

Antiprotons: the magic bullet?

Antiprotons could offer the ultimate in targeted radiotherapy, reports Paula Gould.

Switching from photons to protons for radiotherapy could potentially improve treatment efficacy and reduce the side effects suffered by cancer patients. Protons deposit most of their energy at a precisely-defined depth, so the dose delivered to a target tumour can be raised without damaging nearby healthy tissue.

Initial results from CERN's antiproton cell experiment (ACE), however, have suggested that actually it's antiprotons that are the real "magic bullets" for radiotherapy. Data from CERN have shown antiprotons to be four times more effective than protons at irradiating cells. With just days to go before starting his next round of experiments at CERN last October, Niels Bassler, co-spokesperson of ACE, told Paula Gould about the therapeutic potential of antiprotons.

PG: Why might antiprotons be so effective in radiotherapy?

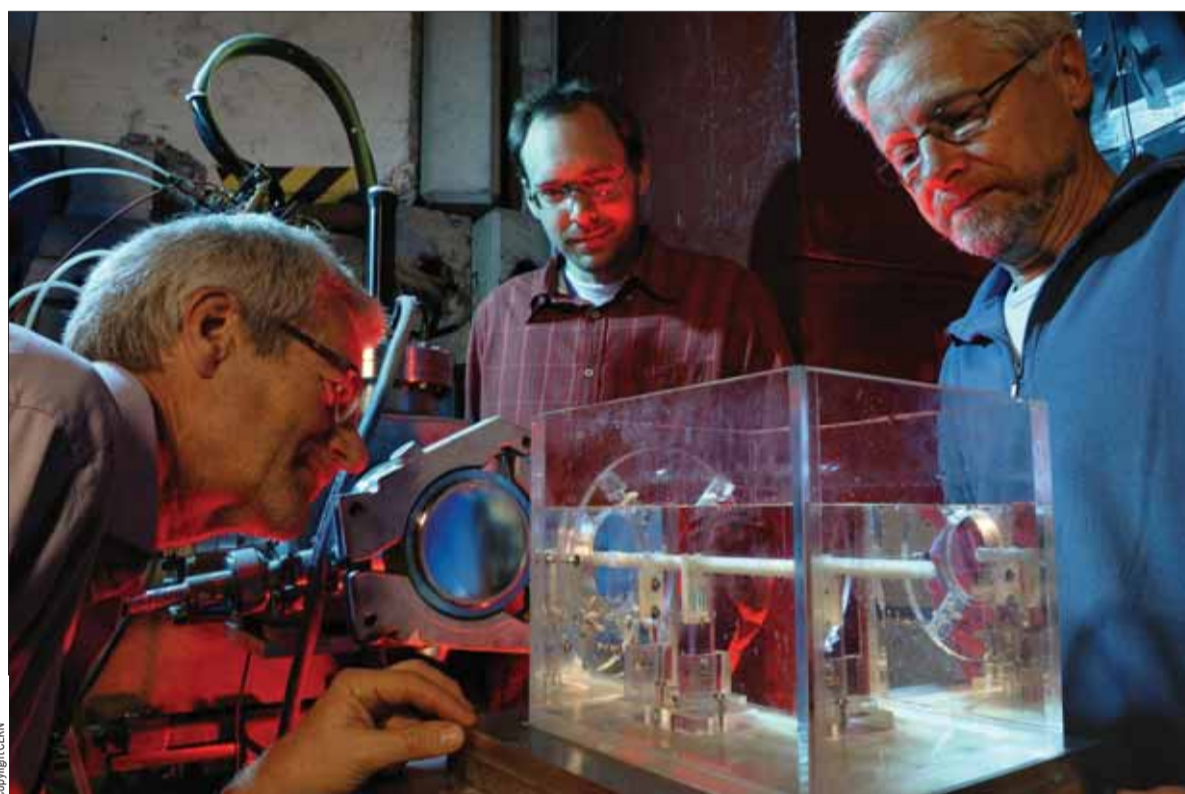
NB: Antiprotons behave like protons when they enter tissue. If you compare the dose-depth curves, in each case you will see a plateau region when the particles are moving and a Bragg peak when the particles stop. However, when antiprotons stop, they also annihilate. This releases additional energy, some of which is deposited locally. So if you compare the size of the Bragg peaks on the depth-dose curves, you see a doubling of dose for the antiprotons.

Is it just about raising the dose?

Not necessarily. In the region of the Bragg peak, we also expect that the relative biological effectiveness (RBE) of antiprotons will be higher than that of protons. This is because secondary particles produced during annihilation, such as helium nuclei, may help destroy surrounding tumour cells.

Your published research discusses the effectiveness of protons and antiprotons in irradiating hamster cells. How have you taken this forward?

Our paper (*Radiother. Oncol.* **81** 233) was based on data acquired in 2003 and 2004. The antiprotons we were working with had energies of just 50 MeV, which meant that the penetration depth into our target was roughly 2 cm. When we returned to CERN last October [2006] we were able to work with 126 MeV antiprotons. This gave us a penetration depth of approximately 10 cm, and a much greater separation between the peak and plateau regions.



Four times better: Niels Bassler (centre) and colleagues work on CERN's antiproton cell experiment.

The ACE team previously reported having problems with antiproton dosimetry. Have you resolved these difficulties?

Getting the dosimetry right in the target region is a nontrivial task owing to the mixed spectrum of particles. But we need to do accurate dosimetry to extract the RBE. In our last series of experiments, we had much success; the results agreed well with Monte Carlo calculations of what the dose should be. We have one week of beam-time in CERN coming up. This will be almost entirely dedicated to radiobiology experiments on hamster cells. Now that we can do the dosimetry, we should finally be able to get a good estimation of the RBE.

Will you then be moving to *in vivo* experiments?

At CERN, the beam fluence is very low. We have dose rates of around 1.2 Gy/hour. It is very difficult to do *in vivo* work with that kind of beam because the cells will repair. In fact, we believe it will be impossible. We really need a dedicated facility, or at least a facility that offers significantly higher antiproton fluence.

Isn't there anywhere in Europe that can offer this?

Not yet. We are hopeful that we will get some beam time at the new Facility for Low-Energy Antiproton and Ion Research (FLAIR) that is planned for the heavy-ion research

centre (GSI) in Darmstadt, Germany. This is still a couple of years away though. Building has not even started.

There are several sites producing protons or heavy ions for particle therapy. Is it just a case of playing catch-up?

Making low-energy antiprotons is a costly process. You need at least two accelerators – one to generate an intense beam of energetic protons for antiproton production, and another to slow down and shape the beam of extracted antiprotons. Whether it is worth the cost is difficult to say right now. Our initial calculations show that based on today's technology, the cost of such a facility would be somewhere in the region of €0.5–1.0 billion (\$0.8–1.6 billion). That's roughly the price of five carbon-ion therapy facilities. Of course, technology is devel-

oping all the time, so we may see new accelerator technologies emerge that can help bring these costs down.

Without any means to make therapeutically useful antiprotons, will your research come to a stand-still?

We can get closer to learning about the clinical efficacy of antiproton radiotherapy without an accelerator. We are modifying a treatment-planning system so we can compare the dose delivered by antiprotons in different cases with that delivered by protons, carbon ions or intensity-modulated radiotherapy. We also want to model the radiobiological effects of the antiproton beam.

Given the investment required, is your investigation into antiproton radiotherapy really worth the effort?

We have to figure out what the clinical benefits are from using this beam and whether this type of therapy is economically feasible – that is true. But there are a lot of spin-offs from this work that may benefit the wider particle-therapy community as well. For example, dosimetry of mixed particle fields, and the modelling of radiobiological effects are both important issues for anyone involved in carbon-ion therapy.

Paula Gould is a contributing editor on *medicalphysicsweb*

EDITORIAL



Welcome to *medicalphysicsweb review*, a special supplement brought to you by the editors of *medicalphysicsweb*.

A unique website for the medical physics community, *medicalphysicsweb* provides in-depth analysis and incisive commentary on the core disciplines of medical physics. Put simply, *medicalphysicsweb* is here to make your job easier – to give you the inside track on the fundamental science, emerging technologies and clinical applications that will underpin future advances in diagnostic imaging and radiotherapy.

This special supplement – the first of three being published this year – is exclusively dedicated to particle therapy. Highlights include the latest research developments and patent applications, updates from some of last year's big trade shows, plus selected abstracts from the prestigious journal *Physics in Medicine and Biology*.

If you've not yet come across *medicalphysicsweb*, please take some time to browse through this supplement and find out what *medicalphysicsweb* is all about. If you like what you see, the next step is to sign up as a member.

Registering as a member of *medicalphysicsweb* is free and takes just a few minutes of your time. Simply log on to medicalphysicsweb.org and hit "sign-up now".

Tami Freeman
Editor, *medicalphysicsweb*

SIGN UP TODAY



- Keep in touch with the latest news, reviews and analysis from *medicalphysicsweb*.

- Register **FREE** as a member of *medicalphysicsweb* today and you'll be entered into our fantastic prize draw for the new iPod Touch.

Childhood cancer: damage limitation

Medulloblastoma is the most common childhood malignant brain tumour. When treated with an appropriate combination of surgery, radiotherapy and chemotherapy, the long-term disease-free survival rates are greater than 60% in high-risk patients and 80% in low-risk patients. However, this prognosis makes it critical to minimize long-term morbidities from radiotherapy.

In particular, the postoperative radiotherapy regime conventionally used to treat medulloblastoma – craniospinal irradiation using opposed-lateral X-rays, plus a boost to the posterior fossa (the tumour bed) – usually results in the patient's eyes receiving significant unwanted dose. The lens is especially sensitive, with the threshold fractionated radiation dose for inducing opacification (cataracts) of the lens estimated as between 8 and 20 Gy.

Now, researchers at Harvard Medical School and Massachusetts General Hospital (Boston, MA) have developed a proton-therapy regime that significantly reduces the dose to the lens of the eye (*Int. J. Radiat. Oncol. Biol. Phys.* 5 1336).

To compare various therapeutic regimes, the researchers first considered a test case: a five-year-old boy with medulloblastoma who was scheduled for proton therapy. They created three treatment plans that would deliver a craniospinal dose of 23.4 Gy and a total posterior fossa dose of 54 Gy: standard craniospinal irradiation using opposed-lateral X-

rays, plus a posterior fossa boost; whole-brain irradiation using opposed-lateral proton fields matched to a posterior-anterior proton spine field; and whole-brain irradiation using opposed-lateral proton fields angled at 20° in a posterior direction.

When compared with conventional X-rays, the opposed-lateral proton beams did not reduce the radiation dose to the lens. Angling the lateral beams by 15–20°, however, led to an average dose reduction of 75% throughout the lens.

The researchers then compared the two proton-therapy set-ups by retrospectively evaluating the lens dose delivered to 39 patients treated with craniospinal proton-beam irradiation. The study included 13 patients treated using traditional opposed-lateral fields, plus 26 patients treated using angled proton-beam fields.

In all cases, when the lateral proton beams were angled by 15–20° to the posterior, the dose to the lens was reduced, with a mean decrease of around 50%. The average maximum dose to any portion of the lens decreased from 74% to 40% of the prescribed dose. Importantly, there was no significant difference in the dose delivered to the planned target volume in the two groups.

“There are no disadvantages to angling the beam that I know of, other than adding to a slightly longer set-up” explained co-author Judy Adams. “This technique became the routine as soon as we planned the first case with it.”

IMPT best for boosting

Intensity-modulated proton beams ideal for boost-dose delivery.

Selective subvolume boosting – delivery of a boost dose to specified regions of a tumour mass – offers a potential way to increase tumour control while reducing complications to normal tissue. The delivery of such non-uniform dose distributions, however, necessitates the use of intensity-modulated irradiation. To this end, US researchers have proposed that intensity-modulated proton therapy (IMPT) may deliver more accurate dose distributions than intensity-modulated X-ray therapy (IMXT).

To compare the options, the researchers – from the University of Wisconsin (Madison, WI) and equipment maker TomoTherapy (Madison, WI) – employed an electronic treatment-planning phantom (*Phys. Med. Biol.* 52 6073). The phantom comprised a 20 cm long cylinder containing a cylindrical base tumour region (the clinical target volume). This tumour region in turn contained six cylindrical boost regions, with radii of between 1.5 mm and 10 mm, arranged in a circle.

By varying parameters including the boost-region dose and the phantom radius, the researchers simulated 112 different delivery scenarios. They then created optimized IMXT and IMPT treatment plans for each phantom variant and compared these plans quantitatively and qualitatively. Several methods of delivering the intensity-modulated radiation were used:

- Step and shoot IMXT (IMXT-SAS),

in which multiple 2D subfields from a multileaf collimator are superposed.

- Helical tomotherapy (IMXT-HT), where radiation is delivered from a linac mounted on a T-style ring gantry that rotates about the patient couch.

- Spot scanning IMPT, in which a proton-beam spot is scanned over a 3D grid in the treatment volume, delivered over 360° (IMPT-SS_{full}) and a 180° arc (IMPT-SS_{half}).

- Distal gradient tracking IMPT, a technique designed to reduce the number of proton-beam spots relative to the spot scanning method, also delivered over 360° (IMPT-DGT_{full}) and 180° (IMPT-DGT_{half}).

One key difference noted between the IMXT and IMPT methods was the higher dose delivered to the normal tissue region by the IMXT delivery. As the phantom radius increased, the integral normal-tissue dose ratios between IMXT and IMPT converged to a factor of approximately two. The dose profiles showed that the boost doses for the IMXT-SAS method did not match the prescribed values as well as the other five methods, a fact that was corroborated by calculations of effective dose-volume histograms.

The researchers also examined the dose uniformity within the base tumour region. This was noticeably worse for the IMXT-SAS method than for the other five methods. The best dose uniformity was exhibited by IMPT-SS_{full} and IMPT-SS_{half}, followed by IMPT-DGT_{full}. The authors note, however, that the focus of this current

study was on the physical dose distributions, and that the clinical consequences of the slightly decreased boost region coverage and increased dose non-uniformity in the base tumour region are unclear.

Upon comparing the phantom plans with the local objective function, the researchers noted that for boost regions larger than 1.5 mm in diameter, boost doses given using the IMPT-SS_{full} method always satisfied the objective function most accurately. IMXT-SAS always showed the worst accuracy of the six delivery methods. None of the methods were able to resolve the smallest (1.5 mm radius) boost region.

The authors concluded that the driving force behind IMPT for selective subvolume boosting must be “the need for reduction in normal-tissue integral dose relative to IMXT and/or the need to completely spare structures distal to the target region”. They also point out that the practical adoption of IMPT for this application will require accurate management of patient motion.

“We plan to continue this work with a study comparing all of the delivery methods for a clinical case in which the boost prescription is non-uniform throughout, and based on a PET image of a hypoxia surrogate,” lead author Ryan Flynn told *medicalphysicsweb*.

Tami Freeman is editor of *medicalphysicsweb*



The Particle Therapy Co-Operative Group, PTCOG, is an organization for individuals with an interest in charged particle radiation therapy. The objectives of the association are to promote global research activities in charged particle radiation therapy, to share and exchange scientific knowledge and to support the organization of dedicated scientific meetings in this field.

Since 2007, PTCOG has had the status of a non-profit association with the domicile in Villigen-PSI, Switzerland. PTCOG 48 will be held in Heidelberg, Germany, in May 2009. In 2010, the meeting will be hosted by the Japanese.

ptcog.web.psi.ch

Sichel Technologies

Smart Marker™

DVS
Dose Verification System

We are at
AAPM booth
number 1120
and also at
ASTRO booth
number 1510

Introducing DVS – The only implantable dosimeter for dose verification and target localization.

See more. Learn more. Visit us at
AAPM and ASTRO.

www.dvssmartmarker.com

Gating system keeps protons on course

Compensating for respiratory motion is an important challenge in proton therapy, reports *Tami Freeman*.

Respiratory motion affects the dose distribution of any external-beam radiation treatment. For proton therapy, however, the implications of target movement are particularly severe. The sharp distal fall-off of the depth-dose distribution – so valuable in enabling proton therapy’s high targeting accuracy – also makes the technique extremely sensitive to any change in radiological depth due to target movement, particularly along the beam direction.

A team of researchers at the Francis H Burr Proton Therapy Center at Massachusetts General Hospital (Boston, MA) has addressed this issue by developing a respiratory gating system for proton therapy of affected sites such as the lung, liver and mediastinum (*Med. Phys.* 34 3273).

Previously, the only way to treat such body sites was to employ large tumour margins, thus ensuring that the proton field covers the target volume for all phases of respiration. The margins need to be expanded not only lateral to the beam direction, as for a photon treatment, but also along the beam direction. This extra coverage considerably increases the normal tissue involvement and thus the treatment toxicity.

By gating the beam in synchrony with selected phases of the patient’s respiration cycle, however, only the

organ motion during the gated phases needs to be considered in the treatment plan. “With gating, the motion margins become much smaller,” lead author Hsiao-Ming Lu told *medicalphysicsweb*. “Due to the particular nature of the particle beam, the saving for normal tissue is more significant in areas behind the target volume.”

Make it real

Lu and co-workers have developed and commissioned a respiratory-gating system for use with range-modulated proton treatment fields. It is based around Varian’s RPM respiratory gating system, which uses a reflector box placed on the patient’s abdomen to monitor their respiratory cycle, selects the appropriate gating level and generates a gating control signal. The team then created a hardware interface to translate this gating signal to the proton-beam control system.

The researchers evaluated the overall performance of their gating system using film dosimetry. A 2D phantom provided motion in accordance with an average patient trajectory (4 cm peak-to-peak motion with a period of 4 s). Using a gating duty cycle of 25% and a pencil-beam aperture to collimate the proton beam, they recorded films for three configurations: no motion; motion without beam gating; and motion with beam gating.



Above: Respiratory-gated proton therapy of a cardiac sarcoma patient. Right: The control system used during the respiratory-gating treatment.



For the stationary case, the dose distribution was clearly centred at the origin. For the case with motion but no gating, this distribution spread out into a line, with peaks at either end corresponding to the maximum and minimum positions. When beam gating was used, the dose distribution re-

localized around the origin, although residual motion during the 25% gating duty cycle resulted in a small spread relative to the stationary distribution.

In order to determine the timing accuracy of the gating process, the team also examined the time delays for various components of the sys-

tem. The total delay between the actual motion and delivery of dose was estimated to be between 65 and 195 ms (130 ms average). The researchers point out, however, that considering the uncertainties involved in other parts of the treatment process, the magnitude of this delay should not cause any concern for most patients.

The respiratory-gating system has been used to perform treatments of lung, liver and cardiac-sarcoma patients at the Francis H Burr Proton Therapy Center, with the first gating treatment performed in February 2006. Lu points out, though, that it’s still too early to make statistically valid conclusions as to the technique’s effectiveness.

The weakest link in the existing system set-up is thought to be the surface-surrogate-based respiration monitoring technique. For certain patients (or possibly most patients at certain times), surface surrogates do not truly reflect the motion of the target volume. “We are developing a fluoroscopy imaging system with automatic seed recognition and tracking so that we can gate the proton beam directly to the exact position of the target volume,” Lu explained.

Tami Freeman is editor of *medicalphysicsweb*

BNCT targets head-and-neck cancers

Head-and-neck cancers that recur following conventional treatment pose a difficult therapeutic problem. Early results from a clinical trial at the Helsinki University Hospital in Finland indicate that an experimental radiation treatment called boron neutron capture therapy (BNCT) shows promise for successful treatment of such recurring disease (*Int. J. Radiat. Oncol. Biol. Phys.* 69 475).

In a prospective phase I/II study, the Helsinki researchers examined 12 patients with inoperable, locally advanced head-and-neck cancers that had recurred following surgery and radiation therapy. Following BNCT, ten of the patients experienced substantial tumour shrinkage, while in seven cases the tumour disappeared completely. The treatment’s adverse effects were moderate and resembled those of conventional radiation therapy.

Heikki Joensuu, professor of oncology at Helsinki University and scientific director of this research programme, reckons that these clinical results open up a whole new field of application for BNCT. Until recently, the technique had only been evaluated for the treatment of brain tumours, with glioblastoma the first target.

“Glioblastoma was selected because its prognosis is extremely poor with

any known therapy,” Joensuu told *medicalphysicsweb*. “Conventional radiation is more effective for well-oxygenated tumour tissue and glioblastomas typically contain poorly oxygenated, necrotic tissue. Boron capture of neutrons produces high-linear-energy-transfer radiation, which we anticipated could destroy the poorly oxygenated glioblastoma cells.”

BNCT also offers potential for use with other difficult-to-treat cancers and a few such cases have already been investigated. Joensuu points out that BNCT is, however, a relatively new technique that still needs to prove its worth against conventional therapies. “BNCT might become incorporated in the primary treatment as a new component of a multispecialty approach in the future - or perhaps even as a sole therapy,” he speculated. “But we are not yet there.”

As such, the clinical usage of BNCT has been pretty limited to date. Joensuu attributes this partly to the therapy’s requirement for access to a nuclear reactor, and partly to unimpressive early results in the treatment of glioblastoma. “But this may now gradually change,” he added. “We believe that BNCT is still in its infancy, and that there is potential to improve the method further.”

Proton therapy: neutron issues

The growing investment in proton therapy is fuelled by the promise of supremely specific dose delivery around the tumour. However, the exquisite specificity of proton therapy has created a new set of challenges for radiotherapy planners. Tightly focused energy delivery might minimize collateral damage, but if the tumour is much larger than the treatment beam, then malignant cells could escape unharmed.

Most proton radiotherapy facilities use passive scattering techniques to expand the treatment beam’s coverage. With this method, a number of material components are placed in the firing line to scatter the incoming protons. The broadened beam is then shaped to the desired size by collimators.

The downside of this strategy is that proton interactions with materials in the beamline will create high-energy secondary neutrons. The high linear energy transfer (LET) of neutrons makes them extremely efficient at ionization, and far more likely to cause cell death than low-LET particles, such as X-rays or protons. If these neutrons reach the patient, then the risk of a second cancer increases significantly.

Given the growing number of pro-

ton therapy facilities worldwide, and their almost-exclusive use of passive scattering technology, this is a risk that should be taken seriously, according to David Brenner and Eric Hall from Columbia University Medical Center (New York, NY).

“The issue of how damaging these low doses of neutrons can be has perhaps not been fully appreciated,” Brenner told *medicalphysicsweb*. “Typical lead times between radiation exposure and a tumour appearing can be 20, 30 or even 40 years. Our concern is that we are setting up a problem for the future.”

The two radiation-physics professors have now calculated the lifetime risk of neutron-induced secondary cancer to patients undergoing proton therapy (*Radiother. Oncol.* 86 165). The lifetime second-cancer risk for a 15-year-old male and female patient came out as approximately 5% and 11%, respectively. But these risks could actually be four times higher or lower, owing to uncertainties in the calculation process, Brenner cautioned.

Brenner is keen to stress that the work should not be used as evidence against proton therapy *per se*. It is more a call for facilities to investigate alter-

native beam-broadening methods. One option would be a switch to active scanning technology, where magnets are used to sweep the proton beam across the tumour. No physical objects are placed in the beamline, so no secondary neutrons are produced at all. This technology is still in its infancy, though in the future, it may become the norm.

For now, changes to passive scattering systems that would minimize neutron production are more likely. Most secondary neutrons are generated by the final collimator, Brenner said. These collimators are typically made from brass or similar materials with a high atomic number. Switching to an alternative, lower-mass, high-density material could cut the neutron dose significantly.

“Proton therapy has a great future ahead of it, but if you can reduce this unwanted dose as much as possible, then you might as well,” Brenner added. “In the short term, passive scattering will probably continue to dominate the market, but there are still ways of reducing the neutron dose with these systems.”

Paula Gould is a contributing editor on *medicalphysicsweb*

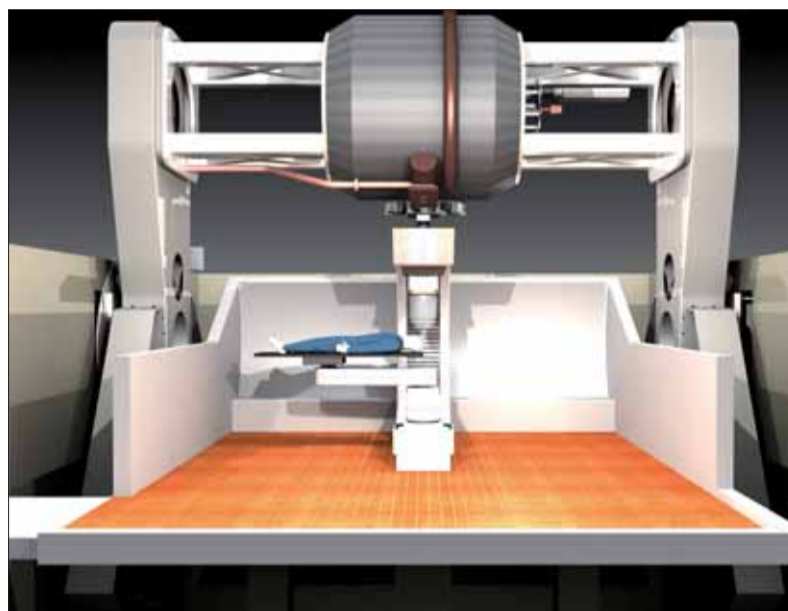
Proton therapy: future planning

Vendors work towards affordable proton-beam radiotherapy, reports Joe McEntee.

Still River Systems, a start-up firm based in Littleton, MA, is thinking big by thinking small. Thinking big in the sense that it wants to transform the economics of proton-beam radiation therapy. To do that, though, the company also needs to think small(ish) – in this case, a single-room, proton-beam radiotherapy system called the Monarch²⁵⁰.

The high cost of particle accelerators compared with X-ray technology kept protons out of mainstream healthcare for many years. Even now, the total equipment cost for a typical proton-therapy system is around \$60 million for an average configuration. Add to that the cost of the building and the associated medical imaging equipment, and the total investment for a proton-therapy facility comes out at around \$140 million. Not cheap.

Interest is growing in proton technology, though, as evidenced by the opening of dedicated clinical proton-therapy facilities in the US, Japan and Europe. Trouble is, sites must generally allow for a purpose-built room to house the accelerator, and then run multiple treatment rooms for the technology to be commercially viable – a requirement that restricts take-up to large clinical institutions.



Next-generation: a 3D rendering of the Monarch²⁵⁰, a compact proton-therapy system under development by Still River Systems.

In contrast, Still River Systems aims to sell pared-down proton sources that fit in a single treatment room. “It’s really a matter of reducing the size, cost and complexity of the accelerator itself,” Kenneth Gall, Still River Systems’ co-founder and CTO, told *medicalphysicsweb*. “Our aim is explicitly to make this technology available to hospital-based treatment centres of any size, even community hospitals.”

Gall and his colleagues have taken an important step towards realizing a clinically practical technology after inking a collaboration agreement with CMS, the St Louis, MO-based specialist in radiation treatment-planning and workflow-management products.

Under the terms of the agreement, the two companies will work together to ensure that CMS’s XiO treatment-planning system interfaces with and

supports the specific planning requirements of Still River Systems’ Monarch²⁵⁰ proton treatment system.

XiO exploits a Linux operating system to provide integrated planning capabilities for a range of treatment modalities, including 3D multileaf-collimator-based IMRT (both sliding window and step-and-shoot), solid-compensator-based IMRT, brachytherapy and proton therapy.

CMS claims to have more proton-therapy facilities using its planning solutions than any other commercial vendor. Its products are being used in conjunction with proton-therapy systems from IBA, Varian/Accel and Mitsubishi.

Precise details of Still River Systems’ technology are being kept under wraps while patents are pending. However, it is known that protons will be delivered from a synchrocyclotron (a cyclotron in which the frequency of the driving RF electric field is varied to compensate for the mass gain of the accelerated particles as their velocity begins to approach the speed of light). This marks a departure from the usual choice of synchrotron or isochronous cyclotron as the particle accelerator.

Joe McEntee is group editor at IOP Publishing

Varian showcases its image-guided, intensity-modulated proton therapy

The ESTRO meeting in Barcelona, Spain, last year saw Varian Medical Systems showcase its capabilities in image-guided, intensity-modulated proton therapy (IG/IMPT). Those capabilities were acquired when Varian paid \$35 million for ACCEL Instruments, a privately held developer of proton-therapy systems and scientific research instruments.

Much like IMRT, the basic principle of IMPT is straightforward enough: modulate the intensity of the incoming beam of protons so as to achieve a higher degree of spatial agreement (or conformality) of the resulting dose distribution with the target volume.

Underpinning this offering is a portfolio that includes superconducting cyclotrons for proton therapy, superconducting magnets (which are sold to large laboratories like CERN in Geneva), speciality linear accelerators for research applications, and X-ray-beam linacs.

Neil Madle, Varian’s head of investor relations, Europe, told *medicalphysicsweb* that the company is in the process of integrating the ACCEL team and product portfolio into Varian. “We’re continuing to develop the software needed for broad clinical deployment of this technology.”



Key component: Varian’s 250 MeV superconducting cyclotron.

He added: “It [ACCEL’s cyclotron] has a technology-leading scanning-beam configuration that lends itself to IMPT in a way that other products in the market do not, limiting the dose that goes beyond the tumour, sculpting around the tumour and the back of the tumour.” That’s particularly important in the treatment of paediatric cancer cases, where clinicians are keen to minimize the exposure of healthy tissues to radiation.

Getting it together

Vendor partnership was a prominent theme at the 49th annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) in Los Angeles, CA, last October.

First out of the blocks at the opening of the trade show, were IBA, the Belgian specialist in particle-therapy systems, and Elekta, the Swedish radiotherapy equipment maker. The two companies announced a tie-up called the Global Particle Therapy Programme, which aims “to optimize the seamless integration of proton-therapy delivery and information management systems within the radiation oncology environment”.

On the Elekta side, this can include an array of Elekta products such as the MOSAIQ workflow management and information system, MOSAIQ proton-therapy module, patient immobilization devices, localization systems, as well as the Elekta Synergy IMRT and IGRT delivery system. On the IBA side, the agreement includes the Proteus proton-therapy system, with the option to add more products in the future depending on customer requirements. Significantly, as well as joint development work, the two companies announced joint sales and marketing activities in this area.

Another one getting with the programme, so to speak, is CMS, the

St Louis, MO-based vendor of treatment-planning and workflow-management products. Under the terms of its agreement with IBA, CMS has committed to provide particle-therapy solutions for a range of clinical requirements. This will include XiO, a treatment-planning platform for photon, electron and proton therapy; the Focal line of distributed planning workstations; and the CMS Direct suite of planning infrastructure and workflow-management products.

Not to be outdone, one of IBA’s rivals in the proton-therapy market, Optivus Proton Therapy (San Bernardino, CA), announced a collaboration of its own: a joint venture with Parsons Commercial Technology Group, a division of Parsons Corporation, to build turnkey proton-therapy centres that “will be completed on time by the most expert team in the field,” according to Optivus’ CEO Jon Slater.

Founded in 1944, Parsons bills itself as “one of the largest, 100% employee-owned management, engineering and construction companies in the US”. Optivus, for its part, was founded by the engineers who designed and installed the world’s first hospital-based proton-therapy centre, at Loma Linda University Medical Center (Loma Linda, CA) in October 1990.

PATENTS

A round-up of the latest international patent applications in particle therapy.

Laser-focused on ion acceleration

Compact particle-selection and collimation devices for delivering ion beams with defined energy spectra are described in international patent application WO/2007/061426.

According to developers at Fox Chase Cancer Center (Philadelphia, PA), the devices are key building blocks for a laser-accelerated ion-therapy system, in which the initial ions have broad energy and angular distributions.

“Superconducting electromagnet systems produce a desired magnetic-field configuration to spread the ions with different energies and emitting angles for particle selection,” notes the filing. “The simulation of ion transport in the presence of the magnetic field shows that the selected ions are successfully refocused on the beam axis after passing through the magnetic field.”

Proton accelerators: doubling up

Researchers at the Fondazione per Adroterapia Oncologica (TERA) in Novara, Italy, have proposed a complex of proton accelerators that combines “reduced energy consumption” with “remarkable compactness”, thereby easing installation in hospital and research facilities dedicated to tumour diagnostics, brachytherapy and particle therapy. According to international patent application WO/2007/054140, the accelerator complex can carry out, either in sequence or simultaneously, both the production of radioisotopes – for medical, industrial and therapeutic purposes – and the therapeutic irradiation of even deep-seated tumours.

Water phantom maps out dose

IBA has developed a water phantom for determining the radiation dose distribution from a particle or photon beam (WO/2007/128087). The phantom comprises a water tank, a means for varying the water level in the tank, and a detector that’s located in a fixed position relative to the water tank and opposite to the beam. The two-dimensional detector includes several sensors to simultaneously measure the dose at various positions. Measurements are performed at varying water levels until the dose distribution in the entire volume of the water tank is obtained.

Biological considerations

Researchers at Hampton University (Hampton, VA) have published details of treatment planning methods for proton- and carbon-ion-therapy that include adequate biological weighting (WO/2007/126782). The treatment plans determine the variability of relative biological effectiveness (RBE) along a beam line and calculate, among other things, the hadron-beam intensity required to achieve a desired biological dose at the treatment site. Typically, three or four RBE values at three or four intervals along the beam line are calculated.

Forward thinking on heavy ions

Particle-therapy vendor IBA has big development plans in carbon-ion therapy, reports *Paula Gould*.

Ion Beam Applications (IBA) has a strong position in the emerging hadron-therapy market. The Belgium-based company has sold 13 proton-therapy systems to date and claims a 55% global market share.

So far so encouraging, but the future of particle therapy is likely to include heavy ions as well as protons, according to IBA's founder and chief research officer Yves Jongen. Hence IBA's development of an accelerator that is capable of producing high-energy carbon ions. Paula Gould spoke to Jongen to learn more about the works-in-progress system.

PG: What are the benefits of using carbon ions for particle therapy instead of protons?

YJ: Some tumours have a core of cells that are deficient in oxygen. Killing these anoxic cells requires a high dose of radiation. Carbon ions have a much higher linear energy transfer than either protons or photons. [This means], in general, they are more effective at treating these tumours that have an anoxic core. Possible applications for carbon ions include non-small-cell lung cancers, secondary metastases in the liver and advanced prostate cancers.

You are not the first to consider using carbon ions for particle therapy. What is particularly novel about your system?

Carbon-ion therapy was pioneered in Europe by the GSI laboratory in Darmstadt, Germany. That technology has now been sold to Siemens. The technology developed by GSI is based on a synchrotron. Four years ago, IBA started to develop carbon therapy using another technology: a superconducting cyclotron. The diameter of the synchrotron is approximately 30 m. The diameter of the cyclotron is 6 m, so it is five times smaller; it is also less expensive and simpler.

How does it work?

This is an isochronous cyclotron. A radio system provides the accelerating voltage and a magnet guides the particles during acceleration. We have an external source that produces a beam of fully ionized carbon ions. These carbon ions (C^{6+}) are injected into the centre of the cyclotron along the axis of the magnetic field and then deflected into a circular orbit. The diameter of the first turn is approximately 6 cm. As the particles pass the accelerating electrode they gain energy, typically 300 kV per turn, and

as they accelerate the diameter of their orbit increases. In this cyclotron, the carbon ions make around 1500 turns. At this point, the diameter of their orbit will be approximately 3 m and they will be travelling at around 75% the speed of light.

What is the energy of your final treatment beam?

It's 400 MeV per nucleon. Because carbon has 12 nucleons, the total energy is actually 4.8 GeV. That gives a penetration depth of 27.5 cm.

But not every tumour will be located at that specific depth.

No, so you need to adjust the energy. That is done by passing the beam through a graphite wedge of varying thickness. You want the peak energy of the carbon beam to correspond with the position of the patient's tumour.

Is your system only suitable for accelerating carbon ions?

Carbon ions might be superior to protons for treating radioresistant tumours, but there will be many other tumours that should be treated with protons. This is why all facilities offering carbon ions should be able to produce protons too. Our cyclotron



Ion man: IBA founder Yves Jongen.

accelerates molecular hydrogen – that is, hydrogen molecules with only one electron and a charge-to-mass ratio of 0.5. When this molecule reaches the correct energy, we fire it at a carbon foil that strips it into two protons.

What is your schedule for development?

IBA is investing €40 million to build a prototype of its new system here in Belgium. Our goal is to have the cyclotron working by the end of 2010 and to have our first patient treated by the end of 2011.

Where will the finished system be installed?

It will be tested at the IBA factory in Belgium and then moved to a demon-

stration site in Caen, France. This is an attractive location. The site is close to the French national heavy-ion accelerator (Ganil) and to several solid-state-physics, radiobiology and medical imaging laboratories. There are also a couple of university medical institutions and a very good engineering school nearby.

Most of IBA's systems have been installed in the US and Asia. Do you expect to see more sites in Europe offering hadron therapy in the future?

Because of its social-security-based healthcare system, Europe has always been a bit reluctant to embrace new therapeutic modalities that could raise treatment costs. That being said, IBA will install two proton-therapy systems in Europe this year – one in Germany (Essen) and one in France (Orsay). A number of other tenders for particle-therapy systems at sites in Europe will be decided this year too. There are tenders out from two sites in Italy and a site in Sweden, and discussions are ongoing at sites in the UK and the Netherlands.

Paula Gould is a contributing editor on *medicalphysicsweb*

journal review

Here's a selection of abstracts from some recent articles published in the journal *Physics in Medicine and Biology* and featured on *medicalphysicsweb*. To view the full articles and browse the journal, visit www.iop.org/journals/PMB

Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy

D Pflugfelder, J J Wilkens and U Oelfke 2008 *Phys. Med. Biol.* **53** 1689–1700

The sharp dose gradients which are possible in intensity modulated proton therapy (IMPT) not only offer the possibility of generating excellent target coverage while sparing neighbouring organs at risk, but can also lead to treatment plans which are very sensitive to uncertainties in treatment variables such as the range of individual Bragg peaks. We developed a method to account for uncertainties of treatment variables in the optimization based on a worst case dose distribution.

The worst case dose distribution is calculated using several possible realizations of the uncertainties. This information is used by the objective function of the inverse treatment planning system to generate treatment

plans which are acceptable under all considered realizations of the uncertainties.

The worst case optimization method was implemented in our in-house treatment planning software KonRad in order to demonstrate the usefulness of this approach for clinical cases. In this paper, we investigated range uncertainties, setup uncertainties and a combination of both uncertainties. Using our method the sensitivity of the resulting treatment plans to these uncertainties is considerably reduced.

PET monitoring of cancer therapy with He-3 and C-12 beams: a study with the GEANT4 toolkit

Igor Pshenichnov *et al.* 2007 *Phys. Med. Biol.* **52** 7295–7312

We study the spatial distributions of β^+ activity produced by therapeutic beams of He-3 and C-12 ions in various tissue-like materials. The calculations were performed within a Monte Carlo model for heavy-ion therapy (MCHIT) based on the GEANT4 toolkit. The contributions from positron-emitting nuclei with $T_{1/2} > 10$ s, namely C-10, 11, N-13, O-14, 15, F-17, 18 and P-30, were calculated and compared with experimental data obtained during and after irradiation, where available. Positron-emitting nuclei are created by



a C-12 beam in fragmentation reactions of projectile and target nuclei. This leads to a β^+ activity profile characterized by a noticeable peak located close to the Bragg peak in the corresponding depth-dose distribution. This can be used for dose monitoring in carbon-ion therapy of cancer. In contrast, as most of the positron-emitting nuclei are produced by a He-3 beam in target fragmentation reactions, the calculated total β^+ activity during or soon after the irradiation period is evenly distributed within the projectile range. However, we

predict also the presence of N-13, O-14, F-17, 18 created in charge-transfer reactions by low-energy He-3 ions close to the end of their range in several tissue-like media. The time evolution of β^+ activity profiles was investigated for both kinds of beams. We found that due to the production of F-18 nuclides the β^+ activity profile measured 2 or 3 h after irradiation with He-3 ions will have a distinct peak correlated with the maximum of depth-dose distribution. We also found certain advantages of low-energy He-3 beams over low-energy proton beams for reliable PET monitoring during particle therapy of shallow-located tumours. In this case the distal edge of β^+ activity distribution from F-17 nuclei clearly marks the range of He-3 in tissues.

Monte Carlo simulations of the dosimetric impact of radiopaque fiducial markers for proton radiotherapy of the prostate

Wayne Newhauser *et al.* 2007 *Phys. Med. Biol.* **52** 2937–2952

Many clinical studies have demonstrated that implanted radiopaque fiducial markers improve targeting accuracy in external-beam radiotherapy, but little is known about the dose perturbations these markers

may cause in patients receiving proton radiotherapy. The objective of this study was to determine what types of implantable markers are visible in setup radiographs and, at the same time, perturb the therapeutic proton dose to the prostate by less than 10%.

The radiographic visibility of the markers was assessed by visual inspection of lateral setup radiographs of a pelvic phantom using a kilovoltage X-ray imaging system.

The fiducial-induced perturbations in the proton dose were estimated with Monte Carlo simulations. The influence of marker material, size, placement depth and orientation within the pelvis was examined.

The radiographic tests confirmed that gold and stainless steel markers were clearly visible and that titanium markers were not.

The Monte Carlo simulations revealed that titanium and stainless steel markers minimally perturbed the proton beam, but gold markers cast unacceptably large dose shadows.

A 0.9 mm diameter, 3.1 mm long cylindrical stainless steel marker provides good radiographic visibility yet perturbs the proton dose distribution in the prostate by less than 8% when using a parallel opposed lateral beam arrangement.

The cautionary tale of neutron therapy

“It’s important that the mistakes made with neutrons are not repeated with charged-particle therapy.”

Bleddyn Jones,
University Hospital
Birmingham, UK

Neutron therapy – tumour destruction via irradiation with a beam of neutrons – was once heralded as a highly promising new cancer treatment. Unfortunately, research based upon an optimistic interpretation of initial experimental evidence produced disappointing clinical results. As the following sequence of events illustrates, the use of partial scientific knowledge in an attempt to improve the treatment of a complex biological condition such as cancer proved ill-advised.

Killing cancer cells in a laboratory environment is considerably easier than curing a malignant tumour situated within or close to essential organs and tissues of the body. In the context of future radiotherapy developments, particularly the use of proton and ion-beam therapy, this tale is highly relevant.

The saga began with the finding that neutrons inflict much greater biological damage than the same dose of 250 keV X-rays. The difference can be quantified by the relative biological effect (RBE), defined as the ratio of the doses of two forms of radiation required to produce the same biological effect. Fast-neutron RBE values of 1.5 to 5 were found in many biological systems, including bacteria, plants and transplanted animal cancers.

The immediate inference from this finding was that neutrons would be ideal for cancer therapy. Yet the first human experiments in the US showed severe toxicity because the relationship between the exposure dose and RBE was not yet known. Further interest arose upon the discovery that high-linear-energy-transfer (LET) radiation, such as fast neutrons, with increased ionization events along micron distances of their tracks, are less dependent than X-rays upon the presence of oxygen to produce cell death.

Many cancers contain zones of very low oxygen tension, which are considered an important cause of radio-resistance. High-pressure oxygen was tested as a means to overcome this problem, but this required patients to be placed within compression tanks. An attractive alternative was the use of cyclotrons to accelerate protons to around 20 MeV or higher and then bombard them onto beryllium targets to produce fast neutrons with high-LET properties.

Trial and error

During the 1970s and 80s, the Medical Research Council in the UK funded three important projects investigating neutron therapy. Firstly, at Hammersmith Hospital in London, clinical studies were conducted using a fixed horizontal beam with relatively poor tissue penetration. However, despite clear evidence that neutron RBE is inversely related to dose-per-fraction in a wide variety of animal tissues, the clinical dose prescriptions used a constant RBE. Thus the dose plan took no account of the increased RBE in normal tissues receiving doses lower than those prescribed to the tumour.

Attempts at randomized trials involved control patients treated with X-rays or cobalt beams at other hospitals. However, no control protocol was specified, resulting in an inappropriately wide variation in applied dose. Much was learned about how to conduct cancer trials properly.

Researchers at the Western General Hospital in Edinburgh carried out stricter in-house randomized trials comparing megavoltage X-rays (with superior tissue penetration) and relatively poorly penetrating fast neutrons. For both radiation classes the beams could be rotated on a gantry. However, the neutron tumour-control rates were disappointing and were accompanied by enhanced normal-tissue toxicity.

Finally, randomized trials at Clatterbridge Hospital in the Wirral, some of which were jointly undertaken with the University of Washington (Seattle, WA), showed that neutrons conferred no clinical advantage. These studies used an extended fast-neutron energy (obtained using 64 MeV protons) that

produced neutron depth-dose distributions equivalent to 5 MeV X-rays.

In other countries, therapy with relatively low-energy neutrons had been tried without recourse to formal comparative trials, and with little convincing success. In retrospect, neutron therapy failed for the following reasons:

- Computations of absorbed dose did not include additional neutron capture in hydrogen-rich tissues, which results in higher energy release in such tissues. These include white matter in the brain and the fat that surrounds most important organs, which is closely associated with their blood supply.
- The well-established finding that RBE varies in different tissues was dismissed, along with the important fact that RBE increases with falling dose, which mitigates the effect of a reduction in physical dose beyond the region of cancer.
- The fact that RBE also varies with cell proliferation rate, so that slow-growing cells have higher values, was not appreciated. It is the slow-growing cells that make up the majority of normal tissue and which contribute to severe tissue damage at extended time periods after irradiation.

Recent mathematical modelling that includes RBE effects shows that neutron therapy would only have worked well for very superficial, slow-growing cancers with little normal tissue coverage. There now remain very few advocates for fast-neutron therapy in the world, although there is some promise for boron neutron capture therapy (BNCT).

Charged particles

Following the fast-neutron cancer trials, the UK funding authorities decided not to invest in further ambitious radiation projects, resulting in a decline in radiotherapy research and scepticism of high-LET radiotherapy. In other countries, more progress has been achieved with charged-particle therapy (CPT) using protons or light ions, again produced from cyclotrons or synchrotrons.

Protons of over 60 MeV have an RBE that’s only slightly higher than megavoltage X-rays, whereas carbon ions have an RBE value of around 3, similar to neutrons. The big advantage of CPT, however, is that as these charged particles traverse through tissue they initially deposit energy at a low LET, followed by a sharp increase to high-LET deposition at the Bragg peak. The tissue depth of this peak can be tailored to each treatment.

At distances beyond the target, there is little or no charged-particle dose, whereas X-rays and neutron beams pass through the entire body thickness. In this way, CPT reduces the total energy deposited in a patient by a factor of between two and 10, depending on location. Because of this superior dose distribution, which allows dose escalation and/or normal-tissue dose reduction to a wider volume of tissue than X-rays, CPT is likely to be more effective than X-ray therapy.

There can be no complacency about X-ray-based radiotherapy, as some patients continue to develop severe, chronic and debilitating side effects following such treatment. But it’s important that the mistakes made with neutrons are not repeated with CPT. New forms of radiotherapy need to be tested in high-quality centres, using the best input from physics, biology and medicine. The major radiotherapy research question over the next few decades will be whether carbon ions are superior to protons in specific cancers.

Advances in understanding the molecular biology of cancer might allow more accurate, earlier diagnosis of cancer. Safe sterilization of small cancers by a few, or even single, exposures might then be possible using CPT. Further fundamental advances in particle physics, including matter-antimatter reactions, may yet provide even more selective forms of radiation therapy. Watch this space. ●

Prof. Bleddyn Jones is a consultant in clinical oncology and applied radiobiology at University Hospital Birmingham and the University of Birmingham Medical School.

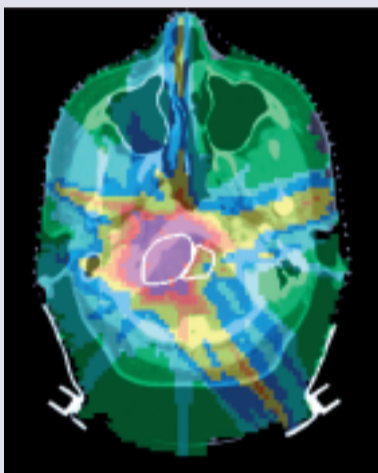
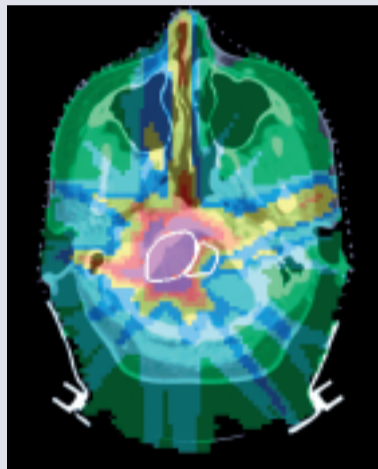
Invitation for authors

Physics in Medicine & Biology

More than 50 years of world-class publication in medical physics

Fast publication • Worldwide visibility • High impact

Editor-in-Chief: S Webb, Institute of Cancer Research and Royal Marsden NHS Trust, UK



If you are working in any of the following areas then we would like to invite your submissions:

- all areas of radiotherapy physics
- radiation dosimetry and metrology
- imaging (e.g. X-ray, MRI, ultrasound, nuclear medicine)
- other radiation medicine applications
- therapies (non-ionizing radiation)
- biomedical optics
- radiation protection
- radiobiology
- body composition



Please submit your research online at www.iop.org/journals/authorsubs
For more information visit www.iop.org/journals/pmb or email us at pmb@iop.org

www.iop.org/journals/pmb

Images: A visual examination of the similarity in plans generated from the nominal non-convex objective function and the relaxed objective function T Halabi, D Croft and T Bortfeld 2006 Phys. Med. Biol. 51 3809–3818

IOP Publishing |  **IPeM**



WIN an iPod Touch with medicalphysicsweb!

Keep in touch with the latest news, reviews and analysis from *medicalphysicsweb*. Register as a member to enter our prize draw to win an iPod Touch.

REGISTER FREE
medicalphysicsweb.org

Terms and conditions apply

VOLUMETRIC MODULATED ARC THERAPY

Elekta VMAT

Conformance. Speed. Ultra-low Dose.

Elekta VMAT delivers dose conformance beyond IMRT capabilities. Delivering a precise dose in minutes, Elekta VMAT targets the exact location of the treatment volume, resulting in better avoidance of critical structures and optimal coverage.

Conformance

One or multiple arcs for precise dose control resulting in better avoidance of critical structures

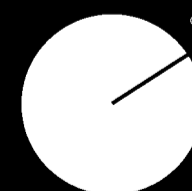
Speed

Dramatically shorter treatment times than current IMRT techniques

Ultra-low Dose

Allows daily 3D volumetric imaging and fewer MUs

Elekta VMAT is pending 510(k) review



ELEKTA

www.elekta.com/vmat