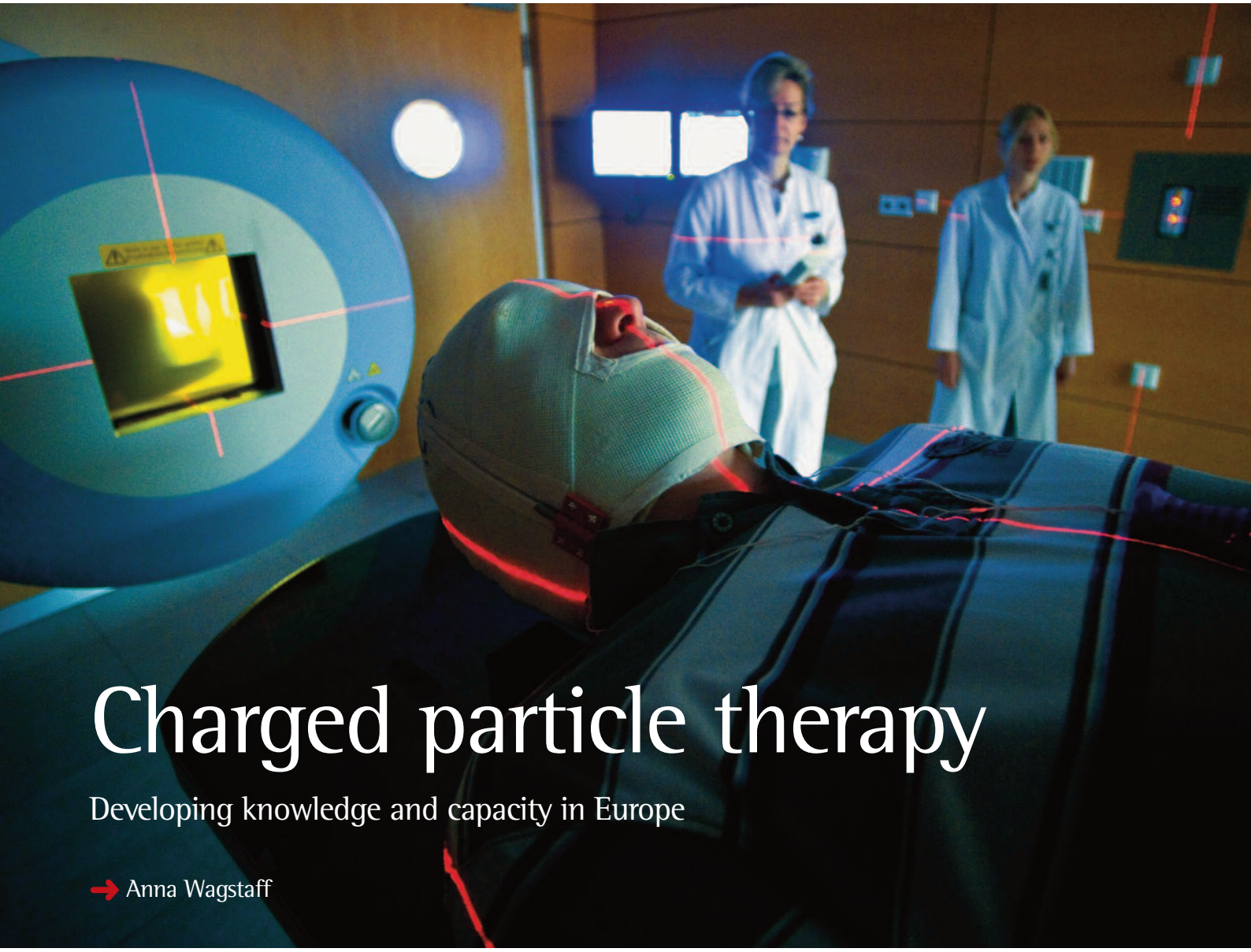


Charged particle therapy

Developing knowledge and capacity in Europe

Anna Wagstaff

Charged particle therapy has been known for 60 years as an alternative radiotherapy, more precise and potentially more safe and/or effective for some patients. But as Europe grapples with the need for equipment and training, there are calls for caution until more robust clinical evidence has been generated about survival and quality-of-life benefits in the longer term.

Ever since radiation was first applied to treating cancer the challenge has been to maximise the damage to cancerous cells while minimising damage to normal tissue – an equation often referred to as the therapeutic ratio. Killing off healthy cells in the pathway of the beam can do irreversible damage to the heart, lungs or brain, affect the ability to eat, talk or swallow, or breach tissue walls leading to fistulas in the bowel or urinary tract. Low-level damage from radiation raises the risk of secondary tumours in the longer term.

One technique with potential for improving the therapeutic ratio in certain cancers has been known since at least 1946. Charged particle therapy replaces the photon (energy) beam of conventional radiation (X-rays, gamma rays or electrons) by a stream of protons or other sub-atomic particles (collectively known as 'hadrons') or by heavier bodies such as carbon ions.

Unlike photons, which deliver most of their energy and biological impact as they enter through the skin, tailing off gradually as they progress through the body, charged particles release relatively little energy as they enter the skin at high speed. Their greatest impact (known as the Bragg peak) is delivered as they come to rest, after which point they have virtually no impact whatsoever (see figure (a)).

In patients a series of Bragg peaks is needed to hit the tumour over its full depth, and this requirement considerably reduces the advantages it has over conventional therapy with respect to tissue damage on the way in (see figure (b)). However, the potential to protect tissue after passing through the tumour is impressive, and is the main reason why charged particle therapy has so far concentrated on ocular melanoma and tumours at the base of the skull, where avoiding damage behind the tumour is particularly important.

The passage of charged particles seems to create much less disturbance to neighbouring tissue than photons, thereby reducing the low-dose toxicity that is known to increase the risk of secondary tumours. Much of the current interest in this type of therapy centres on its potential to improve outcomes in paediatric patients, for whom late secondary tumours are of particular relevance because they have their whole lives ahead of them.

Interest has also been growing in exploring the distinct radiobiological properties of charged particles, which could help identify the sorts of tumours that might be most appropriate for this type of treatment. The biological impact of charged particles in terms of DNA damage is known to be generally higher for charged particles than photons. Calculated in terms of their relative biological effect (RBE) compared to photons, carbon ions have an RBE of 3–4, while that of protons is around 1.1. This raises the possibility that tumours that respond poorly to conventional radiation may respond better to the heavier biological onslaught of carbon ion therapy. This would be of particular benefit in certain cancers of the salivary gland, sarcomas, bone cancers and pancreatic cancers, among others.

Animal and *in vitro* studies have raised hopes that heavy ion therapy might also suppress angiogenesis and metastasis, which are known to be stimulated by X-rays, although this has yet to be demonstrated in patients.

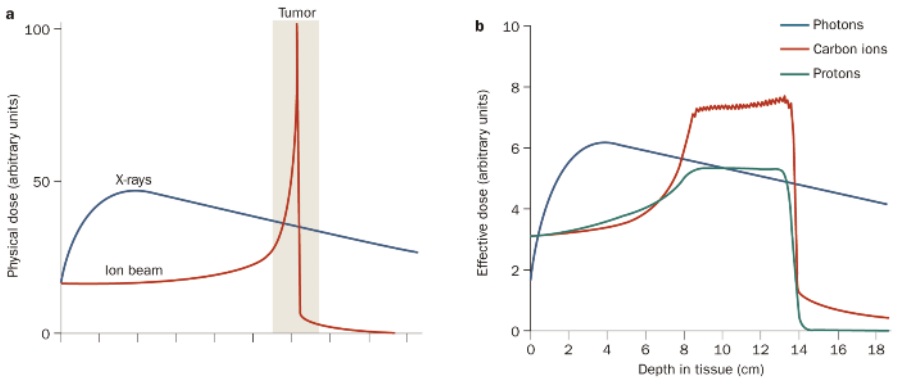
A SLOW START

With all this potential, it might seem strange that charged particle therapy has not developed faster since Robert Wilson published his pioneering paper on The Radiological Use of Fast Protons in the journal *Radiology* back in 1946, or indeed since the first experimental treatments of cancer patients, which were performed in physics research facilities in Berkeley, California (1954) and Uppsala, Sweden (1957).

More than 50 years on, according to the Particle Therapy Cooperative Group, there are still only 20 charged particle facilities currently treating deep tumours (as opposed to surface tumours like ocular melanoma), and only four of these, two in Germany and two in Japan, are using carbon ions.

One problem, undoubtedly, is the size

COMPARISON OF DOSE-TISSUE DEPTH PROFILES



Particle therapy can hit a target more precisely than conventional radiotherapy

Source: M Durante and JS. Loeffler (2010) Charged particles in radiation oncology. *Nature Clin Rev Oncol* 7:37–43. Reprinted by permission from Macmillan Publishers Ltd, 2010

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and the cost of the kit. Charged particle therapy is not something a keen group of young post-docs can dabble in. This is particle physics – not quite CERN, perhaps, which is built to accelerate particles to close to the speed of light – but the principles are the same.

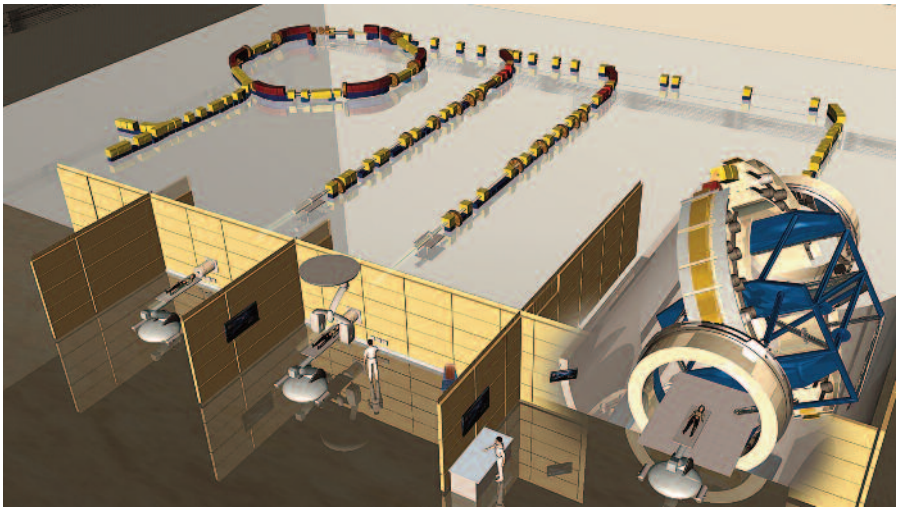
Synchotrons comprise huge circular arrangements of magnets that accelerate the particles, weigh upwards of 100 tonnes and measure around 90 metres in circumference. More advanced facilities also house huge gantries capable of rotating the synchrotron to alter the angle of the beam. Villigen, in Switzerland, and Munich and Heidelberg in Germany, are home to the only European facilities currently using gantries – the buildings that accommodate them have been likened to cathedrals.

The cost of building one of these facilities is estimated at €125 million – rising to €150 million if you want a gantry thrown in. Running costs are also higher, with around twice the level of staff and higher levels of expertise compared with conventional facilities.

In any case, developing the potential of charged particle therapy had to await progress in three-dimensional imaging and computer modelling. Without these, the advantages of the highly concentrated 'Bragg peak' biological impact remained largely theoretical in all but the most shallow tumours, as there was no accurate way to programme the equipment to deliver concentrated damage throughout the tumour tissue, and avoid falling short or, worse, hitting the very organs behind the tumour that charged particle therapy is meant to protect.

Significant improvements in conventional radiotherapy techniques may also have contributed to a lack of urgency in developing charged particle therapy. Conformal techniques, which deliver the full therapeutic radiation dose using multiple low-dose beams that converge on the tumour from many angles, have proved very successful in reducing acute toxicity to healthy tissue, though it is still a little early to draw definitive conclusions about late secondary tumours and survival. The ability to modulate the intensity of the beam according to the density and depth of different parts of the tumour, and the use of powerful software to deliver a finely calibrated treatment plan to a moving tumour (as in the lung) using real-time image guidance, offer further sophistication, while brachytherapy (implanting radioactive pods next to the tumour), is widely used for certain highly localised tumours.

An impressive bit of kit. This schematic representation of the charged particle therapy facilities at Heidelberg University Hospital shows the huge scale of the equipment. The circular arrangement, top left, is the synchotron that accelerates the particles; the large construction at the bottom right of the picture, dwarfing the patient, is the gantry that allows the angle of the beam to be rotated



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As a result, in Europe, the task of making progress with charged particle therapy has been left to a small band of dedicated researchers. Among them is Roberto Orecchia, head of the Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia, Italy, where a new proton therapy facility has recently been completed. The facility is based on a design developed by PIMMS (Proton and Ion Medical Machine Study), a European collaboration involving CERN and charged particle therapy research outfits in Germany, Austria, the Czech Republic and Italy.

That spirit of European scientific collaboration has been a real driving force for Orecchia. In 2002 he helped pull together diverse European efforts in this field through the European Network for LIGht ion Hadron Therapy (ENLIGHT), which links more than 150 clinicians, physicists, biologists and engineers from around 50 European universities and research institutes in 16 countries. "We were a community of scientists who were very interested in developing a new field of research in terms of particle therapy," says Orecchia. "This was not just from a clinical point of view, but to explore the physical and biological characteristics of particles which are very interesting because they can potentially overcome the problem of radioresistance to X-rays. It was also an opportunity to improve the quality of the machine."

Collaboration was strengthened in 2008 with the start of the ULICE programme (Union of Light Ion Centres in Europe). Funded by the EC to the tune of €8 million, it brings together 20 research centres in 11 countries with the aim of

establishing non-competitive European platforms for scientific and clinical research and a coordinated approach to developing the technology, helping countries to set up new facilities and gain experience in this area of therapy. This includes making 691 hours of beam time at the CNAO in Pavia, Italy, and Heidelberg University Hospital in Germany, available to ULICE partner researchers – clinical radiation oncologists as well as biologists and physicists.

Orecchia's own main focus is on developing ways to characterise an individual tumour to exploit the potential of particle therapy to best effect. "Because we have an instrument that is very precise and can be very targeted, the first goal is not only to identify where the target is but also to gather highly detailed information about the tumour biology: cell proliferation, differentiation, quantity of oxygen, a lot of different biological parameters."

These studies should help to identify markers that can guide treatment choice – including which type of radiotherapy to use (conventional, particle, or both), fractionation (how many doses should be administered within what timeframe) and other treatment parameters. "We have to find the molecular basis of a new scheme of fractionation," says Orecchia, who hopes that eventually this could lead to reducing the number of fractions to between one and five sessions, "A big reduction if you consider that when I started in radiotherapy the cycle normally lasted 40 sessions."

Improving the equipment is another area of development. "All the machines in operation now are modelled on equipment designed for physics experiments that has been modified for medical use. One of the ULICE topics is to design a new machine as a concept for medical use." The next generation of magnets he believes could reduce the size of a synchotron by up to 50%. There are also efforts to find alternative methods to accelerate the particles, possibly using a laser beam or dielectric wall accelerator, though these are still at an experimental stage.

With the size of the accelerator reduced, more facilities will be able to afford and accommodate the smaller gantries needed to rotate the beam. Orecchia also hopes that the new generation of particle therapy facilities being developed in Europe will all use active scanning technologies that can modulate the energy of the beam according to the precise shape and characteristics of each part of the tumour.

Robotic patient positioning techniques and image guidance systems for treating moving tumours are also important areas for technological improvement.

Hands-on experience

The clinical and transnational access side of the ULICE programme is coordinated from Heidelberg by Jürgen Debus, head of Radiooncology and Radiation Therapy at the University Hospital who explains, "The idea is that we establish a computer network where everyone can refer potential patients, and a committee decides which patients will be entered into the studies, so we can conduct studies on a pan European level and get a faster recruitment of patients."

Three such studies have already been launched. One compares proton therapy with carbon ion therapy in patients with chordoma. Another is exploring the effectiveness of using carbon ions to treat adenoid cystic carcinoma – a salivary gland cancer that responds poorly to conventional radiotherapy.

A third study is looking at combining conventional and proton therapy for patients with glioblastomas. "Typically 50 Gy, which is a substantial part of the treatment, is delivered in the home institution and delivered to a larger volume, where you suspect there is also microscopic spread," says Debus. "The idea of this study is that these patients are being treated with conventional therapy to large volumes and then there is what we call a 'boost', so if there is macroscopically visible tumour, this area is treated by particle therapy."

Avoiding any break between the photon part of the treatment done at the referring centre and the proton boost will be one of the big challenges for this study. "And in the end the question is: are the results better for this than for treatment with conventional radiotherapy."

The intention, says Debus, is that the patients and their doctors will come to Heidelberg for the 'proton boost'. This supports another aspect of ULICE, which is giving hands-on experience to radiation oncologists from centres that are interested in developing particle therapy, but do not yet have an operational facility. "These people will have the opportunity to get training on the one side and also to bring their patients to the facility, treating them by themselves and then going back home. If they want to start their new facilities, they have already trained personnel and can start right away."

The imperative to invest in highly trained staff to operate this technology is a point strongly emphasised by Debus. "Photons are forgivable with dose

"We have to find the molecular basis of a new scheme of fractionation"

distributions in many situations, they are more robust than for proton dose distributions. So you have to know about the sensitivity of the proton dose distribution and behave accordingly."

The facility at Heidelberg was completed in 2007, but only started treating patients in 2009, concentrating on base of skull tumours, typically tumours which are very close to critical structures such as optic nerve or brain stem. They also treat some patients with 'fixed tumours' of the vertebral column or in the pelvic and sacral area. His facility is now in the process of installing cutting-edge image-guidance equipment that should allow them also to treat patients with certain moving tumours within the next two years.

Looking 10 years ahead, Debus estimates that up to 30% of all radiotherapy treatments in Germany will be done using proton or ion therapy. He hopes that the clinical study platform established by ULICE (the programme comes to an end in 2012) will be able to develop robust, European evidence-based guidelines for which patients need this type of therapy and how to treat them.

Clinical evidence

One person keeping a close eye on this process of building up the clinical evidence for charged particle therapy is Michael Brada, professor of clinical (radiation) oncology at the UK Institute of Cancer Research and a past president (2004–2006) of the European Society for Therapeutic Radiology and Oncology (ESTRO). He caused some ripples with a review article in the *JCO* that he co-authored in 2007, which examined the published clinical evidence for proton therapy and concluded there was none.

A follow-up article by the same authors in *The Cancer Journal* in 2009 presented this stark conclusion: "…despite some tens of thousands of patients treated, the published peer-reviewed literature is devoid of any clinical data demonstrating benefit in terms of survival, tumor control, or toxicity in comparison with best conventional treatment."

The reviews looked at the evidence for chordomas and chondrosarcomas of the skull base, ocular melanomas and prostate cancer – now the main tumour treated by proton therapy in the US. They also looked at 'other tumours' and childhood tumours. The first two really raised eyebrows, because they have become established as heartland 'proton therapy territory' – indeed many facilities treat nothing other than ocular melanomas.

Yet according to Brada et al., the 90% local control rate, 85% cause-specific survival and 90% eye preservation rate are no better than the results achieved by high-precision photon irradiation, at least in small tumours.

Equally, while the results for chondrosarcomas of the skull base may sound impressive at 95% five-year progression-free survival, these tumours, argue the authors, tend to be low-grade indolent tumours often with a long natural history. Results after radical surgery, with or without conventional radiotherapy, show 90%–100% five-year survival, so again no advantage for proton therapy can be shown.

As for chordomas, the 73% five-year disease-free survival figure in a series of 621 patients that gets quoted in various reviews, though undoubtedly impressive, is based on a reporting error of data that were anyway so incomplete they would be unlikely ever to have been accepted by a peer-reviewed journal, says Brada. A closer look at that original study, published in *Strahlentherapie* – not a peer-reviewed journal – reveals that the data show a five-year disease-free survival figure of 64% not 73%, added to which, the number of patients was less than half the quoted number, and more than 40% of these were lost to follow-up.

"It just shows what happens if there is no proper peer review and you don't have any checks in the system, and you have enthusiasts... Everybody believes it and quotes it but actually the results aren't true. Everybody says, 'I want to go and have the treatment at a proton facility.'" Given that proton treatment is expensive, and that the patient may have to bear all costs privately, as well as paying for travel and accommodation, there are huge costs involved in this option, says Brada. "And my take on this is: is the benefit such that you should sell your house to go and have this treatment?"

And so it goes on. In prostate cancer, currently the focus of a marketing campaign by the US National Association for Proton Therapy (quote: "There was no sensation whatsoever, I feel I am healed") – a dose distribution study conducted at Harvard found proton therapy had no advantages over conventional radiation in lowering the risk of acute damage to the rectum, and a slightly elevated risk to the bladder. Low-level toxicity was somewhat reduced, "but is a late second malignancy an issue in prostate cancer?" asks Brada.

This question of clinical relevance, and the need to look at the effect of the treatment in the round, is one Brada keeps returning to. He mentions the example of the spine, where treatment with protons can be focused very precisely at the back

The imperative to invest in highly trained staff to operate this technology is a point strongly emphasised

edge of the vertebral column (see figure).

"What are the side-effects here you want to reduce?" he asks. He acknowledges that the treatment does avoid damage to the heart, "which is good, though I don't think long-term survival is necessarily determined by this." Bowel [colorectal] toxicity is also lower, "But then bowel toxicity is not a very large issue in children." His worry is about what such very precisely targeted therapy might do to the growth of the child in the longer term, and he wonders how much consideration has been given to this aspect of the treatment. "The principle would be that you treat the whole vertebral body so if there is reduced growth it is symmetrical. Now you have a new technique that only treats the back part of the verterbrae. So while you are avoiding some side-effects there are also potential risks. You need to have a very broad view. You mustn't blindly look only at the benefits you also have to measure the risks."

Brada is well aware that he is seen as Mr Negative, raining on the proton therapy parade. In fact he strongly believes that charged particle therapy will prove to be of clinical benefit in specific indications, particularly in avoiding second malignancies in some paediatric cancers and in treating cancers that respond poorly to conventional radiotherapy.

"My bottom line is that it is an interesting new treatment that should be investigated and there are specific situations where it is likely to be of benefit, but you ought to prove that it is of benefit, as you have to do with drugs. There are so many complexities to the treatment that you need to prove that the complexities and problems don't outweigh the technical benefits. I'm an academic and I'm developing new technologies, and the same rigour I require of myself I require of others."

Debus, coordinating the clinical trial platform of the ULICE project, professes a certain sympathy with Brada's argument, but points out that large randomised phase III-type studies are prohibitively expensive: "Who is going to pay?" he asks. "EMEA has big pharma behind it, and they can recoup their initial investment in the costs of the clinical studies by putting that money into the price of a drug. In medical technology you cannot put the price of studies into the price of the device."

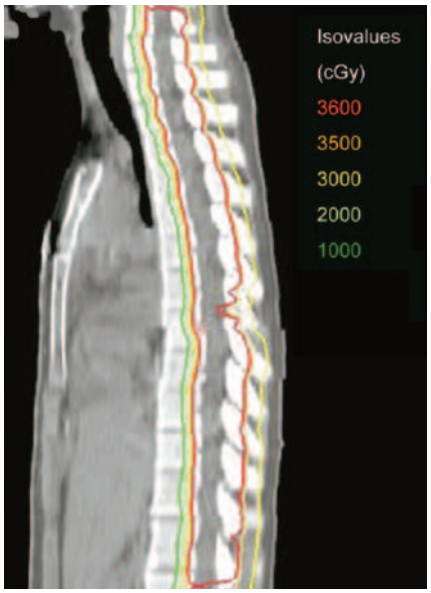
He insists, however, that the approach taken in Heidelberg, and the philosophy behind ULICE, is strongly in support of establishing robust evidence on which to base the selection of patients and tumours that can benefit from proton therapy, even if these studies can never be on the scale required for new medical therapies.

The bigger concern for Brada is what may happen outside the research community. He points towards trends in the US where five new private facilities are set to open next year, no doubt focused on large markets like prostate cancer. Will patients there have their cases discussed by a multidisciplinary team able to weigh up the best options in a disinterested way? Will they be treated by specialists who understand the disease, or simply by experts in proton therapy? Will relevant outcome measures be recorded and analysed? Or will these companies rely on the attraction of their high-tech wizardry to convince patients, and possibly doctors, that their treatment really is superior, without sufficient evidence to back up their claims?

Debus thinks it unlikely that Europe will follow this market-driven route. In Germany a decision was recently taken for proton therapy facilities to be developed at a further three university hospitals. But in the UK, where 20 years ago the proton therapy facility at Clatterbridge had taken a lead in researching this field, Brada is not so sure. Last year the government agreed to invest in a new facility, but put the job out to private contract. "Costs will have to be covered by income from the treatment, which doesn't bode well for research activities," he warns.

The current public spending cuts across Europe will make it harder to win the argument for developing particle therapy capacity within an academic, research-led framework. This makes it particularly important that the sort of inclusive, cooperative Europe-wide network currently organised within ULICE is able to continue after the programme ends in 2012, to shape and influence this area of cancer care led by evidence-based medicine and patient need.

PROTON THERAPY TO THE SPINE



This computed tomography–proton radiotherapy treatment plan shows that the back of the vertebrae will receive doses of up to 3600 cGy, while the bulk of the vertebral bodies are spared. This therapy avoids radiation to the heart and other organs in front of the spinal column, but when used in children there is a risk that, as they grow, the back part of the vertebrae will grow slower than the rest

Reprinted from Krejkarec et al. (2007) Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. *Int J Radiation Oncology Biol Phys* 68:646–649, with permission from Elsevier