How IMRT can become routine

‘Why is IMRT not yet the standard radiotherapy modality?’ asks Marco Schwarz.

Regardless of the specific event considered the starting point for intensity-modulated radiation therapy (IMRT), it’s safe to say that the technique has been around for more than 10 years. How can it be, then, that in 2009 one writes an article examining “how IMRT can become routine”?

The fact is, although some people may think that IMRT is fully mature and now represents the standard radiotherapy technique, this is not entirely the case. It makes sense, therefore, to try to identify the main causes underlying the delayed transition from three-dimensional conformal radiotherapy (3D-CRT) to IMRT.

We should first remember that implementing IMRT following several years of 3D-CRT experience is a completely different challenge to carrying out the same development in a department where 2D radiotherapy is still the de facto standard. While this may be stating the obvious, we tend to forget one important reason why IMRT has not shown a faster adoption rate: when IMRT came into being, CRT (i.e., CT-based 3D treatment planning with conformal apertures, based on delineated contours for both the targets and organs-at-risk) was not the standard for every centre and/or treatment site, even in more affluent parts of the world.

Furthermore, for clinicians in particular, it takes time to move from 2D radiotherapy to CRT than from CRT to IMRT. If we take these aspects into account, the slow pace of IMRT implementation suddenly becomes easier to understand.

Worlds apart

From a technical perspective, the difficulty in transitioning from CRT to IMRT may be explained by one simple observation, Namely, that for quite some time, CRT and IMRT were considered – by most clinicians and by the companies producing radiotherapy equipment – as two different worlds that could not be connected via a smooth path.

Imagine, for example, that you want to treat a patient with prostate cancer and your choice is between a four-field CRT plan and an IMRT plan with 400 control points. Assuming that you are not comfortable with dose escalation, the two plans can in most cases be designed to deliver the same dose to the target, with IMRT allowing you to reduce the volume of rectum receiving higher doses. But in this situation, would you be excited enough by the IMRT plan to immediately transition all of your prostate patients to IMRT?

I am stretching things a bit, but I’m sure that you see the point: in the early days of IMRT, it was extremely difficult to envision it as a logical extension of CRT.

The radiotherapy community needed time to fully grasp the specifics of this new technique and to benefit from IMRT’s additional degrees of freedom without making their lives unnecessarily complicated. In a way, people had to realize that even if you could deliver extremely complex segment patterns, this doesn’t mean that you actually needed to and/or should do for every patient from day one – given that this complexity usually comes at a cost.

But what do we mean exactly by “cost”? If we think about it, it’s not the hardware that’s been the main obstacle to a widespread uptake of IMRT. The real cost lay in the complexity of the treatment-planning and verification process. In my opinion, improvements in treatment-planning software have played an essential role in making IMRT less cumbersome than it was 10 years ago.

Getting used to the concepts that underlie treatment-plan optimization is, in itself, a fair obstacle in the transition from CRT to IMRT. If users of treatment-planning systems are faced with optimization software that makes it difficult to translate clinical requirements into a cost function and to “steer” the optimization towards an acceptable result, IMRT planning becomes a time consuming and frustrating task.

If there’s a single development in treatment-planning worth mentioning here, it’s the possibility of optimizing deliverable plans, as opposed to dose distributions. The experience of the past years has taught us that this is a key step in improving the whole planning procedure.

What is still missing from the optimization modules of most commercial treatment-planning systems is a means to gain insight into the optimization results; for example, the ability to identify which planning objectives are most important in determining a given solution and to evaluate which adjustment to the cost functions could produce better results. When available, such tools will allow the planner to better trust the final plan, which will be not just “2”, but a dose distribution carefully chosen from several realistic alternatives.

The increased complexity in segment patterns that characterizes IMRT was not matched, particularly in the early years, by an adequate increase in the accuracy of dose calculation. With CRT, tasks such as MLC quality assurance and treatment-planning system commissioning were strictly decoupled from the evaluation of the dosimetric accuracy for a single treatment plan. With IMRT, however, this separation mostly disappeared.

Pre-treatment dose verification of each treatment plan thus became a routine part of the IMRT process – a clear indicator that the accuracy of the dose calculation was not fully trusted and that it was difficult to define a priori accuracy criteria for the planning system that were achievable and would provide full confidence in every single plan. In many clinics, the time required to carry out such pre-treatment dose verification is still a real bottleneck hindering large-scale IMRT implementation.

There are two possible solutions to this problem: make the verification process fast and efficient, or somehow avoid the need for it altogether. With regard to the first approach, the possibility of combining all treatment-verification steps, by performing EPID-based in vivo dosimetry during the first treatment session(s) is particularly interesting.

Others argue that there is no reason why the accuracy criteria and approaches deemed valid for CRT should not apply to IMRT too, and that dosimetric pre-treatment verification should be avoided by implementing better dose algorithms in commercial treatment-planning systems. In practice, this means that Monte Carlo dose calculations should become standard.

The large-scale availability of Monte Carlo-based dose calculations in clinical practice has been anticipated for years, but remained largely an unkept promise. One of the causes for this delay, was actually the interest in IMRT, which further shifted the focus from accuracy to speed in dose calculation. We are now at a time where high accuracy and satisfactory speed can be combined. Thus there is no reason why Monte Carlo should not become the standard “dose engine” for IMRT planning in the near future.

From a practical point of view, however, there are two major issues that still cause problems for those planning to immediately transition to IMRT: The human factor and the complete verification process. On the human factor side, it’s important to remember that IMRT is perceived by many as a complex technique that is especially demanding for both planners and physicians.

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MRI-accelerator: the proof of concept

Incorporating real-time image guidance into radiotherapy would ramp tumour targeting more accurately, enabling better avoidance of critical structures and reducing side effects. Such guidance will be of particular benefit if a non-ionizing imaging technique such as MRI is employed. As such, a research team at the University Medical Center Utrecht in the Netherlands is working to integrate a linear accelerator with an MR scanner. Now the Utrecht team has demonstrated proof-of-concept operation of their system (Phys. Med. Biol. 54 N229).

In a step claimed to “open the door to start testing MRI-guided radiation therapy in the clinic”, the team showed that MR imaging with the radiation beam switched on does not degrade the performance of either the linac or the MR scanner.

“The key significance of this work is the fact that we show that real simultaneous irradiation and diagnostic-quality MR imaging is feasible,” said Raaymakers, from UMC Utrecht’s department of radiotherapy. “Before implementation in the radiotherapy clinic we obviously need to make a few more steps, but the proof is there that makes it worth investing in these steps.”

**Design features**

The prototype device comprises a 6MV linear accelerator (Elekta, UK) positioned laterally to a 1.5T Achieva MRI system (Philips, Netherlands), with a source-to-isocentre distance of 1.5 m. Ultimately, the accelerator will be mounted on a ring gantry.

The researchers identified both the MRI and accelerator to enable their simultaneous and unhampered operation. The linac was customised by replacing various steel components with non-ferromagnetic versions, as well as mounting it on a wooden frame (instead of its steel gantry), while the MR scanner was equipped with a replacement magnet and gradient coil.

The MR magnet was built (by Magnet, UK) with the central 15 cm free of coils to let the radiation beam through, giving a maximum irradiation field of 24 cm in the head-feet direction. The magnet is actively shielded, with most of the external field generated by the inner coils cancelled by a field generated from a pair of shield coils. The configuration is tuned to provide a toroidal low-field zone around the magnet. The most sensitive parts of the accelerator are then sited in this low-field region.

The gradient coil, meanwhile, (designed by Philips Research, Hamburg, Germany) has a central 19 cm field free from copper windings and offers imaging performance comparable to that of a standard Achieva coil.

Raaymakers explained that system development posed a variety of challenges on all levels. “The magnet did not fit through the door so we had to break open our radiation bunker, and we got some manuals from Chinese,” he said. “But the scientific breakthrough was this concept of active shielding, which magnetically decoupled the accelerator and MRI to a large extent.”

Finally, the team also redesigned the treatment room set-up. Instead of using the standard RF-shielded room method – placing the MRI inside a Faraday cage – shielding was achieved via two RF cages situated at either side of the MRI bore. In this design, the inner wall of the MRI cryostat becomes an integral part of the RF cage and the sample volume is shielded from the rest of the room, including the accelerator.

“Together, the magnetic decoupling and the RF decoupling made it possible to perform MRI with the radiation beam on,” Raaymakers explained.

**Proof of concept**

The researchers performed initial imaging tests on volunteers (with the accelerator switched off) using standard sequences for prostate, brain and kidney MRI. All images were of diagnostic quality. They then examined the simultaneous use of the MRI and accelerator systems, by performing a 1.5T MR imaging on a pork sample during irradiation. Images taken with the radiation beam on and off were identical, and no degradation of linac performance was seen.

Working towards a clinical prototype, the next step is to incorporate a multileaf collimator, which needs to be non-magnetic. Meanwhile, constructing a gantry for accelerator rotation will facilitate treatments using an arc-therapy approach.

The Utrecht team is currently working with Elekta and Philips on these tasks. “We hope to start the first clinical tests in a year’s time. Whether this involves patients remains to be seen,” Raaymakers told medicalphysicsweb.

He continued: “We are currently discussing with our physicists what the best introduction scheme is. Should we start with palliative patients, start using MRI if improved position verification or should we start with a novel strategy such as irradiation of liver metastases? This choice will determine the technical requirements such as, for instance, full gantry rotation, and the accompanying time schedule.”

Tami Freeman is editor of medicalphysicsweb

**Tumour tracking, with sub-mm precision**

Advances in technology over the past decade have made it possible to image, plan and deliver radiation to a three-dimensional volume with sub-millimetre precision. So long as the target tumour is stationary, that is. Precision planning counts for nothing if the object of interest keeps moving in and out of line.

What’s needed is a delivery system that responds rapidly to tumour motion and reorients the treatment beam accordingly. Researchers from Stanford Cancer Center (Stanford, CA) and Washington University School of Medicine (St. Louis, MO) have now demonstrated that this is possible by combining electromagnetically localized technology with real-time, dynamic multileaf collimator (DMLC) tracking. (J. Radiat. Oncol. Biol. Phys. 74 SU7)

The work was carried out in collaboration with Varian Medical Systems (Palo Alto, CA), and the University of Washington School of Applied and Natural Sciences, University of Minnesota (Minneapolis, MN). The researchers assessed the technical readiness of the prototype device comprising a magnetic positioning system that allows motion-tracking and the RF decoupling made it possible to perform MRI with the radiation beam on.”

Finally, the team also redesigned the treatment room set-up. Instead of using the standard RF-shielded room method – placing the MRI inside a Faraday cage – shielding was achieved via two RF cages situated at either side of the MRI bore. In this design, the inner wall of the MRI cryostat becomes an integral part of the RF cage and the sample volume is shielded from the rest of the room, including the accelerator.

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**Upping the dose via tomotherapy**

Preliminary results from an ongoing clinical trial reveal that helical tomotherapy may enable higher biologically-effective radiation doses to be delivered to non-small cell lung-cancer patients, with lower than expected toxicities. In contrast with most dose escalation studies, the researchers – from the University of Wisconsin School of Medicine and Public Health (Madison, WI) – did not increase the total number of fractions. Instead, all patients received 25 treatment fractions over five weeks, with the dose set according to each individual's likelihood of lung toxicity (TCRT 6 441).

For the 46 patients in the study, the overall two-year survival rate was 46.8%, a large increase over historical rates of 21.5% for the same stage-range of disease. The study showed that higher doses of radiation (typically around 60 Gy in 2 Gy fractions) could be delivered safely using this hypofractionated tomotherapy schedule. Lung and oesophageal toxicities were lower than expected.

Paula Gould is a contributing editor on medicalphysicsweb
The **Calypso® System** is the leading real-time guidance platform for prostate radiation therapy that enables clinicians to keep radiation precisely and continuously focused on the treatment target. The accuracy that comes with continuous real-time tracking improves confidence that you’re hitting the target – and not what’s next to it.

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High-resolution dosimetry is important for all radiation therapy techniques, but more critical for the newer conformal treatment modalities that employ small radiation fields. At the extreme, stereotactic radiotherapy and radiosurgery typically use field sizes of less than 4 cm, and at times as small as 5 mm. Such regimes necessitate tighter target margins and pose stringent dosimetry demands.

There are, however, some big challenges associated with small-field dosimetry. First, as field sizes decrease, the dose becomes inhomogeneous across the beam. Increased collimation also results in steeper dose gradients at the beam edges. If detectors larger than the beam's penumbra are used to measure such fields, they systematically overestimate the beam width — errors that could have significant clinical implications.

What’s needed is a detector with an active width smaller than the beam dimension. Having to perform stereotactic beam dosimetry with high spatial resolution and in real time — requirements that are currently not met by any commercially available product. To fill this gap, UK researchers are developing a small-field dosimeter based on position-sensitive detectors that were originally employed in particle physics (Phys. Med. Biol. 54 445).

The device, called DOSI, is capable of real-time measurements with submillimeter resolution for the research team — from the Rutherford Appleton Laboratory (RAL), University Hospital Birmingham NHS Trust, the University of Birmingham and Swansea University — investigated a prototype DOSI made from monolithic silicon implanted with a linear array of 128 diodes (developed by an earlier RAL collaboration).

The team used the prototype device to characterize 6 MV photon beams from a stereotactic collimator system, with beam diameters ranging from 7.5 to 35 mm. The device's performance was evaluated by measuring the dose distribution, percentage depth dose distribution (PDD), off-axis ratio (OAR) and relative output factor (ROF).

The DOSI data were compared with corresponding results from the hospital's standard dosimeters: a diamond detector and a PointPoint ionization chamber, both optimized for stereotactic measurement. Excellent correlation was seen between DOSI's results and those recorded with the diamond detector, with PDDs in agreement to better than 1% for all depths. The agreement between OARs was better than 3% for all collimators, with ROFs of DOSI and the PinPoint ionization chamber. This is attributed to the volume averaging effects experienced by “large” air-cavity ionization detectors.

“The diodes in DOSI are 0.25 mm wide,” Manolopoulos told medicalphysicsweb. “This is much smaller than the diameter, which is 1 mm diameter at best, and 20 times smaller than the 5 mm diameter PinPoint.” Manolopoulos points out that DOSI is also orders of magnitude faster than its competitors.

Looking to the future, Manolopoulos envisions DOSI being used with advanced radiotherapy techniques. “This is already taking place at UHW, where we are about to start IMRT treatment.”

Brachytherapy: balloon options

Lumpectomy has become a standard treatment for women with early-stage breast cancer. Survival rates for this less radical surgery are equivalent to those of mastectomy, so long as the procedure is performed by a highly experienced surgeon.

The balloon radiation system (BRS) is an example of such an approach with a history that dates back over a decade. The system is based on a balloon-compatible, disposable applicator that can be inserted into the breast, with minimal collateral toxicity and cosmetic outcomes.

The balloon is inflated to allow blistering as needed. A secondary compartment is formed on the breast, with minimal collateral toxicity and cosmetic outcomes.

Researchers at the Technical University of Delft in the Netherlands are developing a new method of radiation dosimetry: radio-fluorogenic co-polymerization (RFCP), which is based on radiation-induced polymerization of a liquid monomer (Phys. Med. Biol. 54 3185).

For both probes, the fluorescence pattern was at the 1% level. For smaller beam diameters, proportional X-ray beams, proton-beam dosimetry performance, they concluded that the RFCP effect could ultimately be used to make 2D and even 3D fluence images of the dose distribution in tissue-equivalent phantoms for testing radiological treatment procedures,” explained John Warman of the university’s Reactor Institute Delft. “If the polymer could be formulated within a quasi-rigid gel matrix, then it would be immobilized and a fixed fluorescence image of the spatial distribution of radiation dose would be created.”

The team examined two potential RFCP solutions: the fluorogenic compound N-(1-pyrenyl) maleimide (MPy), mixed with either methyl methacrylate (MMA) or tertiary-butyl acrylate (BuA). To determine dosimetry performance, they recorded the fluorescence output of each solution while it was moved into and out of the irradiation chamber of a cobalt-60 gamma-ray source.

For both probes, the fluorescence output increased linearly with accumulated dose. When the chamber was raised, the output intensity remained near constant, indicating minimal post-irradiation effects. The higher sensitivity of BuA enabled data with a reasonable signal-to-noise ratio to be obtained using an integration time of just 2 s. Comparing the performances of the two solutions in a radiotherapy-relevant regime (0.27 Gy/min with an accelerated dose of 2.5 Gy) revealed that only BuA/MPy was accurate in this range.

The researchers concluded that RFCP’s linear dose dependence, fast response time and large dynamic range make it suitable for real-time radiation dosimetry. Meanwhile, the possibility of creating a polymer gel could ultimately enable 3D dose imaging during radiotherapy.

“We have been able to produce an optically clear radio-fluorogenic gel matrix in which the spatial resolution of the fluorescence image is 0.1 mm — much smaller than the commercial gel we have used so far,” Warman said. “We hope, in the not too distant future, to demonstrate that the method can be used to image multi-directional X-ray beams, balloon-compatible tracks and the dose distribution around radioisotope sources used in brachytherapy.”

Gel dosimetry: a radio-fluorogenic gel fluoresces after irradiation by a masked 3 MV electron beam.

Researchers at the Technical University of Delft in the Netherlands are developing a new method of radiation dosimetry: radio-fluorogenic co-polymerization (RFCP), which is based on radiation-induced polymerization of a liquid monomer (Phys. Med. Biol. 54 3185).
Protons decrease second-cancer risks

The emergence of lower-cost proton-therapy systems based on compact accelerators enables many more patients to benefit from this highly conformal cancer treatment. To this end, several commercial firms are developing compact systems based on a range of technology approaches. One such company is ProTom International (Flower Mound, TX), which teamed up with MIT’s Bates Linear Accelerator Center (Middleton, MA) last summer to validate its compact proton-therapy system. Now, the partners have announced successful proton extraction and extraction from the ProTom system.

The ProTrain proton system arrived at MIT-Bates earlier this year for validation testing. Following just two months of installation and commissioning, a proton beam was extracted with a beam energy ranging from 30 to 250 MeV. The research team also demonstrated dynamic real-time modulation shaping and extraction from the ProTrain system.

“After completing the formal FDA [Food and Drug Administration] review process in order to make this important new treatment tool clinically available to cancer patients in the US,” said ProTrain’s CEO Stephen Spotts. “We are now ready to begin treating patients, which was a significant step forward for patients receiving prostate cancer treatment in the US.”

One of the main advantages of a small synchrotron is that it can provide independent validation of the system and help identify further potential developments. One of the key advantages of a small synchrotron is its ability to deliver a highly conformal beam with a smaller footprint than a typical large synchrotron.

The ProTrain system is designed to deliver proton therapy with a range of energies, from 30 to 250 MeV, to treat a variety of cancer types, including prostate cancer. The system uses advanced radiation therapy techniques, such as intensity-modulated radiation therapy (IMRT), to deliver the most precise and effective treatment possible.

Advances in cancer detection and treatment have led to large improvements in survival rates. But with increased survival comes an increased need to minimize long-term treatment-related effects. In particular, chemotherapy and radiation therapy are more susceptible to radiation carcinogenesis and have an increased risk of developing second cancers later in life.

Proton therapy offers a theoretical dosimetric advantage over photon radiotherapy, in terms of sparing nearby tissues and organs. As such, it has been proposed as a promising modality for treating central nervous system cancers in paediatric patients. But, while several studies have examined the stray radiation exposures associated with proton therapy, the risks from neutrons generated during the treatment have, in the main, been neglected.

With this in mind, researchers at the MD Anderson Cancer Center (Houston, TX) have compared the risks of developing a second cancer following craniospinal irradiation (CSI) delivered via four modalities: conventional photon therapy, intensity-modulated photon radiotherapy (IMRT), passively scattered proton therapy, and scanned-beam proton therapy, with neutron emissions accounted for in the proton treatments (Phys. Med. Biol. 54 2227).

“Protons focus on prostate cancer”

Long-term survivors of prostate cancer who were treated with radiation therapy face a small but significant risk of developing radiation-induced secondary cancer. Many of these second cancers arise in the normal tissue adjacent to the target, thus it’s been suggested that proton therapy—with its dosimetric advantages—could potentially reduce their incidence. Studies have suggested that using spot-scanned proton therapy for prostate irradiation can reduce the incidence of second cancers compared with intensity-modulated radiation therapy (IMRT). However, as most clinical centres currently use passively scattered proton delivery, for which the production of stray neutron radiation has become a concern, it’s important that this option is also investigated.

Researchers at the MD Anderson Cancer Center (Houston, TX) assessed the relative risks of treating prostate cancer with passively scattered protons and 6 MV IMRT. The studies accounted for contributions from both primary and secondary sources of radiation (Int. J. Radiation Biol. Oncol. 74 616).

To compare the two techniques, the researchers used a commercial treatment-planning system to construct proton treatment plans and IMRT plans for three patients with locally-advanced adenocarcinoma of the prostate. The plans were used to calculate the absorbed dose to the patient from stray radiation for the primary and secondary organs at risk. Secondary doses were determined using Monte Carlo simulations for proton therapy and measurement of primary neutron dose from whole body scans.
Lower energies: reduced costs

There’s no doubt that proton therapy has a great deal to offer clinically: its ability to conform the deposited dose to the intended target improves normal-tissue sparing compared with conventional X-ray therapy. However, with current estimates putting proton-therapy costs at 2.4 times those of intensity-modulated radiation therapy (IMRT), opponents claim that its benefits do not outweigh the additional expenditure.

To redress this drawback, research teams are developing lower-cost proton-therapy systems, using compact accelerators that can be mounted on a rotating gantry and contained within the treatment room. Several approaches are under investigation, including miniaturized synchrocyclotrons, laser-induced plasma wakefield accelerators, and the dielectric wall accelerator (DWA), which uses pulsed electric fields generated inside a high-gradient insulating acceleration tube to speed protons passing through to high energies.

A key factor when designing any new accelerator is specifying the maximum proton kinetic energy that the treatment system must achieve. While the maximum kinetic energy required is generally accepted as 250 MeV (giving a proton range of about 38 cm in water), recent calculations have revealed, actually, that a lower value may be sufficient for the majority of proton treatments.

Researchers from the University of Wisconsin School of Medicine and Public Health (Madison, WI) have quantified the maximum proton energy necessary to treat a given percentage of patients, and examined the implications of this energy threshold when building a gantry-mounted proton-accelerator treatment system (Med. Phys. 36 164). The team analysed 100 randomly selected treatment plans from patients treated with IMRT for cancers of the breast (12), brain, head and neck (28), lung and bronchus (20), abdomen and pelvis (20) and prostate (20). For each case, they calculated the maximum proton-beam energy required to treat the patient using a DWA-based system.

Calculations revealed that treating all patients in the study would need proton energies of up to 240 MeV. However, 90% of patients could be treated at 198 MeV, and 95% at 207 MeV. A beam kinetic energy of 200 MeV immediately prior to entry into the patient was sufficient to treat all breast, brain, head and neck cases, as well as 19/20 of lung and bronchus, 15/20 of abdominal and pelvis, and 17/20 of prostate patients.

Decreasing the maximum kinetic energy from 250 to 200 MeV will decrease the length of the accelerator. This could lead to a significant reduction in the total volume of the treatment system and the size of the treatment room needed to house it,” explained Evan Sengbusch, graduate research assistant in the University of Wisconsin’s medical physics department. “Secondly, accelerating protons to lower energies means that a lower maximum magnet strength is required to deflect and/or bend the proton beam.”

Even with a maximum kinetic energy of 200 MeV, Sengbusch predicts that a DWA proton system will, for now, likely still cost more than existing IMRT set-ups, although “considerably less than current proton-treatment systems”.

The researchers conclude that it’s feasible to significantly lower the maximum kinetic-energy requirements of a compact proton accelerator if the ability to treat a small percentage of patients with rotational therapy is sacrificed. Such a decrease could reduce costs and ease engineering constraints when setting up such a facility, allowing more patients access to this promising treatment modality.

Team work: the research groups of Paul DeLuca and Rock Mackie are studying many aspects of the DWA proton-therapy system.
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PET: predicting drug response

Chemotherapy plays a vital role in the treatment of cancers, but its therapeutic success is not guaranteed. A patient may respond to one drug but not another, or a tumour may mutate and stop responding to a drug. The ability to predict the effectiveness of a particular drug could prevent unnecessary courses of chemotherapy and the associated toxic side effects. PET scanning could provide such a predictor.

Researchers at the University of California, Los Angeles (UCLA) are developing a PET-based tool that could one day allow doctors to evaluate an individual tumour's response to a chemotherapy drug before prescribing therapy, enabling them to personalize treatment to a patient's unique biochemistry.

The UCLA research team has previously created a PET probe by slightly altering the molecular structure of gemcitabine, one of the most common chemotherapy drugs (Nature Med. 14 783). The probe, called 18F-FAC, is activated with positron-emitting particles that allow its movement through the body to be tracked via PET imaging. In a recent small study, the researchers injected the probe into mice with leukaemia and lymphoma tumours, and then imaged the animals an hour later. Gemcitabine is activated intracellularly at a rate controlled by an enzyme called DCK, the activity of which varies significantly among individuals and across different tumour types. The PET scans showed that 18F-FAC accumulated selectively in DCK-positive rather than in DCK-negative tumours (PNAS 106 2847).

“The PET scan offers a preview for how the tumour will react to a specific therapy,” explained first author Rachel Laiing, a UCLA graduate researcher in molecular and medical pharmacology. “We believe that the tumour cells that absorb the probe will also take up the drug. If the cells do not absorb the probe, it suggests that the tumour might respond better to another medication.”

The team now plans to examine whether the probe can predict cellular response to other widely used chemotherapy drugs. “For the first time, we can watch a chemotherapy drug working inside the living body in real time,” explained co-author Caux Radu, assistant professor of molecular and medical pharmacology at UCLA’s David Geffen School of Medicine.

Radu continued: “The beauty of this approach is that it is completely non-invasive and without side effects. We plan to test this method in healthy volunteers within the year, to determine whether we can replicate our current results in humans. If testing in healthy subjects proves safe and effective, the UCLA researchers plan to begin recruiting volunteers for a larger clinical study of the probe in cancer patients.

The Gamma camera: the Dilion 6800 offers molecular breast imaging.

PET scans: 18F-FAC accumulates in DCK-positive (on the left side), but not DCK-negative, tumours.

BSGI proves a valuable option

Breast-specific gamma imaging (BSGI) – a molecular imaging technology based around a high-resolution gamma camera – is proving to be an important tool in the detection and staging of breast cancers. Two recent studies further emphasize the value of this emerging technique, which can visualize less dependent tissue density and discover very early-stage cancers.

The first of these studies compared the sensitivity of mammography, DBy, ultrasonography, MRI and BSGI for detecting invasive lobular carcinoma (ILC). The research team – headed up by co-author Rachel Brem, director of breast imaging and intervention at George Washington University Medical Center (Washington, DC) – performed a prospective study of 26 women with biopsy-proven ILC, all of whom had undergone mammography and BSGI (AJR 192 379).

The mriography and BSGI imaging findings were classified by experienced breast imagers as positive or negative for ILC. Where performed, ultrasonography (25 patients) and MRI (12 patients) results were also examined. The researchers concluded that BSGI was the most effective diagnostic imaging technique, with a sensitivity of 93%. Mammography, ultrasound and MRI demonstrated sensitivities of 79, 68 and 83%, respectively.

“The study is significant because ILC can often be difficult to detect mammographically and is often not palpable at clinical examination,” Brem explained. “BSGI offers improved detection of this form of breast cancer that impacts approximately 10% of new breast-cancer patients every year.”

To perform BSGI, the patient is given a radioactive tracer agent. The gamma-ray emission from this radionuclide is then used to form a digital image showing the metabolic activity of the breast tissue, including its higher metabolic rate, cancerous cells absorb more tracer than healthy cells and thus appear as “hot spots” on a BSGI image.

“BSGI is a physiologic, rather than an anatomic, approach to breast-cancer diagnosis,” said Brem. “It is likely to detect more manageable forms of breast cancer than MRI is because it has the added advantage of detecting the sensitivity for ILC. In fact, it is known that MRI can be limited in the detection of ILC. In addition, the cost of BSGI is significantly less than a breast MRI.”

Extended view

Elsewhere, a research study led by Nathalie Johnson, general surgeon and surgical oncologist at Legacy Good Samaritan Hospital (Portland, OR), demonstrated that BSGI can reveal additional cancers in patients newly diagnosed with breast cancer (Am. J. Surg., 197 199).

Johnson and her team conducted a retrospective review of 138 breast-cancer patients (69 invasive ductal carcinoma, 20 ILC, 32 ductal carcinoma in situ and 17 mixed) in whom BSGI was performed as part of the imaging work-up. BSGI detected additional or more extensive malignancy in the same or opposite breast in 10.9% of these patients. The positive predictive value for BSGI was seen to be 92.9%.

According to Johnson, the biggest benefit of BSGI over breast MRI (often used as a mammography adjunct) is its specificity. “The sensitivity of BSGI is on par with MRI, but the specificity is higher. In addition, when compared to MRI, BSGI is less expensive and easier to use for patient and physician.”

She continued: “The research is important because it helps clarify the role of BSGI in newly diagnosed breast-cancer patients. We have found that these women can have more extensive disease that is not detected by mammography or ultrasonography. This is especially helpful in patients with dense breast tissue where additional evaluation of the remaining breast tissue is necessary.”

In both studies, BSGI was performed with the Dilion 6800 Gamma Camera, a high-resolution, compact field-of-view gamma camera, optimized to perform BSGI. According to its manufacturer Dilicon Technologies (Newport News, VA), the camera was designed to capture up to 16 images, compared with up to thousands of images generated with breast MRI.
Invitation for authors

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Deformable image registration (DIR) is a key tool for determining a point-to-point correspondence between two clinical images. While several recent publications have described innovative DIR strategies and implementations, the translation of image-processing research into clinical application is confounded by the lack of an established method for validating new algorithms.

To determine the efficacy of any DIR algorithm, it’s important to compare its performance against that of an appropriate reference standard. Various standards have been proposed, including those based on synthetically deformed images and high-contrast phantoms. But, according to recent research, the best standard for validating registration accuracy in a clinical setting should be one that’s derived from actual patient image data (Phys. Med. Biol. 54 1849).

To this end, a US Research team has developed a self-contained framework for evaluating the accuracy of DIR-based functional lung imaging from 4D CT images, explained Thomas Guerrero, associate professor of radiation oncology at MD Anderson Cancer Center (Houston, TX). “It quickly became clear, however, that the derived lung-function images were highly variable, depending on the particular DIR formulation used to perform the pulmonary function calculations. Thus we sought to develop a framework for objective evaluation of DIR spatial accuracy.”

The landmark point pairs were generated by a thoracic-imaging expert, who manually registered large numbers of corresponding pulmonary landmark features from five pairs of treatment-planning thoracic 4D CT images. Using a Matlab-based software interface to facilitate manual selection, the expert registered 6726 landmark point pairs over the five cases. Two secondary readers were employed to provide estimates of observer variance.

To demonstrate the practical utility— and statistical necessity— of the evaluation scheme, the researchers examined two DIR algorithms: a gradient-based optical flow method (OFM) and a landmark-based moving-attractor (MLS) algorithm. Both algorithms were used to register the five CT image pairs, and the resulting spatial accuracy determined by comparison with the manually registered landmark data set. The mean spatial registration errors for the OFM and MLS algorithms were 6.90 and 2.05 mm, respectively. Graphical representations of these error data provided further detail as to their nature.

“These algorithms represent two very different strategies for performing DIR of medical image volumes,” co-author Richard Castillo told medicalphysicsweb. “The OFM formulation is driven by the assumption that corresponding voxel intensities remain constant between image pairs, thus the driving force is image similarity, as opposed to spatial accuracy. The MLS deformation, on the other hand, is driven by the assumption that corresponding voxel intensities remain constant between image pairs, thus the driving force is image similarity, as opposed to spatial accuracy.”

The researchers calculated the dose-length product (DLP) for each examination to reflect patients’ radiation exposure during the entire cardiac CT scan. The DLP was calculated by multiplying the CTDIvol by the scan length. Effective dose values were estimated by multiplying the DLP by an appropriate conversion factor. Image quality was assessed by an independent reviewer who checked the visibility of the four main coronary arteries on the CCTA images. The researchers calculated the dose-length product (DLP) for each examination to reflect patients’ radiation exposure during the entire cardiac CT scan. The DLP was calculated by multiplying the CTDIvol by the scan length. Effective dose values were estimated by multiplying the DLP by an appropriate conversion factor. Image quality was assessed by an independent reviewer who checked the visibility of the four main coronary arteries on the CCTA images. The researchers calculated the dose-length product (DLP) for each examination to reflect patients’ radiation exposure during the entire cardiac CT scan. The DLP was calculated by multiplying the CTDIvol by the scan length. Effective dose values were estimated by multiplying the DLP by an appropriate conversion factor.
A 7 tesla MR tomography system at the Max Delbrück Center in Berlin, Germany, is being employed to advance diagnoses and treatments of brain diseases and cancer, as well as open up new possibilities in cardiac research. The machine’s ultrahigh field strength greatly enhances image resolution, and enables it to perform high-speed measurements.

Project partner PTB, the National German Metrology Institute, is now exploring the technical possibilities of the new device and making it suitable for clinical application.

Multiple angles ease screening

Early detection of disease means better chance of survival. That’s the rationale behind cancer screening programmes. Unfortunately, whenever chest radiography has been trialled as a means of seeing out early-stage lung cancer, mortality rates have not reduced.

One reason for the poor performance of chest radiography as a screening tool is its tendency to miss very small pulmonary nodules. Researchers from Duke University (Durham, NC) are now testing a multi-projection X-ray system that promises to do better (IEEE Trans. Nucl. Sci., 56(2), 2009).

Up to 90% of potentially cancerous lung nodules are not seen on standard chest X-rays. Far more small lung nodules are picked up on CT, because the slice-by-slice tomographic technique essentially eliminates the problem of anatomical structures overlapping on 2D views. But the radiation dose associated with a chest CT scan is much higher than that for chest radiography, even if a low-dose protocol is applied. Implementation of a lung cancer screening programme based on CT consequently remains controversial.

“So far, there are only about 30 magnetic resonance tomographs with such a high magnetic field strength, and most of them are used for brain research,” said Bernd Iittermann, head of the PTB’s department of medical metrology. The new whole-body 7 T MR machine will have far more widespread use, providing extremely high-resolution images from the interior of the body. The researchers also hope to use the system to investigate molecular processes in the body, to help combat tumours, for example.

Testing the system to investigate molecular processes in the body, to help combat tumours, for example.
Nanoparticles – in their myriad of shapes and forms – are touted as ideal for a broad range of cancer-management applications. In a hot-bed of research activity, nanoscale-materials are being developed to image the distribution of tumour cells in the body, target and attack to cancerous cells, destroy unwanted cells via ablation or delivering drugs, or – according to the latest claims – all of the above. Here, we take a look at some of the nanotechnology developments reported recently.

- Royal Philips Electronics of the Netherlands has created the first in vivo 3D images using magnetic particle imaging (MPI) – a technique based on visualizing iron-oxide nanoparticles injected into the bloodstream. The team used MPI to scan and deliver magnetic nanoparticles to targeted tumour sites. MPI can capture dynamic concentration changes of the injected nanoparticles, which are swept along by the bloodstream. The team used MPI scanning to capture the distribution of iron-oxide nanoparticles injected into the bloodstream, which can be traced via MRI, while the nanoparticles are sweep along by the bloodstream. The team used MPI scanning to capture the distribution of iron-oxide nanoparticles injected into the bloodstream, which can be traced via MRI, while the nanoparticles are swept along by the bloodstream.

By adding important functional information to the anatomical data obtained from existing modalities, such as CT and MR, Philips’ MPI technology has the potential to significantly help in the diagnosis and treatment planning of major diseases such as atherosclerosis and congenital heart defects,” said Henk van Houten, senior vice-president of Philips Research.

- Many nanomaterials tested in research labs are too toxic for human use. Now, a team of US scientists has developed porous silicon nanoparticles, which glow brightly, last long enough to slowly release cancer drugs, and then break down into harmless by-products. When the nanoparticles were tested in mice, the tumours glowed for several hours and then faded. Close examination of vulnerable organs like the liver, spleen and kidney revealed no lasting changes in mice treated with the nanoparticles (Nature Materials doi:10.1038/nmat2398). The bio-degradable nanoparticles can also be used to help deliver cancer drugs. “The goal is to use the nanoparticles to chaperone the drug directly to the tumour,” said study leader Michael Sailor of the University of California, San Diego (La Jolla, CA). At about 100 nm, these particles are bigger than many others designed to deliver drugs, a factor that’s claimed to improve both their effectiveness and safety.

- A US research team is using hollow gold nanospheres to enhance the cell-killing effects of photothermal ablation. The ultimate aim is to develop a minimally invasive treatment for malignant melanoma. The researchers equipped the nanospheres with a protein fragment that targets melanoma cells while avoiding healthy skin cells. When exposed to near-infrared light, the nanospheres heat up and destroy the cancer cells. In studies in mice, the hollow nanospheres did eight times more damage to skin tumours than the same particles without the targeting peptides. They’re also claimed to be 50 times more effective than solid gold nanoparticles for photothermal therapy. With sizes ranging from 30 to 50 nm, the nanoshells are much smaller than other nanoparticles previously designed for photothermal therapy. The next stage will be to test the nanospheres in humans. Though with the need for extensive preclinical toxicity studies, there’s some way to go yet before the technique could find its way into clinical practice.

The researchers, from the University of California Santa Cruz, the University of California Berkeley, and the MD Anderson Cancer Center in Houston, TX, presented this work at the 237th ACS National Meeting in Salt Lake City, UT.

- Researchers at Purdue University (West Lafayette, IN) have come up with a way to deliver drugs directly to cancer cells using gold nanorods combined with magnetic iron-oxide particles. The magnetic particles can be traced via MRI, while the nanorods are luminescent and can be traced through optical microscopy. While MRI is less precise than optical luminescence in tracking the probes, it can track them deeper in tissue (Angew. Chem. Int. Ed. 48 2759).

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