A CRITICAL EVALUATION OF THE ROLE OF THE CYCLOTRON IN RADIATION THERAPY

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Summary

The present situation in heavy particle radiotherapy is reviewed. The potential of the cyclotron and competing devices is evaluated with respect to dose distribution, dose rate, versatility, size, and cost. Some related non-physical problems characterizing radiation therapy in general are briefly considered. It turns out that compact cyclotrons for 30 to 60 MeV protons will hold their leading position in fast neutron therapy at least, as they do in radioisotope production.

Introduction

In the age of only 8, the cyclotron started in fast neutron therapy at the University of California/Berkeley in 1938[1,2]. Today, nearly 100 isochronous or synchrocyclotrons all over the world are completely or partly dedicated to biomedical applications, predominantly to radioisotope production. About 30 of them are or will be used for radiotherapy to treat,say,3000 patients per year with fast neutrons, ions or pions (see table 1). On the other hand, about 1 million patients are transferred to "conventional" radiation treatment with photons or electrons. Nevertheless, there is appreciable scientific interest in the assessment of biological advantage - based on high LET (linear energy transfer) - or dose advantage (or both) of heavy particles[3,4]. For a few indications in the treatment of cancer and other diseases, they have already been accepted as superior to photons. Most of the targets releasing heavy particles are fed by cyclotrons: at present, there are 22 cyclotrons installed in 27 hospitals and research institutes. There will be 30 cyclotrons in 35 facilities, soon. Fast neutron therapy is being performed with 12 hospital-based compact cyclotrons and 5 DT generators.

Experience compiled since 1975 indicates that biological advantage - if existing at all - can only be evaluated by outermost care for application of dose[5]. Dose distribution is determined by the energy spectrum of the particles and, hence, by the size of the accelerator. Quality of radiation treatment is, however, markedly determined by further essentials:

- adequate dose rate,
- collimation: field shape and shielding, penumbra
- geometry of application: continuously rotating source (isocentric beams)
- treatment planning: based on CAT, NMR(?)
- precise and reproducible localization of the patient
- reliability of equipment
- availability of beam: treatment schedule
- location of the source: minimum distance from radiation therapy department,

and the general technical and organizational support by the physics group, of course.

Dose Distribution, Dose Rate

Radiation applied in percutaneous radiotherapy is primarily characterized by its depth dose, i.e. the dependence of dose on depth in tissue. The latter is determined by the sort of particle used (absorption or "Bragg" curve) and its energy spectrum (see fig.1).

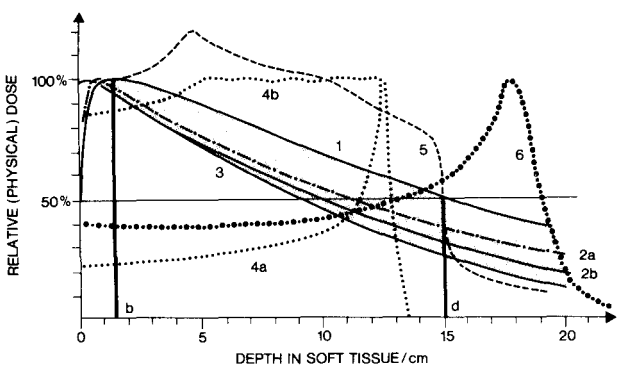

Fig.1: Depth dose curves for heavy particles+: 1. p(66)Be(49) neutrons, SSD=150cm (Ref.6), 2a. DT neutrons, SSD=100cm (Ref.7), 2b. 60Co photons, SSD=80cm, 3. d(16,7)Be neutrons, SSD=120cm (Ref.8), 4. 135MeV protons: a.monoenergetic, b.8 cm spread out Bragg peak (SOBP),(Ref.9), 5. 20Ne ions, 425MeV/u, 10cm SOBP (Ref.3,10), 6. 80MeV pions, 170MeV/c, $\Delta p/p=2\%$

Absorption curves (fast neutrons, photons) are characterized by the depth d of the 50% isodose and the thickness b of the surface layer where dose builts up to the maximum. For treatment of deep seated lesions (tumors) both, d and b should be as large as possible resulting in favourable dose distributions over the target volume and effective skin sparing, respectively. Both parameters increase with energy. As a minimum standard, ^{60}Co photons (E=1,2MeV) are accepted with d=10cm, b=5mm (10x10cm^2 field size, SSD=80cm).

+) SSD=Source Skin Distance

Table 1

PARTICLE RADIOTHERAPY INSTALLATIONS 1984

H = Hospital Gen = DT Generator
RI= Research Inst. S = Synchrotron
C = Cyclotron SC = Synchrocycl.
P = Proposal

Presently operational programs are numbered

Site	Beam, Source	Accel. Type	Manu-fact.	Patient Treatm. since
I. Fast Neutrons				
USA				
1. Houston/Tx. MD Anderson Hospital	H p(42)Be (b)	C	TCC (a)	1972 (1983)
2. Seattle Washington Univ.Hosp.	H p(50)Be	C	Scand	1973 (1984)
3. Cleveland Clinic/Ohio	RI p(46)Be	C		1976
4. Fermi Lab.	RI p(66)Be	LINAC		1976
5. Chicago/Ill. Univ.Hosp.	H d(8,3)D	C	TCC	1981
6. Univ.Penn. Fox Chase Cancer Ctr.	H d-T	Gen	TCC	Jan. 1984
UCLA + VA Med.Ctr.	H p(42)Be	C	TCC	P
GB				
7. London Hammersmith Hospital	H p(40)Be	C	Scand	1966
8. Cladder-bridge Hosp.	H p(60)Be	C	Scand	1984
9. Edinburgh West.Gen. Hosp.	H d(15)Be	C	TCC	1977 (-Oct. 1984)
France				
10.Orleans	RI p(34)Be	C	CGR	1981
Nice	p(50)Be	C		P
Belgium				
11.CYCLONE Louvain-la-Neuve	RI p(65)Be	C	CGR	1978
12.Gand	H d(15)Be p(24)Be ?	C	CGR	?
FRG				
13.Hamburg Univ.Hosp.	H d-T	Gen	AEG/ Rad. Dyn. Inc.	1977
14.Heidelberg DKFZ+Univ. Radiol.Clin.	RI d-T	Gen	Hae-fely	1977
15.Essen Klinikum	H d(14)Be	C	TCC	1978
16.Münster Univ.Hosp.	H d-T	Gen	Hae-fely	1984
Munich Univ.Hosp.	H ?	C	?	P
Japan				
17.Chiba,NIRS	RI d(30)Be	C	CRG	1975
18.Tokyo,IMS	RI d(14)Be	C	TCC	1978
Poland				
19.Krakow INP	RI d(12,5)Be	C (U-120)		1978
South Africa				
Faure,NAC	RI p(65)Be	C		P
South Corea				
Seoul Cancer Res. Hosp.	H p(50)Be	C	Scand	P
USSR				
Dubna,JINR	RI p(640)Be	SC		P
Australia				
Sydney, Pr.Alfred Hospital	H ?	C	?	P
Switzerland				
Zurich Radiol.Clin.	H d-T	Gen	Hae-fely	P

Programs ceased in Amsterdam (1976-81), Dresden (1972-81),and Washington,DC (1975-79).

Site	Beam, Source	Accel. Type	Manu-fact.	Patient Treatm. since
II. Protons				
USA				
20.Cambridge/ Harvard Un.	RI 160MeV	SC		1961
	70MeV	S		P
	H 200MeV	S		P
Argonne Nat.Lab.	RI 50MeV	LINAC		P
Fermi Nat.Lab.	RI 200MeV	LINAC		P
Brookhaven Nat.Lab.	RI 200MeV	LINAC		P
Sweden				
21.Uppsala	RI 187MeV	SC		1957
G.Werner I.	50-250MeV	SC		1984?
USSR				
22.Moscow ITEP/ICEO	RI 70-200MeV	S		1967
23.Dubna JINR/ICEO	RI 90-200MeV	SC		1967
24.Leningrad	RI 1000MeV	SC		1975
Switzerland				
25.SIN,Inj.I	RI 72MeV	C	Philips	1984
Japan				
26.NIRS	RI 70MeV	C	CGR	1979
Belgium				
Louvain-la-Neuve	RI 90MeV	C	CGR	P
South Africa				
NAC,Faure	RI 200MeV	C		1985?
France				
Orsay	RI 200MeV	SC		P
West Germany				
Jülich,SNQ	RI 350MeV	LINAC		P
Heidelberg Radiol.Clin.	H 200MeV	S		P
LBL-Program with 340MeV protons: 1954-57				
III. Heavy Ions				
USA				
27.U.Cal. Berkeley	RI α: 910MeV (184")	SC		1958
	α: ≤10GeV (Bevatron)	S		1975
	$^{12}C^{6+}$: 400MeV/u (BEVALAC)	S		1977
	$^{20}Ne^{10+}$: 425MeV/u	"		
	$^{28}Si^{14+}$: 670MeV/u	"		P
The Heavy Ion Med.Ac.	^{28}Si: 800MeV/u			P

Table 1 (continued)

Site	Beam, Source	Accel. Type	Manu- fact.	Patient Treatm. since
Canada				
Edmonton MARIA	RI	S		P
West Germany				
GSI SIS 12/18	RI	S		P
IV. Pions				
Canada				
28.TRIUMF Vancouver	RI	520MeV H^-	C	1979
Switzerland				
29.SIN	RI	600MeV p	C	1980
USSR				
Dubna,INR	RI	700MeV p (Phasotron)	S	P
LAMPF program (800MeV p): 1974-1982				

(a) TCC = The Cyclotron Corporation, Berkeley CA, USA
Scand = Scanditronix, Uppsala, Sweden
CCR = CGR-MeV, BUC, France
AEG = Allgemeine Elektrizitätsgesellschaft, FRG
(b) p(42)Be: 42MeV protons on Beryllium target

Even with fixed energy of the primary particle, quality of depth dose can slightly be raised (at the expense of a lower dose rate) by either increasing SSD (as flux density goes with $1/r^2$) or in the case of fast neutrons, by "hardening" the spectrum by absorbers of high hydrogen content or - most economically - by the use of thinner targets[12].

Ions and pions, in principle, deposit higher dose at the end of their path (Bragg peak) than at the entrance and in the plateau region. The distal tissue is exposed only slightly by the products of decay and fragmentation (pions, heavy ions) or negligibly(protons). Due to small angle scattering, lateral dose fall off is steep, penumbra and integral dose outside the treatment volume are small. Sparing of overlying (proximal) regions is, however, reduced in SOBP treatment (see curves 4b and 5 in fig.1). Wilson's perception of this dose advantage[13] initiated radiotherapy with protons and heavier ions. The additional high-LET advantage of pions ("pion stars") was suggested by Fowler[14].

For fast neutrons, the impact of dose distribution on particle energies is displayed in figures 2 and 3.

In practice, d ranges from 10 to 15cm corresponding to an average energy of fast neutrons between 15 and 30MeV. Different reactions have been used to produce fast neutrons for radiotherapy, i.e. ^{9}Be(d,xn), d-D, d-T and ^{9}Be(p,n). Correlation of neutron average energy on energy of the primary particles is shown in Fig.3.

For the actually used ^{9}Be(p,n)-reaction with polythene filtering, the free hand fit gives

$E_n = 0.52E_p - 1{,}5\text{MeV}$ ($\pm$ 1 MeV)

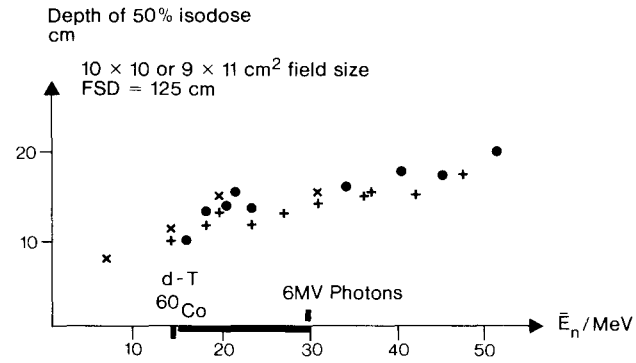

Fig.2: Dependence of depth d of the 50%-isodose of collimated fast neutron beams in soft tissue on average neutron energy (Ref.6,8,15). ●:p-Be with PE-filter, +:p-Be without f., x : d-Be without f.

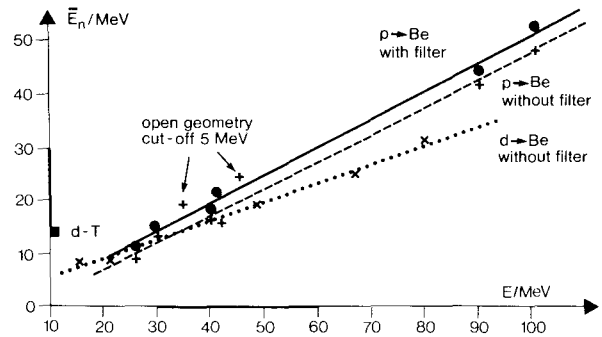

Fig.3: Average energy of collimated fast neutron beams as a function of projectile energy E_p (Ref.6,8,15).

The diagram demonstrates that the proton-Be reactions are equivalent or superior to d-Be reactions at equal energies, the neutron flux density,however,being appreciably lower[16]. As cyclotrons deliver protons of twice the energy they would impart to deuterons it makes sense to switch to the p-Be reactions. This has been accomplished in most cases during the last years. As a consequence, sources of at least 30 up to about 60MeV protons are adequate for fast neutron therapy with emphasis on the higher energies. Modern cyclotrons are,in addition,capable of producing high enough proton beam currents to compensate for the lower neutron yield compared to deuterons. Dose rates of 30cGy/min in 150cm SSD for 40 to 60MeV protons are easily achieved. In view of decreasing relative biological effectiveness and increasing oxygen enhancement ratio a marked advantage from even higher proton energies up to 100 MeV is not to be expected.

Excellent clinical results have been obtained in special cases with the Fermi-Lab neutron beam which is provided by 65MeV protons from a LINAC,however[17]. On the other hand,inferior physical characteristics of fast neutron beams can be partly compensated

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for by special care in treatment planning and application of dose[5]. A compilation of dose rates applied in heavy particle radiotherapy today is given in table 2.

Table 2

APPROXIMATE DOSE RATES OF HEAVY PARTICLE BEAMS USED IN RADIOTHERAPY UNDER APPROPRIATE TREATMENT CONDITIONS

Particle	Ion Beam	Appr.Dose Rate (cGy/min)	Remarks	Ref.
n	16MeV d/100μA	50	SSD=120cm	8
	42MeV p/ 70μA	60	ΔE=15MeV PE-filter	18
	60MeV p/ 30μA	50	SSD=125cm 10cm PE-f.	19
	d-T: 180kV/400mA	10-15 (20?)	SSD=100cm	7
p	160MeV/~nA	200-400	dep.on volume	a
α	225MeV/u ≤10^9/pulse[b]	10-50	(184" SC)	20/ 21
$^{12}C^{6+}$	400MeV/u[c]	1500	(BEVALAC)	"
	≤$2x10^9$/pulse	100	in practice	"
$^{20}Ne^{10+}$	425MeV/u	200-500	max.	"
	$4x10^8$/pulse	100	in practice	
pions	590MeV p 20μA	20 in 1 ltr.	SIN, Ω=1sr	22
	520MeV p 100μA	5-6 (12?) in 1 ltr.	TRIUMF Ω=0.19MeV-sr	d
		18	4cmϕ field	23
	(760MeV p 300μA	10-20	LAMPF Ω=20msr	11)

a) therapeutic doses/practical treatment times
b) frequency modulation rate 64/s
c) 10-17 pulses/min
d) E.W.Blackmore,personal communication 1983

For comparison, photon radiotherapy devices give dose rates of 100-500 cGy/min. 10cGy/min corresponding to about 20-50 cGy/min photon equivalent are regarded as an acceptable minimum in view of patient comfort and patient load.

Tables 1 and 2 indicate that most tasks for heavy particle accelerators in radiotherapy can be overtaken by cyclotrons. We shall now consider their specific potential and discuss alternative devices competing in various domaines.

Radiation Sources

Fast Neutrons

After a partly discouraging summary of clinical experience in fast neutron therapy in 1982[24], a reorientation can be noted[25] based on

- a better understanding of the interaction of neutron beams with biological targets,
- a proper reevaluation of previous results, and
- the expectation to have adequate equipment available, soon.

Following the challenge by the Hammersmith Neutron Therapy Group since 1972[26], manufacturers could provide for compact cyclotrons with proton energies of 40MeV and higher since 1978. Most neutron therapy facilities had switched to higher energies of primary particles (deuterons around 50MeV), then[24]. Dose rates from 0.3 to 0.5Gy/min at SSDs of 1.2 to 1.5m, are available today providing depth doses comparable to modern megavoltage photon beams. Moreover, due to a proposal of Bewley and coworkers[27], variable collimators composed of many sliding steel jaws have been built allowing for remote control of rather irregular field shapes and avoiding the tedious and hazardous changing of bulky collimator inserts (ducts).

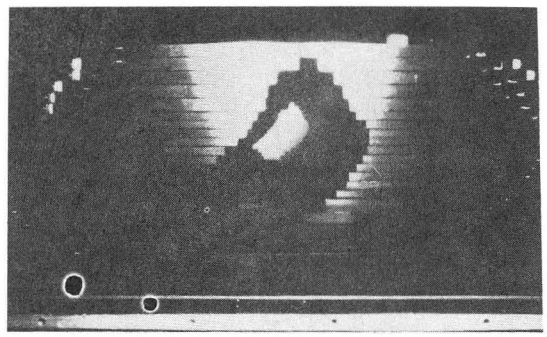

Fig.4: Remotely controlled variable neutron collimator (courtesy of Scanditronix/ Uppsala,Sweden)

Shielding is,however,not as effective for neutrons as for photons or electrons. Due to limitation in size and weight of the collimators leakage is of the order of 1% far outside the beam.

To rotate the neutron source - an essential for modern radiotherapy - the proton beam is deflected by +45° at first and consequently by -135°. Both,magnets and the collimator shield are contained in a gantry several tons by weight being able to rotate by ± 100°,at least (see fig.5).

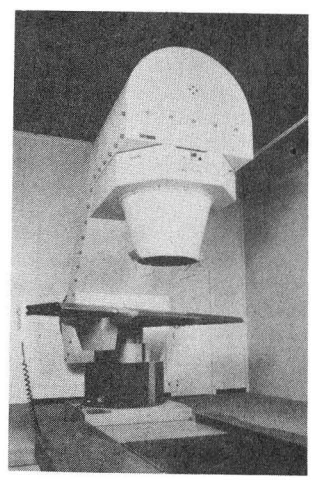

Fig.5: Rotating gantry for fast neutron therapy (courtesy of CGR-MeV, France)

Mechanical stability has to be such that the isocenter (axis of rotation) is maintained in space to within ± 2mm, and the geometry of the beam and focus must not be distorted during rotation to warrant reproducible treatment. Today, 60MeV protons are deemed the reasonable upper limit also in view of design problems and costs (see fig.7).

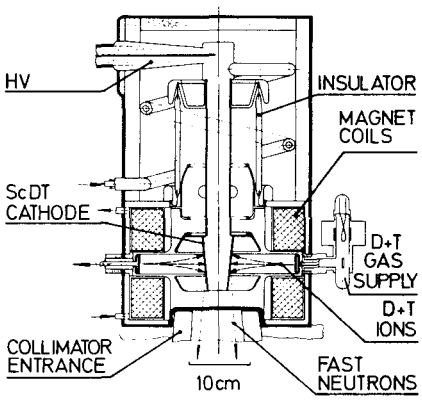

Fig.6: Design sketch of a commercial DT generator tube with simultaneous acceleration of d and t to compensate for the tritium loss in the cathode layer. Constant output of about 15 cGy/min in 1m SSD is maintained for about 300hrs of operation (courtesy of Haefely/Basel, Switzerland)

As a competing device, the DT generator (fig.6) has found its application in neutron therapy despite the low dose rate of actually 15 cGy/min from the following reasons:

- the tube can be operated at low voltages (about 250kV). The power supply is reasonably compact.
- primary particles (d,t) and neutrons are produced in the same reaction chamber, no separate accelerator is needed.
- dimension and weight of the whole assembly are comparable to photon treatment installations housing electron LINACs or betatrons. So,the device is also more readily accepted by medical personnel.
- neutrons are nearly monoenergetic around 15MeV. There is no need of filtering low energy neutrons.
- the price is appreciably lower than any cyclotron neutron installation available today (see fig.7), and the whole installation needs only about half the space (fig.8).

Increasing neutron output to about 20cGy/min seems feasable. Operation and maintenance are as reliable as with cyclotrons,today. The DT generator is an attractive alternative where radiation therapy alone is to be performed. A cyclotron - superior as it be from dose rate and depth dose - would not pay without making use of its additional potential, mainly in the field of radioisotope production.

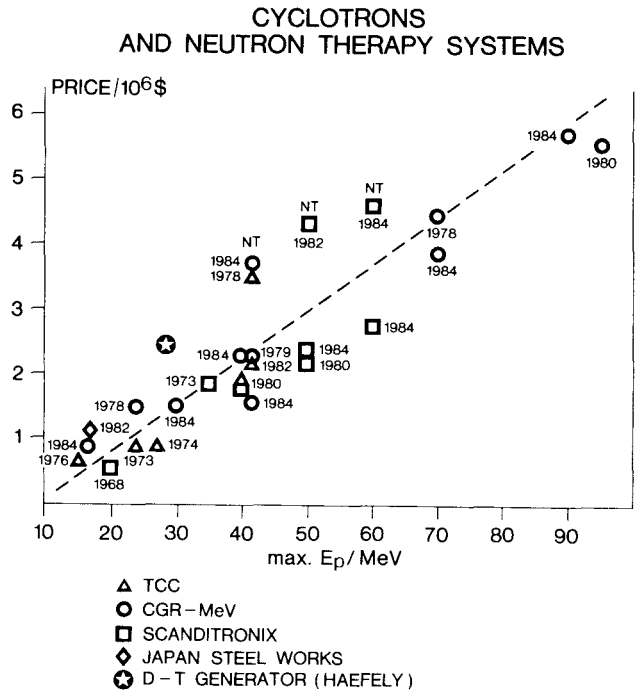

Fig.7: Rough prices for commercial cyclotrons (accelerators only,without peripheral installations) and neutron treatment facilities (NT: rotating gantry plus fixed horizontal beam) in U$ from 1968 to 1984. Surprisingly, prices have remained fairly stable over 15 years irrespective of varying currencies.

A LINAC, as shown by the Fermi-Lab/Chicago group[6,15,24] can be useful,too,as a basis for neutron therapy. From its dimensions, price and operating costs, however, even a modified most recent design[28] would hardly be able to compete successfully with a cyclotron in this field only - it could do so perhaps as a comprehensive facility for fast neutron and proton therapy, and radioisotope production in time sharing operation.

An idea of H.A.Grunder[29], namely to incorporate the Be-target for neutron production into a very compact superconducting cyclotron for 50MeV protons to be mounted directly on a gantry system, will have to manage at least two difficulties: the restricted space available for collimation and shielding as well as the activation of the cyclotron body.

Protons

Proton therapy started in 1954 at the 184" synchrocyclotron of Lawrence Berkeley Laboratory. Without reservations, protons earned success and recognition soon owing to

- the best dose localization achievable at all and
- the radiobiological equivalence to conventional low LET-radiation

which allowed therapists to profit from their experience with photons accumulated over decades.

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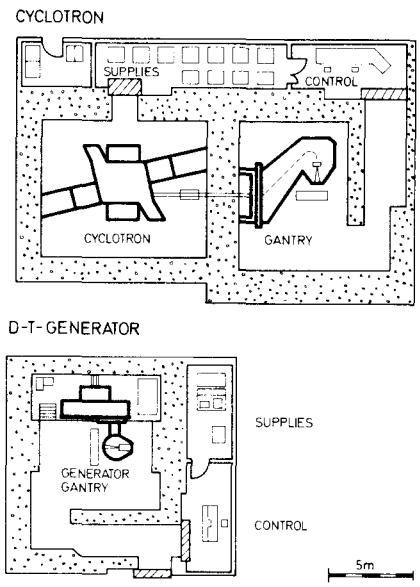

Fig.8: Sketch of the space required for fast neutron therapy installations based on a cyclotron and a DT generator. The cyclotron facility will be about another 50% larger if radioisotope production is also proposed.

Today, 200MeV proton beams from four synchrocyclotrons and one synchrotron in the US,Sweden, and USSR are fully or partly used for therapy. The National Accelerator Centre in South Africa will soon take a 200 MeV SSC with an extensive medical program (p-and neutron therapy, isotopes) into operation (see table 1). 70 to 90 MeV beams for the treatment of eye tumors are (or will be) available in Tokyo, SIN and Louvain-la-Neuve from cyclotrons,too. Proposals for proton therapy at the BNL[30] and Fermi-Lab 200 MeV injector LINACs have not been funded. A 50 MeV proton beam is being built at Argonne Nat.Laboratory for not too deeply seated eye lesions[31],hopefully the starting point for a more powerful installation. The Harvard Cyclotron Laboratory is going to develop a 70 MeV synchrotron as an "eye-machine" and potential injector for a 250 MeV proton synchrotron[32]. New and old plans have come up in West Germany,too.

None of the existing accelerators is being primarily dedicated to radiation therapy nor are they located on a hospital site. The distinguished Harvard Cyclotron Lab. only is a purely "medical" facility, today. Dedicated accelerators for proton therapy are seriously considered in Cambridge/MA and at the ICEO in Moscow.

From space requirements and price, no clinic has been able to afford such instrumentation. With sufficient patient load, operating cost can,however,be covered by charging for treatment as shown by the HCL group[33].

A hospital-based therapy system for "Bragg-peak" proton treatment has to apply 200-250MeV protons (range in soft tissue $\leq$ 25cm) with beam currents of about 10^{10} p/s giving dose rates of several Gy/min in a 1 ltr. volume. Allowing for the beam loss due to "beam flattening" by scattering foils, occluding ring diaphragms, and by collimation, extracted beam currents should be 10-100nA. This seems to put no problems to any existing type of accelerator. Fig.9 shows a comparison in size of the types of 200MeV proton accelerators. The normal conducting SSC(1) seems to rule out from size, weight (>1000t) and cost. At first sight, the normal conducting synchrocyclotron(4) would look most suitable. Its weight of about 300t, however,would cause a high price (> 10M$) and appreciable building costs from heavy foundation. The superconducting SSC(3) could be a good alternative but reliable operation remains to be proven. The most attractive design is a proposal by B.Gottschalk from the Harvard Cyclotron Lab.[34] of a low current 250MeV proton synchrotron weighing about 4t only which he wants to build for about 2M$.

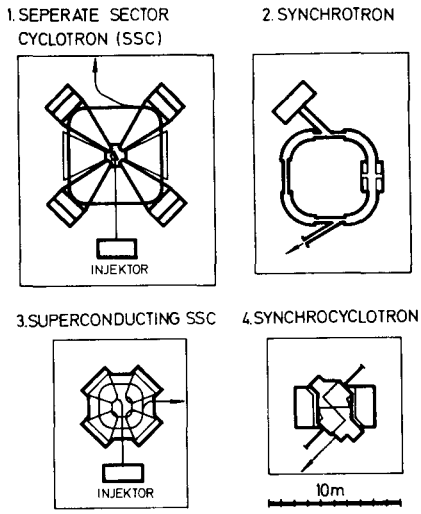

Fig.9: Sketch of 200MeV circular proton accelerators.
1. Ref.35,
2. B.Gottschalk[34],
3. Ref.36,
4. Ref.37

A commercial system, consisting of a synchrotron with appropriate injector (small compact cyclotron?) and three therapy ports with fixed beams has been roughly estimated to cost about 6 M$[38].The configuration, i.e. the choice of the best injector-main ring-combination, remains to be evaluated.

250MeV protons have a magnetic rigidity of $B \cdot \rho = 2.4$Tm. So, with normal conducting ("warm") magnets of, say 1.5T, a bending radius would result of about 1.6m compared to 0.5 - 0.7m for 50MeV p ($B \cdot \rho \cong 1$Tm). Deflecting devices would thus be at least twice as big and heavy as for p(50)Be fast neutron gantries. On the other hand, from the dose advantage of protons, fixed beams from 3 directions: horizontal, vertical and 45° from above would be adequate in this case.

Heavy Ions

Over 27 years, experience has been collected in radiobiology and radiotherapy with heavy ions in Berkeley/California, the only site to provide for both energies and beam currents high enough to irradiate deep seated lesions in human bodies. To cover a range of at least 15-20cm in soft tissue, energies of 150-200MeV/u for ^{4}He up to several hundred MeV/u for heavier nuclei are needed. This is beyond the capability of even the most advanced designs of heavy ion cyclotrons (MSU : K = 500, E = 17-35MeV/u for A $\leq$ 20)[39]. So, the only design principle at present for a medical heavy ion accelerator is the synchrotron. A dedicated facility for ions up to

$^{28}Si^{14+}$ with E ≤ 800 MeV/u is being designed at Lawrence Berkeley Laboratory[40]. GSI in Darmstadt/West Germany plans to perform radiation therapy with the proposed heavy ion synchrotron SIS 12/18[41].

Pions

To date,two big isochronous cyclotrons are holding the position in pion therapy : the 600MeV proton cyclotron at SIN,Villigen/ Switzerland and the 520MeV H^- compact cyclotron at TRIUMF,Vancouver/Canada.
For adequate penetration in water (soft tissue),pions of about 100MeV - with small contamination by decay products - are needed . For sufficient yield, however, the energy should be increased to, say, 500MeV or even more. Basically, every type of accelerator with this capability would do the job provided that the pion flux in the focal spot be of the order of $10^9 \pi^-/s\ cm^3$, to give dose rates of about 10 to 20 cGy/min in 1 ltr. volume[42]. This can be done by either using proton beams of 100 μA or more with an acceptance of the beam delivery system in the usual range (10 to 20msr) or,as at SIN, with a powerful pion collector and focussing system (PIOTRON) of 1 sr. There, 20 μA of 590MeV protons (giving 210MeV/c pions, range in tissue: 31.4cm) are split from the beam (> 100 μA) and dedicated to therapy for 24hrs a day. This is the optimum a therapist can request. A PIOTRON is very expensive (~ 12 M$), however.

At TRIUMF, 5-6 cGy/min of π^- are available at present. Twice as high a dose rate is envisaged by doubling the acceptance of the medical pion beam line. There, therapy has to be adapted to the operation of the cyclotron: long breaks occur as long as polarized protons are scheduled.

As the focus is fixed in space, the pion dose has to be homogeneously distributed over the treatment volume by a precisely controlled motion of the patient in three dimensions ("spot scanning"). This sophisticated device is an essential accessory in pion therapy.

The leading role of the cyclotron in pion therapy is a fact. On the other hand, as proven by the Los Alamos-Albuquerque group, a LINAC, e.g. of the PIGMI type[28], would be appropriate for pion therapy, too.

Competing techniques

By the general progress in low-LET radiation therapy and in diagnostic radiology the lead of heavy particles may shrink. We will only briefly mention:

- increasing versatility and accuracy in MV photon treatment,
- use of radiosensitizers,
- superb diagnostic procedures (CAT,NMR,Ultrasound) to detect and localize cancer early,
- interstitial radiotherapy with implanted radioactive sources or with radioactively labeled antibodies,
- synergistic combinations of radiation with hyperthermia or cytostatic drugs,
- "on-line" control of therapeutic effect ("individual" treatment schedules), etc.

A comprehensive and more competent review on this subject has been given by J.F.Fowler[25].

Non-Physical Considerations

Before drawing conclusions, let me have a look "over the fence". Clinical research in radiotherapy is probably the toughest way to do research at all. Treating human patients with uncommon and sophisticated methods of the kinds presented above means not only that the therapist has to face all the technical problems inherent in high technology equipment such as an accelerator coupled facility. A certain psychological barrier between therapist and physicist has often to be surmounted due to the commonly restricted physical education of the medical and the lack in clinical experience of the physical scientists. Moreover, there are specific difficulties to be solved before a randomized clinical trial can even start concerning

- recruiting patients (statistics)
- ethics (Helsinki Declaration[43]),
- reservations of patients and colleagues,
- strict performance of treatment schedule.

These problems characterize the fundamental difference from research in natural sciences where the experimenter is able to choose his conditions nearly arbitrarily. For successful cooperation of medical and physical research workers reliable equipment, regularly scheduled beam, and technical support in every respect is mandatory.

Economical considerations will gain importance, too. Government and health insurancies have issued regulations to save costs in health care.Hospitals and medical doctors are forced to limit assignment of expensive diagnostic and therapeutic procedures to the outermost acceptable minimum. The overall costs of a conventional radiotherapy treatment are of the order of 300$ calculated for 800 patients treated per year with one megavoltage device[44], this charge being inversely proportional to the patient load. It will be difficult to achieve such figures with heavy particle facilities. At Harvard Cyclotron Laboratory, the patient load over years increased to about 330[33]. Health insurances are,however,willing to compensate for a more expensive but successful new mode of treatment.

Conclusions

Modern heavy particle radiotherapy has been thoroughly prepared and accompanied by extensive research in radiobiology. Nevertheless, inactivation of pathological cell formations in human bodies ("in situ") continues to be an object of experience rather than of proven knowledge. Every new indication, treatment modality, and modification has to be evaluated by randomized clinical trials. Certainly, we are facing another decade of clinical research to demonstrate superiority of heavy particles in certain domaines: i.e. to compare the results of the best possible heavy particle treatment with those of the optimum treatment performed with generally accepted, "conventional" methods. Summarizing these as well as the technical and physical aspects we can state that in fast neutron therapy the cyclotron, especially the small compact cyclotron for protons of 30 to 60MeV will hold its leading position for several reasons:

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1. Progress in design, energy and output current,
2. reliable operation,
3. adaptation to clinical requirements in versatility and physical dimensions,
4. the cost factor (purchase price, operation, staff) is not prohibitive in view of its additional capabilities which can be made profitable use of.

For neutron therapy alone the DT generator is the more reasonable choice.

Application of cyclotrons for 70 to 90MeV protons presently starting in proton treatment of eye tumors will dissiminate soon. For proton therapy of deep seated lesions the most economic accelerator from size, weight, and building requirements seems to be a small and slim low current synchrotron.

There is no doubt that the big synchrotron will continue to be competent for heavy ions. The high current, high energy proton cyclotron feeding a very high acceptance beam line has proven its potential for pion therapy. One should admit, however, that the costs of both dedicated heavy ion and pion therapy facilities considerably limit the chance of their realization as part of a clinical department of radiology.

Favourable results will help to transfer the modality into the armamentum of accepted (and chargeable) radiation treatment as is already the case with proton therapy of eye and brain lesions. A further spread, at least of fast neutron and proton therapy installations can thus be expected, a trend which seems to get compulsion by the growing interest of developing countries cooperating with high technology partners.

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References+

1. J.T.Brennan, IJROBP 3, 143-148, 1977
2. E.J.Hall, IJROBP 8, 2041-2044, 1982
3. M.R.Raju: Heavy Particle Radiotherapy. Academic Press N.Y., 1980
4. J.F.Fowler: Nuclear Particles in Cancer Treatment. MP Handbook 8, A.Hilger Ltd, Bristol, 1981
5. M.Catterall, IJROBP 7, 287-289, 1981
6. I.Rosenberg, M.Awschalom, MP 8, 99-104 and 105-107, 1981
7. K.H.Hoever, Thesis, DKFZ Heidelberg/ Universität Homburg, 1984
8. D.K.Bewley, C.J.Parnell, BJR 42,281-288, 1969, C.J.Parnell, BJR 44, 612-617,1971
9. H.D.Suit et al., IJROBP 3, 115-125,1977
10. E.A.Blakeley et al., LBL Report 11220 UC-48, 73-86, Berkeley/CA, 1980
11. H.I.Amols et al., MP 4, 404-407, 1977
12. D.K.Bewley et al., PMB 29, 341-349,1984
13. R.R.Wilson, Radiology 47, 487, 1946
14. P.H.Fowler, D.H.Perkins, Nature 189, 524-528, 1961
15. W.M.Quam, S.W.Johnson, PMB 23, 47, 1978 S.W.Johnson, PMB23,499, 1978, R.G.Graves et al., MP 6, 123, 1979, K.A.Weaver, MP 6, 193,1979,G.H.Harrison,C.R.Cox,MP6,233,1979 F.M.Waterman et al.,MP6,432,1979,D.K.Bewely et al.,PMB 25,887,1980,G.H.Harrison, MP 7,248,1980,J.C.McDonald et al., MP 8, 39,1981
16. S.Vynckier et al., PBM 28, 685-691, 1983
17. R.Kaul et al., IJROBP 7, 1667-1671, 1981
18. P.R.Almond, IJROBP 8, 2045-2048, 1982
19. D.K.Bewley, PMB 25, 887-892, 1980
20. H.A.Grunder, IJROBP 3, 71-80, 1977
21. J.Alonso, LBL-5610, April 1977
22. C.F.von Essen et al., IJROBP 8, 1499-1509, 1982
23. G.B.Goodman et al., IJROBP 8, 2187-2190, 1982
24. Particle Accelerators in Radiation Therapy. Proc.of the CROS/RTOG Part III, Intern.Workshop, Houston, 1982. IJROBP 8, Dec.1982
25. J.F.Fowler: New Approaches for the Improvement of Radiotherapy. In:J.J.Broese et al., (eds): Radiation Research-Proc. 7th Int.Conf.Rad.Res., Amsterdam 1983. M.Nijhoff Publ.1983, L.Cohen,J.Roy.Soc. Med.75, 394-398, 1982
26. M.Catterall, Proc.Roy.Soc.Med.65, 839, 1972 and BJR 49, 203-205, 1976
27. D.K.Bewley et al., PMB 26, 711-714, 1981
28. PIGMI: A Design Report for a Pion Generator for Medical Irradiations. Compiled by L.D.Hansborough. LA-8880, Los Alamos,Nat. Lab., Sept.1981
29. J.W.Blue, pers.comm.1983
30. W.H.Moore, BNL Report No.16185, 1971
31. R.Martin, St.Kramer, pers.comm.1983
32. B.Gottschalk, pers.comm.1983
33. A.M.Koehler: Harvard Cyclotron Annual Reports.Phys.Dept.Cambridge/MA
34. B.Gottschalk, IEEE Trans.Nucl.Sci.NS-30, 3063, 1983
35. K.E.Scheer, U.Schmidt-Rohr (eds): Strahlentherapie und Diagnostik mit Ionen und π^--Mesonen. BMFT-Projektstudie. Heidelberg 1977
36. U.Schmidt-Rohr, pers.comm. 1983
37. S.Holm, in: J.Carlsson et al (eds): A Clinical Cyclotron Model Program for the Use of 200MeV Protons in Radiotherapy and Nuclear Medicine. Report to the Swedish Board of Technical Development, Uppsala, 1977 ("Larsson-Study")
38. Scanditronix, pers.comm.1983
39. P.Lapostolle, IEEE Trans.Nucl.Sci.NS-30, 1957-1961, 1983
40. E.L.Alpen et al.:The Heavy Ion Med.Accel. Prelim.Design Summary,UCB Pub.-5097,1983
41. GSI Report 82/2.Darmstadt,FRG,Nov.1981
42. H.Wiedemann in Proc.of the Planning Meet. on Biomed.Appl. of the SIN Pion Beam. Zürich, Switzerland, May 1971
43. WHO Chronicle 30, 360-362, 1976 and 35, 212-215, 1981,and Nat.Res.Act., Public Law 93-348
44. D.Greene, BJR 56, 189-191, 1983,and F.Diekmann (ed): Wirtschaftliche Aspekte der Strahlentherapie. Symposium 1.1.-2.2.1980. Fortbildungszentrum Gesundheits- und Umweltschutz e.V., Berlin 1980

+) IJROBP = Int.J.Rad.Oncol.Biol.Phys.,MP = Med.Phys.,PMB = Phys.Med.Biol.,BJR = Brit. J.Radiol.