ACCELERATORS FOR RADIOTHERAPY

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ABSTRACT

Ionizing radiations have been used since the early days of this century to destroy tumors. Different kinds of radiations can be used in radiotherapy : x-rays produced by energetic electrons, electrons, fast neutrons, pions and positive ions. Those radiations are briefly compared considering the dose distribution in the patient body and the advantages of a high Linear Energy Transfer (L.E.T.). Then, different kinds of accelerators used in radiotherapy are briefly reviewed, with emphasis on new developments.

INTRODUCTION

Soon after the discovery of the X-ray, at the turn of this century, it was discovered that X-rays could kill living cells and, therefore, be used for the therapy of cancer. Somewhat later it was recognised that radium emitted energetic gamma rays that had better penetration than the early therapeutic X-rays. In 1936, just after the completion of the 37-inch cyclotron by Ernest.O. Lawrence, and the first fast neutron beams developments, Ernest's brother, John Lawrence, together with Zirkle, Aebersold, Lampe and others started studies on the comparative effects of neutrons and X-rays on various biological systems. In 1939, the new 60-inch cyclotron was accelerating 16 MeV deuterons and was used to start a careful program of radiobiological studies in the field of neutrontherapy and, in december 1939, clinical trials started on patients.
From 1939 to 1943, 226 patients were treated but, due to the lack of fundamental radiobiological knowledge at the time, those initial treatments resulted in a large proportion of problems and the program was discontinued.
In the late forties, electron accelerators, mostly betatrons were built to reach better penetrations with X-rays. However, during the same period, the availability of ^{60}Co sources coming from nuclear reactors made obsolete the use of expensive radium units and the ^{60}Co became the standard source for photon therapy in the world.
It was however recognized that higher energy sources were desirable and in the fifties, numerous high energy betatrons and linacs were built.
At the same time, the development of higher energy proton and heavy ion accelerators for nuclear physics research opened the way for positive ion therapies and, later, for pion therapy.

I. General requirements of radiations for radiotherapy.

1.1 Basic considerations.

In radiotherapy, ionizing radiations are used to destroy undesirable tissues (generally, but not always, cancer tumors) within the body of the patient. Ideally, the radiation effect should be restricted to the zone to be destroyed, and should leave the surrounding normal tissues unaffected.
This goal is however impossible to reach : all radiations travel essentially in straight line through the body and destroy cells in the entrance region, from the surface of the body to the tumor. Most kinds of radiations, like photons, electrons or neutrons have also an effect downstream from the tumor to the exit of the body. Those unwanted effects to normal tissues can be minimized by delivering the radiation to the patient, in different directions, crossing at the location of the tumor.

It is worth noting that our inability to locate the radiobiological effect within the tumor is not only due to the physical characteristics of the beams used but also, often, to an imperfect knowledge of the tumor position and limits.

In addition, the unwanted tissues are often more radioresistants than the normal tissues, which makes the situation even worse. As a result, there is a conflict between the radiation dose needed to achieve a satisfactory tumor control and the dose needed to avoid complications.

1.2 Dose distribution

The dose distribution for X-rays is illustrated by figure 1.

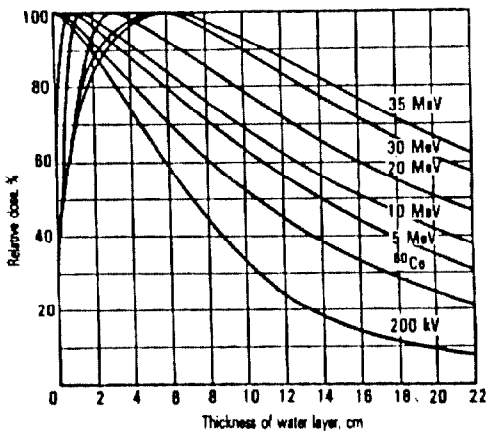

Fig. 1- Depth dose as function of thickness of water layer for 200-kV x-rays, ^{60}Co γ-rays, and betatron x-rays with energies of 5, 10, 20, 30 and 35 MeV.(reprinted from {1}).

If electrons are used instead of photons, we have a reduced dose at large depths. Therefore, for typically available electron energies from linacs, the usefulness of electrons is limited to tumors located close to the surface of the body.

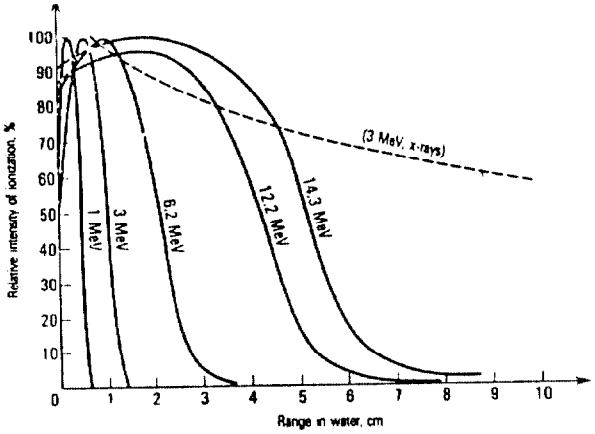

Fig. 2- Ranges of high-energy electrons in water (____) and range of hard 3-MeV x-rays (----).(reprinted from {2}).

Neutrons have dose distribution shapes basically similar to photons, but with generally larger penumbras due to the difficulty to collimate efficiently neutrons. Neutrons produced by D.T. generators have dose distributions comparable to ^{60}Co γ-rays,while fast neutrons produced by a 66 MeV proton beam on a thin beryllium target can be compared to X-rays produced by an 8 MeV linac.

For protons or light ions, the dose distribution shows the well known "Bragg-peak", characteristic of the stopping of heavy charged particles.

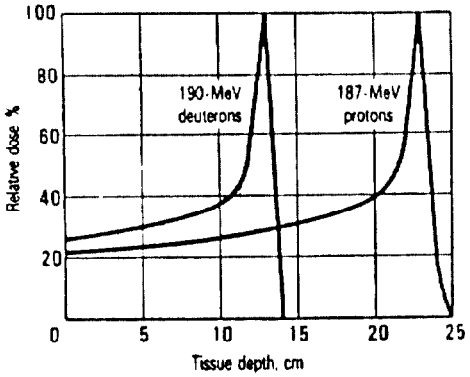

Fig. 3- Depth dose in water for 190-MeV deuterons and 187-MeV protons (after Larsson).(reprinted from {1}).

This peak is actually too sharp to be used on real tumors, and one needs to sweep the energy to broaden the peak.

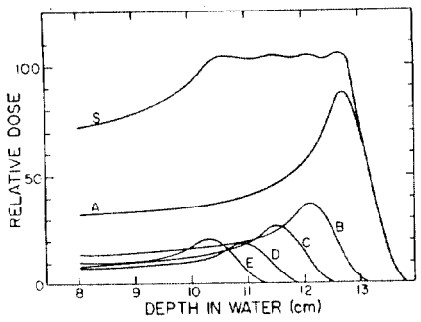

Fig. 4- Modified depth-dose distribution of a proton beam (redrawn from Koehler and Preston, 1972)(reprinted from {3}).

The sparing on normal tissues resulting from the use of protons compared to photons is illustrated in figure 5.

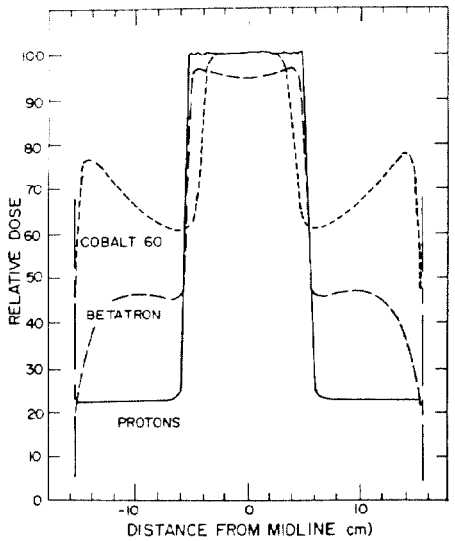

Fig. 5- Dose distribution for ^{60}Co gamma rays, 22-MeV X rays from the betatron, and protons for irradiation of the uterine cervix with four fields in two opposed pairs with their axes inclined at 110° (reprinted from {3}).

1.3 The oxygen effect - low and high L.E.T. radiations

In the fifties, different groups and mainly Gray and his associates in Great Britain demonstrated that the biological effects of a radiation were caused by the combination of both direct and indirect interactions : the direct effect is the destruction or modification of chemical bonds in critical molecules, while the indirect effect is mostly due to the creation of oxidizing free radicals in the tissue water. Thus the presence of free oxygen in the cell enhances greatly the indirect effect.

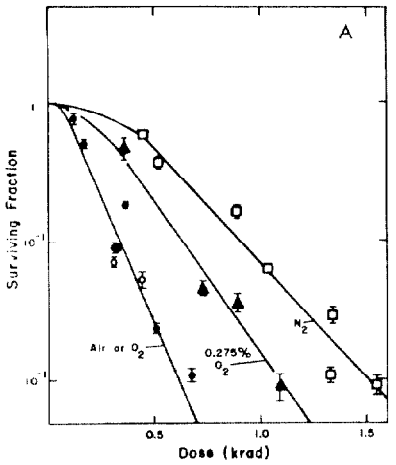

Fig. 6- Survival of human liver cells after 200-kVP x-rays following equilibration with oxygen (-0-), air (-●-), nitrogen (-Â-), and 0.275% oxygen (-Δ-) in nitrogen (reprinted from {4}).

This effect is called the Oxygen Enhancement Ratio (O.E.R.) and is a very serious limiting factor in cancer radiotherapy. Indeed, as tumor tissues are often poorly vascularized and tumor cells therefore less oxygenated, those tumor cells tend to become more radioresistant than the surrounding normal tissues.

It was soon recognized that the O.E.R. was related to energy distribution of the radiation on a microscopic scale. A significant parameter of this energy distribution at microscopic scale is the Linear Energy Transfer (L.E.T.). Numerous experiences have shown that both the O.E.R. and the Relative Biological Efficiency (R.B.E.) of a radiation were connected to the L.E.T.

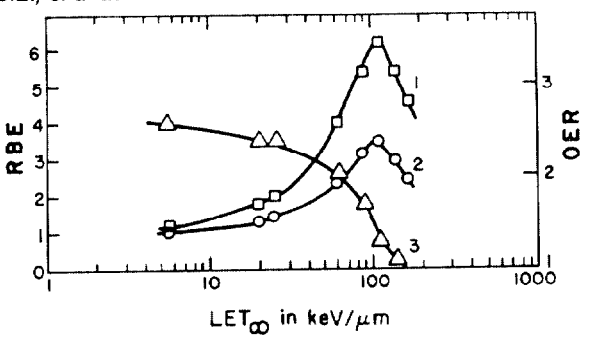

Fig. 7- Variations of RBE and OER as a function of LET_∞ of alpha particles and deuterons, derived from survival curves of cultured cells of human kidney origin. RBE curves 1 and 2 correspond to fractions of 0.5 and 0.01 surviving cells. Curve 3 represents the variation of OER with LET_∞. (Reprinted from {5})

Photons and high energy electrons have low L.E.T.'s from 10^{-2} to 10 KeV/ micrometers. For positive ions, the L.E.T. increases with mass for particles of comparable range.

The biological effect of fast neutrons is essentially due to low energy recoil ions, and their average L.E.T. is therefore very high, around 75 KeV/micrometer.

1.4 Comparison of different kinds of radiations

If we compare the merits of different kinds of radiations used in radiotherapy,combining the dose distribution advantage and the high L.E.T. advantage, we find the classical figure suggested initially by A.M. Koehler.

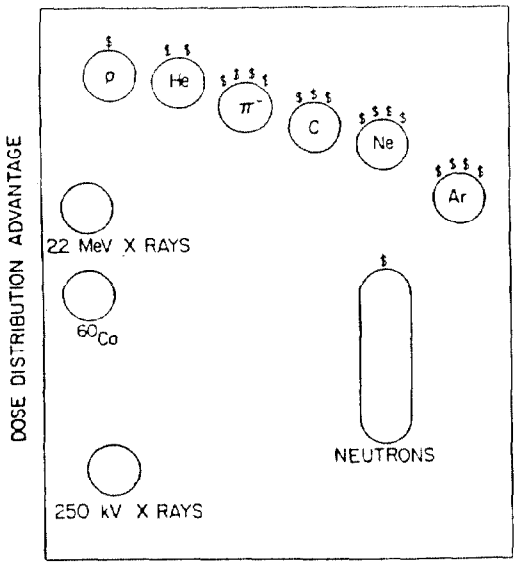

Fig. 8- Schematic comparison of different types of radiations of interest in radiotherapy. The relative price range for particle facilities is indicated by dollar signs. (Reprinted from {6}).

II. Accelerators for radiotherapy

2.1 Electron and photon therapy

Electron and X-ray production accelerators with energies between a few MeV and 40 MeV represent, by far, the largest number of accelerators built for radiotherapy. Although numerous new and interesting developments continue to appear regularly, their technology can be considered as mature and they are produced in large quantities by commercial companies.

2.1.1 Betatron

Betatrons were the first electron accelerators built for radiotherapeutic purposes. Table 1 summarizes the main parameters of some classical betatrons. Betatrons have now been mostly replaced by electron R.F. linacs.

Manufacturer, country	Type	Emergent radiation e^-	Emergent radiation x-rays	Energy range, MeV	Angle of rotation
Allis-Chalmers (U.S.A.)	25 RTM	•	•	10-25	
Brown Boveri (Switzerland)	Asklepitron 35	•	•	0-35	± 105°
Brown Boveri (Switzerland)	Asklepitron 45	•	•	3-45	± 120°
Techsnabexport (U.S.S.R.)	B5M-25	•	•	7-25	± 90°
Siemens (F.R.G.)	18 MeV	•	•	4-18	
Siemens (F.R.G.)	42 MeV	•	•	5-42	± 90°

Table 1 (reprinted from {1}).

2.1.2 R.F. linacs

R.F. linacs are the most commonly used electron accelerators used for electron and photon therapy. Table 2 summarizes the main parameters of some common R.F.linacs.

Manufacturer, country	Type	Emergent radiation e^-	Emergent radiation x-rays	Energy range, MeV	Angle of rotation
Varian (U.S.A.)	Clinac 4/100		•	4	360°
Varian (U.S.A.)	Clinac 6/100		•	6	360°
Varian (U.S.A.)	Clinac 20	•	•	6-20	360°
Varian (U.S.A.)	Clinac 2500	•	•	6-22	365°
Siemens (U.S.A.)	Mevatron 67		•	6	370°
Siemens (U.S.A.)	Mevatron 74	•	•	5-12	370°
Siemens (U.S.A.)	Mevatron 77	•	•	7-18	370°
Philips M.E.L. (G.B.)	SL 75-5		•	4-6	365°
Philips M.E.L. (G.B.)	SL 75-20	•	•	5-20	370°
CGR-MeV (France)	Saturne	•	•	6-20	365°
CGR-MeV (France)	Sagitaire	•	•	7-40	± 105°

Table 2 (reprinted from {1}).

The lenght of a linac increasing with energy, different solutions are used to obtain an isocentric beam.

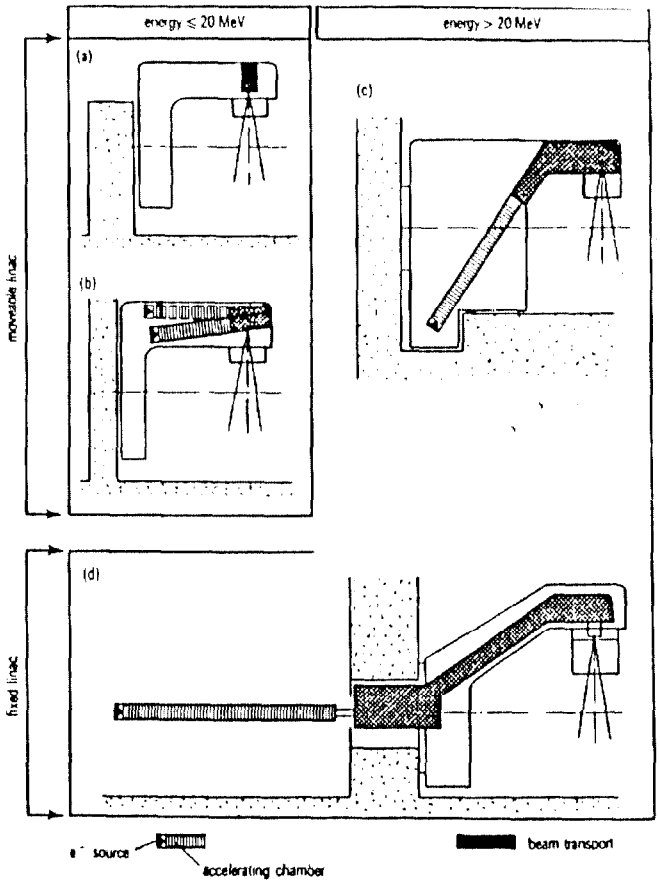

Fig. 9 Location of linacs in facilities for rotating therapy (reprinted from {1}).

Considering the large energy variation of a R.F. linac beam during the pulse, achromatic systems are often used for the beam optics.

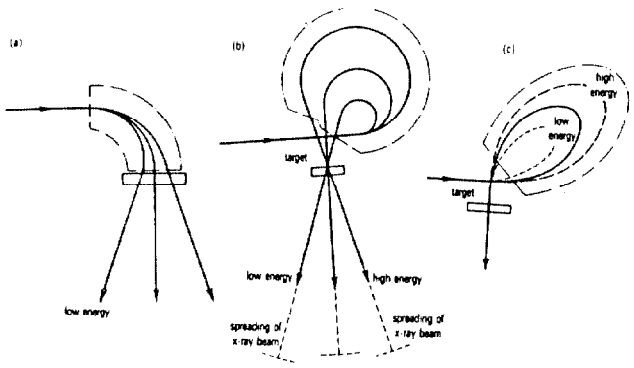

Fig. 10- Paths of electrons of various energies in analyzing-deflecting magnets of radiotherapeutics; (a) magnet with 90° deflection; (b) magnet with 270° deflection, ordinary; (c) magnet with 270° deflection, "pretzel" type (achromatic) (reprinted from {1}).

2.1.3 Microtrons

Circular microtrons and, more recently, racetrack microtrons have been introduced as an alternative to R.F. linacs. They offer the advantage of a small energy dispersion, allowing the use of a beam transport system distributing the beam of a single accelerator to different treatment units.

2.2 Neutron therapy

2.2.1 D.T. generators

The simplest way to generate fast neutrons for neutron therapy is the well known D.T. generator, using 100 ... 300 keV deuterons on a tritiated target. However, large deuteron currents are needed to obtain sufficient neutron fluxes resulting in a rather short target lifetime at such beam powers, and the neutron energy of 14 MeV gives a dose distribution similar to ^{60}Co gamma ray, unsatisfying for deeply located tumors. In addition, the low dose rate obliges to reduce the source to patient distance to typically 80cm. Such a distance is too small for an appropriate collimation of the beam, giving significant penumbras. Therefore the use of D.T. for neutron therapy has been generally discontinued.

2.2.2 Isochronous cyclotrons

A number of classical isochronous cyclotrons have been built primarly as a source of fast neutrons for neutron therapy. They use generally a proton beam, with energies between 30 and 65 MeV to produce fast neutrons by reaction on a beryllium target. Deuterons are also used, and have generally higher neutron production yields but worse dose distribution than protons of similar energy. Classical neutron therapy facilities use a beam transport system together with an isocentric gantry carrying an adjustable neutron collimator. Recently, an attractive new concept, using a superconducting cyclotron rotating around the patient, has been introduced by H.G. Blosser {7}. In this cyclotron, the neutron producing target is hit by the internal beam of the cyclotron, and the yoke is used as part of the neutron collimator.

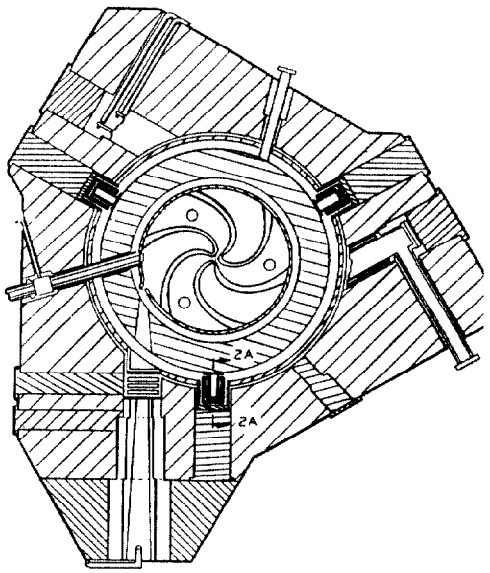

Fig. 11- Median plane section view of the medical cyclotron showing the three spiral hills and accelerating electrodes. Collimators will be of polyethelene concrete mounted in a nonmagnetic collimator snout at the lower left. (reprinted from {7}).

2.3 Pion therapy

Pions have been used for radiobiological studies and for radiotherapy around a number of medium energy proton research facilities. However, the production of pions require such high proton energies and intensities that the construction of an accelerator mainly dedicated to pion therapy would be an excessively large investment and remains therefore quite unlikely.

2.4 Proton and heavy ion therapy

As shown in 1.4, positive ions show a distinct advantage in dose delivery, and have a L.E.T. increasing with the projectile mass. Unfortunately, the energies needed to reach a depth of 25 cm in water range from 200 MeV/A for protons to 400 MeV/A for "light" heavy ions like neon. Accelerators needed to produce those high energies are obviously quite expensive and lie at the limit between the field of large cyclotrons and of small synchrotrons.

2.4.1 Large cyclotrons for positive ion therapy.

A number of old synchro-cyclotrons have been and are still used for positive ion therapy at the end of their useful life in the field of nuclear physics.
In addition, a number of larger isochronous cyclotrons have been planned, but none has been funded up to now. For the production of protons in the energy range 200 ... 250 MeV, at least three technologies can be considered : the synchro-cyclotron (S.C.), the isochronous cyclotron (I.C.) and the synchrotron. Although maximum intensity available from S.C. is quite low, it is perfectly adequate for therapy. A project of superconducting S.C. for proton therapy has been considered by H.Blosser and Cie {8}, while a more classical I.C. structure has been studied for Tsukuba in Japan {9}.

In Europe, a number of radiotherapy groups joined to create the project EULIMA (for EUropean Light Ion Medical Accelerator), a facility able to accelerate ions from protons to neons to energies of 400 MeV/nucleon. The accelerator would be a separated sector, isochronous cyclotron with superconducting coils, having a maximum bending limit K=1600. It would accelerate fully stripped ions produced by an Electron Cyclotron Resonance Ion Source.

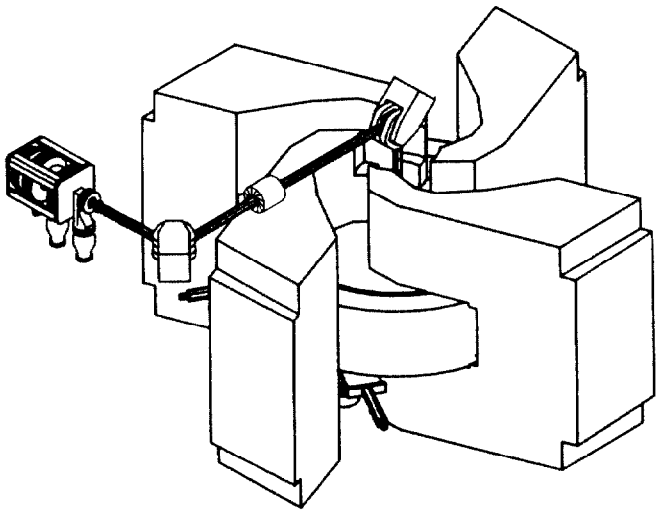

Fig. 12- The EULIMA cyclotron project.

2.4.2 Synchrotrons for positive ion therapy

In addition to facilities operating around nuclear physics research synchrotrons in various parts of the world, a number of small synchrotrons totally dedicated to positive ion therapy have been designed and at least two are in construction.

A 250 MeV synchrotron for proton therapy is presently being built by Fermilab for the Loma Linda Hospital in California. Such a synchrotron fits in a 7 x 7m room, and is injected by a 2MeV R.F.Q. {10}.

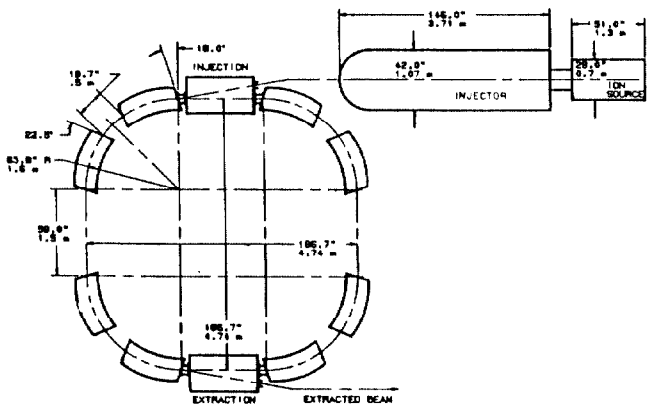

Fig. 13- General Plan of the Accelerator (reprinted from {10}).

A larger synchrotron, able to accelerate heavy ions up to 600 MeV/A is in construction at the N I R S in Chiba (Japan). This accelerator will use P.I.G. ion source, a R.F.Q. linac, an Alvarez linac and two superposed synchrotron rings.

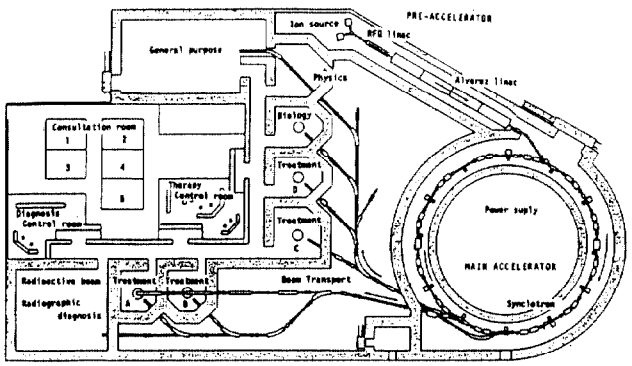

Fig. 14- Preliminary illustration of the NIRS heavy particle medical accelerator and the beam lines for cancer treatment (NIRS) (reprinted from {11}).

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