Inside information...

Medicamundi allows healthcare professionals and the industry to share inside information on the latest technological developments and their medical applications.

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Women’s health:
- Digital mammography
- MR breast imaging
- Near-infrared spectroscopy
- Breast cancer screening
- Cardiovascular disease in women
- Early detection of ovarian cancer

Women’s health:

PHILIPS
Dear Friends,

I am delighted to introduce this issue of Medicamundi, devoted to women’s health. “Women’s health is no longer an isolated phenomenon divorced from mainstream medicine and regarded as a political or feminist issue” [1]. The most obvious differences relate to biology and physiology. Women’s healthcare addresses far more than reproductive health: it includes disease or conditions that occur only in women such as cervical cancer, conditions that occur more frequently in women, like breast cancer, and conditions that are biologically different, such as heart disease.

How can Philips play an important role in women’s health? We start with the needs of the patient and the care provider, understanding their experience through each stage of the care continuum from prevention, screening, and diagnosis to treatment, surveillance, and management. Through a customer-guided approach, we design solutions to meet specific needs. We develop go-to-market models aligned around the customer, providing comprehensive solutions to improve care.

Today, breast cancer is defined by cancer type, and detection is dependent on a variety of factors, including breast density. A comprehensive approach using multiple modalities is now the norm. New guidelines for screening, diagnosis and management can include mammography, a breast ultrasound, and PEPT/CT and information. Women are requesting more accurate, less invasive diagnostics, shorter time between diagnosis and therapy, and, more targeted, less radical treatments. New horizons in staging, grading and prognosis will also drive more personalized treatment regimes.

Heart disease is the greatest cause of death in women worldwide; more than 3 million women die from heart disease every year. We continue to work closely with leading clinicians and patients to understand heart disease in women and provide solutions to improve early detection.

Growth of gynecological procedures is rising. Women expect to have a healthy lifestyle beyond mid-life and no longer accept pelvic conditions and diseases as part of normal aging. Gynecology is an area where we see opportunity for growth in imaging-guided diagnostics and therapy.

It is my hope that this Women’s Health issue of Medicamundi will give readers a clear understanding of the Philips care cycle strategy, and demonstrate our commitment to delivering leading-edge solutions for women’s healthcare needs.

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The Editor-in-Chief and the editorial staff accept no responsibility for opinions expressed by the contributors, and the descriptions of particular medical procedures does not imply approval of the procedures in all countries. Examples of earlier issues of Medicamundi can be found on the Philips website: www.philips.com/medicamundi

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Although not all criteria will be appropriate for every article, the article should meet one or more of the following points:

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Women’s health: an introduction

Women represent more than half the world’s population, have a longer life expectancy than men and consume more healthcare resources. In the USA, for example, women account for two-thirds of the surgical procedures and office visits and approximately 65% of national annual medical bills. Women also make up to 90% of the healthcare decisions for their families [1]. Nevertheless, until relatively recently, the concept of women’s health was primarily related to conditions that occur exclusively or predominantly in women, such as pregnancy, gynecological problems or breast cancer.

However, in 1999, the Society for Women’s Health Research [2] was instrumental in obtaining authorization and funding for a major study conducted by the Institute of Medicine (IOM) of the US National Academy of Sciences. This study was aimed at assessing the state of knowledge on sex-based biology and gender-based medicine, in order to make recommendations for an appropriate agenda for research into women’s health.

In April 2001, the IOM released a report on the study entitled Exploring the Biological Contributions to Human Health: Does Sex Matter? [3]. This was almost certainly the first significant review of the status of sex and gender differences in biomedical research to be published by an independent research organization. It stressed the need for better understanding of the importance of sex differences and how that

Heart Disease – Heart disease kills 500,000 American women each year – over 50,000 more women than men – and strikes women, on average, 10 years later than men. Women are more likely than men to have a second heart attack within a year of the first one.

Depression – Women are two-to-three times more likely than men to suffer from depression, in part because women’s brains make less of the hormone serotonin.

Osteoporosis – Women comprise 80 percent of the population suffering from osteoporosis, which is attributable to a higher rate of lost bone mass.

Smoking – Smoking has a more negative effect on cardiovascular health in women than men. Women are also less successful quitting smoking and have more severe withdrawal symptoms.

STDs – Women are two times more likely than men to contract a sexually transmitted disease, and more likely to experience significant drops in body weight, which can lead to wasting syndrome.

Anesthesia – Women tend to wake up from anesthesia more quickly than men – an average of seven minutes for women and 11 minutes for men.

Drug reactions – Even common drugs like antihistamines and antibiotic drugs can cause different reactions and side effects in women and men.

Autoimmune Disease – Three out of four people suffering from autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and lupus, are women.

Alcohol – Women produce less of the gastric enzyme that breaks down ethanol in the stomach. Therefore, after consuming the same amount of alcohol, women have higher blood alcohol content than men, even allowing for size differences.

Pain – Some pain medications (known as kappa-opiates) are far more effective in relieving pain in women than in men.

Gender differences important to health and disease exist at all levels in the body.

Table 1. Women and men: Ten differences that make a difference.

Information by courtesy of the Society for Women’s Health Research, Washington, DC.

www.womenshealthresearch.org
The Women’s Health Care Cycle

Philips Healthcare recognized the benefits of a program focused specifically on women’s health, and established the Women’s Health Care Cycle program in 2007 with the objective of improving the health and quality of women’s lives worldwide. The care cycle encompasses the whole continuum of care from prevention, screening and diagnosis to treatment, management and surveillance (Figure 1).

Following the patient and the caregivers through every step of the care cycle not only gives a valuable insight into their needs, but also helps the industry to create solutions that will best address their needs. Following this approach provides a greater understanding of the clinical pathways for a particular disease in a particular geographical region, and can show where improvements need to be made.

Today, Philips Healthcare’s Women’s Health program focuses on three key areas of disease in women: breast cancer, heart disease, and gynecology. All three represent important global health issues.

Figure 1. The Women’s Health Care Cycle

Figure 2. Merging of diagnosis and treatment.
Breast cancer is the most frequently diagnosed cancer in women worldwide. Because breast cancer presents in many different ways, a multimodality approach is often required for a comprehensive diagnosis. Philips recognizes this need and offers a portfolio of imaging systems and healthcare informatics solutions. The company is also actively involved in programs that will add value in other points of the breast cancer care cycle.

Heart disease is the greatest cause of death in women worldwide. The World Health Organization reports that more than 3.4 million women die from heart disease every year [4]. Coronary artery disease in women is often clinically different than in men, and women are more likely to present with atypical symptoms. Philips offers a complete portfolio of solutions to support diagnosis in women, and works closely with leading healthcare organizations to provide solutions that address women’s unique cardiovascular needs and help to improve early detection.

Gynecological conditions include benign conditions such as abnormal uterine bleeding, pelvic floor disorders, and infertility, as well as cancer of the cervix, uterus, and ovaries. There were more than one million new cases of gynecologic cancers worldwide in 2008 [4]. Here, novel technologies for imaging can help to provide earlier diagnosis, at a stage when treatment offers a better chance of success, and novel treatment techniques offer less invasive therapy.

One common trend in all these areas is a blurring of the distinction between diagnosis and treatment (Figure 2).

**Breast cancer**

Globally, breast cancer is the most frequently diagnosed cancer in women, accounting for an estimated 1.3 million new cancer cases and 465,000 deaths in 2007 [2]. It is the leading cause of cancer death among women worldwide. The five-year survival from breast cancer is about 89% in the United States, 76% in Europe, and much lower in developing countries [4]. The favorable survival statistics in the developed world is attributed to the detection of cancers at an earlier stage by screening. For example, the overall five-year relative survival of women with breast cancer if detected at an early stage is 98%. The survival drops to 84% when the disease spreads to regional lymph nodes and 28% when spread to distant organs [4]. It has therefore become critical to combat the disease at an early stage.

![Digital mammography](image)

Figure 3. Digital mammography provides superior contrast resolution, of particular value in dense breasts. Images by courtesy of G. Newstead.
At present, there is no single modality that can guarantee the early detection of breast cancer, since the manifestation and progression of the disease varies widely. Screen-film X-ray mammography has been by far the most widely used modality to screen for breast cancer, but with the advent of digital mammography (Figure 3), the clinical community is reaping the benefits of superior contrast resolution and better clinical performance compared with traditional screen-film systems, particularly in women with dense breasts [5]. The digital images also serve as the input for centralized reading and digital archiving as well as computer aided detection (CAD). However, the diagnostic accuracy of X-ray mammography is still limited and breast care is rapidly transitioning to a multi-modality solution-driven approach.

Recent results from the ACRIN 6666 clinical trial demonstrated that combining ultrasound with mammography increased the diagnostic accuracy to 91% compared to 78% with mammography alone [6] at the expense of increasing the number of false-positives. Nevertheless, this has stimulated active technological and clinical investigations to broaden the role of ultrasound for breast cancer screening in addition to its valuable benefits in diagnostic imaging.

Major advantages of ultrasound include the absence of ionizing radiation, the widespread availability, and the relative ease of use. Until recently, however, ultrasound examinations suffered from a relatively low resolution and a high degree of operator dependency, resulting in rather poor reproducibility.

Recent technological advances have significantly increased the scope of ultrasound in breast imaging [7]. The Philips iU22 system with Vision 2009 offers volumetric acquisition (Figure 4), new interventional and contrast tools, and new approaches to improve workflow efficiency, including the new VL13-5 3D linear array transducer with Tissue Aberration Correction (Figure 5). Tissue Aberration Correction corrects for the different speeds of sound in different tissue types, such as fat and glandular tissue in the breast. The result is sharper images with better spatial resolution and less clutter, making it possible to detect smaller and less conspicuous lesions.

Breast MRI (Figure 6) is a supplementary procedure used for further assessment of findings detected by mammography or ultrasound. Typical applications include:
- identification of early breast cancer, particularly in women with dense breast tissue and those at high risk for the disease
- further assessment of lesions, particularly in women with dense breast tissue and those at high risk for the disease
- assessing multiple tumor locations, especially prior to breast conservation surgery
- distinguishing between scar tissue and recurrent tumors
- determining whether a known cancer has spread further in the breast or into the chest wall
- assessing the effect of chemotherapy
- assessing breast tissue density, cysts, enlarged ducts and hematomas
- helping to distinguish between benign and malignant lesions.

The use of breast MRI has substantially increased in recent years. A recent survey of physician members of the Society of Breast Imaging (SBI) indicated that contrast-enhanced breast MRI was offered at 73.8% of the practices and screening breast MRI was offered at 64.0% of practices in the United States [8]. The American Cancer Society (ACS) and the European Society of Breast Imaging recommend screening MRI as an adjunct to mammography for women with an approximately 20% or greater lifetime risk of breast cancer. The ACS recommends breast MRI screening in addition to mammograms for women who meet at least one of the following conditions:
- they have a BRCA1 or BRCA2 mutation
- they have a first-degree relative (parent, sibling, child) with a BRCA1 or BRCA2 mutation, even if they have yet to be tested themselves
- their lifetime risk of breast cancer has been scored at 20%-25% or greater, based on one of several accepted risk assessment tools that look at family history and other factors
- they had radiation to the chest between the ages of 10 and 30
- they have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or may have one of these syndromes based on a history in a first-degree relative [9,10].

Other diagnostic imaging technologies such as MR/optical hybrid imaging, breast specific gamma imaging (BSGI), positron emission mammography (PEM), tomosynthesis, and dedicated breast CT are discussed as potential methods for early breast cancer detection [11-13].

The utilization of multiple modalities for breast care is creating new challenges for the care giver.
It becomes an arduous task to independently review and report on the imaging data from each modality and becomes even more challenging when the modalities are from different vendors. This is driving the need for integrated workflow solutions that can help the physician view, analyze, and report from a single workstation that can communicate seamlessly with modalities from any vendor (Figure 7).

Imaging is at the forefront of the breast care cycle. However, interventional procedures such as biopsies are a crucial part of breast care, which leads to the final diagnosis. Substantial progress has been made in this field transforming it from a surgical procedure to a minimally invasive office-based method. Vacuum Assisted Biopsy is the more recent form of various biopsy techniques, making it possible to extract large tissue samples with excellent integrity, which improves the overall quality of pathology. It is used under stereotactic X-ray, ultrasound, and MR image guidance.

The improvements in imaging and interventional diagnosis make it possible to detect increasingly smaller lesions. This helps to drive the transition from mastectomy to breast conserving surgery, and the adoption of focal therapies such as Accelerated Partial Breast Irradiation (APBI) instead of conventional whole breast irradiation. Balloon breast brachytherapy is one such APBI technique that enables treatment of the lumpectomy cavity in five days, rather than the five to six weeks needed with external beam.
whole breast radiation. The five-year clinical data for balloon breast brachytherapy indicate similar treatment effectiveness as to that of conventional radiation therapy with low toxicity and excellent cosmetic outcome [14]. Various other forms of APBI are currently being actively pursued to further reduce treatment time and enhance clinical effectiveness.

Breast cancer diagnosis and therapy require a multimodality care approach. This means that the workstations must be able to cope with different modalities such as digital mammography, ultrasound, and MRI, as well as emerging technologies such as tomosynthesis and dedicated breast CT. It is, of course, essential for the workstation to be fully integrated with picture archiving and communication systems (PACS) and patient information systems.

**Cardiovascular disease**

Cardiovascular disease is the world’s leading cause of death in women, not only in developed nations, but in developing countries as well. Coronary artery disease is responsible for 294,000 deaths in women annually and is the greatest cause of death in women in the USA (38%), Europe (23%), and China (23%) [15-17]. Prevalence of heart disease in women increases after menopause with the decline in serum estrogen levels. Since older women (>60 yrs) are the largest growing population segment, the public health and economic burden of women’s heart disease will increase significantly in the future. This effect will be magnified in developing countries, where the projected increase in the number of older women exceeds that of developed countries for the same period [18].

Although women under age 55 with heart attacks represent a smaller proportion of all patients with heart disease, they account for approximately 40,000 hospitalizations in the USA each year. Young women also have significantly worse outcomes than men of similar age. About 8,000 women under the age of 55 in the USA die of heart disease annually, ranking it among the major causes of death in this age group [19].

**Clinical issues in ischemic disease**

Differences in the manifestation of heart disease in women and men have been identified in several areas, including etiology, pathophysiology, and clinical presentation. Women have smaller coronary vessels with more diffuse atherosclerosis, microvessels that are more frequently dysfunctional, and less obstructive disease. Ischemic heart disease presents clinical challenges that are not adequately addressed by current techniques developed, tested, and studied in largely male populations. Because women’s ischemic disease often evades detection through traditional diagnostic techniques, it may continue to cause symptoms, but remain undiagnosed until progressing to a critical stage.

Angina is more common in women than men [20,21], but is more often due to microvascular disease with normal non-obstructed coronary arteries. The landmark National Heart Lung Blood Institute (NHLBI) Women’s Ischemic Syndrome Evaluation (WISE) II study showed 60% of women referred to cardiology practices for suspected ischemia did not exhibit obstructive CAD by angiography despite persistent or worsening symptoms [22].

When patients are evaluated for chest pain, cardiologists typically look for an obstructive lesion, i.e. plaque that is blocking an artery; however, in many women, two areas of dysfunction (one in the cells lining coronary arteries and another in the smaller vessels branching within the heart) combine to deprive the heart muscle of oxygen. “Functional”, rather than structural abnormalities of the coronary circulation may provide evidence of ischemic disease in women. Although the diffuse atherosclerosis that many women experience is not seen on coronary angiography, it results in abnormal resistance that limits flow to the heart tissue but without angiographic evidence of blocked artery [22].

The results of the WISE study were summarized as follows: “Ischemic heart disease in women represents an important problem that is difficult to identify early... A heightened awareness of women at risk of IHD and a different approach than that used in men is necessary to allow for diagnosis before late stages develop... But women also are likely to have nonendothelial-dependent microvascular dysfunction, particularly in the early stages of IHD. Limitations to the prevailing diagnostic evaluation of women are now more clearly defined”.

Women have comprised only 25% of participants in heart-related research studies to date. There is a clear need for validated diagnostic methods to provide unequivocal test results in women who are symptomatic for IHD. The WISE results have generated interest in refocusing the diagnostic work-up in women to emphasize functional, rather than structural, abnormalities. Functional capacity, global ventricular function, regional wall motion, and coronary flow reserve show promise of increased effectiveness in the diagnosis of women’s IHD [23].
Imaging modalities
In addition to the tried and tested cath lab techniques, increased understanding of asymptomatic and symptomatic cardiovascular disease in women has created a need for non-invasive techniques to diagnose non-obstructive coronary artery disease (CAD). Stress echocardiography is a widely accepted technique, while SPECT imaging provides valuable metabolic information on existing or incipient ischemia.

Cardiac magnetic resonance offers a complete spectrum of tools to assess cardiac morphology, function, perfusion, viability and coronary vascular dysfunction in a single clinical study [24].

The DXL algorithm
Philips Healthcare has a long-term commitment to developing technologies and solutions for women's heart health. Beginning in the 1970's, Philips has used gender and age-specific criteria in diagnostic electrocardiograph algorithms. The latest DXL Algorithm applies new gender, age and lead-specific STEMI (ST-segment Elevation Myocardial Infarction) criteria to detect acute myocardial infarction in women as well as men. A widespread pattern of ST depression often reflects global ischemia due to left main coronary obstruction, multi-vessel obstructions, or microvascular disease, which is more prevalent in women. The DXL Algorithm incorporates new criteria for these conditions and provides a critical value of “Global Ischemia” to highlight that prompt intervention may be needed.

Gynecology
Gynecological conditions include benign conditions such as abnormal uterine bleeding, pelvic floor disorders, and infertility, as well as cancer of the cervix, uterus, and ovaries.

New therapies for abnormal uterine bleeding
Menorrhagia, including heavy or prolonged menstruation or bleeding between menstrual cycles, affects a significant population of women between the ages of 35 and 54. While the majority of menorrhagia cases are benign in origin, 10% are due to premalignancies or cancer. In the USA alone, over 9 million women suffer from this condition and, in India, it is estimated that 25 million women have fibroid tumors, a primary cause of menorrhagia [25]. At least one-third of menorrhagia cases are caused by uterine fibroids, which can also lead to infertility.

Ultrasound has proven to be a very useful tool for identifying the cause of abnormal uterine bleeding and can help exclude endometrial carcinoma [26]. Transvaginal ultrasound with saline infusion sonohysterography is particularly valuable in triaging certain menorrhagia patients to:
- no further evaluation
- blind endometrial sampling
- visually directed endometrial sampling for focal pathology.

The addition of saline infusion to a standard transvaginal sonogram has also aided diagnosis...
of intracavitary polyps and fibroids within the endometrium. Three-dimensional (3D) volumetric imaging may be helpful in detecting polyps and fibroids when the 2D image is not well defined, and can be useful for monitoring the effects of therapy [27].

Many women delay seeking treatment in order to avoid a major surgical procedure with general anesthesia, such as hysterectomy; however, three million women in the U.S. and Europe are treated for menorrhagia each year. Novel non-surgical treatments for menorrhagia offer new options for women. These procedures, which offer less discomfort and faster recovery time, are prompting more women to seek therapy. The choice of therapy depends on factors such as the cause of bleeding and its severity, and patient’s age and preferences. Non-surgical therapies that can be performed under local anesthesia or conscious sedation include:

**Global endometrial ablation**

Endometrium is treated with thermal ablation, using various energy sources, such as circulating heated saline, cryoablation, hot water balloon, laser energy, microwave ablation, and radiofrequency (RF) ablation.

**Uterine artery embolization (fibroids)**

Particles, such as polyvinyl alcohol, are injected via a catheter into the uterine arteries, resulting in thrombosis and occlusion.

**High-intensity focused ultrasound (fibroids)**

High-intensity focused ultrasound (HIFU) is an emerging therapy technique using focused ultrasound to heat and coagulate tissue deep within the body, without damaging intervening tissue.

In this technique, a specially designed transducer is used to focus a beam of ultrasound energy into a small volume at specific target locations within the body. The focused beam causes localized high temperatures (55 to 90°C) in a region as small as 1 x 1 x 5 mm. The high temperature, maintained for a few seconds, produces a well-defined region of necrosis. This procedure is referred to as ultrasound ablation.

The tight focusing properties of the transducer limit the ablation to the target location. Accurate positioning requires high-resolution images, while effective therapy requires real-time temperature monitoring and adequate post-treatment lesion assessment. To meet these requirements, Philips Healthcare is currently developing a dedicated MRI-guided HIFU system. Increasingly, significant issues in women’s health are emerging in developing countries. Care cycles in these regions can be dramatically different from those in developed countries. For example, factors such as lack of infrastructure, including technology and trained resources, cultural customs and stigmas, and economic issues can have a negative impact on women’s gynecological health. In many areas, a critical need exists for low-cost/high-value, patient-accessible solutions that fit the demands and particular constraints of a given country.

Another dynamic in countries such as China and India is the emerging middle class. There are a growing number of women entering the workforce in middle tier and smaller cities, as well as major urban centers. These women have raised expectations for health care and they need to minimize time away from the workplace due to health issues. As a result, they demand non-surgical, faster recovery therapies for their gynecological conditions.

**Cervical cancer in developing countries**

Cervical cancer continues to be a leading cause of cancer-related death among women in developing countries. It was a major contributor to the one million new cases of gynecological cancers worldwide in 2007. Each year, 80% of the approximately 500,000 new cases and over 250,000 deaths from cervical cancer occur in developing countries [28].

In developed countries, the Pap test and, more recently, HPV testing have been very successful in reducing the incidence of cervical cancer. It is well-established that screening models which work well in the developed world have not been successful in developing countries, due in part to the reliance on laboratory-based screening tests, and to poor patient compliance with a care cycle that requires multiple repeat visits for screening, diagnosis, and therapy. New care models that support screening, diagnosis, and therapy in one visit have shown some promise in overcoming these obstacles.

An important tool for diagnosing and guiding therapy for cervical neoplasias is colposcopy. In colposcopy, magnified visualization of the cervical tissue is used to evaluate abnormal vascular changes that indicate the presence of dysplasia. Digital colposcopes, such as Philips/Goldway SLC-series, can be especially useful for enhancing workflow and quality control in high patient volume settings. In resource-limited settings, digital colposcopy systems support telecolposcopy for improved, timely clinician training and access to center-of-excellence experts from remote sites.
References

Digital mammography has been used for breast cancer detection and work-up of suspected findings in the breast for more than fifty years [1]. After several large clinical trials, mammography has established itself as the primary method for general screening for breast cancer [2-6]. Breast magnetic resonance imaging (MRI) [7, 8] is now recommended as an additional imaging tool for high-risk women. This role is likely to increase. However, at this time, mammography is the only method for which a reduction in breast cancer mortality has been shown in randomized trials [6, 9].

Digital mammography can now deliver better soft tissue contrast than screen-film techniques, better X-ray penetration through dense breasts, and more consistent image quality. Various forms of digital mammography have been commercially available in Europe and the United States for almost a decade. Recent technological trends and results from clinical trials have catalyzed its wider acceptance.

According to the US Food and Drug Administration (FDA), more than 50% of all mammographic units in the United States are digital (6,577 digital out of a total 13,052 mammographic units) [10]. Figure 1 shows the growth of digital mammography in the United States over the past five years, demonstrating a clear acceleration of the trend in recent years.

The rationale for digital mammography

Early investigations on the physical properties of digital mammography provided the impetus for further research [11-15]. These studies suggested that the image noise characteristics of digital systems could be better than for screen-film mammography. Therefore, the high-resolution advantage of screen film might not be as important for detection of microcalcifications in the breast as it was originally assumed.

Moreover, visualization of subtle anatomic detail, such as microcalcifications or soft tissue spiculations, may not be as dependent on spatial resolution as on image contrast and proper exposure: two parameters that present a challenge to screen film but are the strengths of digital imaging techniques.

The ability of digital imaging systems to accommodate a large range of exposure (dynamic range) and the ability to manipulate the contrast of the images after acquisition are important factors that make digital mammography highly desirable. Because of these abilities, digital mammography can alleviate the problems that dense fibroglandular tissue and wide variations in X-ray attenuation often cause in screen-film mammography.

Results from the American College of Radiology Imaging Network – Digital Mammography Imaging Screening Trial concluded that while the overall diagnostic accuracy of digital and screen-film mammography were similar, digital mammography was more accurate in younger women, women with dense breasts, and pre- or peri-menopausal women [16, 17].

Physicians have always viewed digital imaging, including mammography, not only as a technology that may enable better care through improved image quality but also as an important tool for increased productivity. For example,
images acquired at a screening site can easily be transmitted and interpreted at a central location. They can be transmitted to another site for additional consultation. In addition, they can be readily available to the breast surgeons and oncologists.

**The technology**

The development of X-ray detectors that would match or surpass the physical characteristics of mammographic screen-film has been a formidable task. Such detectors must have a pixel size no larger than 100 microns, for an approximate matrix of about 2000 x 2500 pixels or higher.

Moreover, the intrinsic sensitivity of the detector should be high to detect very weak X-ray fluence through dense tissue. At the same time the detector must be able to tolerate very high X-ray fluence in the region of lower X-ray attenuation near the periphery. The electronic noise characteristics should be low so that very low signals through dense breast tissue are not masked.

Two technological approaches have emerged to meet this challenge: amorphous silicon flat-panel detectors used with a scintillator (indirect conversion) and amorphous selenium (direct conversion). The indirect approach uses a thin structured thallium-doped cesium iodide scintillator as the primary detector that is in contact with a pixelated amorphous silicon thin film transistor (TFT) array [18, 19]. Although the scintillator is prone to some light diffusion that can degrade the spatial resolution, this approach has worked well with careful design of the structured scintillator and post processing to preserve high spatial resolution.

The second approach uses amorphous selenium as the primary detector with a TFT readout pixelated array [20, 21]. Selenium is a nearly ideal X-ray detector in the mammographic X-ray energy range. Unlike the indirect conversion approach, X-rays interacting with the amorphous selenium layer in contact with the TFT array are converted directly to electrons, without the intermediate step of scintillation.

Due to the minimal deviation of the electrons from their path in this process (compared to light diffusion in indirect conversion), direct conversion is characterized by high spatial resolution that can be helpful in the detection and characterization of breast microcalcifications. Figure 2 shows a digital mammography system that uses a direct conversion flat-panel detector.

Photo-stimulable phosphor technology, also called computed radiography (CR), has been available for mammography for some time [22-24]. The main advantages of CR mammography are its relatively easy adaptation, which does not require replacing existing mammography units, and the resulting lower initial cost for the transition to digital. CR mammography uses cassettes containing stimulable phosphor plates that replace the screen-film cassettes. Digital images are obtained by electro-optical processing at a plate readout station (Figure 3).

With some digital systems, the X-ray dose to the breast may be lower than that with screen-film systems. This is due to a more efficient X-ray detection and the use of a slightly higher kVp with rhodium or silver filtration. Recent research based on computational simulations suggests that...
a slight reduction in breast compression during digital mammography may also be feasible. However, this needs to be further investigated and confirmed in clinical studies [25].

**Mammography reading**

The large volume of image data and the high image quality requirements of screening mammography necessitate special attention to the image reading environment. Digital mammography images are occasionally printed on high-quality digital film printers, but this deprives radiologists of the opportunity to adjust image display parameters, and is clearly uneconomical and environmentally undesirable practice.

Specialized softcopy reading workstations have been developed for this purpose. Two high-resolution flat-panel displays are now the standard in digital mammography workstations, typically with an image matrix of about 2048 x 2560 pixels, a pixel pitch in the order of 0.16 mm, and luminance exceeding 600 cd/m² (Figure 4). Contrast ratios exceeding 700:1 are attainable and greater than 8-bit resolution at the output is recommended [26].

Some digital mammography systems generate an image matrix that is larger than the native matrix of current image displays, and in such cases the entire breast cannot be viewed in full resolution. However, the zoom mode can be used for easy and fast interaction to view image details in full resolution.

In breast cancer screening, experienced radiologists may read more than 100 cases per hour [27]. Mammography workstations must be able to support this workflow with high data transfer rates, the possibility to define appropriate image hanging and reading protocols, including computer-aided detection (CAD) and double reading, as well as integrated reporting facilities. The transition to multimodality imaging of the breast makes it imperative for the radiologist to be able to review images from various modalities such as digital mammography, ultrasound, and MRI.

This has created both ergonomic and workflow needs that are critical for effective diagnosis. In addition, there is a need for vendor-neutral workstation solutions that can communicate with an imaging modality from any manufacturer. Such solutions are available today that allow visualization of images from multiple imaging modalities. Tools in such systems may include hanging protocols, interactive display or hiding of mammography CAD results, advanced zoom and magnification tools, magnification “lens”, actual size display and measurement, and programmable functions to suit each radiologist’s preference.

However, there are opportunities to enhance workstation solutions to incorporate breast MRI and ultrasound image analysis applications. Emerging imaging technologies such as tomosynthesis and dedicated breast computed tomography (CT) will create the need for additional workstation facilities. Any workstation solution should be capable of full integration with picture archiving and communication systems (PACS) and patient information systems to maximize workflow efficiency and to improve care delivery.

**Research studies**

Digital mammography provides the technological platform for a number of research imaging techniques, ranging from contrast injection mammography and subtraction techniques to tomographic imaging of the breast by digital tomosynthesis or dedicated computed tomography of the breast. While none of these technologies are presently approved for use in screening mammography, they hold the promise of improving the sensitivity and specificity of mammography for detecting early breast cancer.

**Contrast injection mammography**

It is well established that the progression of breast tumors is associated with angiogenesis [28]. Intravenously injected X-ray contrast agents may therefore prove efficacious in early detection of breast tumors. In the early angiogenesis stage,
Digital breast tomosynthesis (DBT) evolved from digital mammography. It consists of acquiring multiple projections of the breast and using them to reconstruct a quasi-tomographic image [32-34]. This requires about six to fifteen projections in an arc, typically up to 60°.

DBT can produce mammogram-like images at different depths. The slice thickness (and spatial resolution) in the z-plane is about 1 mm, but the spatial resolution in the x-y plane is about the same as in standard digital mammography. With improved imaging detectors and techniques, it is now feasible to acquire DBT images with the same radiation dose to the breast as a two-view mammogram. What is uncertain at this time is whether DBT alone is adequate for routine screening, or whether additional mammographic (planar) views will be required for screening.

DBT performs well in visualizing soft tissue abnormalities, but the visualization of very subtle amorphous microcalcifications seems to present a greater challenge than in standard mammography. Therefore, studies indicate that at this time it is difficult to rely solely on tomosynthesis (without any planar views) for the entire examination but this may change as the technology improves.

DBT is well developed and several clinical trials are under way; however, it will have to clear the regulatory process in the USA, Europe and in other countries before it can be used in routine clinical applications.

**Dedicated CT of the breast**

Dedicated CT of the breast is another alternative that was initially attempted more than thirty years ago, but technological constraints have prevented the application of CT technology for routine imaging of the breast [35]. In recent years, with the advent of new X-ray detectors and reconstructions for cone beam geometry, the concept of dedicated breast CT has been revisited.

In a typical implementation of dedicated breast CT, the patient lies in the prone position with the breast pendant through an aperture on a specially designed table [36]. The X-ray source rotates below the table for a tomographic acquisition in cone beam geometry. Dedicated breast CT generates tomographic images with isotropic resolution in three dimensions. The main challenges in breast CT are associated with attaining adequate visualization of microcalcifications, tissue coverage of the axilla and medial aspect of the breast, and in minimizing the radiation dose. This approach is experimental and research into the technological aspects of dedicated breast CT, as well as limited clinical trials, is in progress.

**The future of digital mammography**

High-resolution mammographic imaging detectors and displays that seemed technologically impossible and financially unaffordable a few years ago are increasingly becoming within reach.
of even the smaller clinics. Integration of digital mammography workstations with CAD is now commonplace. At some point, we are likely to see image displays with larger pixel matrices, capable of accommodating the entire breast at full resolution. Imaging workstations that integrate multimodality imaging such as mammography, MRI and positron emission tomography (PET) are also likely to become commonplace. X-ray detectors that use photon counting approaches are emerging for digital mammography and potentially for tomosynthesis and dedicated breast CT [37].

Digital breast tomosynthesis has become the next frontier in transformation from planar to tomographic imaging. More research is needed to establish the role of advanced techniques such as dedicated breast CT and contrast-injected mammography.

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High resolution MR breast imaging

Conventional Magnetic Resonance Imaging (MRI) has good sensitivity for detecting very early breast cancers and pre-cancerous conditions, and is therefore an important screening tool for women who are at high risk for breast cancer [1]. However, improvements in specificity are required, particularly given the high sensitivity of MRI [2]. This is an especially difficult problem when MRI detects very small lesions that may or may not be early cancers. Data currently available suggest that for conventional MRI, the sensitivity for detection of cancers in a high-risk population is between 70% and 80% [3, 4]. However, specificity for detection of early cancers such as Ductal Carcinoma In Situ (DCIS) is as low as 50% [5].

Advances in MRI technology are required to address this problem. Work at the University of Chicago, in collaboration with Philips Healthcare, has developed High Spectral and Spatial resolution (HiSS) MR imaging for improved anatomic and functional imaging of the breast. The results obtained to date demonstrate that HiSS MR images acquired on Philips scanners using Echo-Planar Spectroscopic Imaging (EPSI) have advantages compared to conventional breast images [6-10].

HiSS MR imaging provides a high-resolution spectrum of water and fat signals in each small image voxel [8, 11, 12]. The spatial resolution of HiSS data is equal to that of conventional anatomic images, but additional information related to tissue composition and physiology is available from the detailed lineshapes of water and fat signals in each voxel. For example, deoxyhemoglobin in deoxygenated tumor blood vessels affects resonance frequency and water proton spectral lineshape, and detection of these effects with HiSS can increase sensitivity to tumor neovascularature. Therefore, HiSS provides important new information regarding tissue structure and function.

HiSS MRI should not be confused with the more common biomedical application of spectroscopic imaging to obtain water-suppressed, spatially resolved spectra of metabolites. HiSS images are acquired without water suppression. Images are produced to represent features of the water and fat line shapes, such as signal peak height, line width, resonance frequency, number of resolved components, asymmetry of the water resonance, and changes in these features following contrast media injection. The resulting images increase the quality of anatomic and functional information that is available from MRI [8, 12].

HiSS images are acquired on a Philips Achieva scanner using a specially designed EPSI pulse sequence that provides spatial resolution of up to 400 microns in-plane and spectral resolution as high as 2.6 Hz. Signals are detected with either a 7- or 16-channel dedicated breast coil. Images of the peak height of the water resonance – referred to here as “water peak height images” – provide excellent morphologic detail.

These images can be T1 weighted but their primary source of contrast is very strong T2* weighting without the distortion that typically degrades gradient echo images with long TR. Figure 1 shows slices through a typical water peak height image of a breast with an invasive cancer (arrow, left). This image was acquired with spatial resolution of 500 microns, slice thickness of 1 mm, and spectral resolution of 8 Hz. The strong texture and the absence of fat signal results in clear morphologic detail.

Figure 1, right, shows a Maximum Intensity Projection (MIP) image of four slices, acquired with HiSS, surrounding the slice shown on the right. The connectivity of the parenchyma and blood vessels is more easily visualized in the MIP. Because of the excellent fat suppression in the individual slices, background signal does not accumulate in the water peak height MIP as it does in conventional MIPs.

HiSS is a natural extension of the work of previous investigators, who used low spectral resolution imaging to separate fat and water signals and correct for B1 in homogeneity, and

Investigations and research

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produced substantially improved MR images [13-16]. Recently, advances in MR hardware and software have allowed rapid acquisition of data using EPSI [17, 18] at very high spectral and spatial resolution. This allows resolution of the details of the water and fat line-shapes in each small image pixel [8, 19, 20] with reasonable acquisition times and minimal eddy current distortion.

Work in this laboratory [8, 19-23] and other laboratories [24, 25], demonstrates that HiSS data sets can be used to produce images with significantly improved anatomic detail relative to conventional spin-echo or gradient echo imaging. In the brain, high field data with relatively low spectral resolution can be analyzed in the “time” domain. This produces high-quality images of vasculature and other structures that produce variations in magnetic susceptibility (for example the work of Reichenbach et al. [26], and recent brain imaging at 7T by Duyn et al. at NIH [27]). Hu et al. demonstrated that Susceptibility-Weighted Imaging (SWI) [28] can produce very high quality venograms of the brain.

HiSS is also useful for brain imaging [29]. However, it is more helpful for imaging breast cancers. In breast, because of the large fat content of surrounding tissues and the significant inhomogeneous broadening of the water resonance, it is helpful to acquire data at high spectral resolution and bandwidth, and analyze data in the frequency domain.

In practice, even simple pre-contrast water peak height images are very sensitive to morphologic details, including blood vessels. Figure 2 compares HiSS MR images at a spatial resolution of 500 μm in-plane, slice thickness of 1 mm, with conventional fat-saturated images. Lesions are clearly visible and margins and morphology are well defined in the HiSS images, without the need for contrast agents.

**Advantages of HiSS images:**
Advantages of HiSS images are due to a number of factors:
• more precisely defined anatomy
• improved fat/water separation
• optimal signal-to-noise ratio per unit time
• vascular imaging without contrast agents.

**More precisely defined anatomy**
Spectral data associated with each k-space point can be used to calculate an “ideal” MRI image, that is, an MRI image obtained in the absence of magnetic susceptibility gradients and chemical shift. This is a significant departure from conventional MRI where spatial and spectral information are mixed together. Improved anatomic detail clearly delineates tumor boundaries and internal structure.

**Improved fat/water separation**
Conventional methods use frequency selective saturation, frequency selective inversion, and related methods to suppress the fat signal. This can reduce the signal-to-noise ratio of the water resonance via magnetization transfer effects or partial inversion of the water resonance. $B_0$ gradients result in poor fat suppression with conventional methods. HiSS achieves fat suppression by adequately sampling the proton free-induction decay (FID), producing a fat/water spectrum, fitting the fat resonance, and removing it. If the time over which the FID is sampled is optimized (see below) this approach can increase signal-to-noise ratio rather than reducing it.

**Optimal signal-to-noise ratio per unit time**
Conventional imaging acquires only a single gradient echo. However, optimal signal-to-noise ratio per unit time requires sampling the FID for slightly less than one $T_2^*$. In fact, since the water resonance frequently is inhomogeneously broadened, evaluation of data in the spectral domain reduces effects of destructive interference between different Fourier components and improves the signal-to-noise ratio associated with longer sampling of the FID.

For these reasons - while acquisition of HiSS data typically requires longer run times than conventional data - there is significant potential for improved signal-to-noise ratio per unit time and/or increased spatial resolution.
Vascular imaging without contrast agents

Previous work on animal models of cancer in this laboratory demonstrates that HiSS images can be used to map tumor vasculature without the need to inject contrast agents [30]. In tumors, the imbalance between oxygen delivery and oxygen utilization produces high concentrations of deoxyhemoglobin in blood vessels and this leads to frequency shifts and changes in water signal lineshape [31].

Because the spatial distribution of tumor blood vessels is often very heterogeneous within individual image voxels, small subvoxel clumps of deoxygenated blood vessels can produce shoulders or partially resolved components of the water resonance that are reliably detected in high spectral resolution data. The water lineshape (for example, water resonance asymmetry, shoulders or partially resolved components on the water resonance) can be analyzed to produce images of variations in local magnetic susceptibility.

These images are strongly correlated with images of vascular density around tumors produced from Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI) data. For example, Figure 3 compares an image of water resonance asymmetry produced from a HiSS dataset with a “difference image” produced from DCE-MRI data, showing regions with rapid contrast media uptake. The regions around the tumor that have high vascular density as shown on the DCE-MRI difference image also have strong water resonance asymmetry.

HiSS as a DCE-MRI substitute for detecting early breast cancer

New American Cancer Society (ACS) guidelines for screening of women who are at increased risk for breast cancer are likely to significantly increase the number of women receiving MRI screening exams each year [1]. This increases the importance of new approaches to MRI that increase sensitivity. DCE-MRI is currently the primary tool in MRI detection of breast cancers. Due to their dense and permeable vasculature, breast tumors enhance rapidly and strongly in comparison to normal breast tissue.

While DCE-MRI has obvious advantages, it also has some shortcomings:

• as greater numbers of women are screened with MRI, concerns about nephrotoxicity of contrast agents [32] and other reactions to contrast media become significant.
• diffusive and convective motion of contrast agent molecules blurs tumor edges, handicaps tumor delineation, and morphology assessment. Susceptibility gradients caused by the contrast agent further degrade image quality; particularly at tumor edges where there may be an abrupt change in contrast media concentration. Thus, it would be advantageous for radiologists to examine the “true” morphology of lesions, before contrast agent is injected. In principle, fat-suppressed images can be used for this purpose. However, conventional fat-suppression is often incomplete and image quality is modest.
• DCE-MRI has the highest specificity when acquired with high temporal and spatial resolution – but this is not possible in conventional clinical scans, due to the need to cover both breasts for lesion detection. Temporal resolution is particularly important for detection of DCIS, as shown by Dr. Newstead and co-workers, because DCIS can typically be seen clearly against a dark background in difference images produced from images acquired during the first 30 – 60 seconds after contrast injection [33].
• imaging of tumor morphology and tumor vasculature with HiSS pre-contrast injection may lead to increased diagnostic accuracy.
• HiSS is easily combined with other pulse sequences. For example, the T2, or apparent diffusion coefficient (ADC) of each component of the water resonance can be measured.

Implementation of HiSS MRI on the Philips Achieva Scanner

Collaboration between scientists at Philips Healthcare, Gyrotools, and the University of Chicago has produced a high-resolution EPSI pulse sequence and data processing software. This is integrated into the Philips Operating system so that HiSS scans and image reconstruction can operate routinely in the clinical environment. Optimization of multislice imaging protocols allows full breast imaging using HiSS with clinically acceptable acquisition times (8 – 12 minutes). Further enhancement
of HiSS acquisition speed is expected soon with the development of parallel imaging reconstruction methods for HiSS. Therefore, it is likely that HiSS will provide an important addition to the tools available to radiologists for breast cancer detection and diagnosis.

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Enhanced MR breast imaging

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MRI, together with other new diagnostic methods, has been shown to have the potential to dramatically improve the detection of cancer at a relatively early stage, when it is relatively easy to cure. New ACS guidelines recognize the importance of MRI for early detection of breast cancer. These new guidelines are likely to result in a dramatic increase in the number of women who receive MRI screening exams each year. Based on current guidelines, it is estimated that about 1.5 million women in the USA would qualify for this screening.

As the amount of screening increases, the need for increased specificity will also increase. In addition, while the sensitivity of MRI to invasive breast cancer is very high, improvements in sensitivity to early pre-invasive cancer, and even pre-cancerous lesions, are also needed. This will require improved application of conventional MR methods, improved image analysis and interpretation, and implementation of new methods including metabolic spectroscopy and diffusion-weighted imaging. In addition, a new approach to breast MRI, referred to as "high

The University of Chicago Medical Center (UCMC) is an integral part of the University of Chicago Hospitals. A team of specialized breast radiologists at the Center provides a full range of diagnostic services, including digital mammography, breast ultrasound and dynamic breast MRI, to more than 20,000 patients every year. Recently, the UCMC became the first site in the United States to use Philips Elite Breast Clinical Solution. Comprising the dockable MammoTrak patient support, integrated 16-channel SENSE MammoTrak Breast coil and software for accurate, efficient MR data analysis (DynaCAD), the Breast Clinical Solution provides very high image resolution, excellent breast coverage and an efficient workflow. This article describes the Center’s pioneering work on the application of advanced MR technology to breast cancer.

The UCMC has been using MRI for the detection and diagnosis of breast cancer for over 15 years. More recently, the Center has become especially committed to the use of dynamic contrast enhanced MRI (DCE-MRI). MRI, together with other new diagnostic methods, has been shown to have the potential to dramatically improve the detection of cancer at a relatively early stage, when it is relatively easy to cure. New ACS guidelines recognize the importance of MRI for early detection of breast cancer. These new guidelines are likely to result in a dramatic increase in the number of women who receive MRI screening exams each year. Based on current guidelines, it is estimated that about 1.5 million women in the USA would qualify for this screening.

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Diagnostic MRI

The standard clinical breast examination at the UCMC includes a number of scans, following the flow chart shown in Figure 1.

3D T2-weighted turbo spin echo

A 3D T2-weighted turbo spin echo (VISTA) scan is used to provide preliminary anatomic information and assist the prescription of subsequent scans. It is possible to use the signal intensity and morphologic evaluation of T2 weighted imaging detected masses to improve diagnostic specificity by matching the T2W sequence with the dynamic acquisition slice-by-slice for precise comparison. These scans are acquired rapidly by using multiple spin echoes combined with SENSE. In spite of the rapid acquisition, the image quality is excellent, and suspicious lesions are often detected on these scans. Lesion conspicuity on T2-weighted scans is useful for differentiating cysts and other benign lesions from cancers. Figure 2 is an example of a 3D T2-weighted TSE (VISTA) image, showing a malignant breast lesion.

Diffusion weighted imaging (DWI)

Bilateral diffusion weighted (DWI) scans are performed before contrast injection. Diffusion weighting is useful for detecting the increased cellularity of viable tumors, because the apparent diffusion constant is decreased by restricted diffusion of water inside cells. DWI may also be sensitive to ductal hyperplasia and ductal carcinoma in situ (DCIS) because water within the ducts, which normally diffuses freely, is confined inside intra-ductal cells.

Quantitative measurement of the “apparent diffusion constant” would require several different measurements with different applied gradient strengths. However, to conserve time, our clinical protocol simply uses a single diffusion weighted scan, and the resulting images are evaluated qualitatively to identify regions with an abnormal diffusion rate. An example of a diffusion-weighted image of a malignant breast lesion is shown in Figure 3.

Pre- and post-contrast scans

Bilateral scans are performed pre- and post-contrast. At the UCMC, “eTHRIVE” is used with “SPAIR” to provide fat-suppression with a spatial resolution of 0.76 x 0.76 x 1 mm times 200 slices per dynamic acquisition (Figure 4). This provides excellent morphologic detail pre- and post contrast injection, and images are acquired with temporal resolution of 60 seconds. A high acceleration factor of 6 is achieved using the new 16-channel SENSE MammoTrak Breast coil.

At the UCMC, intensive use of MRI results in the discovery of 250 new cancers each year.

At the UCMC, approximately 750 women receive screening and/or diagnostic MRI scans each year. Many of these patients receive MRI scans secondary to suspicious findings on mammography, primarily in order to search for additional lesions elsewhere in the breast.

Another large group of women comes from Dr. Olufunmilayo Olopade’s Cancer Risk Clinic. This is a specialized clinic within the UCMC. Dr. Olopade is a highly skilled hematology oncologist with proven expertise in cancer risk assessment. She conducts comprehensive evaluations of family history, genetic testing and other risk factors. The protocol followed at the UCMC calls for screening these patients for breast cancer with MRI and Ultrasound every six months, and X-ray mammography every year.

The intensive use of MRI results in the discovery of approximately 250 new cancers each year. The number of percutaneous biopsies (5%) is kept low through the use state-of-the art methods for MR imaging and image interpretation.
Reliable detection of DCIS requires rapid acquisition of the first post-contrast image because DCIS often enhances more rapidly than the surrounding normal parenchyma. Therefore, DCIS can be most clearly visualized by subtracting the first post-contrast images, acquired within the first 30 seconds (i.e. 60 seconds after injection), from the pre-contrast images.

High temporal resolution is also important because it allows accurate assessment of tumor blood flow. At short times after injection, uptake of contrast agent is determined primarily by blood flow and capillary permeability, while at longer times after injection, enhancement is strongly affected by the contrast agent distribution volume.

SENSE with acceleration factors of three or more is critical for proper evaluation of tumor blood flow and for detecting DCIS. With the 16-channel breast coil currently used at the UCMC, SENSE acceleration factors of three to six can be achieved without image distortion and with excellent signal-to-noise ratio.

DCE-MRI data are assessed in two ways. First, subtraction images are viewed, often in three dimensions, to assess the morphology and kinetics of enhancing lesions. An example of a subtraction image is given in Figure 5. Second, plots of signal intensity vs. time are evaluated for regions of interest that are manually selected to include suspicious lesions. These plots are classified using the method described by Kuhl et al., [1] to identify lesions that are likely to be malignant. More quantitative methods that correct for variations in the arterial input function, and for the “native” (pre-contrast) T1, are being developed for routine clinical use, and will soon provide reliable parametric images of tumor blood flow and contrast agent distribution volume.

For lesions that are at least a centimeter in diameter, metabolic single voxel spectroscopy is acquired using a PRESS sequence combined with outer volume suppression. This provides a non-invasive measurement of tumor metabolism and detects metabolites that are markers for malignancy. The most commonly used marker is a high level of choline – a metabolite used in membrane metabolism that is elevated in malignant cells. Proton spectra can be acquired in five minutes with the new 16-channel Mammotak breast coil, which also provides an improved signal-to-noise ratio.

**Patient volume**

The American Cancer Society (ACS) recently recommended the use of MRI in addition to mammography for annual breast screening for women with a 20%-25% or greater lifetime risk of breast cancer [2]. In addition, the Society recommends MRI in addition to mammography for women who:

- have a BRCA 1 or 2 gene mutation
- have a first-degree relative with a BRCA 1 or 2 gene mutation and have not been previously tested
- have received chest radiation treatment between the ages of 10 and 30
- are carriers or relatives of people with certain genetic mutations.

As a result, patient volume for screening with MR can be expected to increase in the years to come.

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Image-guided near-infrared spectral tomography was developed for the detection and characterization of breast cancer because of its unique ability to map hemoglobin, water, and lipid content in tissue. The method uses measurements of light transmitted through the breast at multiple wavelengths to quantify the spectral absorption and elastic scattering properties of tissue.

Breast cancers have been shown to have higher hemoglobin and water content and lower lipid fraction relative to normal parenchyma [1-5]. Because of its modest cost and use of non-ionizing radiation, the technique can be applied to monitor tissue without safety concerns, and integrates with magnetic resonance (MR) breast imaging. Introduction of near-infrared spectroscopy (NIRS) into an existing 3T Achieva MR scanner is demonstrated and representative case studies are presented that show results for intrinsic tumor spectroscopy.

In addition to its potential in breast screening [6], NIRS may hold promise in monitoring the effectiveness of chemotherapy [7]. Cerussi et al, [8] showed that breast monitoring with near infrared light was able to predict chemotherapy response in 11 patients within the first week of treatment. In particular, the absolute concentration of total hemoglobin in tumors and the relative differences in deoxyhemoglobin and water in tumors versus normal tissue demonstrated significant separation of treatment responders from non-responders among the women enrolled in the study.

Cost-effectiveness studies of this approach indicate that the technology should be beneficial in the individualization of neoadjuvant chemotherapy, as long as the initial treatment is less than 90% effective and the cure rate can be increased by as little as 1% through a change to an alternate therapy [9].

Admittedly, optical/NIRS imaging of the breast has exhibited limited success in the screening and diagnostic settings. In several clinical trials, improvements in specificity have been reported because of better lesion characterization [10, 11]. Unfortunately, optical mammography has been unable to characterize small lesions (less than 6 mm) when used alone because of its spatial resolution limitations, which are caused by the excessive light scatter in all tissue.

Indeed, both of the larger breast optical imaging studies described in the literature have either noted the poorer characterization of lesions less than 6 mm [11], or excluded lesions smaller than 8 mm altogether [10]. As a result, the focus on breast cancer screening with NIRS has not led to a technology that has gained clinical acceptance for screening. However, alternative applications continue to be explored and carefully evaluated in order to identify the best possible opportunities for NIRS in breast health care [12].

One promising avenue for NIRS is to focus on its spectroscopic strengths in characterizing tissue without requiring high spatial resolution. Image-guided NIRS makes the strategy possible by using the spatial template of the MR image upon which localized spectroscopy is superimposed. This concept was initially demonstrated for individual wavelength imaging in the breast some ten years ago [13, 14].

A more recent version of the approach has exploited multi-spectral measurements to characterize the fibro-fatty constituents within the breast [15,16]. High-resolution spatial guidance from X-ray or MR has demonstrated an improvement in both the spatial resolution and quantification accuracy of NIRS [17-19]. Initial breast cancer images have recently been reported with the approach [20, 21]. The clinical performance of these coregistered multi-
Modality methods has yet to be fully evaluated in a clinical trial. But the phantom and clinical case studies shown to date clearly indicate that MR-guided NIRS will improve upon the results obtained with stand-alone NIRS imaging.

In this paper, we briefly summarize the MR-guided NIRS system developments that have taken place at Dartmouth Hitchcock Medical Center in collaboration with Philips Research over the last several years. We present several case studies of recent results which illustrate the promise of multi-modality NIRS, not only in terms of improving the performance of optical breast imaging alone, but also in augmenting tumor detection, characterization and monitoring with breast MR.

**Methods**

**Instrumentation**

The optical instrumentation, shown in Figure 1, uses 16 fibers that sequentially deliver light from multiple sources (six separate diode lasers covering the 660-850 nm range) and channel the collected light to a bank of photomultiplier tube (PMT) detectors. Light from the six individual diode lasers is delivered through the fibers to the breast, with an intensity modulation frequency of 100 MHz. The transmitted signals are detected by PMTs matched to each fiber.

The resulting signal is mixed down to low frequency, after which its amplitude and phase are measured through A/D capture at each detector. The phase shift of the 100 MHz light is a direct measure of the scattering path-length that the light has traveled through the breast thus allowing separation of the effects of scatter from absorption using a diffusion-based spectral estimation process.

The fiber optic lines extending from the breast to the data acquisition hardware are 13 meters long, and are non-magnetic. The breast interface has been integrated within the plates of an MR breast RF coil, allowing the NIRS data to be recorded while the scanner is in operation. The patient is positioned prone inside the bore of the magnet (Philips Achieva 3T, X-series) with the breast pendant into the fiber array interface.

While early work was performed with the fibers in a circular geometry, as presented here, a more advanced version of the system conforms to the standard biopsy plates to facilitate clinical workflow. The current design, consisting of 16 fibers, is a prototype that provides one coronal slice of optical measurements. It is possible to incorporate more fibers for multi-slice data acquisition as is routinely performed in standalone NIRS systems.

MRI was used to acquire anatomical features that were integrated within the NIRS image reconstruction procedure [20]. Specifically, 3D T1-weighted Spin Echo (TR/TE = 900/10, flip angle = 18°) MR images were recorded to separate adipose and fibroglandular tissue, which are expected to have distinct optical properties [16]. Regions of interest, determined by Dynamic Contrast Enhanced MR (DCE-MR), were obtained by injecting a bolus of contrast agent (Magnavist) intravenously. A series of T1-W volume images (TR/TE = 10/6, flip angle 20°) were then acquired after each minute, beginning 40 seconds post-injection.

**Image reconstruction**

Tissue absorption and scattering characteristics were determined by simultaneously reconstructing the NIRS data at all wavelengths. Light propagation was modeled by the diffusion equation. This accurately describes signal propagation in tissue when scattering dominates over absorption and when source-detector distances are larger than a few scattering lengths [22].

To form a spectroscopic set of images, a model based estimation algorithm is used that minimizes the mismatch between the NIR data collected and the quantities computed through the diffusion equation [23, 24]. The method...
protocols approved by the Institutional Review Board at Dartmouth Hitchcock Medical Center.

Results

Image guided versus non image guided NIRS

A representative example of NIRS image improvement with MR guidance is illustrated in Figure 2. Here a patient, who was an eventual non-responder to neoadjuvant chemotherapy, was examined on the same day before treatment with a stand-alone (Figure 2a) versus an image guided NIRS system (Figure 2b). Image guidance leads to a dramatic improvement in contrast localization and contrast delineation of background tissue types that is not evident in the stand-alone diffuse image.

Patients

In this case-study report, imaging results from three patients are described. The patients were evaluated during various stages of neoadjuvant chemotherapy for breast cancer treatment. All subjects provided informed consent. They were then imaged according to the research study protocols approved by the Institutional Review Board at Dartmouth Hitchcock Medical Center.

Individual cancer imaging

Three subjects undergoing neoadjuvant chemotherapy were imaged during treatment. These subjects had invasive ductal carcinomas...
(IDCs) confirmed via biopsy. These examples show classic contrasts, where the cancer had higher hemoglobin and water contents because of the increased vascularity expected in tumors. Tumors also typically have a higher cellular packing density because of this vascularity, but scattering contrast was not observed in the non-responding cancer case presented below. Imaging results are shown in Figure 3 and Figure 4.

**Subject 1**
The subject, a 36 year old woman at the time of imaging, had a 3 cm IDC and DCIS lesion in the right breast. Imaging was performed one day after the first cycle of treatment. Results show a decrease in hemoglobin of 20 µM in the region of interest, compared to near 30 µM in the background. Interestingly, the fibroglandular tissue presented lowered hemoglobin that could be due to the large extent of collagen evident in the corresponding mastectomy slice obtained after surgery.

Oxygen saturation in the region was 60% compared to nearly 75% in the background, and water concentration was closer to 40%, compared to 60% in the background. Scattering resulted in an increased particle density near 3.5 x 10¹⁶, and particle size was homogeneous near 1 µm across the image plane. The reading radiologist reported a suspicious lesion appearing in the DCE-MR exam that was not apparent on previous MR scans (lower right enhancement in Figure 3c).

Pathology performed seven weeks later revealed a complete response to chemotherapy with no viable tumor remaining. However, there was residual scar tissue in this location (see Figure 3d) that likely contributed to the lower quantities of hemoglobin, oxygenated hemoglobin, and water as compared to the background. This case is an interesting demonstration of where the NIRS findings could have significant diagnostic potential to eliminate the false positive reading from the MR exam that would have resulted in an additional MR-guided biopsy in most cases.

**Subject 2**
The subject, a 51 year old woman at the time of imaging, had a 7 cm IDC in her left breast. Imaging was performed seven days prior to the first cycle of chemotherapy. MR-NIRS results showed an increase in hemoglobin to greater than 180 µM compared to 40 µM in the background. Hemoglobin oxygenation was 80%, slightly lower than the 85% in the background. Water was elevated to 95% from near 60% in the background.

A slight increase in effective scattering particle size to 0.95 µm compared to a background of 1 µm was found in this region, as well as a lower particle number density, around 0.5 x 10¹⁶ compared to nearly 1x10¹⁶ in the background. It is important to note that in this case the optical system was not able to fully sample the tumor.
course of treatment indicate that total hemoglobin decreased, from about 38 µM to about 20 µM, due to the reduction in the tumor size as a response to treatment. Water diminished in the anterior lesion from about 42% to 38%, most likely because of the reduction in functional vascular tissue in the tumor. Oxygen saturation also decreased, likely because of destruction of functioning tumor vasculature, which restricted tumor perfusion.

Discussion
This study presents MR-guided NIRS for delivery of multi-modality breast exams. The ability to obtain spectroscopic information on both the absorbers present in tissue, and the effective scattering particles, is unique, and has the potential to contribute pertinent diagnostic information. The MR-guided recovery of NIRS parameters in Subject 1 was significant because they allowed identification of lesion features that were not suggestive of cancer.

Ultimately, analysis of the tissue removed during surgery confirmed that the lesion, which was enhanced by DCE-MR, was not malignant but a fibrotic scar left after neoadjuvant chemotherapy. While this case was not in need of highly sensitive diagnostic accuracy, it was complex and the additional characterization of the breast would have helped the attending physicians recommend the best treatment option (for example, of mastectomy or not).

Subject 3
The subject, a 36 year old woman at the time of imaging, had a 3 cm IDC with three satellite lesions in her left breast upon commencement of neoadjuvant chemotherapy. Multiple imaging sessions were performed over the course of treatment. The subject showed complete response to chemotherapy as confirmed by pathology.

The first imaging session occurred one day before her first infusion of chemotherapy. Imaging sessions thereafter were performed within 48 hours of chemotherapy. Figure 5 and Figure 6 demonstrate the volumetric changes in recovered hemoglobin contrast in the regions of interest versus the backgrounds. These MR guided NIRS images were overlaid on the respective DCE-MR views and displayed with VolView software (Kitware, Inc.).

The satellite lesions that were located in the optical fiber plane are visible as increases in hemoglobin over the background, and both are located in the fibro-glandular tissue. In the successive cycle (Figure 6), the volumes of these lesions, as well as total hemoglobin content, decreased.

A summary of the optically recovered properties from three imaging sessions performed over the course of treatment indicate that total hemoglobin decreased, from about 38 µM to about 20 µM, due to the reduction in the tumor size as a response to treatment. Water diminished in the anterior lesion from about 42% to 38%, most likely because of the reduction in functional vascular tissue in the tumor. Oxygen saturation also decreased, likely because of destruction of functioning tumor vasculature, which restricted tumor perfusion.
breast interface will have the optical fibers integrated into biopsy plates, allowing more space for positioning of the breast in the fiber array, which is of particular interest in the ongoing collaboration between Dartmouth Hitchcock Medical Center and Philips Research in Hamburg.

Acknowledgments
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References


Figure 5a. DCE MR images of a patient with an IDC acquired one day before chemotherapy show slight enhancement of one main node with three satellite lesions.

Figure 5b. MR-NIRS images overlaid on 5a). The lesions that were in the plane of the optical fibers of the MR-NIR instrument show increased hemoglobin over the background.

Figure 5c. Color bar used for quantitative analysis of hemoglobin in 5b.

Figure 6a. DCE MR images of the patient from Figure 5 taken within 48 hours after the second cycle of chemotherapy. It is difficult to discern here, but only two lesions enhance, indicating response to chemotherapy.

Note the decrease in hemoglobin between Figure 6b and Fig. 5b, demonstrating the response. Pathology (not shown) taken after the completion of chemotherapy indicated a complete response.

Figure 6c. Color bar has been duplicated here for comparison.

As enrollment in the study presented here is ongoing a more comprehensive summary data will be published in the future. From a system design and performance evaluation perspective, the NIRS components have little impact on MR scanner performance and exam administration. Future versions of the NIRS breast interface will have the optical fibers integrated into biopsy plates, allowing more space for positioning of the breast in the fiber array, which is of particular interest in the ongoing collaboration between Dartmouth Hitchcock Medical Center and Philips Research in Hamburg.


The screening service

For many decades, breast cancer has been the most common form of cancer in women, and the most important cause of death from malignant disease. There are more than 13,000 new cases of breast cancer per year in the Netherlands, and according to the most recent data, 3,300 deaths, among a total population of 16,000,000 [1].

The nationwide screening service for breast cancer, known as BOB from the initials of the Dutch title (Bevolkingonderzoek op Borstkanker) has been set up by the Dutch government for asymptomatic women between 50 and 75 years of age. The primary test offered is X-ray mammography, aimed at early detection of breast cancer in order to reduce the mortality from this disease. The examinations are performed in 14 fixed units at strategic locations in the country, and a
favorable results of these trials and two pilot projects in Utrecht and Nijmegen in the Netherlands, together with a cost/benefit analysis, were the basis for the introduction of breast cancer screening in the Netherlands.

In addition to the reduction in mortality, there are several other indicators that can be used to assess the success of a screening program. These are referred to as surrogate indicators, and include:

- incidence of interval cancers (i.e. those diagnosed after a negative mammographic screening procedure and before the next scheduled screening)
- stage of tumors discovered at screening
- proportion of tumors detected with a diameter less than 1 cm
- ratio between ductal carcinoma in situ (DCIS) and invasive tumors
- proportion of tumors detected with positive lymph nodes.

These surrogate indicators have been shown to provide a good indication of future mortality reduction. We can confidently assert that no other healthcare sector has been so carefully evaluated and supported as breast cancer screening with X-ray mammography.

**Results**

Since its introduction in 1989, breast cancer screening has detected more than 50,000 cases. From the beginning of the program, the surrogate indicators described above have been shown to correlate well with the outcome. From a participation of about 75% in the early years, recent years have shown a slow but steady increase to more than 80%. This shows that screening has now become an accepted phenomenon.

The nationwide screening service is financed directly from taxes, and therefore falls outside the standard healthcare insurance schemes. The government sets a standard of quality that the screening organizations have to meet, with continuous monitoring of the overall figures and performance indicators, and a training and visitation scheme.

**Historical background**

As early as 1968, Wilson and Jungner [2] described a number of criteria that a screening program would have to meet. It is beyond the scope of this article to deal with all of these criteria, but the first essential is to have a practical and effective test. The only validated test for breast cancer that can be applied to a large asymptomatic population is X-ray mammography.

In the latter half of the twentieth century prospective randomized trials were carried out in several countries directed towards estimating the impact of mammographic screening on the reduction of breast cancer mortality. The
The screening program has had an enormous influence on breast cancer care in the Netherlands. The influence of better organization (multidisciplinary breast teams), improved treatment (such as chemotherapy) and improved surgical techniques regularly leads to discussions of what effect can be attributed to which factor. Such discussions are probably irrelevant, because in any case it is evident that mass screening and increased alertness have led to more favorable staging of manifest tumors in the group as a whole.

Cost effectiveness

The mass screening program costs around €45 million per annum. Corrected for inflation, the costs have reduced rather than increased. There are few overheads and the majority of the screening organizations are well run, with high productivity. Since 1994 the efficiency has been increased still further.

Cost effectiveness analyses carried out by investigators at the Erasmus University in Rotterdam, the Netherlands, show that at least 800 fewer women die of breast cancer each year, at a cost of about €4,000 per added year of life. To the best of our knowledge, no other mass screening project even approaches this result.

Since the introduction of breast cancer screening there has been a continuing reduction in breast cancer mortality at both national and regional level. The extension of the age range to 75 in 1998 has been accompanied by a reduction in mortality in the older age group since 2002. From 1989 to 2006, mortality in the 55-75 year old age group was reduced by 24%.

The only detailed performance figures available in the Netherlands are for those women who actually participated in the screening. Extrapolation of the available figures for the population as a whole, and comparison with countries such as Sweden where such an analysis has been carried out, indicates that the reduction in this group is about 40%. In other words, a woman who participates in breast cancer screening reduces her risk of dying of breast cancer by 40%.
Recent developments

The government is currently implementing a program of regional coordination and modernization, in which the existing analogue mammography units are being replaced by new digital systems, linked via a nationwide image management system with a central archive and 25 remote reporting units at various locations in the country, staffed by specially trained screening radiologists.

At present, each region has its own database and the three pilot regions each have a PACS. Philips will be responsible for migration from these to the national archive.

Secure nationwide fiberoptic network

The iSite PACS distributes the images and data via a secure, nationwide fiberoptic network, making them in principle available to authorized healthcare professionals in seconds. An additional benefit is that hospitals will have direct access to the images, eliminating the need for repeated examination and the attendant radiation exposure.

The new service currently comprises nine Regional Screening Organizations, each with one or more Central Units responsible for invitations, process control, and archiving and communicating images and data.

Images and data within the screening units are communicated to the resident workstation using iSyntax, with DICOM communication through the network. Images and data from the mobile units will be recorded on hard disc and couriered to the Central Units.

Implementation

Migration to the new system is already well under way. Two “mirror” Central Archives have been set up in the Eindhoven area, and the first regional central units are on-line.

The nine Regional Screening Organizations are currently being merged into five regions, and all regions are expected to be integrated in the new system by July 2010.

The transition to the new system is complex and far-reaching, requiring the cooperation of all parties, not least the radiologists concerned.

The introduction of nationwide digital screening also requires harmonization of the radiological working procedures, as there are regional differences, some of which are quite significant.

The National Expert and Training Centre has been asked by RIVM to facilitate the transition from analogue to digital screening by providing training specifically directed toward achieving standardized working methods. The training program is compulsory and includes familiarization with the BI-RADS (Breast Imaging - Reporting and Data System) assessment categories, standardized image processing, and...
insight into the effects of this method of working, such as temporary recall peaks.

Considerable benefits are expected when the digital working method has been fully implemented and any teething troubles are overcome. There is good reason to suppose that an even higher level of detection will be achieved, and implementation of the digital system may also be a good opportunity to lower the starting age to 45 years. However, there is still a lot of work to be done in order to fine-tune the system, including developments such as Computer Aided Detection (CAD), automated density scoring, other forms of risk stratification, multimodality imaging, expert panels, continuous on-line quality control, and continuing education.

The screening radiologists in the Netherlands will soon be part of a mammography practice performing close to 1,000,000 examinations per year with 180 similarly trained radiologists and 500 technicians, who will be working together to prevent some 1,000 deaths from breast cancer per year. This is a task that, to the best of our knowledge, does not have its equal anywhere in the world.

References

[1] www.ikcnet.nl


Investigations and research

The role of cardiac MRI in the diagnosis of women’s cardiovascular disease

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More than 400,000 women in the United States die every year from cardiovascular disease (CVD), making it the leading cause of death of women in the US [1]. Despite the advances made in the diagnosis and treatment of CVD in men, the effective diagnosis of CVD in women is limited by their atypical symptom presentation and the reduced sensitivity and specificity of diagnostic testing in women compared to men [2, 3].

Unfortunately, women with CVD also have a higher risk for cardiac events and mortality once diagnosed, increasing the need for tests that diagnose disease at an earlier or even subclinical stage. Thus, there is an urgent and unmet need for new diagnostic strategies in both asymptomatic and symptomatic women with CVD.

The landmark National Heart, Lung, and Blood Institute (NHLBI) sponsored study, Women’s Ischemic Syndrome Evaluation (WISE), made several important contributions to our understanding of CVD in women by [2, 3]:

• defining the unique pathophysiology of CVD in women;
• demonstrating that measurements of coronary vascular dysfunction in women predicted risk of future events;
• outlining the direct unmet need to diagnose women with atypical presentation of CVD.

An abridged summary of the WISE study findings is given in Table 1. To summarize the WISE study findings, women presenting with chest pain are less likely to have obstructive coronary artery disease (CAD) and more likely to have abnormalities of coronary vascular reactivity. Importantly, these abnormalities of coronary flow are tied to the risk of future cardiac events. However, these studies were based on invasive angiography in symptomatic women. Identifying a non-invasive strategy that measures coronary vascular dysfunction could be extended clinically for diagnosis and management strategies in women with non-obstructive CAD [2, 3].

The challenges of imaging women

The challenges encountered by other non-invasive diagnostic modalities highlight cardiac MRI as an ideal non-invasive imaging modality in women. In general, non-invasive modalities face the challenge of detecting disease in women who have smaller epicardial coronary arteries, lower left ventricular mass and smaller left ventricular size than men, and greater chest wall attenuation.

Specific advantages of MRI for evaluation of women include excellent soft tissue characterization and contrast, three-dimensionality, an absolute quantification of blood flow, and overall superior temporal and spatial resolution to image vascular and myocardial abnormalities. In addition, the epidemics of obesity and type 2 diabetes have lead to more women presenting with CAD during childbearing age, creating greater concern for tests involving ionizing radiation: for example, computed tomography (CT) and single photon emission computed tomography (SPECT). MRI is free from ionizing radiation thereby avoiding radiation exposure to sensitive tissues.

Current applications of cardiac MRI

During a single clinical cardiac MRI session, every diagnostic imaging need reported in the WISE study (Table 1) potentially can be met. Currently, cardiac MRI techniques are available to acquire images that can assess morphology, function, perfusion and viability. A combination of any or all of the techniques shown in Table 2 can be collected to investigate evidence of CAD and/or CVD in women.
Measurements of cardiovascular function, including ejection fraction, cardiac output, and total muscle mass, can be obtained reliably with a high degree of accuracy and in a short period of time (Figure 2). Ventricular function can be performed at rest, or under pharmacologically-induced stress, to permit assessment of silent (asymptomatic) ischemic events.

While the anatomical and functional imaging techniques discussed above have become routine for clinical cardiac MRI practice, contrast agent enhancement techniques are often acquired to provide additional information regarding cardiovascular health. Cardiac perfusion images (Figures 3 and 4) can be collected at rest and under stress during the first passage of a contrast agent.

Currently, cardiac MRI is used clinically to study CVD. Further details of these clinical studies are given in this article. The extent to which MRI can be used to diagnose CAD is under investigation. The potential for diagnosing CAD using MRI is also described in this article. A summary of these techniques follows.

### Table 1. WISE study findings and direct needs [2, 3].

<table>
<thead>
<tr>
<th>Study findings</th>
<th>Direct needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional diagnostic tests to identify obstructive disease do not work as well in women</td>
<td>Study symptoms, disabilities, and indicators that are abnormal but not a “typical” presentation</td>
</tr>
<tr>
<td>The “typical” female presentation of Ischemic Heart Disease (IHD) is more complex and multi-factorial than in men</td>
<td>Evaluate combination of symptoms, risk factors and stress-induced imaging markers to improve risk assessment</td>
</tr>
<tr>
<td>There may be gender-specific response to atherosclerotic risk burden mediated by reproductive hormones</td>
<td>Further inquiry as to which functional measures should be considered “at-risk” even without obstructive CAD</td>
</tr>
<tr>
<td>Signs and symptoms of IHD without obstructive coronary disease is a significant health problem for women</td>
<td>New imaging techniques that document the diagnosis of ischemia due to vascular dysfunction</td>
</tr>
<tr>
<td>Estrogen deficiency in premenopausal women with presentation of IHD may be etiologic for obstructive coronary disease during postmenopausal years</td>
<td>Assess role of gender-specific reproductive hormones in IHD etiology, pathophysiology, diagnostic and prognostic assessment, and therapeutic response</td>
</tr>
</tbody>
</table>

### Table 2. Cardiac MR scanning techniques.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Purpose</th>
<th>3T advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright blood</td>
<td>Morphology</td>
<td>SNR and CNR</td>
</tr>
<tr>
<td>Black blood</td>
<td>Morphology</td>
<td>SNR and CNR</td>
</tr>
<tr>
<td>Cine</td>
<td>Qualitative wall motion, ventricular function</td>
<td>SNR and CNR</td>
</tr>
<tr>
<td>Tagging</td>
<td>Quantitative wall motion</td>
<td>Longer tag persistence (can examine diastolic function)</td>
</tr>
<tr>
<td>Phase contrast angiography</td>
<td>Flow quantification</td>
<td>Phase-to-noise ratio increase</td>
</tr>
<tr>
<td>Perfusion</td>
<td>Assess regional blood supply</td>
<td>Lower artifact incidence; greater spatial resolution and coverage</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Assess vessel narrowing</td>
<td>Whole-heart coverage; greater vessel contrast</td>
</tr>
<tr>
<td>Delayed enhancement</td>
<td>Myocardial viability</td>
<td>Greater scar contrast</td>
</tr>
</tbody>
</table>

### Functional cardiac MR can be used to evaluate myocardial motion.
Figure 1. 3T black-blood images. Two chamber, four chamber, and short axis views.

Figure 2. Balanced-Steady State Free Precession (bSSFP) cine images at 3T. End diastole and systole, short axis view.

Figure 3. Stressed first-pass perfusion image at 1.5T (right) shows perfusion deficit (double arrows) in myocardial tissue, in agreement with X-ray angiography findings (left).
gadolinium-based contrast agents. Delayed enhancement techniques use inversion recovery (IR) pulses to visualize the transmural extent of an infarction.

In addition to morphology, function, perfusion and viability assessment, techniques for cardiac vessel angiography, blood flow and myocardial strain measurements have been developed, although they are not used as widely in clinical cardiac MRI practice. Coronary magnetic resonance angiography (MRA) techniques that aim to visualize the coronary vessel lumen have greatly improved over the past few years and now allow artery-targeted or whole-heart coverage (Figure 5) with high spatial resolution in short scan times.

To enhance blood contrast, a T2-preparation pulse suppresses tissues with short T2 relaxation times, such as myocardium. Alternatively, an additional IR preparation in the presence of a gadolinium contrast agent can greatly improve the conspicuity of proximal and distal arteries. Coronary MRA can potentially assess the subset of women who have obstructive CAD. Phase contrast angiography (PCA) can quantify flow in major and some minor vessels surrounding the heart from the phase difference of flowing spins. The image contrast in PCA is obtained from phase subtraction of flow compensated and flow sensitive acquisitions.
Myocardial tagging techniques are similar to functional imaging with the addition of gridded saturation bands or spatial modulation of the magnetization (SPAMM). Myocardial tagging traditionally has been used in cardiac research to observe and quantify wall motion abnormalities by applying material fiducial markers to the tissues with preparatory pulses (Figure 6), thereby allowing direct quantification of motion.

Advances in cardiac MRI

Technical advances in cardiac MRI have strengthened its case as the standard diagnostic tool for women suspected of CVD. Use of vector cardiogram (VCG) algorithms has allowed for more reliable cardiac triggering, which greatly enhances the quality of cardiac cine imaging. Improvements in real-time respiratory navigation permit longer acquisitions for whole-heart 3D image collection allowing higher spatial resolution scans [4, 5].

Cardiac-dedicated phased-array surface coils with as many as 32 elements have led to increased signal to noise ratio (SNR) and reduced scan time using higher acceleration rates [6]. Further improvements in spatiotemporal resolution appear likely from incorporation of novel k-space sampling strategies (for example, k-t BLAST, k-t SENSE) [7]. The “autoviability” technique (Figure 7) uses phase-sensitive inversion-recovery (PSIR) viability imaging to extend the nulling point dynamic range, and thus reduces the dependence on an exact inversion time for delayed enhancement imaging [8].

Lastly and possibly most valuable, the move to a higher static magnetic field with significant increase in SNR and contrast to noise ratio (CNR) has presented an opportunity to increase the utility of cardiac MRI for diagnosis of CVD in women [9-12]. Specifically, vasodilator stress myocardial perfusion imaging and whole-heart coronary MR angiography at 3T have advantages over 1.5T.

The theoretical doubling of SNR can be traded for higher spatial resolution, greater heart coverage with high temporal resolution or shorter scan times, and an increase in vascular SNR and CNR with the addition of T1-shortening contrast agents. A recent study has shown that the dark-rim artifact observed in first-pass cardiac perfusion studies, which can be mistaken for perfusion deficit, occurs more at 1.5T (23%) than 3T (8%) even with equal spatial resolution acquisition [9].

Previously, steady-state free-precession imaging sequences had been restricted to 1.5T due to increased static field non-homogeneities at 3T. Recent technological advances in localized shimming correct the static magnetic field and allowed these techniques to be utilized at 3T, harnessing their ability to double the overall SNR of the acquisition [13]. Table 2 outlines the current cardiac MRI techniques and the possible benefits of 3T for each technique.

Future directions for cardiac MRI for non-obstructive CAD assessment

Impairment of coronary vasoreactivity may appear before the development of obstructive lesions, and coronary endothelial dysfunction potentially can be observed before structural changes are appreciated by angiography [2]. Invasive measurements of coronary flow reserve are predictive of events for women and patients with angina without obstructive coronary lesions [14, 15]. The ability to non-invasively assess coronary vasoreactivity would be particularly important in the diagnosis and treatment of women as an early marker of subclinical atherosclerosis [16-18]. Stress-induced changes in coronary function and blood flow velocity using high-resolution cardiac function and PCA techniques (Figure 8) may indicate the presence of endothelial dysfunction.

Myocardial perfusion imaging is clinically established for hemodynamic assessment of obstructive epicardial stenosis. Additionally, these images help detect perfusion abnormalities that occur only under stress conditions and help to better understand the role of microvascular hypoperfusion in detecting CVD without obstructive CAD.

Importantly, an MR perfusion imaging study by Panting et al. [19] showed that subendocardial ischemia may be responsible for chest pain in women with angina without obstructive CAD. Myocardial perfusion reserve, which can be assessed by comparing stress versus non-stress MR perfusion measurements, is inversely associated with cardiac risk factors and coronary artery calcium in asymptomatic individuals, including patients with non-obstructive CAD [20]. In a similar fashion, this technique may offer a non-invasive assessment of coronary vasoreactivity in asymptomatic individuals at high risk for coronary artery disease.

The WISE study reported that changes in the myocardial high-energy phosphates, phosphocreatine and adenosine triphosphate, from rest to pharmacologically-induced stress might be a marker of CVD without evidence of CAD [3]. In fact, a decrease in phosphocreatine/
adenosine triphosphate ratio during stress indicated a shift toward anaerobic metabolism (in other words, myocardial ischemia) in 20% of women with chest pain without obstructive CAD.

Furthermore, at three-year follow-up, women with a decreased phosphocreatine/adenosine triphosphate ratio during stress at initial examination demonstrated a rate equal to women with obstructive CAD. New developments in cardiac multi-nuclear MR spectroscopy, in particular 31P imaging, are capable of measuring these changes and may potentially be included in a clinical cardiac MR protocol to assess women with possibility of CVD, with and without obstructive CAD [3].

As asymptomatic and symptomatic cardiovascular disease in women becomes better understood, there is a greater need for non-invasive techniques to diagnose non-obstructive coronary artery disease (CAD). Cardiac magnetic resonance has a complete spectrum of tools to assess cardiac morphology, function, perfusion, viability and coronary vascular dysfunction in a single clinical study.
Acknowledgments

The authors would like to thank Tony Fuisz of the Washington Hospital Center and Roderic Pettigrew of the National Institutes of Health for their contributions to this article.

References


In neoadjuvant therapy of breast lesions a needle biopsy is performed in place of conventional excisional biopsy, after which the mass is left in situ in order to determine the effect of the therapy. The rationale for this approach is that removal of the tumor and lymph nodes would also eliminate a valuable gauge for measuring the success of therapy. Leaving the mass within the breast provides a metric to visually determine whether or not the first line treatment is working.

Ultrasound offers an ideal platform for monitoring the effect of therapy. Its advantages include the absence of ionizing radiation, the widespread availability, and the relative ease of use. However, neoadjuvant therapy requires high-quality imaging and accurate measurement for regular and ongoing measurement of tumor volume.

At the University of Kansas Breast Cancer Prevention Center, the effects of neoadjuvant therapy are monitored using the Philips iU22 ultrasound system. The iU22 ultrasound system with Vision 2009 is an "intelligent" system, offering fast acquisition of a complete volumetric data set, with immediate availability of volume imaging, and automated quantification.

Automated quantification

Automatic quantification can detect and measure very subtle changes in the tumor volume. Shrinkage within 48 hours can indicate successful therapy, while continued growth may indicate the need for a new approach, such as changing the drugs or going straight to surgery. Accurate measurement is therefore critical.

We have found automatic quantification to be far more accurate than a physical breast examination performed by a nurse or clinician, and is much less expensive than an MRI scan. The accuracy of the measurement is particularly important because it is essentially a two-dimensional measurement of a three-dimensional volume, so that a very small change in the diameter of the mass indicates a significant change in the volume.

An increase in the size of the tumor is not necessarily an indication of a failed therapeutic effort. A successfully treated tumor may rapidly swell as a response to injury, like a bruise, showing the rapid death of a primary index cancer.

Another, novel indicator is quantification of the vascularization. Changes in the vascularity of a tumor can be observed quickly, painlessly, easily, consistently and often. This information could become an accurate predictor of the success or failure of therapy.

The VL13-5 transducer

The iU22 is provided with the new VL13-5 3D linear array transducer (Figure 1). This transducer combines an easy-to-use ergonomic design with state-of-the-art imaging capabilities, including Tissue Aberration Correction (TAC). TAC is a new technology that corrects for the different speeds of sound associated with different tissue types, such as fat and glandular tissue in the breast, resulting in sharper images with better spatial resolution and less clutter.

3D imaging

The VL13-5 transducer acquires a complete volumetric data set in a single run, while 3D imaging derived from the data set can show the full extent of a tumor, with accurate definition of the tumor margins, including microlobulations, septa, and spiculations (Figures 2, 3). This contributes to precise measurement of the tumor.
dimensions for accurate staging, assessing the effects of therapy and, where necessary, ensuring complete resection.

Another simple but important benefit of 3D imaging is its ability to show the exact position of the biopsy needle. Conventional imaging can give the impression that the needle is within the tumor when, in fact, it lies alongside it.

New insights

3D imaging also provides valuable additional information on tumoral growth patterns and the way cancers spread. We have recently observed that breast cancer tends to spread in the coronal plane, so we have selected our volumetric acquisition in such a way as to maximize diagnostics and evaluation in this plane. In our view, measurements in the coronal plane provide the most accurate measure of breast cancer growth and the most accurate measurement of the response to treatment.

Off-site evaluation

The ability to acquire and store a complete volumetric data set for later evaluation has proved to be a major benefit. The need to maintain patient throughput puts a certain amount of pressure on the radiologists, making it difficult for them to assess masses in the examination room. The iU22 image clips are saved to PACS, allowing the images to be reviewed off-site in a peaceful viewing room, so that the oncologist can study the image data at a high level of detail, without interruptions.

Improved workflow

The iU22 with Vision 2009 has had significant benefits for the workflow. Departments doing breast imaging are constantly under pressure to do faster imaging more consistently. It is critical for the sonographer to spend as much as time as possible looking for cancer rather than typing data during the initial study. The Philips iU22 incorporates a one-button prompt protocol to lead the sonographer through the breast and locate the probe.

Smart protocols overcome the problems of labeling, where the reader had to type in the location in the breast, the distance from the nipple, the radial or antral radial orientation, and so on. This can easily require up to 200 key strokes for a single breast, with the risk of skipping key areas. With the smart protocols, the reader is prompted by a screen-driven message: left breast, 2 o’clock, anti-radial, etc. This avoids time wasted in labeling, and helps to ensure accurate, motivated imaging.

Figure 2. Slice from the 3D data set showing a 7.9 mm malignancy. Precise measurement of the maximum diameter aids early recognition of tumor regression/growth.

Figure 3. 3D imaging provides accurate definition of the tumor margins, showing microlobulations, tumoral septations, and the spiculations surrounding a tumor. The image at lower left shows a tumor diameter of 2.2 mm measured in the coronal plane. This was larger than previously thought, and the patient is now being considered for neoadjuvant therapy.
Recent refinements in sonographic techniques have yielded harmonic imaging, which in turn improves signal-to-noise ratio. Coupled with the use of microbubbles, which can be used intravenously, microvascularity, namely the capillaries within tissue, can be imaged. Years of research with microbubbles in animal models have shown that the transit time of microbubbles in tumor neovascularity differs significantly from that in normal tissues [6]. In addition, tumors tend to have greater vascular volumes and longer washout times. This is reflected as increased area under the curve (AUC) of a time/intensity plot and longer T1/2 in washout phase.

The CE-TVS differs from standard transvaginal sonography in that its inclusion of intravenous injection of ultrasound contrast with a three-minute recording of time intensity curve and its offline analysis. Microbubbles are prepared by shaking for 45 seconds in a specially designed vial oscillator. After an antecubital intravenous line is placed, 3 µL/kg of Definity® (Lantheus Medical Imaging, N Bellerica, MA) is injected through the intravenous line followed by 10 cc saline flush. Pulse inversion harmonics (PIH) affords depiction of the microbubbles.

Standard transvaginal sonography with a C8-4v transvaginal probe on an iU22 Philips ultrasound scanner (Philips Healthcare, Bothell, WA) is used to image the ovary with color Doppler sonography for detection of vascular areas. Once the location of vascularized areas is determined, contrast injection is performed with split screen images using fundamental and harmonic imaging. Maximum intensity projection (MIP) images called the MicroVascular image (MVI) offer an early detection of ovarian cancer.

Clinical Aspects

This year, there will be an estimated 24,000 new cases of ovarian cancer diagnosed and 14,300 deaths in the United States. The incidence of ovarian cancer has been steadily increasing over the past 10 years, with an overall lifetime risk of 1.8% [5]. Despite improvements in median survival through surgical advances and new chemotherapeutic regimens, the overall 5-year survival for women with stage III/IV epithelial ovarian cancer has remained relatively unchanged (15%) over the past 40 years [5].

In contrast, women diagnosed with disease confined to the ovary (stage I), require less morbid surgical intervention, may not require adjuvant chemotherapy, have a significantly improved quality of life, and most importantly have an overall 5-year survival approximating 90%.

Unfortunately, 75% of women continue to be diagnosed with advanced stage disease, which is ample evidence of the inadequacy of a pelvic examination and standard sonography. Therefore, the detection of early stage epithelial ovarian cancer is thought to be the most efficient means to improve survival until the development of an effective therapy.

In recent studies from several medical centers worldwide have shown that contrast enhanced transvaginal sonography (CE-TVS) can detect early stage ovarian cancer. [1, 2, 3, 4]. This major improvement in sonographic detection of tumor microvascular neovascularity has resulted from refinements in sonographic equipment as well as microbubble technology. This overview describes the breakthrough in sonographic techniques that affords early detection of ovarian cancer and a potential use in screening for this “silent killer.”

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Instrumentation and technique

Recent refinements in sonographic techniques have yielded harmonic imaging, which in turn improvements signal-to-noise ratio. Coupled with the use of microbubbles, which can be used intravenously, microvascularity, namely the capillaries within tissue, can be imaged. Years of research with microbubbles in animal models have shown that the transit time of microbubbles in tumor neovascularity differs significantly from that in normal tissues [6]. In addition, tumors tend to have greater vascular volumes and longer washout times. This is reflected as increased area under the curve (AUC) of a time/intensity plot and longer T1/2 in washout phase.

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Clinical advantages

Color Doppler sonography has been used for many years to distinguish between benign and malignant ovarian masses. The relative resistance to flow is determined for selected vessels and is used to distinguish between abnormal vascular compositions from benign lesions. This is a reflection of numerous arteriovenous shunts and

(Philips Healthcare, Bothell, WA) can be reconstructed offline to aid the quantification region of interest (ROI) placement.

Once a region of interest is chosen, QLAB (Philips Healthcare, Bothell, WA) an off-line software program can determine uptake time, peak enhancement, contrast washout and area under contrast enhancement curve.
decreased vascular tone in tumor vessels. However, the vessel impedance values were seen to overlap between benign and malignant ovarian masses.

Contrast enhanced transvaginal sonography (CE-TVS) is based on the depiction of tumor capillary networks. Clearly, there are differences in the orderly branching and tapering vessels in normal tissues and the chaotic branching and vessel caliber of tumor vessels. This is reflected by increased mean transit times.

Figures 1-6 show the CE-TVS in benign and malignant ovarian tumors. Although both lesions had morphologic features suggestive of malignancy, there were significant differences in their contrast enhancement kinetics.
Potential applications

The relatively low incidence (33 per 100,000 in USA) at age 55 and lack of clearly definable risk factors make screening for ovarian cancer a challenge. The fact that less than ten percent of patients ultimately found to have ovarian cancer have a traceable risk factor makes screening a significantly difficult challenge for clinicians.

Figure 4b. Left adnexa: pre-contrast gray scale image (top right image) demonstrates a solid adnexal mass. Peak enhancement PIH (top left image) show extensive vascularity, particularly in the periphery of the ovary. The PIH time-intensity curve (bottom image) of right ovary showed relatively high peak intensity (20 dB), long half washout time (103 sec) and elevated AUC (2323 sec).

Figure 4c. Gross surgical specimen showing normal sized right ovary that contained a cystic area and mildly enlarged and lobuted left ovary. Bilateral serous adenocarcinoma was found in histologic examination.

Screening for ovarian cancer is a challenge because of the relatively low incidence at age 55.

Our recently published data involving 23 masses showed a twofold difference between peak enhancement, threefold difference in washout time, and almost fourfold difference in vascular volume in malignant ovarian tumors when compared to benign. The time to peak, however, was not statistically, significantly different. Figure 7 show this data in statistical terms, with the statistical averages and standard error.
proteomics. If such a serum test becomes available, contrast-enhanced sonography would be clearly indicated as a secondary test as a means to confirm the presence of ovarian cancer and perhaps assess its extent.

However, without the availability of such a serum screen test, contrast enhanced transvaginal sonography serves to have an even greater role.

Clearly, in women with risk factors such as BRCA positive or familial history of breast, ovarian, or endometrial cancer, these women deserve special attention for screening in the hope of early detection.

Another very promising method for early detection of ovarian cancer involves mass spectroscopy of serum protein and gene products, so called proteomics. If such a serum test becomes available, contrast-enhanced sonography would be clearly indicated as a secondary test as a means to confirm the presence of ovarian cancer and perhaps assess its extent.

With fewer than 10% of patients having a traceable risk factor, screening is difficult.
in detecting early stage ovarian cancer. These screening strategies are currently being tested in several trials. Because of the inherent low prevalence of ovarian cancer, it will take years of testing in multicentered trials to conclusively show efficacy. In any event, the use of CE-TVS seems to be quite promising as a means to detect ovarian cancer in its earliest stages.

**Summary**

CE-TVS is a new technique that seems to be quite accurate in sonoographic detection of early stage of ovarian cancer. Its clinical use is currently under investigation in several centers worldwide. It is hoped that this technique can be an effective means to detect early stage ovarian cancer alone or combined with serum testing.

**Acknowledgment**

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**References**


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Color Doppler sonography has been used for many years to distinguish between benign and malignant ovarian masses. The relative resistance to flow is determined for selected vessels and is used to distinguish between abnormal vascular compositions from benign lesions. This is a reflection of numerous arteriovenous shunts and (Philips Healthcare, Bothell, WA) can be reconstructed offline to aid the quantification region of interest (ROI) placement.

Once a region of interest is chosen, QLAB (Philips Healthcare, Bothell, WA) an off-line software program can determine uptake time, peak enhancement, contrast washout and area under contrast enhancement curve.

Figure 1. Endometrioma (benign): Pre-contrast gray scale images (top right image) demonstrate a cystic left adnexal mass with irregular mural thickening. Each enhancement PIH (top left image) image shows moderate level of vascularity within lesions wall. The Pulse Inversion Harmonics (PIH) time-intensity curve of right ovary (bottom image) showed moderate peak intensity (17 dB), short half washout time (68 sec) and moderately increased Area Under Curve (AUC) (1085 sec-1).

Figure 2. Mucinous cystadenoma (benign): pre-contrast gray scale image (top right image) demonstrated a cystic left adnexal mass with irregular thickened wall. Peak enhancement PIH (top left image) images show low level of vascularity within the mural thickening. The PIH time-intensity curve of right ovary (bottom image) showed moderate peak intensity (17 dB), short half washout time (23 sec) and low AUC (322 sec-1).
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INTERMEZZO

Philips Elite Breast Clinical Solution

Designed to combine high patient throughput with high-quality imaging and optimum patient comfort, the Elite Breast Solution comprises the MammoTrak dockable patient support, integrated diagnostic and biopsy coils, and the DynaCAD Enterprise Solution for advanced data analysis and biopsy planning on the MR console.

The MammoTrak dockable patient support has an integrated MammoTrak breast coil with 7 or 16 channels. By allowing the patient to be prepared outside the scanner room while the current patient is still in the scanner, patient preparation time can be shortened and departmental efficiency improved. The patient is simply rolled into the scanner room, already positioned on the MammoTrak, as soon as the previous patient is ready.

Enhanced patient comfort
Care has been taken to make the breast MRI study as comfortable as possible. Patient comfort is particularly important in this type of examination. The patient is therefore positioned feet-first on the patient support, rather than head-first, on a sloping ramp. The most comfortable angle for the ramp was selected following a patient study. The MammoTrak has handgrips on both sides so that even elderly or large patients can be positioned on the coil. The MammoTrak has an adjustable headrest with integrated mirror so that the patient can see out during the examination. Increased space around the patient while she is in the MRI system and the refinements described above overcome many of the problems associated with conventional breast MRI.

The MammoTrak Breast coil
The integrated MammoTrak breast coil comes in two versions:
• New 16-channel SENSE MammoTrak Breast coil
• New open design 7-channel SENSE MammoTrak Breast coil.
Both versions offer improved visualization of the axilla region when compared with conventional breast coils.

The 16-channel integrated MammoTrak SENSE Breast coil provides the required diagnostic breast imaging by optimizing spatial and temporal resolution to visualize smaller lesions, which is important for early detection and improved treatment.
The 7-channel MammoTrak SENSE Breast coil with integrated lighting is designed for breast biopsies, both for medial and lateral biopsies as well as cranial access. The biopsy procedures can thus be separated from the diagnostic procedures if desired by the hospital workflow.

Intuitive biopsy planning from MR console
Breast biopsy is usually a separate procedure from the diagnostic examination. As with the diagnostic examination, the patient is prepared on the MammoTrak outside the scanner room, and then wheeled into the room. After the lesion has been identified, the complete biopsy planning can be done on the MR console using the DynaCAD Enterprise. The system is compatible with core biopsies and vacuum assisted biopsies (VAB).

The DynaCAD shows the optimal trajectory to the breast lesions using the biopsy grid or the pillar. Lateral, medial and cranial approaches are available, ensuring the shortest path to the lesion. The same display as that on the MR console, showing the needle coordinates and position, is also shown on the in-room display near the magnet. It allows the correct needle coordinates to be checked at the magnet, exactly where they are needed. After the needle has been correctly positioned, the patient can be wheeled back into the prep room for the vacuum-assisted biopsy (VAB).

DynaCAD Enterprise
With the Elite Breast Clinical Solution, scans are processed and reviewed via the DynaCAD Enterprise. With a single click, all of the scans are automatically loaded in a pre-configured screen layout, and can be accessed by authorized staff from any computer in hospital. All breast cases are always loaded in the way the physician wants to review them. DynaCAD comes with a full set of processing tools and offers reporting according to the standardized lexicon of the Breast Imaging Recording and Data System (BI-RADS) of the American College of Radiology.

SmartExam Breast
The Elite Breast Clinical Solution is supported by the Elite Breast Ambassador network, providing access to in-depth training courses on breast MRI by leading physicians.

eTHRIVE / VISTA comparison
eTHRIVE, a 3D T1-weighted gradient echo technique, enables fast dynamic scanning with sub-millimeter in-plane resolution optimized for high resolution and good fat suppression. The eTHRIVE technique is based on linear k-space filling with near-isometric voxels. Using VISTA instead of a T2-weighted multislice scan and eTHRIVE with the same voxel size (0.76 x 0.76 x 1 mm), images are matched slice-to-slice between eTHRIVE and VISTA. Matching is in-plane as well as through-plane, with identical dimensions for exact comparison of both image sets (Figure III).

The sagittal multi-planar reconstruction (MPR) views and maximum intensity projections (MIPs) are generated immediately and automatically using the Philips ExamCard*.

*Philips ExamCards contain all the scans required for a complete MR examination in one easy-to-use file. Users share ExamCards via the Philips MRI NetForum Community at www.philips.com/netforum, where ExamCards can be downloaded directly into a Philips MRI scanner.
Women’s health: an introduction
L. Bogdanoff, S. Suryanarayanan and E. Benedict

Until relatively recently, the concept of women’s health mainly comprised conditions that occur exclusively or predominantly in women. However, in 2001 the Institute of Medicine (IOM) of the US National Academy of Sciences released a report stressing the importance of sex differences throughout medical practice. Recognizing the specific needs of women’s health, Philips Healthcare established the Women’s Health Care Cycle program. The care cycle encompasses the whole continuum of care from prevention, screening and diagnosis to treatment, management and surveillance. At present, Philips Healthcare’s Women’s Health Care Cycle program focuses on three key areas: breast cancer, heart disease, and gynecology.

Digital mammography, from planar to tomographic imaging
A. Karellas, S. Vedantham and J. Lewin

Mammography has established itself as the primary method for breast cancer screening, and has been shown to reduce breast cancer mortality. Digital mammography delivers better soft tissue contrast than screen-film techniques, with better imaging of dense breasts, and more consistent image quality. Digital mammography accommodates a wide exposure range and allows post-acquisition contrast manipulation. These characteristics play an important role in the visualization of subtle anatomic detail such as microcalcifications or soft tissue spiculations. Digital mammography also provides a platform for advanced imaging techniques such as dual-energy mammography, contrast injection mammography and tomographic imaging of the breast by digital tomosynthesis.

High resolution MR breast imaging

The University of Chicago, working with Philips Healthcare, has developed High Spectral and Spatial resolution (HiSS) MR imaging to improve anatomical and functional breast images. HiSS data spatial resolution equals that of conventional anatomic images, without the use of contrast agent, with additional information related to tissue composition and physiology available from the detailed line-samples of water and fat signals in each voxel. HiSS images are obtained on a Philips Achieva scanner and an Echo-Planar Spectroscopic Imaging (EPSI) pulse sequence to provide spatial resolution of up to 400 microns in-plane and spectral resolution as high as 2.6 Hz.

Enhanced MR breast imaging
G.M. Newstead

MRI has the potential to improve the detection of breast cancer at a relatively early stage, when it is relatively easy to cure, and can reduce the number of percutaneous biopsies. This article describes the University of Chicago Medical Center’s pioneering work on the application of advanced MR technology to breast cancer, including the use of dynamic contrast enhanced MRI.

A standardized breast examination protocol is presented, including 3D T2-weighted Turbo Spin Echo (VISTA), Diffusion-Weighted Imaging (DWI), and comparison of pre- and post-contrast scans. The Philips Elite Breast Clinical Solution used in the Center is described in an Intermezzo.

MRI-guided near-infrared spectroscopy of breast tumors
C.M. Carpenter, S. Jiang, S. Srinivasa, B.W. Pogue and K.D. Paulsen

This article describes the introduction of near-infrared spectroscopy (NIRS) used within the breast coil of a 3T Achieva MR scanner for dedicated spectroscopic characterization of breast cancers. Absorption spectrum sampling allows quantification of hemoglobin, oxygen saturation and water in the breast. The accompanying scatter data are used to estimate effective particle size and density values. Three case studies show the ability to image tumors during neoadjuvant chemotherapy. Conducted under an Institutional Review Board (IRB) approved research protocol with informed patient consent, the case studies present complex tumor responses where additional NIRS information could aid in the management of treatment decisions.

Nationwide breast cancer screening in the Netherlands
A. Den Heteen and M. Breders

Breast cancer is the major cause of death from malignant disease in women in the world. In the Netherlands, the government provides a free nationwide breast cancer screening service. About a million women are examined per year, representing more than 80% of the target group. The service is currently being modernized, with the existing analogue mammography units being replaced by new digital systems, linked via a nationwide image management system with a central archive. Because of its experience in managing large and complex medical IT solutions, Philips was chosen as the project manager; with Philips iSite PACS as the nationwide image management system.

The role of cardiac MRI in the diagnosis of women’s cardiovascular disease
S.D. Flamm, R.M. Setser, A.Y. Chang and M.S. Kopys

Cardiovascular disease (CVD) is the leading cause of death of women in the United States, yet clinical studies have shown that current diagnostic strategies for assessing CVD in women are not sufficient. Given the unique challenges of imaging women combined with their atypical symptom presentation of CVD compared to men, cardiac magnetic resonance (MRI) may hold the complete spectrum of tools necessary for diagnosis of both asymptomatic and symptomatic women with CVD. The clinically available and developing cardiac magnetic resonance techniques discussed here have the potential to meet the diagnostic needs of CVD in women.

3D ultrasound in neoadjuvant therapy of breast tumors
W.P. Smith

In neoadjuvant therapy a needle biopsy is performed in place of conventional excisional biopsy. The tumor is then left in situ as a gauge for assessing the success of therapy. Accurate measurement of the tumor is critical, and is achieved using a Philips iU22 ultrasound system with a transducer capable of acquiring a complete volumetric data set in a single run. 3D reconstruction provides accurate definition of the tumor volume, while automatic quantification can detect and measure very subtle changes. Shrinkage within 48 hours can indicate successful therapy, while continued growth may indicate the need for a new approach.

Early detection of ovarian cancer with contrast enhanced transvaginal sonography
A.C. Fleischer, A.P. Lyshchik, H.W. Jones III and D.A. Fishman

Contrast enhanced transvaginal sonography (CETVS) has significant potential for the early detection of ovarian cancer. The use of harmonic imaging and microbubbles affords sonographic depiction of tumor microvascularity. In our preliminary experience, there is a four-fold difference in vascular volume and a three-fold difference in washout time between benign and malignant lesions two-fold difference in peak enhancement. It is felt that CETVS may provide an accurate secondary test to distinguish benign from malignant ovarian masses and that further investigation is warranted.
**Introduction aux problématiques de santé de la femme**

L. Bogdanoff, S. Suryanarayanan et E. Benedict

Encore récemment, le concept de santé de la femme englobait principalement des affections touchant exclusivement ou majoritairement les femmes. En 2001, l’Institute of Medicine (IOM) de la United States National Academy of Sciences a publié un rapport mettant en évidence l’importance des différences liées au sexe sur le plan médical.

Afin de mieux prendre en compte les besoins spécifiques aux femmes, Philips Healthcare a lancé un programme d’étude du cycle de soins pour la santé de la femme (Women’s Health Care Cycle). Le cycle de soins couvre toutes les étapes des soins, de la prévention, du dépistage et du diagnostic, jusqu’au traitement, au suivi et à la surveillance.

Actuellement, ce programme se concentre sur trois domaines clés: le cancer du sein, les affections cardiaques et la gynécologie.

**Mammographie numérique: de l’imagerie planaire à l’imagerie tomosynthèse**

A. Karellas, S. Vedantham et J. Lewin

La mammographie s’est imposée comme la principale méthode de dépistage du cancer du sein, et son utilisation a entraîné une réduction de la mortalité liée à cette affection. La mammographie numérique offre un meilleur contraste au niveau des parties molles que la mammographie classique, et permet d’obtenir une meilleure imagerie des seins denses et une qualité d’image plus homogène. La mammographie numérique offre une gamme d’exposition étendue et permet la modification du contraste après l’acquisition. Ces caractéristiques sont primordiales pour la visualisation de détails anatomiques subtils comme les microcalcifications ou les spicules au niveau des parties molles. La mammographie numérique permet également le développement de techniques d’imagerie avancées telles que la mammographie biénergétique, la mammographie avec injection de produit de contraste et l’imagerie tomographique du sein par tomosynthèse numérique.

**Imagerie par résonance magnétique du sein haute résolution**


L’université de Chicago a travaillé en association avec Philips Healthcare au développement de l’IRM haute résolution spatiale et spectrale (HiSS), afin d’améliorer les images anatomiques et fonctionnelles du sein. La résolution spatiale des données HiSS est équivalente à celle des images anatomiques classiques, sans utilisation d’agent de contraste, et est associée à d’autres informations liées à la composition et à la physiologie des tissus grâce à la distinction précise de l’eau et de la graisse au niveau de chaque voxel. Les images HiSS sont réalisées sur un scanner Achieva de Philips et avec une séquence d’impulsions d’imagerie spectroscopique écho-planaire (EPSI) pour fournir une résolution spatiale pouvant atteindre 400 microns dans le plan et une résolution spectrale élevée de 2,6 Hz.

**Spectroscopie proche infrarouge des tumeurs mammaires guidée par IRM**

C.M. Carpenter, S. Jiang, S. Srinivasan, B.W. Pogue et K.D. Paulsen


**Dépistage national du cancer du sein aux Pays-Bas**

A. Den Heeten et M. Broeders

Le cancer du sein est la principale cause de mortalité par affection maligne chez les femmes dans le monde entier. Aux Pays-Bas, le gouvernement propose un service de dépistage national gratuit. Environ un million de femmes sont examinées chaque année, ce qui dépasserait plus de 80 % de la population cible. Ce service est actuellement en cours de modernisation. En effet, les appareils de mammographie analogique existants sont remplacés par de nouveaux systèmes numériques, connectés à un système de gestion d’images national doté d’un système de stockage centralisé. Grâce à son expérience de la gestion de solutions informatiques médicales complexes et de grande envergure, Philips a été sélectionné pour ce projet. C’est le système PACS iSite de Philips qui assurera la fonction de système de gestion national.

**Rôle de l’IRM cardiaque dans le diagnostic des affections cardiovasculaires chez les femmes**

S.D. Flamm, R.M. Setser, A.Y. Chang et M.S. Kotys

Les maladies cardiovasculaires représentent la première cause de mortalité chez les femmes aux États-Unis. Pourtant, des études cliniques ont démontré que les stratégies de diagnostic actuelles des maladies cardiovasculaires chez les femmes sont insuffisantes. L’imagerie chez les femmes présente des problèmes spécifiques. En outre, les femmes atteintes de ce type d’affection présentent des symptômes atypique par rapport aux hommes. De ce fait, l’imagerie par résonance magnétique (IRM) cardiaque semble offrir tous les outils nécessaires pour un diagnostic sûr chez les sujets asymptomatiques et symptomatiques. Les techniques d’IRM cardiaque actuelles et émergentes évoquées dans cet article peuvent permettre de répondre aux besoins spécifiques au diagnostic des maladies cardiovasculaires chez les femmes.
Utilisation de l'échographie 3D dans le traitement néo-adjuvant des tumeurs mammaires

W.P. Smith

Dans le cadre du traitement néo-adjuvant, la biopsie à l'aiguille remplace la biopsie-exérèse classique. La tumeur est ensuite laissée en place afin d’évaluer l’efficacité du traitement.

Une mesure précise de la tumeur est essentielle. Elle est réalisée avec un échographe iU22 de Philips à l’aide d’une sonde permettant l’acquisition d’un ensemble complet de données volumiques en un seul examen. La reconstruction 3D permet d’obtenir une définition exacte du volume de la tumeur et la quantification automatique garantit la détection et la mesure des évolutions les plus infimes. Une diminution de la taille dans les 48 heures indique que le traitement est efficace. À l’inverse, si la tumeur continue à se développer, il est probable qu’un autre traitement soit nécessaire.

Détection précoce du cancer de l’ovaire grâce à l’échographie transvaginale de contraste

A.C. Fleischer, A.P. Lyshchik, H.W. Jones III et D.A. Fishman

L’échographie transvaginale de contraste (CETVS) présente des capacités potentiellement significatives de détection précoce du cancer de l’ovaire. L’utilisation de l’imagerie harmonique et de microbulles permet d’obtenir une image échographique microvasculaire de la tumeur. Dans notre expérience préliminaire, nous avons constaté que les lésions malignes présentent des volumes vasculaires quatre fois plus importants, une durée d’élimination trois fois supérieure et un contraste maximal deux fois plus élevé par rapport aux lésions bénignes. L'échographie transvaginale de contraste devrait constituer un test secondaire précis pour distinguer les masses ovariennes bénignes et malignes. Les recherches vont donc se poursuivre.

Frauenheilkunde: eine Einführung

L. Bogdanoff, S. Suryanarayanan et E. Benedict


Digitale Mammographie – von der planaren zur tomographischen Bildgebung

A. Karellas, S. Vedantham und J. Lewin

Die Mammographie hat sich als bevorzugte Methode für das Brustkrebs-Screening etabliert und trägt nachweislich dazu bei, die Mortalität bei Brustkrebs zu verringern. Die digitale Mammographie bietet einen besseren Weichteilgewebekontrast als die Film-Folien-Mammographie (mit besserer Bildgebung von dichtem Brustgewebe) und liefert eine konsistente Bildqualität.

Die digitale Mammographie deckt einen breiten Belichtungsbereich ab und erlaubt die nachträgliche Kontrastmanipulation nach der Erfassung. Diese Eigenschaften spielen eine wichtige Rolle bei der Visualisierung kleiner anatomischer Details wie etwa Mikrokalkzifikationen oder Spikulabildung im Weichgewebe.


Hochauflösende MRT-Brustbildgebung


Zusammenfassungen Deutsch

Verbesserte MRT-Brustbildgebung
G.M. Newstead


MRT-geführte Nahinfrarotspektroskopie von Brusttumoren
C.M. Carpenter, S. Jiang, S. Srinivasan, B.W. Pogue und K.D. Paulsen


Landesweites Brustkrebs-Screening in den Niederlanden
A. Den Heeten und M. Breinders


Die Rolle der kardiologischen MRT bei der Diagnose von Herz-Kreislauf-Erkrankungen bei Frauen
S.D. Flamm, R.M. Setser, A.Y. Chang und M.S. Kotys

Herz-Kreislauf-Erkrankungen (HKE) sind die häufigste Todesursache bei Frauen in den USA. Dennoch haben klinische Studien gezeigt, dass die gegenwärtigen Diagnosestrategien zur Beurteilung von HKE bei Frauen nicht ausreichend sind. Angesichts der besonderen Herausforderungen der Bildgebung bei Frauen in Verbindung mit der im Vergleich zu Männern atypischen Symptommanifestation von HKE könnte die kardiologische MRT-Bildgebung das gesamte Spektrum an Werkzeugen bereitstellen, die zur Diagnose sowohl asymptomatischer als auch symptomatischer Frauen mit HKE benötigt werden. Die klinisch bereits verfügbaren und die noch in Entwicklung befindlichen kardiologischen Magnetresonanzenverfahren, die hier diskutiert werden, haben das Potenzial, die diagnostischen Anforderungen von HKE bei Frauen zu erfüllen.

3D-Ultraschall bei der neoadjuvanten Therapie von Brusttumoren
W.P. Smith


Früherkennung von Eierstockkrebs mit kontrastmittelverstärkter transvaginaler Sonographie
A.C. Fleischer, A.P. Lyshchik, H.W. Jones III und D.A. Fishman


Resúmenes Español

Salud de la mujer: una introducción
L. Bogdanoff, S. Suryanarayanan y E. Benedict

Hasta hace relativamente poco tiempo, el concepto de “salud de la mujer” comprendía enfermedades que sufrían exclusivamente, o de manera predominante a las mujeres. Sin embargo, en 2001 el Institute of Medicine (IOM) de la National Academy of Sciences estadounidense publicó un informe en el que se subrayaba la importancia de las diferencias de sexo en la práctica médica. Con las necesidades específicas de la salud de la mujer en mente, Philips Healthcare estableció el programa Women’s Health Care Cycle. El ciclo de cuidados engloba todo el proceso, desde la prevención, la detección y el diagnóstico hasta el tratamiento o el control del paciente.

En la actualidad, el programa Women’s Health Care Cycle de Philips Healthcare se centra en tres áreas fundamentales: cáncer de mama, cardiopatías y ginecología.
Mamografía digital, de imágenes proyectivas a tomográficas
A. Karellas, S. Vedantham y J. Lewin

La mamografía se ha impuesto como el principal método en la detección del cáncer de mama, y ha demostrado su eficacia en la reducción de la mortalidad del mismo. La mamografía digital ofrece un mejor contraste de los tejidos blandos que la película radiográfica, con mejores imágenes de mamas densas y una mayor calidad de imagen.

La mamografía digital permite un mayor intervalo de exposición, así como la manipulación del contraste tras la adquisición de imágenes. Estas características juegan un papel importante en la visualización de detalles anatómicos sutiles, como microcalcificaciones o espículas de tejido blando.

La mamografía digital también proporciona una plataforma para técnicas de imagen avanzadas, como la mamografía de energía doble, la de inyección de contraste o las imágenes tomográficas de la mama por tomosíntesis digital.

Imágenes mamarias por RM de alta resolución

La Universidad de Chicago, en colaboración con Philips Healthcare, ha desarrollado la técnica de imagen por resonancia magnética HiSS (alta resolución espacial y espectral) para mejorar las imágenes mamarias anatómicas y funcionales. La resolución espacial de datos HiSS iguala a la de las imágenes anatómicas convencionales, sin necesidad de medio de contraste, con información adicional sobre la composición y fisiología del tejido. El sistema de ecografía Philips iU22 que incorpora un transductor con el que se puede obtener una resolución espacial de hasta 400 micras en plano y una resolución espectral de hasta 0,6 Hz.

Imágenes mamarias por RM mejoradas
G.M. Newstead

La RM puede mejorar la detección del cáncer de mama en una fase relativamente temprana, cuando es relativamente fácil de curar, y puede reducir el número de biopsias por punción.

Este artículo describe el estudio piloto realizado por el Centro médico de la Universidad de Chicago sobre la aplicación de la tecnología de RM avanzada en casos de cáncer de mama, incluido el uso de RM dinámica contrastada.

En este artículo se presenta un protocolo de exploración de mama estandarizado, incluyendo secuencias Turbo Spin Echo de HiSS y la comparación de adquisiciones previas y posteriores al contraste. Las imágenes HiSS se obtienen en una RM Philips Achieva y una secuencia de pulsos de imagen espectroscópica “Echo-Planar” (EPSI) para ofrecer una resolución espacial de hasta 400 micras en plano y una resolución espectral de hasta 2,6 Hz.

Espectroscopia de infrarrojo proximal guiada por RM de tumores de mama
C.M. Carpenter, S. Jang, S. Srinivasan, B.W. Pogue y K.D. Paulsen

En este artículo se explica la introducción de la espectroscopia de infrarrojo proximal (NIRS) que se utiliza para mamas de una RM Achieva 3T para la caracterización espectroscópica especializada de los cánceres de mama. El espectro de absorción permite la cuantificación de hemoglobina, saturación de oxígeno y agua en la mama. Los datos de dispersión asociados se emplean para determinar los valores efectivos de densidad y tamaño de las microcalcificaciones. En estudios de casos muestran la capacidad de obtener imágenes de tumores durante la quimioterapia neoadyuvante.

Detección precoz del cáncer de ovario con ecografía transvaginal con contraste
A.C. Fleischer, A.P. Lyshchik, H.W. Jones III y D.A. Fishman

La ecografía transvaginal con contraste (CETVS) tiene un gran potencial en la detección precoz del cáncer de ovario. El uso de microburbujas e imágenes armónicas permite la representación ecográfica de la microvasculatura del tumor.

En nuestras experiencias preliminares, existe una diferencia cuatro veces mayor en volumen vascular, del triple en el período de lavado y del doble en el realce máximo entre lesiones benignas y malignas. Se cree que la CETVS puede emplearse como segunda prueba de precisión para distinguir masas ováricas benignas de malignas, lo que justifica que continúen las investigaciones.
Technology news

DuoDiagnost* is a remote-controlled fluoroscopy system that’s suitable for all standard R/F procedures. But at the mere touch of a button, you can convert the system into a universal radiography unit – without the need for a second X-ray tube – for all routine radiography procedures including lateral, thorax and tomography studies. The smart combination of radiography and fluoroscopy in one system provides comprehensive clinical functionality in a cost-effective package for virtually all applications.

The latest version of the DuoDiagnost benefits from a new digital image memory that improves workflow and usability. It contains extended image storage capabilities for up to 10,000 images and unlimited backup opportunities via CD. What’s more, it provides extra review functionalities as well as additional DICOM options. And DuoDiagnost comes with a new touch-screen User Interface. Easy to use and intuitive to handle it integrates all advantages of digitization in a compact, elegant Philips design.

*MammoDiagnost VU workstation software is supplied with a high-performance computer, a 250 GB image database, two 5 MP mammography monitors, an additional color navigation monitor and a dedicated workflow keypad.

MammoDiagnost VU - your intuitive workflow for mammography review

Philips Healthcare rounds off its digital breast imaging portfolio with MammoDiagnost VU, a high performance mammography review workstation. Its layout and functionality are designed in line with the two main tasks of mammography – screening and diagnostic reviewing.

Because Philips develops its solutions in constant communication with clinicians, we’re naturally aware of the demands placed on a busy screening center. To allow radiologists to review such a large amount of studies quickly and efficiently, MammoDiagnost VU includes a variety of high-performance features. These include automated breast-tissue alignment, hangings in the user preferred review order, a one-touch keypad to reduce the number of clicks to the absolute minimum, and independent double-blind reading. There’s also a high-performance setup to allow it to be switched between patient exams in less than a second.

*Not available in the USA