Is proton therapy safe in pregnancy?

Scanned protons treat brain tumours in pregnant women with low risk to the foetus.

About one in a thousand pregnant women are diagnosed with cancer. And while many cancers cannot be treated with radiation during pregnancy, it may be possible for brain tumours due to the relatively large distance to the foetus. Proton therapy offers the advantage of reduced integral dose, but scattered and secondary radiation can still pose a potential risk for the radiosensitive foetus.

To determine the degree of such risks, a US research team has investigated the foetal doses from brain tumour treatments with passive scattering and pencil beam scanning proton therapy (PPT and PBS), and 6 MV 3D conformal photon therapy (3D-CRT). They performed dose evaluations using realistic computational phantoms representing 3-, 6- and 9-month pregnancies, implemented in the Monte Carlo platform TOPAS (Phys. Med. Biol. 61 683).

“Our goal was to see whether there would be less of a concern with respect to the foetal dose from proton therapy compared with conventional photon therapy, when treating pregnant patients,” explained Changran Geng from Rensselaer Polytechnic Institute, and Nanjing University of Aeronautics and Astronautics. “The focus was on brain tumours, because tumours closer to the foetus would most likely not be treated with radiation.”

Foetal dose calculations

Geng and colleagues – also from Rensselaer Polytechnic Institute, University of California at San Francisco and Harvard Medical School – simulated a 6.5 × 6.5 × 4.5 cm brain tumour treated with a prescribed dose of 52.2 Gy (RBE). The phantoms (a pregnant female and her foetus) distinguish 31 organs for the mother, plus foetal brain and soft tissue for the 3-month foetus, and foetal brain, skeleton and soft tissue for the 6- and 9-month foetuses.

Foetal dose during photon treatments mostly arises from photons scattered in the patient. For proton therapy, foetal dose is mainly due to secondary neutrons created as protons interact with the treatment delivery system (in PPT) or the patient (in PBS). To address the different biological effectiveness of photons and neutrons, equivalent doses were calculated by applying linear energy transfer (LET)-based quality factors. The mean quality factors for the 3-, 6- and 9-month phantoms were 4.1, 3.7 and 3.6 for PPT, 4.4, 4.3 and 4.4 for PBS, and unity for the photon treatments.

The researchers calculated doses averaged over individual organs and the whole foetus, for three foetal stages and three treatment modalities. The lowest dose was seen for PBS, where the mean neutron-dose equivalent to the whole foetus increased from 1.5 × 10^-3 to 2.5 × 10^-3 mSv per treatment Gy with increasing gestation stage. For PPT, the dose was higher, decreasing from 0.17 to 0.13 mSv per treatment Gy as the foetus grew.

For 3D-CRT, the scattered photon doses to the foetal body were 0.011, 0.024 and 0.030 mSv per treatment Gy, for 3-, 6- and 9-month foetuses. Doses calculated for two different linacs (Varian 2100 Clinac and Siemens Oncor) were highly similar.

For PBS and photon therapy, where the main scattered and secondary radiation is generated in the patient, the soft-tissue dose increases as the foetus grows, attributed to the decreasing distance to the target (the mother’s brain in this study). For PPT, on the other hand, soft-tissue dose decreases as the foetus grows, because the majority of secondary radiation in PPT originates from the treatment head.

CT comparisons

To compare the foetal dose from radiation therapy to that from a CT scan, Geng and colleagues used the commercial software VirtualDose to calculate the foetal dose for a routine brain CT scan of the mother’s head (using a tube voltage of 120 kVp and a tube current of 200 mA for 0.5 s rotational time). The mean foetal dose from a head CT scan increased from 0.018 to 0.038 mGy as the foetus grew. They calculated the ratios of the dose received by the foetus for radiotherapy with a prescribed dose of 52.2 Gy (RBE) divided by that of a CT scan of the mother’s head. For PBS, the mean dose equivalents were only about four times larger than that of the CT scan. For photon therapy, the ratios ranged from 30 to 44 with the growing foetus, while for PPT, the ratios were highest, decreasing from 500 to 180 as the foetus grew.

The researchers note that the absorbed doses to the foetus calculated for the three modalities were far lower than the thresholds for malformation (0.5 Gy), severe mental retardation (0.3 Gy) and lethality (0.1 Gy during the period of pre-implantation).

The excess absolute risk for childhood cancer can be estimated using a linear no-threshold dose-response relationship. PBS at 52.2 Gy (RBE), for example, increases the risk by 1.0 or 0.1 in 10^4 for a 9-month foetus (depending upon the data source used). For PPT, the risk is increased by 56 or 5.3 in 10^5, for photons, the increased risk is about 13 or 1.3 in 10^6. This estimated excess absolute risk is quite low compared to the baseline cancer incidence of 237 in 10^5 (from birth to 15 years).

“Studies like ours are very important to give clinicians confidence when treating high-risk patients.”

Tami Freeman is editor of medicalphysicsweb
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Two ion species, protons and carbon ions, are currently used to treat cancer. Each offers dosimetric and radiobiological benefits over photons in certain clinical scenarios. However, other ions including helium and oxygen can also be generated at some clinics. These, and combinations of ions, could provide better treatment outcomes and should be developed further, argue researchers in a review (Int. J. Radiat. Oncol. Biol. Phys. 428).

“However in many cases, different ions can offer substantial help. Helium, in particular, can be a very good compromise and may soon replace protons as the favourite ion in therapy.”

Reviewing the literature, Durante and colleagues Francesco Tommasino and Emanuele Scifoni described the advantages and limitations of ion species including protons, helium, carbon, and oxygen. As part of their investigation, the researchers conducted in silico dosimetric studies that compared different ions. The studies used the advanced GSI-developed particle treatment planning system TRIP98 and built on previous, similar work by the group. They highlight potential applications where new ion species could benefit cancer patients and those with other conditions, including atrial fibrillation and epilepsy.

Considering the ions’ physical differences, the researchers explained how as atomic number increases, ions deliver higher linear energy transfer (LET), higher dose-per-particle to the tumour and reduced lateral scattering. By reducing scattering, heavier ions offer a way to treat tumours that are adjacent to sensitive structures. Carbon and heavier ions also have a significantly higher oxygen enhancement ratio (OER), and so are better able to kill radioreistant hypoxic tumour cells. However, dose and LET also increase proximal to the Bragg peak with atomic number, increasing normal tissue damage in front of the tumour. Increases in nuclear fragmentation also increase normal tissue dose distal to the Bragg peak.

Consequently, ions with intermediate atomic numbers like helium are a compromise that can better target tumours than protons, but restrict normal tissue damage. For tumours with hypoxic regions, heavier ions such as oxygen or carbon could be used as a boost treatment following irradiation with photons or lighter ions. This combination increases tumour cell killing while limiting normal tissue damage.

To demonstrate the biological effects of the ions, the authors simulated tumour irradiation using TRIP98, and observed large differences in relative biological effectiveness (RBE) between ions. In general, heavier ions produce higher RBE values, both in tumour and proximal and distal normal tissue. The RBE of each ion also varied markedly when the tumour’s OER ratio was altered, emphasizing the importance of an individual’s tumour and healthy tissue biology in selecting the most effective ion.

“The implementation of helium could occur within the next five years at clinics such as the Heidelberg Ion Beam Therapy Center (HIT) in Germany, with other ions to follow,” Scifoni told medicalphysicsweb.

In the meantime, research is needed to develop treatment technology that can better control or mitigate issues of geometric uncertainties. More comprehensive experimental biological data and treatment planning studies are also needed, said Scifoni. “[These will provide] more clear indications suggesting when and how the use of ions other than protons and carbon ions translate into significant improvements in clinical outcomes.”

Jude Dineley is a freelance science writer and former medical physicist based in Sydney, Australia.

**Minibeams can reduce toxicity**

Minibeam radiotherapy uses an array of high-dose, sub-millimetre-sized radiation beams – which gradually broaden and merge – to spare normal tissues while enabling delivery of high doses to target tumours. The premise is that the smaller the treatment field, the higher the tolerance of healthy tissue. Indeed, studies performed using synchrotron radiation have shown that healthy tissue can withstand doses of more than 100 Gy if the field size is small enough.

Now, researchers are investigating whether this novel dose delivery approach could be applied to improve the therapeutic index in hadron therapy. Protons and heavy ions already offer better normal tissue sparing than photons, but it may be possible to increase this advantage further by exploiting the tissue preservation afforded by spatially fractionated minibeams. At the recent ICTR-PHE in Geneva, researchers presented the first dosimetric studies on proton, carbon, and oxygen minibeams, as well as some early in vivo results.

Martínez-Rovira, from the IMNC–UMR1865 at CNRS, presented results from the first dosimetric studies on carbon and oxygen minibeam radiotherapy. In experiments performed at the Heidelberg Ion Beam Therapy Center, Martínez-Rovira and colleagues used a tungsten multislit collimator to create 700 µm-wide minibeams of carbon and oxygen ions, separated by 350 µm and with overall field sizes of up to 20 × 20 mm. The beams were designed to create a spread-out Bragg peak (SOBP) of 50 mm at 80 mm depth in water. The researchers performed beam dosimetry by irradiating a solid-water phantom containing EBT3 radiochromic films. They also assessed and corrected for quenching effects in the films. Measurements revealed that the peak percentage depth-dose (PDD) plot for both the carbon and oxygen minibeams differed in shape from the PDD for a conventional broad-beam SOBP, due to the high ratio of lateral scattering with respect to the dose deposited by the primary beam.

The lateral dose profiles showed patterns of peaks and valleys, demonstrating the feasibility of this approach. The measured peak-to-valley dose ratio (PVD) – a key dosimetric parameter for spatially fractionated radiotherapy – was around 10 in the first centimetres of the phantom for carbon minibeams, progressively decreasing to around five at the SOBP depth of 80 mm. For oxygen minibeams, the respective values were about 10–20, decreasing to around eight at the SOBP.

Martínez-Rovira noted that PVDs in the healthy tissue are similar to those seen in X-ray mini-beams, for which biological effectiveness has been proven. In the tumour, a quasi-homogeneous dose distribution can be obtained by using interlaced irradiations. “This is the first exploratory study that experimentally proves the technical feasibility of hadron minibeam radiotherapy at a clinical centre,” she said.

Speaking in a separate presentation, Cécile Peucelle from IMNC–UMR1865 presented the team’s work on proton minibeam radiotherapy at the Proton Therapy Center in Orsay. Working on the facility’s fixed horizontal beamline, the researchers used brass multislit collimators to generate 100 MeV proton minibeams with widths of 400 or 700 µm, and 3200 or 3500 µm beam spacing. Irradiation of EBT3 films in water-equivalent RW3 slab phantoms resulted in peak-valley dose distributions on the films at all depths except at the Bragg peak, where a near-homogeneous dose distribution was seen.

Spatial fractionation was maintained in the entrance path, due to the PVD values obtained at shallow depths, while a homogenization of the dose profile was observed at the Bragg peak location (where PVD was close to 1).

Peucelle also presented the team’s first in vivo experiments with proton minibeams. In this study, they irradiated the whole brain of healthy rats with a broad proton beam or an array of proton minibeams with a 58 Gy peak dose. Both schemes delivered the same average dose of 25 Gy. Three months after irradiation, rats treated with the broad beam exhibited severe moist desquamation. The minibeam group, on the other hand, exhibited no skin damage and no behavioural changes or clinical symptoms. “These are encouraging results, and a one-year follow up is planned,” she said.

Elsewhere, a team in Germany is also investigating the application of proton minibeams to reduce irradiation side-effects, using an in vivo mouse ear model. The research team, headed up by Thomas Schmid from Technische Universität München and Helmholtz Zentrum München, used the microprobe SNAKE to irradiate the right ears of female mice with 20 MeV protons. The researchers delivered an average dose of 60 Gy to the centre of the ear via both homogeneous and minibeam proton irradiation (a 4 × 4 array of 180 × 180 µm minibeams at a distance of 1.8 mm). The mice had no ear swelling or damage or signs of significant skin reaction after minibeam irradiation, while significant ear swelling, erythema and desquamation developed in the homogeneous field group 3–4 weeks after irradiation. The researchers concluded that proton minibeam radiotherapy leads to reduced side-effects compared to conventional broad-beam irradiation.

Group effort: the biophysics department at the GSI Helmholtz Centre for Heavy Ion Research in Germany.

**Spread out: minibeams gradually broaden as they approach the target.**

**Two ion species, protons and carbon ions, are currently used to treat cancer. Each offers dosimetric and radiobiological benefits over photons in certain clinical scenarios. However, other ions including helium and oxygen can also be generated at some clinics. These, and combinations of ions, could provide better treatment outcomes and should be developed further, argue researchers in a review (Int. J. Radiat. Oncol. Biol. Phys. 428).**
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Prompt gammas go clinical

Prompt gamma imaging is under development as a way to monitor proton therapy in real time, by detecting the gamma photons emitted when the therapeutic beam interacts with nuclei within the patient. At the recent ICTR-PHE in Geneva, Christian Richter reported on the first clinical application of prompt gamma imaging-based proton range verification.

The clinical study was performed at OncoRay in Dresden, using the first prototype of a knife-edge slit camera being developed by IBA. The camera works by directing the prompt gamma rays emitted during irradiation through a tungsten slit collimator, placed perpendicular to the beam. The prompt gammas are incident upon a segmented detector, creating a differential signal which indicates the position of the beam path. If the proton range changes, the prompt gammas pass through the slit at a slightly different angle and hit different detector segments, revealing any range shift.

“Our goal was to evaluate the [prompt gamma imaging] system under clinical conditions, with the final goal of reducing range uncertainties and irradiation of normal tissues,” said Richter. He explained that the slit camera is ideally suited to pencil-beam scanning (PBS) proton therapy, where information is available for every spot and absolute range analysis can be performed. Measurements during passively double-scattered (DS) proton therapy are more complex, as the additional material present in the beam line generates an increased neutron background. In addition, only one prompt gamma signal is recorded for the entire field. However, at Richter’s site, the center only had DS proton therapy available for clinical use, so that is what they used. In August last year, Richter and colleagues used the prototype slit camera to measure the prompt gamma ray depth distribution during treatment of a patient with head-and-neck cancer. The patient received seven fractions of DS proton therapy, using three fields. Richter emphasized that the measurements, which only added minimal extra time, were performed to evaluate the method and were not used to influence the patient’s treatment.

The team performed prompt gamma imaging on one proton field during six treatment fractions, with the slit closed to take a background reading during the other fraction. They evaluated inter-fractional variations in the time-integrated prompt gamma profiles, as well as profiles corresponding to different steps of the modulator wheel (the iso-energy layers). In-room CT was also performed for three fractions to allow dose reconstruction.

Prompt gammas were successfully detected during the six fractions with the open slit. After smoothing and application of auto-detection, the time-integrated profiles revealed inter-fractional global range variations of within ±0.2 mm. “The prompt gamma imaging measurements were in agreement with the control CT-based dose recalculation,” said Richter. He noted that the iso-energy layers could also be measured, and that their profiles were consistent with the time-integrated profiles.

Richter concluded that the team successfully performed the world’s first clinical prompt-gamma-based proton range verification, noting that though the technique is more challenging in DS proton therapy, it is feasible. “We showed that a global range shift of a few millimetres is detectable and that iso-energy layers can be resolved,” he said. Details of the clinical treatment have been published in the journal Radiother. Oncol. (118:232).

The Dresden site will get PBS capability in the next couple of months, and the researchers will then continue the clinical study using both DS and PBS. They also plan to perform phantom studies comparing the slit camera capability for the two delivery modes.

Prompt gammas go clinical

‘Kill-painting’ tackles hypoxia

Tumours containing hypoxic cells are resistant to damage from X-rays, making them challenging to treat using conventional radiotherapy. Ions such as carbon, however, have higher linear energy transfer (LET) and are consequently more effective. The ability to “tune” LET and dose across the tumour volume using scanned ion beams is particularly promising for treating heterogeneous lesions.

Motivated to improve outcomes for patients with such tumours, researchers in Germany and Japan have developed a technique that optimizes ion treatments according to variations in lesion oxygenation. Dubbed “kill-painting”, the approach achieved its goal of uniform cell killing in a phantom tumour in initial tests. In doing so, it avoids the dip in cell killing observed in hypoxic sub-volumes when plans are optimized simply according to dose (weighted by relative biological effectiveness). (Sci. Rep. 5:17016).

“We are able to exploit the advance in the scanning of charged particle beams much better, providing optimal irradiation of tumours with heterogeneous radiosensitivities,” said senior author Emanuele Scifoni, from the GSI Helmholtz Centre for Heavy Ion Research in Darmstadt.

Led by Marco Durante, director of biophysics at GSI, the researchers began with a series of in vitro cell survival experiments measuring oxygen enhancement ratios (OER). A measure of radiosensitivity, this ratio quantifies the increase in dose needed to achieve a given level of cell kill in a hypoxic population, compared to one that is fully oxygenated. At high enough LET, OER approaches unity, making cell kill independent of oxygenation.

The researchers used Chinese hamster ovary cells that have a similar e/β ratio to early responding human tissue. Irradiations were carried out with carbon and silicon ion beams for a range of intermediate LET and hypoxia levels, filling a gap in the data. “This LET region is extremely relevant, since a large part of an ion beam radiation field doesn’t reach LET values high enough to completely get rid of the oxygen effect,” explained first author Walter Tinganelli, who performed the experiments at the National Institute of Radiological Sciences (NIRS) in Japan and GSI, where he now works. “On the biological side, intermediate levels of oxygenation are prevalent in hypoxic tumours rather than entirely anoxic conditions.”

The results were used to validate a model that the researchers have developed to predict OER as a function of hypoxia and LET. An extension of a photon model that predicts OER purely as a function of oxygenation, the new model incorporates an empirical component that takes account of the radiation LET. Model parameters were fitted using data previously reported in the literature. Its predictions matched the experiment results.

The researchers incorporated their model into the TRiP98 ion treatment planning system, and used it to generate a carbon ion treatment plan for a heterogeneous tumour phantom containing three cell populations with different oxygen concentrations. When optimized according to cell survival using kill-painting, uniform survival was achieved. In contrast, survival rates fluctuated in a conventional plan, with a higher cell survival observed in an anoxic volume in the centre of the phantom.

The kill-painted plan also had 20% more dose in the entrance channel of the beam that would result in greater damage to normal tissue, if applied clinically. However, separate calculations revealed that kill-painting provided substantially greater tumour control, which could offset the increase in normal tissue dose.

When the researchers delivered the kill-painted and conventional plans, at the HIMAC accelerator at NIRS and at SRF18 accelerator at GSI respectively, measurements of cell survival matched TPS predictions. Clinical implementation of kill-painting is a long-term goal, says Scifoni. Arguably the biggest challenge is the accurate, high-resolution measurement of tumour hypoxia in vivo. Potential modalities include PET and functional MRI.
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An adaptive lung-cancer proton therapy workflow that makes use of on-board cone-beam CT (CBCT) has been developed by researchers from Belgium, the UK and the US. In the identification of treatment-relevant anatomical changes in patients between radiation doses, CBCT gave similar clinical indicators to regular CT scans (Int. J. Radiat. Oncol. Biol. Phys. doi: 10.1016/j.ijrobp.2016.01.055).

Compared with conventional photon-based radiotherapy, proton therapy allows for greater levels of dose localization, with virtually no exit dose that would result in tissue damage. The procedure comes, however, with certain drawbacks. Patient motion, particularly with pencil-beam scanning, presents one such challenge. Another difficulty lies in proton therapy’s higher sensitivity to anatomical changes—for example, in the lung—which can affect the distribution of the radiation dose.

Tumour enlargement or lung collapse, for example, can result in a shortened beam penetration, reducing coverage of the target. In contrast, tumour shrinkage can result in the radiation beam penetrating further than intended, damaging regular tissues. To compensate for this, regular CT scans are taken during the course of treatment to identify anatomical changes and adjust the therapy accordingly.

One alternative to these routine CT scans lies in the use of CBCT, which uses divergent X-rays to create a 3D image. CBCT comes with a number of advantages, offering highly accurate patient positioning, as well as the capacity to monitor the patient in the treatment position and to rapidly assess the current treatment dose.

In their new study, Boon-Keng Teo, a radiation oncologist at the University of Pennsylvania, and colleagues have developed a CBCT-based workflow for adaptive proton therapy. First, prior to each individual proton treatment, patients are given a CBCT scan. From this, a virtual CT scan is generated by deforming the treatment’s original planning CT scan onto the geometry of the current CBCT scan. An additional correction step accounts for specific anatomical changes such as large tumour regressions—which cannot be handled by the deformable image registration alone.

From this, a fast, range-corrected dose distribution of the intended treatment is calculated. If the identified dosimetric changes are found to be within safe limits, treatment may proceed—else, an offline review of the virtual CT is called for, which may lead to a replan CT to adjust the treatment accordingly.

To test the concept, the researchers compared their CBCT-derived virtual CTs with corresponding, conventional CT scans of twenty lung cancer patients, who exhibited a variety of treatment responses including lung collapse or re-inflation, and tumour growth, shrinkage or density variations.

“A virtual CT generated from a CBCT can give similar dosimetric indicators as a regular CT,” says Teo. “A notable advantage that CBCT can replace evaluation CTs in proton therapy for assessment of anatomical change, and therefore reduce the frequency of CT scans during the course of treatment.”

“This is the first step toward the clinical utilization of CBCT for adaptive proton therapy, which is essential to fully exploit the physical advantages of proton therapy,” says Brian Winie, a medical physicist at Harvard Medical School who was not involved in this study. CBCT, he adds, will allow proton therapy centres to reduce the effects of the range uncertainties that result from anatomical variations during patient travel.

“Adaptive [proton therapy] workflow based on CBCT and deformable image registration may prove valuable to identify critical cases which may require correction strategies,” says Katia Parodi and Guillaume Landry, medical physicists at the Centre Léon-Bérard in Lyon, France.

“The findings pave the way for research that will assess the clinical potential of proton beam dose planning in proton therapy. This work will be of value to other institutions,” said Avery. “We hope to be able to answer these questions within the year.”

This work was supported by the National Institutes of Health, the Department of Defense (NIH/DoD), and the US Army Medical Research and Material Command (USAMRMC).

CBCT suits adaptive proton therapy

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Enhancing radiation therapy for AMD

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries for people over the age of 50. Wet AMD – the more severe form of this eye disease – causes abnormal blood vessels to grow into the retina, damaging the macula and causing loss of central vision. Wet AMD can be treated by injecting anti-vascular endothelial growth factor (anti-VEGF) drugs, or by using photodynamic therapy or lasers to seal the abnormal vessels. But these therapies are not perfect and the disease often continues to progress.

Another option is kilovoltage radiosurgery, which could reduce the need for anti-VEGF injections. Oraya Therapeutics' iRay system, for example, destroys abnormal vessels by irradiating the macula with 4 mm diameter, 100 kVp X-ray beams. This "Oraya Therapy" has already been employed to treat wet AMD in nearly 600 patients. Now, US researchers have investigated the use of gold nanoparticles (AuNPs) to increase the local radiation dose in such treatments, and reduce the dose to surrounding tissues such as the retina, optic nerve and lens (Phys. Med. Biol. 60, 2015).

"As part of our study, we employed Monte Carlo [radiation transport simulations] to determine dosimetric parameters suitable for treatment planning and prediction of therapeutic efficacy during Oraya Therapy of wet AMD," explained Davide Brivio from Brigham and Women's department of radiation oncology, Harvard Medical School. "If successful, the new approach could also be extended to enhance treatment efficacy for other ocular diseases.

Brivio and collaborators – from Oraya Therapeutics and the University of Massachusetts at Lowell – simulated a simplified geometry comprising a layer of AuNPs within endothelial cells, placed 2.4 mm into a water tank. Using nanoparticles with diameters of 10, 20 and 100 nm, and concentrations ranging from 5.5 to 491 mg/g of endothelial cell, they irradiated the water tank with a 4 mm diameter, 100 kVp beam and deposited the dose.

For 100 nm AuNPs with a cellular concentration of 491 mg/g, the researchers observed a large dose peak in the vicinity (within 30 µm) of the AuNP layer, peaking at the AuNP-tissue interface. Similar dose enhancement was seen for irradiation at tilt angles of 0°, 10° and 30°.

To quantify the dose increase, the researchers computed the dose enhancement ratio (DER): the ratio of doses with and without AuNPs. They observed that a nanoparticle concentration as low as 5 mg/g provided a dose enhancement of about 15%, with higher DER obtained at higher concentrations.

Plotting DER as a function of AuNP concentration, with a disk of 4 mm diameter and 2 µm thickness (the volume of macular endothelial cells), enabled the team to devise an empirical model to predict DER from AuNP concentration. This model could be incorporated into the treatment planning process to estimate the effective dose received by macular endothelial cells of a patient given AuNPs.

"The simulation revealed a DER of 1.97 in macular endothelial cells. This implies that these cells can receive the prescribed dose using almost half of the radiation dose, reducing the dose to the retina, lens and optic nerve by 49%, compared with treatment without AuNPs." Next, the researchers plan to address the clinical feasibility of targeted AuNP delivery.

"Targeting sufficiently potent concentrations of the AuNPs specifically to the diseased endothelial cells is crucial," Brivio explained. "Previous studies have demonstrated the feasibility of targeting nanoparticles to these cells with minimal distribution to neighbouring healthy tissue. Motivated by the results of this study, our team is currently optimizing the targeting of the AuNPs in small animals and conducting animal trials towards clinical translation.

The researchers are also optimizing the X-ray spectrum (via filtering) in order to obtain higher dose enhancement while maintaining good beam penetration. "We have discovered that filtered spectra with enhanced flux at lower keV are most advantageous. This could pave the way for further improving radiotherapy effectiveness for wet AMD, but requires further studies," Brivio told medicalphysicsweb. "We are currently also evaluating the benefit of other nanoparticle types besides AuNPs."

Gold nanoparticles target the tumour vasculature

By emitting secondary radiation, gold nanoparticles (GNPs) have the potential to increase the radiation dose to tumours during radiotherapy, with pre-clinical studies implicating damage to tumour vasculature as an important mechanism for tumour cell death.

Using Monte Carlo simulations, researchers in the US have studied in detail the enhancement in vascular dose produced by the radiosensitizers coupled with low- and high-energy X-rays and protons (Med. Phys. 42 (5R)).

"We found that the presence of GNPs in the bloodstream causes areas of high dose to the endothelial cells that can lead to blood vessel damage, which can cut off the blood supply to the tumour and cause tumour regression," said first author Yuting Lin, from Massachusetts General Hospital and Harvard Medical School. Each treatment modality produced spikes in dose that were tens of nanometres wide and sufficiently energetic to kill vascular endothelial cells.

Lin and colleagues used the TOPAS toolkit to simulate the interaction of the radiation beams with 2–20 nm diameter GNPs and calculate the resulting dose distribution. Four beams were simulated: X-ray beams with energies of 130 kVp, 250 kVp and 640 kVp; and a proton beam with a spread-out Bragg peak with a range of 12.7 cm. Prescribed doses of 2 Gy and 30 Gy were delivered, representing a conventional external-beam fraction and a stereotactic fraction, respectively.

The simulations were carried out in a large water phantom. A vessel with an inner diameter ranging from 8 mm to 20 µm and a wall 2 µm thick (the thickness of an endothelial cell) was positioned within it. The researchers modelled irradiations of GNPs homogeneously distributed throughout the vessel and attacked the vessel wall.

The simulations revealed dose spikes of tens of grey – on top of the dose delivered by the beam – at the vessel wall when a GNP interacted with the radiation. The frequency and size of dose spikes increased significantly when GNPs were placed at the bottom of the macula and irradiated with a 4 mm diameter, 100 kVp beam. The probability of dose spikes greater than 30 Gy in a 1 µm section of vessel was 85% for a 250 kVp beam and 30 Gy prescription, when GNPs were distributed throughout the vessel. For the megavoltage photon and proton beams, the corresponding probabilities were just 5% and 1%, respectively.

The probability of dose spikes increased significantly when GNPs were attached to the vessel wall. For the 250 kVp beam, the probability was 100%, compared to 96% and 63% for the megavoltage photon and proton beams. The GNP prescription also produced large dose spikes, albeit less frequently than for the 30 Gy prescription.

Upon clinical translation, GNPs will most likely be used in combination with conventionally fractionated megavoltage radiotherapy in the clinic, said co-author Jan Schueman.

"While GNPs do not interact strongly with these high-energy photons, our current and previous work shows that the low kilovoltage energy component of megavoltage fields increases with increasing treatment depth, resulting in significant radiosensitization," Schueman explained. Nanoparticles that target endothelial cells by attaching to the tumour vasculature as in the study will provide a way to maximize dose enhancement and minimize the number of GNPs required per treatment, he added.

The researchers are optimistic that GNPs can be clinically translated, though this at least five years away, co-author Steven McMahon told medicalphysicsweb. Before clinical trials can begin and FDA approval can be granted, several outstanding but ultimately solvable challenges remain, according to McMahon. The formulation of a GNP with sufficient uptake in the tumour, but limited uptake in organs such as the liver, that also stays in the tumour long enough to enable cost-effective treatments.
ion chambers: a detailed analysis

Ionization chambers used for radiotherapy dosimetry measure the current produced when ions created by the incident radiation are deflected by the chamber's electric field. In an ideal dosimeter, this ionization current is proportional to the absorbed dose, for all field sizes and over a large energy range. In practice, however, ionization chambers differ from the ideal. It's therefore important to understand and isolate the causes of such deviations in practice and using radiation dosimeters.

With this aim, researchers in Australia have devised an experimental technique that can measure the spatial response of ionization chambers and distinguish contributions from the chamber walls, stem and central electrode. They applied the method to 10 common radiotherapy ionization chambers, including thimble chambers, pinpoint chambers and plane-parallel chambers (Phys. Med. Biol. 60 6865).

"Working in a primary standards dosimetry laboratory, I have always been interested in the relationship between ionization chamber construction and energy response," explained lead author Duncan Butler from the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). "During a dosimetry experiment at the Australian Synchrotron, I realised that it would be possible to collimate the high-dose-rate beam to very small dimensions and still produce a measurable signal in an ionization chamber. This made it possible to map the response of the chamber as the radiation struck different components."

Butler and colleagues observed that sub-millimetre-diameter beams of kilovoltage radiation, from the Imaging and Medical Beam Line at the Australian Synchrotron, to irradiate the ionization chambers. They mapped the response of each chamber by scanning it through the beam during gamma irradiation and measuring the ionization current at each position. The resulting 2D dosimetry maps, in which image brightness is proportional to ionization current, revealed the sensitivity of each point in the chamber.

For five thimble chambers examined, the researchers observed several common features, the most obvious of which was a larger contribution from areas where the beam grazes a surface inside the chamber. This increased response at the inside of the chamber walls and the outside of the central electrode is attributed to the release of secondary electrons from the graphite walls at kilovoltage energies. The maps also indicated a small decrease in ionization current near the stem, possibly due to a drop in electric field strength. Monte Carlo modeling of the PTW 30013 Farmer-type chamber confirmed that the grazed surfaces contribute strongly to the overall response at kilovoltage energies.

The authors note that their results are similar to those recently published by German researchers Steffen Ketelhut and Ralf-Peter Kapsch, who succeeded in measuring similar response maps for megavoltage photons and electrons, using slit-scanning and half-beam scanning techniques and a linac (Phys. Med. Biol. 60 6177).

Dosimetric scans of two pinpoint chambers — with cavity diameters of about 2mm — illustrated the high resolution available with this technique. An early model, the PTW 31006, contains a steel electrode, while the recent PTW 31014 uses an aluminium electrode. Line scans through the centre of each chamber revealed that the steel electrode contributes about 12 times more signal than the aluminium electrode.

Finally, the researchers examined three plane-parallel chambers: a Roos chamber, an Advanced Markus chamber and a low-energy soft X-ray chamber. These chambers differ in the size of the cavity and the thickness of the front window. In all cases, they saw an increased contribution from the edge of the cavity, despite the presence of guard rings to minimize ionization near the edge.

Line scans through the centre of the chambers confirmed that the separations between spikes in current coincided with the edges of the air cavities in the Roos and Advanced Markus chambers. The 2D scan of the PTW 33142 soft X-ray chamber showed additional structure in the centre and two rings, which may possibly correspond with the cavity edge and the guard ring. Butler and colleagues also used monochromatic synchrotron beams to observe the enhancement of the photoelectric effect as a function of energy (30 to 110 keV) for the PTW 30003 chamber. One-dimensional scans revealed that the response of the aluminium central electrode was more strongly dependent on energy than the graphite walls. Monte Carlo simulations at each energy agreed well with the measurements.

The researchers note that these findings have application in the design of ionization chambers for radiotherapy and other dosimetry applications. Butler says that a second round of measurements has been proposed.

"We will investigate recombinant electron energy loss at the same high resolution," he told medical-physicsweb. "We also have plans to improve our Monte Carlo model of the chamber and include the electric field in the cavity. Unlike conventional X-ray sources, the synchrotron beam is polarized, so we may be able to see a different response for orthogonal polarizations."

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Can radiotherapy treat Alzheimer’s?

Eliminating amyloid-β plaque is a beneficial treatment strategy for patients with Alzheimer’s disease (AD), helping to slow or even prevent progression of the disease. However, the use of drugs to destroy amyloid-β is limited by the blood–brain barrier (BBB). Now, research in laboratory mice has shown that external-beam radiation can produce a significant reduction in AD-associated amyloid-β plaques, with a subsequent improvement in cognitive function. Prior research has demonstrated that radiation can reduce amyloid-like deposits in extra-cranial disease sites. In this study, researchers at William Beaumont Hospital compared the effects of three doses of radiation administered to 30-week-old male mice with a control group that received no radiation. Randomized groups of three to six mice were irradiated on the right side of their brain with a single 5, 10 or 15 Gy dose. A second series of experiments used fractionated lower-dose irradiation of 1 or 2 Gy, delivered in five to 10 treatments (Radiat. Oncol. 118(4)).

After irradiation, the mice were euthanized for histopathology evaluation. The researchers analysed three stained coronal slices per mouse to compare the number and size of amyloid-β plaques in the irradiated and untreated sides of the brain. Because the number of plaques in each mouse’s cortex varied considerably, the effect of the radiation was determined by the percentage change in absolute plaque number between the two sides, with each animal serving as its own control.

Lead author Brian Marples and colleagues reported a statistically significant reduction in amyloid-β plaques after all single-dose treatments. The largest decrease in amyloid-β plaques after a single radiation exposure was seen with the highest dose and at the longest time post-treatment, at eight weeks. Low-dose fractionated treatments produced greater reductions in amyloid-β plaques: 90.6% with ten 1 Gy treatments, 72% with five 2 Gy treatments and 78% with ten 2 Gy treatments. This compared with a 29.3% reduction seen after a single 5 Gy dose.

“The key aspect of this study is that lower-dose low-LET [linear energy transfer] radiation therapy produces an effect that is independent of the BBB,” wrote the authors. “Treatment efficacy of established AD medications may be enhanced if given in combination with a course of fractionated, non-invasive radiation therapy treatments to further reduce the plaque burden.”

For cognitive testing, 33 mice were trained to locate a platform submerged in a pool of opaque water – a well-established behavioural test used to measure spatial memory function. Nineteen mice received whole-brain irradiation, 14 were controls. Prior to treatment, the two groups did not differ significantly in latency to find the platform. Eight weeks after irradiation, the radiation-treated group displayed significantly reduced latencies compared to the untreated group.

The researchers were encouraged with their findings, because evidence suggested that radiotherapy had an immediate effect on amyloid burden and could translate to an immediate benefit for patients. Marples stated that although the relationship between plaque reduction and cognitive improvement remains controversial, the application of modest-dose brain-targeted radiotherapy to reduce amyloid burden has the potential to offer a widely available, inexpensive new treatment option for all AD patients, irrespective of the extent of cognitive deficit.

“The goal of our future experiments is to determine the temporal dynamics and long-term persistence of the radiation effect, how often and at what dose intensity the radiation therapy needs to be given, and whether prophylactic irradiation can prevent the accumulation of insoluble amyloid burden in pre-symptomatic animals,” said Marples. The team is now conducting pre-clinical research to determine whether the reduction in amyloid could be a consequence of the brain responding to radiation-related chemical events, such as oxidative damage, or a cellular event such as radiation-mediated gliosis or cell death. The researchers are also investigating whether radiotherapy causes local production of cytokines that lead to brain inflammation and BBB disruption.

A phase 1 human trial – called “Phase I feasibility study of low dose whole brain irradiation in the treatment of AD” – is also being developed. Its primary endpoint will be to assess the safety, toxicity and adverse events associated with the use of low-dose fractionated whole-brain irradiation in patients diagnosed with probable AD. The secondary endpoint will be to establish whether this intervention changes the recognised progression of AD through cognitive testing.

Cynthia E Keen is a freelance journalist specializing in medicine and healthcare-related innovations.

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For patients with high-grade glioma brain tumours, radiotherapy, chemotherapy, and surgery remain palliative treatment options, driving research for a cure. Towards this goal, researchers in Australia have combined X-rays, chemotherapy and a radio-sensitizing drug in vitro to more than double tumour cell deaths compared to radiotherapy alone. The combination selectively targets tumour cells and has the potential to reduce side effects in patients (Phys. Med. Biol. 60 7847).

“We were extremely pleased with these results that are unprecedented in vitro on an extremely aggressive glioma cell line,” said study co-author Stéphanie Corde, medical physicist at the Centre of Medical Radiation Physics at the University of Wollongong and Prince of Wales Hospital in Sydney. “We demonstrated that by mixing existing therapies together we could achieve a lot more than any of these therapies alone.”

Corde, first author Sianne Oktaria and colleagues tested the commonly used chemotherapy drug methotrexate (MTX) in their study. A folate analogue, it preferentially accumulates in brain tumour cells as they overexpress cell surface receptors of the molecule. Once in place, the drug inhibits the production of tetrahydrofolate, which in turn inhibits the synthesis of thymidine. Upon irradiation with kilovoltage X-rays, bromine atoms in the BrUdR molecule interacts predominantly by the photoelectric effect, due to its high atomic number. The resulting low energy and high linear energy transfer (LET) secondary electrons have a short range, producing highly localized damage.

The researchers tested the combination therapy in radioreistant 9L rat gliosarcoma cells cultured in flasks. The cells were incubated with MTX and/or BrUdR over two days before being treated with X-ray energies from 50 kVp to 10MV by an orthovoltage unit and linac. Cell populations treated with the two drug combination showed greater cell killing than those treated with radiation alone. The experiments also revealed the enhancement in tumour cell killing had a strong dependence on photon energy. A combination of the two drugs and a 125kV X-ray beam demonstrated the biggest radiobiological effect for a given dose.

Using the 125kVp beam, the combination therapy needed 2.3 times less dose for CIEDs hyperfunctioning compared to 90% of tumour cells in a given population. In comparison, the next most effective X-ray energy was a 6MV beam, where the enhancement in cell killing was by a factor of 1.4.

The physical efficacy of the 125kVp beam in combination with the two drugs is attributable to the bromine atom in BrUdR. Peaking at 40kV, the element’s mass energy absorption is close to the 46kV effective energy of the beam, maximizing the likelihood of interaction between the two. Cell survival data provided evidence that MTX amplifies the biological impact of the radiation-BrUdR combination by limiting the repair of damaged DNA in the tumour cell.

A combination of BrUdR and radiation was less effective than the three-pronged approach. It achieved the same radiobiological effect with 1.6 times less dose than the radiation only control, using the 125kV beam. A combination of MTX and radiation, omitting the radio-sensitizer, provided no advantage over radiation alone.

Subject to further research, Corde envisions clinical trials with an external kilovoltage X-ray beam, using energies slightly higher than the optimal energy confirmed by the study and protecting at least 90% of healthy brain.

“Tunable quasi monochromatic X-ray source would be ideal for the proposed scenario, with photon energies ranging from 30kV to 150kV,” said Corde. As a next step towards clinical translation, the group plans to test the combination therapy in vivo in small-animal models within the next year.

**Trial leader:** Joe O’Sullivan, from CCRCB at Queen’s University Belfast.

**Trial studies radiation combination**

Queen’s University Belfast, in partnership with the Belfast Trust, is leading the first trial of a combination cancer therapy for patients with advanced prostate cancer. The ADR-RAD trial will enroll 30 patients with advanced prostate cancer (where the cancer has spread to the bones) over the next 18 months. The treatment combines two existing forms of radiotherapy: volumetric-modulated arc therapy (VMAT) to target prostate cancer cells in the pelvis; plus internal radiotherapy with radium-223 to target disease in the bones. Radium-223 is a relatively new drug that’s given intravenously.

Once in the bone, it emits alpha radiation that travels less than a millimeter (between two and 10 cells deep) and delivers a high dose near to cancer cells in the bone.

“This is the first trial of its kind anywhere in the world,” said Joe O’Sullivan, who is leading the trial at the Northern Ireland Cancer Centre at Belfast City Hospital. “It is hoped that combining the two forms of radiotherapy will be more effective than existing hormone treatment in targeting prostate cancer cells at multiple sites and extend the life expectancy of men whose treatment options are otherwise limited. We expect results from the initial trial within two years, with the view to then embarking on a larger trial with a greater number of patients.”

**Lead minimizes pacemaker dose**

Lead shields provide a simple and inexpensive way to reduce radiation delivered to pacemakers during radiation therapy, according to a study by scientists in Canada. The protection is modest in many instances, but can in some cases reduce radiation by 40%, cutting the risk of pacemaker failure (J. Appl. Clin. Med. Phys. 16 41).

An ageing population has led to ever greater numbers of people receiving cardiac implantable electronic devices (CIEDs), and many of those at some point have to undergo radiation therapy. There are two main types of CIED: the regular pacemaker and an implantable cardiac defibrillator; which in addition to the pacemaker’s normal function can defibrillate. Either type is susceptible to radiation damage.

There are guidelines for the maximum amount of radiation that CIEDs should receive, but failures are unpredictable and can occur under the stated thresholds. Studies have shown that as little as 0.5 Gy of ionizing radiation can bring a CIED to a halt, while 0.05 Gy is enough to slow down a CIED, causing a patient discomfort. To reduce the risk of any damage, therefore, some clinics cover the area directly above a CIED with a lead sheet wrapped in plastic – but quite how effective this is, no one has been sure. “My impression is that lead sheets are not widely used to protect pacemakers and other cardiac devices during radiation therapy,” said Louis Archambault of Université Laval in Quebec. “However, at our clinic we’ve always seen lead shielding as an essentially ‘free’ method to reduce dose to these devices. They are inexpensive to make and they are easy to place on the patient.”

Archambault and colleagues have investigated the effectiveness of lead shields for CIEDs by performing clinically realistic radiation treatment on a phantom head and torso. They used two treatment methods: 3D conformal radiation therapy, which sends the radiation beam from different angles, and intensity-modulated radiation therapy (IMRT), which in addition uses a multi-leaf collimator to regulate the dose.

Using a plastic scintillation detector, the researchers performed extensive dose measurements on the phantom at different depths close to the beam edge, with and without the CIED. This allowed the measurements to be modelled in a standard treatment planning system, and also be used to create a dose prediction model. In the final step, the researchers treated the phantom with beam configurations from real patient cases, allowing them to test the precise dose reduction offered by the lead shield.

On average, the lead shielding reduced dose to the CIED by 19±15%. The reduction was greatest for breast cancer cases at 31±15%, and in isolated cases reaching as much as 40%. Importantly, the results also showed that the dose prediction model was far more accurate than the treatment planning system, with the former deviating only 14% from measurements and the latter deviating 71%.

“I think our work demonstrates that a lead shield is a simple and inexpensive method for reducing dose to a CIED,” said Archambault. “Even if the dose reductions are modest most of the time, [the shield] can nevertheless represent over 40% reduction in some cases. Because there are no data supporting a fixed dose threshold below which a CIED is completely safe from perturbation, any dose reduction should be welcomed if it does not add a burden on the clinical workflow.”

Archambault steps short of recommending widespread usage of lead shields, however, as there may be better types of shield available.

“We are currently working with a cardiologist to perform a vast retrospective analysis of patients with pacemakers and other CIEDs treated in our clinic,” he says. “Our aim is to better understand the causes of CIED abnormal events seen during or shortly after radiation therapy. This work should help us establish guidelines for the use of CIED shielding.”

Joe Cartwright is a freelance journalist based in Bristol, UK.
The first MRI-guided radiation treatment took place in January 2014, at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. The treatment was performed using ViewRay's MRIdian, which integrates a 0.35 T MRI with three gamma-emitting cobalt-60 sources. Two years down the line, at the Siteman Cancer Center, director of radiation oncology physics at Washington University School of Medicine, explains how the system has impacted the centre’s radiotherapy programme.

“Several things have changed how we treat patients. For one, we are able to see things that we haven’t seen before. Also, during treatment we can see where the tumour is,” said Mutic. “We can deliver radiation with much more certainty now, so we can treat with smaller margins or maybe treat a patient we wouldn’t have treated previously.”

MR guidance also enables the use of different types of radiation treatments. One such example is stereotactic body radiotherapy (SBRT), which utilizes high doses of radiation in a short course of therapy, and relies on precision target localization. The Siteman team has used SBRT to perform a number of single-fraction breast treatments, which would not previously have been possible. “Because we have the MR, we can see the targets much more clearly and have a greater confidence that we’re treating what we’ve supposed to,” Mutic said.

Mutic points out that the Siteman Cancer Center is also now performing on-couch adaptive treatments—as routine. For each fraction, the patient is scanned on the treatment couch, a new plan is created and quality assurance is performed prior to treatment. The adaptive treatment planning process takes roughly 10–20 minutes, and almost 200 adaptive treatment fractions have been delivered in this way. In addition, patients are imaged throughout radiation delivery. The MRIdian currently records images at 4 frames/s, with 8 frames/s capable in the pipeline for later this year. For treatment of moving targets, this functionality enables gating to be performed directly on the target or the normal anatomy, without the need for surrogates.

To date, the Siteman team has treated 26 different disease sites using MRI-guided radiotherapy, with breast, lung and gastrointestinal tumours the most common cases. “The system was designed to function as a regular treatment machine to fit with the rest of our practice by treating a bit of everything on it,” explained Mutic. “The same people that are treated on a linac can also use this system.”

Mutic and colleagues are currently running three clinical trials using the MRIdian. The first of these involves treatment of oligometastases with as high a dose as possible, based on isolotoxicity to normal structures. The second study, which is still in its early stages, investigates the ability of using improved image guidance to escalate dose to stage III lung tumours, while treating less normal lung tissue. The third trial exploits MR guidance to reduce the volume of irradiated normal tissue. “The idea is that if we can see the treatment volume better on the MR image, then we can reduce the margins,” said Mutic. Early results have demonstrated the ability to shrink the irradiated volume by 55%.

“We have succeeded in what we wanted to do—to make a viable clinical device that anybody can use routinely every day,” Mutic concluded. “From showing the practicality of MR-guided radiotherapy, we’ve realised why the idea of online adaptive radiotherapy. I can really say it is now 100% routine.”

VMAT plan can lower skin dose

Intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) deliver highly conformal radiation dose distributions, directly targeting tumours while avoiding or minimizing dose to organs-at-risk. But skin is not necessarily spared, especially if hot spots are inadvertently created. In fact, severe skin reactions have been documented in head-and-neck cancer patients who received IMRT. Could VMAT techniques be potentially less harmful?

With respect to patients with prostate, brain, and head-and-neck cancers, the answer is yes, according to a retrospective study comparing IMRT and VMAT treatment plans for different tumour locations. While achieving the same target coverage, the VMAT plans reduced the radiation dose to the skin in all regions of the body. Additionally, a comparison of traditional vs. potential boost regimens with integrated boost regimens for head-and-neck cancer patients revealed that the traditional approach decreased the hot spot skin dose to the shoulder (Med. Dosim. 41:80).

The investigation was undertaken by medical physicists at Vanderbilt University School of Medicine. George X Ding and Gregory Penoncello prepared VMAT and IMRT treatment plans for 19 patients: nine with head-and-neck cancer with complex-shaped targets, five with brain cancer with different lobes involved, and five with prostate cancer, with and without involved nodes. Each plan was created to achieve the same coverage with the same organ constraints.

For head-and-neck treatments, IMRT plans used seven fields at varying angles, and VMAT plans used two full arcs, both with 6 MV photons. The mean skin dose did not vary largely between either type of plan. VMAT reduced the hot spot dose by an average of 6.5%, but with a large variation in the difference.

For prostate treatments, IMRT plans used seven fields and VMAT plans used two full arcs for patients with nodal involvement: five fields (IMRT) and one full arc (VMAT) were employed for a patient with out nodal involvement. All plans used 10 MV photons. The mean skin dose did not vary largely for either type of pelvis plan. However, VMAT decreased the hot spot dose in the pelvis by an average of 36% compared with IMRT.

Although the reductions in mean skin dose and hot spot dose by VMAT were impressive for head-and-neck and prostate cancer treatments, the authors emphasized that the sparing capability of VMAT is a case-based situation. Because VMAT doses can be delivered over a large range of angles, the dose can spread out more than in static-field IMRT. However, if the number of static IMRT entry beams were increased, the skin dose would decrease. Additionally, skin dose value is dependent upon its distance from the target. If the tumor is deep, beams have to travel through more tissue. The closer to the surface a target is, the higher the skin dose will be. This explains why skin in shoulder areas is more susceptible to developing skin toxicities.

“The results from this study provide a dosimetric explanation of skin reactions observed in patients; it presents useful information to help clinicians make informed decisions in selecting optimum treatment techniques,” wrote the authors. “At Vanderbilt-Ingram Cancer Center, the most appropriate treatment techniques are selected based on an individual patient’s needs.”

“The purpose of our study is to provide information for radiation oncology cancer treatment teams to work with in order to avoid the need to make both types of modality plans for each patient,” Ding told medcityweb. “And while there is a significant advantage for the VMAT technique, because VMAT delivery is faster, it will be used only when it is the best clinical choice for a patient, a decision that needs to be made in a case-by-case basis.”
ViewRay unveils plans for MRIdian Linac

ViewRay, creator of the cobalt-based MR-guided radiotherapy system MRIdian, has announced the development of the MRIdian Linac, a linear accelerator-based version of its treatment system. Speaking at the 36th Annual Cowen Healthcare Conference last month, ViewRay’s CEO Chris Raanes explained the rationale.

“We’ve had great progress since the launch of the MRIdian. We’ve treated patients at four top cancer centres around the world and in the first two years it has been used to treat over 25 different types of cancer,” he said. “The only significant push back that the company has seen is that some people just don’t like the cobalt radiation source.”

Raanes explained that ViewRay has developed a Double Focused beam-shaping technology that renders the cobalt beams equivalent to those produced by a linac. Indeed, MRIdian users have already published data showing the equivalence between the two. However, customers are still generally more familiar with linacs, prompting the company to move in this direction.

Raanes said that he was initially tempted to keep the MRIdian Linac development quiet for now, and make a bit splash at one of the big conferences later this year. “But when you’ve got as far as we have, we feel it is time to talk about it to the world,” he explained. “We actually have one of these systems up and running now, we are way ahead of our schedule, and we have proved all the concepts.”

Presenting images of a patient inside the linac-based system, along with what he described as a “beautiful” treatment plan, Raanes explained that the new device exploits the beam-shaping technology that ViewRay developed for the cobalt sources. “When you put that same technology in front of a linac, you end up with the sharpest beams in the industry,” he claimed. “There is nothing out there that compares to the sharpness of the plans that we see.”

So how did ViewRay address the complex problem of combining a MR system with a linac? Raanes cited two key breakthroughs: RF “Stealth Cloaking” and magnet shield technology. The first of these enables clear MR imaging inside the MR field, by “absorbing the RF and keeping it away from where it doesn’t belong”. Images of a patient “absorbed in the linac, undistorted, in the same footprint,” said Raanes.

The magnet shield technology addresses the other challenge: how to make a magnetic void right in the middle of the MRI field and that’s why we can fire straight beams, undistorted, in the same footprint,” said Raanes.

Referring back to ViewRay’s Double Focused technology, Raanes explained that the resulting sharp beams enable the MRIdian Linac to create stereotactic radiosurgery (SRS) treatment plans with equivalent quality to those from specialized SRS systems. “We now can take on anything from the toughest criteria for intracranial treatments, down to the simplest 3D conformal palliative type of treatments,” he added. “We have broadened our market to do anything that a standard or specialized radiotherapy system can do.”

Finally, Raanes mentioned the company’s “pop-apart MRI technology”, which enables easy access for installation of the system in existing vaults. He noted that the MRIdian Linac will have the same small compact footprint as the cobalt-based MRIdian system, and that users with the existing MRIdian will be able to upgrade to the linac option.

ViewRay anticipates applying for FDA clearance and CE Mark approval in the second half of this year. “You’ll see the first scientific papers at two big conferences – AAPM and ASTRO,” said Raanes.

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For brain tumour patients undergoing surgery, the proportion of tumour removed is a major factor determining prognosis. However, diseased tissue may look like healthy brain, making it difficult for surgeons to locate the tumour margin. Meanwhile, histological analysis of excised tissue can take tens of minutes, extending the operating time in theatre. Expensive in-theatre MRI has also shown limited benefit.

Addressing this, researchers in the USA have developed optical imaging technology for rapid, objective assessment of tissue samples during surgery. Stimulated Raman scattering (SRS) microscopes image tissue architecture on a cellular level, and an automated machine learning classifier scores the images for the likelihood of tumour infiltration. In their latest study, the collaboration used this approach to accurately classify biopsy samples from 22 neurosurgery patients (Sci. Transl. Med. 7, 297ra163).

“This technology has the potential to eliminate some of the guesswork of brain tumour surgery,” said Daniel Orringer, senior author and neurosurgeon at the University of Michigan in Ann Arbor. The approach stimulates Raman scattering using two lasers tuned to match the vibrational modes of lipids and proteins. The resulting images display lipids in green and proteins in blue, enabling protein-rich tumour cells to be detected.

The tissue classifier combines three indicators of tumour infiltration extracted from the SRS images – tissue cellularity, a protein-to-lipid ratio – into a single score. Ranging from zero to one, a higher score indicates a higher probability of tumour infiltration. The classifier generates the score using a generalized additive model. The model is trained using an SRS image database of normal and diseased tissue independently assessed for tumour infiltration using conventional haematoxylin and eosin (H&E) microscopy.

The researchers used SRS microscopy images from 19 patients with glioblastoma and three with epilepsy. As expected, there were marked qualitative differences between the two groups and between different types of tumour and normal brain tissue. Overall, tumour-infiltrated tissue exhibited higher cellularity, a protein-rich composition and a lower density of axons. In a blinded online survey of three neuropathologists, the researchers demonstrated the utility of the images in detecting and identifying that the degree of tumour infiltration matched that of H&E staining. They obtained very good agreement between the two techniques in a sample of seven patients.

A subset of 1477 images from 18 patients was used to assess the classifier. The classifier was trained with one half of the images and used to score the other half. It performed well, identifying tumour-infiltrated tissue with an average sensitivity of 97.5% and specificity of 98.5%.

By combining imaging with a quantitative score, the technique has an advantage over quantitative approaches such as Raman spectroscopy, said Orringer. “As a surgeon, I’m much more likely to trust a numerical readout that makes sense given the tissue architecture. SRS microscopy allows surgeons a metric they can trust and verify.”

In ongoing work, the collaboration is developing SRS microscopes suitable for clinical use, including a handheld probe for in situ assessment of tissue during surgery. Though the probe may be more convenient than ex vivo analysis, testing is needed to assess its performance in the more demanding measurement environment of the surgical cavity. “We are working on understanding the tradeoffs in image quality that might come with the handheld imaging system,” said Orringer. “Once we have both an ex vivo and in vivo system available to test side by side, we’ll determine which system – or both – we’d like to put our energy into developing.”

Imager boasts high sensitivity

Imaging technology that could enable more accurate brain tumour excision and improve patient survival has been demonstrated in the lab by a Canadian–US collaboration. The imaging system, which uses an electron-multiplying charge-coupled device (EMCCD) to detect a fluorescent biomarker in tumour cells in situ, is orders of magnitude more sensitive than current state-of-the-art technology (Biomed. Opt. Express 6, 5063).

“The improved level of sensitivity we demonstrated is especially relevant for low-grade gliomas and invasive cancer found towards the periphery of the tumour, where there are often lower levels of fluorescence signal produced,” explained Michael Jermyn from the Montréal Neurological Institute and Hospital at McGill University and Polytechnique Montréal.

Typically, surgeons rely on visual assessments and time-consuming pathology tests in theatre, plus pre-operative MRI, to localize the tumour. Increasingly though, researchers are working on tools that will enable more accurate on-the-spot assessments during surgery.

Fluorescence imaging detects the light emitted from molecules such as protoporphyrin IX (PpIX) upon excitation with a light source. PpIX is selectively synthesized and retained in tumour cells upon administration of the pro-drug 5-aminolevulinic acid. Already in clinical use in Europe, the strategy typically uses commercially available neurosurgical microscopes and is carried out in low ambient light. Surgeons assess tissue qualitatively, either with images captured by the microscope’s CCD camera or through pieces. However, the approach has limited sensitivity and specificity.

Addressing this, Jermyn and colleagues’ latest system connects an EMCCD – a high-gain sensor suited to short exposures and low-light conditions – to the neurosurgical microscope, via a fibre-optic bundle. The system has a 4.5 cm diameter field of view.

The collaboration compared the new imager to two other fluorescence-detecting devices they had previously developed. The first was a sensitive handheld probe that measured fluorescence at single points and was already undergoing clinical studies. The second was a state-of-the-art imager that integrates a neurosurgical microscope with a CMOS sensor. Previous research revealed the imager was 10–20 times less sensitive than the probe and could not reliably detect low-grade gliomas, motivating the development of the EMCCD system.

The researchers compared the systems using several phantoms comprising a lipoprotein suspension that simulated brain tissue and a range of PpIX concentrations. The tests revealed that the sensitivity of the EMCCD system varied linearly with PpIX concentration, including at the low concentrations found in low-grade gliomas. It was also one to two orders of magnitude more sensitive than the CMOS system and of comparable sensitivity to the handheld probe. This was despite estimated signal losses of around 30% in the fibre-optic bundle.

In other tests, the team imaged seven samples of excised rat brain that contained tumour. Images from the EMCCD system were compared with those captured by the microscope alone. Contrast ratios – image intensity in a 5 × 5 pixel area of fluorescing tumour normalized to that of non-fluorescing tissue – were assessed in each sample. A simple comparison revealed greater contrast ratios using the EMCCD system and that the fluorescence levels it reported correlated well with measurements by the probe.

Advancing their research, the collaboration is now fabricating a next-generation EMCCD system, which will be tested in operating theatres at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire and the Montréal Neurological Institute and Hospital. “These studies will assess the detection capabilities during surgery and may pave the way for clinical trials investigating the effectiveness of the imaging system on treatment outcome,” said Frédéric Leblond, senior author and director of the Laboratory of Radiological Optics at Polytechnique Montréal.

In the longer term, the imager may complement a second handheld probe also developed in Montréal and planned for clinical trials in 2016. Measuring Raman scattering, the probe has successfully detected low-grade glioma and invasive cancer cells.

β-decays guide surgery

Radioguided surgery uses a radiolabelled tracer administered prior to surgery to guide lesion resection. Preferential tracer uptake by the tumour helps the surgeon identify tumour residuals and hopefully achieve complete tumour resection. Current methods mostly use gamma-emitting radiotracers, but the high penetration of gamma photons through tissue means that any tracer uptake in nearby healthy tissue generates a non-negligible background signal. This approach also exposes medical personnel to radiation.

Speaking at ICTR-PHE in Geneva, Riccardo Faccini from INFM and Sapienza University presented an alternative: radioguided surgery based on β decay. Electrons travel just a few millimetres in tissue, eliminating background signal and allowing for large tracer uptake in nearby healthy organs. This also enables use of a lower radio-pharmaceutical activity and reduces the dose to medical staff.

Faccini described the team’s prototype intraoperative β detection probe. The 1 cm-diameter probe has a chamber of β-terphenyl (a scintillator with high sensitivity) and a 2 × 2 × 2 cm sensitive area. In tests on phantoms, the probe exhibited a spatial sensitivity of about 2 mm. One potentially significant use of β guidance is in neurosurgery, where complete removal of a brain tumour is vital and other radiotagged techniques are limited by high tracer uptake in brain tissue. To investigate this possibility, Faccini and colleagues examined the somatostatin analogue DOTATOC labelled with the β-emitting radionuclide 111In. Faccini presented the first validation results, using the β detection probe to evaluate 111In-DOTATOC uptake in a patient with meningioma.

In an initial step, the researchers administered 111In-DOTATOC and performed PET imaging to estimate tracer uptake. A tumour-to-normal tissue ratio of about 14 was observed. The day before surgery, the patient was injected with 8 mCi of 111In-DOTATOC. During surgery, tumour samples were extracted for evaluation. Results showed that the probe could detect residuals as small as 0.2 mL. The signal from larger tumour samples was 100 counts per second (cps); smaller 0.2 mL samples exhibited signals of approximately 40 cps, while signals from healthy tissues were below 5 cps. The researchers also confirmed that there was a low level of radioactivity in the surrounding tissue.

Next, Faccini and colleagues plan to extend the clinical studies to gliomas and neuroendocrine tumours, and are developing a new application with different beta-emitting radiotracers. Other tasks include developing specific radiotracers, and improving the probe, for example by enabling endoscopic use.
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Researchers at Sunnybrook Health Sciences Centre made history by using focused ultrasound to non-invasively open the blood–brain barrier (BBB) for the first time. The procedure, performed last November, provided temporary and targeted BBB opening, with the aim of more effectively delivering chemotherapy to the patient’s malignant brain tumor.

The BBB is a protective layer of tightly joined cells that lines the blood vessels of the brain and prevents harmful substances from entering the surrounding tissue. Unfortunately, it also stops certain drugs from reaching targets in the brain in adequate concentrations, and has been a persistent impediment to treating neurological conditions such as brain tumors, Alzheimer’s disease, Parkinson’s disease and epilepsy. Safe, temporary opening of the barrier in a targeted area is a long-sought goal.

With this aim, the Sunnybrook research team — led by neurosurgeon Todd Mainprize and physicist Kullervo Hynynen — infused the chemotherapy agent doxorubicin, plus microscopic gas-filled bubbles into the patient’s bloodstream. The microbubbles are smaller than red blood cells and pass harmlessly through the circulation. They then used Insightec’s ExAblate Neuro — an MRI-guided focused ultrasound system — to sonicate targeted blood vessels in the patient’s BBB, in two regions near to the tumor.

The device uses 1024 transducers within a helmet to focus ultrasound through the skull and onto the target. Acoustic modeling based on a pre-treatment CT is used to compensate for skull aberrations (where the skull deforms and shifts the ultrasound beam). Focusing ultrasound on the vessels repeatedly compresses and expands the circulating microbubbles, causing them to vibrate and loosen the tight junctions of the cells that comprise the BBB.

After sonication, Mainprize and colleagues imaged the patient’s brain using MRI with gadolinium contrast agent, which cannot usually cross the BBB. Grids of bright dots seen at the sonicated points indicated that the BBB had opened, enabling the contrast to leave the blood vessels and enter the patient’s brain. The researchers believe that the chemotherapy drugs were thus also able to flow into the targeted part of the brain tumor.

The procedure took 2.5 hours in total, during which time the patient was awake in the MRI scanner, and did not feel any effects from the treatment. The following day, she underwent her scheduled surgery to remove the brain tumor.

“We are encouraged that we were able to temporarily open this barrier in a patient to deliver chemotherapy directly to the brain tumor,” said Mainprize. “Some of the most exciting and novel therapeutics for the treatment of malignant brain tumors are not able to reach the tumor cells because of the BBB. This technique will open up new opportunities to deliver potentially much more effective treatments to the targeted areas.”

This treatment was the first in a pilot study of up to 10 patients to evaluate the feasibility, safety and preliminary efficacy of this approach. Study participants are already scheduled for traditional neurosurgery to remove parts of their brain tumor. If the pilot is successful, the team plans a second trial, and are currently in discussions to assess the best next approach to gain the most information and the largest patient impact.

As well as enabling drug delivery, this non-invasive BBB-opening could find application in treating a range of other neurological conditions. Hynynen, who has been performing pre-clinical studies of this approach for about a decade, has demonstrated that the combination of focused ultrasound and microbubbles can also stimulate the brain’s natural responses to fight disease. For example, the temporary opening of the BBB appears to facilitate the brain’s clearance of a key pathologic protein related to Alzheimer’s and improves cognitive function.

A recent study from the Queensland Brain Institute in Australia further corroborated Hynynen’s research, demonstrating that BBB opening with focused ultrasound reduced brain plaques and improved memory in a mouse model of Alzheimer’s disease. Based on these two pre-clinical studies, a pilot clinical trial of focused ultrasound to treat Alzheimer’s is being organized. Other groups are investigating applications in treating Parkinson’s disease, opening targeted blood vessels in the patient’s bloodstream.

Temporary opening: MR images of the patient’s brain recorded after sonication exhibit bright dots in the places where the BBB was opened.

**Cardiac catheter, treats, monitors**

A proof-of-concept experiment with a combined high-intensity focused ultrasound (HIFU) and local harmonic motion (LHM) imaging catheter has shown that the minimally invasive catheter can function as a therapeutic and monitoring tool for cardiac ablation. The study, from the University of Toronto, demonstrated the catheter’s potential to produce and detect cardiac-ablation lesions.

The current gold standard in cardiac-ablation therapy is radiofrequency (RF) ablation. This RF treatment is limited to the production of transmural lesions in the ventricles, and treatment-monitoring techniques are currently not available for most RF-ablation procedures. A fully ultrasound-based system has the potential to produce and detect deep lesions, according to lead author Mathew Carias, a graduate student in the Department of Medical Biophysics at the University’s Sunnybrook Research Institute. Such lesions are created to destroy diseased or abnormal tissue, such as cardiac cells that cause the heart’s electrical signal to malfunction and cause irregular heartbeats (Ultrasound Med. Biol. 42 1964). LHM imaging, an elastographic technique that uses both therapeutic and diagnostic ultrasound transducers, is based on the principle that harmonic motion can be estimated and imaged in tissues in which a time-varying force has been externally applied with focused ultrasound transducers. Importantly, this ability to continuously monitor lesion formation without discontinuing therapeutic ultrasound, its ability to measure lesion formation at multiple tissue depths overcomes current challenges related to knowing lesion-depth penetration during cardiac-ablation therapies. It could also provide a more cost-effective approach to treatment monitoring, compared with techniques such as magnetic resonance thermometry.

For these reasons, Carias and co-author Kullervo Hynynen constructed and tested a combined HIFU and LHM catheter. They initially created a catheter-sized LHM device to detect tissue displacements, testing this on phantoms and ex vivo cardiac samples. They next created a side-facing intravascular catheter in which two embedded angled therapeutic transducers were placed alongside an imaging transducer. This design enabled lesion formation at the same time as acquisition of amplitude-motion-mode ultrasound images that enabled tissue displacement to be estimated. The researchers used this second device to perform an in vivo experiment using a six-month-old 40 kg pig. The left ventricle was used to attempt three lesions on its endocardial surface, and the right ventricle was used to create five lesions on its epicardial surface. Sections of the ventricles that had been exposed to ultrasound were evaluated for overall depth of coagulation into the ventricle wall. The transducers were characterized according to their overall acoustical power output and pressure-field formation, and were determined to have an efficiency of approximately 25%. Measurements in cardiac tissues before and after lesion formation revealed a decrease in displacement amplitude, corresponding to an increase in tissue stiffness. Continuous measurements throughout the sonication showed decreased amplitudes in both ex vivo and in vivo experiments.

“Four of five epicardial attempts gave rise to lesion formation on the surface, and two of three endocardial attempts gave rise to lesions,” the authors wrote. “Endocardial lesions were difficult to locate for histologic examination due to the tortuosity of the intracardiac morphology.”

Based on their results, the authors recommend that additional experiments are performed to enable clinical use of the device. These include the formation of larger lesions, design of a therapy controller that will enable automatic lesion detection through an online surgical platform, and increased robustness of lesion localization. A controller with automatic amplitude threshold detection would detect when treatment is complete and halt the sonication. They also recommended an investigation to determine the threshold value that gives rise to the most successful treatments.

Carias told medicalphysicsweb that he and his colleagues are currently developing protocols and methods that could be used as a treatment controller, and are also developing threshold values. “I am currently determining the correct amount of energy needed to make a catheter for clinical use. This includes making slight design changes to the catheter itself so that it could be used more safely in a clinical environment,” he explained.
Capsule detects GI tract disease

A method for imaging and characterizing the oesophageal wall using a tethered capsule has been developed by researchers from Harvard Medical School and Strasbourg University. The technology, which uses optical coherence tomography (OCT), may provide a simple and convenient method for diagnosing upper gastrointestinal tract diseases such as Barrett’s oesophagus.

The diagnosis and subsequent treatment of many diseases of the upper gastrointestinal tract often call for endoscopic examination. Unfortunately, this is typically expensive, uncomfortable, requires patient sedation and only provides limited information on surface tissues. Subsequent biopsies can provide additional information, but only from limited sample sites. This can be especially problematic when attempting to diagnose diseases with patchy presentations, such as Barrett’s oesophagus – in which oesophageal tissues change to resemble those that line the intestine.

A tethered capsule is to use OCT, an imaging technique that uses back-scattered, near-infrared light – in a manner analogous to ultrasound – to create micron-resolution images. In their work, Harvard Medical School’s Guillermo Tearney and colleagues have developed an OCT capsule for imaging the oesophagus. As the capsule is swallowed, or retracted by its tether, it creates 360° cross-sections up and down the oesophagus. From the data generated, it’s possible to distinguish between regular and abnormal tissues. Being only 11 x 24.3 mm in size, the capsule can be easily swallowed. Compared with endoscopy, this makes the procedure more comfortable for the patient – who need not be sedated – and simpler, as it can be performed in a non-specialized setting without a physician.

The capsule device comes with some technical challenges, however, the most problematic being the time-consuming nature of manually characterizing the data collected. To address this, Tearney and his team have developed a computer algorithm capable of mapping the imaged tissues and identifying the presence of Barrett’s oesophagus. In a clinical trial, the algorithm’s tissue characterization produced a 94% match with those conducted manually by an expert.

Furthermore, the automated system can provide feedback to the capsule operator about the level of tissue contact between the capsule and the oesophageal wall. The highest quality images are produced with full contact, which is typically ensured by peristalsis, but can be lost if the oesophagus expands. As the capsule can be easily re-engaged by giving the patient a sip of water, however, this feedback capacity will allow sections to be re-imaged if needed and ensure a complete dataset is acquired.

“This study demonstrates that tethered capsule endomicroscopy has the potential to be an efficient, non-endoscopic screening tool to identify those who may benefit from an upper endoscopy and to fill a gap in our current screening paradigm for Barrett’s oesophagus.”

Having demonstrated its potential, Tearney and colleagues are now moving to further develop their screening technology, with an eye to decreasing processing times and conducting comparisons between their algorithm’s output and histopathology as the gold standard. They are also investigating whether this technique might also be used for the diagnosis of other gastrointestinal tract cancers and conditions such as allergic esophagitis and coeliac disease. According to the researchers, the technology might find wide clinical application within a few years.

Pancreatic cancer is predicted to become the second leading cause of cancer mortality by 2030, yet no adequate molecular imaging tools exist to aid in the staging, monitoring and treatment of the disease. To address this shortfall, a research team headed up at the Memorial Sloan Kettering Cancer Center has developed three probes for PET, near-infrared fluorescence (NIRF) and dual-modal (PET/NIRF) imaging of pancreatic ductal adenocarcinoma. PET and NIRF optical imaging offer complementary clinical applications, enabling non-invasive whole-body imaging to localize disease and identification of tumour margins during surgery, respectively (PNAS 112 15850).

The probes were created using site-specific modification of an antibody that targets CA19.9, the most common pancreatic cancer biomarker. Each probe showed exceptional uptake and contrast in antigen-positive tumours, with negligible non-specific uptake in antigen-negative tumours. The researchers evaluated the dual-modal probe in an orthotopic murine pancreatic cancer model, observing the probe’s capacity to delineate metastases and map the sentinel lymph nodes via tandem PET/CT and NIRF imaging. “These imaging tools have tremendous potential for further preclinical research and for clinical translation,” the authors write.
Far-IR light measures blood glucose levels

A research team led by Yuji Matsuura of Tohoku University has developed a non-invasive method for measuring blood glucose using far-infrared light. People with diabetes traditionally monitor their daily blood glucose levels by sampling blood from their fingertips. To eliminate this invasive procedure, glucose measurement methods are being developed based on selective absorption by glucose of some wavelengths of near-infrared light. This approach is not ideal, however, as near-infrared light is not only weakly absorbed by glucose, but also by water, protein and haemoglobin.

Instead, the researchers are investigating the use of far-infrared light with wavelengths of around 10 µm, which is strongly absorbed by glucose and should deliver more sensitive and accurate measurements. As far-infrared light only penetrates a few microns into the skin’s surface, the team developed a novel measurement technique comprising a small prism attached to the ends of flexible hollow-optical fibres to radiate the far infrared light. Using this method, it is possible to irradiate the oral mucosa of the inner lips that, unlike skin, have no thick horny layer. Experiments showed that the device could measure blood glucose levels with a less than 20% margin of error, which Matsuura believes is good enough for clinical use.

OCT spots dangerous plaques

Combining optical coherence tomography (OCT) with near-infrared autofluorescence (NIRAF) imaging may help identify coronary artery plaques that are likely to rupture and cause a heart attack, report researchers from the Wellman Center for Photomedicine at MGH. OCT provides images of tissue microstructure, while NIRAF provides information on the molecular composition of tissue, together creating a powerful tool for investigating coronary artery disease. In a first study in patients, the researchers examined whether a catheter-based OCT–NIRAF device could identify rupture-prone sites within plaques, particularly fibroatheromas, which consist of a core of dead cells covered by an often-thin fibrous cap (JACC: Cardiovascular Imaging doi: 10.1016/j.jcvi.2015.11.020).

The study included 12 patients receiving cardiac catheterization. Results confirmed that the OCT–NIRAF procedure was as safe and feasible to perform as conventional OCT, with no additional time required. Images of coronary arterial segments revealed elevated NIRAF signal in areas where OCT suggested the presence of a fibroatheroma, and even higher in lesions with thin caps or at sites of plaque rupture and clot formation. “Overall, we believe that the combined OCT–NIRAF examination provides information on molecules within arterial plaques and other features associated with a higher risk of an acute coronary event,” said co-senior author Gary Tearney. “But right now this is a hypothesis, and our findings need to be borne out in larger studies, which we plan to have underway later this year.”
Three-dimensional breast imaging methods such as breast CT overcome the shortcomings of 2D mammography, in which overlapping structures can obscure cancerous lesions. Performing breast CT with synchrotron radiation (SR-BCT) enables the use of phase-contrast techniques, which produce images with high soft-tissue contrast. Now, researchers in Italy are planning the first clinical study of phase-contrast SR-BCT (Phys. Med. Biol. 61 569).

“Inconventional attenuation-based X-ray imaging, the radiographic contrast comes from differences in the volume density and composition between tissues. Attenuation-based mammography is limited by the intrinsically low contrast between glandular (healthy) and tumour tissue,” explained Giovanni Mettivier from the University of Naples “Federico II” and INFN. “On the other hand, in phase-contrast imaging, the image contrast comes from comparatively higher differences in electron density of tissues, giving the possibility of better sensitivity through an increased contrast. Now, researchers in Italy are planning the first clinical study of phase-contrast SR-BCT (Phys. Med. Biol. 61 569).

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The SYRMA-CT project: dosimetry group members (left to right): Christian Fedon, Antonio Sarno, Francesca Di Lillo and Giovanni Mettivier. The SYRMA-CT team plan to only irradiate part of the breast underestimates the delivered dose, with the amount of underestimation increasing as the irradiated volume is reduced.

The researchers also examined MGD, MGDv, and MGDt, for a glandular fraction of 50%, at 38 keV (one of the energies to be employed in the SYRMA-CT project), as a function of the height of the irradiated volume. MGD showed a linear dependence on height, while MGDt increased sub-linearly. MGD, was almost independent of the height of the irradiated volume, and assumed values similar to MGD for the whole-breast irradiation.

The authors propose that in breast imaging exams where only partial irradiation is planned, MGD, is the most suitable metric for expressing the glandular dose to the breast. For SYRMA-CT, they plan to use their MC code to estimate the dose to glandular breast tissue prior to each X-ray exam. "It will be the basis of the dosimetric protocol for pilot breast CT scans at the Elettra synchrotron radiation facility, to be submitted to the regulatory board for study approval."

Mettivier told medicalphysicsweb.
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An algorithm that generates reproducible, personalized maps of neural networks in the brain using functional MRI (fMRI) has been demonstrated by an international collaboration. The non-invasive approach could enable more efficient planning of neurosurgery for brain tumours and disorders such as epilepsy. Other potential applications include the guidance of brain stimulation techniques used to treat neurological and psychiatric conditions (Nature Neurosci. 18 1853).

Functional networks in the cerebral cortex, like those responsible for speech and decision making, vary significantly between individuals. Consequently, neurosurgeons must map them prior to surgery to limit damage. However, the standard means of doing this – cortical stimulation – requires the direct placement of electrodes on the brain and to date there has been no viable non-invasive alternative.

“fMRI has already been used for pre-surgical mapping, but with limited success due to its low reliability,” said first author Danhong Wang of the Athinoula A Martinos Center for Biomedical Imaging at Massachusetts General Hospital and Harvard Medical School. “We believe a more reliable and accurate mapping technology will greatly expand the clinical use of fMRI.” The research was led by Hesheng Liu, director of the Laboratory for the Study of the Brain Basis of Individual Differences.

Functional mapping of the brain is an active area of research and so-called “parcellating” algorithms are under development by several groups. However, the collaboration’s iterative algorithm is unique in that it exploits a priori knowledge of functional brain anatomy. It uses an atlas of 18 brain networks as a template and starting point, projecting them onto the individual’s blood oxygen level dependent (BOLD) fMRI data. The atlas was derived from the scans of 1000 individuals in previously reported work.

The parcellation algorithm compares each of 18 network-averaged reference signals derived from the template with fMRI data from single points in the individual’s scan. Points that correlate strongly with any of the 18 reference signals are averaged to derive more personalized “core” signals for each network.

Reference and core signals are then iteratively averaged together to update the reference signal, eventually converging to a final, personalized set of networks. Each time they are averaged, the core signal is preferentially weighted depending on several factors. For example, core signals are assigned a greater weight than the atlas-derived reference signals at anatomical locations known to have greater inter-subject variability, based on data previously reported by Liu’s group.

The collaboration confirmed the algorithm’s reproducibility and that it could detect differences between individuals in two fMRI data sets of 25 and 100 volunteers. In the first set, for example, where subjects were scanned five times over six months, intra-subject reproducibility quantified using a Dice coefficient was 83%. Analysis of the second set also demonstrated reproducibility when the algorithm was applied to resting state scans and concatenated scans where the volunteers were given tasks to activate specific networks.

The researchers validated the algorithm against invasive cortical stimulation in eight pre-surgical epilepsy patients and compared its performance to other parcellation methods. They included simple application of the population-defined networks used by the algorithm and conventional task-activated fMRI scans where networks are identified using statistical techniques.

Algorithm results were consistent with the cortical stimulation data, providing a closer match than the other methods, quantified using receiver operating characteristic curves. For example, the algorithm gave an area under the curve of 0.91 compared to 0.76 for task activation fMRI.

“We have shown that sensory and motor networks can be accurately mapped in a few patients prior to brain surgery,” said Liu. “We must [now] validate the localization of cognitive networks, such as the language networks, using invasive measures in a large group of patients.”

The collaboration hopes to eventually replace invasive cortical stimulation with this technique. “My optimistic expectation is that a non-invasive functional network parcellation will be used routinely in the clinic, at least as a prescreening technique for invasive tests, within five years,” Liu told medicalphysicsweb.
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