Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Discovery that Harmonic Ultrasound Modes using Microbubbles can Differentiate Benign from Malignant Liver Tumours, Producing a Major Improvement in Outcome

1. Summary of the impact (indicative maximum 100 words)

Questions about the benign or malignant nature of liver tumours are common and pressing since they determine how the patient is managed. Benign masses are frequently encountered; they usually do not require intervention but are easily mistaken for malignancies with conventional imaging methods. Work at Imperial College demonstrated that microbubble contrast agents have the special property of lingering in both normal liver tissue and in benign solid masses, whereas malignancies do not retain microbubble. The discovery of this property at Imperial has led to their use worldwide as a diagnostic tool. In 2012 NICE recommended their use as being cost-effective for this use.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Martin Blomley, late Professor of Radiology (1995-2006)
Professor David Cosgrove, Professor of Clinical Ultrasound (1997-2004) now Emeritus
Dr Christopher Harvey, Senior Lecturer (2001-present)
Professor Edward Leen, Professor of Radiology (2007-present)
Professor Adrian Lim, Professor of Radiology, Consultant Radiologist (2003-present)

Microbubbles are gas particles a few microns in diameter supported by a thin membrane (1). They decay spontaneously in the circulation after 2-3 minutes. During early clinical trials in 1996, Imperial researchers noticed that, after intravenous injection, microbubble signals could still be obtained from normal liver parenchyma after disappearance of the microbubbles from the bloodstream (2). Research at Imperial confirmed that microbubbles survive for longer in the sinusoidal vasculature of the liver (and, as found by Professor Lim, also in the spleen) (3). This discovery by the Imperial team at Hammersmith Hospital has become defined as the “late phase”.

The key finding was that the common solid benign masses such as haemangiomas and focal nodular hyperplasia also share this property, whereas malignant masses such as metastases and primary liver cancers (hepatocellular- and cholangio- carcinomas) do not. This crucial observation, by Imperial researchers, made available a fast, safe and inexpensive test that has revolutionised the investigation and management of patients being assessed for liver malignancy (4). Other imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) can also achieve this, but they are more expensive, less immediate and less widely available.

In 2000 Dr Harvey demonstrated that microbubbles could be used as tracers following bolus i.v. injection (5). Real-time haemodynamic information, that is analogous to that obtained using radionuclide tracers, can be derived by monitoring the arrival of microbubbles into the arterial supply of an organ or region of interest (such as a tumour). By following the changing signal intensity in real-time as the microbubbles arrive and disappear, time-intensity curves can be created, from which several features can be extracted and turned into functional images. This dynamic approach was put to effect in the liver where Professor Blomley and colleagues found that an accelerated transit between the supplying hepatic artery and the draining hepatic veins is a marker for liver metastases and for cirrhosis. An important development of this use of microbubbles as tracers is in monitoring the vascular response of tumours to treatments directed against their neovascular supply to allow early tailoring of treatment (6).

An extension of the Imperial group’s observations on the behaviour of microbubbles is their ability to define very precisely the microvascular perfusion of tissue (6); Professor Leen has translated this into an important use in immediate monitoring of the interstitial ablation of tumours. Before this Imperial work the clinical treatment approach for a planned ablation would be; the ablation would be performed and the patient would be sent for a contrast-enhanced CT scan. If the treatment has not been adequate (as determined by the CT), the patient must return on a separate occasion to the interventional room for further ablation. Using microbubbles, the adequacy of the treatment can be assessed immediately after the ablation session, in the same room, with demonstrated savings in time, cost and effectiveness.

3. References to the research (indicative maximum of six references)

(1) Blomley, M., Cosgrove, D. (1997). Microbubble echo-enhancers: a new direction for ultrasound? *Lancet*, 349, 1855-1856. DOI. Times cited: 38 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(2) Blomley, M.J., Albrecht, T., Cosgrove, D.O., Jayaram, V., Eckersley, R.J., Patel, N., Taylor-Robinson, S., Bauer, A. and Schlief, R. (1998). Liver vascular transit time analyzed with dynamic hepatic venography with bolus injections of an US contrast agent: early experience in seven patients with metastases. *Radiology*, 209, 862-866. Times cited: 68 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 6.33

(3) Blomley, M., Albrecht, T., Cosgrove, D., Jayaram, V., Butler-Barnes, J. and Eckersley, R. (1998). Stimulated acoustic emission in liver parenchyma with Levovist. *Lancet*, 351, 568. DOI. Times cited: 104 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(4) Albrecht, T., Blomley, M.J., Cosgrove, D.O., Taylor-Robinson, S.D., Jayaram, V., Eckersley, R., Urbank, A., Butler-Barnes, J. and Patel, N. (1999). Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. *Lancet*, 353, 1579-1583. DOI. Times cited: 143 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(5) Harvey, C.J., Blomley, M.J., Eckersley, R.J., Heckemann, R.A., Butler-Barnes, J., Cosgrove, D.O. (2000). Pulse-inversion mode imaging of liver specific microbubbles: improved detection of subcentimetre metastases. *Lancet*, 355, 807-808. DOI. Times cited: 111 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(6) Blomley, M.J., Cooke, J.C., Unger, E.C., Monaghan, M.J., Cosgrove, D.O. (2001). Science, medicine, and the future - Microbubble contrast agents: a new era in ultrasound. *BMJ*, 322, 1222-1225. DOI. Times cited: 153 (as at 6th November on ISI Web of Science). Journal Impact Factor: 17.21

Key funding:

- Medical Research Council (MRC; 1995-1998; £159,000) “Realising our Potential” (Ropa), Principal Investigator (PI) D. Cosgrove, Supported Dr Martin Blomley 3 years + equipment to study Harmonic Mode Ultrasound.
- MRC (1999-2003; £585,000), PI M. Bromley, Career Development Grant.

4. Details of the impact (indicative maximum 750 words)

Impacts include: practitioners and services, health and welfare, public policy and services
Main beneficiaries include: practitioners, patients, NHS, NICE, World Federation of Ultrasound in Medicine and Biology (WFUMB), European Federation of Ultrasound in Medicine and Biology (EFSUMB) (both professional Associations).

During clinical trials of early versions of microbubbles prior to their licensing and commercialisation, observations by Professors Blomley and Cosgrove in the Imperial team led to the discovery of what has become known as the “late phase” in which microbubbles are retained in normal liver beyond their survival in the blood stream. Liver lesions that wash out in the late phase are potentially malignant; those that retain the microbubbles are almost always benign. This discovery enables a fast, safe and inexpensive test that has revolutionised the investigation and management of the large group of patients undergoing liver imaging to detect primary or secondary liver involvement with cancer. Other imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) can also achieve this, likewise depending on the use of contrast agents, but they are more expensive, less immediate and less widely available.

The Imperial microbubble group demonstrated that microbubbles can be used as tracers following their intravenous injection as a bolus, providing haemodynamic information that is analogous to that obtained using radionuclide tracers and the equivalents for CT and MRI. However, the use of microbubbles as tracers have significant advantages which underlie the 2012 NICE recommendations for use:

- They are confined to the vascular space whilst other agents diffuse into the interstitial space complicating their behaviour.
- The required mathematical modelling is simpler.
- They have been found to be a marker for liver metastases and for cirrhosis.
- While conventional size measurements (the RECIST and WHO criteria) fail to demonstrate early tumour response or resistance, the changes in microbubbles flow characteristics give early indications of a patient’s particular tumour.
- MBs provide individualised information such that follow up expensive treatment regimens can be individually tailored.

These observations formed the basis for the recommendation by NICE that licensed microbubble is preferred when examining abnormal-looking areas in the liver [1]. To quote from the NICE Recommendations (page 19) [1] “Compared with contrast-enhanced ultrasound, contrast-enhanced CT was as effective but more costly,… Contrast-enhanced MRI with gadolinium cost £1063 more per person than contrast-enhanced ultrasound…” The European and World Federations of Ultrasound in Medicine Guidelines (2008 and 2013, translated into Spanish, Italian French and Chinese), all rely heavily on research from the Imperial team [2, 3].

Similarly, use of microbubbles has been undertaken in the spleen by Professor Adrian Lim and this is featured in the EFSUMB Guidelines 2012 [4].

An important practical development of the Imperial group’s observations on the behaviour of microbubbles is their ability to define very precisely the microvascular perfusion of tissue. This has led to significant cost savings. Professor Leen has translated this into an invaluable diagnostic application in monitoring the increasingly used interstitial ablation of tumours using any of a number of local thermal therapeutic approaches, most commonly radiofrequency ablation. These treatments seal off the blood supply, demonstration of which confirms the adequacy of the ablation. In the traditional approach, under real-time ultrasound guidance, a planned amount of tissue destruction is attempted, for example a tumour together with a 2cm “safety margin” of surrounding liver or kidney. Then the patient is sent for a contrast CT scan; if the ablation has not been adequate, they must return to the interventional room for further treatment, usually in a new treatment session after a second general anaesthetic. Following successful ablation, the flow of MBs is eliminated, and this can be monitored with contrast enhanced ultrasound immediately after the treatment, which can be extended if necessary. This results in savings in time, cost and effectiveness, as evidenced in an Italian study in which they say “Cost-effectiveness and reduction of patients' discomfort related to the need of re-treatment are the two most outstanding advantages of CEUS in this field.”

The clinical application of this method was featured in a recent BBC-4 programme (POP! The Science of Bubbles) which included a clinical section showing Professor Lim scanning a patient at Charing Cross Imperial College Trust [5]. This underpins the wide impact that these discoveries have had, extending beyond the medical community to the general public.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] NICE, diagnostic guidance 5 (2012): SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast- enhanced ultrasound imaging of the liver. www.nice.org.uk/dg5. Archived on 8th November 2013.

[2] Claudon, M., Dietrich, C.F., Choi, B.I., et al. (2013). Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound in Medicine & Biology*, 39 (2), 187-210. DOI.

[3] Translated guidelines

- France guideline translation: Correas, J., Tranquart, F., Claudon, M. (2009). [Guidelines for contrast enhanced ultrasound (CEUS)--update 2008]. *J Radiol*, 90, 123-38.
- Ripolles, T., Puig, J. (2009). [Update on the use of contrast agents in ultrasonography: a review of the clinical guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)]. *Radiologia*, 51 (4), 362-375. DOI

[4] Piscaglia, F., Nolsoe, C.,Dietrich, C.F. et al., (2012). The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall in der Medizin*, 33 (1), 33-59. DOI

[5] BBC-4 screening “POP! The Science of Bubbles” broadcast May 2013. The clinical section shows Professor Lim performing a clinical contrast-enhanced ultrasound scan in Charing Cross Hospital, Imperial College in April 2013. http://www.youtube.com/watch?v=zCJQ_SsSddk