HADRONIC RADIOTHERAPY ACCELERATORS

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RADIOBIOLOGICAL CONSIDERATIONS

The name *hadronic radiotherapy* is now being recommended by accelerator physicists, although it has not become, as yet, generally accepted. Despite the advantages of modern electron linacs, extensive clinical experience with photon therapy has shown that some tumours, called radioresistant, respond poorly to photon therapy, and that sometimes even nonradioresistant tumours cannot be given a tumouricidal dose because of the unavoidable associated dose to neighbouring healthy tissue. Hadronic radiotherapy uses particles such as *neutrons, protons, pions, helium,* or *heavier ions* to treat radioresistant tumors and those located near critical body structures such as the spinal cord. Initial research in hadronic radiotherapy was performed using accelerators built for basic physics research. At present, there are a few hospital-based accelerators built for and dedicated to neutron and proton therapy, but much of the hadron therapy research continues to take place in physics laboratories. In this respect, the development of hadron therapy closely parallels the development of photon therapy. Advances in accelerator technology are making hadron therapy possible, although hadron therapy will not be as ubiquitous as photon therapy in the foreseeable future.

If you compare the depth dose distribution for X-rays, γ-rays and electron beams with the distribution of a proton beam for a deep-seated tumour you can easily see that the proton beam delivers most of its radiation dose at a precisely determined, energy-related point, called the *Bragg peak.*

Heavy charged particles exhibit a completely different interaction mechanism with matter than electromagnetic radiation such as X and gamma rays or bremsstrahlung. Electromagnetic radiation interacts with the target material via the Compton effect, photoeffect and pair production. The primary intensity of the beam decreases exponentially with the penetration depths and the beam does not have a finite range. In addition, the lateral scattering of the primary beam due to Compton scattering and the scattering of the secondary electrons is large.

Swift heavy charged particles when passing through matter, dissipate their energy mainly via interaction with the electrons of the target material. Because of the large difference between the electron mass compared with the mass of the atomic nuclei, the deflection of the projectile ions is very small and only a multiple collision process can cause a net deflection of the particle beam. Due to the reaction kinematics, the mean deflection of these electron collisions becomes even smaller for heavy ions (Kraft, 1990).

In radiobiology, particle beams are often characterized by their *linear-energy-transfer* (LET) distribution. The LET of a particle is defined as the energy expended in creating ion pairs in the medium and is equal to the *restricted* stopping power. The LET for 1-MeV electrons is 0.25 keV/mm. For neutrons produced in the reaction 50 MeV d + Be, the LET distribution ranges from 1.5 to 500 keV/mm, with a peak near 8 keV/mm and 100 keV/mm. Particles with LET values less than 30-50 keV/mm are called low-LET particles, whereas those with larger LET values are categorized as high-LET particles. High-LET particles are more biologically damaging because they cause more directly and indirectly ionizing events per unit track length.

The radiobiological rationale for high-LET radiotherapy is threefold [Kraft, 1990]: (a) Cells cannot repair the more extensive damage incurred by high-LET radiation as easily as they can repair low-LET radiation damage. (b) Tumour cells are often hypoxic, i.e. they lack oxygen because of an inadequate supply of blood to the tumour. Such cells are more responsive to high-LET than to low-LET radiation. This difference in response is due in part to the reduced production of oxidizing radicals under hypoxic conditions for low-LET radiation. (c) For low-LET radiation, cells exhibit varying degrees of radioresponsiveness depending on whether or not they are actively

dividing. Certain cells are resistant to low-LET radiation when they are in the resting phase of the cell cycle. This radioresistance has clinical ramifications in terms of the types of tumours that might be most effectively treated with high-LET hadrons. It is suggested that high-LET particles may be advantageous in treating slowly growing tumours .

Summing up, it can be stated that: (1) protons and light ions easily permit a conformal therapy, which otherwise requires about ten X-ray fields. From this point of view, fast neutrons behave like X-rays. Heavy ions have a 'fragmentation tail' that makes them impractical in therapy, so that light ions, such as carbon or, perhaps, oxygen, are today considered to be optimal, (2) high-LET radiations have a different radiobiological effect which makes them more suitable for radioresistant tumours,(3) neutrons have high-LET values, but are not useful in conformal therapy. Light ions, such as carbon, have again the advantage of physical selectivity and high-LET, being much better therapy tools than pions and neutrons, and (4) among ions, it is only protons that have been used in large enough number of cases.

ACCELERATORS FOR NEUTRON THERAPY

Neutron therapy was the first form of hadron therapy to be used clinically. By 1980, 19 institutions had treated a total of nearly 6,000 patients. By 1987 the total number of patients irradiated with neutrons in about 20 facilities the world over was roughly 10,000; at present (1997) this number is probably over 20,000.

In the USA, more intensive work on neutron therapy was started as early as the 1970s, using cyclotrons and rf linacs intended initially for physics research. The preliminary results proved to be quite promising, so much so that the National Cancer Institute initiated a 10-year research project with the aim of designing clinical facilities and implementing clinical trials as the third stage of the project. In the years 1971-1989, 7 facilities covered by the NCI project were provided with funds totalling $69.5 million (Zink et al, 1989).

Fast-neutron therapy is no longer considered to be experimental. Clinics currently treating an average of about ten patients per day are located at Fermi National Accelerator Laboratory in Batavia, Illinois; the University of Washington in Seattle, Washington; Harper Grace Hospital in Detroit, Michigan; and the National Accelerator Centre in Faure, South Africa [3].

Opinions on the efficacy of neutron therapy vary. From the analysis of the results of therapy on the 10,000 cases of inoperative radioresistant tumours published in (Zink S. et al 1989) it was found that control rates vary from 71% for salivary gland tumours and melanoma to 48% for bladder cancers and 33% for recto-sigmoid cancers. In spite of these quite diverse results, they are probably the best that are achievable at present (Lennox, 1989). Similarly, positive opinions have been recently published in (Russel et al, 1987; Saroja K.R. et al, 1993). The early success of neutron therapy was spoiled by late effects that were so severe that most of neutron trials have now been terminated. However, the question of turning neutron therapy into a routine treatment modality is still open, which is evidenced by the lack of any final conclusions from the many-year long US neutron therapy program (Zink S. et al 1989).

A distinctive feature of the present-day neutron therapy facilities equipped exclusively with cyclotrons is that this therapy is being combined with the production of radionuclides, especially those with short half-lives (Scharf W.H. 1994). Recently, installations have been set up, in which, in addition to production of radionuclides and neutron therapy, proton therapy can also be implemented. The aim of such programs is not only to extend the scope of therapeutic modalities and to combine the various types of treatment, but also to improve beam utilization and the cost-effectiveness of therapy as the treatment costs are still quite high. Recently, clinicians and medical physicists have focused their attention on the method of *Boron-Neutron Capture Therapy*, known as *BNCT method*.

Boron neutron capture therapy is a treatment proposed for deep, inoperable brain tumours (Nakagawa Y.). The principle of BNCT is to selectively destroy cancer cells by loading them with boron compounds and then introducing neutrons to convert the boron nuclei into pairs of short-range ions which deliver their energy within the cancer cell.

The *boron neutron capture therapy* (BNCT) modality consists in saturating the tumour tissue with ^{10}B atoms incorporated into an appropriate pharmaceutical, and then irradiating the tumour with epithermal (to 20 keV) neutrons. Fast neutrons (energy> 100 keV) are too penetrating and cause damage to both normal tissue and tumour cells through ionizing radiation. Thermal neutrons will not penetrate far enough to reach tumours under the surface. Thus, epithermal neutrons energy between

0.025 eV and 20 keV must be used. These moderate energy neutrons are thermalized by hydrogen atoms as they pass through the overlaying tissue. If the ^{10}B concentration in tissue is assumed to be 10 to 100 ppmw, irradiation requires 10^{12} to 10^{13} epithermal neutrons per cm^2, which corresponds to a dose of about 8 Gy.

Statistical data indicate that there are about 11,000 new cases of high grade gliomas in the United States alone (Laramore G.E.). Current BNCT protocols utilize one radiation treatment. However, there is some radiobiological data indicating that it would be advantageous to utilize a small number of fractions rather than a single fraction to allow normal brain tissue to repair damage from the low linear energy transfer (LET) radiation contaminant in the epithermal beam and also to allow tumour cells to redistribute into more sensitive phases of the cell cycle. There is the potential to convert certain nuclear reactors into BNCT treatment centers but as a practical matter, there are probably only about 4-5 reactors in the United States that could be easily modified to produce suitable treatment beams. Assuming that it would be possible to treat approximately 10 patients a week at each of these centers, there would be a throughput of 500-600 patients per year per facility. This would enable 2000-3000 patients to be treated, resulting in a strong demand for new treatment centers.

A sophisticated, dual-energy linear accelerator used in radiotherapy departments costs around $2M and the cost of the treatment room is approximately $500K. This $2.5M investment returns a typical yearly cash flow of approximately $1.25M if it treats a typical "mix" of 30 patients per day. Assuming that the same ratio of cost to cash flow would apply to a nonreactor-based BNCT treatment facility, this would put the acceptable total initial cost for the facility at $20M. The above figure should be considered a conservative number. A greater charge for a BNCT course of treatment would allow for a higher facility cost as would accepting a lower return on capital.
Since the anticipated market in the United States is only 15-20 units, it might be difficult for a company to recoup its research and development costs. It appears that greater potential profit would occur from operating the facility rather than manufacturing the treatment device and therefore, a "franchising approach" might be more tenable with a portion of the profits returning to the manufacturer (Laramore G.E.).

The neutron generation yields significantly increase with the initiating particle energy electrons, protons and deuterons with energies of 10 to 50 MeV (Kushin V.V. et al,). Since the technique of accelerating particles to such high energies is fairly costly, the work on the development of a hospital accelerator for BNCT has now been mostly focused on the application of a beam of protons or deuterons with moderate energies between 2 and 5 MeV.
At the present time there are several competing designs for proton accelerators for epithermal neutron beam production. Perhaps the most advanced work has been done on the Tandem Cascade Accelerator (TCA) design (Yanch J.C. 1993). According to the last report (Shefer R.E. et al), a 4 mA, 4.1 MeV unit has been under construction. The accelerator itself would weigh approximately 900-1000 kg, be approximately 6 m long, and require 25 kW of electrical power to operate. This scale is certainly compatible with installation in a clinical facility. Initial operation of the accelerator was scheduled for Spring, 1995.

Another accelerator design is the radiofrequency quadrupole (RFQ) which is being designed to produce a 2.5 MeV proton beam at 50 mA current (Wang C. et al, 1993). The basic RFQ design is well known since this type of accelerator is frequently used as part of the injector stage for high energy physics research machines. The pre-clinical RFQ linac has been designed for installation in an existing shield room at UCSF (Hamm R.). The 2.5 MeV proton RFQ is capable of producing approximately 10^{12} n/s for target and moderator development, as well as for biological studies with boronated pharmaceuticals. The use of proton linac accelerators (Lennox A.J.) as well as pulse machines (Friedman L. et al) and others have recently been also considered.

PION RADIOTHERAPY ACCELERATORS

The potential for *negative p^- mesons (pions)* for therapy was recognized by FERMI and others soon after the pion capture phenomenon was observed. FOWLER and PERKINS in 1961, were the first formally to propose pions for radiotherapy.

Pions for therapy are produced by protons with energies > 400 MeV striking a beryllium or graphite target. Linacs, cyclotrons, and synchrotrons can be used to accelerate the protons. The pion therapy has the advantage of low-LET dose to healthy tissue in the plateau region upstream from the tumour and high-LET

dose at the end of the beam range in the tumour.

The clinical use of pions was only possible when accelerators became available which produced beams with intensities of the order of 10^8 pion s^{-1}; Higher intensities were achieved in the 1970s with the advent of the high intensity medium energy accelerators called *meson factories* (proton energy 500-1000 MeV, intensities of several hundred μA). Among the best known meson factories are LAMPF (Los Alamos Meson Physics Facility, rf linear proton accelerator with 1 mA beam intensity) and TRIUMF (Tri-University Meson Facility, Canada) and PSI (Paul Scherrer Institute, Switzerland). TRIUMF and PSI use large isochronous cyclotrons with maximum energies of 520 and 588 MeV respectively.

The pion radiotherapy programme in Los Alamos was discontinued in 1982 after treating about 230 patients and the programme in Switzerland is also recently being discontinued after treating about 500 patients. Although some favourable tumour responses were obtained, the results were inconclusive. Pion therapy is still being carried out heroically in Vancouver (Raju M.R. 1994). It looks as if the pion therapy dose not seem to a prospective method of treatment.

PROTON RADIOTHERAPY ACCELERATORS

Protons deliver the dose at a relatively uniform low level until they have lost a significant fraction of their energy, at which point the dose increases reaching a sharp peak close to the end of the proton range. The exact position of this Bragg peak in dose can be controlled by steering or collimating the proton beam for transverse movement and by modifying the impact proton energy for longitudinal movement. This allows fine control of the dose distribution and significantly reduces the potential for damage to surrounding tissues. Over 15,000 patients have now been treated by this method, and for a number of tumours dramatic improvement in success rates have been clearly demonstrated (Thornton A.F. and Suit H.D.,1992; Pedroni E.).

At present, two major applications of proton beams are encountered in clinical practice. These are, firstly, the use of relatively low energy protons: $E_p \leq 80$ MeV or higher energy degraded beams, specifically for the treatment of the ocular tumours using field sizes smaller than 10 cm^2; and secondly, the treatment of large or deep-seated lesions using higher energy beams ($E_p \geq 150$ MeV) with small or large fields.

A disadvantage of photons (X-rays and γ-rays) and fast neutrons is that they give their maximum dose near the skin at the entrance and a lesser dose in deeper tissue. On the other hand, as already mentioned, proton beams have the favorable characteristics of the Bragg peak, a peak dose just before the protons stop in the tissue and no dose deposition beyond it. If the energy and the energy spread of a proton beam are adjusted so that the spread-out Bragg peak occurs in the tumour, radiation damage to normal tissue between the entrance skin and the tumour decreases greatly compared with any conventional modality.

The Bragg peaks of heavy ions are as sharp as those of protons. However, in contrast to protons their dose is deposited in the region beyond the distal edge of the Bragg peak to some extent because of the fragmentation of the incident particles. Biomedical effectiveness of heavy ions is higher than that of protons. It is still an open question whether this characteristic is an advantage in clinical use, because the heavy ions probably heavily damage normal tissue as well as the tumour.

The biological effectiveness of proton beams is almost the same as that of photons. This fact insures utilization of huge amounts of biological knowledge and clinical experience of conventional radiation therapy for proton beams. Different kinds of particle radiotherapy modalities are compared with each other in Figure 1 in bar graphs. The proton beams are capable of well-focused dose concentrations in tumours. As compared with pion and heavy ion generators, proton generators have the advantage of smaller size and lower cost. Indeed, it is be possible to install a proton beam facility in a hospital. Therefore, by summing up all the advantages of proton therapy, it may be safely stated that, among all unconventional and experimental techniques,this modality stands the best chance of becoming a fully routine form of therapy. It is because we are now witnessing intensive transformation of general use accelerators into dedicated hospital accelerators.

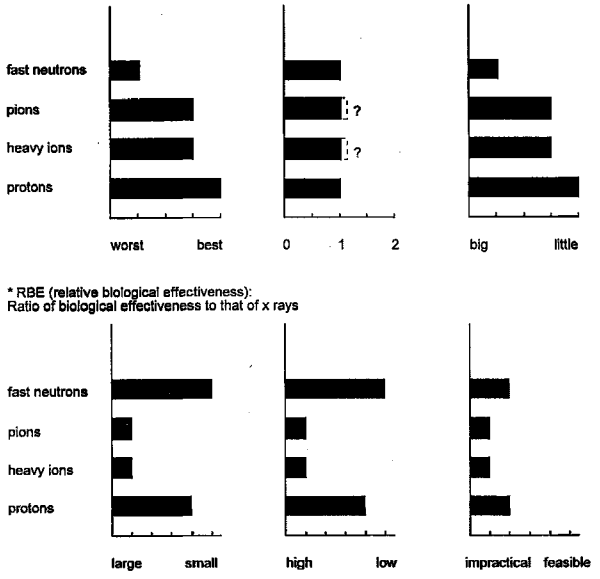

Fig. 1

There are now (1997) 16 operating proton therapy centers in the world; four are in the USA, six in Europe, three in Russia, two in Japan and one in South Africa. At eight centers, the accelerator is a cyclotron, at five, a synchrocyclotron, and at three, a synchrotron. At six centers, the maximum proton energy is < 100 MeV. Six centers can provide proton beams with variable energy and six centers can deliver proton beams with diameters > 10 cms. Data on the above centres are listed in Table I, together with the number of irradiated patients as of Jan 1,1995, whereas the designed and proposed new facilities to be implemented within the next decade or so are listed in Table II. It may be expected that by the end of this century about 10 facilities will have been built, including 7 installations for proton therapy and 3 installations for heavy ion therapy.

Table I. Accelerators for proton therapy(as on Jan.1,1997)

Institution	Accelerator	Energy [MeV]	Year of operation	No. of patients on Jan. 1, 1996
Donner Lab. Berkeley USA	Synchrocyclotron	340	1954-57	30
Werner Inst. Uppsala, Sweden	Synchrocyclotron	85	1957-76	73[4]
Harvard Cycl.Lab. USA	Synchrocyclotron	160	1961	6626
Dubna, Russia	Synchrocyclotron	90-200	1964-74	84
Inst. Teoret. i Eksp. Fiziki, Moscow,Russia	Synchrotron	70-200	1969	2877
LIJF, St Petersburg, Russia	Synchrocyclotron	70-1000	1975	969
Nat.Inst.Nucl.Phys.Chiba, Japan	Synchrocyclotron	70	1979	86[2]
PMRC, Tsukuba, Japan	Synchrotron	250	1983	462
SIN[5], Villingen, Switzerland	Cyclotron isochron.	70-590	1985	1785
Werner Inst., Uppsala, Sweden	Synchrocyclotron		1989	65[4]
Clatterbridge Hospital, Bebington, England	Cyclotron isochron.[3]	62	1990	656
LLUMC, Loma Linda, USA	Synchrotron	70-250	1990	1262
Louvain-la-Neuve[7], Belgium	Cyclotron	90	1991	21
Nice[8], France .	Cyclotron	65	1991	636
CPO Orsay[9], France	Synchrocyclotron	70-200	1991	673
NAC [0], South Africa	Cyclotron	200	1993	106
IUCF[6], USA	Cyclotron	200	1993	1
UCDavis, USA	Cyclotron	68.5	1994	50
TRUMF, Canada	Cyclotron	180-520	1995	5

[1)] July 1994; [2)] June 1993; [3)] Set in operation in June, 1990; [4)] Treatments with a 72 MeV stationary (fixed) beam resumed after reconstruction May 1993; [5)] At present Paul Scherrer Institut (PSI); [6)] Indiana University Cyclotron Facility, Bloomington, USA; [7)] Universite Catholique de Louvain, Louvain-la-Neuve, belgium; [8)] Centre Antoine Lacassagne-Cyclotron Biomedical, Nice, France; [9)] Center for Protontherapy (CPO) - Orsay Synchrocyclotron Cedex; [10)] National Accelerator Centre at Faure, republic of South Africa.

For cancer therapy the maximum energy required for the beam is 250 MeV for protons and about 400 MeV/n for carbon and oxygen ions, with maximum intensities of the order of 10^{11} protons/s (or 10-30 nA averaged over a 30-60 second treatment time) and 10^{9}-10^{10} ions/s. A dedicated facility should be located inside a hospital, which means within a highly populated area accessible to the general public, so that the radiological impact outside the therapy department should be virtually zero. To reduce the cost per treatment, one

accelerator should serve several treatment rooms. A peculiar aspect is the possibility that one ore more of the treatment rooms be equipped with a rotating isocentric unit (a "gantry") to perform patient irradiation from any angle, and this must be taken into account in the shielding design. In Europe there are a few accelerator facilities where proton therapy is carried out, but they are mainly limited to proton energies of 60 to 70 MeV [50] for the treatment of ocular tumours and only two of them are located in a hospital (Nice in France and Clatterbridge in the UK). Due to the complexity, size and cost of a general purposed facility, there is only one project for a large hospital-based hadron-therapy facility - in Italy - but several for upgrading existing accelerator facilities for clinical use. Undoubtedly, the main advantage of the Italian project (Amaldi U. and Silari M., 1994; Silari M.) is an attempt to create a national network of proton therapy facilities.

Table II. Proposed new facilities for proton and ion beam therapy (as of December 1997)

INSTITUTION	PLACE	TYPE	1ST RX?	COMMENTS
P.S.I.	Switzerland	p	1996	200 MeV, var.energy, gantry, dedicated line
Berlin	Germany	p	1996	72 MeV cyclotron; eye treatment beam line.
G.S.I.Darmstadt	Germany	ion	1996	first Carbon beam in the medical cave 7 June 1995
KVI Groningen	The Netherlands	p	1997?	plan:- 200 MeV accel.; 2 rms; 1 gantry; 1 fix.
NPTC (Harvard)	MA U.S.A.	p	1998	at MGH; 235 MeV cyclotron; gantry; 4 horiz beam
NC Star	NC U.S.A.	p	1999?	synchrotron; 70-300 MeV; 2 horiz; 1 gantry
Regensburg	Germany	p	1999?	gantry; 1 fixed beam; 1 eye beam.
Hyogo	Japan	ion	2000	protons & ion; 2 gantries; 1 horiz; 1 vert; 1 45°deg.
TERA	Italy	p (ion)	2000?	H- accel; 60-250 MeV p; +BNCT; isotope prod.
AUSTRON	Austria	ion	?	protons and light ions
Beijing	China	p	?	250 MeV synchrotron.
Brookhaven	NY U.S.A.	p	?	linear accelerator.
Clatterbridge	England	p	?	upgrade using booster linear accelerator.
ITEP Moscow	Russia	p	?	3 horiz. -1 fix beam, 2 gantry, 1 exp., H- accel.
Jülich (KFA)	Germany	p	?	exp. beam line; plans for therapy.
Kashiwa	Japan	p	?	no details yet; will start construction in 1996
Kraków	Poland	p	?	60 MeV proton beam.
Kyoto	Japan	p	?	250 MeV synchrotron; gantry; 1 fixed horiz. beam.
Munich	Germany	p	?	64 MeV protons; eye treatments
Proton Develop.	IL USA	p	?	300 MeV protons; therapy & lithography
Tsukuba	Japan	p	?	230 MeV; 2 rms; 1 vert+ 1 h beam; 1 gantry

The aim of the *Progetto Adroterapia* (Hadrontherapy Project) is to set up a nationwide network of proton therapy centres which has been named RITA (Rete Italiana Trattamenti Adroterapici, Italian Network for Hadrontherapeutical Treatments). The centre of the network is occupied by the Centre for Oncological Hadrontherapy which will have four rooms for proton treatments. This hospital-based *Hadrontherapy Centre* should be a "centre of excellence" and it is conceived to provide, within a hospital which has already available all other facilities, the techniques and the tools that are related to the state-of-the-art radiation therapy. The facility will aim at the treatment of 1000 patients/year and is designed with a relatively easy upgrading path to ion treatments. A room for the production and use of thermal and epithermal neutrons for boron neutron capture therapy is also foreseen. The other nodes of the RITA network are various *Proton Therapy Centres*, which should make use of relatively cheap and compact proton accelerators to be installed, due to their reduced space requirement, in a number of hospitals distributed over the entire nation. Following such preparatory work, the patients will be referred to the closest or more convenient centre for hadron treatment. Some patients may be treated locally with conventional radiation and receive elsewhere only a proton (or ion) boost.

A real innovation would be represented by the development of a compact accelerator. Such an accelerator should satisfy the following requirements (or at least most of them): (1) it should accelerate a minimum of $2 \cdot 10^{10}$ protons/s to at least 190 MeV; (2) it should be built (including ancillary systems) in less than 300 m^2 (shielded area and service space); (3) it should consume less than 250 kW and (4) it should cost, with one external beam (but without civil engineering) less than 10 M$;

this figure should include the cost of controls and beam delivery, but the cost of the injector can be excluded if it is also used to produce PET radionuclides for the same hospital. An effort has been undertaken within the Progetto Adroterapia in this direction. Four options are presently being considered: (1) a synchrotron using pulsed magnets with a peak field of 4 T; (2) a linear accelerator; (3) a superconducting cyclotron and (4) a weak focussing synchrotron of the LLUMC type but of reduced circumference. The demonstration of the feasibility of one (or more) of these designs would represent a significant technology transfer from a research organization to industry and the medical field.

One especially notable initiative in the U.S. was the commissioning of a 250-MeV proton synchrotron at the Loma Linda University Medical Center in Loma Linda, California. The accelerator was designed and built by the Fermi National Accelerator Laboratory (Cole F.T. et al 1990). It is the first *dedicated proton accelerator facility* built for a hospital. The proton facility has three rotating-gantry rooms, two fixed horizontal beam-line rooms, one for small-field treatments (eye and brain) and large-field treatments, and the other for research. The first patient was treated in the eye beam in October 1990, and the second beam line, the horizontal beam line with a 250-MeV beam was put into clinical use in March 1991. The patient treatments began in June 1991 using the beam delivered by one of the gantries. At present, i.e in January 1995, 1000 patients have already been treated in this facility (Table II).

In Japan, proton therapy is being realized at two facilities: at the National institute of Radiological Sciences (NIRS), Chiba, and the Particle Radiation Medical Sciences Center (PARMS), University of Tsukuba. At the NIRS, protons are accelerated to an energy of 70 MeV with a range of 36 mm, and the PARMS uses 500 MeV protons from the High Energy Physics Laboratory (KEK). As a consequence of very promising results of clinical studies, the medical community in Japan is aggressively pursuing acquisition of new dedicated proton facilities.

A new dedicated medical synchrotron with an energy variable in steps of 120, 180, and 230 MeV was originally planned for construction at Tsukuba. The designed beam intensity was to have been 20 nA, which corresponds to $1.25 \cdot 10^{11}$ protons per second. Two modes of extraction, fast and slow, are planned. Two treatment rooms with horizontal and vertical (up and down) beams are planned (Fukumoto S. 1991). Tsukuba changed its main accelerator from a synchrotron to a compact cyclotron in 1992. There are two reasons for the change: (1) The cyclotron is supplied by IBA and Sumimoto with a guaranteed beam parameters, (2) Cyclotron cw beams are more convenient for a scanning system of beam delivery than that of a slow-extracted synchrotron beam. University of Tsukuba will submit the plan to the Ministry of Education as a project which will start in the 1996 fiscal year.The construction of a 250-MeV AVF separate-sector cyclotron is nearing completion at the Osaka University in Japan. The machine is planned to be used for medical sciences as part of an interdisciplinary research program. However, anticipating the beam-time demand for this machine by the physics community, another new facility is being considered. There is also a proposal to build a 250-MeV synchrotron for medical use at Kyoto University. Kobe is the capital of Hyogo prefecture. On Jan.17,1995 theis area suffered from a disastrous earthquake. A particle beam facility is being planned there by local government. This was the most advanced project implemented in Japan. Three kinds of particles: protons, helium and carbon ions were to be delivered. Its engineering design would was to be started in early 1995, and the whole facility is to be completed by the end of 1998. Although the offcials of the Hyogo prefecture are enthusiastic, the damage caused by the earthquake may affect the timetable.

Several medical accelerators have been designed in Russia. Specially notable is the design of a very compact synchrotron, accelerating protons to 200 MeV with a high magnetic field of 5-10 T, the orbit length of 4.7 m, and the repetition rate of 10 Hz developed at the Budker Institute of Nuclear Physics (BINP) in Novosibirsk. Recently, in cooperation with ENEA-INN-FIS a more conservative version has been considered: the use of 4 Tesla warm 3.5 msec pulsed dipole magnets that allow a synchrotron with only 6.4 m of circumference [58]. The work has been carried out with the view of applying it in the Italian project Progetto Adroterapia. The total surface of the accelerator and the therapy complex will be 300 m^2 and the rough cost estimation is 10 M$.

The number of facilities for proton therapy envisaged for the USA is estimated at 15-20, whereas that for Italy at only 3 to 4. Though it is lower, by almost one or two orders of magnitude, than the number of the existing facilities for conventional therapy, it reflects the need for a commercial production of proton therapy installations.

The realization in the U.S.A. of the second hospital-based proton radiotherapy facility of the world has been recently approved (Gall K.P. et al, 1993). The new centre will be built at the Massachussetts General Hospital of the Harvard Medical School in Boston (Northeast Proton Therapy Centre), which has the largest experience in proton therapy. The beam will be delivered by a cyclotron, which is quite significant in that the first dedicated facility at Loma Linda was equipped with a proton synchrotron, The contract for the facility in Boston, including beam delivery system and gantry, has been assigned to a European company - IBA Belgium. This will certainly have positive consequences for the future of proton therapy in Europe (Pedroni E.). The first dedicated facility for proton therapy in Japan will be also equipped with a cyclotron (Jongen Y et al., 1993) .

At present, some of specialists and commercial companies are proposing, or working on a system specially dedicated to proton therapy. Ion Beam Application S.A. (IBA), Belgium, proposes a commercial equipment specially designed for in-hospital operation [60, 61]. The basic configuration of the IBA proton therapy system comprises the following elements: (1) a 235 MeV isochronous cyclotron, able to deliver beams of up to 1.5 mA, but hardware-limited at 300 nA in order to limit the maximum possible dose rate to the patient; (2) an energy selection system transforming the fixed energy beam extracted from the cyclotron into a variable energy beam (235 to 70 MeV range) provided with energy spread and emmitance limitations and verification; (3) a beam transport and switching system connecting the exit of the energy selection system to the entrance points of a number of gantries and fixed beam lines; (4) three gantries fitted with a nozzle, and a system consisting of two horizontal beam lines, the large field one being equipped with a nozzle. For beam spread-out on the gantries and on the large field line, both beam scattering and beam wobbling are available; (5) a global control system including, in addition to an accelerator control unit, three independent, but networked therapy control stations; (6) a global safety management system independent of the global control system; and (7) a robotic patient positioning system.

A few companies propose other systems, most of them being at a conceptual stage. These various systems may differ because of different concepts regarding the gantries, the nozzles, the patient positioners or the safety and control systems. However, the concept proposed for proton acceleration is probably that which best differentiate one system from another. For example, the proton therapy system for the Loma Linda University Medical Centre based on a proton synchrotron was built by a team regrouping the Fermi National Accelerator Laboratory, the Loma Linda University, the Lawrence Berkeley Laboratory and SAIC (Science Applications International Corporation), a private company based in San Diego, CA, USA. SAIC is now working on a proton therapy system based on a second generation synchrotron, taking advantage of the experience gained from Loma Linda. One of the main objectives is to achieve the intensity performances required for proton therapy. ACCTEK Associates, Inc. is promoting for commercial use its concepts of equipment for proton therapy including a H^- synchrotron with charge exchange extraction. Other companies or persons are working on proton therapy systems based on a linac [13, 64] and a superconducting cyclotron (Mandrillon F. et al.1994) .

AccSys Technology Inc. put forward the idea of a compact proton linac with the side-coupled structure and its rf power system (the major portion of accelerator) similar to those used by Siemens Medical Laboratory for conventional electron radiotherapy linacs. This significantly reduces the cost of the linac to less than $8.0 M. AEA Technology have proposed to investigate the novel idea of using linear accelerators to boost the energy of the 24 existing and suitable medical cyclotrons throughout the world. This will provide the required high energy proton therapy facilities at a suitably reduced cost (Nightingale et al. 1992).

A proposed 238 MeV Superconducting Cyclotron for proton radiotherapy has an outer radius of 1.45 or 16.0, depending on the 185 MeV or 238 MeV version, its the total body weight being 75 and 90 tons, respectively (Mandrillon F. et al).

There is no debate on the clinical superiority of the proton beams over the photon beams. Since the clinical value of proton radiotherapy has been fully ascertained, the wider application of this modality will be mainly dependent on the financial side. According to W.T.Chu [66] the capital cost of a proton facility is lower than, or at least comparable to, that of a conventional linac facility (electron/photon) of equivalent clinical capability. To be valid, the comparison must be made between two kinds of facilities that can treat comparable numbers of patients with the same cancer-cure rate. In

other words, the cost of one proton facility should be compared with that of several linac facilities which can perform a comparable number of 3-dimensional conformal therapy deliveries within a given time. Based on very conservative figures, the conclusion is that one proton facility can treat the same number of conformal therapy patients as ten linac facilities. As the useful life of a proton accelerator is estimated at 25-35 years and that of linacs is 10-12 years, these ten linacs must be replaced at least once during the lifetime of a proton accelerator. W.T.Chu also points out that the capital cost of conventional photon treatment is about 25% of the entire treatment. The delivery cost of radiation therapy is dominated by the labor and not by the facility cost. The capital cost of proton facilities can be easily absorbed if the clinical results are superior to those from photon treatment. When the costs are about the same for both proton and photon treatment modalities, it is clear that protons will win over photons in every clinical analysis (Chu W.T., 1994).

LIGHT ION RADIOTHERAPY ACCELERATORS

Ions such as neon, carbon and oxygen with high LET are effective against radiation resistant and anoxic tumours, which are difficult to treat with protons or X-rays. The possibility of using these ions was investigated from 1977 until 1992 at LBL, Berkeley (Lennox A.J. 1994). The Bevalac at Berkeley has now been decommissioned for lack of funds. A still older machine at Berkeley, the synchrocyclotron, treated around 2050 patients with helium beams, but was shut down in 1987. Thus, limited clinical experience exists for light ion beams. But biophysical experiments performed over the last 15 years at Berkeley and Darmstadt, bore strong evidence for the physical and biological superiority of light ions over proton beams (Bohne D. 1992).

The effects of heavy ions on slowly growing tumours were found to be comparable to the effects of neutrons but the sparing of normal tissues is expected to be better for heavy ions. The clinical impression is that heavy ions may play a useful role in the management of slowly growing sarcomas, chordomas and prostate cancers (Raju M.R. 1994).

The goal of the treatment of ocular melanoma (Lennox A.J. 1994) is to select a beam direction (or equivalently, a direction in which the patient gazes) so that the tumour is treated adequately and critical structures of the eye such as the lens, fovea, and optic nerve receive only minimal dose.

Since Autumn 1994 a very comfortable light ion accelerator complex is operating at NIRS, Chiba, Japan (Hirao Y. et al, 1992; Tsuji T. et al, 1994). The HIMAC (Heavy-Ion Medical Accelerator in Chiba) project was started in 1984 as one of the projects of "Comprehensive 10 year Strategy for Cancer Control", and the construction of the building and installation of all facilities were completed at the end of 1993. This is the first heavy ion synchrotron complex dedicated to medical use in a hospital environment. The aim of the HIMAC project is to establish therapeutic advantage of ion beams in cancer treatment.

The major part of the accelerator consists of a two-ring synchrotron, two ion sources, an RFQ linac, an Alvarez linac and a high-energy beam transport system. There are three treatment rooms - vertical, horizontal, and vertical and horizontal beams - as well as rooms for physics and radiobiological studies. In the initial pilot study, clinical trials will be performed on the treatment of head and neck, CNS and lung tumours, the first patients having been treated since Autumn 1994 using carbon ions. As irradiation technique develope, other tumour sites, including the liver, uterine cervix, bladder and prostate, will be evaluated as possible candidates for heavy ion therapy (Tsuji T. et al, 1994).

HIMAC required ion species chosen in the atomic number range between 2 (helium) and 18 (argon) as a result of basic research on relative biological effectiveness and that of clinical trials at LBL. The maximum required range of ions in tissue was determined from the range-energy relationship for silicon, which is one of the heaviest and most suitable ions for the deep-seated and radio-resistant tumour therapy. This maximum energy of 800 MeV/u could provide the range in tissue considerable greater than 30 cm for ions lighter than silicon. The dose rate requirement for any ion beam is 5 Gy min^{-1} to permit completion of one fractional treatment within one minute. The maximum field size is 22 cm in diameter (Hirao Y. et al, 1992).

Ion therapy is expected to be much more expensive than proton therapy, as seen from a comparison of the costs of the HIMAC Facility - over 300 M$ - with the cost of the Loma Linda proton facility (60 M$) in the USA. The higher cost of ion therapy can be justified

only in two ways (Chu W.T. et al 1993) (1) by the need of high LET associated with adequate precision, or (2) by the need of extremely high dose precision. The task of the new ion facility in Chiba is to provide answers to these and many other questions.

A European initiative for the implementation of a light ion accelerator into an existing hospital environment developed in the late '80s: European Light Ion Medical Accelerator (EULIMA). This project was financially supported by the European Community Medical and Health Research Programmes and the studies were based on radiation research centers and accelerator laboratories in France, Belgium, Germany and Switzerland, and focused on the choice of a proper accelerator and beam delivery system. The EULIMA project was terminated at the end of 1991, because no European government wanted to provide the construction funds for the accelerator and associated equipment (Bohne D. , 1992).

The beam requirements for heavy-ion medical machines kept fairly stable over the years, with fluctuations of 20% in energy and a factor of 5 in intensity. A typical figure is 5 Gy per liter and minute, which corresponds to 10^8 particles per second for Ne ions spread over one liter target volume. This number is easy to meet for various choices of the machine.

For a nuclear physics machine the term flexibility is of paramount importance, because one does not know in advance, what research fields turn out to be most rewarding. Simplicity of operation and reliability are widely sacrified for this somewhat irrational term flexibility. It is hard to keep machine builders away from this philosophy in case of a medical accelerator. For the design of medical accelerators there are some issues which are not relevant for nuclear physics machines: for example,the extreme care in beam control in respect to patient safety. This implies a fast beam switch-off capability and monitoring redundancy. The time structure of the beam extraction needs some concern in case of a synchrotron when combined with a magnetic scanning system (Bohne D. , 1992).

Detailed overviews on the implementation of heavy-ion accelerators for medical purposes have been presented in recent publications (Bohne D, 1992; Chu W. T. et al 1993). The common denominator of all this work has been to considerably reduce the costs, which are decisive in making heavy-ion radiotherapy more popular. At GSI a heavy-ion synchrotron SIS has been in operation since 1990 with a maximum energy of 2 GeV/u, much higher than necessary for radiotherapy. SIS is designed for a three orders of magnitude higher beam intensity than necessary for cancer treatment. German proposal uses a parasitic beam from the GSI synchrotron [16] in collaboration with the University Clinic of Radiology in Heidelberg and the German Cancer Research Center (DKFZ). Treatment of patients is expected to begin in 1996 starting with light ion beams, probably carbon. Radiobiological experiments and instrumentation tests are under way. The project has been funded by the German government. The medical beam line, the instrumentation and the medical building should be ready by the end of 1995. The overall cost in the prices of 1993 is estimated at about 13 million DM, i.e. about 9 million US dollars.

Some groups are planning to develop heavy-ion therapy after implementing proton therapy. These include the German COSY/Jülich project and the Italian TERA project (Amaldi U. and Silari, 1994) . At the COSY accelerator at Jülich another medical beam is being prepared; initially planned with protons, it will later be used also for ion therapy. In Austria, plans are under way to implement heavy-ion and neutron-capture therapy in the AUSTRON project. This project for a spallation neutron source involves a 1.6 GeV synchrotron cycling at an impressive 25 Hz, with 100 kW on target. The complex will include proton and ion therapy, and is planned for the year 2000 (APO).

CONCLUSIONS

Charged particle accelerators have gained a permanent position in the field of conventional radiotherapy. In industrial countries every eighth man or woman stands a chance of being treated with radiation produced in accelerators. These countries have reached a saturation point in radiotherapy accelerators as concerns the number of machines used at a moderate cost of treatment. However, in developing countries the situation is diametrically opposite: more than 80% of world's population has no or very difficult access to accelerator therapy. Therefore, the problem that is still pending is that of designing and developing a new generation of low cost medical accelerators for conventional therapy acceptable for less advanced countries.

As for unconventional radiotherapy we are witnessing a transformation period of proton therapy into a fully routine method of treatment. Intensive work, mostly on radiotherapy neutron

accelerators for BNCT and on heavy-ion machines, has every chance of success in the not too distant future.

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