MRI guides radiation treatments

Clinical treatment has now started on the ViewRay MR-guided radiation therapy system.

The ViewRay MR-guided radiotherapy system has been used for the first time to perform real-time continuous MR imaging during a patient treatment. This breakthrough treatment took place in January of this year at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine (St Louis, MO), where the ViewRay system is now in regular clinical use.

MR guidance enables the clinician to visualize a patient’s tumour and surrounding anatomy in real-time and ensure that the radiation beam remains on target as the tumour moves. “This has never been done before,” said Michael Saracen, ViewRay’s senior director of marketing. “Previously, it had not been possible to visualize what was going on during the whole treatment. Now, we can make movies of it.” Tami Freeman caught up with Saracen to find out more.

TF: How does ViewRay’s device differ from other MR-guided radiotherapy systems?

MS: ViewRay’s system uses cobalt-60 sources, rather than integrating the MR scanner with a linac. Cobalt-60 was somewhat of an arcane technology that delivered low doses, but ViewRay uses highly activated cobalt and three heads that fire simultaneously to provide an equivalent output to a 4 MV linac. The system also uses double focused multileaf collimators that provide the sharpest beam penumbra possible and deliver equivalent performance to a standard linac.

What treatments have been performed to date?

One of the first treatments was stereotactic body radiation therapy (SBRT) for lung cancer. 3D conformal and intensity-modulated radiotherapies have also been performed. The centre has already treated a wide variety of disease sites including lung, stomach, colon, bladder, ilium, abdomen, breast and mediastinum, to name but a few. The system is really being used for everything, to name but a few. The system is now in regular clinical use.

Are adaptive treatments being performed?

Knowing that this has never been done before, the Washington University team is moving slowly towards the adaptive stage. They are collecting data with the goal of defining protocols. For example, if the targets are within a percentage threshold during a treatment then it’s good to go; if not, then maybe the doctors need to replan. With the ViewRay system, you can do that at the console while the patient is on the table. I believe in the next month or two they plan to start incorporating that as well, they’re very eager to start using this.

So it’s possible to perform online changes during treatment?

Yes the ViewRay system is capable of doing that. When James Dempsey designed this almost 10 years ago, that’s what he had in mind. The system includes autocontouring tools and ultrafast Monte Carlo dose calculation that can, for example, create a 9-beam prostate plan in just 20s.

Are there any other ViewRay systems in use yet?

A total of six systems have been purchased, with three currently in the installation phase. One system is now being used for imaging studies at the University of Wisconsin in Madison, and UCLA has finished the RF shield and is now installing the system. Typically, once a system is delivered, it’ll be used for imaging studies for a month or two and then the team will install the sources and perform the dosimetry. Interestingly, because it is cobalt-based, and cobalt is the standard by which all radiation is measured, some commissioning elements of the ViewRay system can actually be much faster than for a standard linac.

Is the Siteman Cancer Center solely using the device clinically?

It’s a research centre, so they’re taking the approach that it’s not just about treating 20 patients a day. Alongside the clinical treatments, the researchers are also performing imaging studies. They are working on getting a bunch of abstracts out for forthcoming meetings – there’s a lot of activity on that front.

“Previously, it had not been possible to visualize what was going on during the whole treatment. Now, we can make movies of it.”

Tami Freeman is editor of medicalphysicsweb.
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How to optimize MRI-linac gradient coils

Hybrid MRI-linacs offer a promising new approach to image-guided radiotherapy, delivering soft-tissue-based position verification during treatment. Such systems are often designed with two gradient coils to accommodate the accelerator and the patient in the gap. The rapid pulsing of these coils, however, induces electric fields and currents within the patient, a phenomenon that needs to be evaluated for patient safety.

Potential health risks of electric field induction by pulsed gradient coils include stimulation of the peripheral nerves and muscles and/ or induction of retinal light flashes.

If the patient is positioned between split coils at right-angles to the magnets, the field orientations are very different to those seen in conventional MR scanners. In addition, the gradient field produced outside the imaging region by a split coil has a different spatial distribution to that produced by a standard non-split coil.

"Further research is needed to work out the optimal design of the gradient coils and positioning," explained Stuart Crozier, Director of Biomedical Engineering at the University of Queensland in Australia.

With this aim, Crozier and colleagues performed a detailed simulation study to evaluate the electric fields and associated current densities induced in a patient being scanned in an MRI-linac system.

Hybrid strategy ups target dose

Hybrid adaptive radiotherapy using MRI provides higher doses to treatment targets compared with conventional treatments in patients with cervical cancer, according to a retrospective treatment planning study by researchers in Canada. The strategy exploits the soft-tissue detail provided by MRI and uses scans over the course of therapy to both guide the positioning of the patient’s tumour and replan the treatment, correcting for target motion and deformation (Radiother. Oncol. doi: 10.1016/j.radonc.2013.11.006).

“We found that the integrated strategy is remarkably successful even for the most difficult cases of cervical cancer,” said Young-Bin Cho, who conducted the study with colleagues at the Princess Margaret Cancer Centre in Toronto.

Traditionally, cervical cancer patients are positioned for treatment using X-ray-based imaging of bony landmarks in the pelvis, with a single treatment plan prepared for the duration of therapy. However, the treatment target can move relative to the bony anatomy and pelvic soft-tissue anatomy can change significantly over the course of treatment, reducing a plan’s effectiveness.

The researchers investigated the impact of soft-tissue MRI-based positioning and replanning over conventional approaches, simulating treatments in 15 patients. Each patient had already been treated and received CT and MRI scans for treatment planning, plus weekly MRI scans over their five-week treatment course. The weekly scans were carried out using an MRI simulator with the patient positioned as for treatment.

Simulated soft-tissue and bony positioning approaches – both using MRI – were combined with either zero, one or four (weekly) replans. The updated plans, generated from the weekly scans, were applied after a week’s delay to mimic clinical workflow. Online replans based on the weekly MRIs were also simulated, but these were introduced without delay. Patient anatomy at each treatment fraction was assumed to be the same as that seen on the preceding weekly scan,

In general, a hybrid strategy that used soft-tissue image guidance and offline replanning provided superior treatment volume coverage. The improvement was marked in five cases identified as difficult and increased with the frequency of replanning. In these cases, weekly replans resulted in D98 values – the dose to 98% of the target volume – that exceeded 95% of the prescribed dose.

According to ICNIRP guidelines, the 99th percentile value of the induced electric field (E99%) should remain below 0.8 V/m for tissues exposed to a time-varying magnetic field between 400 Hz and 3 kHz. The highest value of E99% (0.9021 V/m) was seen for the axially-oriented model in position 1, induced by the CC. This value was 22.6% higher than that calculated for a conventional non-split coil in the same position.

The researchers also simulated voxel models with 2 mm resolution, to study the distribution of peak induced current densities inside the body. For the flanged coil (FC), peak current densities occurred in different organs for different body positions, orientation and gender, while peak electric fields mostly occurred in the skin and fat tissues.

The highest current densities (0.7658 A/m) occurred in cerebrospinal fluid (CSF) in the axially-oriented model in position 2. The highest electric field was in the skin of the radially-oriented model in position 2, while the largest E99% (0.9543 V/m) occurred in the fat tissue of the radially-oriented model in position 2.

Repeating these simulations for the split z-gradient coil (ZC) revealed that most peak current densities occurred in the CSF, while peak electric fields occurred mostly in skin and fat tissues. The maximum current density (0.6006 A/m) was in the CSF of the axially-oriented model in position 1. The maximum electric field (5.6357 V/m) was in the skin of the axially-oriented model in position 1. The largest E99% (0.6661 V/m) was in the fat tissue of the radially-oriented model in position 2.

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The authors concluded that the amplitudes and distributions of the current density depended both on the body position and orientation. In addition, both electric fields and current densities were higher for the axially-oriented than the radially-oriented models. "The findings in this paper can help when designing and positioning both electric fields and current densities occurred in different organs for different body positions, orientation and gender, while peak electric fields mostly occurred in the skin and fat tissues.

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PET/CT shows promise for brain studies

Simultaneous PET/CT combines the sensitive molecular imaging of PET with soft-tissue contrast and functional information from MRI. One potentially important application for PET/MRI is quantitative brain studies, which demand high performance and stability from both modalities. With this in mind, researchers from the University of Tübingen in Germany have evaluated the quantification accuracy, homogeneity and stability of two PET/MRI systems.

To prevent adverse interaction between the two instruments, simultaneous PET/MRI systems employ avalanche photodiodes (APDs) instead of photomultiplier tubes (PMTs) for PET detection. However, are highly sensitive to temperature changes or bias voltage shifts. PET detectors based on APDs must therefore be systematically evaluated before use in demanding investigations.

“High stability of the PET/MR system is a prerequisite for functional brain studies,” explained lead author Holger Schmidt. “Our main motivation was to test whether existing APD-based PET/MR systems are capable of performing dynamic PET scans using short half-life radiotracers, such as 18F-FDG in low-dose exams with 18O-labeled water. While standard PET and MR quality checks are already carried out, more detailed investigations of the feasibility of such studies are missing so far.”

Schmidt and colleagues first evaluated the quantification accuracy of small lesions measured using two APD-based PET/MRI systems: the BrainPET brain scanner and Bio- graph mMR whole-body scanner. For comparison, they also assessed the Biograph mCT, a state-of-the-art PET/CT scanner. (Invest. Radiol. doi: 10.1097/RIR.0000000000000201).

The researchers used the three systems to acquire PET images of a cylindrical phantom containing eight spheres (with diameters of 4–8 mm) filled with [18F]-fluoride solution at different positions inside the PET field-of-view (FoV). They calculated “recovery values” for all images, defined as the measured activity concentration divided by the decay-corrected true activity concentration. The BrainPET system exhibited the highest recovery values – up to 99.0% for 8 mm spheres – and could better detect the smaller spheres. The whole-body PET/MRI, meanwhile, showed similar performance to the PET/CT scanner, with recovery values up to approximately 60% for the 8 mm spheres. However, the variability of recovery values for different sphere positions was higher for the BrainPET (up to 7.4%) than the PET/MRI (up to 4.1%) and PET/CT (up to 4.3%) systems.

The use of MR-derived (rather than CT-based) attenuation correction to reconstruct images from the whole-body scanner led to an underestimation in PET activity of up to 7.2%. The researchers also evaluated the effect of activity outside the PET FoV on PET quantification. For the whole-body PET/CT and PET/MRI systems, high activity concentrations outside the PET FoV had little or no influence on sphere activity quantification. The BrainPET, however, exhibited an activity-dependent recovery gradient, resulting in activity underestimations of up to 80% near the outside source. This is most likely due to erroneous scatter correction.

To investigate the long-term PET stability of the whole-body PET/MRI system, the researchers recorded a 5 min scan of a [18F]-FDG cylinder phantom 14 times over eight days. The PET detector showed good long-term stability, with standard deviations (SD) for the 14 measurements of 0.10%, 0.10%, 0.11% and 0.03%, for prompt, random and true counts and single count rate, respectively. The SD of the recovery values in the resulting PET images was 0.3%.

Energy spectra of each crystal and position profiles of each detector block revealed no distinct deviations between the different measurements. This long-term stability implies that reliable PET measurements can be performed, with no problems due to temperature variations of the APDs causing gain variations. They also checked the influence of MR scanning during PET acquisition, finding no influence of simultaneous MR on counts, count rates or recovery values.

For functional MRI (fMRI) studies, the stability of the scanner must be tested according to the functional Bioinformatics Research Network (fBIRN) protocol. The researchers tested the stability of the whole-body PET/MRI system by scanning a stability phantom using an echo planar imaging sequence for blood-oxygen-level-dependent measurements. They performed fMRI with an idle PET system, with [18F]-FDG sources inside the PET FoV and with the PET system turned off and saw no PET-related changes. Measurements showed that the percentage fluctuation (0.07%) for all PET states and drift (between 0.16 and 0.28) were well below the fBIRN recommendations.

Schmidt and colleagues concluded that the homogeneity and accuracy of APD-based PET detectors were comparable with those of bulky PMT-based detectors. The stability of the whole-body PET/MRI system was also comparable with that of stand-alone systems, allowing for quantitative PET and fMRI measurements, assuming that suitable attenuation correction is applied.

As the BrainPET system showed problems with stability, the researchers plan to use the whole-body PET/MR system for future functional brain studies. “We are performing a clinical trial on brain tumours and are planning several trials for investigating different diseases using diverse short half-life radiotracers,” said Schmidt.

MRI addresses lung screening

Screening high-risk individuals for lung cancer can identify malignant nodules sooner and at earlier stages than they might otherwise have been detected, saving lives in the process. But every CT scan performed, even if detected, saves lives in the process. But every CT scan performed, even if detected, saves lives in the process. But every CT scan performed, even if detected, saves lives in the process.

German researchers have conducted a study to investigate the potential of MRI for detecting cancer-suspicious lung lesions. Gregor Sommer, from the department of radiology at the German Cancer Research Center (DKFZ) in Heidelberg, and co-researchers proposed to work in demanding investigations.

In the ongoing German Lung Cancer Screening and Intervention trial (LUSI), who had either a pulmonary nodule greater than 10mm or a lesion with a calculated doubling time less than 46 studies, and two lesions in the remaining four datasets. On MR, one radiologist identified half of these (27) lesions; the other radiologist identified 25. Two malignant nodules were missed by both radiologists. The false negative ratio was 52%. The overall sensitivity of MRI was 48% (26/54) and the specificity was 88% (29/33). The sensitivity of the MR images was 78% for malignant nodules and 36% for benign ones.

Based on the findings of their study, the researchers believe that MRI has the potential to replace low-dose CT as the primary tool for lung cancer screening, provided that its sensitivity and specificity for detection of malignant lung nodules can be confirmed in further clinical trials as being greater than 75% and 90%, respectively. They pointed out that MRI offers the possibility of shortened screening intervals for individuals as being greater than 75% and 90%.

Phantoms eye ultralow-field MRI

The National Institute of Standards and Technology (NIST) in the US has developed two prototype phantoms for calibrating ultralow-field (ULF) MRI systems, which operate at microtesla magnetic field strengths. “Tissues that may look the same in clinical MRI can look very different in ULF MRI, which provides new contrast mechanisms,” explained NIST physicist Michael Boss. “Our hope is that we can move this technique along to attract more interest from industry vendors.” ULF MRI scanners are also simpler in design, lighter and less expensive than regular MRI systems.

The NIST prototypes offer a quantitative means to assess ULF-MRI performance, validate the technique, and directly compare different experimental and clinical MRI scanners. The phantoms comprise short plastic cylinders containing six or 10 jars filled with various salt solutions that become magnetized in a magnetic field. Tests using conventional MRI at 1.5 and 3 T, and an experimental ULF-MRI scanner at between 107 and 128 kHz, showed that the prototype phantoms were well matched to ULF-MRI applications and allowed direct comparison of ULF and clinical MRI performance (Magn. Reson. Med. doi: 10.1002/mrm.23060).
Focus on: MRI

Scans identify cancer spread

Whole-body, diffusion-weighted MRI can reveal the spread of cancer in patients with myeloma, reducing the reliance on painful bone marrow biopsies. That’s the conclusion of a study from the UK’s Institute of Cancer Research (ICR) and Royal Marsden NHS Foundation Trust. Twenty-six myeloma patients were scanned before and after treatment. In 86% of cases, experienced doctors correctly identified whether patients responded to treatment; accurately identifying non-responders in 80% of cases. The researchers also assessed visible changes on the scans using the apparent diffusion coefficient (ADC). Changes in ADC correctly identified treatment response for 24 of 25 myeloma patients (Radiology doi:10.1148/radiol.131131529).

“Three is the first time we’ve been able to obtain information from all the bones in the entire body for myeloma in one scan without having to rely on individual bone X-rays,” said ICR’s Nandita deSouza. “We can look on the screen and see straight away where the cancer is and measure how severe it is. The scan is better than blood tests, which don’t tell us in which bones the cancer is located. It also reduces the need for uncomfortable biopsies, which don’t reveal the extent or severity of the disease.”

A metabolic MRI technique has the potential to detect the ischaemic myocardium associated with early-stage heart disease with unprecedented sensitivity, according to a proof-of-concept study by researchers at the University of Philadelphia in Pennsylvania. The researchers used creatine chemical exchange saturation transfer (CrEST) MRI to map deficiencies in the metabolite produced by necrotic myocardium. Unlike other cardiac imaging techniques, CrEST does not need a contrast agent or expose the patient to ionizing radiation (Nature Medicine 20:209).

“Measuring creatine with CrEST is a promising technique that has the potential to improve clinical decision making while treating patients with heart disorders and other diseases, as well as spotting problems sooner,” said senior author Ravinder Reddy.

In clinical practice, ischaemic myocardium can be identified with nuclear medicine stress tests using radiopharmaceuticals, but they expose the patient to ionizing radiation. A second clinical approach, anatomical MRI using a gadolinium contrast agent GdDTPA, can distinguish between healthy and necrotic myocardium, but cannot identify ischaemia in tissue that is still viable.

Creatine maps: healthy myocardium (left) shows noticeably more creatine than infarcted heart tissue (right). Arrow indicates infarcted tissue region.

The technique is also contraindicated in patients with severe kidney disease. Measurements of local changes in metabolism that occur with early-stage heart disease, before myocardium suffers permanent damage, offer an alternative approach.

CrEST works on a standard 3 tesla scanner and exploits the naturally occurring exchange of protons between the amine groups of the creatine and surrounding water molecules, which happens around 1000 times each second. During the scan, the nuclear magnetizations of the amine protons are saturated using a radiofrequency pulse from the MRI scanner specially tuned to their resonant frequency, making their net signal zero. As the protons are exchanged, more saturated protons accumulate in the water, reducing the signal from the water by an amount proportional to the concentration of creatine in the tissue. The CrEST image is formed by subtracting the saturated image from a second non-saturated image and normalizing the difference using the non-saturated image.

The researchers first compared the CrEST against 31P MRS spectroscopy(MRS) using excised samples of partially necrotic myocardium taken from a pig. CrEST was significantly more sensitive, producing MR signals over 70 times greater than MRS measurements on the same samples. In a second study, scans of two healthy pigs in vivo showed uniform distributions of creatine. In two sheep and one pig that had partially necrotic myocardium, CrEST-measured creatine levels were significantly lower in these regions compared to surrounding healthy tissue. Finally, in an analogy of a cardiac stress test, the researchers scanned the calf muscles of three volunteers after exercise. CrEST detected the expected rise and subsequent fall of creatine generated by the muscle activity and the variations were validated by 31P MRS measurements made under identical conditions.

In ongoing work, the researchers plan to demonstrate the differentiation of ischaemic but viable myocardium from necrotic tissue in animal models using CrEST, and are optimizing the technique for the first in vivo cardiac scans in humans. Clinically, Reddy says CrEST could eventually be used for both diagnosis and post-treatment follow-up.

Other potential applications include the diagnosis and further study of other heart pathology, including cardiac hypertrophy and neurological conditions associated with creatine deficiency.

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A close look at neural activity

A PET insert that enables simultaneous PET/MRI scans overcomes previous hurdles relating to the combined use of PET and functional MRI (fMRI) to analyze brain function. The insert enables the combination of images from both modalities, allowing researchers to directly compare PET and fMRI measurements showing the brain during activation and at rest (Nature Medicine 19 1184).

The feasibility of combined PET/MRI in small animals and humans has been previously demonstrated. However, the technique has not been used before to compare brain function between these two modalities by acquiring highly spatially and temporally correlated multiparametric data, according to the study authors.

The researchers, from the Werner Siemens Imaging Center at the Eberhard Karls University Tübingen in Germany, have begun to use simultaneous PET/MRI to explore functional processes in the brains of laboratory rats. Bernd Pichler, chair of the centre’s Department of Preclinical Imaging and Radiopharmacy is overseeing the project, with lead author and post-doctoral researcher Hans Wehrle. The PET insert tool was developed and built at the University of Tübingen.

Functional MRI uses blood oxygen level-dependent (BOLD) contrasts and allows researchers to depict changes in blood oxygenation that are associated with brain function. The BOLD effect displays the complex interactions of blood oxygenation and cerebral metabolic rate of oxygen (CMRO₂), cerebral blood flow (CBF) and changes in cerebral blood volume (CBV).

PET imaging, meanwhile, can help explain the metabolic basis of the fMRI signal and provide complementary information. The PET tracer can quantify changes in brain activity that are reflected by increases and decreases in the cerebral metabolic rate of glucose, as well as the baseline brain activity resulting from excitatory synaptic activity and metabolic plasticity.

The researchers explained that simultaneous [¹⁸F]FDG-PET and BOLD-fMRI acquisitions allowed the study of neuronal activity using both PET, which provided glucose-metabolic level data over a period of minutes using a sustained stimulus, and fMRI, which provided vascular-level data and information about oxygen metabolism in a few seconds using block-design stimulus. The stimulus consisted of stimulating the whisker pads of eight laboratory rats. When the researchers stimulated a whisker pad in 30 s time blocks, BOLD-fMRI images showed that the contralateral whisker barrel field of the brain was strongly activated.

They also observed strong BOLD activation in several other areas of the brain. The PET stimulus was permanently applied for 45 minutes. The data acquired during this time revealed several additional activated areas that were not seen on the BOLD-fMRI images, and which are known to be involved in pain processing, emotion and attention. In total, the fMRI images identified a total of nine known neural networks. The PET images identified seven glucose metabolism-related networks.

In certain brain regions, the researchers identified mismatches between glucose metabolism-related brain activation measured with PET and oxygenation-related signals measured with MRI. They attributed this to the fact that PET and fMRI methods are sensitive to different components of the metabolic-haemodynamic coupling. They suggested that further PET/MRI studies using the capability to observe multiple metabolic scales could help clarify these issues.

“PET/MRI is an excellent tool that can be used to explore and potentially help to explain the enigmatic nature of the BOLD signal in activated and resting states. Our study clearly shows that an interplay between multiple techniques and disciplines is needed to further enhance knowledge about how the brain works,” the authors concluded.

Sodium MRI aids breast imaging

Investigators from Brigham Young University and the University of Utah have created a breast cancer screening device based on sodium MRI, which acquires MR data from sodium nuclei (rather than the hydrogen nuclei used in the vast majority of MR images). As sodium concentrations are thought to increase in malignant tumours, the method could potentially improve assessment of breast lesions and reduce false positives.

The team developed a novel composite array comprising a 7-channel sodium receive array, a large sodium transmit coil, and a 4-channel proton transceive array for combined proton/sodium 3T breast MRI (Magn. Reson. Med. doi: 10.1002/mrm.24860).

The device produced images with up to five times better signal-to-noise ratio than previous sodium imaging efforts. High-quality images were obtained in 20 minutes, suggesting that sodium MRI breast scans could be implemented clinically. “The images we’re obtaining show a substantial improvement over anything that we’ve seen using this particular MRI technique for breast cancer imaging,” said senior author Neal Bangerter. “We believe this can aid in early breast cancer detection and characterization while also improving cancer treatment and monitoring.”

The team’s goal is to produce a device capable of obtaining both sodium and proton images without repositioning the patient.
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Streamline your planning process!
First patient treated with DMLC tracking

A dynamic multileaf collimator has been used to track a moving tumour with a therapeutic X-ray beam for the first time in Sydney, Australia.

Last November, Tony Saunders, a 76-year-old prostate-cancer patient from the city received radiotherapy using the adaptive technology that corrects for tumour motion during treatment. His treatment at Royal North Shore Hospital is part of a clinical trial supported by Varian Medical Systems that will quantify the dosimetric and clinical benefits of DMLC tracking over conventional non-tracking treatments.

“This trial is the first clinical implementation of MLC tracking, and with Calypso guidance represents the most accurate and precise treatment of prostate cancer,” said Paul Keall, director of the Radiation Physics Laboratory at the University of Sydney, who started to develop the technique in 1999 while an assistant professor at Virginia Commonwealth University in Richmond.

“It does feel really wonderful to see the technology that so many people have worked so hard on for so long come to fruition and be realised in a patient treatment,” said Keall.

Implemented on a Varian Trilogy linear accelerator at the Northern Sydney Cancer Centre, the technique adapts the treatment aperture to track the moving tumour during treatment. Real-time data on the tumour location is provided by the Calypso 4D localization system that uses electromagnetic transponders implanted in the prostate. Unlike other previously implemented tumour tracking approaches, DMLC tracking does not rely on a surrogate for tumour motion, such as the patient’s external contour, and therefore also does not require a correlation model to relate tumour and surrogate motion.

How to view the treatment beam

Air scintillation—the weak emission of light due to excitation of nitrogen gas by ionizing radiation—has previously been used to study cosmic ray showers entering the atmosphere and as a means to count alpha emitters. Previously, however, the technique has not been considered in the context of clinical radiotherapy.

Now, researchers from Stanford University School of Medicine have assessed whether air scintillation produced during radiotherapy can be visualized and used to monitor the treatment beam. They found that an electron-multiplication CCD camera could successfully image air scintillation induced by megavoltage electron beams and kilovoltage X-ray beams (Med. Phys. 41 010702).

“We believe that air scintillation imaging gives us a unique opportunity to look at patient radiation treatment over many fractions, without any disruption in clinical workflow,” said lead author Guillem Pratx told medicalphysicsweb.

“We often assume that treatment machines always deliver the exact same radiation dose during fractionated treatment as measured during QA; with air scintillation, we have a non-intrusive way of verifying this assumption.”

“The main application we envision is beam monitoring during treatment. We think that there would be an advantage in having a camera in the treatment room that monitors radiation delivery in real-time. This could be used to document every treatment fraction, or to discover hardware malfunctions and other errors before they can lead to patient harm.”

Pratx and colleagues first investigated air scintillation produced by a 50 kVp/30 mA X-ray beam. They prepared the room by eliminating background light sources and placed the camera 3.4 m from the source. Images showing the conical shape of the X-ray beam could be produced with an exposure time of just 10 s. The intensity of the air scintillation—which is produced mostly in the 300–430 nm range—decreased with distance from the source as the beam diverged.

Next, the researchers imaged a megavoltage electron beam inside a linac vault. Here, they could not remove all sources of ambient light and instead used a short-pass filter to block photons above 440 nm.

The positional data are fed into the DMLC tracking software and used to translate the treatment aperture according to the tumour motion. An updated set of leaf positions are then calculated, within system constraints, to deliver the new aperture. The modified leaf sequences are passed to the DMLC controller for actuation, adapting the treatment aperture within 220 ms of detecting a change in tumour position. Future versions will adapt to tumour rotation and deformation.

The trial is the next step in the development of the technology that has previously been tested with clinical treatment plans delivered to a moving phantom and in vivo in pigs. Thirty prostate-cancer patients will receive 40 fractions of volumetric-modulated arc therapy (VMAT) using the tracking technology. Data collection is estimated to finish by mid-2013.

The recorded motions of the tumour and the DMLC will be used to reconstruct the delivered dose distributions, as well as the distribution that would have been delivered had DMLC tracking not been used. A comparison of the two, along with the original treatment plan, will enable improvements in tumour coverage and bladder and rectum sparing to be quantified.

“We hypothesise that Calypso-guided MLC tracking will reduce tumour underdose and associated normal tissue overdose from 30%–33%, in some cases, to less than 3% in all cases,” Keall told medicalphysicsweb.

Keall and his co-workers plan to publish preliminary results after the accrual of data from the first 10 patients. Beyond the trial, they hope to exploit the accuracy of the technique to provide stereotactic body radiotherapy for prostate patients moving in time, combining treatment courses from 40 fractions down to five. They also plan to apply the technique to other tumour sites in the abdomen and thorax where more extreme intrafraction motion occurs, including the lungs and pancreas.
**Tabletop source eyes microbeam therapy**

Microbeam radiation therapy (MRT), in which a tumour is irradiated with an array of high-dose, microscopically thin X-ray beams, shows great promise for brain tumour treatments. Studies in animal models demonstrate that MRT can selectively eradicate tumour cells while sparing normal tissue. However, the technique’s current reliance on a synchrotron radiation source is a major roadblock for potential clinical translation.

In a quest for an alternative X-ray source for microbeam radiation, researchers from the University of North Carolina (UNC) at Chapel Hill have developed a tabletop MRT system based on a carbon nanotube (CNT) field emission source array technology (invented in the laboratory of Jianping Lu and Otto Zhou at UNC and commercialized by startup XInRay Systems). Using a hybrid approach that integrates image-guidable beam delivery, they have determined the microbeam targeting accuracy in mice bearing small brain tumours (Phys. Med. Biol. 59 1283). “Instead of a single small focal spot, a distributed CNT X-ray source array spreads the thermal power over a long narrow focal line on the anode. It’s equivalent to having a large number of high-power X-ray tubes irradiating the target at the same time,” explained first author Lei Zhang. “In this way, a CNT field emission cathode can generate higher microbeam flux than conventional X-ray tubes.”

The prototype MRT system includes the CNT-based irradiator and a high-resolution CNT-based micro-CT scanner, also developed by the team. The irradiator comprises a linear CNT field emission cathode array, an electrostatic focusing lens and a tungsten anode. For this study, the X-rays were collimated into a 280 μm wide microbeam.

Zhang and colleagues studied 14 tumour-bearing mice. To identify the tumour location with respect to the microbeam position, they proposed an image guidance protocol based on registration of X-ray images with MR images. One day before treatment, the mice were imaged with a 9.4 T MR scanner. The 2D shape, size and location of the tumour were clearly visualized in the MR image and the average tumour size was 1.4 ± 2.2 mm.

On the day of irradiation, the mice were anaesthetized and immobilized in customized holders using hardware including two ear bars. Two-dimensional X-ray projections recorded by the on-board micro-CNT scanner showed bone structures such as the skull, jaw and spinal cord, as well as the ear bars. These images were scaled, aligned manually with the sagittal MR images and used to calculate the distance from the tumour centre to the ear bars.

The researchers irradiated the first two mice with a single microbeam of 138 Gy entrance dose. The second pair was irradiated with two parallel microbeams with centre-to-centre distance of 900 μm and an entrance dose of 108 Gy per beam. The remaining mice were irradiated by three microbeams, with a 900 μm pitch, delivering 48 Gy each. The average dose rate at the mouse head entrance plane was 1.16 Gy/min.

To verify beam delivery, the researchers placed Gafchromic films at the entrance and exit planes of the mouse head during irradiation. Selected films were scanned and analysed to create dose profiles, which were then compared with the prescribed treatment plans.

An example analysis of films from a mouse treated with three microbeams showed an entrance beam width of 280 μm, consistent with tube calibration results. The measured peak dose of each beam was also consistent with the prescribed value. The second-generation CNT-MRT system can generate microbeams with the necessary energy, beam width and PVDR to produce similar therapeutic effects to those seen in synchrotron MRT studies. The researchers have now managed to measure the Cerenkov radiation emitted during radiotherapy, as the radiation penetrates the tissue, and is in most cases proportional to the dose. The trick is to see it above the ambient light, which is why Pogue and colleagues are working on to human clinical trials with the system becomes established and more widely used, it will likely lead to other innovations in radiation therapy delivery, because no one has ever been able to image radiation delivery before with real time visualization of the deposited dose and the mapping to the patient anatomy,” he says.

With the animal tests already successful, the researchers are moving on to human clinical trials with 12 subjects. They expect the trial to finish early next year, and will decide then what the next stage will be. “The unique part about this system is it could be implemented with essentially no extra work, because it is simply imaging of the patient during their normal treatment,” commented Pogue. “The cameras would need to be permanently positioned in the room, but this is already done for video imaging of the microbeam path, and we are monitoring for breathing movement.”

**Cerenkov light emission tracks radiotherapy dose**

Scientists in the US have demonstrated that Cerenkov light emitted during radiation therapy on a live animal can reveal the radiation dose being administered. The technique could enable doctors to make sure that the correct radiation doses are administered to humans undergoing radiation therapy. (J. Biomed. Opt. 18 110504).

It is important to carefully regulate the amount of radiation that a patient receives when undergoing radiation therapy, to minimize the risk of side effects. Unfortunately, knowing exactly how much radiation the body is healthy, normally, treatment is planned according to computer simulations of the body, generated with CT scans. One or two times during a treatment course, a patient can also have a detector inserted into them to estimate the amount of incident radiation. But these methods aren’t foolproof; a patient could dose weight, for instance, leading to a relatively high dose.

One new approach to measuring radiation dose is to make use of Cerenkov radiation, which is emitted when electrons and other charged particles travel through a dielectric medium faster than light would travel. Cerenkov radiation is poten-tially visible as flashes of light during radiation therapy, as the radiation penetrates the tissue, and is in most cases proportional to the dose. The trick is to see it above the ambient light, which is why Pogue and colleagues are working on to human clinical trials with the system becomes established and more widely used, it will likely lead to other innovations in radiation therapy delivery, because no one has ever been able to image radiation delivery before with real time visualization of the deposited dose and the mapping to the patient anatomy,” he says.

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The impact of cell signalling

Cell response to ionizing radiation depends not only on physical parameters such as dose, but also on biological and genetic factors. Recent research has revealed intercellular signalling to be one such factor that makes a significant contribution to cell killing in vitro, both in irradiated cells and their non-irradiated neighbours. Based on in vitro data, researchers in Northern Ireland have developed a model that incorporates this effect and used it to assess the radiobiological impact of intercellular signalling on clinical radiotherapy plans (Int. J. Radiat. Oncol. Biol. Phys. 87 1148).

“One common argument brought up against the data from the in vitro signalling experiments is that they’re so different to what’s normally assumed clinically that they can’t possibly translate into a clinical setting,” said Stephen McMahon, first author and physicist at the Centre for Cancer Research and Cell Biology at Queen’s University Belfast. “As far as we could see nobody had actually modelled that, which was part of the motivation for doing our work.”

Intercellular signalling, or bystander effects, occur when irradiated cells secrete a signalling molecule that diffuses through the surrounding tissue to activate, initiating damage in neighbouring cells. The group noticed the phenomenon when they observed deaths in cells that could not solely be attributed to the dose they had received. “[Potential implications] include an effective broadening of beams, which may reduce the benefit of extremely tight dose conformity, initiating damage in neighbouring cells,” they wrote. “The group noticed the phenomenon when they observed deaths in cells that could not solely be attributed to the dose they had received.”

The model assumes cell damage occurs from direct “hits” of radiation and indirectly from signal propagation between irradiated cells and their neighbours. A simplified version of the phenomenon, it also assumes homogeneous diffusion of cellular signals as a starting point for investigation. The diffusion function is a function of $\lambda$, a constant that describes the exponential decay in signal strength following irradiation and $R$, the spatial range of the signal.

The model was applied to calculate the survival of a population of human fibroblast cells in 3D conformal, intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) plans in 10 prostate cancer patients. Physical dose distributions were compared with distributions adjusted to the uniform physical dose required to produce the same cell death as when signalling effects were accounted for. A value for $\lambda$ was derived from in vitro measurements and a range of biologically feasible values were chosen for $R$.

Signalling had the greatest impact on tissue outside of the treatment fields. Contributions from nearby in-field tissue resulted in greater cell killing and signalling-adjusted doses. For example, in the IMRT plans, the physical median mean bladder dose over the 10 patients was 23.5 Gy, compared to 33.4 Gy when signalling was accounted for.

The reverse was seen in cells in the treatment beam’s path, though the effect was less marked. In the IMRT plans, the physical mean planning target volume dose of 74.5 Gy compared to a signalling-adjusted dose of 71.3 Gy. Here, a lack of signalling from cells outside the beams meant the model predicted less cell damage compared to the scenario assumed clinically, where damage is independent of the dose received by neighbouring cells.

Nevertheless, adjusting for signalling resulted in no dramatic departures from the physical dose distributions. It also made no significant difference to comparisons of the different treatment techniques, leading the researchers to conclude that the in vitro observations on which the model is based can be reconciled with clinical experience.

“I, for example, had predicted massive treatment failures in IMRT compared to 3DCRT that would have suggested something was wrong with the model as we know that’s not the case clinically,” said McMahon.

Fortunately, everything has come out looking fairly sensible thus far, suggesting that this is an area worth more investigation.”

Future work by the researchers will include comparisons of model predictions with clinical data, in vitro testing and further in vitro investigations.

Plan incorporates tumour shrinkage

Radiation doses delivered to lung tumours may be efficiently escalated over a course of radiotherapy using a method that predicts tumour shrinkage, according to a preliminary planning study by US researchers. The technique, called robust planning targeting (RPTP), uses a geometric model and is significantly less labour-intensive than existing adaptive approaches that require re-planning treatments mid-course (Int. J. Radiat. Oncol. Biol. Phys. 88(4)).

“In principle, RPTP should work at least as well as adaptive radiotherapy, but with a much reduced workload,” said Perry Zhang, physicist at the Memorial Sloan-Kettering Cancer Centre, New York. Shrinking tumour volumes are commonly observed over the course of radiotherapy in patients with non-small cell lung cancer (NSCLC). Now, predicting tumour regression before the patient sets foot in the treatment bunker may not be restricted to a single treatment plan. “We can usefully take advantage of regression as typically seen in many lung tumours, even though we don’t know the exact form of the regression,” said Zhang.

The researchers developed the shrinkage prediction model based on in vivo tumour data, obtained from one planning CT scan and weekly (GTV$_{orig}$) for patients already treated for NSCLC. The shrinkage of the tumour from the volume observed in the pre-treatment CT scan represented a progressive shrinking of the tumour over the course of radiotherapy in each patient. “This is related to regression and shrinking volume over the course of treatment. Intensity-modulated treatment plans were calculated for planning target volumes (PTV) generated from the GTVs. PTV$_{orig}$ was prescribed a standard clinical dose that increased with each PTV shell, where PTV$_{orig}$ received the maximum dose achievable that restricted doses to surrounding organs-at-risk (OAR) to acceptable levels.”

The dosimetric performance of RPTP was compared with other planning approaches, including adaptive radiotherapy. The researchers found that PTV$_{orig}$ over-lapped with the true PTV (PTV$_{true}$) derived from the GTV on the final CBCT scan by 76.0–88.3%. Averaged over all patients, the RPTP approach delivered the highest dose to PTV$_{true}$ with a moderate improvement seen over the adaptive, replanned approach. RPTP resulted in a mean PTV$_{true}$ dose that was 5.7 Gy higher than the adaptive approach, while the mean PTV$_{true}$ was 0.4 Gy higher.

There were no significant differences in doses to the lungs and spinal cord between RPTP and the three other planning approaches.
A simpler way to image with protons

Proton radiography and proton CT employ high-energy proton beams to create planar or tomographic images of patients. Using protons rather than X-rays to image a patient enables more accurate treatment planning calculations. But the cost and technical complexity of traditional proton detection systems currently limit their clinical use.

"Conventional proton radiography based on individual tracking of protons requires fast data-acquisition systems in order to acquire radiographies in a tolerable time," explained Mauro Testa, from Massachusetts General Hospital and Harvard University Medical School.

To address these limitations, Testa and colleagues propose a new proton radiography technique based on time-resolved dose measurements. The method requires only a 2D dosimeter array and the clinical proton beam. What’s more, it can create a radiographic image in about 100 ms, using a dose of just 0.7 cGy. The team has performed a proof-of-principle study using a prototype diode-array dosimeter (Phys. Med. Biol. 58 R215).

Proton therapy delivered via parallel opposed proton beams is used to provide hadron therapy to specific tumour sites (or target volumes). A simpler way to image with protons is created by traversing the patient with an adjustable wheel. The first Bragg peak (near the maximum dose) and the last Bragg peak (near the zero dose) are used to define the dose region of interest. Time-dose measurements can be acquired using a fast CCD camera, Testa told medicaledphysicsweb. "This detector allows a sampling time of 2 ms," said Testa.

One important potential application of proton radiography is pre-treatment range verification, using a low dose "scout-beam" to image the patient in the treatment position. Comparing measured WEPL values to those computed by the treatment planning system could improve calculation of the exact beam range needed to cover the target volume. When treating medulloblastoma patients, for example, this could significantly reduce the skin dose.

With this in mind, the researchers compared proton radiography of a human skull with conventional X-ray imaging. The lower resolution seen for the proton radiography was partly due to the inherent multiple Coulomb scattering of protons in the patient, which leads to image blurring. However, the detector spatial resolution played a key role, with sub-millimetre resolution easily achievable with a commercial X-ray panel, but limited by the diode pitch in the proton detector.

The team also examined the potential of real-time imaging of a Lucite cube moving with 1D and 2D sinusoidal motion, creating movies using a single radiographic image for each frame. For both movies, the cube’s trajectory were distinctly recognizable, with the centre of the cube and the motion table position within millimetre agreement.

Proton CT (pCT) is particularly advantageous for treatment planning as it removes the need to convert X-ray Hounsfield units into relative dosimetry. Using pCT makes it advantageous for treatment planning, as it reduces the skin dose.

Testa and colleagues performed pCT on a cylindrical Lucite phantom containing various rod inserts. They recorded radiographic projections at angles from 0 to 178°, using interleaved measurements to increase spatial resolution. Reconstructed pCT images clearly showed the lung, air and bone inserts. The RSP value for Lucite obtained from the images was close to the actual value, while RSP values calculated for the inserts were somewhat biased towards to that of Lucite. The accuracy of the obtained RSP values was impacted by the detector’s limited spatial resolution. A full-scale detector with higher spatial and temporal resolution should increase calculation accuracy, as would accounting for multiple Coulomb scattering in the reconstruction algorithms.

“We are currently working on a new detector design that utilizes a scintillating screen coupled with a fast CCD camera,” Testa told medicaledphysicsweb. “This detector allows sub-millimetre spatial resolution and a sampling time of 0.1–1 ms. We plan to use it to acquire higher resolution CT images and to perform an end-to-end validation study of the range tuning method for medulloblastoma cranial fields.”
Proton rescanning: which works best?

Active spot scanning is the delivery method of choice for most new particle therapy facilities. Treating mobile targets with spot scanning, however, is limited by interplay effects between tumour and beam motion, which lead to target dose inhomogeneities. One way to mitigate such effects is to use rescanning – either volumetric scanning, where dose is delivered across a series of full-volume rescans, or layered rescanning, which delivers all scans in one energy plane before moving to the next.

To compare the two schemes, researchers from ETH Zurich and the Paul Scherrer Institute (PSI) in Switzerland have performed a detailed simulation study modelling the interplay effects for a range of system and beam delivery scenarios. In particular, they examined the impact of the beam position adjustment time (BPAT), the speed at which a particular delivery system can move the beam from one spot to the next (Phys. Med. Biol. 58 7905).

"Active scanning is particularly sensitive to organ motion, and has thus been used sparingly up to now to treat mobile tumours," said ETH's Kinga Bernatowicz. "Rescanning is one promising motion mitigation technique, and in this study we investigated its effectiveness for different delivery scenarios under the assumption of different delivery speeds and characteristics typical of currently available commercial systems."

Bernatowicz and colleagues performed 4D dose calculations for two clinical liver cases, with large and small tumour volumes, simulated for up to seven rescans. For each case, they simulated four BPAT scenarios. Motion was simulated with a typical breathing period of 5s. They assessed the resulting plans to determine the impact of rescanning on treatment delivery time and dose homogeneity. The researchers focused first on single-field plans. They examined four BPAT scenarios: two with a fast lateral BPAT of 4 ms, and depth (energy) BPATs of 80 ms and 1 s (scenarios 1 and 2, respectively); and two with a slower lateral BPAT of 10 ms and energy BPATs of 80 ms and 1 s (scenarios 3 and 4, respectively).

For systems with fast energy BPATs, dose homogeneity improved as the number of rescans increased. No significant difference in performance was seen between the two rescanning methods, although layered rescanning showed a higher dependence on the selected phase. For both patients, layered rescanning led to a smoother change in dose homogeneity with increasing rescan number, whilst volumetric rescanning showed more fluctuations.

For scenario 2 (fast lateral changes and slow energy changes), results were similar to those described above. However, if both BPAT values were slow (scenario 4), clear differences in the two scanning methods appeared: layered rescanning performed best after 2–4 rescans, while for a higher number of rescans, both methods gave similar results.

For scenarios with fast energy changes, layered and volumetric rescanning required similar treatment delivery times to achieve satisfactory dose homogeneity. For systems with longer energy adjustment times, however, layered rescanning achieved dose homogeneity in a noticeably shorter treatment time.

"Our study indicates that using multiple SFUD [single-field uniform dose] plans per field leads to a similar improvement in dose homogeneity as rescanning, and that smaller amounts of rescanning per field are necessary when using multiple field plans," Bernatowicz explained. The team is now working on experimental validation of the simulated results.

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LET painting improves outcome

Heavy ion therapy produces high-linear-energy-transfer (LET) Bragg peaks that offer one way to tackle hypoxic – or oxygen deficient – tumours that respond poorly to radiotherapy. However, if delivered across an entire tumour, high LET can also result in the excessive exposure of adjacent healthy tissue and unacceptable side-effects.

Instead, researchers in Denmark and Germany are investigating the targeted approach of LET-painting, where high-LET radiation is steered into the hypoxic portion of a tumour only. In an initial modelling study, they predict superior tumour control compared to the current clinical standard of non-painted treatments that assume normoxic – or oxygenated – tumour composition (Acta Oncol $53$ 21).

‘LET-painting could quite dramatically increase tumour control, without increasing the side effects that are normally associated with high-LET radiation,’ said Niels Bassler, first author and physicist at Aarhus University.

The researchers compared the tumour control probabilities (TCP) calculated for LET-painted and non-painted carbon-12 and oxygen-16 treatment plans in a patient who had already been treated for oropharyngeal cancer.

Non-painted plans mimicked existing clinical approaches, using two coincident pairs of opposed, scanned beams, each delivering a spread out Bragg peak (SOBP) that gave a uniform dose and largely uniform dose-averaged LET across the entire tumour volume. TCPs for these plans were calculated for two scenarios: the first assumed a normoxic tumour, as is the current practice in centres delivering carbon-12 treatments, while the second took tumour hypoxia and the associated radioreistance into account.

Painted plans were calculated for a range of hypoxic volume sizes up to 10 cm$^3$, centred on a hypoxic volume identified in the patient’s tumour. The plans that were delineated using F-18 fluoroazomycin arabinoside (FAZA) PET imaging. The same field arrangement was used as in the non-painted plans, but the parts of each field incident on the hypoxic volume were ramped, the SOBPs delivering 100% of the dose at the proximal edge of the volume and 0% dose at the distal edge.

The opposed ramped fields elevated dose-averaged LET across the hypoxic volume compared to the surrounding non-hypoxic tumour. Total energy fluence was fixed across all the plans, pinning the value that gave a TCP of 95% in the clinical planning standard of the non-painted plans that assumed a normoxic tumour. This ensured fair comparisons of the painted and non-painted approaches.

LET painting proved feasible, demonstrating consistently superior TCP values to the clinical reality of a non-painted plan delivered to a hypoxic tumour; this returned a TCP of 0%. However, this advantage dropped off sharply as hypoxic volume increased, with TCPs of the order of 50% or more only observed in volumes less than 1 cm$^3$ in the oxygen-16 plans and less than 0.5 cm$^3$ in the carbon-12 plans.

The trend arises from the different contributions of the plateau and the entrance window and a spherically focused 10 MHz acoustical transducer.

For clinical application, Parodi and colleagues are aiming to develop an ionoacoustic imaging system with a penetration depth of more than 10 mm and sub-millimetre resolution. Ultimately, they hope to combine anatomic ultrasound imaging prior (or even in parallel) to treat with ionoacoustic imaging of the Bragg peak during ion beam therapy.

To test the potential of this approach, the LMU team performed proton beam experiments at the Maier-Leibnitz-Laboratory’s Tandem accelerator. They used 20 MeV protons to irradiate a water phantom with pulsed beams of varying pulse length (1.5 ns – 4 µs). The ensuing acoustic signals were detected using a 3.5 MHz, cylindrically focussed ultrasound transducer and a spherically focussed 10 MHz transducer.

For beam intensities above 10$^4$ protons/pulse, a clear acoustic signal could be acquired. The signal showed three spikes, attributed to the Bragg peak, the entrance window and a reflection. The distance between the first and second of these spikes is proportional to the ion beam penetration depth and can be used to assess beam range. The measured range resolution agreed with that seen in simulations. “Sub-millimetre resolution of the Bragg peak position seems to be possible, quantification is ongoing,” said Parodi.

Very recently, the LMU team has begun to investigate ionoacoustic tomography, using a 64-channel ultrasound transducer array. Parodi noted that the team has now recorded its first 3D images. She concluded that ionoacoustic detection offers a direct way to observe the energy range of the ions in tissue, with the potential for 2D and 3D imaging with sub-millimetre range resolution. The minimum detectable signal was so far found to be 10$^4$ protons/pulse, representing a 10$^{-2}$ eV energy threshold.

The next steps will involve testing the ionoacoustic effect using more realistic targets and higher-energy ion beams from conventional and novel high-dose-rate sources, as well as simulating the entire imaging process and exploring the technique’s applicability to various clinical treatment sites.
CERN unifies medical physics research

CERN has transferred a great deal of technology into the field of medical physics over the years, from adaptation of its high-energy particle detectors for PET scanning to the design and development of dedicated accelerators for particle therapy. Now, CERN is consolidating all of its diverse activities in the medical physics arena, with the creation of a new office for medical applications. “Since the start of this year, we are trying to combine all of our research on medical applications at CERN into one coordinating office,” explained CERN’s Director-General Rolf Heuer, speaking at the recent ICTR-PHE meeting in Geneva, Switzerland.

Heading up the office for medical applications is Steve Myers, formerly CERN’s director of accelerators and technology. Myers’ first task in his new role was to set up a brainstorming workshop to help guide the direction of the fledgling programme. The workshop, which took place immediately after the ICTR-PHE meeting, saw around 80 leading experts from around the globe come together to discuss matters such as accelerators and gantries, clinical perspectives, biomedical research and radioisotope production, detectors and dosimetry, and the application of large-scale computing.

One of the first projects that Myers will oversee is the transformation of CERN’s Low Energy Ion Ring (LEIR) into a biomedical facility. LEIR is a small accelerator currently used to pre-accelerate lead ions for injection into the Large Hadron Collider (LHC). But it only does this for several weeks each year, leaving a lot of spare beam time. Importantly, the ring also has an energy range that matches that of medical accelerators (440 MeV/u for carbon ions). CERN has now confirmed that LEIR can be converted into a dedicated facility for biomedical research. This “BioLEIR” facility will provide particle beams of different types at various energies for use by external researchers.

Myers explained the rationale for developing such a facility. He pointed out that although protons and carbon ions are already in extensive clinical use for treating tumours, and other species such as oxygen and helium ions are under investigation, there’s still a lack of controlled experiments that directly compare the effect of different ions on cancer cells under identical conditions. “The big advantage here is that we don’t treat patients,” he said. “Our aim is to provide a service, so researchers don’t have to do experiments at a clinical site, they can come here instead.”

As well as radiobiology experiments, LEIR is lined up for use in detector development, dosimetry studies and basic physics investigations such as ion beam fragmentation. The facility would work in the same way as particle physics experiments are carried out at CERN: researchers propose experiments, which are peer reviewed by a panel of experts who select suitable projects, and CERN controls the beam time allocation.

Before this can happen, however, LEIR needs some hardware modifications. CERN researcher Adrian Garonna presented a status update on the ongoing design studies. He emphasized that LEIR will continue to be used as a lead ion accumulator for the LHC and other heavy ion experiments. The challenge, therefore, is to redesign LEIR for biomedical experiments, using the simplest and most cost-effective configuration, but while maintaining its current operational performance for the LHC.

Firstly, Garonna told the ICTR-PHE delegates, the current front-end is tailored for use with heavy ion sources and requires at least three weeks to swap between heavy and light ions. What’s needed is a dedicated front-end, comprising a light ion source and a radiofrequency quadrupole (RFQ) optimized for light ions, that will offer fast switching between species. The beams will be injected into and accelerated in LEIR up to a kinetic energy of 440 MeV/u for carbon ions. Garonna and colleagues have identified a suitable commercial light ion source (the supernanogon electron cyclotron resonance source) that can provide hydrogen, helium, carbon, nitrogen, oxygen and neon ions.

The next task is modification of the extraction system, which is currently designed to transfer high-brightness, 200 ns pulses to the Proton Synchrotron. Here, the goal is to create a dedicated resonant extraction system that delivers long spills (1–10 s) with uniform intensity for biomedical experiments. Such a slow extraction scheme could be implemented using minimal new hardware, explained Garonna, by installing an electrostatic septum and two magnetic septa. The CERN team has also demonstrated the feasibility of two potential resonance driving mechanisms: quadrupole driven extraction, which is easy to implement; and RF knock-out, which delivers better beam quality but requires installation of new hardware.

Finally, Garonna detailed a first proposal for two experimental beamlines for LEIR: a horizontal beamline running at up to the maximum energy (440 MeV/u) and a vertical beamline with a reduced energy of up to 75 MeV/u. The adjacent hall next to the ring, currently used for storage, will also need to be fitted out as an experimental area suitable for various biomedical experiments. The total cost of the infrastructure developments will likely come in at around €15 million. And while CERN has provided seed funding for this project, the majority of the money needs to be sourced from elsewhere. So when can we expect to see the BioLEIR facility opening its doors to the international research community? Myers predicts that the full funding should be sourced during this year. Once this is achieved, the site could be up and running roughly two years later.

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Gelatin phantoms calibrate PET

Accurate volume estimation is imperative when using PET for tumour staging and treatment planning. Currently, PET systems are calibrated using phantoms made from hollow spheres filled with radioactive liquids. But the presence of a non-radioactive wall at the edge of such a sphere can cause inaccuracies. Instead, researchers in Sweden suggest that a wall-less gelatin phantom will improve PET activity quantification and volume delineation (Phys. Med. Biol. 59 1097).

Previous studies on PET quantification phantoms have shown that the presence of a non-active wall decreases the lesion-to-background contrast. This creates inaccuracies in quantification, particularly when imaging a small sphere where the wall represents a large portion of its overall volume. The presence of cold walls has also been shown to affect the measured standard uptake values, which reduce as wall thickness increases.

To address these shortcomings, Marie Sydoff and colleagues at Lund University’s Department of Medical Radiation Physics in Malmö have developed a simple method for creating radiomide-doped gelatin phantoms without non-active walls. To compare these with conventional phantoms, they used a Jaszczak phantom containing three hollow spheres filled with radio-isotopes (with diameters of 15.6, 22.5 and 27.9 mm) and then frozen to create solid phantoms. The other half of the solution and water to the other half. The gelatin solution was heated, poured into spherical aluminium moulds (with diameters of 15.6, 22.5 and 27.9 mm) and then frozen to create solid spheres. The other half of the solution was used to fill the hollow plastic spheres. Finally, all six spheres were mounted in the Jaszczak phantom.

The researchers dissolved $^{18}$F-FDG in water to an activity concentration of approximately 80 kBq/ml, simulating a clinical situation. They added gelatin granules to half of the solution and water to the other half. The gelatin solution was heated, poured into spherical aluminium moulds (with diameters of 15.6, 22.5 and 27.9 mm) and then frozen to create solid spheres. The other half of the solution was used to fill the hollow plastic spheres. Finally, all six spheres were mounted in the Jaszczak phantom.

The spheres were imaged with a Gemini TF PET/CT system (from Philips Healthcare) using a matrix size of 144 x 144, a voxel size of 4 x 4 x 4 mm, and a scan time of 8 min/bed position. Measurements were made with the spheres surrounded by water (zero background), and with background fractions of 0.08, 0.1, 0.13 and 0.2.

After PET image reconstruction and attenuation correction, the data were processed to calculate the background-corrected relative threshold $T_{rel}$ for all of the spheres. $T_{rel}$ provides an intensity threshold with which to delineate the volumetric edges of a tumour or spherical phantom. For the largest spheres and the lowest background fraction (0.08), $T_{rel}$ was lower for the hollow plastic sphere (99.7%) than for the gelatin sphere (41.4%). With the highest background (0.2), $T_{rel}$ was 33.7% for the large plastic sphere and 41.1% for the large gelatin sphere.

The researchers plotted $T_{rel}$ as a function of the five background fractions. With zero background activity, the $T_{rel}$ values for the gelatin and hollow spheres were practically the same. As the background activity increased, however, $T_{rel}$ for all of the hollow spheres decreased while $T_{rel}$ for the gelatin spheres remained practically constant.

“When we used the $T_{rel}$ values for volume calculations, the values obtained from the hollow spheres showed increasing overestimation of volume with increasing background activity levels,” explained Sydoff. “This makes the $T_{rel}$ values for the gelatin spheres more accurate for structures in an active background, which is always the case in patient measurements.”

The authors conclude that threshold values estimated using spheres with non-active walls should not be used for tumour delineation in patients, especially for small volumes within a high-activity background. With the gelatin spheres, however, the background corrected threshold method can be employed to define tumour volume from PET images.

The researchers now plan to study the effects of plastic walls in micro-PET systems, where phantom walls are a much bigger problem, since the volumes are far smaller. “I am also looking at the possibilities of using this method of volume estimation on structures other than spheres, to be able to implement it in real patient measurements such as within oncology, for example,” said Sydoff.

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Performing PET functional measurements in very small animals can be difficult, due to the limited blood volume that can be sampled and rapid changes in blood radioactivity after the radiotracer is injected. To overcome this process, Japanese researchers have developed the CD Well, which uses microtiter-sized sample volumes to measure whole blood and plasma for dynamic PET studies in mice and rats. The goal was to develop a system that measures time-activity curves for arterial whole blood (wTAC) and plasma (pTAC) separately (Phys. Med. Biol. 58 7889).

A quantitative PET study requires concurrent acquisition of pTAC and wTAC data to estimate the behaviour of dose to certain tumour subvolumes in target tissue using compartment model analysis. For a small rodent, the volume per sample for TAC analysis is limited to 4 or 5 µl. This is considerably less than the volume of samples needed for metabolite analysis and pTAC and wTAC measurements, and the restriction that no more than 10% of the animal’s total blood volume should be sampled to prevent adverse physiological effects.

The small volume of these micro-samples is a limiting factor when they are centrifuged to separate plasma from blood cells, and then used to perform volume and radioactivity measurements, according to lead author Yuichi Kimura, a professor at Kinki University. The CD Well overcomes this difficulty because it uses only a minute volume of blood. The apparatus contains 36 U-shaped channels. Each holds a maximum of 4 µl of blood. The hydrophilic-lined channels have tapered inlet openings at each end, one used to sample a drop of blood and the other serving as an air vent. Each channel has a precise, uniform rectangular cross-sectional area of 200 × 500 X 10 µl to radiolabel a volume of sampled blood to be obtained from the length of the sample in the channel.

The small size of the CD Well enabled it to be placed next to a rodent during the blood sampling. This shortens the catheter length, reducing distortion of the TAC due to dispersion and minimizing the total volume of blood loss,” the authors wrote. Its size also reduces the delay between the true and measured TAC, as well as distortion of the TAC shape caused by dispersion due to the transit of sampled blood through the catheter; delay and dispersion being the major factors that cause inaccurate TAC.

After serial sampling is completed, the CD Well is centrifuged to separate plasma from blood cells and then scanned with a flatbed scanner to define the regions of plasma and blood cells. The measured length is converted to volume. The apparatus is then exposed to an imaging plate for 20 minutes to measure positions and times of gamma rays from the channels, after which it is scanned by a phosphor imaging plate scanner with a spatial resolutions of 100 µm/pixel and a 16-bit output resolution. The two images are processed with a dedicated software program. The scanned image, which depicts locations of whole blood and plasma, is superimposed on the imaging plate derived image to acquire the radioactivity concentrations in Bq/µl in whole blood and plasma separately.

Kimura and colleagues reported that it is a valid technique. Radioactivity concentration measurements by the CD Well were not significantly different from those obtained by conventional manual methods. The researchers use the CD Well to measure blood volume directly, individual differences in blood specific gravity do not affect the result.

A new take on PET registration

A new way of validating PET imaging and the segmentation of tumour images with histopathological data has been developed by researchers in the US. The technique synthesizes PET images from autoradiography images of excised tumours and could provide a more informed basis for customized PET-guided radiotherapy that selectively boosts dose to certain tumour subvolumes (Radiator. Oncol. doi:10.1016/j.radonc.2013.12.017).

“While the scientific community is excited about PET-guided fully personalized radiotherapy, not everyone is aware of the fact that we are yet to demonstrate spatial correlation between even the most common of PET tracers and any of their assumed identities,” said lead researcher Marian Axente, who carried out the research at Virginia Commonwealth University Medical Centre in Richmond, VA, and now works at Stanford University in California.

A common approach to histopathological PET validation is to register in vivo PET scans of a tumour with histopathological images acquired after its excision. However, registration techniques have limited accuracy because the two images may not align. To solve this problem, the team developed a system that uses the CD Well research system to sample blood from a tumour, and then synchronizes the images of the blood with histopathological sections (Neoplasia 5 586).

When blood is drawn from tumours, a large perfusion defect consistent with myocardial infarction is evident when both modalities were used to image a mouse with a surgically induced myocardial infarction. “MicroSPECT readily identified a large perfusion defect consistent with myocardial infarction involving the cardiac apex and anterolateral left ventricular wall, which could not be seen by microCT,” the authors wrote. MicroSPECT also offered an advantage in imaging myocardial infarction in that both function and radiotracer distribution data could be obtained from a single acquisition without the need for additional specialized contrast agents. Another advantage is its nanomolar sensitivity in detection of molecular probes, with a 10³ greater sensitivity than currently available MR techniques.

The primary disadvantage compared to MRI was the use of ionizing radiation. “While this level of radiation exposure can contribute to effects on cardiac imaging, it could potentially become an issue in cancer studies by affecting the progression of some tumours,” they observed.

The advantages of microSPECT

State-of-the-art microCT and microSPECT scanners can produce images with high enough spatial and temporal resolution to quantitatively evaluate the cardiac function of laboratory mice. According to researchers at Duke University both of these imaging technologies offer advantages over MRI, the “gold standard” for in vivo murine cardiac imaging (Med. Biol. 107 013006).

In a direct comparison study, the researchers also discovered that microSPECT had several advantages over microCT. This finding may be particularly valuable, because the microSPECT scanner utilized is in commercial production, whereas the microCT is unique to the Duke research laboratory. In vivo cardiac imaging of mice is a useful tool for researchers of human cardiac disease and for developers working on new clinical treatments. However, the small size of a mouse’s heart and its rapid heart rate make the acquisition of high-quality images challenging. Duke’s dual-source microCT system produces what lead author Nicolas Befera and colleagues believe is the highest spatial resolution currently available for 3D cardiac microCT imaging. The lab also owns a U-SPECT/CT system from MILabs of the Netherlands that fitted with a 0.35 mm multi-pinhole collimator. The research team combined both systems to acquire images of a mouse with myocardial infarction, as well as six control mice, all of which were anesthetized for the procedures. For the 4D microCT, mice were injected with a liposomal blood pool contrast agent, immediately after which sampling was performed using retrospective cardiorespiratory gating. Image acquisition took up to 5–10 minutes, with a delivered radiation dose of 360 mGy.

MicroSPECT, mice were injected with technetium tetrofosmin, and images acquired. Since the CD Well measures blood volume directly, individual differences in blood specific gravity do not affect the result.

Increased accuracy: first author Marian Axente and colleagues have come up with a new technique for PET image registration.

A new way of validating PET imaging and the segmentation of tumour images with histopathological data has been developed by researchers in the US. The technique synthesizes PET images from autoradiography images of excised tumours and could provide a more informed basis for customized PET-guided radiotherapy that selectively boosts dose to certain tumour subvolumes (Radiator. Oncol. doi:10.1016/j.radonc.2013.12.017).

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