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Proton beam therapy: more than a leap of faith?

Proton beam therapy continues to hotly divide medical opinion. As the UK steps up its investment as part of reforms to cancer treatment, **Jonathan Gornall** talks to experts around the world about the strengths and limitations of this controversial therapy

Jonathan Gornall *freelance journalist*

London, UK

On Sunday 17 June a group of almost 20 children and their parents gathered at London Zoo. To the casual observer it could have been a birthday party, but it was a special day for every one of these children, who ranged in age from 18 months to 5 years.

This was a reunion of some of the 160 NHS cancer patients who have been sent overseas since 2008 for proton beam therapy. The treatment has divided medical opinion in the UK since the announcement in April that the Department of Health was to spend £250m (€318m; $394m) building two treatment centres in England, at the Christie Hospital in Manchester and University College Hospital in London.[1]

All the children at the zoo had been treated at the ProCure Proton Therapy Center in Oklahoma City, one of three centres (two in the United States and one in Switzerland) to which the NHS sends patients. In the past year, ProCure has treated 30 patients referred by the NHS.

Among them was Thomas Adams who, in January last year, at the age of 18 months, was found to have an anaplastic ependymoma, a rare and aggressive brain tumour. He had surgery at Alder Hey, followed by chemotherapy, but a scan three months later showed the tumour had returned. This time his parents were presented with another option: more surgery, followed by proton beam therapy.

Both Thomas's parents are hospital doctors in Liverpool—he's a registrar in obstetrics and gynaecology, she's in genitourinary medicine—but before Thomas became ill they, like most people, knew little about proton therapy.

It was, the parents wrote on their blog before the treatment, "supposed to be less dangerous in the young brain as the particles . . . do not spread beyond where they are targeted, and as such have less potential to cause developmental problems for children. However, there is not a lot of long term follow-up data and as such we feel that we are taking a leap of faith in science."[2]

In May 2011 they flew to Oklahoma for two months of treatment. A year on, Thomas remains well and is developing normally. "The debate," says his father now, "is a bit different when you are on the other side."

Critics say the NHS should not be spending so much money on a treatment that has not been subjected to randomised controlled trials and for which there is little evidence of long term efficacy or safety. In April, an article in the *BMJ* questioned whether the government's £250m investment was premature.[3] "For most indications," reported a review of the evidence in February, no firm conclusions could be drawn about the superiority of protons over photons and it was "sobering to observe that no phase III trials have been performed."[4 5]

Advocates, on the other hand, insist the physics speaks for itself.[6] They say proton beams can be focused on a tumour and deposit no exit dose beyond the target area, thus minimising damage to surrounding healthy tissue. A report by a working party of the National Radiotherapy Advisory Group in 2006 concluded that proton therapy was "a safer and more effective treatment than the best available x-ray therapy," especially for some cancers in children and tumours in adults close to critical structures.[7]

The debate has been clouded in the UK by a focus on the widespread use of proton therapy in America for the treatment of prostate cancer.[3] This is a red herring, says Adrian Crellin, a consultant clinical oncologist at St James's University Hospital, Leeds and the Department of Health's national lead for proton beam therapy: "We have quite specifically excluded prostate cancer as a standard indication for treatment because there's no evidence."

In fact, the application of proton therapy in the UK is limited to just 15 rare cancers— three adult and 12 paediatric—that have the clearest evidence, including base of skull chordomas and chondrosarcomas and primary paraspinal tumours. Referrals to overseas treatment centres, which will continue until the NHS units are up and running in 2017, are subject to approval by a national clinical panel that takes account of a range of other

jgornall@mac.com

factors, including the timing of radiotherapy in relation to other treatment and the stage and pathology of the cancer.[8]

Development of the technology

Proton therapy is not a new concept. "Nobody could say of UK plc that we have jumped on a bandwagon that has just left the station," says Ed Smith, a consultant clinical oncologist at the Christie. "We are coming to this many years down the line."

The use of protons in therapy was first proposed in 1946 by Robert Wilson, an American physicist who had worked on the atomic bomb and who postulated that the nature of the proton's Bragg curve—which shows a sudden increase in ionisation density as the particle slows down, followed by a rapid drop in the dose—could be exploited to avoid damage to tissue surrounding tumours.[9]

Over the next few decades experiments, and some treatments, were carried out in laboratories around the world, but it was just over 20 years ago, by which time computing and imaging technologies had developed sufficiently, that the world's first hospital based proton therapy unit opened for business.

Loma Linda University Medical Center in southern California is generally credited with this breakthrough, in 1990, but in fact the UK got there first.

In 1984 the Medical Research Council set up a cyclotron, a type of particle accelerator, at the Clatterbridge Centre for Oncology on the Wirral, to run a series of trials comparing the treatment of tumours with conventional x rays and neutrons. As it became clear that treatment with neutrons was no better and even worse than conventional x ray therapy,[10 11] the cyclotron was switched to producing protons for the treatment of ocular melanomas. The first two patients were treated in June 1989 and, although the cyclotron lacks the necessary energy to treat deeper seated cancers, Clatterbridge has been operating ever since as a national referral centre for rare ocular tumours, treating up to 130 patients a year.

Expansion

Since 1990 the number of proton therapy centres overseas has escalated, with 10 in the US alone by June 2011 and more planned. In the UK the wider application of protons was proposed in 2006, when the then Labour government asked the National Radiotherapy Advisory Group, whose 26 members include oncologists, physicists, and radiotherapists, to plan for a "world class service in the longer term."

At the time, says Crellin, a member of the advisory group, up to 20 NHS patients a year were already being sent abroad for proton treatment on an ad hoc basis. "The costs were extraordinarily high, because they were all one-offs, [and] some of the justifications were based more on pressure from families than evidence."

In its report, delivered in February 2007, the National Radiotherapy Advisory Group said it considered that the worldwide literature was "now sufficient to justify the use of proton treatment for a number of indications" and estimated there was an "immediate need" for about 400 patients a year, mainly children, "in whom important improvements in treatment and reduced long term side effects can be achieved." It recommended that at least one treatment centre should be set up in England and that in the meantime a clinical panel should be formed to screen applications for patients being sent abroad.[12]

Both of these recommendations were enshrined in the government's Cancer Reform Strategy in 2007.[13] In April the following year the NHS National Specialised Commissioning Group set up the clinical reference panel, chaired by Crellin, which sent abroad its first 11 patients in 2008-9, and in August 2009 hospitals were invited to bid to provide proton beam therapy services.[14] In April this year it was confirmed that the NHS would build two centres, at a cost of £250m.

Economic benefits

Since the first 11 patients were sent overseas by the panel in 2008-9, the numbers have increased steadily: 20 were treated in 2009-10, 50, in 2010-11 and 79 in 2011-12. Of the 160 patients treated overseas so far, 107 have been children and 53 adults. Over the next few years, however, as more facilities become available, far more patients will be treated abroad—by 2014-15 the NHS expects to be sending up to 400 patients a year for treatment, at an annual cost of £30m.[1]

Set against these costs, and with the two UK centres expected to treat a total of about 1500 patients a year, it is clear that the £250m investment could quickly represent a saving for the NHS. However, says Smith, the true economic benefit to the NHS could lie in the long term savings associated with not having to treat patients for secondary cancers.

"If my primary concern was with the grand economic scale of things, then yes I would say we are certainly not going to be seeing benefits of this in the next five or 10 years. But this is a far sighted programme . . . the holy grail [of radiotherapy] is to treat just the tumour, and not the normal tissue, and proton beam therapy is a very important step towards that."

Safety questions

Yet the NHS embrace of proton therapy is in contrast to the caution expressed by the US Agency for Healthcare Research and Quality. In September 2009—one month after the Department of Health gave the go ahead to develop proton centres in England—the agency concluded that while proton therapy might be "considered by some clinicians to be better than traditional radiation" for treating several types of cancer, there was "limited evidence about its safety compared with other types of radiation therapy."[15]

The agency singled out for criticism a key paper from two senior members of the pro-proton camp that had appeared in the *Journal of Clinical Oncology* in 2008. The authors, from the University of Texas MD Anderson Cancer Center and Harvard's Department of Radiation Oncology, had argued that as "virtually no dose is administered distal to the target volume and substantially less dose is administered than x-rays proximal to the target volume . . . 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."[16]

This line of reasoning, said the agency, was "unsubstantiated, because it indiscriminately equates increased precision in delivering the planned radiation treatment with positive patient relevant outcomes . . . even the theorised reductions in the rate and severity of harms with particle beam therapy rather than conventional therapies have not yet been convincingly demonstrated in well-designed comparative studies."

Three years on, the agency's view is unchanged. Though acknowledging that there are "commonly accepted indications, such as tumors of the eye, skull base, and spinal cord," it remains concerned that "No randomized controlled trials and only a few well-conducted cohort studies have compared proton beam radiation to other treatments."[17]

It is, says Crellin, important to see such concerns "within the context of what has happened in the United States, which is that people have rushed headlong into treating prostate cancer [with protons], for which there is remarkably little evidence. I'm not surprised there is a very cynical view about it, but if you read most of the literature about the sorts of things that are on our prioritised list, there's not really much argument about those things."

It is still too early to draw conclusions from the proton treatment of the first 160 NHS patients sent overseas, though Crellin expects to be able to produce an initial survival curve analysis later this year. There is, he says, "no evidence of anything disastrous going on [but] we've been quite tight, if you like, on our priorities in selecting patients who are deemed to be curable and who therefore will come into the category of getting advantage from the [absence of] late side effects."

Evidence based treatment?

Although children are expected to account for only a fifth of the cases that will be treated in the UK, 60% of those sent abroad for proton therapy so far have been children. Children have the greatest potential gain, in terms of development and longevity, and it was deemed right to focus on them because treatment slots were limited, says Crellin. They are also particularly vulnerable to x ray damage and, while "there's almost no difference between the IMRT [intensity modulated radiation therapy] distribution and the proton distribution as far as the tumour is concerned, the low dose outside the tumour is where the gain is."[18 19]

However, Cecile Ronckers**,** epidemiologist for the Dutch Childhood Oncology Group, and Geert Janssens, radiation oncologist at Radboud University Nijmegen Medical Center, both in the Netherlands are more sceptical. "Evidence that less normal tissue irradiation or a lower dose results in a clear risk reduction of radiation induced second malignancy is based on retrospective data and still a matter of debate," they said.

Supporters say that some of the best evidence of the potential of proton therapy for preventing secondary malignancies in patients of any age comes from a retrospective study in 2008 of 503 patients treated with proton therapy at the Harvard Cyclotron.[20] Outcomes were compared with those of 1591 matched patients treated with conventional photon radiation and taken from the US National Cancer Institute's Surveillance, Epidemiology and End Results registry. After a median follow-up of 7.7 years in the proton group and 6.1 years in the control group, 6.2% of the proton patients developed a second malignancy, compared with 12.8% of patients treated conventionally.[20]

Ronckers and Janssens agree that the study is important but are doubtful whether it is good evidence. "It is a single study, its results were only reported in meeting abstracts and oral presentations, and it is surrounded by questions about validity."

When Manchester and London are up and running, the treatment list will be expanded to include more adult cases, says Crellin. Nevertheless, it will remain "pretty stingy" by US standards and limited, in the words of the panel's guidance, to "cases where critical normal tissues impose dose constraints or considerations of potential late effects from irradiation of the normal tissues make even optimised photon options such as intensity modulated radiotherapy (IMRT) unacceptable."

This, says Crellin, is "what one can justify now." If it came to treating common tumours with proton beams, then "absolutely there have got to be randomised controlled trials, because the differences may be relatively small." But he says for some of the rare or paediatric cancers the small numbers of cases would make trials "almost impossible . . . We've got indications on our list where there are ten or a dozen [cases] in the world in a year."

When it comes to paediatric cancers, the principle of equipoise becomes especially important. "It would be quite difficult to justify irradiating a large amount of a growing child when you don't have to," he says. There is also evidence that for the rare adult cancers "the dose that is ideal to give is higher than you could possibly achieve with conventional IMRT; we know we can do it safely and the results are very good, so in a sense time has already moved on."

Not everyone is convinced that randomised controlled trials are unnecessary, or that they would be difficult to execute. "It is clearly a more complex picture than just the physical distribution," says Ian Kunkler, consultant in clinical oncology at the Edinburgh Cancer Centre, "and the randomised trial is the only way that you are going to exclude potential sources of bias."

He sees the development of the NHS proton centres as an opportunity for the UK to take a lead in international research, joining forces with other countries to run multicentre trials capable of recruiting sufficient numbers.

"Clearly it's very important that we shouldn't have to send children and their families abroad. But obviously it is an expensive facility to provide, and I am keen to see that the investment is maximised, in terms of not only treating paediatric patients, where I don't think there's any disagreement about the benefits, but also of using the facility for evaluating [protons] for other sites, where the benefit is unproven."

There is, he says, a lesson to be learnt from the neutron trials in the 1970s and '80s, "where there was a conviction among some parties that neutrons had a theoretical benefit and this was shown not to be true in a randomised trial." Neutron treatment had appeared to offer some improvement in local control, says Kunkler, but "the level of late normal tissue damage was much higher than was anticipated. The point is that you need clinical trials as the framework for assessing particle therapy in which the effect on the tumour and the effects on the normal tissue are extremely carefully documented and these patients are followed up for five or ten years to see what the balance is in terms of tumour effect versus normal tissue effects."

Future directions

Stuart Green, director of medical physics at University Hospitals Birmingham, named as the third centre in the event of an expansion of the proton service, believes health economics makes the case for proton therapy.

"All kinds of cancer treatments are improving," he says. "The number of patients surviving long term cancer treatment is going up and . . . that means we have to put all our efforts into treating to the same degree of efficacy against the tumour, but with minimal toxicity, because those patients and the health service are going to have deal with those long term consequences of treatment. And that makes the argument for proton therapy."

While the NHS restricts the type of cancers that can be treated by proton therapy, ProCure, its service provider in the US, does not. Given the high investment costs and the increasing number of centres, operators are required to adapt their thresholds to be successful. Like all US proton therapy providers, ProCure treats prostate cancer and Eugen Hug, ProCure's chief medical director, makes no apologies for that. He is familiar with charges

Neutron therapy: warning on acting too soon

Clinical trials using the UK's first medical cyclotron to compare the effects of fast neutrons with conventional x rays were carried out at Hammersmith Hospital in the 1970s. Researchers reported that "The advantages to the neutron-treated patients were statistically highly significant"; the tumour had regressed completely in 37 out of 52 patients treated with neutrons, compared with only 16 of the 50 treated with photons.[21] A follow-up study, two years later, found that "with one exception, local control in the neutron series has persisted without recurrence."[22]

However, a longer term study at the Department of Clinical Oncology in Edinburgh, where another cyclotron unit had been installed by the Medical Research Council (MRC), found similar tumour control rates, and cause specific survival rates in the two groups, and the researchers concluded that there was "no evidence in this study of a therapeutic advantage for treatment with neutrons."[23]

There was even worse news in store for neutrons. In the wake of the ambiguous Hammersmith and Edinburgh findings, another cyclotron was set up by the MRC in 1984, at the Clatterbridge Centre for Oncology on the Wirral. Two studies comparing the treatment of head and neck and pelvic cancers with neutrons and x rays ended badly. In 1990, four years in, the pelvic trial was stopped because of increased mortality among patients treated with neutrons for cancer of the cervix, bladder, or rectum.[10] When the five year study of 178 patients with advanced head and neck cancer ended in March 1991, it was found that although the initial response rate had been better with neutrons, "permanent local control and survival were not improved, and the incidence of late normal tissue toxicity was increased."[11]

that, to cover their costs, proton centres are treating cancers, especially prostate cancer, despite a lack of evidence that it is effective and the fact that costs are twice those of radiotherapy and three times those of surgery.[24] But, he says, "for a patient who is seeking the least amount of potential risks from prostate cancer treatment, I think that protons are indeed a viable option. The problem that arises there is, does a perceived reduction of maybe a couple of per cent of risk justify the increased cost? Now here we are at a socioeconomic question and not a medical question, because that would always be 'Do the least amount of harm you can do.'

"There is," he adds, "almost universal acceptance of protons as a superior treatment modality for children, because of course with a young child you have to minimise any radiation given. The question then is, well, when does it stop being relevant? We could probably assume it's relevant for a 20 year old, because he has another 50 or 60 years to live; the question is where does society draw the line?"

Hug has been working with protons for 20 years—before joining ProCure in May last year he was director of the Center for Proton Therapy at the Paul Scherrer Institute in Switzerland, served as professor and chair of proton radiotherapy at the University of Zurich, and has also worked with Massachusetts General Hospital and the Harvard Cyclotron Laboratory in Boston.

Protons, he says, are "the next logical evolutionary step" in the development of radiotherapy and he, like many in the field, believes the debate is taking place only because of "the perceived cost of protons, and I think the costs will come down because protons are still a rapidly evolving technology." ProCure, he says, is working towards making protons available at a similar price to photons, "so as to simply take the wind out of the sails of this argument."

Nevertheless, he acknowledges the need for evidence to convince the sceptics: "We need to be able to demonstrate a clinically meaningful benefit for the patient and that's either on tumour control, on cancer cure, or in reduction of short term or long term side effects"—and he believes such evidence will soon be available.

"Right now, we are lagging behind a little bit, but we are in a very important transition period. We already have a quite extensive use of protons in clinical practice, and now we have trials ongoing that will be available in three or four years."

But Ronckers and Janssens maintain there are still a lot of technical limitations to proton therapy—for example, there is no good online imaging system for gating tumours that move during respiration. "A lot of technical gadgets routinely used on the modern photon machines remain to be developed for proton machines. A nice example concerns imaging of the tumor during one fraction or one treatment course. Generation of adaptive treatment planning remains a major challenge for clinical physicists involved in proton therapy. As a result, an unnecessary large volume of healthy tissue is irradiated to a high dose. Taking into account all the technical caveats of proton therapy, a much more limited range of indications than is now represented in medical literature and popular media will really benefit.

ProCure is working with the Proton Collaborative Group on clinical trials and is currently evaluating a randomised study that will compare photons and protons. Of the 1200 patients treated by ProCure since August 2008, 1000 have been recruited into prospective studies.

It is also Crellin's intention that in the UK "all patients who receive proton therapy will be part of some defined protocol which will be evaluated."

We have to justify the investment in proton therapy, he says, but in terms of the "the whole overall cancer treatment budget it's a drop in the ocean. Think about the cancer drugs fund—£200m a year, almost all of which is on non-curative treatments.

"As long as we are rigid about evaluating, and re-evaluating everything within a prospective, auditable study to make sure that we can produce outcomes, then I think it's actually something the NHS should be jolly proud of. There is no other country in the world that has done it in quite this systematic way."

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