Cancer: see, reach, treat

An academic-industry partnership between **Johns Hopkins University School of Medicine** and Philips has yielded quantitative methods to evaluate liver cancer. Their 3D visualisation technique offers a more accurate representation of the tumour and could radically improve treatment

CANCER IS THE leading cause of death worldwide, accounting for over 8 million deaths in 2012. Alarmingly, liver cancer, which accounts for an eighth of all cancer deaths is also the only cancer that in increasing in incidence. There are over 800,000 new cases of primary liver cancer – cancers originating in the liver – and more than 300,000 cases of secondary liver cancer – cancers that originate from other organs, such as the colon, and metastasise to the liver – worldwide every year.

At present, liver cancer can only be cured either through ablation, inserting a needle through the skin and into the lesion and then burning it, or through surgery, either transplanting a new liver or removing the cancerous lesion. However, because the disease has close to no symptoms in the early stages, most patients are diagnosed in the later stages, when surgery and ablation are no longer options. As the range of treatment options is poor, so are the clinical outcomes – the median survival rate is less than one year.

IMAGE-GUIDED THERAPIES

Nevertheless, there is hope. Interventional oncology, a growing field, offers clinicians routes to treat patients who are unsuitable for ablation or surgery. Liver cancers are primarily supplied by the hepatic artery, while healthy liver tissue is supplied by the portal vein, providing a separate vascular pathway to reach the tumour. Therefore, delivering drugs directly to the hepatic artery is effective in the management of liver cancer patients.

Over half of liver cancer patients undergo image guided therapies, such as transcatheter arterial chemoembolisation (TACE). TACE involves the simultaneous local delivery of chemtherapy and 'beads' that block the arteries feeding the tumour, and is directed by real-time X-ray images. By positioning the TACE catheter close to the tumour, good results can be obtained, and with fewer side effects than less targeted approaches. TACE is more selective in drug delivery, and therefore can enable a higher dose of chemotherapy while maintaining a low level of systemic toxicity. Evidence shows that patients with primary liver cancer have better symptom control after TACE than those only receiving supportive care. As a result, TACE has been incorporated into all guidelines regarding the treatment of these patients. It has also become the staple of intermediate stage primary liver cancer treatment, and is being increasingly used to treat secondary liver cancer too.

AN EMERGING PARTNERSHIP

However, TACE is a palliative therapy; it cannot cure patients. What's more, it relies extensively on clinician input and subjective decision making, which can affect the outcome of the procedure, leading to non-specific drug delivery and tumour recurrence. The potential is high, but the protocols need to be more systematic.

Looking to provide these advances, and ultimately improve prognosis for patients of this devastating cancer, is the Geschwind Lab, initially a part of Baltimore's Johns Hopkins University School of Medicine and now Yale University School of Medicine. Laboratory leader Dr Jean-François "Jeff" Geschwind is Professor of Radiology, Surgery and Oncology, and Chairman of the Department of Radiology and Imaging Sciences at Yale University.

Working closely alongside Geschwind is Dr MingDe Lin, a Senior Researcher for Philips Research North America. Lin and Geschwind are Principal Investigators of a National Cancer Institute (NCI)-funded academic-industry partnership between John Hopkins University School of Medicine and world-renowned technology company Philips, which aims to 'see, reach and treat' liver tumours.

SEE

The first major goal of the project is to better 'see' liver tumours, by developing enhanced X-ray imaging hardware and software. This is an important first goal, as liver tumours are most often discovered accidentally by other medical imaging techniques, including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), when patients are examined for alternative maladies. Furthermore, TACE requires real-time X-ray imaging in order to guide the clinician in where to deliver the drugs. Geschwind's group recently made a significant improvement to image acquisition during TACE by creating an entirely new imaging method called dual-phase C-arm cone beam computed tomography (DPCBCT), which relies on an intra-arterial injection of contrast medium. "Given that the liver tumour is supplied by the hepatic artery, this provides direct visualisation of the tumour-feeding blood vessels and the tumour parenchyma," Lin explains.

This method acquires two cone beam CT (CBCT) scans back-to-back, one in the early and one in the delayed arterial phase, and requires only one

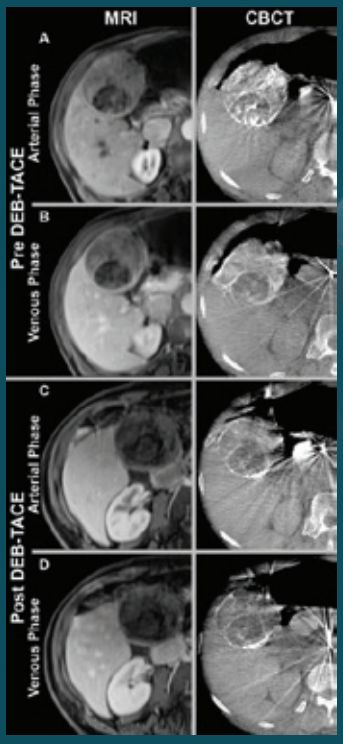

Figure 1: A–D, Representative T1-weighted axial enhanced arterial and portal venous phase MR images (left), and axial enhanced early or arterial and delayed or venous phase CBCT images (right) from a 73-year-old man with right-lobe HCC. MR images were acquired approximately 1 month before and after DEB-TACE therapy, whereas dual-phase CBCT images were acquired prior to and immediately following DEB-TACE. A, Baseline arterial phase MR and early arterial phase DPCBCT pre-DEB-TACE images. B, Baseline venous phase MR and delayed arterial phase DPCBCT pre-DEB-TACE images.. C, 1 month follow-up MR arterial phase and immediate post-DEB-TACE DPCBCT early arterial images.. D, 1 month follow-up MR venous phase and immediate post-DEB-TACE DPCBCT delayed arterial images. Note the similarity between MR and DPCBCT in enhancement patter before and after treatment, which in our study was found to be predictive of response.

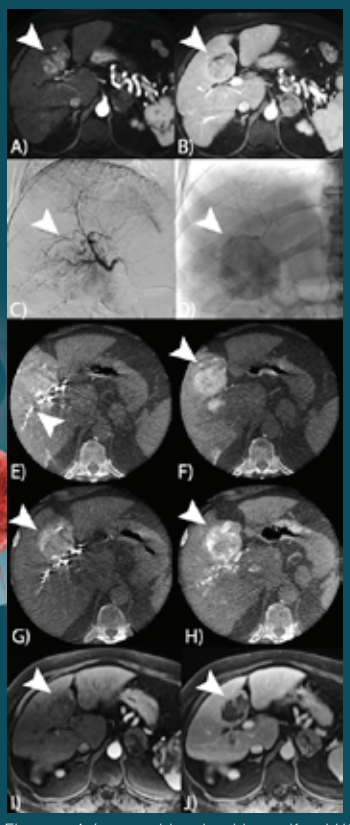

Figure 2: A 61 year-old male with a unifocal HCC in segment 4 of the liver, seen on pre-procedural CE-MRI as a hypervascular tumor on the arterial phase (A) and as a hypoattenuating tumor on the portal venous phase (B). Pre-treatment right hepatic angiography shows a tumor blush (C and D). Pretreatment DPCBCT demonstrates the 3D hepatic arterial anatomy on the arterial phase (E), and the tumor enhancement on the delayed phase (F). Immediately after the first DEB-TACE treatment, a DPCBCT was performed to assess technical success of embolization. The early arterial (G) and delayed parenchymal (H) phases images predicted intra-procedurally the same tumor response when compared to the post-TACE follow-up CE-MRI obtained 1 month later, on the arterial (I) and portal venous phases (J).

contrast injection; a marked improvement on traditional methods. Moreover, this form of CBCT significantly enhances the visualisation of liver tumours compared to conventional diagnostic imaging methods like contrast-enhanced CT, because the contrast medium is injected *directly* into the liver. DPCBCT has been shown also to be able to detect more lesions completely than 2D intraprocedural imaging traditionally used (specifically fluoroscopy and DSA).

The results of a clinical study demonstrated that enhanced images of tumours acquired by DPCBCT during the TACE procedure could be used to predict how primary liver tumours would respond to drug-eluting beads (which slowly release chemotherapy agents) up to a month after administration. Not only does the method improve treatment planning, it also improves treatment itself. DPCBCT enables intra-procedural feedback so that a more complete treatment could result. In consequence of these astounding results, DPCBCT has since been made part of routine clinical practice for TACE at Johns Hopkins and is suggested for other treatment centres to follow.

REACH

Once a tumour has been visualised, reaching it becomes the next stage in the treatment process. Accurately locating the tumour enables the targeting of treatments, which makes therapy both more specific and potent, as well as reducing side effects.

Thus, to complement DPCBCT, the team at Philips Healthcare developed a piece of navigation software called EmboGuide, a live 3D image guidance tool to improve the delivery of TACE. As the vascular pathway to the tumour can be highly variable between patients, EmboGuide helps to direct the catheter to the tumour site with the aid of live images and software guidance, very much like GPS. It assists the clinician in reaching the tumour via the arterial tree, and has been shown to make tumour-feeding blood vessels easier to detect.

TREAT

At present, radiological biomarkers are used to assess tumour response to TACE. This process is vital to further treatment decisions, yet there remains no universally accepted standard for assessing tumour response.

Response Evaluation Criteria in Solid Tumors (RECIST) guidelines are widely used to assess response to systemic chemotherapy, however, they cannot be applied to TACE because the treatment mechanism is different. The high concentration of chemotherapeutic drug used in TACE along with the embolisation of the tumour feeding blood vessels causes changes in tumour viability with minimal changes in tumour size. As a result, the European Association for Study of the Liver (EASL) introduced guidelines based around the use of contrast enhancement, a surrogate marker for tumour viability, as an independent imaging biomarker. More recently, modified RECIST (mRECIST) was proposed, aiming to improve

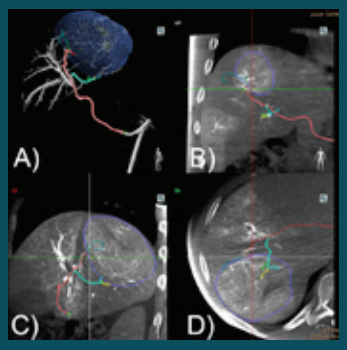

Figure 3: Early arterial phase DPCBCT is shown in coronal (B), sagittal (C), and axial (D) planes. The arterial tree and tumor feeding arteries are visualized using various line colors with the segmented tumor as the blue outline. The tumor segmentation and the extracted vessels are represented as a 3D rendering in (A).

further on the EASL guidelines.

Both methods are more effective at assessing treatment response than RECIST, but their ability to predict survival is most reliable *months* after TACE has been administered. This prevents immediate treatment decisions – which could be vital for cancer patients. Furthermore, mRECIST is only 1D, and EASL 2D, providing a one axial slice view of the 3D image volume: only a portion of the heterogeneous tumour. Put simply, they do not accurately represent the full tumour volume.

The advent of 3D tumour segmentation methods has initiated a move towards quantitative image analysis of the entire tumour. The Geschwind Lab has made an important contribution to this transition, developing their own 3D analysis method called quantitative EASL (qEASL). qEASL is a semi-automatic segmentation-based 3D technique, developed

THE TEAM IS THE FIRST TO PROVE THE SUPERIORITY OF A WORKFLOW EFFICIENT 3D QUANTITATIVE, SEMI-AUTOMATED IMAGE ANALYSIS TECHNIQUE OVER MANUAL MEASUREMENTS IN LIVER CANCER PATIENTS AFTER LOCAL THERAPIES

EMBOGUIDE: THE THREE STAGE PROCESS

1. Automatic identification of the tumour-feeding blood vessels, from the early arterial phase of the DPCBCT
2. The tumour is semi-automatically segmented, either from the delayed phase of the DPCBCT or from contrast-enhanced imaging (MRI or CT) taken before the procedure
3. The software automatically suggests the most direct vascular pathway for drugs to reach the tumour

A prospective clinical trial is currently underway to prove that EmboGuide can reduce procedure time, the dose of contrast medium, and the X-rays required, as well as improve patient outcomes by systematically positioning the drug delivery catheter.

with Philips Healthcare, that can directly calculate both tumour volume and the amount of dead tumour tissue. The image analysis is applied on contrast-enhanced MR or CT images that are already acquired as part of routine clinical care and addresses the limitations of manual 1D and 2D measurements. At present, decisions about whether to re-treat a patient after the first round of therapy are based on imaging biomarkers. But a radiologist usually measures these manually. This method is inefficient, difficult to reproduce, and often shows limited correlation with genuine tumour pathology. The 3D technology in qEASL takes the guesswork out of evaluating treatment outcomes. Furthermore, when used before and after treatment, it can predict patient survival.

The lab's research – presented at a number of conferences last year, including the Society for Interventional Radiology (SIR), the World Congress on Interventional Oncology (WCIO), and the Radiological Society of North America (RSNA) annual meetings – validated the software by comparing qEASL results to pathology, and demonstrated that what is measured through imaging represents what is happening in reality, verifying that qEASL could effectively predict patient survival better than current methods.

In the first study, the researchers compared the new 3D analysis with the standard 2D response assessment method, finding an error margin of under 10 per cent for predicting the amount of dead tumour tissue, while the 2D method strayed by as much as 40 per cent from the genuine values. In a series of follow-on studies, analysing over 300 liver tumours in 123 patients, the 3D technique demonstrated a greater ability to predict survival between patients who responded to therapy and those who did not, compared to the conventional technique.

Aside from being pathologically and prognostically accurate, the system is also workflow-efficient. It rapidly enables 3D segmentations, in a period of one to two minutes. However, as it is semi-automatic, it still allows input from the radiologist to modify the process when necessary, for example to manually correct the tumour edge.

A REVOLUTION IN TUMOUR ANALYSIS

The team has reported a number of astounding successes, testament to the advantages of a strong academic-industry partnership. "We have high technology and clinical expertise working together to help answer challenging clinical questions. There is a high level of translational research, that at the end of the day, results in improved patient care," Lin elucidates.

As a result of these achievements, Philips is presently in the process of translating the qEASL prototype into a product. On the academic side, Geschwind's team is conducting global and multi-institute studies to further expand the range of applications for their 3D quantitative analysis towards other therapies (such as systemic chemotherapy) and other regions of the body (such as brain tumours). Ultimately, they aim to lead a paradigm shift: from 1D and 2D qualitative estimates to 3D quantitative measurements – across all imaging modalities and for many diseases. Furthermore, dual-phase CBCT is considered the gold standard for intra-procedural liver lesion detection by an increasing number of physicians and, together with EmboGuide, is already commercially available outside of USA, while it has recently been 510k approved in USA.

PRODUCT LAUNCH

The team is the first to prove the superiority of a workflow efficient 3D quantitative, semi-automated image analysis technique over manual measurements in liver cancer patients after local therapies. Progress has been rapid; Philips is already in the process of translating the qEASL prototype into a product. The Johns Hopkins researchers also intend to present the results of their multi-centre studies at the Radiological Society of North America (RSNA)'s annual meeting this year, with Philips planning to launch the product simultaneously.

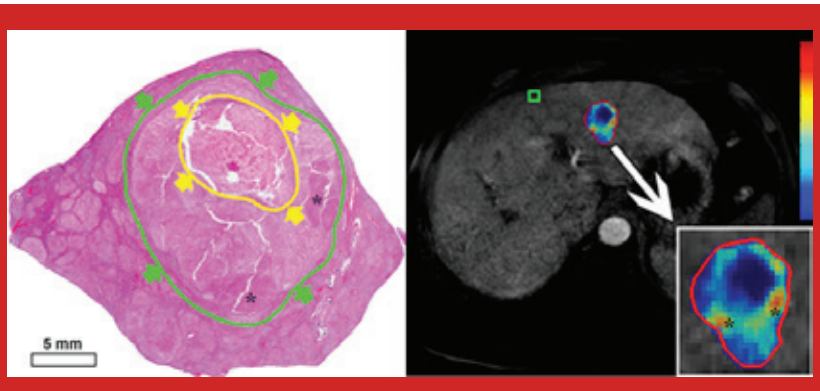

Figure 4: The left panel shows a representative slide with the histosegmentation technique (yellow area represents necrosis, green area enclosed the entire tumor). The right panel shows the qEASL color map of the tumor (magnified – red representing maximum enhancement and blue representing no enhancement/necrotic tumor tissue, normalized by the background enhancement in the green box). Corresponding, high viability tumor areas are asterisked.

SEE, REACH, TREAT THE TUMOUR AND ASSESS RESPONSE

OBJECTIVES

- See – to develop improved X-ray imaging hardware and software in order to better visualise lesions
- Reach – to create novel image guidance software to enhance tumour targeting
- Treat – to develop 3D and quantifiable measures of treatment success to assess the response

KEY COLLABORATORS

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