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Prospects for Proton-beam Radiotherapy

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Proton beams are already being employed for radiation therapy in 15 centres worldwide and over a dozen more are planned. Good clinical results have been reported in uveal melanomas and in sarcomas of the skull base. Calculated dose distributions for the treatment of brain, lung, head and neck and pelvic tumours predict an improvement relative to multiple-field or conformal photon radiotherapy. Protons may well provide high-precision radiotherapy that will lead to improved treatment of certain tumours in specific anatomical locations.

Key words: proton radiotherapy, conformal radiotherapy, dose distributions, radiotherapy machines
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INTRODUCTION

IMPROVEMENT OF local tumour control is a major aim in the strategy to cure more patients of cancer. During the past few years, major developments have taken place in techniques of radiation planning and delivery, in particular, in so-called conformal radiotherapy [1, 2]. This approach gives the promise of increasing the radiation dose to tumours, whilst reducing the dose to surrounding normal tissues, and in specific tumour sites this should lead either to increased local tumour control and to a reduction in radiation morbidity. Proton-beam therapy has the ideal physical properties to deliver such an optimal radiotherapy treatment. Energies in the region of 250 MeV are required to treat deep-seated lesions, and so far these have only been available in a few centres. This may provide the ultimate approach to high-precision conformal radiotherapy. The magnitude of the clinical benefit is not yet clear: theoretical studies are under way to estimate this and, within the next few years, further clinical results will come from a number of centres in various countries where proton therapy machines are being installed.

RATIONALE

Basis for the use of proton beams in radiation treatment

The impetus for efforts to improve radiotherapy dose distributions comes from continued failure to achieve local control in a significant proportion of cases, particularly in advanced stages of disease at many anatomic sites. In the U.S.A., it has been estimated that the treatment of the primary tumour is unsuccessful in some 200 000 patients per year [3]. The equivalent number of cases in the U.K. is around one fifth of this, or 40 000 patients per year. Suit also demonstrated that greater success in controlling the local disease will lead to improved patient survival, in spite of the losses due to metastic disease [3].

Although there is no doubt that reduction in treatment volume carries the potential for improved radiotherapy, there are legitimate questions regarding the magnitude of the gains to be realised and the cost of achieving them. Previous clinical experience has shown that technical developments in radiation therapy, which have made significant reductions in treatment volume, have resulted in more patients being cured. Substantial improvements in therapy have followed the progression from orthovoltage to cobalt-60 to megavoltage machines. No radiobiological advantage is conferred by these higher energy beams, but previously untreatable tumours such as prostate and bladder cancer are now regularly eradicated. Ten-year survival results in Hodgkin's disease improved from 23 to 62% following the introduction of megavoltage treatment [4], and from 33 to 70% for tumours of the oropharynx [5]. In carcinoma of the cervix, the Princess Margaret Hospital Group in Toronto documented an improvement in survival from 25 to 40% in a prospective randomised study, comparing cobalt-60 treatment with therapy using a 22 MeV Betatron Unit [6].

The radiation dose that can be tolerated by a normal tissue without serious damage is greater for small than for larger treatment volumes. Therefore, reducing the amount of normal tissue that is included in the target volume will allow the dose to the tumour to be increased. The expected increase in normal-tissue tolerance as a result of conformal dose distributions should permit doses that are 10–20% higher than in current conventional therapy [3]. The consequent gain in tumour control probability will depend on the slope of the dose–response curve for local control. Information on the steepness of these curves is available for a number of tumour types. A typical value for the slope of the dose–response curve for tumour control is $\gamma_{50} = 2$ (i.e. at the steepest point of the tumour control curve, a 1% increase in dose results in a 2% increase in local control). An increase in the target dose of 20% would thus roughly translate into a 40% increase in local control rate.

Proton therapy is most attractive when the following conditions exist: (1) incomplete local tumour control is achieved by present treatment modalities, whether by surgery, conventional radiotherapy, or both; (2) there is a low probability of metastatic spread; (3) evidence for a dose–response relationship in tumour control is available; (4) adequate tumour dose is limited by the proximity of vital structures.

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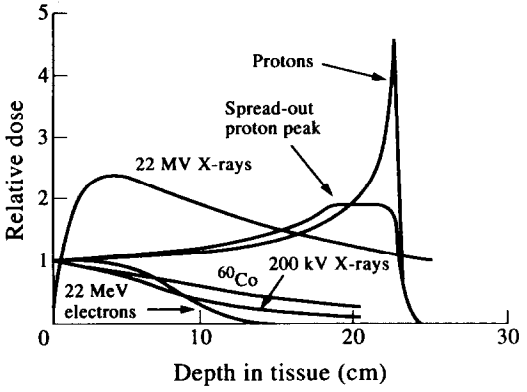

Figure 1. Comparison of depth–dose distributions for X-ray, γ-ray and electron beams with that for a proton beam. This chart compares the energy-loss characteristics of various types of radiation used in the treatment of cancer.

The physics of proton beams

Protons have 2000 times the mass of electrons. As a consequence of this large mass, high-energy protons travel virtually in straight lines in matter, in marked contrast to electrons of similar penetrating power which are scattered appreciably except at the very beginning of their range. A second, equally important, consequence of this straight-line travel is that a beam of monoenergetic protons (i.e. all having the same energy) will stop at almost exactly the same depth. Again this is not the case with electron beams.

A plot of energy deposition versus depth of penetration for a monoenergetic proton beam shows that the absorbed dose increases very gradually with increasing depth and then suddenly rises to a narrow peak at the end of the proton range. This is known as the Bragg Peak. Figure 1 shows this property of proton beams in comparison with the depth–dose properties of high-energy X-rays, ^{60}Co γ-rays and 22 MeV electrons, all radiation qualities in frequent use in radiotherapy.

Production of a clinically useful beam

The very sharp depth–dose distribution for a monoenergetic proton beam is rarely useful for treating a tumour without some modification. Tumours generally occupy an extended volume in the body, and some way must be found to irradiate this volume uniformly. The most common way of doing this is to *spread out* the Bragg peak. This is illustrated in Figure 2. The energy of the beam is modified during treatment, either by passive scattering or by some form of active scanning [7].

Relative biological effectiveness (RBE) of high-energy protons

Protons at the very end of their range (i.e. in the distal part of the Bragg peak) are densely ionising and have an increased linear energy transfer (LET). In spite of this, spread proton beams with sufficient penetration for clinical radiotherapy have an overall RBE that is only slightly higher than unity. They are, therefore, classed as low-LET radiation and their biological effects are similar to those produced by X-rays, γ-rays or high-energy electrons. In the planning of proton therapy, this is a distinct advantage because the spectrum of types of normal-tissue reactions is likely to be the same as are produced by current radiotherapy machines. The relative incidence of 'early' and 'late' reactions is likely to be similar to current experience giving a measure of safety in moving to this new type of radiation.

The most significant radiobiological question is whether proton radiation has precisely the same biological effect per unit dose as conventional therapy. There have been a number of laboratory studies of the RBE of protons. Early work showed a range of RBE values, roughly 0.7–1.3 [8, 9]. More recently, published values have been close to 1.0 [10]. Clinical studies of proton therapy have often assumed an RBE of 1.1, thus allowing a slight safety factor. It has become conventional for proton therapy doses to be specified in terms of Cobalt Gray Equivalents (CGE) and these have usually been obtained by multiplying the actual dose in grays by 1.1.

Protons are not neutrons

The physical and radiobiological properties of proton and neutron beams are very different. The benefit of neutron beams is thought to lie in their greater RBE, mainly against hypoxic tumour cells; the benefit of protons lies in greater precision of dose delivery (Figure 3). Research into the therapeutic value of neutron beams has gone on for many years. However, during the past decade, the future for neutron therapy has come into question. In the U.K., two of the three installations (Hammersmith and Edinburgh) have been closed and treatments have been curtailed at the third (Clatterbridge). Although the reasons for this decline are controversial, it does seem that high LET radiations tend to produce increased late normal-tissue damage [11]. It is possible that shorter overall treatment times may help to off-set this disadvantage [12]; also, the use of a multi-leaf collimator has recently been shown to reduce the late

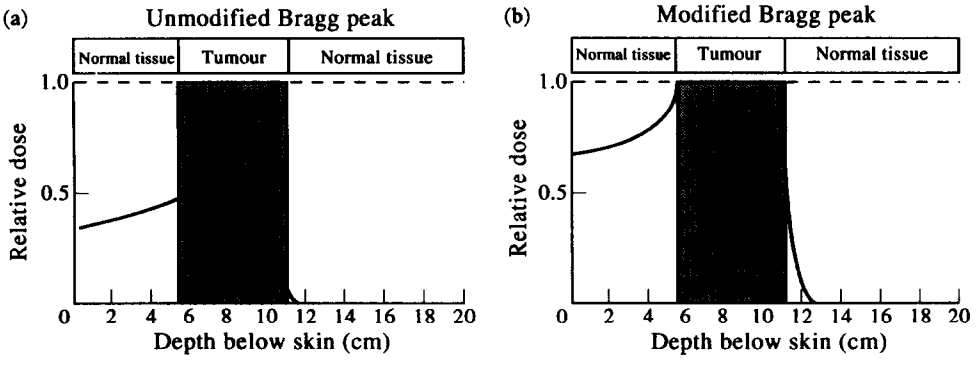

Figure 2. (a) A monoenergetic proton beam deposits most of its energy at its stopping point in tissue (i.e. in the Bragg peak). The dose anterior to the target volume is lower than with conventional irradiation, and there is almost no dose to tissues beyond the peak. (b) By varying the energy or otherwise modulating the beam, the Bragg peak region can be made to encompass the target volume for a large tumour, while still delivering a reduced dose to surrounding tissue.

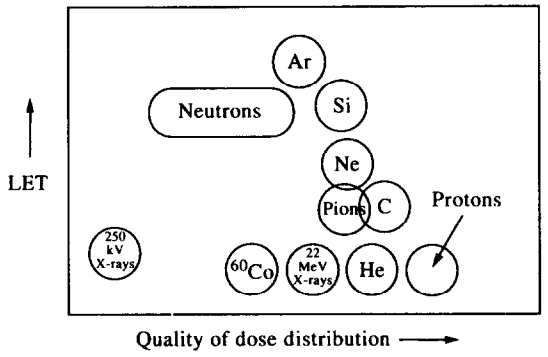

Figure 3. Conventional and novel radiations for clinical radiotherapy differ in terms of the quality of dose distribution that they provide, also in their LET. From Fowler [40].

complications of neutron radiotherapy [13]. Since similar types of high-energy accelerator are required for both neutrons and protons, it is important not to confuse these two types of radiation.

CLINICAL RESULTS WITH PROTON THERAPY

Progress so far in the use of protons for radiotherapy

Well over 15 000 patients have been treated with heavy charged particle beam therapy in 17 centres (Table 1). The majority, over 11 000 patients, have been treated with protons. Approximately 46% of all proton treaments have been for patients with benign intracranial lesions, such as pituitary adenomas and arteriovenous malformations. Thirty-two per cent of patients had orbital tumours, most commonly uveal melanomas. The most common types of lesion treated by protons in other sites have been tumours of the skull base and cervical spine sarcomas. The selection of patients has been weighted towards those whose lesions could be treated with machines that were designed for basic particle physics research with fixed horizontal beams. This greatly restricts flexibility in treatment technique, in comparison with isocentrically mounted linear accelerators. Many proton facilities used so far have had proton energies sufficient only to treat relatively superficial tumours. Additional limitations on patient accrual have occurred because many units have been sited in physics laboratories remote from hospital sites.

Table 1. Current proton therapy installations

Location		Date of first treatment	Recent patient total
Harvard	U.S.A.	1961	6010
Moscow	Russia	1969	2550
St Petersburg	Russia	1975	719
Chiba	Japan	1979	86
Tsukuba	Japan	1983	354
PSI (SIN)	Switzerland	1984	1363
Dubna	Russia	1987	24
Uppsala	Sweden	1989	34
Clatterbridge	U.K.	1989	463
Loma Linda	U.S.A.	1990	682
Louvain-la-Neuve	Belgium	1991	21
Nice	France	1991	216
Orsay	France	1991	235
NAC	South Africa	1993	6
Indiana	U.S.A.	1993	1

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A number of new proton therapy centres are now planned (Table 2). Some of these will have high-energy beams mounted on gantries capable of isocentric movement and will be sited in dedicated medical facilities. For the first time, this will give the opportunity for systematic evaluation of protons for deep-seated and common tumours.

Uveal melanoma. Uveal melanoma is rare, yet a comprehensive review by Suit and Urie [14] collated results from over 2800 patients treated with protons. Exceptionally high doses of radiotherapy have been given, using doses of 70 CGE in five fractions or 60 CGE in four fractions. Impressive actuarial local control rates of 96% have been described with most failures occurring on the margins of the high-dose field or elsewhere within the globe. Overall, 5-year survival rates of 80–88% are very satisfactory and functional results are also good, with useful visual function remaining in the majority of eyes treated, preservation of the acuity being dependent on the distance of the melanoma from the fovea and optic disc [15]. The Harvard group are currently conducting a randomised phase 3 study comparing 70 CGE and 50 CGE (both in five fractions) with the aim of reducing normal-tissue complications whilst maintaining local control.

Sarcomas of the skull base. Chordoma and chondrosarcoma of skull base are also rare, but considerable experience in treating them with proton beams has been built up by the Harvard and Berkeley groups over the last 15 years [16–19]. Results on 320 patients have recently been summarised [14]. The dose that can safely be delivered using conventional photon beam radiotherapy is limited to about 55 Gy, and retrospective reviews suggest that local control is about 35% at 3 years [20–24]. Proton doses of 65–75 CGE using 1.8 CGE per fraction have been given and local control probabilities of 91 and 83% reported for skull base chondrosarcomas and 65 and 33% for chordoma [19, 17]. Factors related to the chance of recurrence were histology, tumour volume, site of disease (skull base better than cervical spine) and tumour dose, recurrence being most likely in areas of relative under-dosage. Treatment-related morbidity appears to be low.

Table 2. New facilities for proton and ion-beam therapy, under construction or planned

Institution	Place	Expected
PSI	Switzerland	1994
HIMAC Chiba	Japan	1994
TRIUMF	Canada	1994
Novosibirsk	Russia	1995?
Berlin	Germany	1995
Munich	Germany	1995
GSI Darmstadt	Germany	1996
ITEP Moscow	Russia	1996
Proton Development NA	Illinois, U.S.A.	1996
Jülich (KFA)	Germany	1997
KVI Groningen	Netherlands	1997?
NEPTC (Harvard)	U.S.A.	1998
Clatterbridge	U.K.	?
Tsukuba	Japan	?
Chicago	U.S.A.	?
TERA	Italy	?
Krakow	Poland	?

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These results are substantially better than with conventional photon-beam treaments, but no prospective randomised studies are planned in view of the rarity of the tumour. Detailed dosimetry comparisons with "conformal" photon-beam therapy have also not been made. Other intracranial tumours treated successfully in small numbers by the Harvard group include meningiomas (16 of 16 recurrent or inoperable tumours attained local control) and craniopharyngioma (14 out of 14 were successfully controlled) [14]. A Soviet group have also reported promising results treating cavernous sinus meningioma [25].

Other tumours. The only phase 3 prospective randomised study comparing photon and proton beam therapy has been undertaken at the Massachusetts General Hospital and Harvard Cyclotron Laboratory in prostate cancer. 191 patients with T3–4 N0–2 cancer were treated with photon beam radiotherapy to the pelvis (50.4 Gy), and then randomised to either a shaped photon boost of 68.4 Gy using lateral fields or a proton boost to 75.6 CGE using a perineal field [26]. The treatment code has not yet been broken for outcome (overall local control 87%, survival 81%, 5 years post-treatment). Late radiation effects have been more common in the high-dose arm with an actuarial probability of developing rectal bleeding of 34%, compared to 16% for the photon arm ($P = 0.013$), but no patient had greater than RTOG grade 2 toxicity. Similarly, haematuria was more common in the proton arm (14 versus 8%, $P = 0.25$). Rectal toxicity was clearly related to the volume of rectal wall irradiated. Comparisons of efficacy between the randomised arms of this important trial are eagerly awaited, but it should be noted that in phase 1/2 studies of conformal radiotherapy using photon beams the prostate dose has been escalated to 80 Gy [27, 28].

A small study in oesophageal cancer has reported results in 11 patients treated with 250 MeV protons to a dose of 80–88 CGE [29]. 10 of 11 achieved local control, 1 patient developing serious morbidity. The Soviet group have also reported promising results in breast and uterine cancer [30].

ESTIMATES OF THERAPEUTIC GAIN

Comparison of dose distributions achievable by proton and photon beams

Although the number of sites treated with proton beams has been limited, a significant body of work has compared the dose distributions of protons and photons at a variety of sites.

Brain tumours. For paediatric brain tumours, Archambeau and co-workers [31] demonstrated, for a thalamic astrocytoma, that dose escalation from 54 Gy (photons) to 74 CGE for protons was possible with a decreased integral dose to normal brain; similarly Tatsuzaki and associates [32] demonstrated a 46% reduction in normal brain irradiated to high dose using protons rather than photons for the treatment of a cortical glioblastoma.

Head and neck cancer. In the treatment of the head and neck region Miralbell and colleagues [33] have demonstrated potential reductions in dosage to the brain stem, optic nerve and retina using protons rather than photon treatment for maxillary sinus cancers. For carcinoma of the tonsillar region, Slater and associates [34] have shown proton beams can deliver higher doses to the target volume whilst reducing radiation to salivary glands and mandible.

Lung cancer. In non-small cell lung cancer, Langer and Kijewski [35] have demonstrated that proton-beam techniques can increase tumour dose by at least an additional 10 Gy while maintaining a dose of 20 Gy to $< 30\%$ of the contralateral lung volume.

Pelvic tumours. Smit [36] estimated for cervix cancer, treated with a 200 MeV proton beam, that a volume reduction of up to 60% in the high-dose volume could be achieved with proton therapy when compared with the photon therapy. He calculated that a 20% dose increment might be reasonable with an expected 40% improvement in local control rate without an expected increase in complications. For the post-operative treatment of rectal cancer, Tatsuzaki and colleagues [32] demonstrated that the volume of bowel treated to the 90% isodose could be reduced by approximately 50% using proton rather than conventional photon beam arrangements. Suit and Urie [14] have demonstrated a similar (50%) reduction of bowel exposure when using protons to treat pelvic lymph nodes from prostatic adenocarcinoma. Levin [37] has described a technique for radical para-aortic lymph node irradiation in cervix cancer using high-energy protons with or without initial photon-beam therapy. The distributions that were obtained suggested that doses up to 80 CGE could be delivered without significant toxicity to cauda equina, kidney or bowel. Using conventional photon therapy, it is not possible to deliver radical doses of radiotherapy adequate to reliably eradicate macroscopic disease either in the pelvis or para-aortic lymph nodes, and proton-beam therapy offers the opportunity for addressing whether such treatments may impact on the survival of patients with pelvic tumours.

Studies at the Royal Marsden Hospital (RMH) and Institute of Cancer Research (ICR)

Although the radiotherapy planning studies described above encourage the view that there will be significant benefits from the use of proton beams, in our opinion they are not yet fully conclusive. An important limitation of some previous assessments has been to compare proton beam treatment with conventional photon beam therapy. Photon beam treatment has moved on and state-of-the-art treatment now demands the use of 3D beam shaping or conformal radiotherapy [1]. The necessary comparison is between the best dose distributions obtainable from conformal proton-beam therapy compared to proton beams. A project is under way in the Physics Department of the RMH/ICR in which, for a number of tumour sites, estimates are being made of the expected gain in terms of tumour control for a fixed level of normal-tissue damage. A study on prostate cancer is now complete [38]. This compared a 2-field proton with 3-field or 6-field megavoltage conformal X-ray techniques for 20 cases of advanced prostate cancer. An example of the results is shown in Figure 4. In the proton plan, the 30% isodose encompasses a smaller volume of rectum and bladder, and no part of the femoral head receives more than 50% of the prescribed dose. There was evidence of a distinct advantage for protons in about one-third of the cases. Success in the remaining cases was limited because the target volume included the wall of the rectum. It would now be possible on the basis of state-of-the-art 3D-planning to select those cases that should benefit from proton therapy; in such a common disease these would comprise a substantial number of patients. Similar studies for cancer of the bladder, lung, brain and head and neck region are underway, both here and in other institutions.

The numbers of patients likely to benefit from proton therapy

A comprehensive study of the potential benefits of proton therapy has recently been presented in a working report by

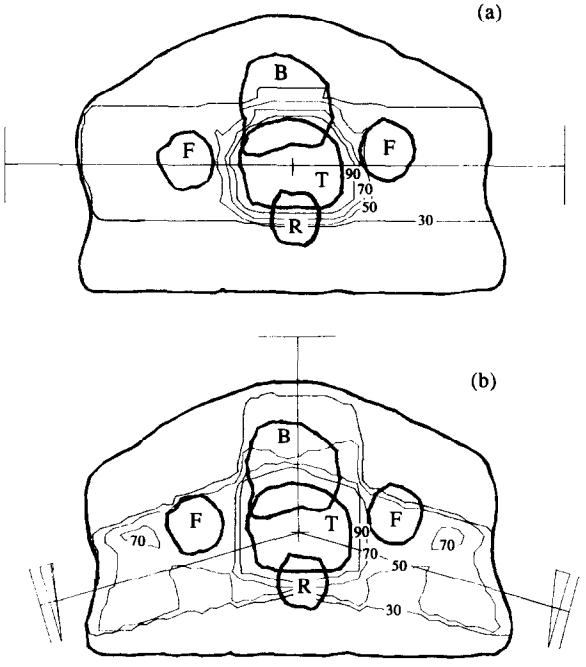

Figure 4. A comparison of dose distributions in the central CT slice through the pelvis (a) for a 2-field proton plan employing passive scattering; (b) for a 3-field 15-MV X-ray plan. The isodoses shown are normalised to 100% at the isocentre. T, target volume; R, rectum; B, bladder; F, femoral heads.

Bonelli and associates [39]. Tumours that are likely to benefit from high-precision treatment with protons were divided into the following four categories:

(A) Highly localised tumours of the brain and head and neck, characterised by their close proximity to vital structures. For these conditions, a proton beam provides unique advantages which have already been clinically demonstrated. (Examples: uveal melanoma, sarcomas of the skull base.)

(B) Localised tumours in other sites which are inadequately controlled by conventional radiotherapy because of their low radiosensitivity. Protons offer the prospect of increasing the tumour dose without exceeding the tolerance of surrounding normal tissues.(Examples: prostate cancer, undifferentiated thyroid tumours.)

(C) Tumours for which local control might be improved by adding a proton 'boost' to conventional treatment. (Examples: head and neck tumours, oesophageal cancer.)

(D) Advanced conditions for which conventional photon radiotherapy is ineffective and where treatment may be improved by giving all or part of it with protons. (Examples: pancreatic tumours, gliomas.)

Patients in group A might well travel long distances to be treated at a single proton facility. Those in group B would be accrued from a geographical region. Those in groups C and D would come from the population close to the treatment centre. The number of cancer patients presenting per year in Italy within each of these categories was estimated by Bonelli and associates [39] from Italian tumour registries: A (450–650); B(960); C(790); D(200). The total of these estimates is 2400–2630 cases per year.

PROTON ACCELERATOR OPTIONS

The technology for accelerating charged particle beams to high energies has largely been driven by the needs of the high-energy physics community. The energies involved are often orders of magnitude higher than those required for proton radiotherapy. Consequently, there are no off-the-shelf products. There are considerable differences between the accelerators used in the various proton therapy centres around the world, which, with two notable exceptions (Loma Linda in the U.S.A. and Clatterbridge in the U.K.), have all made use of existing nuclear physics machines. There are three main candidates for consideration: the cyclotron, the synchrotron and the linear accelerator. It is assumed that a maximum energy of around 250 MeV (range in water of 38 cm) is required in order to be able to treat deep-seated tumours in any part of the body.

Cyclotron

A cyclotron consists of a large magnet that produces an intense and uniform magnetic field within an evacuated flat disc-like chamber. The particle beam moves along a spiral trajectory starting from the centre of the chamber. An electric field is alternated between the two halves of the disc (the two 'dees'), and it is the resulting impulse that accelerates the particles. For low energies and, therefore, low particle speeds, a constant frequency alternating field is satisfactory. Particles as heavy as protons increase their mass significantly as they approach therapeutic energies, and this requies increased sophistication. The most straightforward solution is a fixed-energy cyclotron. This is known as isochronous operation. Low-energy cyclotrons are already in widespread medical use for the production of short-lived radioisotopes for use in positron-emission tomography (PET). It is possible to extract the beam at different energies but, again, this adds to the complexity. If the extraction energy is always constant, an alternative is to reduce the energy of the beam to the desired level by the use of beam degrader.

To summarise, the fixed-frequency, fixed-energy, non-superconducting cyclotron is technologically the simplest solution for accelerating protons up to the energies required for the therapy of deep-seated tumours.

Synchrotron

In a synchrotron, the beam circulates along an orbit of fixed diameter within an annular vacuum tube. The magnetic and the accelerating radiofrequency fields are synchronously varied as the speed of the particles increases. The group at Loma Linda in California chose this type of accelerator. The main advantage offered by a synchrotron is its energy variability. It is even possible to change the energy between cycles and so modulate the depth of the Bragg peak without the use of absorbers. The potential disadvantage of a synchrotron is that it is more complex than a cyclotron due to the requirement of rapid field variation, as compared with a fixed-frequency and fixed-field machine. However, there are many successful synchrotrons in existence that are far more complex than the ones required for therapy.

Linear accelerator

Linacs are familiar to radiation therapists and are widely used to accelerate electrons to energies of 20 MeV or higher. As indicated above, there are additional technical problems to be solved with heavier particles such as protons. Two companies recently proposed designs that overcome these difficulties, but so far such a machine has not been built.

Gantry

To be able to aim beams from different directions at a tumour without moving the patient is a standard requirement in conventional radiotherapy, and this will be essential in order to fully exploit the superior depth-dose characteristics of proton beams in a variety of sites in the body. A 'gantry' is a mechanical device for steering the particle beam. Gantries for proton therapy will inevitably be more costly than for electrons as the magnetic fields required to bend the particle trajectories are much larger. The engineering solution adopted at Loma Linda is very elaborate and costly; they have paid the penalty of being first to design such a device. This pioneering effort has cost of the order of 44 million U.S. dollars, including the building. Loma Linda has one gantry in clinical use, and two more have been built and are about to go into clinical use. Much less bulky and expensive designs are now being suggested by various commercial companies, though none has so far been built and tested.

Choice of accelerator type: summary

No one type of accelerator is obviously superior to all the others. The cyclotron is the simplest, cheapest and most reliable option, but it involves sacrificing energy flexibility. The synchrocyclotron provides the most sophisticated solution and the linear accelerator is a feasible option. In each case, a gantry would be essential, but this is technically a separate question from the type of accelerator.

SUMMARY AND CONCLUSIONS

1. 250 MeV protons have almost ideal physical properties for the precision radiotherapy of deep-seated tumours. Proton therapy is being introduced into a number of major radiotherapy centres worldwide.
2. Protons will certainly lead to improved dose distributions, but the impact of this on local tumour control is at the present time hard to judge. Research projects are under way that seek to provide a firm theoretical basis for the introduction of this new treatment and for the appropriate selection of patients.
3. The radiobiological properties of high-energy protons are similar to those of conventional X-rays and electrons. Proton therapy therefore has none of the uncertainties and perhaps detrimental properties of neutron therapy. Experience so far built up in the treatment of ocular melanomas and other tumour types provides assurance that no unexpected forms of tissue damage will arise.
4. Protons may well provide high-precision radiotherapy that will lead to improved treatment of certain tumours in specific anatomical locations. Proton therapy will never be appropriate for the majority of cancers, but could provide an excellent and cost-effective treatment for an important minority.

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Oestrogens, Proteases and Breast Cancer. From Cell Lines to Clinical Applications

H. Rochefort

Human breast cancer is characterised by its high frequency of metastasis and its oestrogen responsiveness, allowing specific anti-oestrogen therapy. Oestrogens are promoting agents that stimulate early steps of mammary carcinogenesis. The availability of several oestrogen receptor (ER)-positive and ER-negative human breast cancer metastatic cell lines has allowed characterisation of several hormone-regulated genes, some of which are involved in growth and metastasis. Moreover, these models have allowed examination of the mechanisms by which hormone antagonists (anti-oestrogens and anti-progestins) act on their respective receptors to inhibit tumour growth. By contrast, no convenient *in vitro* models are available to investigate the mode of action of oestrogens and anti-oestrogens on non-malignant mammary cells. Among the oestrogen-regulated genes, some are also regulated by growth factors, such as the cathepsin D gene, whose overexpression in primary breast cancers has been associated with relapse and metastasis in several retrospective clinical studies. The mechanism and consequences of cathepsin D overexpression on metastasis are reviewed. From these studies on cell lines, new immunological and genetic probes have been raised that can be applied to breast cancer tissue to titrate in patients expression of different genes involved in the control of mammary tumour growth and invasion. These tissue markers should help to stratify primary breast cancers according to their ability to metastasise and respond to therapies and consequently to choose the best therapy. Over the next decade, these studies should lead to new therapeutical approaches of breast cancers which resist classical systemic therapies.

Key words: breast cancer; oestrogens, cathepsin D, metastasis, phagocytosis
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INTRODUCTION

OESTROGENS HAVE been proposed to stimulate the growth of breast cancer since studies by Beatson [1] and Lacassagne [2]. The mechanism underlying this effect has been investigated by studying oestrogen receptor-positive (ER+) breast cancer cell lines [3]. The development of these model cell lines has provided extensive information, some unexpected, concerning mechanisms and clinical applications. Decisive steps in this area have been to define oestrogen-induced genes and proteins, to develop specific antibodies and cDNA probes, and to use these probes on tumour biopsy specimens for defining prognosis.

Present and future studies should reveal the mode of action of these markers in controlling decisive steps in tumour promotion and in defining the mechanism for their altered expression in breast cancer.

In this article, I will consider: