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Hadron accelerators in cancer therapy

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Abstract

The application of hadron accelerators (protons and light ions) in cancer therapy is discussed. After a brief introduction on the rationale for the use of heavy charged particles in radiation therapy, a discussion is given on accelerator technology and beam delivery systems. Next, existing and planned facilities are briefly reviewed. The Italian Hadrontherapy Project (the largest project of this type in Europe) is then described, with reference to both the National Centre for Oncological Hadrontherapy and the design of two types of compact proton accelerators aimed at introducing proton therapy in a large number of hospitals. Finally, the radiation protection requirements are discussed.

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1. INTRODUCTION

The applications of particle accelerators in biomedicine are many and varied [1,2]. They range from the widespread use of small electron linacs for radiation therapy, to the application of 10-20 MeV proton cyclotrons for radionuclide production or elemental analyses, to the use of 50-60 MeV proton accelerators for neutron therapy or proton treatment of eye melanomas, to the recent larger hadron accelerators installed in hospitals for cancer therapy with proton or ion beams. Here we will only focus our attention on the use of hadron accelerators in cancer radiation therapy. We shall just mention that after several years of clinical trials no definitive conclusions have yet been drawn on the actual advantages of fast neutron therapy over conventional (photon and electron) radiation therapy modalities. The enhanced radiobiological effectiveness shown by fast neutrons is somewhat spoiled by the sub-optimal achievable dose distributions. It can be expected that tumours which are eligible for neutron therapy will, in the long run, be the best candidates for radiation therapy with light ions. On the other hand, boron neutron capture therapy (BNCT) shows some promising features which are boosting the development of compact clinical machines providing the required neutron fluence rates. An overview of the most recent developments in BNCT can be found in ref. [3].

The use of hadron beams (protons and light ions such as carbon, oxygen and neon) in cancer radiation therapy has grown considerably since the first trials in the mid-fifties and now a few hospital-based facilites are in operation, with a few others being built or designed. A very comprehensive and up-to-date review of the field can be found in refs. [4,5]. The rationale for the use of protons in radiation therapy relies on the superior dose distribution which can be achieved with respect to photons and electrons: this is due to the low lateral scattering undergone by protons, their well-defined range and the increasing ionization (i.e., dose deposition) with increasing penetration in tissue, which produces the well known Bragg peak (Fig. 1). Ions heavier than protons show an even improved dose distribution and the additional advantage of an increasing biological effectiveness (RBE) at the end of range [6].

The depth of the Bragg peak depends on the initial energy of the protons and its width on the energy spread of the beam. By varying the energy during the irradiation in a well controlled manner, one can superimpose many narrow Bragg peaks and obtain a Spread Out Bragg Peak (SOBP). Although this implies an increase of the skin dose, the overall dose distribution is still far better than that achieved in conventional radiation therapy. Fig. 2 shows the range-energy curves in tissue for protons and various ions. From these curves it is easily seen that, in order to irradiate deep seated tumours, the maximum required energy for protons and carbon ions is 200-250 MeV and 350-400 MeV/u, respectively. All the clinical needs can thus be satisfied with proton energies in the range 60 - 250 MeV and beam intensities of the order of 5×10^{10} - 10^{11} protons/s. For light ions the corresponding figures are 120 - 400 MeV/u and 10^{9} - 10^{10} ions/s, according to the type of ion. These requirements represent the basic specifications which must be met by a hadron accelerator designed for cancer therapy.

The actual specifications which must be met by a proton or ion radiation therapy facility to provide a reliable and effective tool against cancer are much stricter. The performance specifications of the accelerator and of the beam transport and delivery systems must satisfy a number of clinical requirements. These specifications are expressed in forms of *energy range, energy variability, beam intensity, lateral penumbra, distal dose fall-off, source-to-surface distance, time structure of the extracted beam, raster scanning system specifications* and beam abort time. An exhaustive discussion on this subject may be found in ref. [7] and in the references therein quoted.

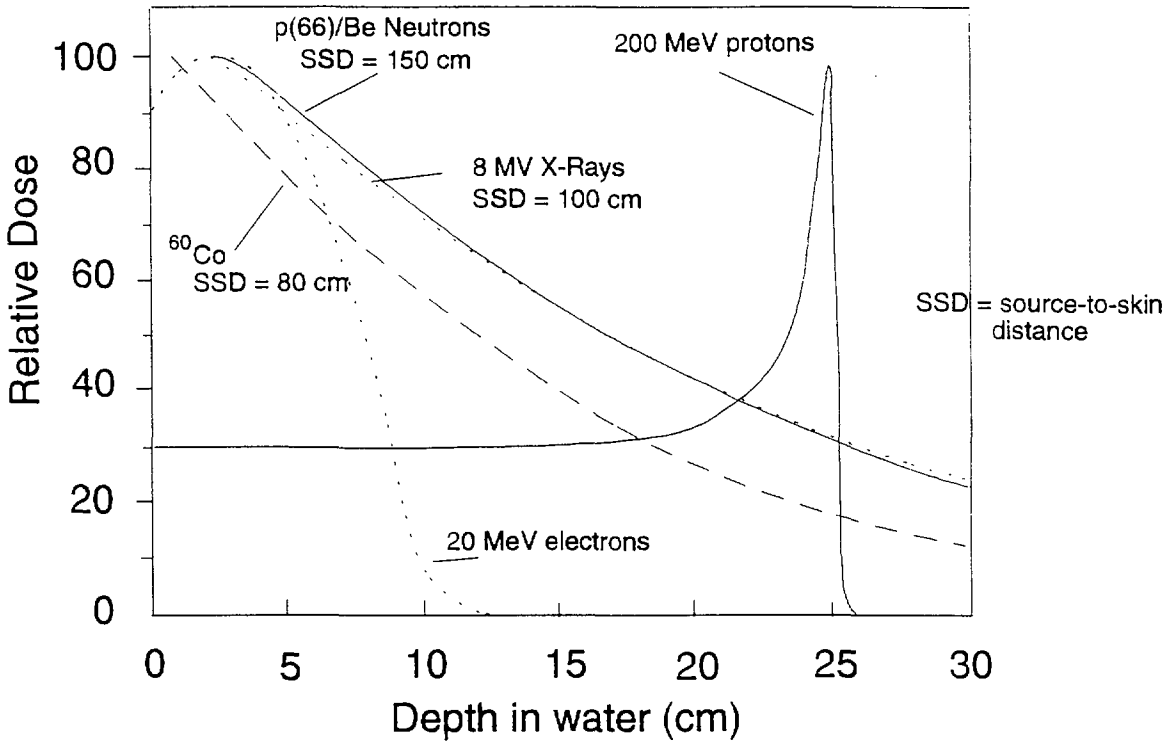

Figure 1. Depth-dose curves for photons (from a Cobalt source and a 8 MV linear accelerator), electrons, neutrons and 200 MeV protons. With protons the highest doses is released near the end of their range in tissue giving raise to the Bragg peak.

2. ACCELERATOR TECHNOLOGY AND INSTRUMENTATION

The hadron accelerators which are the best candidates for medical use are the cyclotron, the synchrotron and, more recently, the linac, as will be discussed in Section 6. The obvious advantages offered by a conventional cyclotron working at fixed energy (i.e., fixed frequency and fixed field) are simplicity and reliability of operation and continuous beam. This continuous beam yields beam intensities well exceeding the requirement for therapy and sufficient for other potential applications such as radionuclide production and neutron therapy. The disadvantage with a fixed energy accelerator is that the beam has to be degraded in energy down to the value corresponding to the maximum depth of penetration for the given treatment. This is done by means of an absorber placed just outside the extraction port of the accelerator, before the beam is transported to the treatment room. Degradation of beam energy implies degradation of beam quality; this has to be compensated by analyzing the beam in momentum, with loss of beam intensity and activation of components in the beam transfer line. Therefore, according to the amount of energy degradation required, for a given beam intensity to be delivered at the isocentre, an higher intensity must be accelerated in the machine. The proton intensity required for therapy is of the order of a few nA and cyclotrons can deliver extracted beams of several tens of μA, so that in this respect the above requirement does not constitute a restriction. Nevertheless since the extraction efficiency in a proton cyclotron is not particularly good (60-70%), the higher is the beam current accelerated in the machine, the higher are the prompt radiation generated and the induced activity in the vacuum chamber. In principle, the absorber can be placed in the treatment room at the end of the transfer line (which presents the

advantage that the magnets in the beam line operate at fixed field), but in this case no clean-up in momentum can be made and reaction products from the degrader can reach the patient. This is particularly critical in the case of treatment of ocular melanoma, where only 70 MeV are required and degradation of the beam quality subsequent to the energy reduction would therefore be much pronounced.

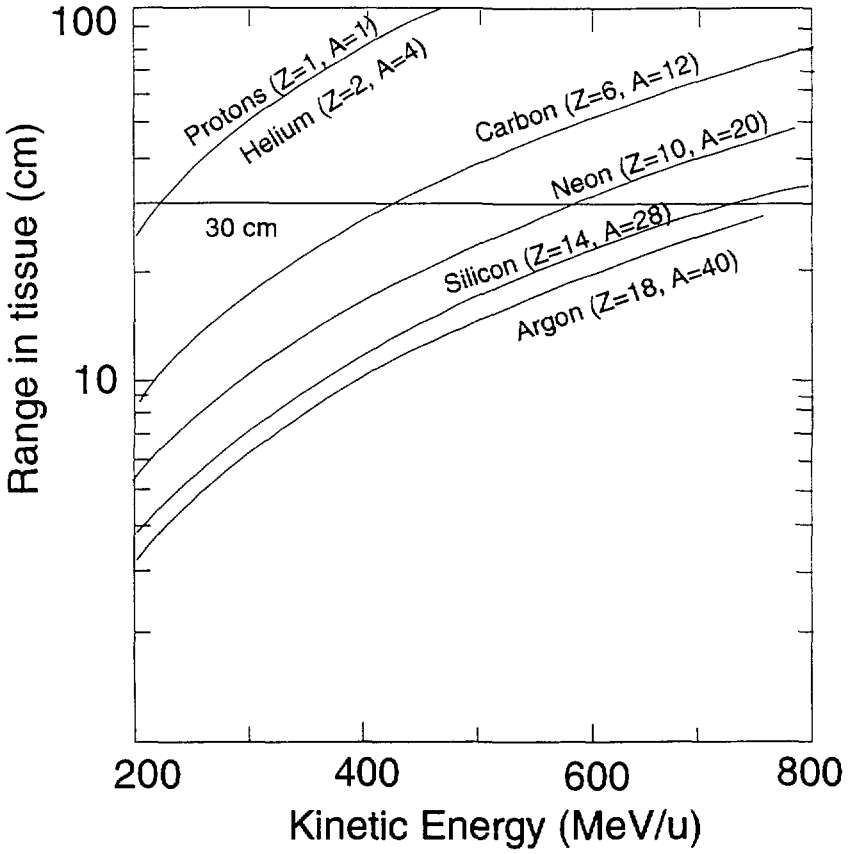

Figure 2. Range-energy curves in tissue for protons and light ions.

Whereas a cyclotron is made up of a large magnet and the particle beam, in the course of the acceleration process, moves along a spiral trajectory starting from the machine centre, in a synchrotron the beam circulates along a fixed orbit and the magnetic and radiofrequency fields vary according to the acceleration process. The obvious example for the synchrotron solution is the facility at the Loma Linda University Medical Center (LLUMC) in California [8] described in the next Section, where a Radio Frequency Quadrupole (RFQ) injects 2 MeV protons into a compact synchrotron of 20 m circumference which then accelerates the beam to a final energy in the range 70 - 250 MeV. The main advantage offered by a synchrotron is its energy variability. An interesting possibility is that the energy of the extracted beam can be varied from one cycle to the next in steps as small as 1 MeV, so that the modulation of the Bragg peak can be achieved without the use of absorbers, thus preserving beam quality and reducing the amount of shielding required. In this case it is obvious that the same rapid adjustment of the magnetic field is necessary for the magnets in the beam line and in the gantry. This possibility should not be underestimated since the use of absorbers causes scattering and straggling that increase the transverse and longitudinal size of the beam and blur its edges. On the other hand the accelerator is more complex than a cyclotron working at fixed frequency

and fixed field, because of its peculiar operating principle relying on rapid field variation. However many synchrotrons far more complex that the ones required for therapy are in operation worldwide.

To allow full flexibility in patient treatment, the accelerator should be coupled, via a beam transfer line, to an isocentric beam delivery system called "gantry". A gantry is a rotating mechanical structure which supports and positions the terminal tract of the beam transfer line (the bending, focusing and steering magnets, as well as the "nozzle") in order to focus the proton beam on the patient's tumour from any desired angle in the plane of rotation, as is routinely done in conventional radiotherapy. In this way a full conformation of the dose distribution (especially for tumours having a complex shape) can be obtained and the dose delivered to the surrounding healthy tissue be reduced. The gantry can be isocentric or eccentric (in which case the gantry and the couch rotate around a common point, the isocentre), as the unit designed at the Paul Scherrer Institut (PSI), Villigen, Switzerland [9]. An isocentric gantry of the "corkscrew" type, similar to that installed at LLUMC, is shown in Fig. 3. The radial dimension is determined by the source to isocentre distance, which should be large enough in order to minimize the skin dose. This geometry achieves a minimization of the overall swept volume. The outer diameter of the gantry shown in the figure is about 11 m with a distance between the exit of the last dipole and the isocentre of 3.4 m. Another design (using an in-plane configuration) but with similar overall space occupation has been adopted at the Northeast Proton Therapy Center (NPTC) under construction in Boston.

To achieve a conformal irradiation of the target volume, the beam has to be spread both longitudinally (i.e. in depth) and transversally. This can be achieved either with "passive" or "active" methods. Modulation of the beam energy is necessary to obtain a SOBP matching the entire tumour extension in depth. With a fixed energy accelerator this is obtained with a rotating absorber of variable thickness placed in the beam path, or via a so called range shifter (an absorber made up of a combination of different thicknesses of material). With a synchrotron energy variation can be achieved on a pulse to pulse basis, as discussed above. Lateral beam spreading can be achieved with a passive device. This system makes use of a double scatterer: the first spreads the incoming pencil beam, the second flattens the dose distribution in order to obtain a large and uniform irradiation field. Lateral and distal shaping are obtained by means of a collimator and a compensating bolus. Better results in conformal therapy can be achieved by an active scanning method, either voxel or raster. In this case an optimized dose delivery without the use of any patient specific hardware is obtained. Magnetic beam scanning fully displays its advantages when, instead of irradiating regularly shaped areas, scanning is limited to the cross section of the target volume including only a small safety margin around it. With voxel scanning the overall volume to be treated is subdivided in unit volumes which are irradiated in sequence, with the beam switched off while adjusting the scanning elements for the irradiation of the next unit volume (technique adopted at PSI). With raster scanning the beam is scanned continously across a slice at a given depth and the dose delivery is controlled by the scanning speed and/or by the beam intensity (technique adopted at the Gesellschaft für Schwerionenforschung, GSI, in Darmstadt, Germany).

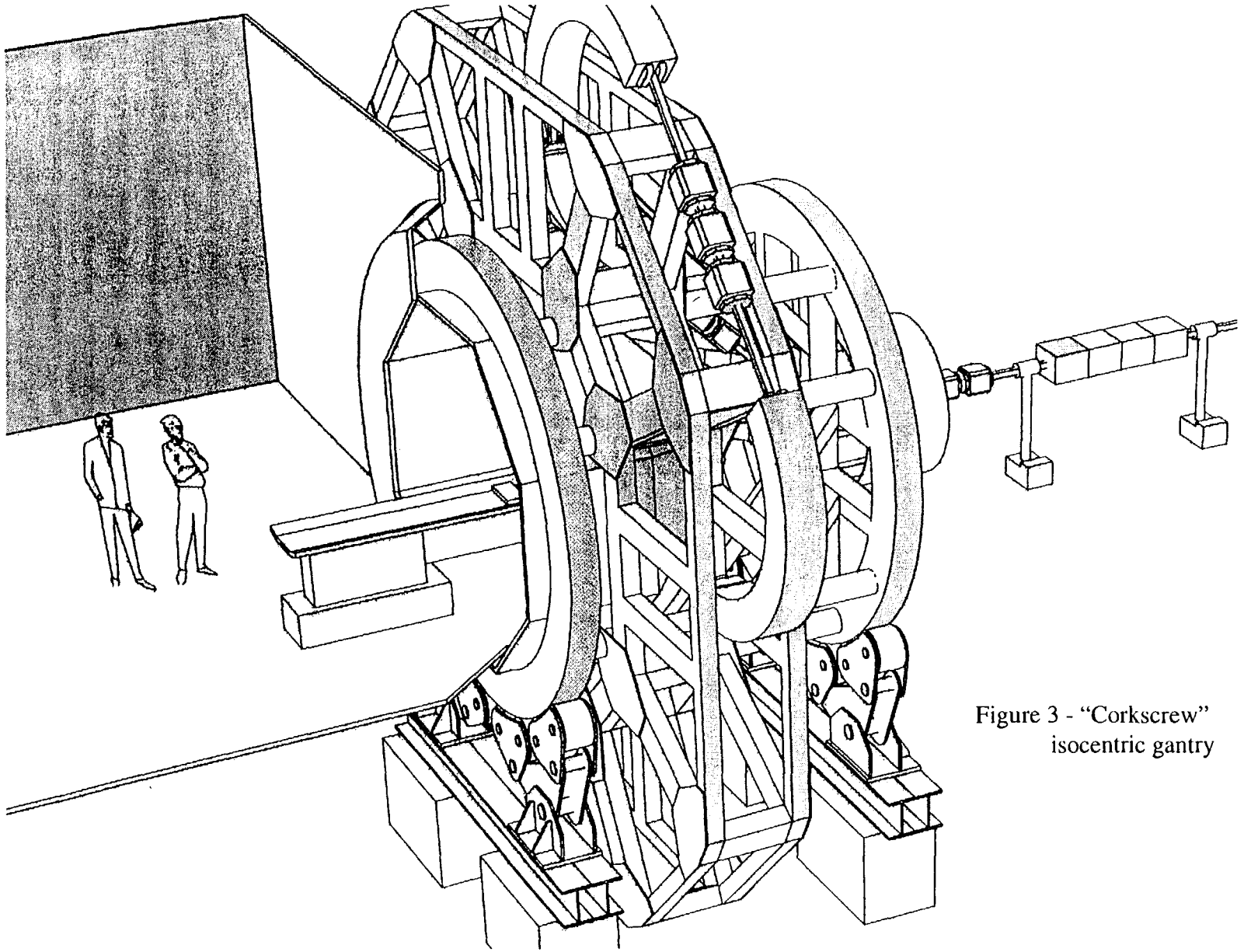

Figure 3 - "Corkscrew" isocentric gantry

3. FACILITIES

At present, several protontherapy centres are in operation in North America (United States and Canada), Russia, Japan, South Africa and Europe. Most of the clinical experience (more than 18000 patients treated until January 1997, to whom 1100 patients treated with pions and 2600 treated with ions should be added) has so far been obtained at research institutions which have devoted, at some stage, part of the accelerator time to medical uses. Loma Linda is the first hospital-based proton radiotherapy facility for treatment of deep-seated tumours (Fig. 4). The NPTC under construction at the Massachusetts General Hospital (MGH) in Boston, USA, will be the next, where patient treatments will start in 1998 [10]; it will have two isocentric gantries with an in-plane configuration but with equivalent performances of the "corkscrew".

The only centre with experience in light ion therapy was for a long time the Lawrence Berkeley Laboratory (LBL) in the USA, which unfortunately terminated its clinical activity in February 1993 [11]. LBL was equipped with a fixed horizontal beam and with a "wobbler" beam spreading system. A hospital-based centre for light ion radiotherapy (HIMAC, Heavy Ion Medical Accelerator in Chiba) has started operation in Chiba (Japan) in 1994 [12]. The centre is equipped with a combination of fixed horizontal and vertical beams and about 200 patients have been treated until now with carbon ions. Together with GSI (see below), this facility will provide in the next years crucial information on the effectiveness of ion therapy and will define the needed protocols.

Japan is the country which is presently making the largest investments in hadrontherapy. In addition to the two existing centres (HIMAC and the proton therapy program operated by the Proton Medical Research Centre at KEK, in Tsukuba), six projects are at different stages of development, four already funded and under construction and two at the phase of proposal: 1) a hospital-based facility run by the National Cancer Centre is almost completed in Kashiwa; it will be equipped with a 235 MeV cyclotron built by IBA/Sumitomo and with two isocentric gantries; 2) a multi-purpose facility is under construction at the Wakasa-wan Energy Research Centre in Tsuruga, provided with a 200 MeV synchrotron; it will have two fixed beams (one horizontal and one vertical) but no gantries; 3) construction has started in the Hyogo prefecture of a facility for treatements with both protons and carbon ions, equipped with a 600 MeV/u synchrotron; 4) the construction of a hospital-based proton facility has been approved in Tsukuba, but the type of accelerator is not yet decided; 5) a proton facility based on a synchrotron is proposed by Kyoto University and 6) a preliminary design has been completed for a proton therapy centre in Shizuoka.

Let us now briefly review the situation in Europe. Hospital-based centres for treatment of ocular melanomas are in operation at the Centre Antoine-Lacassagne (Nice, France) and at the Douglas Cyclotron Unit (Clatterbridge, UK). Eye treatments are also given at non-hospital facilites: PSI in Villigen (Switzerland), CPO in Orsay (France), UCL in Louvain-la-Neuve (Belgium) and GWI in Uppsala (Sweden). At PSI a medical beam line provided with an isocentric gantry, a new room and a medical annex building have been constructed and patient treatment has just begun [9]. The facility is intended for experimental cancer therapy and will treat a maximum of about 100 patients per year. A similar project is under way at GSI in Darmstadt, but treatments will be performed with carbon ion beams [13]. Radiobiological experiments and tests of instrumentation are in progress and patient treatments should start this year. The facility will treat approximately 70 patients per year. A proposal also exists for setting up a beam line dedicated to proton therapy at the cooler synchrotron COSY in Jülich

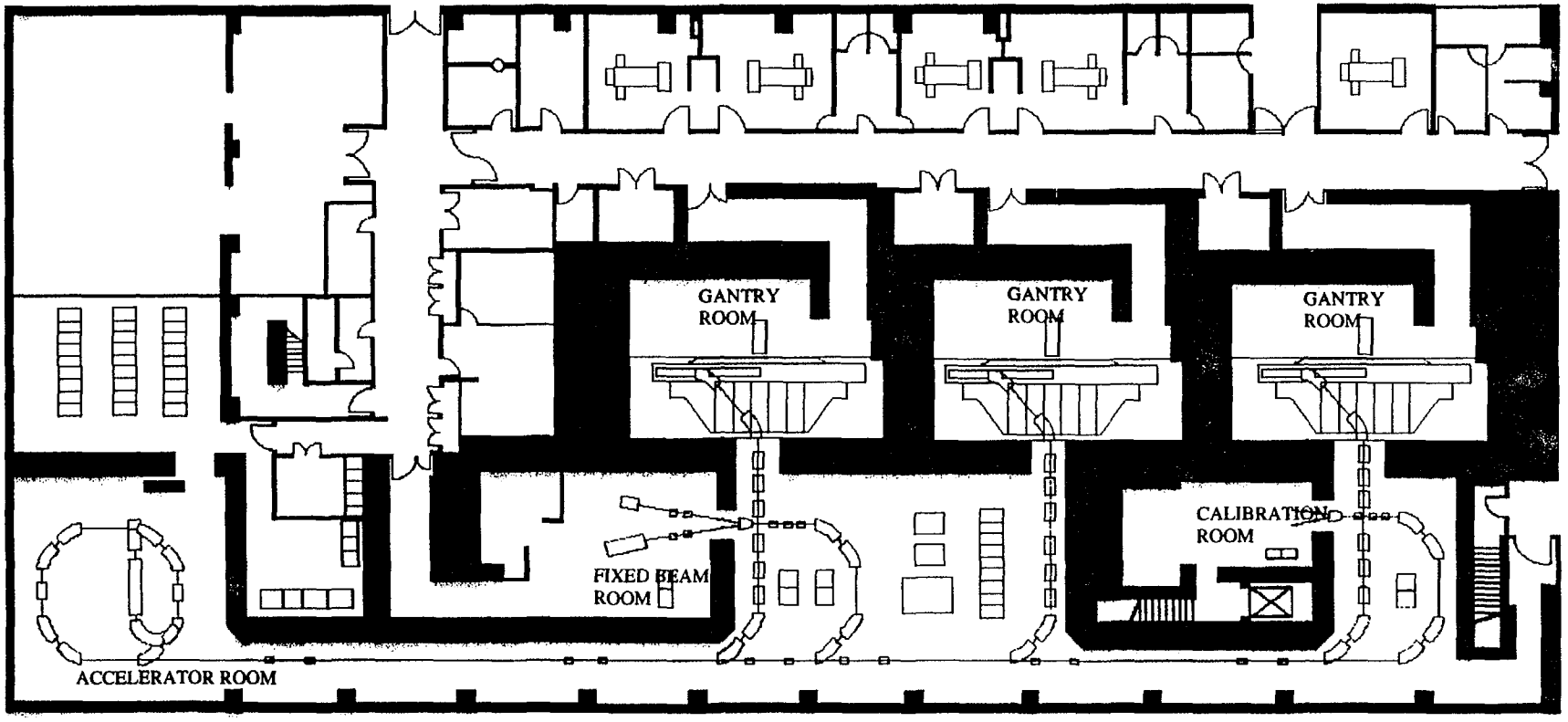

Figure 4. Loma Linda University Medical Center, California, USA (adapted from ref. [4]).

(Germany) [14], but there are no recent progress on the project. The facility is intended to be equipped with an isocentric gantry. At the Hahn-Meitner-Institute in Berlin (Germany) a project is under way for a proton therapy facility dedicated to the treatment of ocular melanomas using the 72 MeV beam of the VICKSI cyclotron. Treatments are planned to start sometimes this year [15]. Another project is the upgrade of the existing proton therapy facility at the Douglas Cyclotron Unit (Clatterbridge, UK). A design has been completed for a booster linac to raise the proton energy from 62 MeV to 200 MeV [16], but the project is not yet funded. Plans also exist for setting up proton therapy at KVI in Groningen (The Netherlands) using the AGOR cyclotron; the first treatment is scheduled in 1998. Research on ion cancer therapy is also part of the AUSTRON project [17,18]. A preliminary study has also been made to assess the feasibility of adapting to proton therapy the ISIS synchrotron at the Rutherford Appleton Laboratory in the UK [19]. The only plan for a large hospital-based facility is the project for the Hadrontherapy Centre to be built in Italy and discussed in the next Section. The design of the accelerator is carried out at CERN as a joint venture between Italy (TERA), Germany (GSI) and Austria (AUSTRON).

4. THE TERA PROJECT

The aim of the TERA Project (Hadrontherapy Project) [20] is to set up a nationwide network of protontherapy centres which has been named RITA (Rete Italiana Trattamenti Adroterapici, Italian Network for Hadrontherapeutical Treatments). The centre of the network is occupied by the National Centre for Oncological Hadrontherapy (Centro Nazionale di Adroterapia Oncologica, CNAO). This hospital-based *Hadrontherapy Centre* should be a "centre of excellence" and it is conceived to provide the techniques and the tools that are related to 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. The other nodes of the RITA network are various *Protontherapy 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 throughout the country. Multimedia connections established among the centres will allow physicians and medical physicists to discuss the cases by exchanging CT, MR and other diagnostic images and possibly plan the best treatment at a distance. Following such preparatory work, the patients will be referred to the closest or more convenient centre for hadron treatment. For example, some patients may be treated locally with conventional radiation and receive elsewhere only a proton (or ion) boost.

5. THE NATIONAL CENTRE FOR ONCOLOGICAL HADRONTHERAPY

The CNAO (Fig. 5) [20-22] will be provided with: 1) two treatment rooms equipped with an isocentric gantry capable of transporting protons up to 250 MeV; 2) one room equipped with one horizontal beam line for irradiation of eye tumours and 3) one room with one horizontal beam for experimental activities with both protons and light ions (dosimetry, radiobiology, calibrations, etc.). A future update of the facility foresees the addition of a small room served by the proton beam from the injector, for thermal neutron production for BNCT. The possibility also exists for the production of positron emitting radionuclides for PET diagnostics (^{11}C, ^{13}N, ^{15}O and ^{18}F).

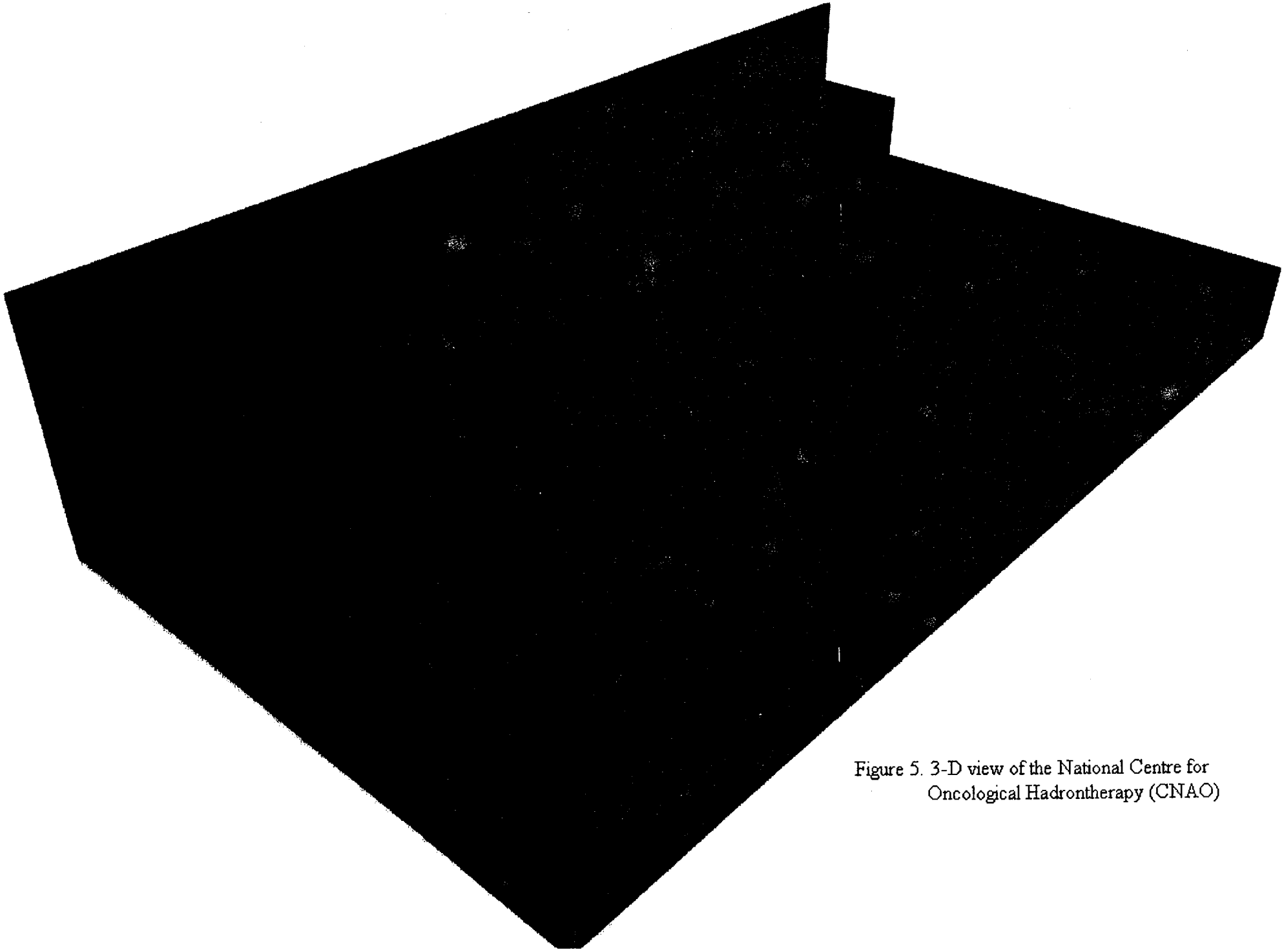

Figure 5. 3-D view of the National Centre for Oncological Hadrontherapy (CNAO)

The complex will consist of two buildings: an underground, heavily shielded area (the "bunker") housing the accelerators and the treatment rooms, and a surface building above ground with conventional facilities and office space. The bunker has a surface area of about 70 x 40 m^2 and consists of three underground levels. Level -3 houses the accelerator and the treatment rooms, level -2 houses the auxiliary equipment (such as power supplies and cooling units) and rooms for dosimetry and treatment planning, level -1 is reserved for office space and diagnostics units (MR and CT scanners).

The main accelerator is a synchrotron capable of providing 60-250 MeV proton beams with an average intensity of about 10 nA [20-24]. The injection energy in the synchrotron is 11 MeV. The injector is an RFQ + DTL structure, delivering average currents of 50-100 μA, sufficient for producing positron emitting radionuclides for PET diagnostics [25] and thermal and epithermal neutrons for BNCT [26-28]. After a sufficient clinical experience is gained with proton treatments, the accelerator will be upgraded to start treatments with light ions. The complex will be modified to accelerate fully stripped light ions up to ^{12}C or ^{16}O to a final energy in the range 120-400 MeV/u, with minor interventions on the ring and the addition of a second ion source and injector. A synchrotron has been preferred as it easily provides pulse-to-pulse energy variability over fine steps, as required by the clinicians. In addition, the cyclotron and linac options are ruled out by the request of future upgrade to light ion acceleration. After initial operation with ion beams with one horizontal beam line, the building can be expanded with the addition of one or two additional treatment rooms for ions.

6. THE COMPACT ACCELERATOR PROJECT

Another main goal of the TERA project is the development of a "compact" proton accelerator for hospital installation. Such an accelerator should satisfy the following requirements (or at least most of them): 1) it should accelerate a minimum of $2x10^{10}$ 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. Four options were studied: 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 the research field to industry and the medical field. The four designs are thoroughly discussed and compared in ref. [29] and a brief overview is given in ref. [30]. Here we will only discuss the two designs which are most promising, i.e. the linac and the superconducting cyclotron.

Linear accelerator. Medical electron linear accelerators (6-25 MeV) are commonly used for radiation therapy, where they have largely replaced cobalt-60 units. The typical RF frequency of these machines is 3 GHz, for which many RF power supplies are commercially available. To develop a compact proton linac one is therefore tempted to use this frequency, although it is unusual for accelerators, as such a high frequency is not compatible with a large bore aperture (i.e., high proton intensity). However, the proton current required for therapy is so low (a few nA) that the use of a 3 GHz structure becomes feasible.

The linac [31] shown in Fig. 6 is designed for a maximum energy of 200 MeV. The accelerator is made up of a 428.3 MHz 7 MeV RFQ+DTL injector, followed by a 7-70 MeV

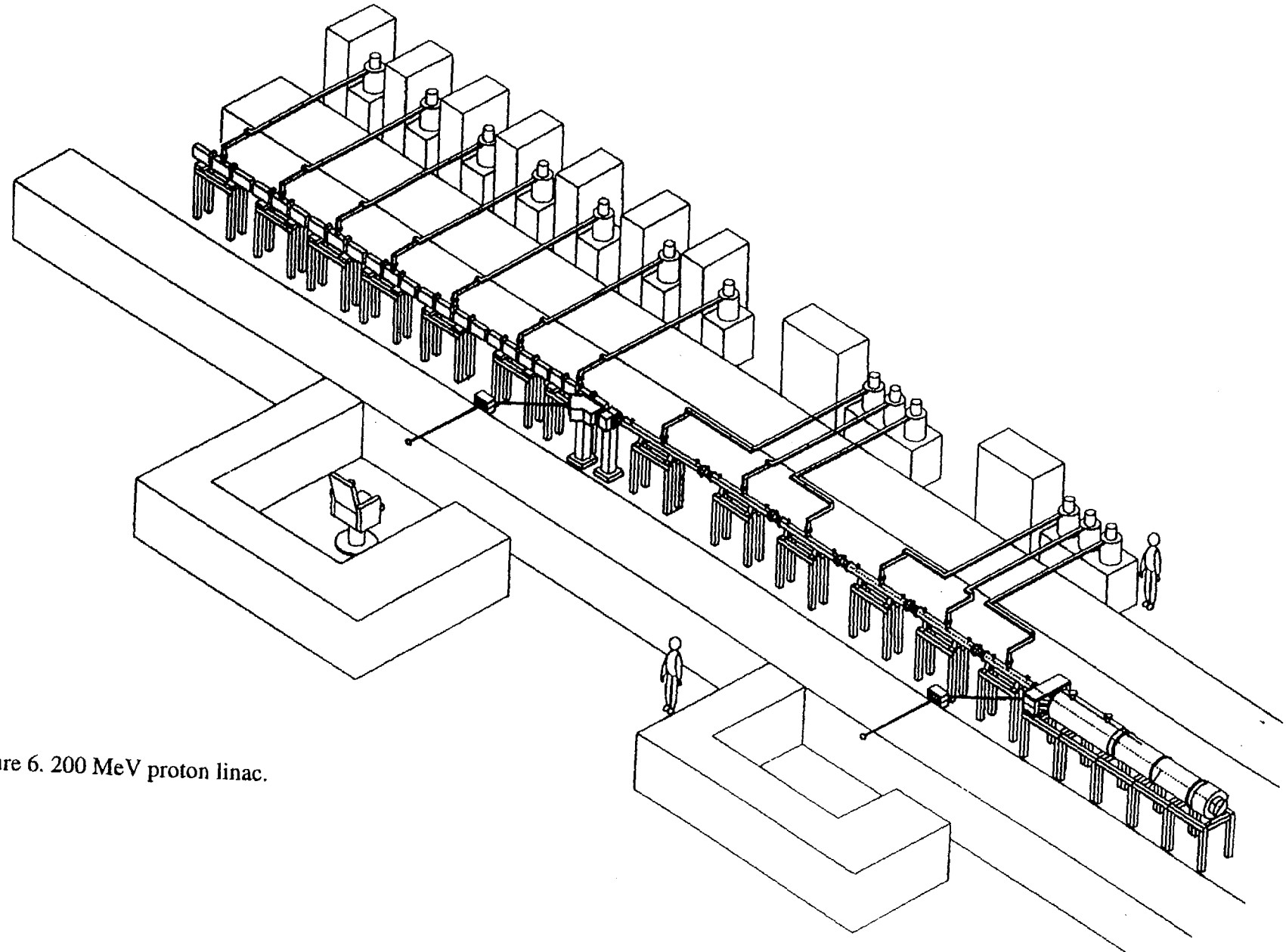

Figure 6. 200 MeV proton linac.

section based on an innovative 3 GHz Side Coupled Drift Tube Linac (SCDTL) divided in 6 modules; each module, less than 2 m long, consists of a number of tanks and requires less than 1.5 MW peak power; focussing is achieved by permanent magnet quadrupoles. The SCDTL is followed by a 70-200 MeV variable energy Side Coupled Linac (SCL) operating at 3 GHz. The SCL is made up of 7 independently powered modules (5 MW klystrons), the 3 lower-energy ones composed of 4 tanks and the 4 high-energy ones composed of 3 tanks. The facility should be equipped with one beam at a fixed energy of 70 MeV (from the exit of the SCDTL) for eye treatments and one gantry transporting the 200 MeV beam from the exit of the SCL. The energy can be varied in steps by switching off some of the SCL tanks.

Superconducting cyclotron. A superconducting cyclotron is an interesting solution for a hospital-based accelerator, since size and cost are inversely proportional to the magnetic field, operation costs are much reduced with respect to a room-temperature cyclotron and superconductivity is a well-established technique, already used in hospitals (MR imaging). A superconducting cyclotron accelerating deuterons to 50 MeV has been designed and built at the Michigan State University and is in use at the Harper Grace Hospital in Detroit for neutron therapy [32]. A small superconducting cyclotron (12 MeV) for the production of PET radionuclides is marketed by Oxford Instruments [33].

The cyclotron studied is a joint project between the University of Milan and the Centre Antoine Lacassagne in Nice. The accelerator, designed for a fixed energy of 200 MeV, has a three sector configuration and uses three RF cavities located in the valleys. The extraction radius is 0.7 m. To simplify the construction and the operation of the cyclotron and to reduce cost, the following solutions have been adopted: 1) the isochronous field is obtained by shimming the poles, thus avoiding the necessity of trim coils; 2) the superconducting coils are operated in the persistent mode by shortening them with a superconducting cable; 3) there is no LHe liquifier, but the cryostat only requires a periodic refilling (about once a fortnight); 4) acceleration is achieved with 3rd RF harmonic; 5) use is made of an internal proton source. The estimated power consumption of the cyclotron is 120 kW. The magnetic field at the centre is 2.53 T. The extracted proton current for therapy application is limited to 500 nA.

7. RADIATION PROTECTION REQUIREMENTS

Proton accelerators employed in radiation therapy are intermediate energy machine which produce secondary radiation (neutrons and photons) from beam interaction with accelerator components (such as the magnets), beam delivery devices (such as collimators) and the patient. Although the beam intensity is much lower than that typical of research accelerators (a few 10^{10} protons/s versus values larger than 10^{13} protons/s), yet the fact that such machines should normally be installed inside a hospital and/or in highly populated areas calls for a shielding design which should reduce the radiological impact on the external environment essentially to zero. Typical required shielding thicknesses ranges from 1.5 m of ordinary concrete up to 4 m (to attenuate the forward secondary emission in the case, for example, of a treatment room with a fixed horizontal beam). The shielding design obviously depends on whether one should ensure dose equivalent limits compatible with occupational exposure of with the general public. This distinction is important because at least part of the facility is accessed by people accompanying the patients undergoing therapy. Experimental and calculated shielding data for the energy range of interest for medical accelerators and some results of shielding measurements can be found in refs. [34-46].

A peculiar situation with a medical proton facility is the use of isocentric gantries. The fact that the beam can be rotated 360 degrees in one plane imposes specific equirements on the shielding walls of the room, as well as accurate assumption on the use factors of the shields. Access to the treatment room needs to be through a two or three leg maze [47], several metres long, to avoid the use of a massive shielding door which would be impractical in a medical facility. At most, a polyethylene door like those ones used in conventional radiation therapy departments equipped with electron linacs may be installed. Interlocks must obviously prevent access to the accelerator hall and to the treatment room when the beam is present, but the possibility of fast beam abort and immediante entrance into the treatment room must be ensured in the case the patient needs assistance. Due to the low beam intensities involved in the operation of the accelerator and the short irradiation times, air and material activation do not usually represent a major problem.

8. CONCLUSIONS

Advantages and disadvantages of different options for a medical proton accelerator, whether it should be in particular a cyclotron or a synchrotron, have been largely addressed, but no definitive answer has been given and is likely to not exist. There are several factors which have to be balanced: fixed versus variable energy extraction, time structure of the extracted beam (continuous versus pulsed), flexibility versus simplicity of operation, reliability, space requirements, capital and running costs, etc. As a point of fact, a synchrotron was chosen at LLUMC, and a cyclotron for the NPTC under construction at the Massachussetts General Hospital in Boston. For ion acceleration, the synchrotron seems to be the only choice.

The linac may also prove to be a successful accelerator for proton therapy, while the use of a superconducting magnet can drastically reduce size, weight and the possible cost of a cyclotron. The next few years will hopefully bring interesting technological developments to this field, not only on the accelerator side, but also in the beam delivery systems. The development of more compact gantry systems is as important as the construction of compact proton accelerators. If these advances do come about, it is possible that proton (and possibly ion) therapy will become a widespread clinical tool.

9. ACKNOWLEDGEMENTS

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