ACCELERATORS FOR MEDICAL APPLICATIONS

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Abstract

About 50% of the ten thousands particle accelerators at present running in the world are devoted to medical applications. The main areas of use are: (i) radioisotope production, (ii) conventional radiotherapy with electron and photon beams, (iii) oncological hadrontherapy. In this review paper it is shown that in all these areas there are new developments which are scientifically interesting and/or economically promising.

1 INTRODUCTION

Approximately 50% of the 10'000 or so accelerators running in the world are devoted to medicine and/or biology. Table 1 reproduces the statistics presented in a recent paper by W.H. Scharf and O.A. Chomicki [1].

Table 1. 1994 statistics of all the running accelerators and update for 1995 [1].

CATEGORY	*NUMBER IN USE*
"High Energy" research accelerators	~112
Accelerators in industry	~1500
Ion implanters Surface modification	> 2000 ~ 1000
Synchrotron radiation sources	~ 50
BIOMEDICAL ACCELERATORS – Radiotherapy – Research (including biomedical) – Medical radioisotope production	 *>4000* *~ 800* *~ 5000* *~ 200*
Total in 1994	~ 9962
Total estimated in 1995	*~ 10000*

As shown in Table 1, 80% of all the biomedical accelerators (4'000 in 1994) are devoted to radiotherapy with either X-rays (to be discussed in Sections 3) or hadron beams (Section 4). Section 2 is devoted to some remarks concerning the applications of accelerators to the production of medical radioisotopes, a subject that is also covered in the paper by D. Lewis [2].

2 RADIOISOTOPE PRODUCTION

In 1994, the world turnover of business connected with medical radioisotope production was 1.2 M$ [1]. Three subjects will be touched upon here:

1. production of isotopes for PET applications,
2. production of isotopes for nuclear medicine,
3. neutron sources as substitutes for nuclear reactors.

2.1 Accelerators for PET

PET applications are reviewed by T. Jones [3]. Still it is worth making two remarks on the accelerators that produce the four PET isotopes: ^{11}C, ^{13}N, ^{15}O and ^{18}F.

Firstly, until now these isotopes have been produced with cyclotrons accelerating protons (and much less frequently deuterons) to energies lower than 15-20 MeV. Recently some firms have offered and sold linacs accelerating about 10^{-4} A of protons to 10-12 MeV for the same purpose. It is too early to say how many users will chose linacs instead of cyclotrons for this application. Still it is important to underline, that in a mature field, accelerators of a different design can be introduced with the realistic hope of an economic return. The RF-Focused Drift-tube (RFD) linac [4] is another possible contender.

Secondly, usually a PET centre has a cyclotron and one, sometimes more, PET cameras. However a better use of the facilities could be made by serving more centres with a single accelerator. As can be seen from the data of Ref. [5], this is already done in Germany but not at all in the other European countries, which will probably follow the trend.

Table 2. 1995 statistics of cyclotrons and PET Centres in Europe [5].

	Cyclotrons	PET Centres	Ratio
GERMANY	17	30	*~ 55%*
EU-GERMANY	41	44	*~ 95%*
EU	58	74	*~ 78%*

2.2 Nuclear medicine applications

Production of isotopes for nuclear medicine requires proton energies greater than 15-20 MeV. (Cyclotrons used in these applications are usually multiparticle machines having K>18). About hundred cyclotrons, produced by eight firms, are at present running in the world. The list of isotopes is long and only some of the most interesting ones are recalled here to underline the variety of the applications:

- ^{67}Ga diagnosis of cancer and infections,
- ^{81m}Kr diagnosis of ventilatory disorders of the lung,
- ^{111}In antibodies label, study of the cerebral fluid,
- ^{123}I studies of the thyroid and of the blood flow,
- ^{195m}Hg studies of the blood flow rate,
- ^{201}Tl myocardial scintigraphy.

Highly enriched targets are needed to produce radioactive isotopes which comply with the pharmaceutical licences. Collection rates of the separators are of the order of milligrams/hour, so that the starting material is expensive. Isotope separators capable of producing large currents are thus essential components of all these facilities. Their characteristics appear in Fig.1, which also shows the currents and the energies of some existing and proposed accelerators for nuclear medicine applications [5].

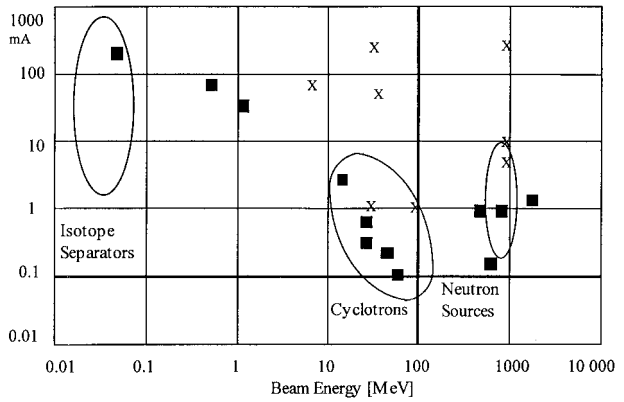

Figure: 1 Energies and currents of the separators and accelerators used for nuclear medicine ("cyclotrons") and as intense neutron sources (crosses=existing facilities; squares=projects) [6]. The closed curves indicate typical values of the parameters of these three types of sources.

Bulk radiopharmaceuticals are produced by cyclotrons which have been engineered to combine reliability with ease of maintenance. On the larger cyclotrons negative hydrogen ions are accelerated [7]. The beam powers are now of the order of 15 kW, and are ten times larger in the future nuclear medicine proposals of 100 MeV cyclotrons or proton linacs [8].

2.3 Accelerators as substitutes for reactors

At present, radiopharmaceutical production by neutron activation is carried out at reactors having large thermal neutron fluxes (~2 10^4 neutrons $s^{-1}cm^{-2}$). These are therapeutically and economically very important sources, since about 90% of all nuclear medicine procedures utilize ^{99m}Tc, whose precursor ^{99}Mo is produced in reactors. Moreover ^{125}I and ^{192}Ir for cancer therapy are produced through neutron capture and neutrons are also utilized in Boron Neutron Capture Therapy (BNCT), for which a new line has been built with EU funds at the Petten reactor.

Many of these reactors are approaching the end of their useful life and spallation neutron sources are at present being considered for radiopharmaceutical uses. Recently spallation sources have also been proposed for energy production (Carlo Rubbia's Energy Multiplier) and for nuclear waste transmutations [9]. The challenge is the production of high-power proton beams: in the design presented by IBA (ADONIS) the energy is 150 MeV and the current is 2 mA [10]. Certainly this field will flourish in the next few years, if the necessary investments to build the first prototype cyclotrons and linacs can be found.

3 LINACS FOR RADIOTHERAPY WITH X-RAYS AND ELECTRONS

3.1 The future of megavoltage X-ray therapy

Electron linacs are the most used X-ray source in cancer radiotherapy (RT). As shown in Fig. 2, the rate of installation of new 3 GHz linacs has been very large, particularly in the United States, so that today about half of the 4000 accelerators used in the world (Table 1) are in the USA.

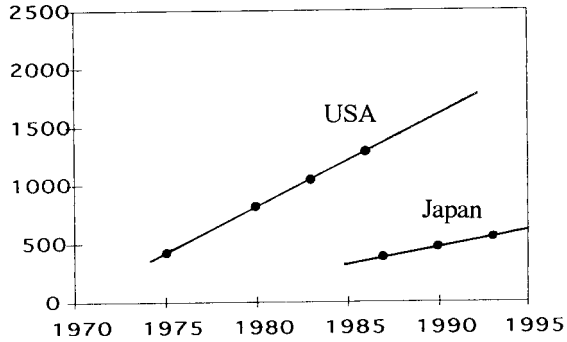

Figure: 2 Time dependence of the number of electron linacs installed in the USA and Japan. (Data from Ref. 1,11).

In the USA, the replacement of cobalt "bombs" by linacs has been very rapid: the ratio R= (cobalt sources/linacs), which was 2.5 in 1975, had gone down to about 0.6 in 1985 [12]. At present the ratio R is about 1.5 in the rest of the world while it is less than 0.5 in the States, where there is a linac for every 150 000 inhabitants. This is even too much, since it corresponds to less than the optimal value of 250 patients/year for each linac. To understand this figure it has to be stressed that electrons are used only in 10-15% of all the treatments and that with X-rays a tumour is irradiated typically 30 times (5days x 6weeks) with a total dose of about 30x2Gy = 60J/kg. Thus 250 patients/year corresponds to about 7000 sessions/year; each session lasts about 15, mainly spent in positioning the patient.

In the sixties travelling wave linacs were used. From the seventies standing wave linacs in the range of 5-25 MeV and of higher gradient (about 15 MeV/m) are used. They are short and light, so that they are easily mounted on a rotating system and the patient can be irradiated from any angle. They are also very reliable, the typical fraction of time-on being 98%. They are considered to be better RT sources than cobalt bombs, both because of the higher penetration (Fig. 3) of the photons (megavoltage X-rays, in the parlance of radiotherapists) and the easier handling and disposal. The substitution will continue worldwide, so that the potential market is large, in particular if developing countries are taken into account. A single figure should suffice: only 50 linacs are at present installed in Indian hospitals [12].

3.2 Conformal radiotherapy

High-energy photons have an unfavourable dose distribution (Fig. 3). Thus in a typical treatment, two opposite beams of X-rays are used so that, for a given dose to the tumour, the dose absorbed by the upstream healthy tissues is reduced. Four cross-fired beams are also used; still the contour of a regularly shaped tumour can be followed with a precision which is at best *centimetric*. For irregular shapes the situation is even worse.

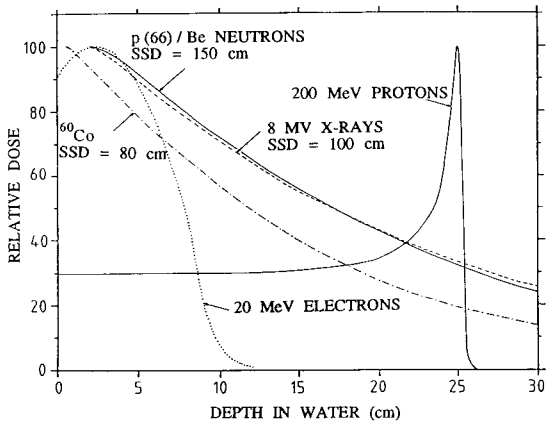

Figure: 3 Dose-depth curves in water of various beams of radiation.

Only recently multiple (up to twelve) crossing beams have been used in the so called *conformal radiation therapy* (CRT) which, based on very accurate 3D imaging and treatment planning, can follow contours with *millimetric* precision. In CRT the energy absorbed by the healthy tissues is globally the same but is more uniformly distributed over the surrounding healthy tissues than in normal RT. This is very important when the tumour is very close to one (or more) critical organs that cannot be irradiated. Since the dose to the tumour is limited by the dose that can be absorbed by the critical organ(s), in CRT larger doses can be given to the tumour. Note that a 10% increase of the dose corresponds to a 15-20% increase in the probability of local control of the tumour: even a small increase in the dose is therapeutically worthwhile.

4 ACCELERATORS AND TECHNIQUES OF HADRONTHERAPY

4.1 Deep hadrontherapy

Fifty years ago, Bob Wilson remarked that the Bragg peak of monoenergetic protons (shown in Fig. 4) and of other charged hadrons, easily allows what is now called a "conformal" treatment of deep sited tumours [13]. To reach 25 cm in soft tissues the kinetic energy of the protons has to be at least 200 MeV. For carbon ions, the most used hadrons after protons, one needs 4500 MeV, i.e. 375 MeV/u. Since the width of the Bragg peak of monoenergetic particles is very narrow, to irradiate thick targets the energy of the charged particles has to be modulated in time either by an absorber of variable thickness or by changing the energy of the accelerator.

With a *Spread Out Bragg Peak* (SOBP) of 8-10 cm, the distall fall-off of the dose takes place in 2-3 mm and the surface dose for proton (carbon ions) is typically 70% (50%) of the peak dose at 20-25 cm depth. These conditions are much more favourable than those of X-rays (Fig. 3). Due to the convenient *macroscopic* energy distribution, a truly conformal radiotherapy can be performed with only one or two directions of incidence of the charged hadron beam. Moreover the total energy delivered to the surrounding healthy tissue is definitely lower than in X-rays conformal radiotherapy (CRT). This allows an even larger tumour dose than in CRT for sites which are surrounded by critical tissue, as in the brain.

What about neutral hadrons? Neutron beams have been used in Berkeley since 1938 for oncological treatments [14]. Indeed, about 50 MeV protons are sufficient to produce fast neutrons which, however, have a depth dose distribution not very different from megavoltage X-rays (Fig. 3). The advantage is that the deposition of energy is due to very low energy protons, which have a much larger stopping power (or LET=*Linear Energy Transfer*) than the electrons set in motion by high-energy photons: more than 100 MeV/cm instead of a few MeV/cm. As a consequence of the different *quality* of the radiation field, neutrontherapy is suited to treat *radioresistant* tumours, i.e. the slowly growing hypoxic tumours which are insensitive to both X-rays and protons and represent about 10% of all tumours treated with X-rays. Neutrontherapy, after the treatment of about 18000 patients, is at present being given up because this most useful *microscopic* feature is more than counterbalanced by the unfavourable *macroscopic* dose distribution. On the other hand, light ions, and in particular carbon ions, have the dual property of a favourable dose distribution (crucial for a conformal radiotherapy) and of a large LET (necessary for the cure of radioresistant tumours).

At the end of 1995 about 16000 patients had been treated with proton beams over the world [15] and about 100 with carbon ions at HIMAC (Heavy Ion Medical Accelerator Centre) in Japan [16]. The pioneering work done in LBL with helium ions (about 2000 patients) and neon ions (about 500 patients) was discontinued in 1992 [17]. As mentioned above, nowadays carbon ions (Z=6) are considered to be better suited than helium (Z=2) and neon (Z=10) ions for the treatment of radioresistant tumours, because the LET (which for a given velocity is proportional to Z^2) is less than 100 MeV/cm at the entry point (so that in the first traversed layers they behave roughly as X-rays and protons) but is definitely larger than 100 MeV/cm in the SOBP which covers the tumour.

Protontherapy of eye melanomas, requiring 60-70MeV protons, is performed in many, including European Union (EU) centres. Deep seated tumours are treated in one dedicated hospital-based centre (at the Loma Linda University Centre in California [18]) and in ten centres which originally were, or still are, nuclear research centres:

CPO	Orsay,	GWI	Uppsala,
HCL	Boston,	ITEP	Moscow,
IUCF	Indiana,	JINR	Dubna,
LINPh	St.Petersburg,	NAC	Faure,
PMRC	Tsukuba,	PSI	Villigen.

It is seen that only two of them are in EU (CPO and GWI). The HIMAC facility in Chiba (Japan) is fully

dedicated to ion therapy [16]. Together with Loma Linda, this is the only hospital based dedicated hadrontherapy centre. As discussed in Subsection 4.3, in the next years the situation will change, in particular outside Europe.

4.2 Beam spreading systems

Fig. 4 represents the two methods adopted for conformally irradiating a tumour target :

(i) By widening the beam with an absorber, which acts as a scattering medium, a funnel of charged particles is produced, as done for the neutral photons used in RT; collimators and absorbers are used to shape the field.

(ii) With two dipole magnets, a pencil beam is directed in the chosen direction and the target is irradiated by moving the pencil beam and varying its energy.

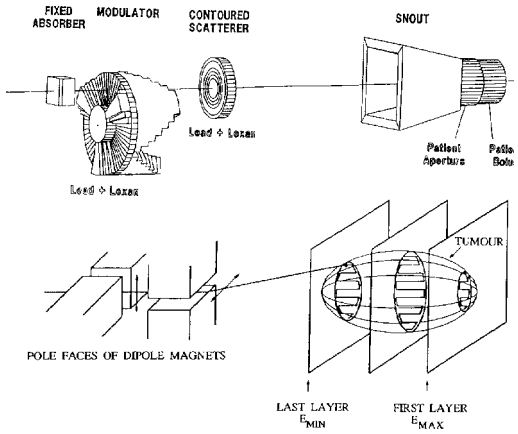

Figure: 4 "Passive" and "Active" beam spreading systems. An active system can be based either on *raster scanning* (as in TV) or on *voxel scanning*.

For the about 20000 patients treated so far with charged hadrons only passive beam spreading systems have been used. They are installed at the end of the beam transport system. In all centres these lines are fixed, while in Loma Linda they are the last part of three 10 m high *rotating isocentric gantries*, which allow irradiation from any angle. The alignment procedure is long: typically 20-30 minutes. Active systems have been recently tested in PSI and GSI and will be used on patients towards the end of 1996. At PSI a compact gantry and a voxel scanning system for protons has been constructed [19], while the carbon beam of the GSI synchrotron will be used to irradiate patients with a horizontal raster scanned pencil beam [20]. In future all facilities will have active spreading systems, but medical doctors still prefer the passive method which is proven and guarantees a uniform irradiation in the transverse plane. Active systems will have to be very reliable to be accepted.

4.3 Potential patients and new funded centres

In Europe (3.2 10^8 inhabitants), about 50% of all the tumours are irradiated with high energy photons. This corresponds to about 600'000 new X-ray treatments per year, which implies about 60'000 patients with radioresistant tumours, who could profit from iontherapy. To substantiate this large figure many clinical trials are needed at HIMAC, GSI and possibly other new iontherapy centres. For protontherapy solid results exist for brain, eye, spinal cord tumours and a few other sites. Salivary glands, prostates and cervices have also been treated. A conservative analysis made in the framework of the TERA programme (described in the *Blue Book* of Ref.[21]) concluded that about 5% of X-rays patients would profit (i.e. about 30'000 in Europe). In a study for Europe Gademan obtained much larger figures: 280'000 patients, of which about 25'000 first priority cases [22]. Since a multigantry centre can treat about 1000 patients/year (each one for 20 sessions lasting 20-30 minutes each) one conservatively concludes that in Europe there is space for at least *twenty* protontherapy centres aiming at improving the local control of tumours close to critical organs. But to be *economically competitive* with CRT, as shown by P. Chauvel et al in the *Green Book* of Ref. [23], the cost of protontherapy should be about 1000 DM/session, which implies an investement not larger than 20 MDM for the accelerator and three gantries; present costs are about 50% greater. This is a worthwhile technical challenge.

By the year 2000 there will be at least three new dedicated facilities for protontherapy. Two of them (one in the USA and the other in Japan) are based on the cyclotron designed by IBA [24]. For the Japanese tender IBA has teamed with Sumitomo(SHI). The American Centre (NPTC) will have two rotating gantries; it is being built in Boston by Mass. General Hospital (MGH) and utilizes all the knowledge collected at the Harvard cyclotron.

The third funded proton accelerator is of novel design and will be built in Rome with funds from Istituto Superiore di Sanita' (the Italian National Institute of Health). The 3 GHz proton linac has been designed in the framework of the TERA Collaboration under the leadership of M.Weiss [25,26] and solves the challenge of accelerating low-energy protons with a high frequency linac, in itself a scientifically interesting problem.

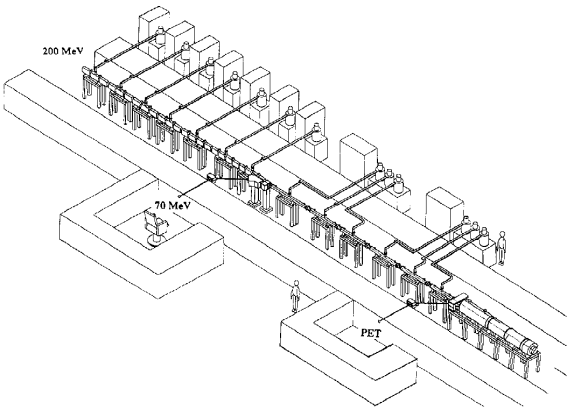

Figure: 5 The low current 3 GHz protontherapy linac to be constructed in Rome by ENEA,ISS and TERA under the direction of L. Picardi (ENEA).

As shown in Fig. 5, the high-frequency linac is made of three sections: a ten MeV injector of lower frequency (which can also produce PET isotopes), a new accelerating structure named *Side Coupled Drift Tube Linac* (SCDTL) and a conventional *Side Coupled Linac* (SCL). Each SCDTL tank contains 4, 5 or 6 drift tubes about 1cm long and with a 4-6 mm diameter hole. Permanent magnets located between adjacent tanks focus the accelerated beam. The SCDTL section accelerates protons to 70 MeV, and it is what is financed at present. The SCL part will be built next and bring the beam to 200 MeV. With small modifications the SCL can also be used as a *booster* of a 60-70 MeV proton cyclotron [25]. The non-profit TERA Foundation is looking at present for partners interested in transforming their cyclotrons into a 200 MeV variable energy facility for protontherapy.

4.4 European design of a medical synchrotron for protons and ions

Since 1992 the TERA Foundation has been engaged in the design of a medical synchrotron for protons of more than 250 MeV and carbon ions of at least 375 MeV/u [21]. G. Brianti is the Chairman of the Project Advisory Committee. Since 1995 CERN experts have contributed to the design of the accelerator. In June 1996, an agreement was signed with six oncological Hospitals to form a Consortium and build the *National Centre for Oncological Hadrontherapy* (CNAO) in Milan.

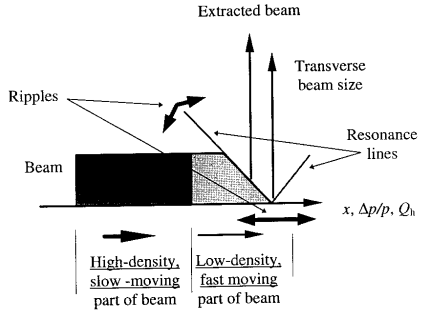

Figure: 6 By feeding the resonance with a fast moving beam the effects of the ripples are reduced.

At the beginning of 1996, under the leadership of Philip Bryant, a new collaboration between CERN, TERA, AUSTRON and GSI began working on an improved design of a proton/carbon synchrotron and the rotating gantries. For a medical synchrotron, the intensity of the extracted beams poses no special problem, since 10^{11} p/s and 3 10^{9} ions/s are sufficient. The issue is the time uniformity of the spill since, due to the magnet ripples, synchrotron pulses have time structures at many frequencies; this makes an accurate active spreading of the beams particularly difficult. At HIMAC this problem has been partially solved with a very accurate (to few 10^{-7}), but costly, stabilisation of the magnet power supply [16].

The new study of the medical synchrotron is thus taking time uniformity of the extracted beam, which lasts about one second, as the highest priority, as already done at LEAR for much longer time scales. The work is not yet completed, but the main idea behind a solution, possibly to be combined with other methods, can be explained with reference to Fig.6, in which the transverse beam size is represented as a function of the coordinate x. Due to the unavoidable ripples in the dipoles and quadrupoles, the resonance lines (drawn at 45°) can be thought to oscillate continously in the directions indicated by the arrows. When the beam is pushed to the resonance, or viceversa, the movement of the resonance lines produces a time disuniformity. To reduce the effect the part of the beam which is closer to the resonance can be made to move much faster, so that the extracted beam is less sensitive to the ripples. This activity is another good example of how medical applications give rise to scientifically interesting accelerator problems.

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