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Review

Particle Beam Therapy (Hadrontherapy): Basis for Interest and Clinical Experience

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The particle or hadron beams deployed in radiotherapy (protons, neutrons and helium, carbon, oxygen and neon ions) have physical and radiobiological characteristics which differ from those of conventional radiotherapy beams (photons) and which offer a number of theoretical advantages over conventional radiotherapy. After briefly describing the properties of hadron beams in comparison to photons, this review discusses the indications for hadrontherapy and analyses accumulated experience on the use of this modality to treat mainly neoplastic lesions, as published by the relatively few hadrontherapy centres operating around the world. The analysis indicates that for selected patients and tumours (particularly uveal melanomas and base of skull/spinal chordomas and chondrosarcomas), hadrontherapy produces greater disease-free survival. The advantages of hadrontherapy are most promisingly realised when used in conjunction with modern patient positioning, radiation delivery and focusing techniques (e.g. on-line imaging, three-dimensional conformal radiotherapy) developed to improve the efficacy of photon therapy. Although the construction and running costs of hadrontherapy units are considerably greater than those of conventional facilities, a comprehensive analysis that considers all the costs, particularly those resulting from the failure of less effective conventional radiotherapy, might indicate that hadrontherapy could be cost effective. In conclusion, the growing interest in this form of treatment seems to be fully justified by the results obtained to date, although more efficacy and dosing studies are required. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RADIATION THERAPY, either alone or combined with surgery, can produce enduring loco-regional disease control in a wide variety of cancers. The chance of tumour eradication with radiation depends on tumour-related factors, such as radiosensitivity, volume, location and dissemination path, as well as factors related to the irradiation modality, such as the treatment plan and targeting accuracy. Higher doses of radiation generally give improved local control and possibly longer disease-free survival [1–4], but it is important to ensure that the radiation tolerance of adjacent normal tissues is not exceeded.

Recently, highly sophisticated three-dimensional treatment planning systems have become available. Powerful tools, such as integrated multimodality imaging, beam's eye view, three-dimensional dose distribution and dose–volume histograms [5], can now provide a complete representation of the volume to be irradiated. On-line imaging systems and the use of digitally reconstructed radiographs (DRRs) allow verification of patient positioning during each treatment session and comparison with positions in previous sessions [6]. Another major advance has been the development of three-dimensional

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conformal radiotherapy: this optimises targeting to an anatomical region by means of multileaf collimators containing multiple pairs of thin leaves that can be moved independently to obtain any desired field shape [7]. Modulation of the beam intensity profile, either through beam scanning, dynamic beam shaping or elaborate beam modulators, can further improve control of dose distribution [8]. Finally computer control of the whole radiotherapy process allows complex treatments with custom-shaped or modulated fields in much shorter treatment times than is possible with conventional equipment and also allows accurate use of non-coplanar irradiation beams [9].

These impressive developments mean that higher doses of photon radiation can be delivered to a more precisely defined target volume, while leaving adjacent normal tissues and organs relatively unscathed. It is precisely these advances that have stimulated renewed interest in the use of particle beams, resulting in new designs for hadron units and the construction of new facilities. In fact, the superior physical selectivity of charged hadron beams could not be fully exploited without the improved target definition, meticulous treatment planning and highly accurate delivery recently developed for conventional photon therapy.

Hadrons are subatomic particles subject to a strong nuclear force—a force that binds particles together within the atomic nucleus. The name hadron is derived from a Greek word meaning 'strong'. Hadrons are themselves composed of quarks, thought to be among the ultimate constituents of matter. Typical hadrons are the familiar protons and neutrons that make up atomic nuclei and, by extension, those nuclei themselves. The hadrons currently employed in radiotherapy are neutrons and protons and the nuclei of light atoms such as helium, carbon, oxygen and neon (without, or with, some of their attendant electrons); the latter are generally referred to as light ions. These beams have physical and radiobiological characteristics which differ markedly from those of conventional radiotherapy beams composed of gamma rays or X-rays: charged hadrons (protons and light ions) interact more readily with matter (have enhanced ballistic selectivity) allowing well-defined distribution of the dose in depth; while light ions deposit a large fraction of their energy at the end of their track, resulting in intense local ionisation that is considered highly effective against radiation-resistant tumours [10–13].

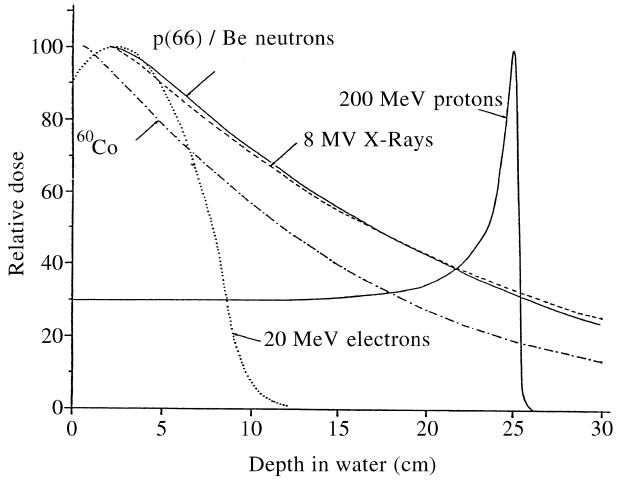

Figure 1. Depth–dose curves for photons (from a cobalt source and an 8 MeV linear accelerator), neutrons and 200 MeV protons. With protons, the highest dose is released near the end of their range giving rise to the 'Bragg peak'. The proton peak is high and narrow because the protons are monoenergetic. For each beam the source to skin distance (SSD) is indicated.

This review discusses the clinical indications for, and expected advantages of, hadrontherapy. In addition, the accumulated clinical experience with particle beams, as reported by the major hadrontherapy centres, is reviewed; the intention being, where possible, to compare findings with those obtained using state-of-the-art photon therapy techniques. Doses are usually expressed in the cobalt-Gray equivalent (CGE) unit. This is the dose given multiplied by the relative biological effectiveness (RBE) of the radiation beam employed. The RBE varies with equipment but mainly with the susceptibility of tissues to radiation; it is a constant (value 1.0) for photons, 1.1–1.3 for protons and 3.0–6.0 for neutrons [13]. Figure 1 compares depth dose curves for photons and various particle beams.

CLINICAL EXPERIENCE WITH HADRONTHERAPY

To date, 43 centres worldwide have treated patients with hadrontherapy; irradiation with neutrons has been conducted in 23 centres, and approximately 15 000 patients have been treated with protons or light ions at energies in the range 60–250 MeV (suitable for irradiation of superficial and deep structures) at 20 different centres. The Loma Linda University Medical Center (LLUMC), California, U.S.A., is the only hospital-based facility so far using protons with energies as high 250 MeV; it is equipped with three isocentric gantries —structures that can rotate to move the terminal tract of a beam transfer line to vary the incidence of the beam on the stationary patient, as in conventional radiotherapy. At least six new hospital-based facilities are being constructed or are under consideration.

Two centres have experience with light ions: the Lawrence Berkeley Laboratory (LBL) which closed in 1993 and the Heavy Ions Medical Accelerator Center (HIMAC), Japan, which started operating in 1994. At GSI in Germany, carbon ion treatment was due to begin in early 1998. In Italy, the TERA project is planning the construction of a National Centre for Oncological Hadrontherapy equipped with a synchrotron to produce protons and light ions. Construction is planned to start in 1998 with completion scheduled for 2002 (Tables 1 and 2).

Neutrons

Experience accumulated in centres for neutron therapy around the world has demonstrated that neutron radiation is of benefit in salivary gland cancers, advanced prostate cancers and certain sarcomas [14–17]. However, results with many other tumours have shown no advantage over conventional X-rays. Most randomised clinical trials comparing neutron with photon therapy have failed to demonstrate that neutron irradiation results in improved survival and have revealed a disturbingly high incidence of severe late effects [18]. These results are in part related to technical problems, such as less effective collimation, inadequate beam energies and poor shaping that characterise laboratory-based neutron therapy units [19]. Because of its greater biological efficacy, densely ionising radiation requires careful collimation and precisely targeted dose delivery to avoid severe late effects in healthy

adjacent tissue [20]. Current clinical studies are being conducted using modern, high-energy hospital-based neutron generators, where treatment planning and dose delivery facilities are comparable to those available for photon therapy [21, 22]; these will permit comparison with standard radiotherapy and define the role of, and indications for, neutron irradiation. Preliminary findings of this ongoing research Indicates that neutrons are mainly useful for locally advanced, non-metastatic, 'radioresistant' tumours.

Boron neutron capture therapy (BNCT) is attracting increasing interest. Boron compounds can be concentrated in tumour cells and then irradiated with low energy neutrons [23–25]. The boron nuclei capture neutrons and the subsequent nuclear reaction gives rise to alpha and lithium particles of high linear energy transfer (LET: density of energy deposition along the track of the particles within tissues) and short range, which transfer all their energy to the boron-containing tumour cells. BNCT is under study for brain tumours, melanomas and hepatic tumours. The effectiveness of this technique is expected to increase as boron compounds become available with more specific selectivity for tumour cells and as procedures for monitoring the blood concentration of boron improve [26, 27].

Protons

The clinical use of proton therapy began in 1954. The majority of patients have been treated in non-hospital-based centres, using beams of fixed energy often not ideally suited to clinical use and requiring modulation by absorbers placed at the end of the beam transport system. Patient access to such centres was often restricted, since physics research programmes took priority. This led to the use of unconventional fractionations not based on evidence-based radiological practice. In spite of these limitations, clinical results were encouraging for several types of tumour, with improved local control reported by several groups [28, 29], which prompted the design of hospital-based equipment provided with rotating gantries. The first of these was inaugurated at LLUMC in 1990; a number of others are under construction [30, 31].

The main clinical indications for proton therapy are proximity of the target area to critical structures (where maximum selectivity of dose distribution is of paramount importance), low tumour radiosensitivity necessitating high-doses; and a high benefit to cost ratio [32]. For the restricted number of tumour types that meet these criteria, such as uveal melanomas [33–35] and chondrosarcomas and chordomas of the base of skull [36] and spinal region [37], proton therapy may be superior to photon beam therapy.

For other malignancies, including tumours of the brain [38–40], head and neck [41, 42], oesophagus [43], prostate [36, 44], rectum [45], female reproductive system [46–48], as well as soft tissue sarcomas [49], where improved local control is likely to result in higher rates of definitive cure, protons therapy has been claimed to have an advantage over conformal photon radiotherapy or combined radiotherapeutic–surgical approaches. However, these were all comparative treatment studies in small series of patients and require confirmation in larger series. Some non-malignant lesions, such as arteriovenous malformations (AVMs) and pituitary adenomas, can also be successfully treated with protons [50].

To facilitate the conduct of clinical trials, the U.S. National Cancer Institute and the American College of Radiology have established the Proton Therapy Oncology Group (PROG). Several phase III and phase I–II trials are being carried out under the auspices of PROG (Table 3).

Light ions

The development of light ion radiotherapy has been slower than that for lower LET radiation because of the complexity of light ion accelerators and because the physical and radiobiological behaviour of these particles require extensive investigation before routine clinical use is justified. The Lawrence Berkeley Laboratory, California, U.S.A., which closed in February 1993, accumulated the greatest experience so far. Between 1975 and 1992, 1314 patients were irradiated, most with helium nuclei (α particles), that deposit energy very much like protons, and 427 patients were irradiated with neon ions. Neon ions are high LET particles with an average RBE of 2.5.

The diversity of tumours treated, the small number of patients treated each year, and the wide variety of doses and

Table 1. *Operating proton and light ion centres*

Centre	Particles	Date of 1st treatment
MGH–HCL, U.S.A.	Protons	1961
Moscow, Russia	Protons	1969
St Petersburg, Russia	Protons	1975
Chiba, Japan	Protons	1979
	Light ions	1994
Tsukuba, Japan	Protons	1983
PSI, Switzerland	Protons	1984
Dubna, Russia	Protons	1987
Uppsala, Sweden	Protons	1989
Clatterbridge, U.K.	Protons	1989
Loma Linda, U.S.A.	Protons	1990
Louvain-la-Neuve, Belgium	Protons	1991
Nice, France	Protons	1991
Orsay, France	Protons	1991
NAC, South Africa	Protons	1993
IUCF, U.S.A.	Protons	1993
UCSF–CNL, U.S.A.	Protons	1994
TRIUMF, Canada	Protons	1995

Table 2. *Planned hadrontherapy centres*

Centre	Particles	Date of 1st treatment
GSI, Germany	Light ions	1997
Berlin, Germany	Protons	1997
KVI Griningen, The Netherlands	Protons	1998
NPTC Boston, U.S.A.	Protons	1998
Kashiwa, Japan	Protons	1998
NC Star, U.S.A.	Protons	1999?
Regensburg, Germany	Protons	1999?
Hyogo, Japan	Light ions	2000?
PROTOX, U.K.	Protons	2001?
TERA, Italy	Protons	2002?
	Light ions	?
AUSTRON, Austria	Light ions	?
Beijing, People's Republic of China	Protons	?
Central Italy, Italy	Protons	?
Clatterbridge, U.K.	Protons	?
ITEP Moscow, Russia	Protons	?
Juelich, Germany	Protons	?
Krakow, Poland	Protons	?
Kyoto, Japan	Protons	?
Proton Development NA Inc. IL, U.S.A.	Protons	?

Table 3. *PROG active protocols*

Phase I/II randomised study of charged particle radiation in the treatment of chordomas or low-grade chondrosarcomas of the base of skull or cervical spine (PROG 85-26)
Prospective study of patients with recurrent or incompletely excised benign intracranial meningiomas for the evaluation of treatment results with combined proton and photon irradiation to doses of 55.8 or 63.0 CGE (PROG 92-13)
Phase I/II study employing proton therapy for the treatment of squamous cell carcinoma of the oropharynx (PROG 92-14)
Phase I/II study of hyperfractionated, accelerated radiation therapy for advanced paranasal sinus carcinoma employing combined proton and photon irradiation (PROG 92-15)
Phase III trial employing conformal photons with proton boost in early stage prostate cancer: conventional dose compared to high-dose irradiation (PROG 95-09)

fractionations employed do not allow satisfactory comparison of light ion results with those using photons or other particles [51]. Nevertheless, there are indications of improved outcomes for certain types of tumours, meriting further investigation as newer facilities come on-line.

The first hospital-based centre for light ion therapy, the Heavy Ions Medical Accelerator Center (HIMAC), started operating recently in Japan. Preliminary phase I–II studies are ongoing for several tumour sites, with progressive dose escalation based on normal tissue morbidity and tumour responses [52].

RESULTS AT SPECIFIC SITES

Eye

Uveal melanomas lend themselves to treatment by fixed hadron beams of lower energies than required for deeper tumours. From 1976–1995, 2242 patients were treated at the Massachusetts General Hospital–Harvard Cyclotron Laboratory (MGH–HCL) with a 60 MeV proton beam to a dose of 70 CGE (RBE=1.1), given in five fractions. Historical comparison with patients treated by eye enucleation showed improved 3-year survival [33–35].

A large retrospective series was analysed using the size categories of the Collaborative Ocular Melanoma Study [53]. Actuarial metastasis-free 5-year survival was 86 and 68% for intermediate (IT) and large size tumours (LT), respectively; with 10-year survival 79 and 60%. Tumour re-growth occurred in 2.4% of patients with LT and in 0.5% patients with IT. Re-growth following enucleation was observed in 15 and 5%, respectively. Useful vision was preserved in over 25% of LT and 66% of IT patients. An updated analysis of 1006 MGH–HCL patients reported 5-year actuarial local control at 96%, with eye preservation in 90% [54]. Owing to the very high control rate, a phase III trial has been initiated for doses of 50 CGE versus 70 CGE.

Helium ion beams have been used at LBL for uveal melanomas, with dose escalation from 50 to 80 CGE. Regression rates similar to those found by MGH–HCL (up to 93%) were reported. However, at doses above 70 CGE, anterior chamber complications, mainly neovascular glaucoma, became more frequent than with other conservative approaches, such as plaque brachytherapy [55, 56].

Radiation therapy for retinoblastoma aims to avoid radical surgery. Proton beam radiation therapy can reduce the size of the treated volume so that in theory, eye structures, orbital bone and soft tissues can be spared and the incidence of complications is reduced. A high precision proton beam was used at MGH–HCL to irradiate 12 young patients with retinoblastoma at doses in the range 40–46 CGE. Local control was achieved in all and after a mean follow-up of 3.5 years, no enucleation was necessary. Two cataracts were reported as radiation-related complications [57]. These results are comparable to those obtained with surgery or radioactive plaque therapy. Several irradiation techniques are being studied for retinoblastoma and preliminary results indicate that homogeneous target coverage is achieved and irradiation to adjacent normal tissues reduced [58]. This may result in decreased incidence of second tumours and better cosmetic outcome.

Macular degeneration is the leading cause of severe visual impairment in patients over 65 years in the U.S.A. Current treatment is laser photocoagulation which always produces visual compromise. Preliminary results on 21 patients treated at LLUMC with protons in a single fraction of 8 CGE have been published. Fluorescein angiography demonstrated regression or stabilisation in 10/19 cases (53%), while visual acuity was improved or unchanged in 15 (79%) [59]. At MGH–HCL a protocol employing either 16 or 24 CGE, in two fractions, is being employed. Preliminary conclusions are that age-related macular degeneration can be treated effectively by proton irradiation. However, since proton beam facilities are in very short supply, a careful evaluation of costs versus benefits is necessary [60].

Base of skull

Chordomas and chondrosarcomas of the base of the skull are very close to dose-limiting structures (optic pathways, brainstem and spinal cord). Local failure is the main reason for relapse; distant metastases occur rarely. Primary treatment aimed at secure local control offers the best chance of cure [61]. Surgery and conventional radiotherapy provide 5-year progression-free survival in the range 17–33% for chordomas at all sites [62–64]. A recent Mayo Clinic review on base of skull chordomas reported 33 and 24% progression-free survival after 5 and 10 years [65], respectively. In four recent series [66–69], 5-year survival for patients with base of the skull chondrosarcoma ranged from 43–90%. The radiation doses in all these studies were moderate, usually under 60 Gy, because of the risk of damage to surrounding tissues.

Proton beam therapy in such tumours may improve local control by using higher dose radiation, yet keeping the risk of damage to critical structures low. From 1975 to 1993, 133 adult patients with chordomas and 130 with low-grade base of skull chondrosarcomas were treated with fractionated proton radiation therapy at MGH–HCL [70, 71]. Surgery first debulked the tumour and produced a favourable geometrical configuration for radiotherapy. The median doses given were 68.7 CGE (range 36.0–79.2) for chordomas and 68.4 CGE (range 66.6–72.0) for chondrosarcomas. Local control at 5 and 10 years was 59 and 43% for chordomas and 98% for chondrosarcomas. Local recurrence-free survival was significantly better in males than females. During follow-up, 40 chordoma patients developed local recurrences and 8 distant metastases. No patients with low-grade chondrosarcoma developed metastases. Major complications (unilateral or bilateral blindness, brain or brainstem necrosis) occurred in 8%. Thus, progression-free survival in patients receiving

proton therapy appears markedly better than published results with conventional radiotherapy.

To improve the determination of the optimal dose, a randomised prospective trial has been initiated by PROG (PROG 85-26). Low risk cases (base of skull chondrosarcoma and males with base of skull chordomas) are being randomised to receive between 66.6 and 72 CGE, while high risk patients (cervical spine chondrosarcoma, cervical spine chordoma and women with base of skull chordoma) are being randomised to between 72 and 79 CGE.

A large series of patients with tumours arising in or extending to the base of the skull were treated with helium and neon ions at LBL [72]. With a median dose of 65 Gy, the 5-year actuarial local control rates were 85, 78 and 63%, respectively, for meningioma, chondrosarcoma and chordoma. Improved three-dimensional treatment planning and treatment delivery techniques resulted in a reduction of serious late complications: 41% for patients treated before 1986, 20% for patients treated between 1987 and 1992.

At MGH–HCL, 16 patients with benign meningiomas of the base of the skull were treated with combined protons and photons from 54 to 72 CGE. This group was compared with 24 patients who received photons only at 45–50 Gy. A trend towards better local control was evident at higher doses in the former group [73]. A comparative proton and photon treatment planning study was performed at MGH–HCL. The dose localised more accurately to the target area with protons than with photons [57]. Based on these results, a randomised prospective study (PROG 92-13) of two dose levels (55.8 versus 63.0 CGE) in patients with incompletely excised and recurrent sphenoid ridge and parasellar meningiomas was begun in 1994.

Central nervous system

Although postoperative adjuvant radiotherapy significantly increases median survival for malignant glioma, the best results at present are 2-year survival rates of approximately 30% for glioblastoma multiforme and 57% for anaplastic astrocytoma [74, 75]. A dose escalation study up to 80 Gy using three-dimensional conformal radiotherapy with photons for high grade astrocytoma obtained a median survival of 16 months and a 2-year survival rate of 20% [76].

A Radiation Therapy Oncology Group (RTOG) randomised study compared neutron boost with photon boost following 50 Gy conventional whole brain radiotherapy [77]. Median survivals were similar in the two arms, but autopsies on 20% of patients revealed proliferative tumour tissue in all patients irradiated by photons, but in none of those receiving neutrons. Based on these results, RTOG designed a new study with a 'field-within-a-field' boost, but no improvement in overall survival was found [78].

At MGH–HCL, a protocol for grade IV malignant gliomas has been implemented. After maximal surgical resection, high dose hyperfractionated protons/photons are given to three progressively smaller target volumes. The smallest volume (defined by the contrast enhanced rim) is irradiated to 90 CGE in 50 fractions over 5 weeks; 25 patients have been treated and all failures have been in tissue outside the 90 CGE treatment volume [57].

At the Proton Medical Research Center (PMRC) of Tsukuba, Japan, 13 patients with malignant gliomas were treated with protons alone or proton boost, achieving local control in 50% of anaplastic astrocytoma and 0% of glioblastoma multiforme; median survival was 25 and 13 months, respectively [28].

16 malignant glioma patients treated with neon ions at LBL did not show improved survival; 2 patients died from brain necrosis, considered related to the high RBE (4.0–4.5) [51].

In spite of these modest results, clinical investigations with hadrons for the treatment of high grade gliomas are continuing in several centres. Careful dose escalation with light ions and protons and the use of BNCT, are being explored.

Stereotactic proton beam irradiation was used at MGH–HCL to irradiate acromegalic patients with intrasellar pituitary adenomas. At 5 years the remission rate was 50%, with visual impairment in 1.8% [79]. Because of different pretreatment levels of growth hormone, which predict outcome, reliable comparison with conventional photon radiotherapy could not be made [80]. A study on tolerance doses reported 10% major complications for up to 55 CGE with conventional fractionation, but this incidence was probably related to predisposing factors, such as diabetes mellitus-induced vasculitis [81].

At MGH–HCL irradiation has been used since 1961 to treat arteriovenous malformations. A single fraction of 10–50 CGE is used, depending on lesion size and expected toxicity [82]. A complete obliteration rate of 20% has been reported, probably due to the low doses employed, with a complication rate of 0.3%. A new iterative multi-modality system for delineation of target volume was recently inaugurated. This spares a relatively large amount of normal brain tissue when large and complex arteriovenous malformations are treated with stereotactic protons [83]. LBL reported superior effectiveness overall with stereotactic Helium ion therapy; their obliteration rates were higher and related to lesion size, reaching 94% for lesions less than 4 cm^3. However, the morbidity rate was 12%. Doses ranged up to 35 CGE. Reduction of radiation doses in the latest series [84] resulted in a lack of early morbidity. Longer follow-up is required to evaluate long-term control rates at these lower doses.

A recent attempt to compare the dose distributions of different stereotactic techniques found that protons had a distinct advantage (in terms of dose uniformity to tumour and sparing of adjacent brain tissue) for large and irregular target volumes [85].

Prostate

The radiobiological characteristics of neutrons suggest that they would be particularly effective for treating slowly proliferating tumours, such as prostate adenocarcinomas [86]. An RTOG randomised clinical trial that compared mixed neutrons and photons with conventional photons in locally advanced prostate carcinomas found that the mixed-beam modality had a persistent and significant advantage in terms of loco-regional control (with 5 and 10-year rates of 85 and 70% versus 62 and 58%, respectively), and overall survival (5 and 10-year actuarial survivals of 70 and 46% versus 53 and 29%, respectively) [87, 88].

An NTCWG randomised trial showed significantly improved clinical and histological local control rates for neutrons compared to photons, that have not yet translated into improved overall or cancer specific survival [89]. A recent update of the NTCWG study confirmed the significant difference in loco-regional recurrence rates between the two arms (40% for photons and 14% for neutrons at 7 years)

Table 4. Summary of results obtained with particle beam to treat cancers of head and neck, lung, bone and soft tissues, oesophagus, liver, biliary duct, pancreas, bladder and cervix

Treatment centre [Ref.]	Disease/tumour site	No. of patients	Treatment	Results	Comment
NTCWG [94–96]	Advanced head and neck cancers (stage III–IV)	178 patients, 169 evaluable	Randomised: neutrons (20.4 Gy) versus photons (70.0 Gy)	Initial response with neutrons better; 3 year local control and survival not different	Early toxicity similar, late toxicity higher (40 versus 18%) in neutron arm
MGH–HCL [57]	Carcinoma of paranasal sinus	36 patients, 20 evaluable	Combined photons and protons up to 76 CGE	15 no evidence of disease, 5 partial response	
MGH–HCL [97]	Primary and recurrent sarcomas of head and neck	27 patients	Combined photons and protons (mean dose 68.5 CGE)	3 and 5 year local control 71 and 51%; trend for better local control with target doses of at least 70 Gy	Good results attributed to selectivity of proton dose distribution
PMRC [28]	Locally advance T3–T4 head and neck tumours	10 patients	Protons 80% $\geq$ 70 Gy 50% $\geq$ 80 Gy	Two patients developed local failures salvaged by surgery	
LBL [98]	Heterogeneous group of head and neck tumours	98 patients	Neon ions	Actuarial local control rate at 2 years: 60% for non-SCC and 35% for SCC	Further use of charged particles justified for tumours that abut or surround critical tissue
RTOG [99, 100]	Inoperable, primary or recurrent salivary gland tumours	32 patients, 25 evaluable	Randomised: photons versus neutrons	Better 10 year local control and survival with neutrons (56 versus 17%) but not better overall survival. High incidence of distant metastases	Fast neutrons have RBE 8 for salivary gland tumours, cf. 3.0–3.5 for normal tissue
University of Hamburg [101]	Recurrent salivary gland tumours	33 patients	14 MeV neutrons	5 year survival 45%, control 43%, one patient suffered severe late effects	Result superior to photons (median local control rate 28%)
LBL [51]	Salivary gland tumour	18 patients	Neon ions	5 year actuarial local control 61%	Improved outcome versus photons
University of Washington [102]	Non small-cell lung cancer	102 patients	Randomised: neutrons versus photons (60 Gy in each arm)	No differences in local control or overall survival	
NTCWG [103]	Non small-cell lung cancer	200 patients	Randomised: neutrons (20.4 Gy) versus photons (66.0 Gy)	Survival advantage for neutrons for squamous cell histology	Trend to better survival with neutrons in patients with favourable prognostic factors
University of Washington [104]	Unresectable sarcomas	16 patients	Neutrons	Local control rates approximately 50% superior to photons	
LBL [105]	Soft tissue and bone sarcomas	17 patients	Helium and/or neon ions	Results at 5 years: actuarial local control 48%, survival 41%	Over 50% of patients succumbed to distant metastases despite chemotherapy
RTOG [106–108]	Oesophagus, bladder, cervix	132 patients	Neutrons	Preliminary results not promising	Further investigation not recommended
LBL [109]	Locally advanced oesophageal, gastric and biliary tract cancers	65 patients	Helium ions 60–70 CGE	Median survival 8 months	Results not better than photons
PMRC, Tsukuba [110]	Oesophageal carcinoma	15 patients	Protons mean dose 80.4 Gy	All patients had complete response; 3/15 recurred locally after 8, 16 and 44 months	High-dose proton radiation resulted in high local control and survival rates
PMRC, Tsukuba [111]	Hepatocellular carcinoma	34 patients	Protons 50–87 Gy	2 year local control in 12/18 (67%)	No severe side-effects
LBL [112]	Pancreatic cancer	49 patients	Randomised: helium ions (60–70 CGE) versus photons (60 Gy)	No significant difference in local control and survival	

[90]. However, in this study, and that performed by Chuba and associates [91], neutron therapy was associated with increased late complications, such as bladder, rectal and musculoskeletal toxicity resulting in hip stiffness, which appeared to be related to technical factors, such as beam energy, collimation and treatment planning.

A series of 241 patients with prostate cancer was irradiated with neutrons at the University of Washington cyclotron, equipped with a fully rotational isocentric gantry, variable multileaf collimator, three-dimensional treatment planning and computer controlled systems [92]. This study confirmed improved local control with neutrons and low (10%) major toxicity, with no patients requiring colostomy for bowel complications.

At MGH–HCL, a randomised study compared conventional photon boost with conformal proton boost in advanced stage prostate cancer. It showed significantly improved local control for poorly differentiated tumours using proton boost (up to 75.6 CGE), but grade 1+2 rectal bleeding and urethral stricture were more frequent [93]. Based on this experience, a PROG randomised trial for T1–T2 prostate cancers comparing two different proton doses (79.2 versus 70.2 CGE) was started in 1996.

12 patients with locally advanced prostate cancer have been treated with neon beam irradiation at LBL. The 5-year actuarial local control rate was 75% with one major radiation-related proctitis that required colostomy [51]. The authors suggested that these promising results should be further investigated in phase III clinical trials.

Other sites

Table 4 provides a summary of the results obtained using particle beams to treat tumours of other sites.

COSTS

Most studies on particle beams were carried out using physics laboratory accelerators and did not usually require cost-of-treatment analyses. Following the accumulation of evidence that hadrontherapy may be more effective than conventional therapy in selected cases, careful cost analysis and long-term comparison with state-of-the-art photon radiotherapy techniques becomes mandatory. Any advantage in terms of increased cure rate or reduction of acute and late complications rates will result in cost savings for salvage treatments and treatment for iatrogenic morbidity, and these must be included in the analysis.

It is clear, nevertheless, that more clinical data are needed, and in particular randomised comparative trials must be performed in order to unambiguously identify tumours for which hadrontherapy is superior to modern conventional radiotherapy and to enable precise assessment of the magnitude of the clinical gain, including the benefits of avoided later treatments, saved patients' work time and quality-adjusted life years.

Hadrontherapy centres are undoubtedly more complex and more costly than conventional photon therapy units. However, the costs of radiotherapy in general, including hadrontherapy, are much lower than the costs of all other types of therapy for malignant diseases [32, 113–115]. Thus, proton therapy, for example, is not more expensive than many of the therapies available offered by many national health services and private insurance plans. The best available European data [116] indicate that the average cost of cancer treatment is 15 000 DM ($8000) per patient, conventional radiotherapy costs 7000 DM ($3700) per patient, while an intensive course of chemotherapy, as applied in leukaemia, for example, costs 60 000 DM ($24 000). These figures do not include the cost of any subsequent chemotherapy given to control metastases. Conformal X-ray therapy for prostate cancer costs, in Italy, the equivalent of 16 000–17 000 DM ($8500–9000). A course of hadrontherapy requires 20 000 DM ($10 500), but this would be more than justified for those tumours where hadrontherapy is significantly more effective than conformal X-ray, or even other conventional therapies. A target of around 20 000 DM ($10 500) per treatment was proposed by the Design of Compact Proton Accelerators Project and accepted by the Italian Ministry of Health in their financing of this project in 1995 [117]. The costs of treatment at the National Centre for Oncological Hadrontherapy in Italy are projected to be considerably higher since this will be a centre of excellence and research, providing not only proton therapy but more expensive treatments with carbon ions. It has been estimated that a 20 session course, 30 min each session, will cost between 25 and 30 million Italian Lire (approximately 25 000–30 000 DM; $13 000–16 000) in 1995 figures.

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