PRESENT STATUS AND FUTURE TRENDS OF HEAVY PARTICLE RADIOTHERAPY

D T L JONES
Medical Radiation Group, National Accelerator Centre, P O Box 72, Faure, 7131 South Africa

Fast neutron therapy began as long ago as 1938 and subsequently proton, alpha particle, heavy ion, pion and neutron capture therapy have been used. To date it is estimated that in excess of 45 000 people have undergone some form of particle therapy. In the future it is expected that fast neutron therapy will be used for selected tumour types for which neutrons are known to show improved cure rates. The future trends in charged particle therapy will be driven by increasing commercialization. The future of neutron capture therapy will depend on current clinical trials with epithermal neutron beams and the development of new tumour-seeking drugs.

1. Cancer treatment

Cancer can broadly be defined as the uncontrolled growth and proliferation of groups of cells. In industrialised societies about 30% of people suffer from cancer and about half of these die from the disease. About half of all cancer sufferers (i.e. 15% of the population) receive radiation therapy (possibly in conjunction with surgery and chemotherapy). The prognosis in individual cases varies greatly and depends on tumour type, stage of diagnosis, general health of the patient, etc. A patient who survives for 5 years after commencement of treatment is regarded as having been cured.

Cells from the primary tumour can metastasize (spread to other parts of the body) and about 30% of all cancer patients have metastases at diagnosis. Radiotherapy and surgery are both localised foms of treatment and are generally only used to treat the primary tumour and are responsible for 90% of cancer cures (about 45% for each modality). Chemotherapy is used to treat metastases and the 5-year survival rate is only about 10% [1].

From the above statistics it is clear that even modest improvements in cancer treatment will benefit a large number of people. A very important factor to consider when assessing the cost-benefit of cancer treatment is the cost of *not* curing a patient. This can be very high and may involve risky salvage surgery, chronic health care, etc. The cost may be as much as 4-5 times the cost of curing a patient.

The objective of radiation therapy is to maximise the effect of the radiation on the target and to minimise the effect on surrounding normal tissue. This is done by increasing either the physical dose differential or the biological effect differential between the target and normal tissue. This requires correct choice of treatment modality, proper treatment planning, accurate treatment, etc.

Radiation is usually not administered in a large single dose (except in special circumstances) but is divided into several treatment sessions or fractions (between 3 and 40, depending on the condition being treated). This technique allows normal healthy cells which suffer sublethal damage [2] (i.e. which sustain some damage but are not killed) in the previous session to repair (recover), while the cancer cells are unable to recover during this period. The limiting factor in radiation therapy is always the amount of damage which normal tissue can sustain.

2. Rationales for heavy particle therapy

Some of the physical properties of particles used in radiotherapy are given in Table 1. A range of 26 cm in water is regarded as the minimum requirement for a therapeutic ion beam, although a range of greater than 30 cm is preferable.

Table 1: Physical properties of particles

PARTICLE	CHARGE	MASS	ENERGY FOR RANGE OF ~26 cm IN WATER
e	-1e	$1m_e$	70 MeV
π^-	-1e	$273m_e$	100 MeV
n	0	$1839m_e$ = 1.009u	-
^{1}H (p)	+1e	$1836m_e$ = 1.008u	200 MeV
^{4}He (α)	+2e	4u	200 MeV/u
^{12}C	+6e	12u	380 MeV/u
^{20}Ne	+10e	20u	525 MeV/u
^{40}Ar	+18e	40u	730 MeV/u
BNCT ^{4}He ^{7}Li	+1e +1e	4u 7u	[7 μm] [5 μm]

The biological effects of different radiations depend not only on the dose delivered, but also on the microscopic dose distribution, which is expressed in terms of LET (linear energy transfer) and is equivalent to dE/dx in the language of nuclear physics. Densely ionizing radiations such as neutrons, pions and heavy ions are high-LET radiations while photons, electrons and high energy protons are low-LET radiations. The higher the LET, the greater the biological effect of a given type of radiation. The lower the energy of a particular radiation the higher is its LET and therefore its biological effect. Ions consequently have higher

LET values near the end of their range. Typical LET values for various types of radiations are given in Table 2. For ion beams the values refer to high-energy particles.

Table 2: Typical LET values

RADIATION	LET (keV/μm)
Cobalt-60 γ-rays	2
250 kV x-rays	3
Protons	3
∝-particles	5
π^- mesons	10
Carbon ions	15
Neon ions	50
Fast neutrons	75
Argon ions	150
Boron neutron capture	150

Another important reason for using these radiations concerns the cell cycle effect [4]. Cells are most sensitive to radiation in the mitotic (dividing) phase of the cell cycle. However, they are relatively tolerant in the resting phase and, since slowly cycling tumours contain a larger proportion of cells in the resting phase at any given time, these tumours are resistant to conventional radiations. Fast neutrons and other high-LET radiations are therefore generally used for treating large, slow-growing or radioresistant tumours. The physical characteristics of high-energy fast neutron beams are similar to those of high-energy x-ray beams (Figs. 1, 2).

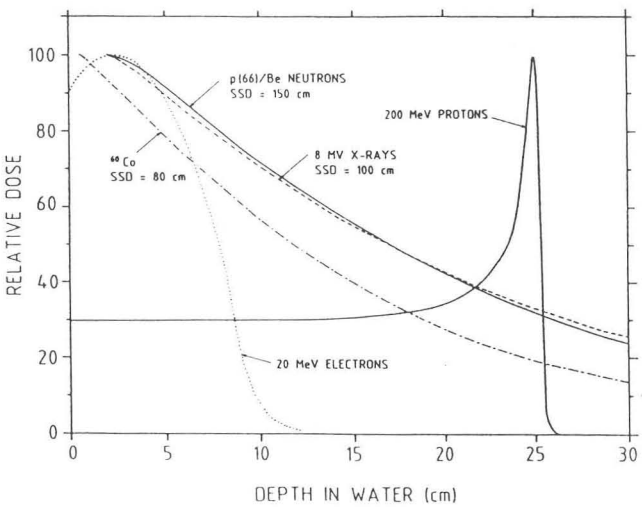

Figure 1: Depth dose curves for a p(66)/Be neutron therapy beam and a 200 MeV proton therapy beam [5] compared with conventional radiotherapy beams

Per unit dose high-LET radiations are more efficient at killing cells than low-LET radiations. With low-LET radiations a larger proportion of cells suffer repairable [2] damage than with high-LET radiations where the damage is largely irreparable. One of the main rationales for high-LET therapy lies in the so-called oxygen effect [3]. Because the proliferating tumour cells can reduce the blood supply to the centre of large tumours, the cells in this region can become deprived of oxygen. Cells which lack oxygen are resistant to conventional types of radiation (photons and electrons) but are much less resistant to high-LET radiations.

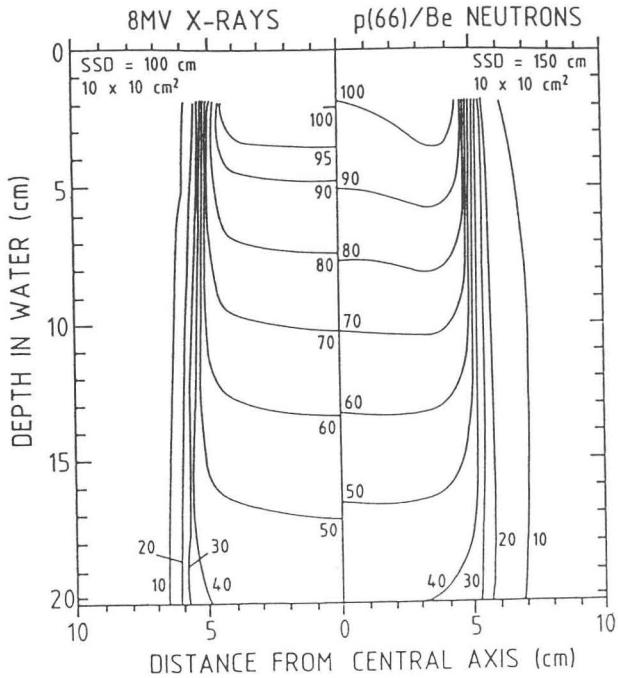

Figure 2 Isodose curves for a p(66)/Be neutron therapy beam (right) [6] compared with a typical 8 MV x-ray beam (left).

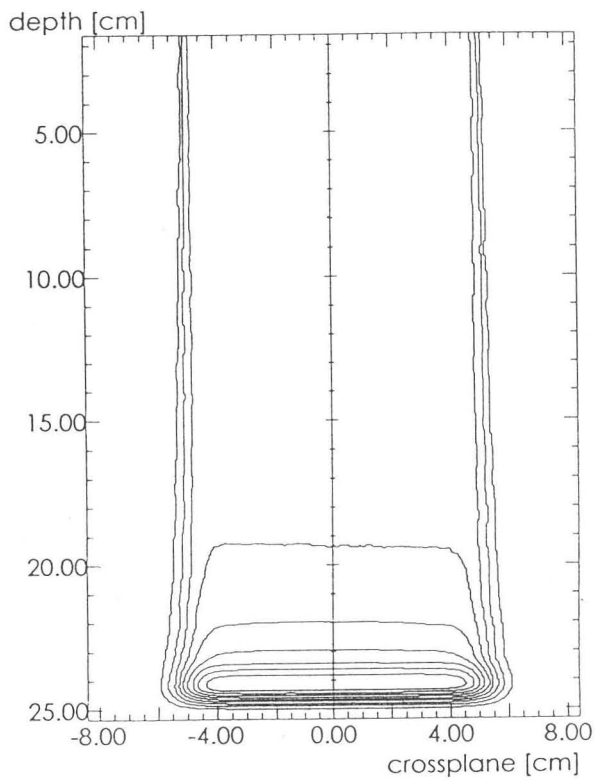

Figure 3: Isodose (10%-90%) curves for an unmodulated 200 MeV proton therapy beam [7].

The other main rationale for using hadrons lies in the physical selectivity of some of these particles (i.e. the ability to conform the dose to the target). Protons and other ions have unique dose distributions (Figs. 1,3). These beams exhibit a relatively flat entrance dose region (plateau) followed by a sharp dose peak (the Bragg peak) in which the particles lose most of their energy. The dose distributions of all charged particles have sharp distal and lateral dose fall-offs, which are illustrated in the case of a 200 MeV proton beam in Fig 3. For protons there is no radiation beyond range end, while for heavier ions (^{12}C, ^{20}Ne, etc.) nuclear fragmentation of the incoming ions results in the formation of lighter ions which deposit energy beyond the primary Bragg peak. Nuclear fragmentation (Fig. 4) increases with increasing atomic number of the ion species. On the other hand, the lateral and distal dose fall-offs of the primary beam decrease with increasing atomic number as multiple scattering and range straggling respectively are less. Bragg peaks have to be spread out to cover the target and this can be done either by active electromagnetic or mechanical techniques. The physical properties of ion beams are best utilized for eradication of well-defined lesions close to critical structures, which in principle can be relatively easily avoided. Heavy ions are also high-LET radiations and have biological advantages. The physical dose for heavy ion beams is decreased with depth to compensate for the increasing relative biological effectiveness (RBE) to provide a biologically equipotent effect across the tumour. This is illustrated in Fig. 4 for the case of a ^{12}C beam. For protons a constant RBE (with respect to photons) of 1.0 - 1.1 is usually assumed.

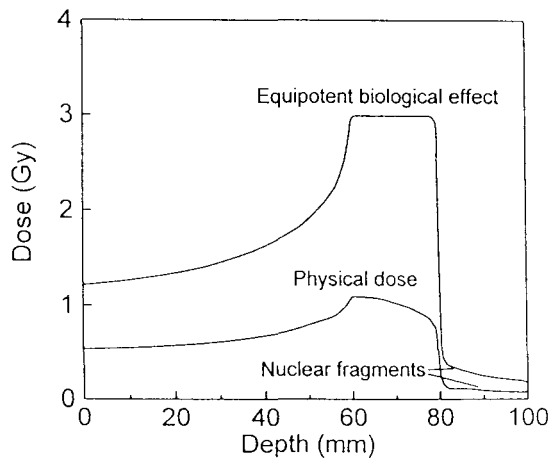

Figure 4: Schematic representation of how the Bragg peak of a ^{12}C beam is spread out to achieve an equipotent biological effect.

Boron neutron capture therapy (BNCT) is a special type of high-LET radiation therapy that attempts to achieve a selectivity at the cellular level. The rationale is to incorporate ^{10}B atoms selectively in the cancer cells and then bombard those atoms with thermal neutrons to produce a neutron capture reaction with subsequent emission of He and Li nuclei with ranges of 5 - 9 μm (less than 1 cell diameter). The radiation selectivity of BNCT results from the fact that the capture cross-sections for thermal neutron capture in tissue elements (which are far more abundant) are two orders of magnitude less than for capture in ^{10}B. To meet the criteria of selectivity and effectiveness, there must be a significantly higher boron cocentration in tumour than normal tissues and at least 30 μg/g ^{10}B in the tumour.

3. Historical aspects

The story of hadron therapy begins with the construction by Ernest Lawrence and his associates of the first cyclotrons at Berkeley in the early 1930s. Shortly after the discovery of the neutron by Chadwick in 1932 [9] at the Cavendish Laboratory in Cambridge, Ernest and John Lawrence (a physician and brother of Ernest) and their co-workers at Berkeley were experimenting with the effects of fast neutrons on biological systems [10]. On the 26 September 1938, the first patients were treated with neutrons (d(8)+Be) on the 37 inch cyclotron at Berkeley [8]. Single fractions only were administered. This pilot study on 24 patients was regarded as most successful and led to the construction of the dedicated 60 inch Crocker Medical Cyclotron [11]. A total of 226 patients were given fractionated treatments with neutrons (d(16)+Be) on this latter machine between 1939 and 1943, before the cyclotron was expropriated for the atomic bomb programme.

Although some remarkable cures were obtained, many patients suffered severe side effects [12] and neutron therapy fell into disrepute. Later analyses of the treatments showed that the increase in RBE when fractionated treatments are given was not taken into account [13] as the effect was not known at the time. Only after extensive radiobiological investigations of the effects of neutrons [14] was neutron therapy started again in the mid-1960s at Hammersmith Hospital, London [15], and later at other centres. Fast neutrons are high-LET particles and are therefore generally more effective for treating large, slow-growing or radioresistant tumours.

In a remarkable paper the therapeutic possibilities of both fast and slow (by means of the thermal neutron capture process) neutrons had been postulated by Locher in 1936 [16]. Patients were treated by BNCT using thermal neutron beams at the Brookhaven National Laboratory (BNL) and the Massachusetts Institute of Technology (MIT) in the USA between 1953 and 1961 [17,18]. The results of the treatment of glioblastoma multiforme were very poor and the treatments were discontinued. BNCT treatments began in Japan in the late 1960s and the early results showed some promise, particularly for the treatment of more superficial tumours for which thermal neutron beams had adequate penetration [19]. These treatments continue to this day. The promising results that were obtained in the Japanese programme together with some supporting evidence from fast neutron therapy gave some impetus to the field and from 1994 BNL, MIT and later the European Centre at Petten, the Netherlands have treated patients with

epithermal beams from reactors. These beams are more penetrating (Fig. 5) and can be used for treating deeper seated tumours.

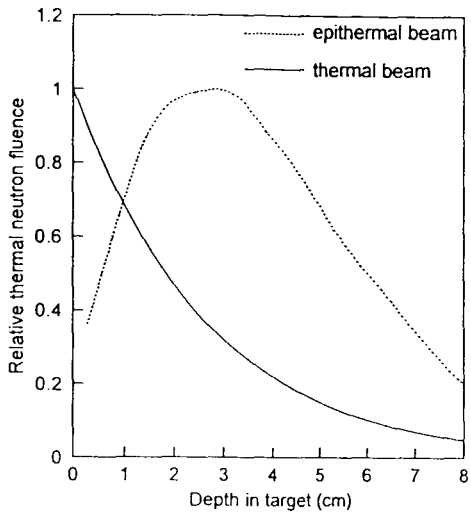

Figure 5: The relative thermal neutron fluence as a function of depth for typical thermal and epithermal neutron beams.

Robert Wilson first proposed the use of protons and heavier ions for therapy in 1946 [20]. The pioneering experimental work of Tobias and his associates a few years later confirmed Wilson's predictions [21]. Between 1954 and 1957 patients were treated with protons on the 184 inch synchrocyclotron at Berkeley by Tobias, John Lawrence and others [8]. The machine was upgraded and the energy became too high for proton therapy and from 1957 alpha particles were used for therapy. From 1975, heavy ions (mainly Ne) were used for patient treatment on the BEVALAC at Berkeley [22]. The treatment facilities were closed in 1992.

Although Yukawa had postulated in 1935 [23] that protons and neutrons were held together by mutual exchange of pi-mesons, these particles were only discovered by Perkins and others in 1947 [24,25]. They were first formally proposed as a therapeutic modality in 1961 by Fowler (nephew of Lord Rutherford) and Perkins [26]. Only negative pi-mesons (π^-) are useful for therapy and are only produced in nuclear reactions when protons (or electrons) of energies greater than 400 MeV strike a heavy target.

Negative pi-mesons have the unique characteristic of being captured by nuclei in the medium near the end of their range. The capture nucleus disintegrates into ionizing fragments of short range (the "star formation") which have a mixture of high- and low-LET components (Fig. 6). The properties of pions were first investigated at Berkeley [27, 28] and were first used for treatment at Los Alamos in 1974 [29] and later at TRIUMF, Canada and the Paul Scherrer Institute (PSI), Switzerland. All programmes have now been terminated as the clinical results did not show significant advantages.

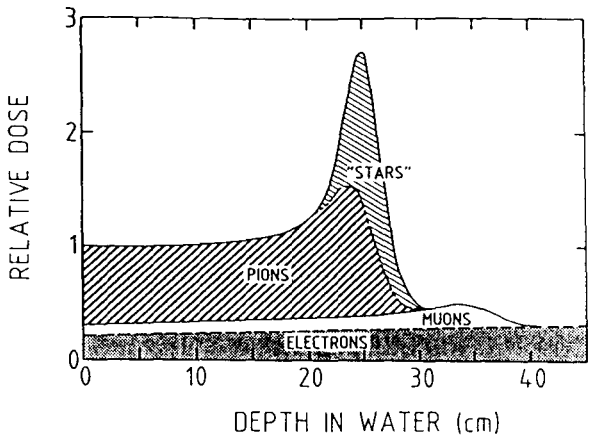

Figure 6: Depth dose curve for a negative pi-meson beam [8].

4. Heavy particle therapy facilities

The most common accelerators currently used to produce heavy particle therapy beams are cyclotrons (fast neutrons, protons and pions) and synchrotrons (protons and heavier ions). To date all BNCT has been with reactor beams, although there are proposals for using low-energy electrostatic generators to provide epithermal beams. The requirements for an ideal heavy particle therapy facility (excluding BNCT) are given in Table 3.

Table 3: Requirements for ideal heavy particle therapy facility

LOW CAPITAL AND OPERATING COSTS	
COMPACT	
LOCATED IN LARGE HOSPITAL	
RELIABLE	
SIMPLE TO OPERATE	
ISOCENTRIC GANTRY	
MULTILEAF COLLIMATION (neutron) BEAM SCANNING (ion)	
FIELD SIZES UP TO 30 cm x 30 cm	
DOSE RATES:	>3 Gy/min (ion) >0.5 Gy/min (neutron)
PENETRATION:	>30 cm (ion range) >15 cm (50% depth dose/neutron)
EFFECTIVE SAD:	>3 m (ion) >1.25 m (neutron)

Many of the early fast neutron therapy facilities and some newer ones were closed because of several factors: the physical beam properties were hopelessly inferior, the location of the facilities was inconvenient, beam configuration and collimation were inadequate or there were problems with patient accrual. Tables 4 and 5 show existing low- and high-energy fast neutron therapy facilities respectively. The former have limited application because of inferior beam penetration. Tables 6 and 7 show existing low- and high-energy proton therapy facilities respectively. The former are used almost

exclusively for the treatment of eye lesions (mainly uveal melanoma and age-related macular degeneration [ARMD]).Table 8 shows heavy ion therapy facilities. Current BNCT facilities are listed in Table 9.

High-LET radiations are most effective for treating large, slow growing or radiation resistant tumours such as those of the salivary gland, paranasal sinus, head and neck, prostate, bone and breast; soft tissue sarcoma, uterine sarcoma and melanoma. Beams exhibiting physical dose selectivity are most suited for treating lesions (not necessarily malignant) close to critical structures, such as uveal melanoma, ARMD pituitary adenoma, meningioma, arteriovenous malformation, prostate, acoustic neuroma, chondrosarcoma and chordoma; and prostate, cervix and paranasal sinus tumours. BNCT has been used to treat mainly patients with gliobastoma multiforme and some malignant melanomas. To date more than 20 000 patients are estimated to have been treated with fast neutrons, more than 22 000 have been treated with protons and about 3 000 with heavier ions [44]. Exactly 1100 patients have received pion therapy [44] and less than 300 have received BNCT.

Table 4: Low-energy fast neutron therapy facilities

PLACE	COUNTRY	SOURCE REACTION	MEAN ENERGY (MeV)	SAD (cm)	BEAM DIRECTION	COLLIMATOR TYPE
Obninsk	Russia	Reactor	-	-	-	-
Garching	Germany	Reactor	1.8	545	Horizontal	Inserts
Chelyabinsk	Russia	d(0.5) + T	14.3	-	-	-
Tomsk*	Russia	d(14) + Be	5.9	-	-	-
Minsk*	Belorus	d(14) + Be	5.9	-	-	-
Essen*	Germany	d(14.3) + Be	6.0	125	Isocentric	Inserts

*Cyclotron

Table 5: High-energy fast neutron therapy facilities

PLACE	COUNTRY	SOURCE REACTION	SAD (cm)	BEAM DIRECTION	COLLIMATOR TYPE	FIRST TREATMENT	NO. OF PATIENTS (Apr 1998)
Orleans	France	p(34) + Be	169	Vertical	Inserts	1981	1729
Beijing°	China	p(35) + Be		Horizontal	Inserts	1991	
Detroit MI	USA	d(50) + Be	183	Isocentric cyclotron	Multirod	1990	913
Seattle WA	USA	p(50) + Be	150	Isocentric Horizontal	Multileaf Inserts	1984	1778
Seoul	South Korea	p(50) + Be	150	Isocentric	Variable jaws	1986	310
Nice*	France	p(60) + Be	170	Vertical	Multileaf	1993	57
Louvain-la-Neuve	Belgium	p(65) + Be	162	Vertical Horizontal	Multileaf Inserts	1978	1810
Batavia IL°	USA	p(66) + Be	190	Horizontal	Inserts	1976	2532
Faure	South Africa	p(66) + Be	150	Isocentric	Variable jaws + multiblade trimmer	1988	951

+Operations suspended °Linac

Table 6. Low-energy proton therapy facilities

PLACE	COUNTRY	MAX. CLINICAL ENERGY (MeV)	RANGE IN ICRU MUSCLE (cm)	BEAM DIRECTION	FIRST TREATMENT	NO. OF PATIENTS (Jul 1998)
Davis, CA	USA	60	3.1	Horizontal	1994	162
Clatterbridge	UK	62	3.3	Horizontal	1989	817
Nice	France	65	3.6	Horizontal	1989	1010
Chiba	Japan	70	4.1	Vertical	1979	96
Villigen	Switzerland	72	4.4	Horizontal	1991	2487
Vancouver	Canada	72	4.4	Horizontal	1991	37
Berlin	Germany	72	4.4	Horizontal	1998	3
Louvain-la-Neuve	Belgium	90	6.5	Horizontal	1991 - 1993	21

All accelerators are cyclotrons

Table 7: High-energy proton therapy facilities

PLACE	COUNTRY	MAX. CLINICAL ENERGY (MeV)	RANGE IN ICRU MUSCLE (cm)	BEAM DIRECTION	FIRST TREATMENT	NO. OF PATIENTS (Jul 1998)
Cambridge MA*	USA	160	17.9	Horizontal	1961	7694
Uppsala*	Sweden	200	26.2	Horizontal	1957	220
Moscow*	Russia	200	26.2	Horizontal	1969	3039
Faure*	South Africa	200	26.2	Horizontal	1993	263
Bloomington IN* a	USA	200	26.2	Horizontal	1993	1
Orsay*	France	200	26.2	Horizontal	1991	956
Dubna* a	Russia	↓200	26.2	Horizontal	1967	124
Villigen*	Switzerland	↓230	33.3	Isocentric	1996	9
Boston MA* b	USA	235	34.5	Isocentric & Horizontal	(1998)	
Kashiwa* b	Japan	235	34.5	Isocentric & Horizontal	(1998)	
Loma Linda CA*	USA	250	38.3	Isocentric & Horizontal	1990	3433
Tsukuba*	Japan	↓250	38.3	Vertical & Horizontal	1983	576
Berkeley CA*	USA	340	63.9	Horizontal	1954 - 1957	30
St. Petersburg*	Russia	1000	328.3	Horizontal	1975	1029

↓ Degraded beams *Cyclotron +Synchrocyclotron *Synchrotron
a Operations suspended b Commissioning in progress

Table 8: Heavy ion therapy facilities

PLACE	COUNTRY	ACCELERATOR	ION	NO. OF PATIENTS*	PERIOD
Berkeley CA	USA	Synchrocyclotron+ Synchrotron+	He	2054	1957 - 1992
Berkeley CA	USA	Synchrotron+	Heavy Ions*	433	1975 - 1992
Chiba	Japan	Synchrotron	C	389	1994 -
Darmstadt	Germany	Synchrotron	C	2	1997 -
				824	
				2878	

+BEVALAC *Ne mainly, + C, Si, Ar *July 1998

Table 9: BNCT facilities

THERMAL BEAMS
JAERI Research Reactor 4, Tokai, Japan
Kyoto University Research Reactor, Kyoto, Japan
EPITHERMAL BEAMS
Brookhaven Medical Research Reactor, Upton NY, USA
Massachusetts Institute of Technology Reactor II, Cambridge MA, USA
European High Flux Reactor, Petten, The Netherlands

5. Beam delivery: fast neutron and ion beams

For fast neutron therapy, the reactions d+T, d+Be and p+Be are used for neutron production [30, 31]. Neutrons from the d+T reaction have inferior properties in terms of beam penetration, lateral penumbra and dose rate [30] and this reaction is currently used at only a few centres. For modern high-energy facilties, the p+Be reaction is preferred (except for the Detroit d + Be facility [32]), since the same machine can accelerate protons to twice the energy of deuterons and thus provide more penetrating beams.

Although some fixed beam arrangements are still used, isocentric facilities are desirable. Nevertheless, with a versatile patient support system and good treatment planning fixed beam facilities have given good clinical results for selected tumour types (eg. salivary gland, prostate, soft tissue sarcoma, bone sarcoma, melanoma). Flexible beam shaping (eg. multileaf collimator [33], multiblade trimmer [34]) is desirable, but good dose conformation can be achieved with a variable rectangular collimator or fixed inserts if proper beam blocking is done. Sophisticated 3-dimensional treatment planning is essential

Passive scattering systems [35] (i.e. double scatterers with occluding rings or contoured scatterers) are used at most proton and ion therapy facilities to spread the beam laterally. To modulate the Bragg peak in depth rotating variable thickness propellers [36] or ridge filters [37] are used. The particle ranges for treatment are changed by either interposing passive degraders in the beam or, in the case of synchrotrons, by changing the beam energy. Magnetic beam scanning is used at two centres (Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany [38] and the Paul Scherrer Institute (PSI), Villigen, Switzerland [39]) Isocentric beam delivery is not as important as for neutron therapy, but is nevertheless desirable and three types of gantries, all with very different design features,

have been built to date: the corkscrew gantry (Loma Linda University, USA [40]), the compact eccentric gantry (PSI) [39] and the conventional 90° gooseneck gantry (Northeast Proton Therapy Center, Boston, USA and National Cancer Center, Kashiwa, Japan) [41]. Several other types of gantries have been proposed including a 60°-bend gooseneck gantry for ^{12}C ions at GSI [42] and the so-called Riesenrad gantry (proposed Med-AUSTRON project, Wiener Neustadt, Austria) [43]. Non-orthogonal fixed beam arrangements (Hyogo Prefecture facility, Japan and National Accelerator Centre, South Africa) [44] are also being designed. Together with a versatile patient support system and scanned beam delivery such facilities provide a viable cost-effective alternative to isocentric facilities.

Beam scanning with charged particles will likely be the standard method of beam delivery at future facilities. Scanning is used for both beam spreading and for intensity modulated dose delivery. Scanned beams reduce the integral dose to normal tissue because proximal edge conformation can be achieved. There is less activation of components and less exposure of patients to background radiation. Scanned beams, because of the small effective source size, also have smaller penumbrae than passively scattered beams. No patient or field specific devices are required, the dose delivery patterns are automatically computer generated, resulting in less personnel input and increased patient throughput. Conformal therapy with inverse planning optimization should result in less fields per treatment. However, scanning systems are very complex and therefore intrinsically less reliable. Dosimetry is more difficult and the problems associated with organ and patient motion are more severe. The effects of the latter can be reduced to some extent by multiple scans, increasing the elemental beam size or decreasing the overlap between adjacent beam positions.

Lateral beam spreading is done with two magnets which move the beam in two dimensions over the treatment area in a continuous or discrete fashion. Alternatively, one scanning magnet can be used to scan the beam in one dimension (strip) and the patient or the scanning magnet can be moved to move the strip to the next position. As for passive beam modification systems depth variation is accomplished by interposing degraders in the beam in the case of cyclotrons (eg. at PSI [39]) or by changing the beam energy in the case of synchrotrons (eg. at GSI [38]).

6. Future trends

It is likely that a few new fast neutron therapy facilities will be built. There are proposals for new facilities in China, Germany, Poland, Slovakia and South Africa. Most existing high energy facilities will continue to operate since neutron therapy has been clearly established to be the treatment of choice for certain tumour types in randomized clinical trials (particularly for salivary gland [45] and prostate [46] tumours). Improved treatment planning will probably have to be done (in which RBE and gamma contamination will be taken into account). Inverse planning and intensity modulation, although very difficult, may have to considered. The enhancement of fast neutron therapy using neutron capture of thermal neutrons produced in the body is already receiving a lot of attention [47]. Modifications of the fast neutron sources to provide more low energy neutrons will be required. The use of predictive assays and more appropriate patient selection will play a role in the future. Accelerators suitable for fast neutron therapy can also be used for isotope production and for the treatment of eye lesions if proton beams of energies greater than 60 MeV are used for neutron production.

The future of neutron capture therapy will depend on the results of the current clinical trials with epithermal reactor beams. Because of the problems of locating reactors in hospitals, neutron capture therapy will probably be done in future on low-energy accelerator-based hospital facilities with isocentric capabilities. Properly synchronized fractionated treatments (radiation and drugs) will be given. Small proton accelerators providing neutrons in the p(2.5 MeV)+Li reaction are favoured at present [48]. Proton beam currents of up to 50 mA are required, but target heat removal is a severe problem. Other possibilities include neutron production by high intensity D-T generators, ^{252}Cf , spallation and photonnuclear reactions. New capture nuclei (eg. ^{157}Gd) will be considered while more efficient tumour seeking drugs will have to be developed. To date, only glioblastoma multiforme and malignant melanomas have been treated and identification of more clinical indications will be necessary to expand the usefulness of BNCT..

There is probably no future for pion therapy. The clinical results were not encouraging and the facilities are extremely expensive and pions really have no physical or biological advantages over heavy ions.

A few new heavy ion facilities are likely to be built and one is already under construction. However, these are very expensive facilities and the number will be limited. Some convincing evidence that heavy ions are a better treatment modality than protons needs to be produced. The use of radioactive beams for treatment is likely to be undertaken so that real time visualization of the dose distributions will be possible.

Many new hospital-based proton therapy facilities will be built. Several are already under construction. Lower cost turn-key therapy facilities need to be provided for the hospital environment. Most facilities will have isocentric gantries with beam scanning capabilities. It is likely that practically all new hospital-based facilities will be provided by commercial companies. The economies of scale will bring the costs down and with multiple treatment rooms such facilities will be cost-effective when compared with conventional radiotherapy machines which only have one treatment station. There are many proposed new ion therapy facilities [44], but a large number remain unfunded.

[1] J .H. Kogelnik in *Advances in Hadrontherapy*, eds. U. Amaldi, B. Larsson and Y. Lemoigne (Elsevier Science BV, Amsterdam, 1997).

[2] M.M. Elkind and H. Sutton, *Nature*, 184, 1293, (1984).

[3] L.H. Gray, *Brit. J. Radiol.* 30, 403 (1957).

[4] T. Terasima and L.J. Tolmach, *Nature*, 190, 1210 (1961).

[5] D.T.L. Jones, A.N. Schreuder and J.E. Symons, in *Proc 14th Int. Conf. On Cyclotrons and their Applications*, ed. J.C. Cornell (World Scientific, Singapore, 1996) p 491.

[6] D.T.L. Jones et al., in *Hadrontherapy in Oncology*, eds. U Amaldi and B Larsson (Elsevier Science BV, Amsterdam, 1994) p301.

[7] D.T.L. Jones in *Ion Beams in Tumor Therapy*, ed. U Linz (Chapman and Hall, Weinheim, Germany, 1995) p350.

[8] M.R. Raju, in *Heavy Particle Radiotherapy* (Academic Press, New York, 1980).

[9] J. Chadwick, *Nature*, 129, 312 (1932).

[10] J.H. Lawrence, P.C. Aebersold and E.O. Lawrence, *Proc. Natl. Acad. Sci. U.S.A.* 22, 543 (1936).

[11] R.S. Stone, J.H. Lawrence and P.C. Aebersold, *Radiology* 35, 322 (1940).

[12] R.S. Stone, *Amer. J. Roentgenol.* 59, 771 (1948).

[13] G.E. Sheline et al., *Amer. J. Roentgenol.* 111, 31 (1971).

[14] J.F. Fowler and R.L. Morgan, *Brit. J. Radiol.* 36, 115 (1963).

[15] M. Catterall, *Eur. J. Cancer* 10, 343 (1974).

[16] G.I. Locher, *Amer. J. Roetgenol.* 36, 1 (1936).

[17] W.H. Sweet and M. Javid, *J. Neurosurg.* 9, 200 (1952).

[18] L.E. Farr et al., *Amer. J. Roentgenol.* 71, 279 (1954).

[19] H. Hatanaka and Y. Nakagawa, *Int. J. Radiat. Oncol. Biol. Phys.* 28, 1061 (1994).

[20] R.R. Wilson, *Radiology*. 47, 487 (1946).

[21] C.A. Tobais, H.O. Anger and J.H. Lawrence, *Amer. J. Roetgenol. Radiat. Ther. Nucl. Med.* 67, 1 (1952).

[22] J.R. Castro et al., *Cancer* 46, 633 (1980).

[23] H. Yukawa, *Proc. Math. Phys. Soc. Japan*, 17, 48 (1935).

[24] D.H. Perkins, *Nature* 159, 126 (1947).

[25] G.P.S. Occhialini and C.F. Powell, *Nature* 159, 186 (1947).

[26] P.H. Fowler and D.H. Perkins, *Nature*, 189, 237 (1961).

[27] E. Gardner and C.M.G. Lattes, *Science* 107, 270 (1948).

[28] S.P. Richman et al., *Rad. Res.* Suppl. 7, 182 (1967).

[29] M.M. Kligerman et al., *Int. J. Radiat. Oncol. Biol. Phys.* 4, 263 (1978).

[30] D.K. Bewley, in *The Physics and Radiobiology of Fast Neutron Beams* (Adam Hilger, Bristol, U.K., 1989).

[31] R.L. Maughan, *Brit.. J. Radiol.* Suppl. 24, 204 (1992).

[32] R.L. Maughan and M Yudelev, *Med. Phys.* 22, 1459 (1995).

[33] A Brahme et al., *Radioth. Oncol.* 1, 65 (1983).

[34] D.T.L. Jones et al., *Strahlenther. Onkol.* (in press).

[35] A.M. Koehler, R.J. Schneider and J.M. Sisterson, *Med. Phys* 4, 297 (1977)

[36] A.M. Koehler, R J Schneider and J.M. Sisterson. *Nucl. Instrum. Methods* 131, 437 (1975).

[37] B. Larsson, *Brit. J. Radiol.* 34, 143 (1961).

[38] T.H. Haberer et al., *Nucl. Instrum. Methods. Phys. Res.* A330, 296 (1993).

[39] E. Pedroni et al., *Med. Phys.* 22, 37 (1995).

[40] A.M. Koehler, *Report No. LBL* 22962 (Lawrence Berkeley Laboratory CA, 1987).

[41] J. Flanz et al., *Nucl. Instrum. Methods Phys. Res.* B99, 830 (1995).

[42] M. Pavlovic, *GSI-Preprint-97-50* (Gesellschaft für Schwerionenforschung mbH, Darmstadt, Germany, 1997).

[43] R. Pötter and K. Poljanc, *Private communication* (1998).

[44] J.M. Sisterson in *Particles*, Number 22 (Harvard Cyclotron Laboratory, 1998).

[45] G.E. Laramore et al., *Int. J. Radiat. Oncol. Biol. Phys.* 27, 235 (1993).

[46] K.J. Russell et al., *Int. J. Radiat. .Oncol. Biol. Phys.* 28, 47 (1993).

[47] G.E. Laramore et al., *Int. J. Radiat. Oncol. Biol. Phys.* 28, 1135 (1994).

[48] D.A. Allen and T.D. Beynon. *Phys. Med. Biol.* 40, 807 (1995).