

# NEW DEVELOPMENTS IN MEDICAL IMAGING TO DETECT BREAST CANCER

*Breast cancer is still one of the most common cancers in women.*

**CHRISTOPHER L VAUGHAN, BSc (Hons), PhD, DSc (Med)**

*Emeritus Professor of Biomedical Engineering, and Founding Director, MRC/UCT Medical Imaging Research Unit, Faculty of Health Sciences, University of Cape Town, and Chief Executive Officer, CapeRay Medical (Pty) Ltd, Westlake Business Park, W Cape*

*Kit Vaughan's experience over the past three decades includes a post-doctoral fellowship in orthopaedic engineering at Oxford University, a tenured professorship at the University of Virginia, and 14 years as the Hyman Goldberg Chair in Biomedical Engineering at the University of Cape Town (UCT). During this latter period he helped to pioneer the medical device industry in South Africa, contributing to Disa Vascular, Acorn Technologies, Lodox Systems, and the Leatt Corporation. Kit is a Fellow of the International Academy for Medical and Biological Engineering, and his qualifications include a BSc (Hons) in applied mathematics and physics (Rhodes), a PhD in musculoskeletal biomechanics (Iowa) and a DSc (Med) in biomedical engineering (UCT).*

*Correspondence to: C Vaughan (kit@caperay.com)*

It is estimated that 1 in 4 South Africans will be affected by at least one cancer diagnosis in their lifetime, with breast cancer being the most common cause of death in women. Clinical studies have shown that early detection has caused mortality rates to fall by up to 50%, and the earlier the detection, the greater are the chances of survival.<sup>1</sup> Various medical imaging modalities are used to detect breast cancer, the most common being X-rays (mammography), ultrasound, magnetic resonance imaging (MRI) and various radionuclide techniques.<sup>2</sup> The purpose of this article is to review these and other novel medical imaging modalities.

*It is estimated that 1 in 4 South Africans will be affected by at least one cancer diagnosis in their lifetime, with breast cancer being the most common cause of death in women.*

The American College of Radiology has developed, published and trademarked a quality assurance tool called BI-RADS, an acronym for Breast Imaging-Reporting and Data System. The system was designed to standardise patient reporting in two domains: assessment categories, with a numerical code between 0 and 6, allowing for concise and unambiguous sharing of patient records between clinicians; and breast composition categories, with a numerical code between 1 and 4, indicating the density of breast tissue (Table I). The BI-RADS classification system applies to medical images of the breast acquired by X-rays, ultrasound and MRI.<sup>3</sup>

*Various medical imaging modalities are used to detect breast cancer, the most common being X-rays (mammography), ultrasound, magnetic resonance imaging (MRI) and various radionuclide techniques.*

## X-rays

Screen-film mammography, the use of X-rays and analogue film have been the 'gold standard' for imaging the breast since the mid-1960s.<sup>3</sup> In addition to its ability to allow visualisation of soft-tissue abnormalities,

mammography is also able to depict subtle calcifications, which may be indicative of cancer. Screen film, however, suffers from a number of drawbacks: limited dynamic range and contrast, granularity and susceptibility to poor processing of the photographic film. The past decade has seen the emergence of full-field digital mammography (FFDM), a technique that captures an electronic image of the X-rays transmitted through the breast, which is steadily replacing analogue mammography.

**Table I. The Breast Imaging-Reporting and Data System (BI-RADS), a quality assurance tool designed and endorsed by the American College of Radiology for use with mammography<sup>3</sup>**

Assessment		Composition	
Category	Description	Category	Description
0	Incomplete	1	Almost entirely fat
1	Negative	2	Scattered fibro-glandular densities
2	Benign findings	3	Heterogeneously dense
3	Probably benign	4	Extremely dense
4	Suspicious abnormality		
5	Highly suggestive of malignancy		
6	Known biopsy-proven malignancy		

The sensitivity (percentage of true positives) of mammography is approximately 75%, while the specificity (percentage of true negatives) is in the region of 90%. Sensitivity falls to less than 50% in women who have dense breasts (BI-RADS 3 or 4) (Table I), although FFDM performs significantly better than screen film for pre-menopausal women younger than 50 years of age.<sup>2</sup> FFDM also exposes patients to a lower radiation dose and, when implemented via a slot-scanning geometry, the dose is further reduced while the image quality is enhanced.<sup>4</sup>

One of the limitations of mammography is that the standard two-dimensional (i.e. planar) projection has overlapping of healthy and pathological tissues. Not surprisingly, cancerous lesions can be hidden, especially when the surrounding tissues are dense.<sup>5</sup> Digital breast tomosynthesis (DBT) is a technique in which 10 - 12 projection views

over an arc of about 30 degrees are acquired, and the 3D volume of the breast is reconstructed from the multiple 2D projections.<sup>2</sup> Early clinical results show that, in comparison with FFDM, DBT has higher conspicuity (Fig. 1) and performs better in dense breasts.<sup>5</sup>

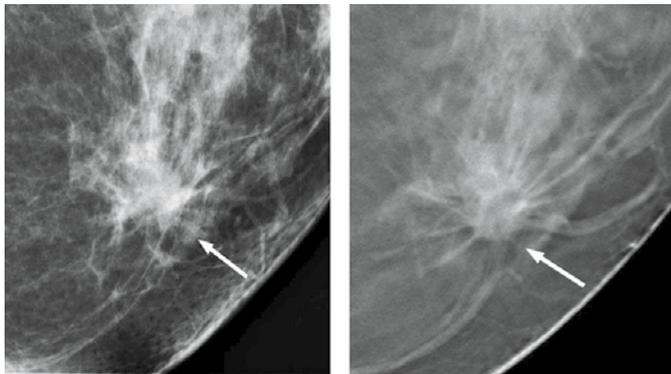


Fig. 1. A clinical case showing a low-grade invasive ductal carcinoma, comparing full-field digital mammography (left) and digital breast tomosynthesis (right). These images are courtesy of Dr Steven P Poplack of the Dartmouth Hitchcock Medical Center, New Hampshire.

Another approach utilising X-rays, that overcomes the tissue superposition problem, is breast computer tomography (BCT), a technique in which the patient lies in a prone position on a bed. An aperture in the bed enables the pendant breast to be imaged by a C-arm, consisting of an X-ray source and flat-panel digital detector that rotates around the breast.<sup>2</sup> BCT provides excellent 3D anatomical detail and the ability to visualise soft-tissue lesions, but performs poorly when cancer is located within microcalcifications that are less than 150 microns in size. Aside from dose concerns, another limitation of BCT is its inability to image the axillary region of the breast where the lymph nodes – and therefore potential cancers – are located.

### Computer-assisted diagnosis

Computer-assisted diagnosis, also referred to as computer-aided detection or CAD, has been available as an accredited tool since the late 1990s. Because images of the breast from FFDM, or even ultrasound and MRI, are available in digital format, they lend themselves to pattern recognition algorithms that can be implemented on a computer. A CAD system for detecting breast cancer will typically be ‘trained’ on

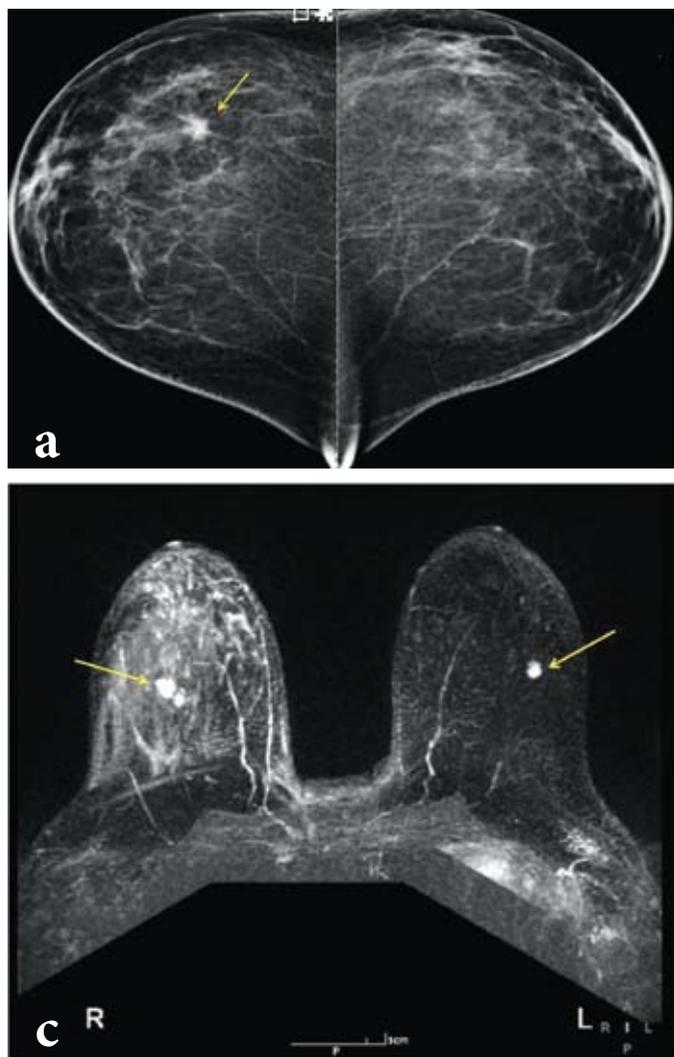
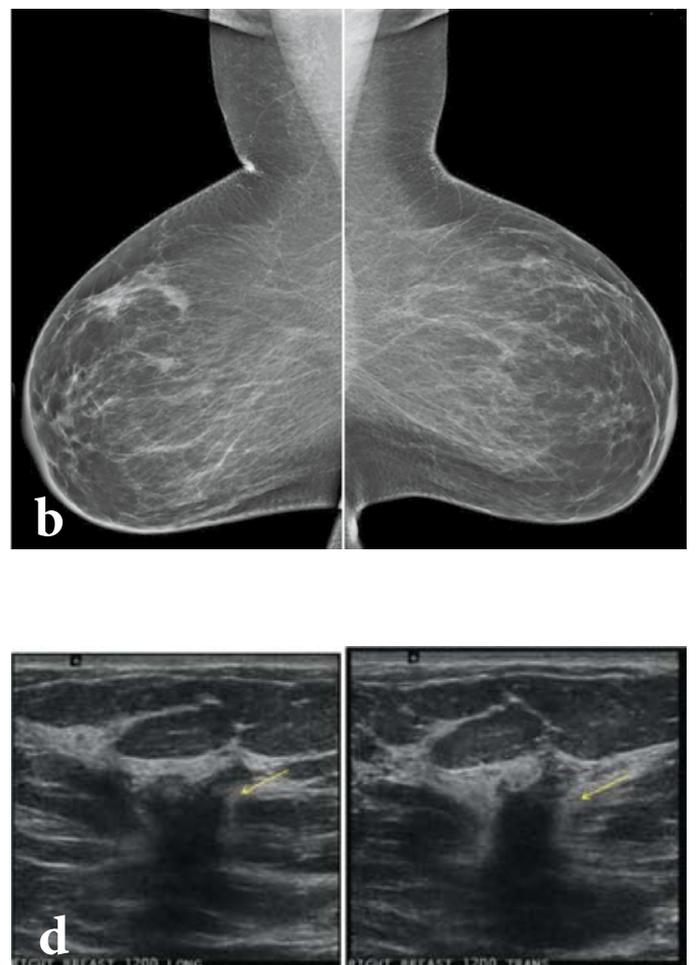


Fig. 2. A 46-year-old patient, who denied any lumps or pain in either breast, presented for a second opinion. Craniocaudal (a) and mediolateral oblique (b) digital X-rays of the left and right breasts. These images reveal an irregular speculated mass in the right superior breast, although, on physical examination, no palpable lump was found. An ultrasound image (c) of the right breast shows the presence of a hypoechoic mass. A follow-up magnetic resonance image (d) identified the carcinoma in the right breast as well as the presence of an additional mass in the left breast. Needle biopsies confirmed invasive ductal carcinoma and the patient proceeded to have bilateral lumpectomies. These images and case study are courtesy of Dr Stamatia Destounis of Elizabeth Wende Breast Care in Rochester, New York.



a few thousand images, some of which have known cancerous lesions. Once the algorithm has been optimised to recognise different forms of breast cancer, it can then be presented with an image that it has never encountered before.

***A CAD system for detecting breast cancer will typically be 'trained' on a few thousand images, some of which have known cancerous lesions.***

CAD systems have the ability to segment different structures, to identify specific features and to evaluate and classify these structures. CAD has been shown to improve sensitivity in breast cancer detection (i.e. it identifies lesions missed by the radiologist), but at the expense of specificity: there is an increase in false positives.<sup>6</sup> These latter findings can provoke anxiety, not to mention unnecessary biopsies, although some women and their physicians may decide this is an acceptable trade-off to identify additional cancers. It is highly likely that, as multiple imaging modalities become more prevalent, the real power of CAD will emerge.

### Ultrasound

Medical ultrasound, in which sound waves 100 - 1 000 times higher in frequency than those detectable by humans are employed to generate images of tissues within the body, has been used in clinical practice to detect breast cancer for over half a century.<sup>7</sup> Compared with other modalities, such as digital X-rays and MRI, ultrasound has a number of key benefits: it is non-invasive, relatively inexpensive and portable, and has excellent temporal resolution. The basic principles of ultrasound are simple: a wave is generated by a transducer and propagates through the tissues; the wave is partially reflected at the interface between different tissues; the reflection is detected by the same transducer; and the time of the reflection, plus the speed of sound in the tissue, yields the position of the tissue interface.

While the spatial resolution of ultrasound is quite limited (~1 mm), it has the major advantage of being able to identify lesions embedded in dense breast tissue.<sup>3,7</sup> This means that ultrasound is an important adjunct to FFDM, increasing the sensitivity, even though the number of false positives may also increase.<sup>1,8</sup> Other interesting developments include the use of contrast-enhancing agents<sup>9</sup> and automated breast ultrasound (ABUS), a promising technique that eliminates operator dependency and produces 3D images of the breast.<sup>10</sup>

### Magnetic resonance imaging

Unlike X-rays or CT, MRI uses no ionising radiation. Instead, it utilises a powerful magnetic field to align the orientation of hydrogen nuclei in the body and, via a coil that acts as a radio-frequency transmitter, alters the alignment of the nuclei. The magnetic field thus generated is detected by the MRI scanner and this information enables the reconstruction of the underlying tissues. In the case of breast imaging, the development of a special bilateral coil has facilitated simultaneous imaging of both breasts.<sup>2</sup> MRI not only produces 3D morphology of breast tissue, but also provides physiological (i.e. functional) information such as vascular density changes associated with angiogenesis.

Clinical trials of MRI have demonstrated that it can provide an accurate diagnosis, the extent of disease and the ability to detect cancers in the contralateral breast that are mammographically occult (Fig. 2). It performs particularly well in women who have a high risk of hereditary breast cancer and is recommended as an adjunct to mammography for these patients. MRI has a sensitivity of 90% and a specificity of 72%, with the promise of improving this latter figure with the application of magnetic resonance spectroscopy.<sup>2</sup> MRI is an expensive modality and is therefore used as a diagnostic rather than a screening tool.

### Radionuclide imaging

Radionuclide imaging of the breast covers a number of different forms of nuclear medicine scans, from positron emission mammography (PEM) to breast-specific gamma imaging to molecular breast imaging (MBI).<sup>3</sup> The common thread running through these techniques is the injection of a radiopharmaceutical agent, with the image captured by specialised detectors. In the case of PEM, the radionuclide tracer is fluorodeoxyglucose, the decaying positrons interact with electrons in the lesion, and the resulting photons strike a scintillator coupled to a photodiode. In studies comparing PEM to MRI, the former shows increased precision in identifying benign and cancerous lesions, thus reducing unnecessary biopsies.<sup>2</sup>

***Clinical trials of MRI have demonstrated that it can provide an accurate diagnosis, the extent of disease and the ability to detect cancers in the contralateral breast that are mammographically occult.***

In the case of MBI, the radionuclide tracer is technetium-99m sestamibi and a dual-head camera – one on either side of the breast makes use of cadmium zinc telluride (CZT) digital detectors.<sup>3</sup> Images can be acquired in the craniocaudal (CC) and mediolateral oblique (MLO) projections, thus facilitating direct comparison with mammography. Interestingly, in a large clinical trial comparing MBI with screening mammography in over 1 000 women with dense breast tissue (and therefore at increased risk of breast cancer), 2 - 3 times more cancers were detected with MBI than with mammography.<sup>11</sup> There are, however, three major disadvantages to MBI: lengthy imaging time (40 minutes); elevated radiation dose associated with the radionuclide; and high cost of the procedure.

### Multimodality imaging

The images and clinical case study in Fig. 2 illustrate the power of utilising more than one imaging modality. Because mammography performs poorly in women with dense breasts, the argument has been made to combine ultrasound with mammography for screening.<sup>1,8</sup> In these cases, however, the images have been acquired sequentially, using separate pieces of equipment. Furthermore, in hand-held ultrasound the image quality is dependent on the skill of the operator and the two sets of images (ultrasound and X-rays) cannot be co-registered. Recognising this shortcoming, there is now a concerted effort to develop a single system that is capable of simultaneously acquiring images using both modalities.<sup>2</sup>

An ambitious approach, still in prototype form, is a system that incorporates dual modalities: DBT is combined with MBI.<sup>12</sup> The system facilitates co-registration of the two modalities (one anatomical, the other functional) and, because the images are effectively in 3D, diagnosis is enhanced. In a limited clinical trial of 17 women, sensitivity was 86% while specificity was 100%. With further development this system could make a meaningful contribution as a diagnostic tool for the detection of tumours and the characterisation of breast cancer.

### Investigational imaging modalities

Although the traditional breast imaging techniques are well understood and broadly applied, there is nevertheless considerable research activity exploring the efficacy of alternative technologies.<sup>2</sup> One such approach integrates both thermo-acoustic and photo-acoustic techniques to achieve dual contrast imaging (microwave and light absorption).<sup>13</sup> The basis for this system is the high contrast in di-electric properties between a malignant tumour and normal adipose breast tissue. Early results on breast phantoms appear promising but a proper clinical trial is still required.

Researchers at the University of Bristol have developed a breast cancer detection system that uses radar-based microwaves.<sup>14</sup> *In vivo* microwave imaging of breast tissues suggests that di-electric properties correlate well with radiographic density. The system incorporates a hemispherical array of radar antennae that conform to the shape of the pendant breast. In a limited clinical trial, comparing the experimental

approach with mammography, the 3D microwave system detected a tumour in the correct location.

Thermography, the remote measurement of skin surface temperature with an infrared camera, has been applied to breast cancer detection for over half a century.<sup>15</sup> Despite a large body of published work, breast thermography remains controversial and is unlikely to replace mammography as a screening tool.

References available at [www.cmej.org.za](http://www.cmej.org.za)

## IN A NUTSHELL

- When considering medical imaging options, it is important to distinguish between **screening**, where the vast majority of women have no disease, and **diagnosis**, where there is a high suspicion of a lesion.
- In the case of screening, an ideal system would have both sensitivity and specificity values of greater than 90%, including women with dense breasts.
- While such a system does not yet exist, a promising candidate would appear to be a dual-modality device that combines full field digital mammography (FFDM), digital breast tomosynthesis (DBT) and automated breast ultrasound (ABUS).<sup>2</sup>
- The application of computer-assisted diagnosis (CAD) would further enhance the utility of the system. However, to have significant impact in reducing mortality, such a system would have to support high patient throughput and be widely available.

## SINGLE SUTURE

### *New disease found*

An 18-month wait for a diagnosis may seem extreme, but not when the medical disorder in question was formerly unknown.

In 2008, the US National Institutes of Health established the Undiagnosed Diseases Program (UDP) to help people with mysterious conditions. This week it announced its first big discovery: the genetic and molecular basis of a previously unexplained condition that causes painful calcification of the arteries.

Currently, only 9 individuals are known to have the disorder, dubbed 'artificial calcification due to CD73 deficiency'. Researchers analysed the DNA of 5 affected siblings and found that they all had mutations of the NT5E gene, which codes for the CD73 enzyme that produces adenosine – a molecule that helps prevent the arteries from calcifying. The findings offer targets for a treatment.

The discovery is impressive to its speed and technical prowess, says William Gahl, director of the UDP. 'The role of adenosine was not known before.'

*New Scientist*, 5 February 2011, p. 5.