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Radiotherapy with beams of carbon ions

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Abstract

In cancer treatment, the introduction of MeV bremsstrahlung photons has been instrumental in delivering higher doses to deep-seated tumours, while reducing the doses absorbed by the surrounding healthy tissues. Beams of protons and carbon ions have a much more favourable dose-depth distribution than photons (called 'x-rays' by medical doctors) and are the new frontiers of cancer radiation therapy. Section 2 presents the status of the first form of hadrontherapy which uses beams of 200–250 MeV protons. The central part of this review is devoted to the discussion of the physical, radiobiological and clinical bases of the use of 400 MeV u^{-1} carbon ions in the treatment of radio-resistant tumours. These resist irradiation with photon as well as proton beams. The following section describes the carbon ion facilities that are either running or under construction. Finally, the projects recently approved or proposed are reviewed here.

(Some figures in this article are in colour only in the electronic version)

Contents

		Page
1.	Radiotherapy developments: from x-rays to hadrontherapy	1863
2.	Status of protontherapy	1865
3.	Advantages of carbon ion beams	1866
4.	Clinical results and number of potential patients	1872
5.	Facilities treating patients with beams of carbon ions	1874
6.	Carbon ion facilities under construction	1875
7.	Planned facilities for carbon ions and ENLIGHT	1878
	Acknowledgment	1879
	Appendix. List of the main acronyms used in the text	1879
	References	1880

1. Radiotherapy developments: from x-rays to hadrontherapy

The driving force in the more than hundred-year history of conventional radiotherapy was the search for higher precision and greater biological effectiveness of the applied dose. The former could be reached by increasing the energy of the photons yielding a shallow decay of the dose in depth (figure 1) and a smaller lateral scattering. The higher effectiveness was tested by the additional application of hyperbaric oxygen, heat or drugs as radiation sensitizers. But there was no breakthrough in sensitizing tumour cells, combined with acceptable side effects in normal tissues. Finally, it was the higher physical precision that contributed to the elevated tumour control rate in conventional radiotherapy with x-rays and, in about 10% of the patients, with electron beams. The recent transition from electromagnetic radiation to hadron beams is very much in line with the historical development of radiation therapy.

In the developed countries, every year about 20 000 oncological patients, out of 10 million inhabitants, are treated with high-energy photons. As sources of radiation, radiotherapists use electron linear accelerators (linacs) which are 1–1.5 m long. About 8000 such accelerators are used worldwide to treat patients. As shown in figure 1, the absorbed dose owing to a beam of MeV photons (usually called 'x-rays' by medical doctors) has a roughly exponential absorption in matter after an initial increase. The maximum, for beams having a maximum energy of 8 MeV, is reached at a depth of 2–3 cm of soft tissue. At a depth of 25 cm the dose is about one-third of the maximum.

To increase the dose to the tumour—and thus the tumour control rate—it is essential to 'conform' the dose to the target. In order to selectively irradiate deep-seated tumours, radiotherapists use multiple beams usually pointing towards the geometrical centre of the target (cross-fire technique). These irradiation techniques are applied by having the structure containing the linac rotate around a horizontal axis (gantry). The most recent *intensity modulated radio-therapy* (IMRT) makes use of 6–10 entrance ports. The beams may be non-coplanar and their intensity is varied across the irradiation field by means of variable collimators ('multi-leaf collimators') that are computer controlled.

Hadrontherapy is a radiotherapy technique that uses 'hadrons', i.e. collimated beams of compound particles made of quarks. 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. Because of 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). (For a given biological effect, the RBE is defined as the ratio between the cobalt-60 gamma absorbed dose, which is needed to produce the wanted effect, and the dose of the radiation under study.) In the clinical trials, neutrons produced a greater tumour-control rate especially for radio-resistant tumours [1]. But because of the poor depth-dose distribution (figure 1), the biologically high effective dose was also large for the normal tissue outside of the target volume leading to severe side effects. Therefore, in the last few years most countries have terminated neutron therapies.

The next big hopes were the negative-pion beams which produced an additional boost of dose at the end of the pion's range. There the negative pions were captured by the target nuclei and released additional energy. Although, the dose improvement at the end of the range could be confirmed in 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 [2]. Today, the proposed use of antiprotons represents, in many respects, a revival of the basic ideas of pion treatment, but considering the cost and the complication involved, its advantages with respect to the multiple charged ions discussed in this paper are by far not obvious.

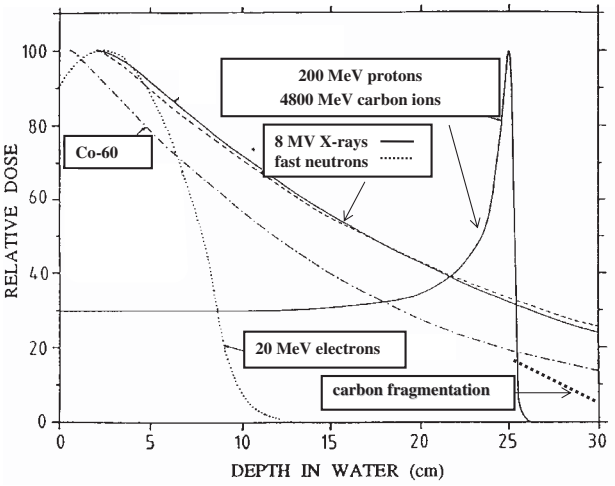

Figure 1. Depth dependence of the deposited dose for different radiations. Because of the Bragg peak it is said that the dose distribution is 'inverted' with respect to the almost exponential, and much less favourable, behaviour produced by a beam of high-energy photons.

The clinical use of protons and carbon ion beams was first proposed by R Wilson [3], who measured in 1946 at the Berkeley Cyclotron, depth profiles with a significant increase in dose at the end of the particle range, the so-called Bragg peak (figure 1), which had been measured fifty years before in the tracks of alpha particles by W Bragg.

In 1954, the first patient was treated at Berkeley with protons, followed by helium treatment in 1957 and neon ions in 1975 [4]. 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 characteristic, i.e. the electric charge, which makes their beams easy to detect and to control by means of magnetic fields. This was also because of the fact that, in those early times, the computer power available was too poor for a control system of an active beam scanning as described below.

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 20 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 m. Till now only synchrotrons are used to produce carbon ions of about 400 MeV per nucleon (400 MeV u^{-1}). In fact, their magnetic rigidity of approximately 6 Tm is about three times larger than the one of 200 MeV protons so that about 20 m diameter synchrotrons are needed when fields in the range 1.5–2 T are used.

For mono-energetic charged hadrons, the Bragg peak of figure 1 is very narrow so that the energy of the particles has to be changed during the irradiation to produce a *spread-out Bragg peak* (SOBP), and thus cover the tumour depth. In cyclotrons, the beam energy cannot be varied so that some movable energy absorbers and a magnetic selection system have to be used to adapt the range of the particles to the depth of the target to be irradiated. However, in synchrotrons the energy of the extracted beam can be varied at will, which is an essential advantage for conformal treatment.

Relatively simple 'passive spreading systems' have been used in all hadrontherapy centres till 1997. In this approach, a first 'scatterer' widens the pencil beam; their energy is adapted to the distal form of the tumour by using appropriate absorbers. Downstream of the scatterer,

the transverse form of the irradiation field is defined by collimators. A complete description of all passive methods is given by Chu *et al* in [5]. Only in 1997, at GSI [6] and PSI [7], the novel 'active spreading systems' have been developed where the charged hadrons are magnetically guided over the treatment area and modulated in intensity (*intensity modulated particle therapy* = IMPT).

2. Status of protontherapy

Most existing particle therapies use protons delivered in fixed horizontal beam lines combined with passive scattering systems. In the competition for a better dose conformity, the IMRT with photons reached the same quality as horizontal passive modulated proton beams. Consequently, the protontherapy centres of recent conception feature isocentric 'gantries' to improve the conformity of the treatment avoiding the healthy tissues. In this way, radiotherapists have the option of rotating the direction of the therapeutic proton beam around the patient just as they do for x-ray treatments. For conventional therapy with x-rays, the gantries have two tasks: to distribute the unwanted entrance dose over a larger volume and to enable the use of the best entrance channels. For the use of the inverted ion dose profiles, only the second point of an optimal entrance remains valid.

The magnetic rigidity of 200 MeV protons is such that a standard magnetic channel capable of doing so has a typical total radius of 4–5 m. For this reason, fixed (mainly horizontal) proton beams have been used worldwide till 1992, when the first hospital-based centre became operational at the Loma Linda Medical Centre (California). As shown in table 1, the new proton facilities usually have more *gantries*, which are large and heavy mechanical structures and which rotate around a horizontal axis supporting bending magnets and quadrupoles.

Since good review articles on protontherapy have been written by Pedroni *et al* [8] and Goitein *et al* [9], here we limit ourselves to commenting briefly on table 1 that lists the proton centres and the corresponding numbers of treated patients.

Most of the 40 000 patients have been treated with proton beams, produced by accelerators built for nuclear and sub-nuclear physics. Since the turn of the century things have changed. Now, five commercial companies offer turnkey centres of proton therapy featuring isocentric 'gantries' (two based on cyclotrons and three on synchrotrons): ACCEL [11], IBA [12], Hitachi [13], Mitsubishi [14] and Optivus [15].

These are 'hospital-based' centres in the sense that they have more than one irradiation room devoted to hadrontherapy of deep-seated tumours and are run in strict connection with one or more hospitals. Typically, in such a centre between 15 000 and 25 000 irradiation sessions (lasting 20–30 min each) are held every year. Since an average proton treatment needs 20–25 sessions, a typical centre will provide protontherapy to 1000 patients and more every year.

At the end of 2004, there were *three* dedicated hospital-based centres for deep protontherapy in the United States and *four* in Japan. In USA, the second hospital centre (NPTC) is located close to the Massachusetts General Hospital (Boston) and the third one is the Midwest Proton Radiotherapy in Bloomington (Indiana).

The centres under construction are in Houston (Texas)—where the Hitachi medical synchrotron has been selected by the MD Anderson Cancer Center—and in Gainesville (Florida)—where the Universty of Florida Shands Medical Centre has chosen the IBA Cyclone 230.

In Europe, the Paul Scherrer Institute launched a new project (PROSCAN) at the end of the year 2000. The proton beam, from the superconducting cyclotron produced by ACCEL, serves both the existing eccentric gantry and a new isocentric gantry and, to actively distribute the dose, an improved version of the PSI spot scanning technique will be implemented [7]. The Rinecker Proton Therapy Centre in Munich (Germany) has selected the same accelerator.

Table 1. Number of patients irradiated with protons by January 2005 [10].

Centre	Start	Stop	Acc.[a]	Beam(s)	Max. en. (eV)	Total (pts)	Date of total
LBL, Berkeley (USA)	1954	1957	S	Horiz.	230	30	
GWI, Uppsala (Sweden)	1957	1976	C	Horiz.	185	73	
HCL, Cambridge (USA)	1961	2002	C	Horiz.	160	9 116	
JINR, Dubna (Russia)	1967	1996	S	Horiz.	200	124	
ITEP, Moscow (Russia)	1969		S	Horiz.	200	3 785	Dec. 04
LINPh, St. Petersburgh (Russia)	1975		SC	Horiz.	250	1 145	April 04
NIRS, Chiba (Japan)	1979		C	Horiz.	70–90	145	April 02
PMRC(1), Tsukuba (Japan)	1983	2000	S	Vert.	250	700	
PSI-72, Villigen (Switzerland)	1984		C	Horiz.	72	4 182	Dec. 04
TSL, Uppsala (Sweden)	1989		C	Horiz.	200	418	Jan. 04
Douglas, Clatterbridge (UK)	1989		C	Horiz.	62	1 372	Dec. 04
LLUMC, Loma Linda (USA)	1990		S	H + 3 gantr.	250	9 585	Nov. 04
UCL, Louvain (Belgium)	1991	1993	C	Horiz.	90	21	
CAL, Nice (France)	1991		C	Horiz.	65	2 555	April 04
CPO, Orsay (France)	1991		SC	Horiz.	200	2 805	Dec. 03
iThemba LABS (South Afr.)	1993		C	Horiz.	200	468	Nov. 04
MPRI(1), Indiana (USA)	1993	1999	C	Horiz.	200	34	
UC Davis, Calif. (USA)	1994		C	Horiz.	200	632	June 04
TRIUMF (Canada)	1995		C	Horiz.	70	89	Dec. 03
PSI-200, Villigen (Switzerland)	1996		C	Horiz.	250	209	Dec. 04
HMI, Berlin (Germany)	1998		C	Horiz.	65	546	Dec. 04
NCC, Kashiwa (Japan)	1998		C	H. + 2 gantr.	230	300	Oct. 04
HIMBC, Hyogo (Japan)	2001		S	H. + 2 gantr.	250	483	June 04
PMRC(2), Tsukuba (Japan)	2001		S	H. + 2 gantr.	250	492	Dec. 04
NPTC, MGH Boston (USA)	2001		C	H. + 2 gantr.	230	973	Dec. 04
INFN-LNS, Catania (Italy)	2002		C	Horiz.	62	82	Oct. 04
WERC, Wasaka Bay (Japan)	2002		S	H. + V.	200	19	Oct. 04
SHIZUOKA (Japan)	2003		S	H. + 2 gantr.	235	100	Dec. 04
MPRI(2), Indiana (USA)	2004		C	H. + 2 gantr.	200	21	July 04
WANJIE, Zibo (China)	2004		C	H. + 3 gantr.	230	01	Dec. 04
Total						40 801	

[a] C = cyclotron, S = synchrotron, SC = synchrocyclotron.

In this centre, to be completed in 2005, the ACCEL cyclotron serves four gantries and a horizontal beam [16].

Three centres based on the IBA cyclotron were being built in the East, two of them in China and one at the National Cancer Center in Seoul [17]. The Chinese locations are the Wanjie Tumor Hospital in Zibo, opened at the end of 2004, and the Sino–Japanese Friendship Hospital in Beijing [18].

The last entries of table 1 justify the statement that protontherapy is booming and will continue to spread as one can expect that in the medium term for every 10 million inhabitants 1000–2000 patients will be treated with proton beams that have almost the same biological effectiveness (RBE) as x-rays but, because of the Bragg peak, always give a smaller dose to the healthy tissues surrounding the tumour and thus cause less adverse effects.

3. Advantages of carbon ion beams

In the rest of this paper, we concentrate on the therapy with ion beams and, in particular, of carbon ions stripped of all their electrons. Unfortunately in 1992, the Berkeley programme, which was successfully going on for twenty years at the Bevalac, was discontinued. Since

then, the only two places where patients have been treated with beams of carbon ions are the GSI Laboratory at Darmstadt (till the end of 2004, more than 250 patients were irradiated with an 'active' spreading system of IMPT) [6] and the Japanese Centre HIMAC (Heavy Ion Medical Accelerator Centre) [19] in the Prefecture of Chiba in Japan (more than 2000 patients were treated with a 'passive' spreading system). A second Japanese centre went into operation in 2002 in Hyogo [20] and two centres are under construction in Europe: one in Heidelberg (Germany) and the other in Pave (Italy). They are described in the next section together with other recent developments.

Carbon ions are advantageous in radiotherapy because of *four* physical and biological properties:

1. Carbon ions deposit their maximum energy density in the Bragg peak at the end of their range, where they can produce severe damage to the cells while sparing both the transversely adjacent and deeper located healthy tissues.
2. Beams of carbon ions can easily be formed as narrow focused and scanning pencil beams of variable penetration depth, so that any part of a tumour can be accurately irradiated with optimal precision. They penetrate the patient with minor lateral scattering and longitudinal straggling. Indeed, lateral and longitudinal scattering is about 3 times smaller than for protons. Being charged, they can easily be formed as narrow focused and scanning pencil beams of variable penetration depth, so that any part of a tumour can be accurately irradiated with optimal precision.
3. Carbon beams have a favourable depth profile of the RBE. This is the main advantage with respect to protons: at high energies, in the entrance channel mostly repairable damages are produced, corresponding to low RBE values, while in the last 2–3 cm of the range the RBE significantly increases to values between 2 and 5, depending on the type of tumour. Moreover very radio-resistant tumours show the largest increase in RBE.
4. The location where the dose is deposited by carbon ions can be determined by means of on-line positron emission tomography (PET). The on-line PET control permits exploitation of the millimetre precision of a focused carbon beam, with its high biological effectiveness for targets that are close to or inside a critical structure, such as optical nerves and spinal cord.

As far as point (1) is concerned, there is no essential advantage of heavier ions like carbon over protons in the irradiation of homogeneous tissues. However, in the case of non-homogenieties, the larger lateral scattering of protons—point (2)—is converted into large dose spikes at the transition from low to high density. On the other hand, the fragmentation of the carbon ions produces a 'tail' in the dose distribution after the distal drop of the Bragg peak (figure 1) and implies an irradiation of the immediately downstream tissues with a dose that is 10–20% of the plateau value in the SOBP.

For ions the global dose delivered must take into account the biological effectiveness mentioned under point (3). This delicate subject is discussed in the rest of this section.

Towards the end of the range the single track *linear energy transfer* (LET, equivalent to the energy loss $\mathrm{d}E/\mathrm{d}x$ and measured usually in $\mathrm{keV}\,\mu\mathrm{m}^{-1}$) reaches a maximum value. In ion–atom collisions 80% of this energy is transferred to target electrons that are emitted preferentially with low kinetic energy, forming an 'electron cloud' around the trajectory of the primary ion, i.e. the ion track. Radiobiological effects are produced mostly by electrons. It is the higher electron-density, and consequently the ionization-density, that yields a greater biological effectiveness.

The main target of the radiation attack is the DNA inside the cell nucleus. DNA is a very complex system and its integrity is essential for cell survival. Therefore, the DNA is

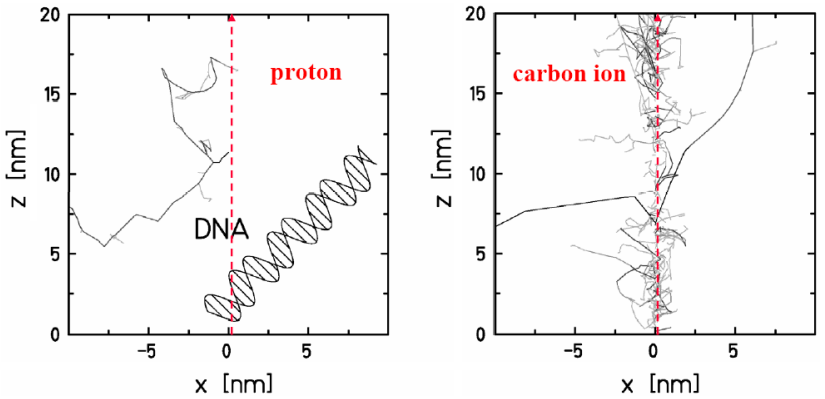

Figure 2. The structure of a proton and a carbon track in nanometre resolution are compared with a schematic representation of a DNA molecule. The higher density of the secondary electrons, produced by carbon ions, creates a large amount of clustered DNA damage.

highly protected by an extremely elaborate repair system so that DNA violations, like single or double strand breaks, are rapidly restored. But when DNA is exposed to very high local doses—where local refers to the scale of a few nanometres as shown in figure 2—the DNA lesions become concentrated or clustered and the repair system fails to correct the damage. In this case, the dose is more effective compared with sparsely ionizing radiation and the RBE is larger than 1.

It has been shown, for carbon beams, that the location of elevated RBE coincides with the Bragg maximum. In particular, for many cells and many biological reactions, the RBE becomes definitely larger than 1 (i.e. these ions are much more effective than photons or protons) when the LET becomes greater than about 20 keV μm^{-1}, i.e. in the last 40 mm of a carbon track in water or in biological tissue. While in the initial part of an approximately 20 cm range in matter (what is called by radiotherapists 'the entrance channel'), the LET is smaller than 15 keV μm^{-1} and the ionization density produces mostly repairable damage. The reason why a LET of 20 keV μm^{-1} is so discriminating can be *very qualitatively* understood as in a few nanometre thickness of a fibre, a few nanometres thick, made of a DNA helix and the water molecules that surround it, 20 keV μm^{-1} corresponds to an *average* energy deposition of 100–200 eV that causes, on average, the production of a dense cluster of 4–5 ionizations.

The LET values of light ions are summarized in table 2 for the range corresponding to 200 MeV protons (262 mm of water). One can see that the LET of carbon ions is larger than 20 keV μm^{-1} in the last 40 mm of their range in water, while for helium this only happens in the last millimetre. For protons, the range of elevated effectiveness is restricted to a few micrometres at the end of the range—too small to have a significant clinical impact. For ions heavier than carbon the range of elevated RBE starts too early and extends to the normal tissues located before the tumour. After the work done at Berkeley with neon and helium ions, in the beginning of the 1990s, carbon ions were chosen as optimal for the therapy of deep-seated tumours as the increased biological effectiveness, owing to the variation of the LET along the track, could be restricted mainly to the target volume [21].

The RBE depends upon the position along the single-track Bragg peak and thus also along a SOBP, as shown by the *in vitro* measurements reproduced in figure 3. To obtain a flat 'biological' dose along the peak, it is necessary to have a non-uniform distribution of the 'physical dose', as shown in the left panel of figure 3.

The RBE effects are the combination of a physical effect, the ionization density, and of a biological phenomenon, the DNA repair capacity of the cell. Because of the high effectiveness

Table 2. The energies of column 2 correspond to a range of 26.2 cm in water. The other columns give LET values at different residual ranges.

Charged particle $^{M}N^{Z}$	E (MeV u^{-1}) Range = 262 mm	LET (keV μm^{-1}) at various residual ranges in water (mm)				
		262	150	70	30	1
$^{1}H^{+1}$	200.0	0.5	0.6	0.8	1.1	4.8
$^{4}He^{+2}$	202.0	1.8	2.2	3.1	4.4	20.0
$^{7}Li^{+3}$	234.3	3.7	4.6	6.2	8.9	40.0
$^{11}B^{+5}$	329.5	8.5	10.0	13.5	19.0	87.5
$^{12}C^{+6}$	390.7	11.0	13.5	17.5	24.5	112.0
$^{14}N^{+7}$	430.5	14.5	17.5	22.5	31.5	142.0
$^{12}O^{+8}$	468.0	18.0	21.5	28.0	39.0	175.0

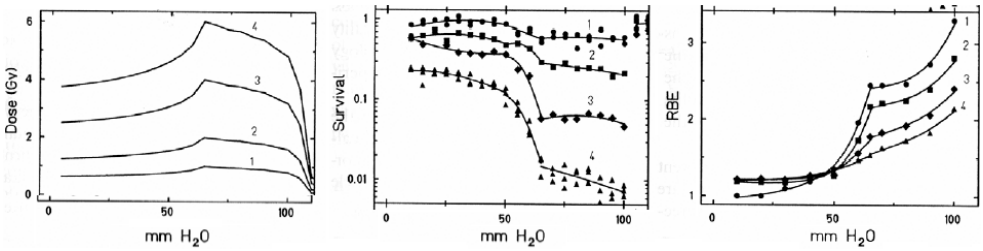

Figure 3. Comparison of the physical absorbed dose (left panel) and measured cell survival of CHO cells (central panel) in an SOBP for various doses. RBE values calculated from the measured cell survival are shown in the right panel. The dose has to decrease at the distal part in order to achieve a homogeneous biological effect over the simulated tumour [22].

to suppress the repair, ion beams are most suited to slow growing and good repairing and, therefore, which tumours are *radio-resistant* to photons or protons. There, the biological effect, i.e. the killing of tumour cells, is increased 3–5 times as compared with conventional radiation.

For a quantitative calculation of the RBE effects, a theoretical model, the local effect model (LEM) has been developed at GSI [23, 24]. It allows the optimization of the treatment planning according to biological parameters and is based on measurable parameters such as the track structure, the size of the cell nucleus and the x-ray sensitivity of the tissue. In the calculation, a number of tracks are spread over the cell according to the required dose. Then, for small compartments of the cell nucleus, the local dose produced by these tracks is calculated. According to this local dose, the probability of the induction of a lethal lesion is obtained from the measured x-ray dose effect curve. This value is then weighed with the size of the local compartments in comparison with the total size of the cell nucleus. Finally, these contributions are integrated over the whole cell nucleus, yielding the induction probability for the inhomogeneous distribution of dose given by the carbon ions that traverse the nucleus. The most important physical parameter of LEM is the radial dose distribution inside a particle track, varying with the energy and LET. On the biological side, the repair capability of the cell is expressed through the ratio of the α coefficient of the linear dose term to the β coefficient of the quadratic dose term of the x-ray dose effect curve, usually written in the following form:

$$\ln(\text{fraction of surviving cells}) = \alpha D + \beta D^2.$$

In figure 4, the most advanced photon treatment plan using IMRT with 9 fields is shown. This is compared with a two-field carbon treatment plan using IMPT and the treatment planning system is based on LEM [24]. In the LEM approach, the point-by-point RBE of the tumour to be treated (and of the healthy tissues to be avoided) is not derived from *in vitro* data, but

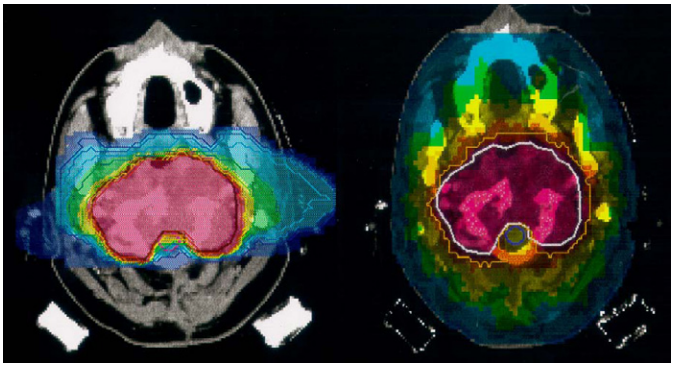

Figure 4. Comparison of treatment plans with 2 fields of carbon ion (IMPT—left panel) and with 9 fields of x-rays (IMRT—right panel) [23]. In both cases the conformity to the target volume is good but for carbon ions the dose to the normal tissues is much smaller.

can be determined from the intrinsic repair capacity as given by the parameters α and β of the dose response curve of the same tissue to the photons. The very successful experience of more than two hundred patients treated till now at GSI with this treatment planning fully confirms the basic rationale of these calculations.

The IMPT plan of figure 2 has been obtained by making use of the properties mentioned under points (1), (2) and (3). In this case, and in most others, the advantage of an inverse dose profile, with the high dose and high LET at the end of the range (figure 1), allows reducing the dose to the normal tissues outside the target volume by a factor of 2–3. This applies also to protons, yet carbon ions are more effective for radio-resistant tumours. These types of tumours are thus the elective targets in a carbon ion facility, while protontherapy is well adapted to other cases in which a tumour is close to the organs at risk that cannot be irradiated. These arguments are important since a protontherapy facility is about 30% cheaper than a carbon ion centre, which requires a total investment cost of about 100 M€.

How is IMPT implemented in practice? The inverse dose distribution of particles having a well defined range allows division of the target volume into slices of equal particle energy and treatment of each slice separately by moving the beam in a raster-like pattern over the area where the raster pattern is sub-divided into small volumes called voxels. The necessary particle fluence for each voxel is calculated before the treatment and the beam in it moved from one position to the next when this number of particles is reached. 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. three-dimensional pixels), which are treated in 2–6 min. 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, in which the third dimension is scanned by moving the patient's bed), as described in [6, 7]. All the newly built hadrontherapy facilities will have the possibility of treating patients with active three-dimensional scanning systems.

Scanning allows treating any irregular shaped tumour with a precision given by half the width of the beam. In figure 5 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.

A last advantage—point (4)—of particle beams, and especially of ions like carbon, is the '*in situ*' production of positron emitters like carbons 10 and 11 and oxygen 15. Because

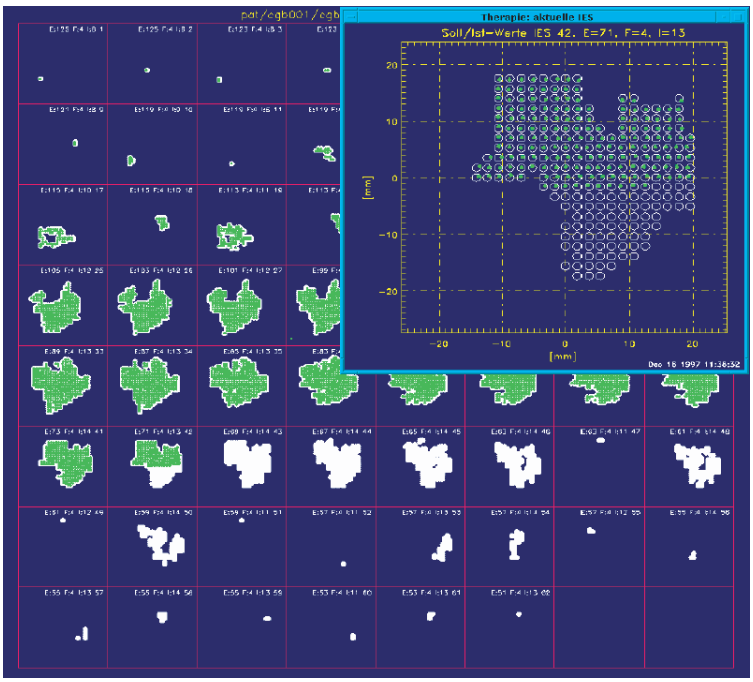

Figure 5. Iso-energy slices of a tumour treated at GSI with carbon ions. In each panel one slice is shown out of 62. In the magnified panel, the circles are the planned target positions; the green point represents the measured positions of the centre of the beam. But the beam diameter is larger than the circles and overlaps many positions, yielding a homogeneous dose distribution.

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 (figure 6). Tobias [25] proposed this technique in the early 1970s at LBL. The technical realization at the GSI pilot project is due to Enghardt [26] of FZR Dresden.

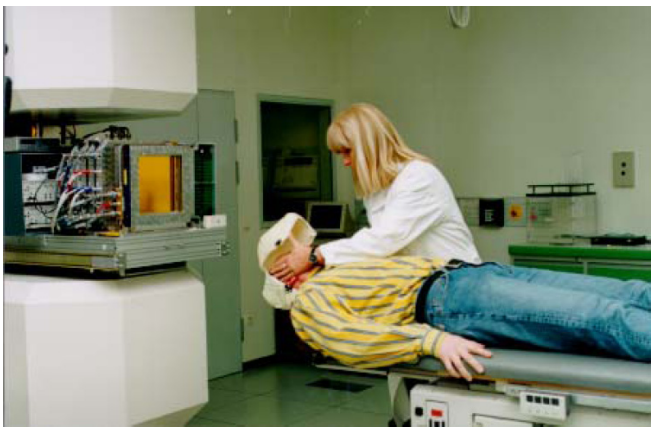

Figure 6. The GSI horizontal beam has been used to treat mainly intracranial and head and neck tumours. The two white boxes, placed above and below the patient, contain the detectors for the on-line PET determination of the dose distribution.

Many patients have to undergo surgery before radiation treatment leaving operation holes, so called vacuoles, in the irradiated area. The range of the carbon ions changes because of liquid and mucus accumulating in these vacuoles. Then the PET control indicates whether the treatment planning has to be done again because of substantial geometrical alterations. In addition, PET control gives—for the first time in 110 years of radiotherapy—an '*in situ*' control of the treated field that also checks all the calculations and calibrations of the energy losses used for treatment planning. The iterative procedure of the range measurements and the CT calibration for the planning procedure and the control via PET monitoring yields the final millimetre precision of the carbon treatment. In principle, it is also possible to perform a PET analysis for the range distribution in proton treatment by using the oxygen 15 isotopes produced when neutrons are removed from the oxygen nuclei contained in the irradiated tissue. However, to date, the proton community is just starting to develop such a tool to control the precision of proton irradiations [27].

4. Clinical results and number of potential patients

In a conventional treatment with x-rays, a total dose of 60–70 Gy (1 Gy $= 1\,\mathrm{J\,kg^{-1}}$) is deposited in a tumour target in typically 30 sessions to give time for re-oxygenation of hypoxic—and, therefore, radio-resistant tumour cells and for the transition of tumour cells from radio-resistant cell cycle stages to more sensitive stages. In addition, the unavoidably irradiated healthy cells have a chance to repair the radiation damage. In fact, because of the non-optimal dose distribution of x-rays, a large amount of healthy tissues are unnecessarily irradiated, especially when large tumours are treated through many ports.

In conventional radiotherapy, the doses given to the healthy tissues are the real limiting factor. The recent introduction of IMRT increases the doses given to the healthy tissues but distributes it over a large volume and thus allows an increased dose to the tumour targets. This is very beneficial because even a modest 10% increase of the dose deposited in a tumour gives, typically, an increased probability of about 20% of the local control of the tumour itself. This implies that passing from 60 to 66 Gy, for instance, the control probability increases from 50% to 60%, a not negligible gain.

This fact is independent of any clinical trial and is the strongest argument in favour of protontherapy: since proton and x-ray beams produce practically the same biological effects on the irradiated cells, a better spatial distribution is certainly useful to either reduce the side effects or to increase the tumour control probability or to a achieve a balance mixture of the two. It has to be remarked that both proton and x-rays effects are not exactly equal, so that in clinical practice an average RBE value of 1.1 is used for the doses given in a proton SOBP. However, this difference is small and in the proton/x-rays comparison the main issues are the treatment cost—2–3 times larger for protons than for x-rays [28]—and the general availability—limited by the economically driven necessity of building large centres with many rooms served by a single accelerator.

As discussed in the last section, carbon ion treatments are based on a different rationale: better physical conformity *and also* larger biological effectiveness, resulting in better control rates for radio-resistant tumours. In this case, the physical dose has to be locally multiplied by an RBE value that depends upon the tissue and the irradiation conditions. Both radiobiological data and their modelling enter in the RBEs used for healthy and tumour tissues, and their validity has to be confirmed by the clinical results of the irradiations which, by now, refer to almost 2500 patients.

Description of the clinical results of carbon therapy is beyond the scope of this paper. Thus, as far as the Japanese experience is concerned, we refer to a

recent review paper that summarizes the HIMAC results and quote only some of them [29].

Patients with early-stage non small cell lung cancers (NSCLC) that could not be operated have been treated with different dose-fractionation schedules: 18 fractions in 6 weeks, 9 fractions in 3 weeks and 4 fractions in 1 week. For the shortest one the local control rate was 73% at three years. At present, a phase I/II study is in progress by treating these patients with a single dose of 28 GyE delivered through four ports. (Note that the equivalent dose GyE is obtained by multiplying the physical dose—measured in grey—by the local value of the RBE, so that the physical dose is typically about 9 Gy.) Short schedules are also being studied for hepatocellular carcinomas: in the last phase II study the three-year local control rate was 90% using a 4 fraction/1 week regimen. For locally advanced prostate tumours of high risk patients (PSA $> 20\,\mathrm{ng\,ml^{-1}}$), the local control rate at six years was 82%, after a combined treatment with hormones and carbon ion beams (66 GyE in 20 fractions). Finally, with 70 GyE in 16 fractions the local tumour control rate for bone and soft tissue sarcomas—which are very radio-resistant tumours—was 88% after three years and the three-year survival rate was 54%.

Thus, carbon irradiations at Chiba showed that the fractionation schedule can be shortened below 10 fractions and the total dose can be reduced still more, yielding better tumour control than the high dose photon treatment. These improved results are due to the higher carbon-RBE for radio-resistant tissues. This is a typical feature of ions heavier than protons and cannot be mimicked by greater global doses using photons or protons.

At Darmstadt, three-year tumour control rates for chordomas and chondrosarcomas, which were a subsection of the large variety of tumours treated at NIRS, are 100% and 84%, respectively, for a similar tumour dose [30]. These values are significantly better than those reported for conventional radiotherapy, using also an accelerated fractionation scheme of 20 fractions in 20 days.

For details and comparisons of all these results with the clinical outcomes of other types of treatments, we refer to the original references. As far as the number of potential patients is concerned, detailed analyses have been made in Germany [31], Italy [32], Austria [33] and France [34] by groups of radiotherapists who have applied, to the national data, specific criteria for each tumour site. Different approaches are 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 patients receiving conventional radiotherapy at all the twelve Austrian centres. In France, five large radiation therapy departments have been surveyed for 1 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 also too consistent, as quantitatively confirmed by the table of [33] in which the indications of the four groups of radiotherapists are compared site by site. As an overall summary it can be stated that

(i) about 1% of the patients treated today with x-rays should 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.

Overall, 15% of the approximately 20 000 patients treated for every 10 million inhabitants, with conventional radiation would receive a better treatment with hadron beams. This corresponds to about 2500 proton treatments and about 500 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 1500 patients a year in about 30 000 sessions) for every 10 million people and a carbon ion centre for every 50 million people. This is indeed the conclusion reached by the Italian association for radiotherapy and oncology AIRO [32].

As far as costs are concerned, it has been said that a proton treatment costs 2–3 times more than a conventional treatment [28]. The economy of carbon treatment is different. As shown by radiobiological experiments and confirmed by clinical experience, with carbon ions the usual cellular repair mechanisms have little effect so that there is no point in delivering 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 (in Japan down to the limit of a single fraction!) is a great advantage for very effective use of the costly infrastructure and—if confirmed by the ongoing 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.

5. Facilities treating patients with beams of carbon ions

In 1994, the first patient was treated at NIRS in Japan with carbon ions where the construction of HIMAC (Heavy Ion Medical Accelerator in Chiba) was promoted by Y Hirao. As discussed in the previous section, more than 2000 patients have been treated and very promising results have been obtained. At HIMAC, the choice was made not to construct rotating gantries but to have a horizontal and a vertical beam in a single treatment room. The other two rooms feature horizontal beams. Passive spreading systems were used for many years, but in 2003 a simplified active system was implemented called 'layer stacking' [35]. Presently, the introduction of active scanning is in preparation.

In the Centre HIBMC in Hyogo, the first patient was treated with protons in May 2001. This centre, constructed by Mitsubishi Electric, is based on a single linac injector and a 29 m diameter synchrotron for protons and carbon ions. It features three treatment rooms for protons (two of them with gantries) and two rooms for ions featuring a horizontal, a vertical beam and also an inclined beam. By the end of 2004, about 200 patients had been treated with protons and 50 patients with carbon ions [10].

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

In the summer of 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 [6]. With the start of the patient treatment the project leadership turned to the Heidelberg Clinic.

There were four novel features of the GSI pilot project:

(i) the IMPT using the active 'raster' scanning system described above;

(ii) the fully automatic control of the GSI accelerator complex, which can be handled by an operator trained for standard x-ray equipment;

(iii) the sophisticated models and codes that take into account the RBE of different tissues in treatment planning according to the LEM [24].

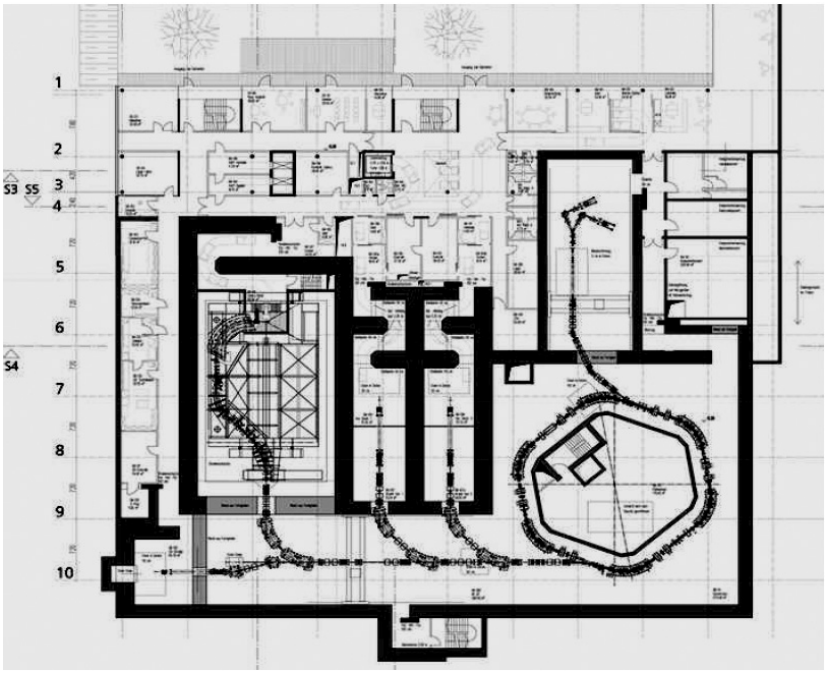

Figure 7. The Heidelberg facility HIT (Heidelberg Ion Centre) features three treatment rooms. One of them hosts a rotating carbon ion gantry of new design. A single 7 MeV u^{-1} linac injects in the synchrotron both protons and carbon ions. The construction status of HIT can be checked by visiting the site www.arge-sit.de.

(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 fragment into β^+ radioactive nuclei [28].

6. Carbon ion facilities under construction

Based on the successes of the pilot project, the Heidelberg Ion Therapy Centre (HIT) was proposed [31] and approved in 2001 (figure 7). The civil engineering work could start in November 2003. The total estimated cost of 78 M€ is shared one-to-one between the Federal Government and a bank loan of the Heidelberg hospital. The first patient treatment should take place at the beginning of 2007.

HIT is a very ambitious project that applies all the techniques and methods developed in the framework of the pilot project and features the first carbon ion gantry, which weighs about 600 tons (figure 8).

HIT is a joint project of the Heidelberg Clinics and GSI in the sense that the responsibility for accelerator is given to GSI. The irradiation system and the medical equipment will be supplied by Siemens Medical Solutions. The construction of the buildings and the operation is with the Heidelberg Clinics.

At the end of 1995 one of us (U Amaldi) with the help of M Regler, drew the interest of the CERN management to the design of an optimized synchrotron for light ion (and proton) therapy. At the beginning of 1996, the study of such a synchrotron was started at CERN under the leadership of P Bryant with the acronym PIMMS (*Proton and Ion Medical Machine Study*).

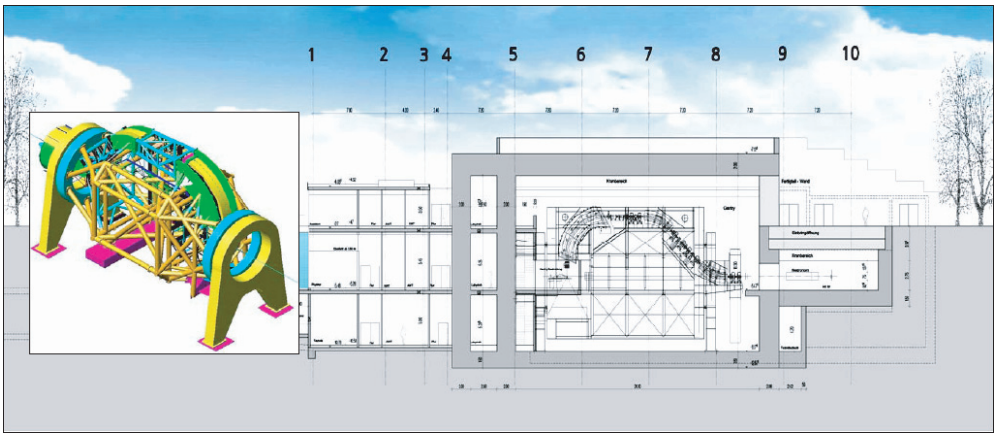

Figure 8. The GSI isocentric gantry for carbon ions. It is about 25 m long and vertically occupies three floors.

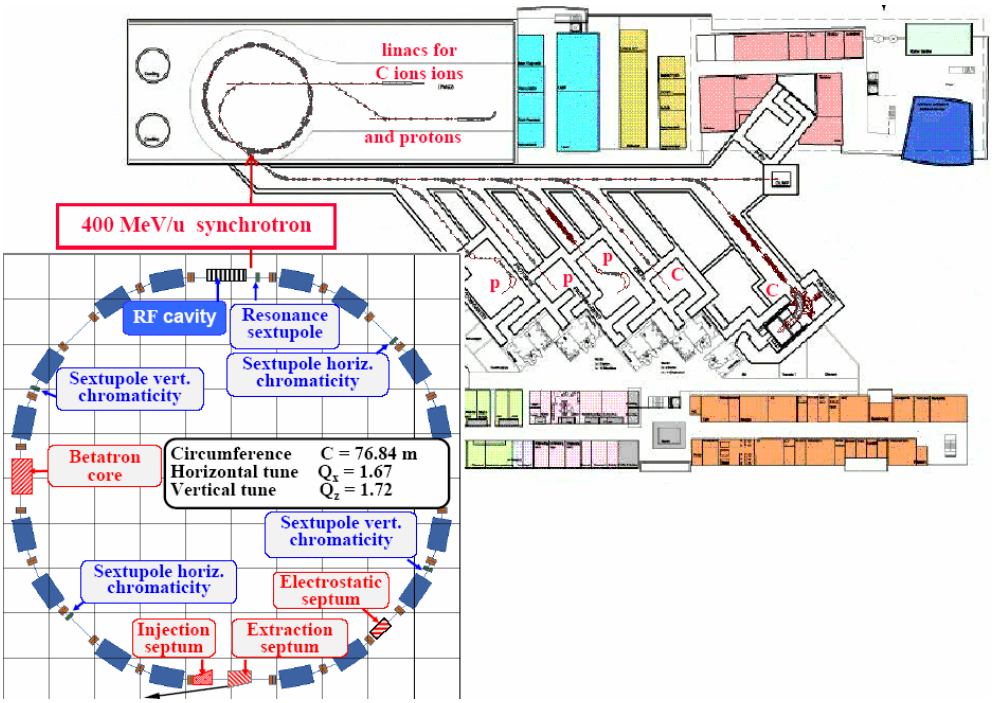

Figure 9. The general layout of the facility designed in the PIMMS [35]. The beam distribution line is long as it has the special feature that various functions are performed by different modules. The covered area is 15 000 m^2.

PIMMS was a collaboration of CERN, Med-AUSTRON (Austria), Oncology 2000 (Czech Republic) and TERA (Italy). GSI contributed and gave an expert's advice.

The study was closed and published at the beginning of the year 2000. The outcome of this four-year study is a complete design that combines many innovative features so as to provide an extracted pencil beam of particles that is very uniform in time, can be varied in energy and adjusted in shape (figure 9). These are pre-requisites for the application of the technique

of IMPT. A short list of the special features of the PIMMS design includes two injector linear accelerators, one for protons (20 MeV) and the other for carbon ions (7 MeV u^{-1}), two dispersion-free zones for injection and RF acceleration, a slow extraction scheme based on a 'betatron core' and 'rotators' to optimize the beam optics of the rotating gantries [36].

The PIMMS group had the mandate of designing the synchrotron and the beam lines of a light ion hadrontherapy centre without any financial and/or space limitation. In fact, PIMMS was not intended to be ever built in its final layout. It was rather an open design study from which different modules could be taken for the design of various centres according to their requirements.

The second European centre is being built in Pavia, a university town located 30 km southwest of Milano. CNAO (the '*Centro Nazionale di Adroterapia Oncologica*') has been designed by TERA, a non-profit foundation created in 1992 and recognized by the Italian Ministry of Health in 1994. Following PIMMS, TERA worked out a design that would be less expensive than PIMMS and still retain the most important features of PIMMS. In the PIMMS/TERA design of figure 10 [37]: (i) the sources are inside the ring and a single 7 MeV u^{-1} injector of the GSI design for HIT is used for all ion species, (ii) a multi-turn injection scheme is adopted, (iii) for extraction both a betatron core (as in PIMMS) and an RF knock-out system (as in HIMAC and HIT) are implemented, (iv) the beam lines are shorter and, thus, less expensive than the ones in PIMMS.

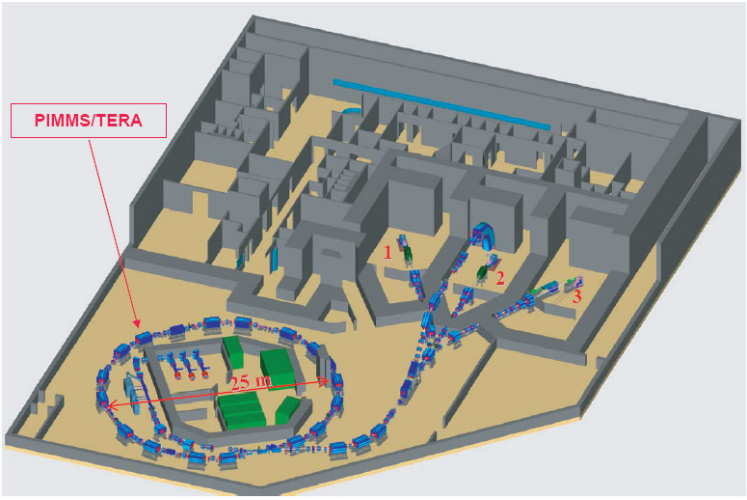

Figure 10. In the PIMMS/TERA design, the sources and the single injector are inside the ring and the beam lines are shorter than in PIMMS, so that the layout is more compact. Three treatment rooms are served by four active spreading systems [36].

In 2001, the Italian Government created the CNAO Foundation which, in the following years, received other funds from the private foundations and the local authorities. The founders of CNAO are, with TERA, the two largest university hospitals in Lombardy (seated in Milano and Pavia), the two largest comprehensive oncological hospitals in Italy are (Istituto Nazionale dei Tumori and European Institute of Oncology, Milano) and the Italian National Neurological Institute (Milano). In September 2003, TERA completed the specifications and the technical drawings of all the components of the high-tech part of the Centre, that have been worked out in collaboration with INFN—in particular the *Laboratori Nazionali di Frascati*—and also CERN and GSI.

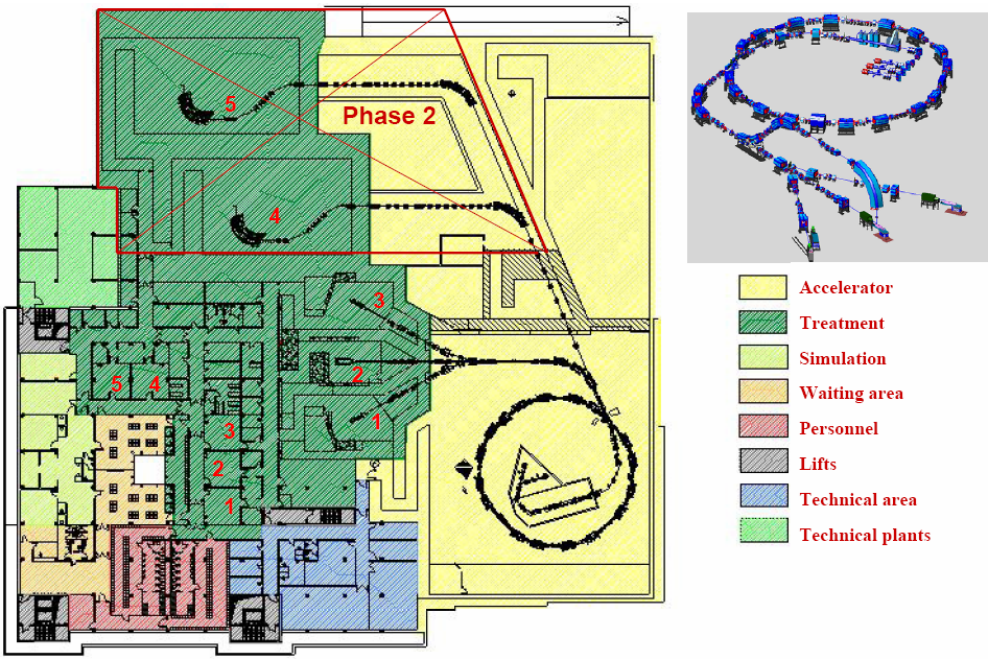

Figure 11. Layout of the CNAO underground bunker. Initially the bunker will not feature the two very large gantry rooms that will be built and equipped with gantries at a later stage.

The CNAO Foundation is in charge of the construction, together with INFN, commissioning and running of the facility. In 2004, the components were ordered and the civil engineering construction was tendered out. CNAO has decided that the layout of figure 10, with three treatment rooms, constitutes phase 1 of the centre, but that in the beginning the underground building will be constructed allowing for the possibility of adding two gantry rooms that will be equipped only in phase 2. The layout of underground floor scheme for the final project is shown in figure 11. The facility is foreseen to be ready by the end of 2007.

7. Planned facilities for carbon ions and ENLIGHT

In this section, we complete the information concerning the possible uses of the PIMMS/TERA design. In the fall of 1998, the University Claude Bernard of Lyon commissioned TERA with drawing up 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 but featured two gantries for ions identical to the GSI one. Following this preliminary study, the Lyon University signed a contract with CEA (Saclay) and IN2P3 of CNRS to produce a report to be presented to the French authorities. The first volume of the ETOILE project [38] is based on the PIMMS/TERA synchrotron. A second volume was issued in 2004, which is centred on the health care and the economic aspects of the Lyon project [39].

In 2003, a similar project was presented to the French Government by the Basse-Normandie Region: ASCLEPIOS was proposed to be built near GANIL, the ion accelerator Centre in Caen [40]. In May 2005 the French government decided that the first national carbon ion centre will be built in Lyon.

The PIMMS/TERA synchrotron is also the heart of the centre proposed by the Karolinska Institute and Hospital, which is described in a paper published in 2001 [41].

In 1998, the Med-Austron team presented to the Austrian authorities the PIMMS project shown in figure 9 [42]. In the following years, a complete study was performed comparing the GSI project for Heidelberg and the PIMMS/TERA design. The proposal, described in a volume issued in 2004 [43], is based on the PIMMS/TERA synchrotron and a modified PIMMS design for the extraction lines. At the end of 2004, the Austrian Government, the State of Lower-Austria and the town of Wiener Neustadt granted a substantial part of the required funding and initiated the creation of the organizational structure to advance the project.

The designs described above are preliminary and will be frozen only after the financial framework for the construction and the running are defined.

The five European projects (sited in Heidelberg, Pavia, Wiener Neustadt, Lyon or Caen and Stockholm) have teamed with ESTRO (the European Society for Therapeutic Radiology and Oncology), EORTC (the European Organization for Research and Treatment of Cancer), CERN and GSI to form the *European Network for Light Ion Hadron Therapy*. In 2002, ENLIGHT was financed for three years by the European Commission. The activities that are going on can be easily guessed from the list of the six working packages:

1. Epidemiology and patient selection.
2. The design and conduct of clinical trials.
3. The preparation, delivery and dosimetry of ion beams.
4. Radiation biology.
5. *In situ* monitoring with PET.
6. Health economic aspects.

The existence of this network, and of its potential follower, guarantees that the future of carbon ion therapy in Europe is on a sound footing and that the foreseen facilities will be run for the benefit of all European patients [44].

Finally, it should be mentioned that the industry has meanwhile shown its interest in the upcoming market of heavy particle therapy. As described above, five companies are selling proton therapy units. In the heavy ion market, Mitsubishi has designed a 'micro HIMAC', a synchrotron for combined proton and carbon therapy, ACCEL and IBA are working on carbon ion superconducting cyclotrons and Siemens Medical Solutions has designed a combined proton–carbon facility on the basis of exclusive licences of the GSI patents and know-how. In 2005, other companies are organizing themselves to get into this promising market. The strong interest of industrial companies in ion therapy indicates the large potential of this novel strategy for combating cancer.

Acknowledgment

UA gratefully acknowledges the generous financial support given to TERA by the Monzino Foundation (Milan).

Appendix. List of the main acronyms used in the text

Bragg peak		Increase of the energy deposition to a maximum value at the end of a charged particle range in matter
CNAO	Centro Nazionale di Adroterapia Oncologica	Foundation created by the Italian government in 2001 to realize the ion therapy centre designed by TERA. The Centre is under construction in Pavia

CT	Computer tomography	From x-ray images taken under different directions, a three-dimensional image of sections of the human body is produced
GSI	Gesellschaft für Schwerionenforschung	German National Laboratory for Heavy Ion Research where patients are treated with carbon ions since 1997
HIMAC	Heavy Ion Medical Accelerator at Chiba	The first centre to treat patients with carbon ions built by the National Institute for Radiological Sciences (NIRS) located in Chiba. First patient: 1994
HIBMC	Hyogo Ion Beam Medical Centre	The second world centre for carbon ion therapy located in Hyogo. The first patient was treated in May 2001
HIT	Heidelberg Ion Therapy Centre	The centre is being built by GSI for the Heidelberg Clinics. HIT is foreseen to treat patients in 2007
IMPT	Intensity Modulated Particle Therapy	Small pencil beams of different energies are guided over a three-dimensional target volume dissected into 'voxels'. By modulating the beam fluence of the different voxels a homogeneous biological effect over the target volume can be reached. Usually 2 ports are sufficient for a conformal treatment
IMRT	Intensity Modulated Radiation Therapy	Photon beams from 5 to 10 different ports are directed to the same target volume in a cross-fire technique. By modulating the intensity of each individual beam by a computer-controlled multi-leaf collimator a good conformity of the irradiated volume can be reached
LEM	Local effect model	By considering the local effects on the cell nucleus, RBE values for an ion irradiation are calculated on the basis of the local dose distribution around the particle tracks and the x-ray response
LET	Linear energy transfer	LET is linear energy transfer to the biological target. This is equal to the local energy loss $\mathrm{d}E/\mathrm{d}x$, if the created electrons do not leave the biological target
MedAustron	Medical facility of the AUSTRON project	Austrian project for the installation of an ion therapy centre at Wiener Neustadt, Austria. MedAustron participated in PIMMS
PIMMS	Proton Ion Medical Machine Study	Study performed at CERN of an optimized synchrotron and beam lines for ion therapy
PET	Positron emission tomography	In conventional PET, the measurement of the annihilation signal of positron emitters injected in the body allows determination of the size of the organs and their functions. In particle therapy, PET is used 'on-line' to trace the positron emitters produced by the primary beam
RBE	Relative biological effectiveness	Ratio of a x-ray dose to a particle dose that produces the same biological effect. For many biological systems $1 < \mathrm{RBE} < 4$
SOBP	Spread out Bragg peak	To treat an extended volume the Bragg maximum of beams of different energies are superimposed yielding a flat dose or a flat biological effect on the target
TERA	TErapia con Radiazioni Adroniche	Italian Foundation for the development of hadrontherapy in Italy and Europe. TERA participated in PIMMS

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