The earlier, the better

Dr Wei Huang discusses his research on cancer imaging techniques and reveals what his team’s latest discoveries could mean for the diagnosis and treatment of cancer.

What led you to switch research fields from neurodisorders to cancer?

I joined the Memorial Sloan Kettering Cancer Center (MSKCC) as a magnetic resonance imaging (MRI) physicist in 2003. Prior to this, my main research focus was using MR spectroscopy (MRS) to study various types of neurodisorders, such as Alzheimer’s disease and multiple sclerosis. As you can imagine, all of MSKCC’s research is focused on cancer. Therefore, after joining the Center, my first research effort was to use MRS to improve breast cancer diagnostic accuracy. The motivation behind this is the high false positive rate in breast cancer detection by current state-of-the-art breast imaging methods, such as X-ray mammography, ultrasound and MRI, which leads to many unnecessary biopsies of benign breast lesions.

Why did you focus your studies on applying MRI techniques for cancer detection and the assessment of therapeutic response?

My colleagues and I discovered that, with much better signal-to-noise ratio compared with MRS, and therefore better ability to detect smaller lesions, dynamic contrast-enhanced MRI (DCE-MRI) can be used to significantly improve breast cancer diagnostic accuracy. This, in turn, leads to a reduction in unnecessary biopsies, especially when the imaging data are analysed quantitatively using a pharmacokinetic model.

With cancer treatment entering an era of precision (or personalised) medicine, I believe imaging will play an important role in treatment decision making. An imaging method like MRI is non-invasive and can provide a 3D high-resolution survey of an entire tumour’s heterogeneous response to therapy – something that an invasive procedure like biopsy cannot do. If imaging can provide accurate predictions of therapy response in the early stages of treatment, then non-responding patients can be switched to, or stratified for, different treatment arms. This will spare them from ineffective and potentially toxic drugs, and has tremendous implications for patient wellbeing and healthcare cost efficiencies.

How does DCE-MRI provide early prediction of cancer response to treatment?

In standard cancer imaging, guidelines such as response evaluation criteria in solid tumour (RECIST) are used to measure tumour size changes for evaluation of response to treatment. However, many research studies show that tumour size change is not a good early predictor of treatment response, especially in the era of targeted cancer treatment.

Cancer cells are not necessarily killed immediately after administering targeted therapy. Instead, biological tumour functions are altered at an early stage of treatment before there is actual tumour shrinkage. Therefore, functional imaging methods are better equipped than conventional anatomic imaging for early prediction of therapy response. DCE-MRI is one functional imaging method that measures tumour microvasculature; it provides early prediction of cancer therapy response by detecting early changes in tumour microvascular properties following the initiation of therapy.

Can you outline your team’s work on developing new software tools to aid clinical decision making?

We have taken a ‘big data’ approach, whereby all kinds of data – including clinical, genomic, proteomic and imaging data – will be combined for planning personalised treatment strategies. Supported by the National Cancer Institute, we are building web-based software for clinical decision making. This tool will allow a physician to input a patient’s DCE-MRI data for processing with the shutter-speed model. This enables us to obtain the imaging biomarker results in the tumour and combine the imaging results – which can include more than just the DCE-MRI results – with the patient’s clinical and molecular (genomic and proteomic) data. This aids decision making by enabling the plotting of the data points of individual patients to be treated among those from previous patients with known clinical outcome (such as overall survival) following treatment.

How do you envision the DCE-MRI shutter-speed model will impact the diagnosis and treatment of cancer in the future?

DCE-MRI has already been widely used in research and early phase clinical trial settings to evaluate cancer response to treatment. For some cancers, such as breast cancer, DCE-MRI is already part of clinical work-up for cancer detection. There is improving consensus and standardisation in DCE-MRI data acquisition and analysis to advance reproducibility and repeatability. DCE-MRI will therefore be translated into everyday clinical practice as a functional imaging method (not just for anatomic observation) for cancer diagnosis and therapeutic monitoring.

I believe the capability of the shutter-speed DCE-MRI method, in providing comprehensive imaging of tumour functions (vascular and metabolic), will make it an indispensable tool for the diagnosis and treatment of cancer in the near future.
IMAGING TECHNIQUES ARE important not only for aiding early detection of cancer, but also for determining the precise stage and location of the disease. This enables doctors to prescribe effective, tailored treatments and, where necessary, perform direct surgical procedures. Numerous imaging methods are currently used for early detection of cancer, such as ultrasound, nuclear imaging and computed tomography scans. However, there can be problems with determining the exact form of cancer – for example whether it is indolent or aggressive – when using these conventional methods.

Researchers at Oregon Health and Science University, USA, are working on the development of an advanced functional imaging technique to evaluate cancer response to therapy.

A PHYSIOLOGICAL PHENOMENON
Dr Wei Huang and his colleagues have developed a dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) technique in the hope that it will lead to sensitive and reproducible quantitative imaging methods. The potential benefits of this new technology are significant and far reaching. First, while no one can predict how a patient will respond to specific treatments, DCE-MRI could predict therapy response in the early stage of treatment and spare non-responding patients from receiving ineffective and toxic treatments. Second, the technology could help improve the clinical management of individual cancer patients. Third, the time it usually takes to evaluate the efficacy of novel therapies could be notably reduced.

Conventional pharmacokinetic techniques for DCE-MRI data analysis are based on tracer kinetic models, which have been developed for nuclear imaging procedures such as positron emission tomography (PET). These modalities acquire their imaging signals from the tracer molecule that is delivered to the body through intravenous injection. This means that there is no cause to worry about water exchange between in vivo tissue compartments.

However, in MRI, water molecules are the source of the imaging signal, meaning that it is important to take water exchange across cell membrane and blood vessel wall into account. "The MRI signal is related to tissue contrast agent concentration indirectly through interactions between contrast molecules and water molecules," Huang elucidates. "Since most MRI contrast agents (generally gadolinium chelates) do not enter inside cells..."
while both extra- and intra-cellular water contribute to MRI signal, it is important to account for inter-compartment water exchange – a real physiological phenomenon – in pharmacokinetic modelling of DCE-MRI data.”

SHUTTER SPEED
Although conventional pharmacokinetic models for DCE-MRI data analysis exist, the team has developed a shutter-speed model that takes the physiological phenomenon of water exchange across tissue compartments into account and improves the accuracy of data analysis. This leads to the correction of systematic errors in the conventional models and results in more accurate discriminations between benign and malignant breast lesions. Using the shutter-speed model could therefore reduce the number of unnecessary biopsies performed in clinics, which in turn could benefit patients’ wellbeing and reduce healthcare expenditure.

Huang and his team have also found that the shutter-speed model is sensitive to functional changes in breast tumours caused by therapy. This could enable doctors to ascertain whether or not the treatment prescribed is effective.

NEW DIMENSIONS
The shutter-speed model has recently led to an exciting discovery for the team. DCE-MRI is generally considered to be an imaging method capable of measuring microvascular properties, and is therefore used in that capacity. However, the model’s abilities as a marker of cellular energetics metabolism have now been shown.

“The development of the shutter-speed model has opened a new, additional dimension for clinical application of DCE-MRI, such as in vivo metabolic imaging with spatial resolution of MRI scale, which is superior to spatial resolution of conventional metabolic imaging methods such as PET,” Huang explains. “This discovery will have important implications for the imaging of cancer and other human diseases.”

It is clear that DCE-MRI has significant potential; however, there are limitations that still need to be addressed. For example, there is a lack of standardisation in both image data acquisition and analysis, and, until this is achieved, the technology cannot be widely applied in clinics.

The shutter-speed model takes the physiological phenomenon of water exchange across tissue compartments into account, leading to the correction of systematic errors and providing more accurate discriminations between benign and malignant breast lesions.

There are three approaches to analysing the data acquired through DCE-MRI: qualitative, semi-quantitative and quantitative. While the first two approaches are commonly used, the latter is more desirable for DCE-MRI because it generates imaging biomarkers of real tissue biology. However, issues with using this approach still remain, as Huang highlights: “Both the accuracy and precision of those biomarkers can be affected by many factors in data acquisition details and selection of pharmacokinetic model used for analysis. Briefly, the big limitation of DCE-MRI is its inadequate reproducibility and repeatability”.

The hope is that increasing awareness of the potential benefits of DCE-MRI could lead to a positive change among research and clinical communities, one that will see a consensus for standardisation. If researchers and scientists around the world use the standardised processes and methods to acquire and analyse the DCE-MRI data, then there is a genuine possibility that the technology could be translated into everyday clinical practice.