THE HARMONICS OF COLLABORATION

Imaging physicist and clinical radiologist pair to give liver cancer a new look

When Dr. Stephanie Wilson presents images at radiology seminars and conferences showing that ultrasound can diagnose the nature of a liver mass with equal, and at times better, accuracy than computed tomography (CT) or magnetic resonance imaging (MRI), she often finds her audience surprised and impressed: ultrasound is cheaper, more accessible, faster and produces fewer adverse effects. Those at Wilson's talks surprised by ultrasound's ability to diagnose liver masses—which are extremely common and can produce weeks of worry among patients waiting for CT or MRI—are diminishing in number, however. One reason for this shift in awareness is the appearance of some of those new ultrasound images on the January 2007 cover of *Radiology*, the largest circulation and arguably most prestigious journal in medical imaging. The images are from an article that marks the outcome of a prolific collaboration between Wilson and Dr. Peter Burns, a senior scientist in imaging at Sunnybrook Research Institute (SRI).

Wilson, who served as the first female president of the Canadian Association of Radiologists and is a professor of radiology at the University of Calgary, is an expert on liver disease. Burns is a physicist and the chair of the department of medical biophysics at the University of Toronto. Together with Burns' unique technology, developed and commercialized at SRI, the two have made ultrasound a practice-changing method of diagnosing liver masses in Toronto and, increasingly, internationally.

The story of ultrasound's rise to prominence as a liver imaging technique began more than a decade ago in Burns' lab at SRI, where he and his colleagues developed methods to detect and image microbubbles that would later be used for contrast enhancement in patients undergoing liver ultrasound. Microbubbles are microengineered pockets of gas, smaller than a red blood cell, surrounded and stabilized by a thin layer of protein or lipid—a sort of microscopic soap bubble. They're made from harmless materials found in the body, and only a few drops need be injected into a vein. The bubbles circulate and, when excited with ultrasound waves, ring and produce harmonics, like musical overtones. Burns pioneered an imaging technique called pulse-inversion to capture those harmonics, effectively illuminating blood flow in tissue in real time, and producing an immediate and remarkably detailed picture. The invention was recognized as seminal in the field of ultrasound physics. Says Wilson, "Peter is a brilliant scientist and a very clever investigator."

Translating this science into a method that can be used in clinical practice to image the liver required that Wilson and Burns take several steps. First, the bubbles needed to be approved for clinical use, which was achieved in Canada with the help of their early data in 2002. The European Union and several other countries followed soon thereafter, although the bubbles are still not approved for clinical use in the U.S. by the Food and Drug Administration. (Burns is optimistic that this will change soon.)

Lack of approval in America, which made ultrasound trials using microbubbles less feasible in the U.S., did, however, help Burns and Wilson present a successful case for funding clinical trials in Canada. One of the first trials they set up, at the University Health Network in downtown Toronto where Wilson was then based, was to determine if ultrasound could diagnose liver masses with sufficient accuracy. The study showed it could do, so they next ran a trial in the same Toronto clinic comparing ultrasound to the standard liver imaging techniques of CT and MRI. The trial generated a huge amount of data, and after a long period of analysis, *Radiology* accepted the results with the resounding affirmation of a cover spread, securing ultrasound's place as a viable, and in some instances superior, imaging technique.

A striking finding from this study was that in 25% of patients ultrasound caught one important sign of cancer that CT and MRI did not. "That's a very significant finding," says Burns. He says that this didn't mean CT or MRI led to missed cancer diagnoses; rather, CT and MRI might have been indeterminate, and other signs led radiologists using those methods to suspect cancer. But, as Burns notes, "The problem with an indeterminate test is that it sends patients on to more tests or biopsies, so having a definitive test is much more useful. In these 25% of cases, ultrasound was definitive."

Dr. Peter Burns

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Herein lies one reason — streamlined diagnosis — why ultrasound, when used to image liver masses, has a positive impact, even on a clinical practice that uses CT and MRI. Traditionally, when radiologists discover a liver mass using conventional ultrasound imaging, they report it to the patient's physician, and the physician refers the patient for CT or MRI. The patient then goes home and waits, eventually to return for a scan that is much more expensive than ultrasound and requires time to process the results. The new contrast-ultrasound, on the other hand, is performed in real time when the mass is first detected, bypassing the referral and scan-scheduling process and providing instant results.

Another benefit of ultrasound is fewer adverse effects. The contrast-enhancement agents for CT and MRI can produce negative side effects. In addition, CT imparts a whack of radiation — a concern for all patients, but particularly for women of childbearing age. Wilson notes that research in the U.S. has shown that CT scans may be responsible for up to 2% of cancers in that country.

Following their *Radiology* cover article, Burns and Wilson teamed again and joined other colleagues in a Toronto-based 1,040-person trial to analyze the impact of ultrasound on the care of patients with liver masses. Results showed that in 45% of cases patients' care was changed favourably. "It's always conceivable," says Burns, "that a diagnostic test can make lives more complicated, ring false alarm bells, cause more confusion and testing. But this test seems successful in that it reduces the number of subsequent investigations and shortens time to diagnosis for patients who are frequently very anxious."

Thousands of patients around the world now benefit from contrast-ultrasound liver imaging, especially those in Southeast Asia. Many Asian countries have high rates of hepatitis B and C, which increase the risk for liver cancer dramatically. Toronto, with many people of Southeast Asian origin, also has elevated hepatitis rates. These patients require regular liver scans, part of a strategy to catch cancer early should it develop, and many in Toronto are now routinely scanned with ultrasound at the University Health Network. China, with an enormous population, has made significant use of Burns' invention and continues to expand its implementation.

While contrast ultrasound for liver imaging has become a standard of care in areas of China and Toronto, its recognition and use elsewhere is also increasing. Although it requires a highly skilled operator, a potential hindrance to rapid clinical adoption, Wilson finds growing implementation among her colleagues in Calgary. Moreover, the European Association for the Study of the Liver published guidelines for liver diagnoses that include microbubble ultrasound. The "Barcelona Guidelines," which Burns calls the bible of diagnostic algorithms for the liver, included contrast ultrasound as a definitive method for liver diagnosis. And for his contributions to the field, Burns was awarded the 2008 William Fry Memorial Award of the American Institute for Ultrasound in Medicine, its highest recognition for lifetime achievement in basic science research. But as a physicist, says Burns, "The most valued reward is to see one's work impact patient care. For that reason, and because of the distance it has travelled, we are very happy about this work. Such collaborations between basic scientists and clinicians are the most important we have in medical research." JO

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