Providing **support**
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Proton therapy:
A policy for scientific research

Executive Summary

- Brain Tumour UK recognises that proton therapy has the potential to treat a small proportion of brain tumours more effectively and with fewer long-term side effects than conventional radiotherapy with photons.
- However, there is little high quality scientific evidence that proton therapy offers clinical advantages over photon therapy.
- Brain Tumour UK believes the lack of high quality evidence could reduce opportunities for patients in the UK to benefit from proton therapy, if its advantages are real.
- Brain Tumour UK is committed to evidence-based medicine and believes that randomised, controlled trials (RCTs) should be undertaken to quantify the efficacy of proton therapy.
- Brain Tumour UK believes that the UK Government should support the implementation of a European Hadron Therapy Register that will undertake high quality scientific research.
- A specific proportion of the healthcare research budget should be ring-fenced for proton therapy and managed by an indepedent organisation such as the Medical Research Council.
- Brain Tumour UK believes that the Register should be created in 2010 and begin research immediately, so that preliminary evidence on proton therapy is available when the UK's first proton therapy centre becomes available around 2013, in order to guide further research.
- Research should be a mandatory part of the contract for the UK's own proton therapy unit.

What is proton therapy?

Proton therapy is a type of hadron (or particle) radiotherapy. It uses beams of proton particles to treat cancer. Conventional radiotherapy x-rays use photons.

The proton beam is created in either a cyclotron or a synchrotron particle accelerator. These machines energise the protons and fire them at the tumour. The energy in the protons damages the vital DNA of cancer cells and has the potential to destroy the cancer. But radiotherapy can damage healthy cells, too. Scientists hope that the physical properties of protons mean that this damage can be minimised.

In theory, the distinctive charge and mass of protons means that their harmful energy should not spread so far after hitting the tumour. The advantages include:

- a tumour could be given a larger and more lethal dose of radiation than is possible with conventional radiotherapy;
- or the tumour could receive the same dose of radiation as with conventional radiotherapy, but with fewer harmful side effects. This might allow a patient to tolerate greater doses of chemotherapy.

Proton therapy may therefore be better than conventional photon radiotherapy for treating certain types of brain tumour, because the "dose distribution" of the radiation is more closely confined to the tumour. This may benefit children in particular, by reducing their exposure to the long-term harmful effects of radiation [Figure 1].

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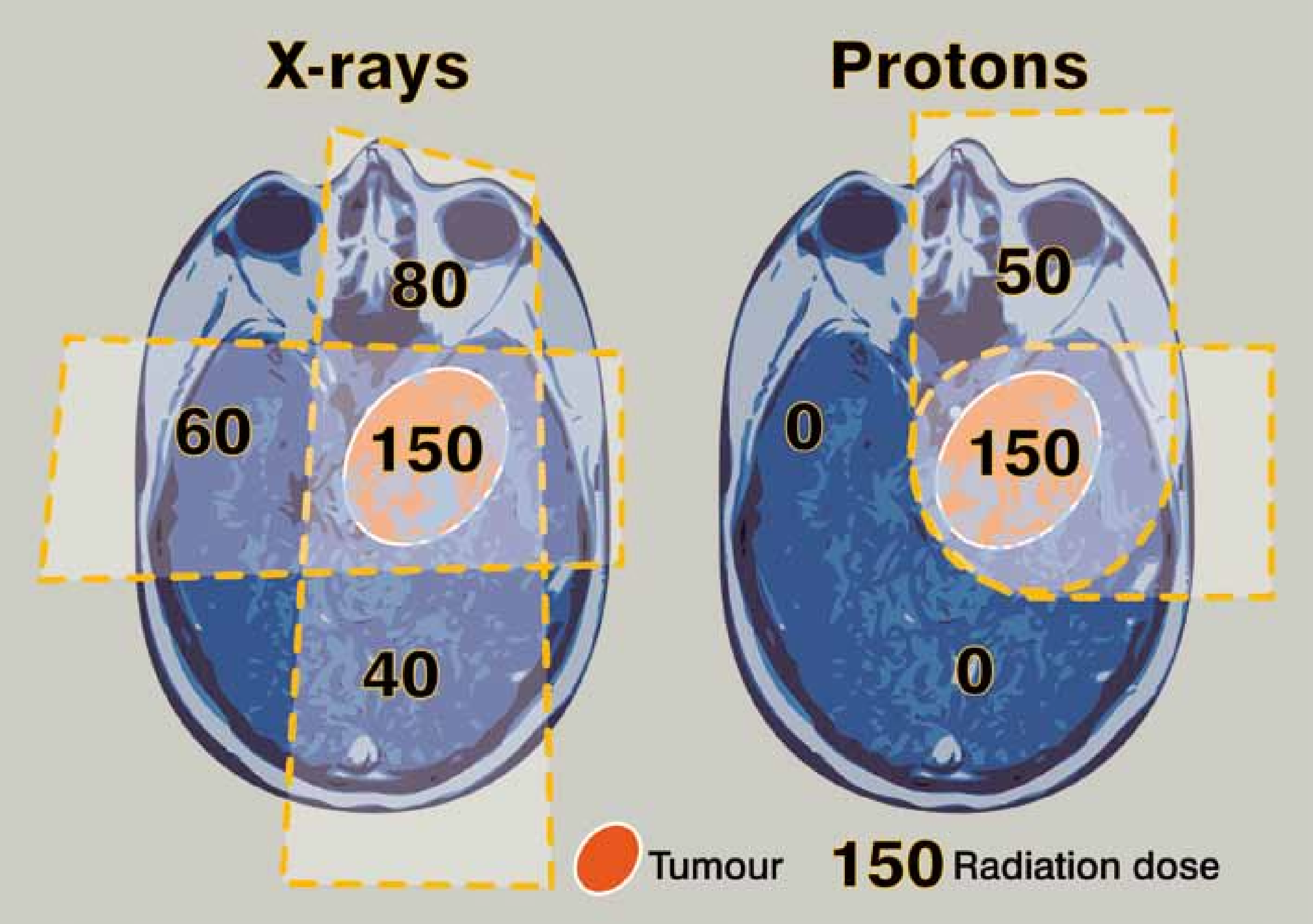

Figure 1: This illustration shows how, in theory, radiation spreads more widely in the brain when X-rays are used compared to proton therapy. Proton therapy may therefore be better for treating certain types of brain tumour and tumours in children in particular, because the "dose distribution" is more closely confined to the tumour. However, some experts question whether this dose distribution can be achieved in practice and point out that other potentially harmful particles, such as neutrons, could still cause long-term side effects.

The need for high quality research

On 18 August 2009, the Department for Health announced that hospitals in England were being invited to bid to provide the UK's first proton therapy centre. The accompanying press release stated:

> "For patients, especially children, with highly specific types of cancer that occur in the retina, base of the skull and near the spine, proton beam therapy can be better than conventional radiotherapy as it precisely targets the tumour, giving better dose distribution and not harming vital organs.[1]"

However, recent correspondence in the *Journal of Clinical Oncology* and elsewhere suggests that there is virtually no high quality evidence that proton therapy is better than conventional radiotherapy. Although the supporters of proton therapy have high hopes for its clinical benefits [Box 1], the lack of high quality evidence for these benefits is already showing signs of limiting Government commitment to proton therapy expenditure. The Government's strategy group for proton therapy called for two facilities to be built in the UK, but only one has been offered by the Government[11].

It is difficult to organise high quality clinical trials, particularly when the number of patients available for such studies is quite small. There are many opportunities for bias to creep into clinical trials. But such trials can be delivered through careful, international collaboration and they are vital. In April 2006, Professor Alistair Munro, a deputy editor of the *British Journal of Radiology*, warned:

> "If particle therapy does have a role in cancer management, then that role needs to be carefully defined, on the basis of evidence, not opinion."[2]

Box 1: The potential for proton therapy

The advocates of proton therapy have identified those patients who are most likely to benefit from proton therapy. Some experts dispute the claims of benefit for these tumour types and argue the claims are not supported by high quality evidence.

Delegates from an Anglo-French conference in 2008 agreed that the strongest evidence suggests that proton therapy is best suited to:

1. Tumours that are relatively radiation resistant and are next to healthy tissue which limits the radiation dose that can be used. They said: "These include chordoma and chondrosarcoma brain tumours of the skull base."
2. Tumours in children, particularly where the tumour is large. Proton therapy may offer advantages over conventional radiotherapy by reducing the risk of children developing secondary cancer later in life and by reducing the effect that radiotherapy has on the child's growth and glands which regulate the body (the endocrine glands). They said: "There is clear evidence that the use of proton beams can reduce unnecessary dose in many non-target structures. The most dramatic example of this is in medulloblastoma."

The authors added: "It is possible to make an argument for proton therapy for many other cancers but, although the physics evidence base is highly suggestive of benefit, the published medical evidence is limited."[14]

In 2009, a Proton Therapy Advisory Group for the Department of Health, chaired by Dr Adrian Crellin, identified the following range of cases suited to proton therapy and the potential number of children and adults in the UK who could be treated:

Paediatric (childhood) conditions	No. of cases per annum
Chordoma/Chondrosarcoma	15
Rhabdomyosarcoma	
Orbit	5
Parameningeal & Head & Neck	15
Pelvis	10
Osteosarcoma	3
Ewings	9
PNET (Extra-osseous Ewing's)	5
Ependymoma	25
Low Grade Glioma	5
Optic Pathway Glioma	12
Craniopharyngioma	15
Medulloblastoma (PNET)	70
Hodgkins	5
Retinoblastoma	5
Meningioma	3
Intracranial Germinoma	10
Nasopharynx (Head & Neck)	15
Difficult Cases (Esthesion-euroblastoma/Neuroblastoma/Liver)	5
Very Young Age (Extra Cases)	20
Paediatric Total	**252**

Adult conditions	No. of cases per annum
Choroidal melanoma	100
Ocular / Orbital	25
Chordoma – base of skull	60
Chondrosarcoma – base of skull	30
Para-spinal / Spinal Sarcoma – including chordoma	180
Meningioma	100
Acoustic Neuroma	100
Craniospinal NOS (Pineal)	10
Head & Neck & Paranasal Sinuses	300
Primitive Neuro Ectodermal Tumour (PNET) (medullo/intracranial)	30
Difficult Cases	300
Adult Total	**1235**

Source: A Framework for the Development of Proton Beam Therapy Services in England[11]

He observed:

> "The peer-reviewed literature contains little evidence upon which we might base decisions concerning the efficacy and cost-effectiveness of particle therapy. … Good evidence for cost-effectiveness is non-existent: such studies as have been performed have been methodologically unsound and poorly reported. The onus is now firmly on the advocates of particle therapy to expose their results to peer review rather than simply presenting them to meetings of like-minded people."[2]

In September 2006, the National Radiology Advisory Group (NRAG) published a review of the evidence for proton therapy[3]. Many scientific studies were summarised. However, the review did not assess the *quality* of the studies. This was an unfortunate omission, because more detailed reviews have now questioned the quality of the scientific evidence base for proton therapy.

Professor Michael Brada and colleagues reviewed the available evidence for proton therapy for brain tumours in 2007 and commented:

> "The investment in clinical facilities offering proton therapy should not simply follow enthusiasm and belief in the new technology but should be firmly based on objective outcome data demonstrating the real additional value of protons over photons using the criteria of evidence-based medicine."[4]

Their analysis concluded, starkly, that: "The claim by proton therapy supporters that protons are the treatment of choice for chordoma and chondrosarcoma is no longer tenable based on the currently available evidence."[4]

Also in 2007, a team from the Cochrane Library's Cancer Network undertook a systematic literature review of the clinical and cost-effectiveness of hadron therapy (HT) including proton therapy[5]. During this thorough review, from a highly respected body with a deep commitment to evidence-based medicine, more than 770 papers were examined. But the review found that the number of randomised, controlled scientific trials "was too small to draw firm conclusions" about proton therapy. Although the researchers found that "proton irradiation emerges as the treatment of choice for some ocular [eye] and skull base tumours", they concluded:

> "Existing data do not suggest that the rapid expansion of hadron therapy as a major treatment modality would be appropriate. Further research into the clinical and cost effectiveness of hadron therapy is needed."[5]

"Further research into the clinical and cost effectiveness of hadron therapy is needed."
Cochrane Cancer Network

There are hardly any randomised, controlled clinical trials which have robustly tested the theoretical advantages of proton therapy. In randomised, controlled trials (RCTs), two groups of randomly-selected patients are treated with the traditional therapy or the new therapy. The results from the two groups are compared, and also checked by other scientists in a process called peer-review. This is the best way of assessing whether a new treatment really is better than the old treatment.

In 2006, Munro illustrated the dangers of failing to undertake RCTs:

> "We were, after all, enthusiastic early adopters of neutron therapy and spent the best part of 25 years finding out that, in the long run, we might have been better off putting our efforts elsewhere."[2]

It took "meticulous clinical studies" by Professor William Duncan and his team to find "that fast neutron therapy offered no significant advantage over conventional therapy with photons".

Unfortunately, the advocates of proton therapy argue that RCTs directly comparing protons with photons are not possible. They point out that because they know the dose distribution of protons is certain to be better than that of conventional photon radiotherapy, it would be ethically unjust to compare the two kinds of treatment on patients. In 2008, Professors Michael Goitein and James Cox argued:

> "It is therefore hard to imagine how any objective person could avoid the conclusion that there is, at the very least, a high probability that protons can provide superior therapy to that possible with x-rays in almost all circumstances. It is primarily for this reason that the practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays.[6]"

Professor Herman Suit and colleagues similarly concluded: "there is no medical rationale for clinical trials of protons as they deliver lower biologically effective doses to non-target tissue than do photons for a specified dose and dose distribution to the target"[7].

But Professor Eli Glatstein and colleagues from the University of Pennsylvania School of Medicine disagreed. They pointed out:

> "Given the fact that the analysis by Brada *et al* does not show clear evidence of a clinical superiority for protons, then it is difficult, in our opinion, to see why it would be "unethical" to perform such randomized trials. ... Despite the contention by Goitein and Cox that protons are superior to photons, it is fair to say that there remains enough uncertainty in the medical community that randomized clinical trials can be justified. In fact, such trials are on strong ethical ground based on the principle of clinical equipoise, a situation that exists when there is collective professional uncertainty about treatment.[8]"

Dr Brett Lewis points out that high quality evidence is particularly important when health service budgets are under pressure:

> "We must have the courage to generate high quality, disinterested, and unbiased data. This is especially true in the current era, when changes in practice result in higher reimbursement rates, and when the United States taxpayer is increasingly held hostage to spiralling medical costs. We must broaden our perspective to realize that we are not the only ones whom we must convince with evidence. As long as they entrust us with their lives and with their pocketbooks, the public has a right to hold us to our own highest standards. Only in this way do we hope to retain the trust and respect of the patient, the public, and each other.[9]"

Proton therapy costs around twice as much as conventional image-guided and intensity-modulated radiotherapy solutions[10]. The advocates of proton therapy argue that the higher costs of constructing and running proton therapy centres are outweighed by the benefits. It is claimed that there is "a net benefit of around £40,000 per child" from using protons over conventional x-rays. Regrettably, the assumptions made and evidence used in reaching this figure have not been published. No comparative figures are available for adults and obtaining them would apparently require "a combination of clinical assumptions and modelling techniques", rather than actual evidence[11].

In a letter to the *Journal of Clinical Oncology,* Drs Fergus Macbeth and Michael Williams commented:

> "As leading providers of proton therapy in the US, [Goitein and Cox] are not objective and their vested interests (intellectual, professional, and reputational, rather than financial) are not fully declared.[12]"

Macbeth and Williams went on to argue:

> "There is no reliable, objective evidence that proton therapy improves clinical outcomes, either survival or quality of life. Recent reviews identify 40,000 patients who have been treated worldwide. Four randomized controlled trials have been performed, but all are proton-proton comparisons of different dose levels in the treatment of ocular melanoma, prostate cancer, and base-of-skull tumors. They shed no light on whether protons are better than photons. There have been five comparative studies and 44 case series. The only tumors for which there is any evidence for the superiority of protons on the basis of clinical results is in the treatment of base of skull chordomas and ocular tumors. ... Widespread introduction of proton therapy for an ever increasing range of indications would be folly without better evidence of effectiveness.[12]"

Recently, Professor Goitein has attempted to pour oil on these troubled waters. Although he maintains that "many otherwise desirable trials are not feasible on ethical grounds", he has proposed that a number of trials should be undertaken including: retrospective non-randomized clinical trials; prospective non-randomized clinical trials; and prospective-randomized clinical trials[13].

It remains to be seen whether these proposals will meet all the expectations of fellow clinical researchers by offering sufficient RCTs to compare proton therapy directly with conventional x-rays.

Advancing evidence-based medicine

The fact that many experts challenge the evidence for proton therapy does not mean that it is not beneficial. Brada and colleagues stressed that the lack of evidence "does not mean that protons may not be useful in selected tumors. It should be a stimulus for more research, particularly in the form of appropriately designed and powered prospective studies".[4]

Glatstein and colleagues argue that:

> "In our opinion, some of the largest gains for protons are likely to be found in conjunction with other modalities, such as surgery and chemotherapy. ... We believe this trend toward multimodality treatment ultimately yielding improvements in survival will continue, and we think that proton treatments will facilitate that to a major degree. ... The only conclusive way to demonstrate this, however, is with carefully constructed randomized prospective clinical trials.[8]"

Brain Tumour UK is concerned that the lack of high quality evidence could reduce opportunities for patients in the UK to benefit from proton therapy, if its advantages are real.

Current proton therapy systems are enormous, very expensive structures, but small units designed to fit into a standard radiotherapy room are being developed by companies such as Still River Systems. Without evidence to demonstrate clinical advantage and to justify new expenditure, health services may be reluctant to replace conventional technology with these new proton devices when they become available.

Brain Tumour UK agrees that RCTs must be implemented to properly quantify the clinical efficacy of proton therapy. The UK has an excellent healthcare infrastructure that would allow some trials to take place. But a proton facility will not be completed in the UK for at least five years. And we doubt that there are enough patients in the UK alone to allow sufficiently rapid results to be obtained from RCTs.

We therefore support a proposal from the Cochrane Cancer Network for a Register to allow scientific research to be expedited:

> "We may be able to make better use of the data that is already being generated by existing centres. Establishing a European Hadron Therapy Register (EHTR) to hold anonymised data on patients treated by European centres providing hadron therapy would provide a simple but effective solution to the current lack of coherent published data.[5]"

The Cochrane Cancer Network highlights the potential benefits of such a Register [Box 2] and this has been welcomed by clinicians including Macbeth and Williams:

> "If [proton therapy advocates] are adamant in their refusal to allow randomized controlled trials, they should at least encourage and take part in other large-scale comparative studies. A hadron therapy registry would form the basis for careful case-control studies, and provide some information despite the problems of establishing randomized trials. Or are they anxious that the emperor may in fact be naked?[12]"

Box 2: A European Hadron Therapy Register

The Cochrane Cancer Network argues that a European Hadron Therapy Register could be used to:

- define the extent to which patients who have been treated with hadrons are representative of the totality of patients with particular types of tumour;
- identify the research questions that need to be asked by providing a reliable and current repository of knowledge concerning the clinical efficacy of hadron therapy;
- provide a useful infrastructure, and a compendium of experience, upon which to build future studies and clinical trials;
- examine the number and geographical distribution of potential patients and relate this to the location and capacity of those centres that are either functioning or planned;
- permit prospective collection of uniformly defined data on both costs and effectiveness of hadron therapy;
- inform future studies and help ensure that valuable time and resource is not wasted in setting up and attempting to prosecute randomised studies that, because of poor accrual of patients, turn out to be non-viable.

Hadron therapy research will require a considerable degree of international and interdisciplinary collaboration to produce viable trials that deliver on time. The collaborative involvement of hadron therapy centres in an EHTR project might make it simpler to obtain and compare accurate information on the real costs (both capital and revenue) of the treatment. Investment in linking clinical trial and case series data prospectively and/or retrospectively to economic data is recommended in order to allow a realistic assessment of the potential of hadron therapies.

We appreciate that, given commercial pressures and sensitivities, this will not always be possible for the privately funded initiatives. For all publicly funded programmes the recording, sharing and public dissemination of such information should be part of standard operating procedures.

The use of existing comparative and non-comparative clinical data could be enhanced by stratification (such as division by tumour and stage) and by comparison with standard treatment of matched patients treated with traditional radiotherapy or different forms of hadron therapy.

Funding high quality research

Brain Tumour UK believes that the UK should take the lead now on establishing and co-ordinating such a Register, with major funding from the Government. We believe that the Register should be operated by a body that is strictly independent of the current advocates of proton therapy, such as the Medical Research Council (MRC), to ensure that all research is free of unintended bias.

The current framework for proton therapy provision in the UK "includes capacity of 5% for research into new applications of the treatment. It is also anticipated that high quality prospective studies will also be undertaken on the impact on clinical management of all patients undergoing PBT treatment[11]".

Whilst Brain Tumour UK welcomes the commitment to research in this framework, we believe that a clearly defined proportion of the UK's health research budget should be ring-fenced for proton therapy research and managed by an independent arbiter, such as the MRC.

Brain Tumour UK believes that the Register should be established in 2010 and begin research immediately, so that when the UK's first proton therapy centre becomes available around 2013, preliminary evidence on proton therapy is available to guide further research.

Proton therapy in the UK

Brain Tumour UK welcomes the Government's commitment to build a proton facility in the UK. But it is not clear where the funding for this unit will come from.

Currently, the NHS favours public-private investment for large infrastructure projects. But when a technology is both novel and, to a large extent, unproven, there is a danger that the commercial imperative to secure a return on investment will obscure opportunities for high quality scientific research and leave those patients most likely to benefit from the unit at the back of the queue.

Brain Tumour UK therefore believes that the Government contract for the new facility must make the delivery of high quality research a mandatory priority, with control of the research programme held by the MRC or similar independent body.

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