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European Developments in Radiotherapy with Beams of Large Radiobiological Effectiveness

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Hadrontherapy/Particle therapy/Large RBE radiations/European hadrontherapy projects/Carbon ion centres.

This paper reviews the European activities in the field of tumour therapy with beams which have a Radio Biological Effectiveness (RBE) larger than 1. Initially neutron beams have been used. Then charged pions promised better cure rates so that their use was pursued in the framework of the 'Piotron' project at the Paul Scherrer Institute (Switzerland). However both approaches did not meet the expectations and in the 80s the EULIMA project became the flagship of these attempts to improve the effects of the delivery of radiation doses of large RBE with respect to photons, electrons and even protons. The EULIMA ion accelerator was never built and it took more than ten years to see the approval, in Heidelberg and Pavia, of the construction of the HIT and CNAO 'dual' centres for carbon ions and protons. In 2008 they will start treating patients. The developments that brought to these construction projects are described together with the special features of these two facilities. The third European dual centre is being built by Siemens Medical Systems in Marburg, Germany, while other facilities have been approved but not yet fully financed in Wiener Neustadt (Austria), Lyon (France) and Uppsala (Sweden). Finally the collaboration activities of the European Network ENLIGHT are presented together with the recent involvements of European industries in the construction of turn-key dual centres and the development of a new accelerator concept for hadrontherapy, the 'cyclinac'.

THE BEGINNINGS: FROM NEUTRONTHERAPY TO EULIMA

In the context of improving radiotherapy by better targeting and/or achieving a larger effectiveness, the transition to hadron beams like neutrons, protons, pions and heavier ions could have been predicted. In this paper, devoted to radiation of large *Relative Biological Effectiveness*, RBE, protons are not considered.

Due to their higher penetration depth, low energy neutrons were the first hadrons used in radiotherapy, in particular to control radio-resistant tumours due to the large RBE of the recoiling protons and ions. At Berkeley before World War II Ernest Lawrence, John Lawrence and collaborators used fast neutrons to treat tumours.[1)] In Europe the first neutron irradiation were made at the Hammersmith hospital under the direction of M. Catteral in 1969[2)] but in the last years neutron therapies have been terminated in most European countries: because of the poor depth-dose distribution of low energy neutrons the biologically high-effective dose is large also in the normal tissues outside the target volume causing severe side effects. High energy neutrons which have a better depth dose profile exhibit a much lower RBE values that diminish the wanted effectiveness. A good indication for neutron treatment has been salivary gland tumours which are rather superficial,[3)] but these are also sensitive to carbon ion therapy. This modality is still used to some small extend at the research reactor Garching FRM II in Munich.[4)]

Boron Neutron Capture Therapy is a topic of research in a European project at the nuclear reactor of Petten, Netherlands.[5)] There by the end of 2006 some thirty glioblastoma patients have been treated with mixed success. In 2007 the future of this clinical activity will be reviewed.

After neutrons the next big hopes were negative-pion beams producing an additional boost of dose at the end of the pion's range. There the pions are captured by the target nuclei and release additional energy. Although the dose improvement at the end of the range could be confirmed in physics measurements, the clinical trials performed at PSI

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(Switzerland) at the 'Piotron' facility in the years from 1980 to 1993 could not demonstrate an improved cure rate and the pion trials were terminated worldwide after the treatment of some 800 patients.[6–8)]

Today the proposed use of antiprotons 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 paper are by far not obvious. The way in front of the proponents of this large radiobiological effectiveness therapy is still long but it has to be underlined that recently an interesting paper has been published on the measurements performed at CERN on the RBE of stopping antiprotons.[9)] In this paper the RBE of antiprotons is compared with the one of protons, the hadron which has in practice the same effectiveness as high energy photons and is most used in the clinical practice.[10,11)]

Heavier ions 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 2800 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 proposal of a reduction of other tumours when the pituitary would be inactivated. In these treatments a general RBE of 1.6 was used as multiplication factor of the absorbed dose.[12)] Concerning the primary goals, the inactivation of the pituitary, the precision of the helium therapy and the RBE were correct and this type of precision therapy can be regarded as a first step towards heavy ion radiosurgery. About twenty years later argon beams were tried at the Bevalac in order to increase the effectiveness against hypoxic and otherwise radio-resistant 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, lighter ions, first silicon ions for two patients and then neon, were used for 433 patients until the Bevalac stopped operation in 1993.[13)] In the same year HIMAC started to treat patients.

Coming back to the subject of this paper, in 1987 a very 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.[14)] EULIMA, the European Light Ion Medical Accelerator project, financed by the European Commission, was led by Pierre Mandrillon (Laboratoire du Cyclotron, Nice) and involved many European laboratories and centres. Initially the project, by making use of the Berkeley experience, foresaw the use of O^{+8} ions, but during the study a worldwide consensus was reached that a better choice is C^{+6}. In the design the long range possibility was also kept open to treat patient with radioactive beams.[15)]

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.[16)] In this report the advantages and disadvantages of the superconducting 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. Moreover 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 at their disposal facilities similar to the Heavy Ion Medical Accelerator at Chiba and the Hyogo Ion Beam Medical Center.

The rest of this paper is devoted to the developments which brought to the creation of a European network of centres devoted to hadrontherapy with beams of heavy charged particles different from protons.

EUROPEAN RESEARCH IN RADIOBIOLOGY

The use of ions in cancer therapy requires the understanding of the basic radiobiological phenomena in tumours and in healthy tissues. In the beginning at Berkeley the increase in the relative biological effectiveness (RBE) for ions with respect to photons was believed to be related to the physical parameters of the beam, being the same for different tissues. Although cell experiments with cell lines of different repair capacity did show the problems of this approach, it had to be used because of the 'passive' dose delivery system employed. In such a case the variation of the RBE with depth determines the shape of the beam modulators and cannot accommodate all the combination of tissue types and tumour extensions.[17)]

Since 1980 a large programme of systematic studies of RBE, with many important European contributions, has been carried out by the GSI radiobiology group at various accelerators, such as Unilac (Darmstadt), Ganil (Caen), Bevalac (Berkeley), the Tandem Van De Graff (Heidelberg) and, later, at SIS (Darmstadt). This research has concentrated on the effects of high LET (and thus large RBE) radiations on very different biological objects, from sub-cellular systems - such as DNA and chromosomes - to biological systems that are very resistant to extreme environmental conditions and are used in space research.

The experiments used more than a hundred thousand biological samples and ion beams from very light to very heavy elements. The research identified the systematic dependence

of RBE on physical and biological parameters – mainly the capacity of cells to repair DNA damage - as the most important factor, which was then theoretically modelled for use in treatment planning. In particular, the work showed that for beams of carbon ions the section of the particle track with increased RBE coincides with the few centimetres before the Bragg peak, while for lighter ions it is concentrated only in the last few millimetres. For heavier ions, such as the argon, silicon and neon ions, used previously at Berkeley, it causes significant damage in the normal tissues before the tumour.

A review of the many European results of interest for ion therapy is outside the scope of this paper. The interested reader can consult Refs[18,19] for the GSI work and Ref[20–25] for some contributions to this field by French, Italian and Swedish research groups.

ACCELERATORS AND BEAMS FOR ION THERAPY

Advantages and disadvantages of cyclotrons and synchrotrons have been listed in the first Section in connection with the EULIMA project.

For reaching deep-seated tumours (more than 25 cm of water equivalent), the needed energies of these accelerators 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 track are the two physical reasons which make carbon irradiations qualitatively different from proton irradiations, which in turn behave similarly to photon. Quantitatively, the enormous amount of radiobiological information collected can be summarized by stating that for radio-resistant cells the RBE of carbon ions is definitely larger than 1 when the Linear Energy Tansfers (LET) is larger than about 20 keV/μm. Protons, which reach such a high LET only in the last mm of their range, behave biologically and clinically essentially as photons.

In practice energetic protons are obtained either with cyclotrons (normal or superconducting) or with synchrotrons having a diameter of 6–7 metres. Till now only synchrotrons have been built, first in Japan and now in Europe, to produce carbon ions of about 400 MeV/u. The magnetic rigidity of these ions equals 6.3 Tm, *i.e.* is three times larger than the one of 200 MeV protons so that 20 metre diameter synchrotrons are needed when fields in the range 1.5–1.7 tesla are used. Since 2007, as discussed in the last Section, superconducting cyclotrons not very different from the one studied for EULIMA almost twenty years ago are being put on the market.

As mentioned above, in cyclotrons the beam energy cannot be varied, so that there is the problem of needing the relatively slow displacement of absorbers to vary the energy, and thus the range, of the particles. Downstream of the absorbers a magnetic energy selection system (ESS) has to be used to clean the absorbed and scattered beam. In an ESS neutrons are produce which, in turn, produce unwanted radioactivity. Instead in synchrotrons the energy of the extracted beam can be varied within about 1 second, the typical time in between two spills, which is an advantage for conformal treatment.

Clearly the energies needed for hadrontherapy are large in comparison with the 10–20 MeV of the electron linacs used in conventional radiotherapy. This is the reason for the much larger dimensions, weights and power consumptions of the corresponding accelerators. On the positive side one has to register the fact that the needed currents are small: in the case of active spreading about 1 nA for protons and less than 0.1 nAe for carbon ions. Thus the technical problems are dictated by the particle energy and not by the current.

As far as the monochromaticity of the beam is concerned, it has to be recalled that for a 400 MeV/u carbon ion the fall-off of the Bragg peak (from 80% to 20%) is about 10 mm. Since the ion range is roughly proportional to $E^{1.8}$, not to spoil the peak properties at a depth of about 25 cm the energy spread of the distal dose deposition should not be larger than $0.55\ (10/250) \approx 0.2\%$.

For an active dose delivery the energy has to be adjusted in many steps during the irradiation to produce the desired superposition of Bragg peaks, which possibly takes into account the local average RBE of the mixed radiation field and thus uniformly covers the 3D tumour target. Relatively simple ‘passive spreading systems’ have been used in all hadrontherapy centres till 1997. Only in 1997 at GSI[26] and PSI[27] the novel ‘active spreading systems’ have been developed where the charged hadrons (protons and carbon ions) are magnetically guided over the treatment area and modulated in intensity (*Intensity Modulated Particle Therapy* = IMPT). Since a few years all centres feature active scanning systems even if very few have been used till now to treat patients.

The protontherapy centres of recent conception feature isocentric ‘gantries’ to improve the conformity of the treatment avoiding at best the healthy tissues. The magnetic rigidity of 200 MeV protons is such that a rotating gantry supporting a magnetic channel capable of doing so has a typical radius of 4–5 m. By now, many commercial companies offer turnkey centres of proton therapy featuring isocentric ‘gantries’ equipped for the active spreading of the dose. This is very difficult in the case of carbon ion treatments because of the three times larger rigidity with respect to protons. In the EULIMA collaboration a study was performed of a carbon ion gantry[28] and other suggestion have followed. However, as discussed in the following, the only centre which will feature a gantry is the one being constructed at Heidelberg.

THE GSI PILOT PROJECT

Starting in 1988 one of us (G.K.), together with G. Gademann and G. Hartmann, proposed a two-step project: installation of an irradiation unit for experimental patient treat-

ment at the new heavy ion accelerator SIS of GSI and, as a second phase, the construction of a dedicated heavy ion therapy unit at the Heidelberg University hospital.

In summer 1993 the construction of the therapy cave at GSI started and in December 1997 the first two patients were treated with the novel intensity modulated 'raster' scanning technique.[29] With the start of the patient treatment the project-leadership turned to the Heidelberg Clinic.

There are four novel features in the GSI pilot project:

(i) the IMPT system that uses the active raster-scanning system as mentioned above;
(ii) the fully automatic control of the GSI accelerator complex, that can be handled by an operator trained as operator of standard X-ray equipments;
(iii) the sophisticated models and codes that take into account the RBE of different tissues in treatment planning.[29,30]
(iv) the two gamma ray detectors placed above and below the patient to determine 'on-line' the exact location and shape of the irradiated volume because, when penetrating the body, the incident carbon ions produce β^+ radioactive nuclei.[31]

For a quantitative calculation of the RBE effects, a theoretical model, the Local Effect Model (LEM) has been developed at GSI[29,30] and implemented in a treatment planning system TRIP which, by the beginning of 2007, has been used successfully for more than 300 patients. The GSI-DKFZ treatment planning system allows the optimization of the treatment according to biological parameters and is based on measurable parameters as the track structure, the size of the cell nucleus and the X ray sensitivity of the tissue.

In Fig. 1 the most advanced photon treatment plan using Intensity Modulated Radiation Therapy with 9 fields is shown. This is compared to a two-field carbon treatment plan using Intensity Modulated Particle Therapy and the treatment planning system based on LEM.

To deliver the dose the ion beam in moved from one position to the next without turning off the beam. When one slice is treated, the energy of the beam is reduced for the next slice. In practice, the complete target volume consists of 10'000–30'000 voxels (*i.e.* 3D pixels), which are treated in 2–6 minutes. As mentioned above, intensity control raster (or voxel) scanning was introduced by GSI for carbon ions (in three dimensions) and by PSI for protons (in a two-dimensional version, since the third dimension is scanned by moving the patient's bed), as described in Refs[26] and[27].

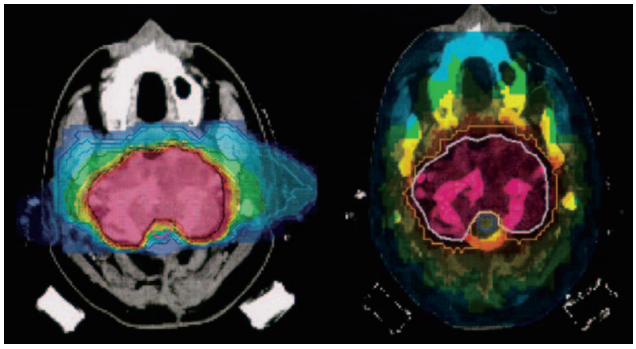

Fig. 1. Comparison of treatment plans with 2 fields of carbon ion (IMPT – left panel) and with 9 fields of X-rays (IMRT – right panel). In both cases the conformity to the target volume is good but for carbon ions the dose to the normal tissues is much smaller.

Scanning allows treating any irregular shaped tumour with a precision given by half the width of the beam. In Fig. 2 the iso-energy slices of a tumour are shown together with one iso-energy slice in an enlarged scale where the calculated beam positions are given as circles and the measured ones as points. In order to reach a good homogeneity the pencil beam has a half width that covers approximately three beam positions in the vertical and horizontal directions.

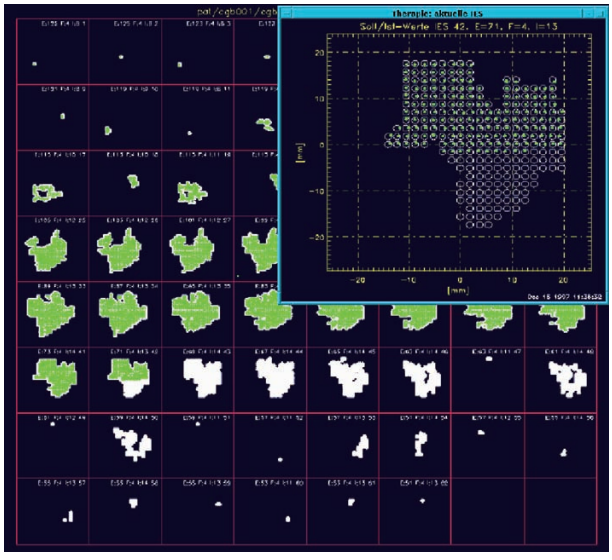

Fig. 2. Iso-energy slices of a tumour treated at GSI with carbon ions. In each panel one slice is shown out of 62. In the magnified panel, the circles are the planned target positions; the green point represents the measured positions of the centre of the beam. The beam diameter is larger than the circles and overlaps many positions, yielding a homogeneous dose distribution.

A last advantage of particle beams, and especially of ions like carbon – point (iv) of the list –is the 'in situ' production of positron emitters, mainly ^{11}C and ^{15}O. Because the stripping of one or two neutrons is a minor perturbation, the residual carbon ions form a maximum of β^+ activity close to the Bragg maximum of the stabile carbon ions. By monitoring the positron emitting isotopes by a PET camera during and shortly after the beam application, the actual stopping points of the beam can be controlled. C. A. Tobias proposed this technique in the early 70's at LBL.[32] The technical realisation at the GSI pilot project (Fig. 3) is due to W. Enghardt, of FZR Dresden.[31,33] A prerequisite for online PET is an

Fig. 3. The GSI horizontal beam has been used to treat mainly intracranial and head and neck tumours. The two white boxes, placed above and below the patient, contain the detectors for the on-line PET determination of the dose distribution.

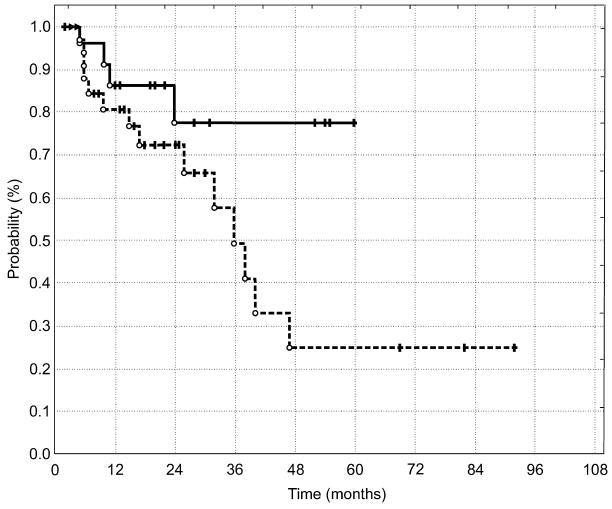

Fig. 4. Local control rate of salivary gland tumours are compared for about 30 patients in each arm: the lower curve represents patients treated with photon IMRT only. For the patients in the upper curve, 6 out of 20 fractions were replaced by carbon treatment.[34)]

active beam delivery system that avoids a large amount of neutrons activating the treatment area.

The iterative procedure of range measurements and CT calibration for the planning procedure and the control via PET monitoring yields the final millimetre precision of the carbon treatment.

The treatments at the GSI pilot project were performed in cooperation with the University Radiotherapy and DKFZ, Heidelberg and FZR Dresden and yielded the same good tumour control as in Chiba.[34,35)] By the beginning of 2007, more than 300 patients had been treated.

Here a comment is in order on the quality of a tumour treatment. The 5 year tumour-free patient survival is the first aim of a treatment, but a primary tumour can produce metastases even a long time after it was removed. If metastases occur a good local control-rate does not mean patient cure but helps in many cases to prolong the patient's life and to reach a better quality of life, depending on the patient's general conditions and on the type of tumour. In Fig. 4 the local tumour control rate up to 5 years is shown for salivary gland tumours where, in the course of a conventional treatment, 6 of 20 fractions were given with carbon ions compared to treatments where all fractions are given with photons. The 5 year local control rate rises by about 50%: this is a great success but unfortunately this type of tumour has a 30–40% probability to produce metastases.

For carbon treatments those patients should be selected that have the largest benefit according to the bio-physical properties of these particles. Slowly growing tumours are very radio-resistant against photons because of their great repair capacity. Because carbon ions kick down the repair capacity for these difficult tumours a great benefit was expected and then realized. For a complete carbon treatment, 5 year tumour-control rates of 80% have been reached, again much better than other treatments. This is true for both treatments, at Chiba and Darmstadt. But a greater conformity of the beam delivery with the scanning system reduces the side effects and increases the quality of life, so some of the patients were even able to do their professional work during and immediately after treatment.

A similar good response is now expected for prostate tumours which are radio-resistant too. The high RBE for these treatments will allow reducing the burden to the surrounding normal tissue, like rectum and bladder, and should therefore reduce the side effects. But prostate treatment has the problem that the organ can be at different positions from day to day and that it can move during treatment. Therefore a boost strategy of six carbon fractions within a larger field photon treatment has been applied for the first patients treated at GSI. In total 30 patients will be treated with carbon ions and 30 without to prove whether the predicted advantages can be realised in the clinical practice. The result of these treatments will be analysed towards the end of 2009.

POTENTIAL EUROPEAN PATIENTS OF PROTON AND CARBON ION THERAPY

As far as the number of potential patients is concerned, detailed analysis have been made in Germany,[36)] Italy,[37)] Austria[38)] and France[39)] by groups of radiation oncologists who have applied to the national data specific criteria for each tumour site.

Different approaches have being used. In Germany and Italy the data of existing tumour registers have been used by estimating, site by site, what fractions of the patients would be advantageously treated with proton and/or carbon beams. In Austria a nationwide survey was performed on the pat-

ients receiving conventional radiotherapy at all the twelve Austrian centres. In France five large radiation therapy departments have been surveyed for one day and for each patient it was determined whether a proton or carbon treatment would have been preferable to a conventional irradiation.

The results of these different approaches are even too consistent, as quantitatively confirmed by the summary table appearing in Ref.[38] in which the indications of the four groups of radiation oncologists are compared site by site. Note that this comparative work has been done in the framework of the European Network for Light Ion Therapy (ENLIGHT) discussed in the following.

As an overall summary it can be stated that

(i) about 1% of the patients today treated with X rays must be irradiated with protons since the outcomes are definitely better than the ones of conventional therapy (Category A of the Italian survey);
(ii) about 12% of the X-ray patients would profit from a proton treatment but further clinical trials are needed to quantify, site by site, the clinical advantages (Category B patients);
(iii) about 3% of the X ray patients would profit from carbon ion therapy, but many more dose escalation studies and clinical trials are needed.

An independent study made in Sweden concluded that 14–15% of the patient should be treated with protons.[40]

Overall, one can state that 15% of the about 20'000 patients treated in Europe, every 10 million inhabitants, with conventional radiation would receive a better treatment with charged hadron beams. This corresponds to about 2600 proton treatments and about 600 carbon ion treatments per year. If the actual average recruitment rate could be as large as 50%, these figures would require – in the medium term – a protontherapy centre (treating 1300 patients a year in about 30000 sessions) every 10 million people and a carbon ion centre every 50 million people. This is indeed the conclusion reached by the Italian association for radiotherapy and oncology AIRO.[37]

As far as costs are concerned, it has been calculated that a proton treatment costs 2–3 times more than a conventional treatment.[41]

The economy of carbon treatments is different. As shown by radiobiological experiments and confirmed by the clinical experience of NIRS, since with carbon ions the usual cellular repair mechanisms have little effect there is no necessity to deliver the dose in the 20–30 fractions used in X ray and proton therapy. The possible *shortening* of the treatment to less than 10 fractions (at HIMAC down to the limit of a single fraction) would be a great advantage for a very effective use of the costly infrastructures and – if confirmed by more clinical trials – will reduce the cost of the treatments and may become one of the main reasons behind the future rapid diffusion of light ion therapy. In this connection it should not be neglected that there is still a rational for carbon *fractionated* delivery: the sparing of normal tissues in the entrance channel where carbon acts more like sparsely ionizing photons. The balance between these opposite arguments is probably tumour-type dependent.

THE HEIDELBERG ION THERAPY CENTRE HIT

With the new century Europe has made important steps in the development and construction of hospital-based 'dual' centres for carbon ions and protons. Based on the successes of the GSI pilot project, the Heidelberg Ion Therapy centre (HIT) designed by GSI was approved in 2001 and the civil engineering work began in November 2003. This centre features the HICAT synchrotron made of six long bending magnets,[42] two horizontal beam lines and the first carbon-ion rotating gantry, which is 25 m long and weighs 600 tonnes.[43]

HIT is a project of the Heidelberg university hospital. The total cost is close to 100 M€. Half of this investment is given as research money by the Federal government while the other half is a bank credit to the hospital

The responsibility for the buildings is with the university building office. In contrast to the name, this institution does not belong to the university but to the state government. GSI is responsible for the accelerator from the ion sources to the high energy beam lines. Siemens Medical Solutions has taken over the responsibility for the raster scanning system and the beam delivery control to the patient, which is the most critical part of a ion therapy facility but also the most underestimated one: the treatment planning system has to produce a steering file for the scanner system that guaranties a correct and reproducible 'isodose' (in case of protons) or a correct 'iso-effect' (in case of carbon ions) on each voxel of the target volume. This procedure has to be in agreement with local regulations as well as with the European legislation.

At the beginning of 2007 the construction phase of the building is completed and the injector is in operation. Beams from the synchrotron are expected in spring 2007 and the first patient should be treated by the beginning of 2008.

The synchrotron ring, shown in Fig. 5, has a diameter of about 20 metres. The first design was produced in 1992 as a contribution to the EULIMA project and further developed in the next years.[44] The HIT injector, which is a RFQ followed by an 'interdigital' structure of the type developed since long at GSI by H. Ratzinger and collaborators,[45] accelerates to 7 MeV/u protons, carbon ions and, possibly, other ions as helium or oxygen.. The RF knock-out technique used in NIRS[46] has been adopted for extracting a beam which is uniform in time.

HIT is an ambitious project that - by applying all the techniques and methods developed in the framework of the pilot project - will be a centre of clinical and medical physics research. Jürgen Debus is Medical Director and Thomas

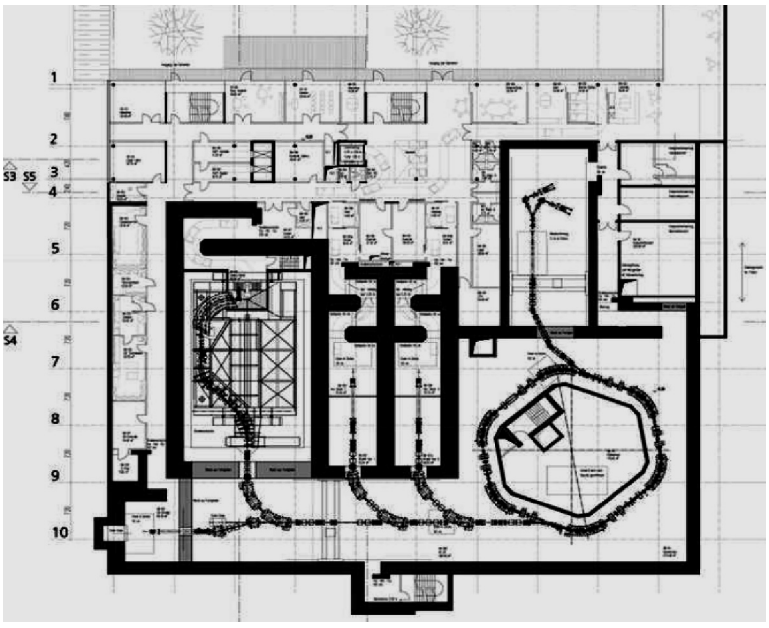

Fig. 5. The Heidelberg facility HIT (Heidelberg Ion Centre) features three treatment rooms. One of them hosts a rotating carbon ion gantry of new design. A single 7 MeV/u linac injects in the synchrotron both protons and carbon ions. The construction status of HIT can be checked by visiting the site www.arge-sit.de.

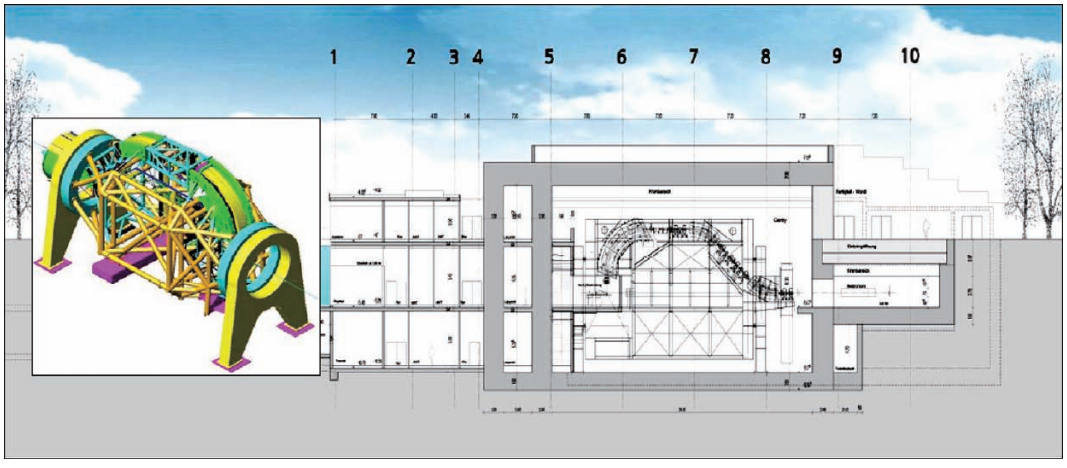

Fig. 6. The GSI isocentric gantry for carbon ions is about 25 m long and vertically occupies three floors. It will be ready by the end of 2008.

Haberer Technical Director. The centre features a gantry which weighs about 600 tons (Fig. 6), consumes up to 400 kW and will allow the comparison of proton and ion therapies performed in optimal and similar irradiation conditions. Moreover, since the necessity of having a gantry for the future ion facilities is still under discussion, the HIT gantry, as a first prototype, will contribute to answer this question.

On the clinical side the European legislation has set a high threshold for a general application of ion beams: in principle each new tumour type has to be treated with a few patients and after a 5-year-observation the authorities will decide whether this is an acknowledged procedure for patient cure. HIT, together with CNAO discussed in the next Sections, will play an essential role for all other particle therapy facilities in Europe.

THE PROTON ION MEDICAL MACHINE STUDY PIMMS AT CERN

At the end of 1995 one of us (UA) - with the help of Meinhard Regler of the Med-Austron project - attracted the interest of the CERN management in the design of an opti-

mized synchrotron for light-ion therapy. Once completed, such a design would be freely available to all the European countries ready to invest the required funds in the construction of a National facility. In 1996 the activity was started at CERN under the acronym PIMMS (*Proton and Ion Medical Machine Study*).

PIMMS was a collaboration among CERN, Med-AUSTRON (Austria), Oncology 2000 (Czech Republic) and TERA (Italy). Philip Bryant of CERN was the Project Leader. During the years 1996–2000, CERN contributed also with the part-time assistance of many of its staff members. TERA, Med-AUSTRON and Oncology 2000 invested in the study 25, 10 and 3 man years respectively. GSI contributed with expert's advice and participation in regular meetings of the Project Advisory Committee chaired by Giorgio Brianti.

The two volumes of the final report were distributed in 1999–2000.[47,48] The outcome is a design that combines many innovative features, so as to provide an extracted pencil beam of particles that is very uniform in time and can be easily adjusted in shape.

A list of the special features of the PIMMS design includes:

1) two dispersion-free zones for injection and RF acceleration in a lattice made of 16 short and cheap bending magnets;
2) single-turn injection from the inside of the ring;
3) slow extraction based on the excitation of a "betatron core"[49] while all the currents in the other machine components are kept unchanged and the lattice satisfies the "Hardt condition"[50];
4) an 'empty' bucket that increases the velocity of the particles entering the extraction resonance, thus reducing the intensity fluctuations of the extracted beam[51];
5) separated functions for the high-energy beam lines, so that the sectors used for varying the horizontal and vertical dimensions of the pencil beam used for scanning the tumor are independent[52];
6) a mobile cabin gantry (named Riesenrad gantry) for carbon ions[53];
7) "rotators" to make the beam optics of each gantry independent of the gantry rotation angle.[54]

Applying the above mentioned design criteria, the PIMMS implementation had three rooms for protontherapy (two of them equipped with rotating gantries) and two rooms for the irradiation with carbon ions.

No costing was done, but a rough estimate indicates that the realization of the layout of PIMMS would require a total investment definitely larger than 150 M€. The high cost should be no surprise, since PIMMS mandate was the production of the best possible design without monetary constraints.

THE ITALIAN NATIONAL CENTRE FOR ONCOLOGICAL HADRONTHERAPY CNAO

In the years 1992–1999 the TERA Foundation, created to advance hadrontherapy in Italy and Europe, made two attempts to obtain from the Italian Health Ministry the funds needed to build the National centre CNAO by choosing as its location firstly Novara (the town where the Foundation has its seat) and later Milan. Two full projects were prepared and two books produced[55,56] but the times were not yet ripe.

In the years 1999–2003 TERA used many parts of PIMMS and modified others in order to reduce space and costs and produced the more compact and flexible "PIMMS/TERA project" of Fig. 7:

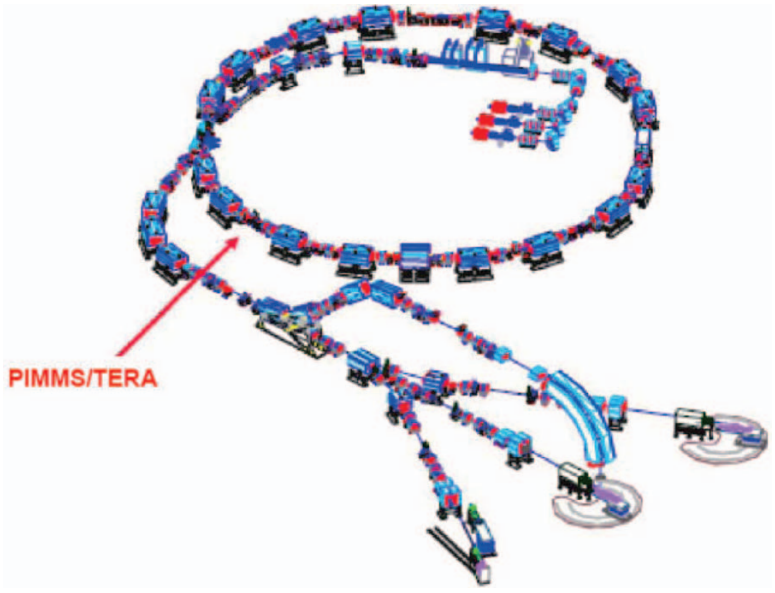

Fig. 7. The sources and the injector are inside the PIMMS/TERA synchrotron making it very compact. Initially three rooms will be built, but two gantries are foreseen for the second phase.

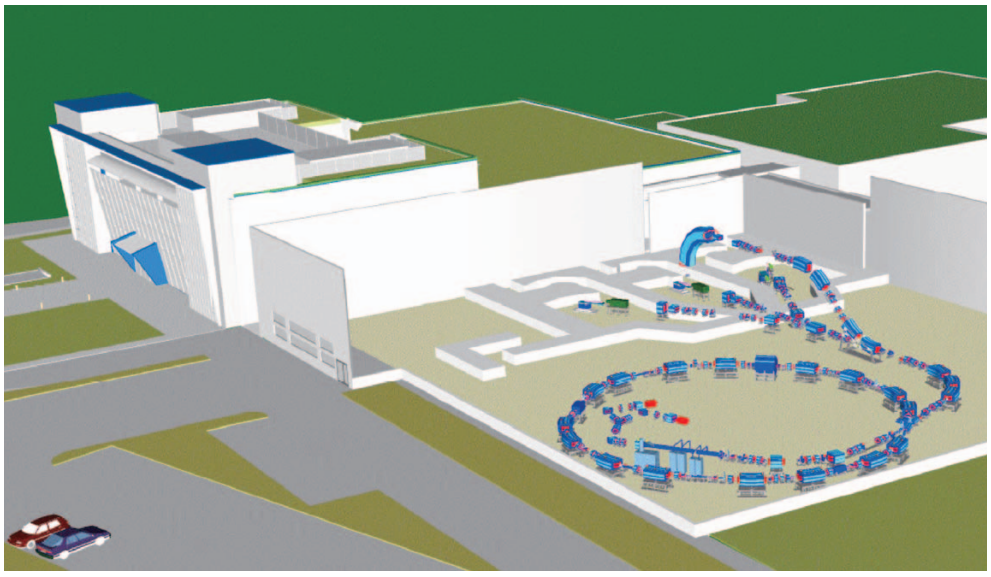

Fig. 8. The Phase 1 of the Italian National centre CNAO features three treatment rooms. In the central one patients are irradiated with a horizontal and a vertical beam. Two gantry rooms will be added so that, when completed in Phase 2, the centre will feature five treatment rooms. The first patient will be treated in 2008.

1) a single 7 MeV/u injector for all ion species from proton to carbon was used; for such injector the design made by GSI for the Heidelberg centre[36,44] was adopted;
2) a multi-turn injection scheme was chosen;
3) a RF knock-out system was implemented, in addition to the betatron-core extraction, similar to the one used by HIMAC and HIT;
4) the beam lines were made shorter and, thus, less expensive than the PIMMS ones, but with this simplification some of the nice properties described above were lost.

In 2001 the Italian Government created the CNAO Foundation and attributed to it a first installment of 20 million Euros. Founders of CNAO are, 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*. The final project was prepared by TERA in the years 2002–2003 and at the beginning of 2004 CNAO hired 25 people from TERA to constitute the core group responsible for the construction and running of the facility. The same year many institutes took construction responsibilities, in particular INFN which assures also the co-leadership of the project. Other European laboratories involved are CERN, GSI and CNRS- IN2P3 of Grenoble.

Phase 1 of CNAO has three treatment rooms, as shown in Fig. 8. The total investment is 90 M€, 80% of which have been granted by the Italian Health Ministry. In February 2007 the synchrotron hall (which is shown at the right in Fig. 8) was completed and the mounting of the components initiated. More details can be found in the contribution by S. Rossi to the conference EPAC 06.[57]

The building on the left of Fig. 8 has three floors and is devoted to the reception of patients, to the visits and to the offices and laboratories of the 120 people who will work there at the end of a running-in period of three years. Roberto Orecchia is Medical Director and Sandro Rossi Technical Director.

The aim of the Phase 1 is to deliver 19000 sessions per year, 80% with carbon beams and 20% with proton beams. The patients will be prepared and aligned on movable beds outside the treatment rooms and the bed locked in the irradiation position by automatic alignment systems.

The figure represents Phase 1 of the centre with three treatment rooms, but the building on the back of Fig. 8 has been constructed to allow for the possibility of adding two ion gantry rooms that will be equipped in a second construction Phase, so that eventually CNAO will be a dual centre with five rooms.

OTHER EUROPEAN PROJECTS AND ENLIGHT

In fall 1998 the University Claude Bernard of Lyon commissioned TERA a preliminary proposal of a hadrontherapy centre based on the PIMMS design and featuring two carbon ion gantries and a horizontal line. TERA prepared a report describing a centre that is similar to the design prepared for CNAO. Following this preliminary study, the Lyon University signed a contract with CEA (Saclay) and IN2P3 of CNRS to produce two reports presented to the French

authorities.[58,59] In 2003 a similar project was proposed to the French Government by the Basse-Normandie Region: ASCLEPIOS, to be built near GANIL, the ion accelerator Centre in Caen. In June 2005 the Lyon ETOILE project was approved by the French government. At the beginning of 2007 construction funds were attributed by the state, the region and the town.

In Sweden the PIMMS/TERA synchrotron was for a long time the heart of the centre proposed by the Karolinska Institute and Hospital which is described in a paper published in 2001.[24] At the beginning of 2007 the Karolinska accelerator is planned to be a superconducting cyclotron for ions whereas the Uppsala plans are for a proton facility.

In 1998 the Med-Austron team presented to the Austrian the proposal of a dual centre to be built in Wiener Neustadt. The first design was based on the PIMMS/TERA synchrotron and a modified PIMMS design for the extraction lines.[60,61] At the end of 2004 the Austrian Government, the State of Lower-Austria and the town of Wiener Neustadt granted 40% of the required funding. At the beginning of 2007 the government of Lower Austria took the decision to finance, build and operate MedAustron. The tendering procedure will start in 2007 and the centre should start operating in 2012.

In 2002 the five European projects (sited in Heidelberg, Pave, Wiener Neustadt, Lyon and Stockholm) teamed with ESTRO (the European Society for Radiotherapy), EORTC (the European Organization for Cancer Research), CERN and GSI to form the *European Network for Light Ion Therapy*, which was financed for three years by the European Commission. The activities, which have being concluded in 2005, can be guessed from the list of the six Working Packages:

1. Epidemiology and patient selection
2. Design and conduct of clinical trials.
3. Preparation, delivery and dosimetry of ion beams.
4. Radiation biology.
5. In-situ monitoring with Positron Emission Tomography.
6. Health economic aspects.

The work done is documented in a series of reports[62] and in a contribution to ScienceDirect.[63]

Between 2006 and 2007 a larger group of institutes and hospitals from 15 countries has come together to prepare a new proposal for the EU Framework Programme FP7 under the name ENLIGHT++.[64]

The existence of this network, and of its potential follower, guarantees that the future of carbon ion therapy in Europe is on a good track and that the foreseen facilities will be run for the benefit of all European patients.

EUROPEAN TURN-KEY DUAL THERAPY CENTRES AND FUTURE DEVELOPMENTS

Industry has shown its interest in the upcoming market of

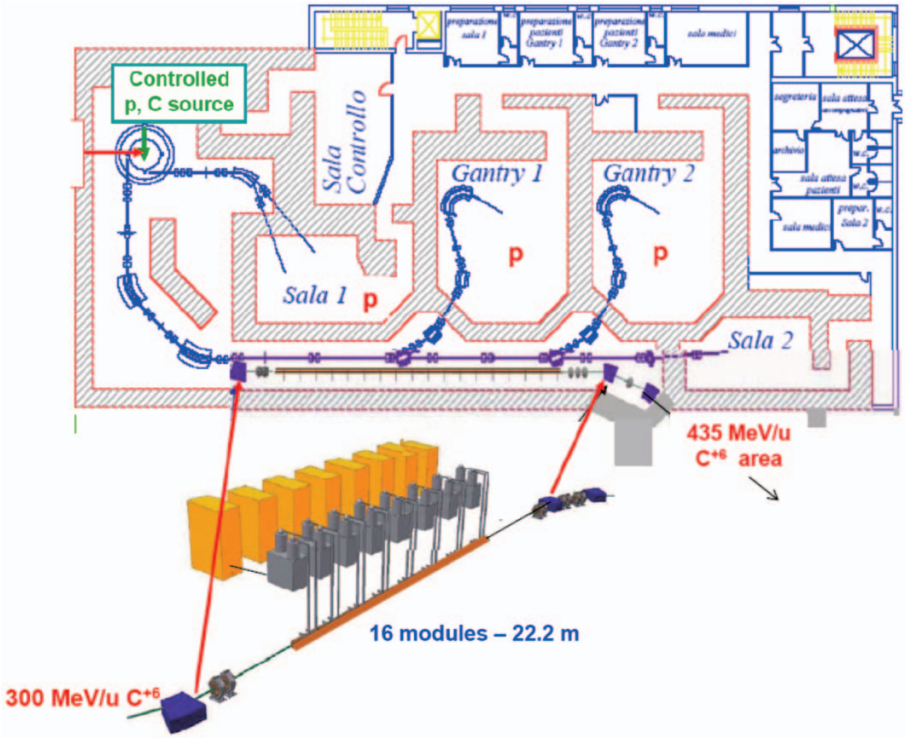

Fig. 9. A hadrontherapy centre as the one of Fig. 5 can be upgraded with CABOTO to boosts the energy to 435 MeV/u corresponding to a 33 cm range in water. LIBO is made of 16 modules and is 22 m long.

hadrontherapy by proposing solutions based on synchrotrons and cyclotrons. Five companies are already selling proton therapy units. In Japan, Mitsubishi produces since many years a synchrotron for combined proton and carbon therapy.[65] The facility in construction at Gunma University is based on a new compact synchrotron design which has 18 bending magnets.[66]

In Europe, Siemens Particle Therapy offers a combined proton-carbon facility on the basis of exclusive licenses of the GSI patents and know-how.[67] The synchrotron, which has 12 bending magnets, has been designed by Danfysik.

At the beginning of 2007 a commercial company is discussing with the CNAO Foundation the licensing of the synchrotron design which is being built in Pavia.

As discussed in the first Section, a superconducting (SC) cyclotron for accelerating carbon ions to 400 MeV/u was proposed at the end of the 80s by the EULIMA group but never built. In 1989 Blosser and its group at Michigan State University proposed a 400 MeV/u SC cyclotron.[68,69] More recently a similar SC cyclotron has been designed in Korea.[70]

In 2006, a 400 MeV/u SC cyclotron has been put on the market by IBA as an alternative to the synchrotrons used till now in Japan and Europe to accelerate carbon ions to $\geq$ 400 MeV/u.[71] The IBA cyclotron weights 700 tons and has a 6 m diameter.

Some years ago a 250 MeV/u SC cyclotron was designed by scientists of the LNS laboratory in Catania, which belongs to the Italian National Nuclear Physics Institute (INFN).[72] As in the other SC cyclotrons for hadrontherapy, the accelerated particles are hydrogen molecules deprived of one electron (H_2^+) and carbon ions (C^{+6}). These particles, which have Q/A = 1/2, are extracted through the same port with a stripping foil and with a conventional deflector respectively. Later the energy was increased to 300 MeV/u.

Following an agreement signed in 2006 with INFN, the executive design was performed by IBA and, from the beginning of 2007, the 5 metre diameter SC cyclotron is a IBA commercial product.[73]

The LNS group has proposed to build a proton and carbon ion centre based on this 300 MeV/u cyclotron at the Cannizzaro hospital (Catania). The preliminary layout, shown in Fig. 9,[74] features three proton rooms, two of them being equipped with gantries, and a room with a horizontal beam ("Sala 2") for therapy with carbon ions of energy smaller than 300 MeV/u.

Carbon ions of 300 MeV/u have a 17 cm range in water. Fig. 10[75] shows that, according to the HIMAC experience, such a range is sufficient to treat 70% of the Head and Neck tumours, 65% of the brain, esophagus and lung tumours, 55% of liver tumours but only a very small fraction of bone and soft tissue sarcomas, prostate, uterus and rectum tumours.

To reach a depth of more than 30 cm of water TERA has proposed to add, for an investment of about 10 M€, a linear carbon ion accelerator *CABOTO* (CA*rbon* BO*oster* for T*herapy* in O*ncology*) to the IBA/LNS cyclotron.

The linac, shown in Fig. 9, stays in the corridor of the proton magnetic transport channel and brings in 22 metres the carbon ions extracted from the cyclotron from 300 MeV/u to 435 MeV/u, which corresponds to a range in water of 31 cm.

Each of the 16 modules runs at 3 GHz, and is very similar

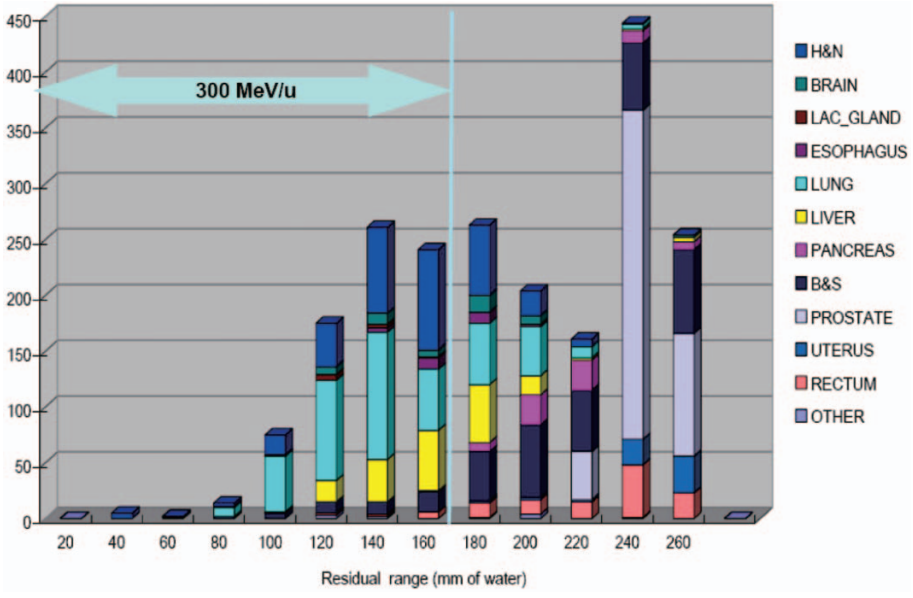

Fig. 10. On the vertical axist he number of patients is plotted while the horizontal axis represents the water equivalent depth of the maximum range used for each patient. The about 2000 HIMAC patients had the tumours indicated in the inset.[75]

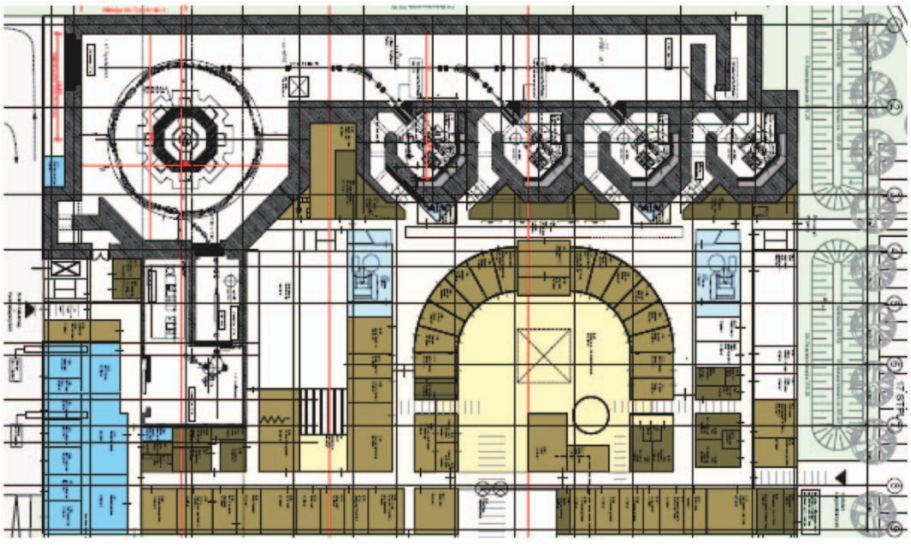

Fig. 11. The design of the Marburg facility is based on an extended study of the clinical workflow. Three treatment areas with a horizontal beam line and one with a 45° oblique beam will be used in an optimal way to shorten the treatment time for the patient (Rhön-Klinikum-AG and Brenner and partners architects).[77)]

to the prototype constructed by a collaboration of TERA with CERN and INFN that accelerated protons from 62 to 74 MeV.[76)] The structure adopted is of the Side Coupled Linac (SCL) type. This LIBO (LInac BOoster) together with the cyclotron is a novel accelerator system for hadrontherapy called "cyclinac". The time and intensity structure of a cyclinac is better suited to the active dose distribution approach, called "spot scanning" and developed at PSI[27)], than those produced by cyclotrons and synchrotrons. In fact, the carbon 'spots' are delivered at a rate of 400 Hz and, before delivering each one of them, in less than 2 milliseconds the number of ions can be chosen and the 3D position in space can be adjusted at will (transversely and in depth) on a $(20\ \mathrm{cm})^2$ area.

A cyclinac is also intended to be the heart of IDRA, the "Institute for Diagnostic and RAdiotherapy", which is a multipurpose facility for the production of both radiopharmaceuticals for diagnostic and therapy, and high-energy protons for therapy.

Going back to dual centres based on synchrotrons, in January 2006 contracts for a completely privately financed carbon/proton centre were signed by the Rhön-Klinikum-AG, which owns more than 40 German hospitals, including the Giessen-Marburg University clinics, and Siemens Medical Solutions, Division for Particle Therapy.[77)]

The Marburg facility, shown in Fig. 11, is designed for the treatment of 2000 patient a year and aims for a good patient comfort and low treatment costs, below 20000 € per patient, which is the same goal of short and efficient treatment times. To this end the workflow has been optimized. The patients will be immobilized outside the treatment caves and computer controlled Robots will position the patient in front of the beam. Possible misalignments will be detected with fluoroscopy and corrected by the robot system.

The Rhoen Klinikum has specialized in the application of high technology like computer guided heart surgery and high technology diagnostics. Therefore it is expected that the Marburg ion therapy will be a great progress towards the general application of this therapy to all the patients who deserve it.

When it starts to operate in 2010, the Marburg Heavy Ion Therapy will demonstrate that in Europe hadrontherapy with ion beams has left the research area and arrived in the clinical environment.

CONCLUSION

In conclusion, the recent strong interest of industrial companies in ion therapy indicates the large potential of this strategy for fighting cancer that has its roots in the instruments developed for fundamental research in subatomic physics. Europe has increasingly contributed to its development and the outlook is positive: in a few years it will host many hospital-based centres for the treatment of tumours which require the special efficacy of large RBE radiations and will have in place a coordinated network for common activities and exchanges.

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