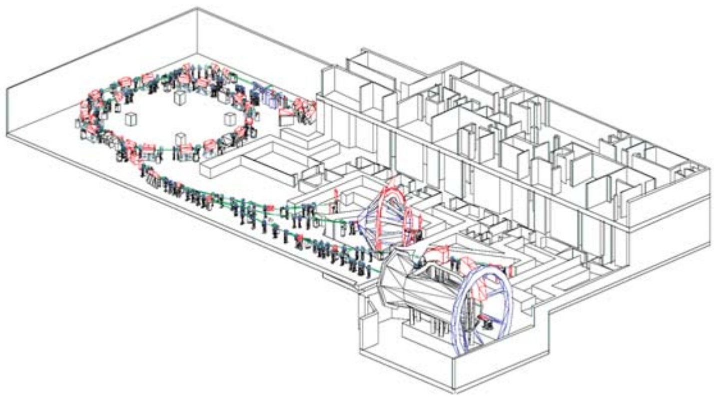

Figure 21. Perspective view of the first centre designed for the Mirasole site by TERA using a modified version of the PIMMS layout. The single injector linac is placed outside of the synchrotron ring. The ion gantry is very similar to the one built for HIT in Heidelberg.

In the second phase, TERA introduced other important modifications and improvements to the original design of the synchrotron and of the beam lines developed by PIMMS, producing the "PIMMS/TERA" design: the single linac for protons and carbon ions is located inside the ring and the three treatment lines are short.
In May 2001 the Italian Health Minister Umberto Veronesi created, following a TERA request, the CNAO Foundation "to realize the 'Centro Nazionale di Adroterapia Oncologica' proposed and designed by TERA".
In November 2001, after the change of Government that followed the political elections and a new review by an ad-hoc ministerial Committee, this decision was confirmed and further funds allocated by the Health Minister Girolamo Sirchia, thus concluding a procedure covering a ten year long period of frustrating experiences of public and private presentations, production and distributions of short and long documents and approvals of CNAO by various Commissions, the first one having been obtained - as said above - in 1995. Since 2002 the Health Ministry has been financing the CNAO foundation with ten million Euro per year.
One fundamental reason of the eventual success of this long standing endeavour was certainly the 'political' decision by TERA of not choosing too early the site of the centre, a decision that (after the first two attempts in Novara and Mirasole) was left to the public authorities which would contribute for the largest part of the construction funds.

☐ THE CNAO FOUNDATION

The CNAO Founders are the same institutions that had been chosen to create the Mirasole Foundation: with TERA, two large University hospitals (Ospedale Maggiore in Milan and San Matteo in Pave), two oncological hospitals (the public Istituto dei Tumori and the private Istituto Europeo di Oncologia, both in Milan) and the national neurological Institute Carlo Besta. Since 2004 INFN is Institutional Participant of CNAO.

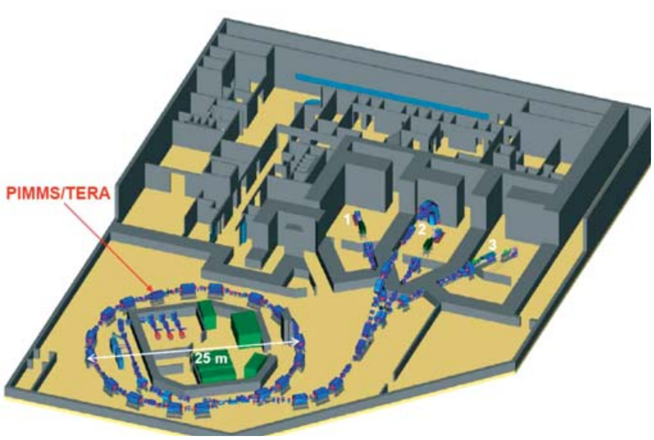

Figure 22. The layout of the Italian National centre designed by TERA features three treatment rooms with four beams, three horizontal and one vertical. It was also foreseen that two carbon ion gantries would be added in a second construction phase.

In November 2001 Erminio Borloni - top-manager of important private and public companies - was nominated President of the CNAO Foundation. In July 2002 an instrument of understanding was signed by the presidents of the CNAO and TERA Foundations. On its basis, TERA agreed to give to CNAO the intellectual property of all the technical documents it will produce since then in connection with the national centre. After fourteen months, in October 2003 TERA delivered to CNAO about 3,000 pages of specifications and technical drawings - to which CERN, GSI and INFN also contributed - thus concluding the activity started twelve years before. The overall layout of the PIMMS/TERA project is shown in Figure 22.
At the end of 2003 TERA passed to CNAO

Foundation 16 full-time staff members (physicists and engineers) and 9 part-time consultants. Sandro Rossi - who had been for many years TERA Technical Director - was chosen as CNAO Technical Director and Roberto Orecchia, TERA Vicepresident, was nominated CNAO Medical Director. From 2005 Graziano Fortuna of the Legnaro Laboratories was Technical co-Director in view of the large responsibilities taken by INFN in the construction and the running-in of the centre. At present Claudio Sanelli of the INFN Frascati Laboratories covers this role.

In January 2003 the Government announced the construction of the national centre in Pave, close to the Policlinico San Matteo, one of the five hospitals which, together with TERA, are the founders of the CNAO Foundation. About 30,000 m[2] were made available free of charge by the Province of Pavia for its construction. At the end of 2003 CNAO chose Calvi-Tekne as Architecture Bureau which produced the project of Figure 23.

Figure 24 shows the plan of the underground floor, where the synchrotron and the treatment and waiting rooms for the patients are located[(24)]. The areas for the two ion gantries will be built as Phase 2 of the project but the five rooms for the preparation of the patients are there from the beginning.

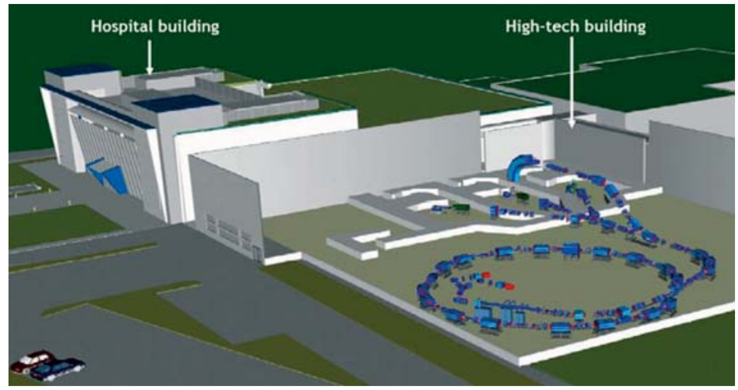

Figure 23. The project being realized in Pave by the CNAO Foundation features two separate buildings (*Courtesy of the CNAO Foundation*).

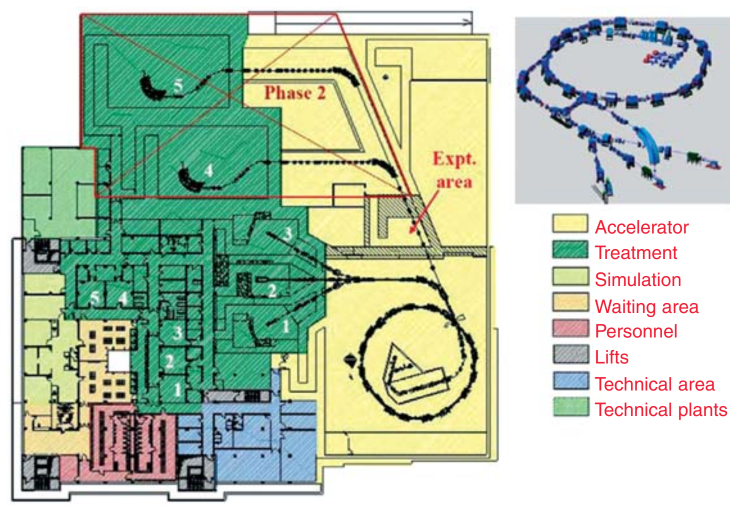

Figure 24. The layout of the underground floor prepared for the CNAO Foundation by the consortium Calvi-Tekne. Initially the bunker will not feature the two gantry rooms that will be built and equipped with gantries at a later stage (*Courtesy of the CNAO Foundation*).

Figure 25. The front side of the hospital building and the synchrotron hall in September 2007 (*Courtesy of the CNAO Foundation*).

The two photos of Figure 25 have been taken in September 2007.
The installation in Pave will be completed in summer 2008, seventeen years from the distribution of the report proposing it[7].
This is a convenient point where to stop this double review of the history of hadrontherapy from the beginnings till the nineties and of the Italian developments initiated around that time. The reader who would appreciate a more complete discussion of the rationale, the techniques and the development of carbon ion therapy can browse a review article I have written with Gerhard Kraft for Reports on Progress in Physics[1].

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