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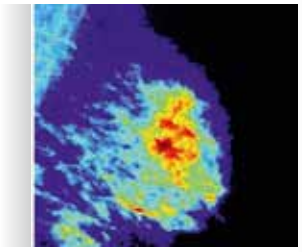
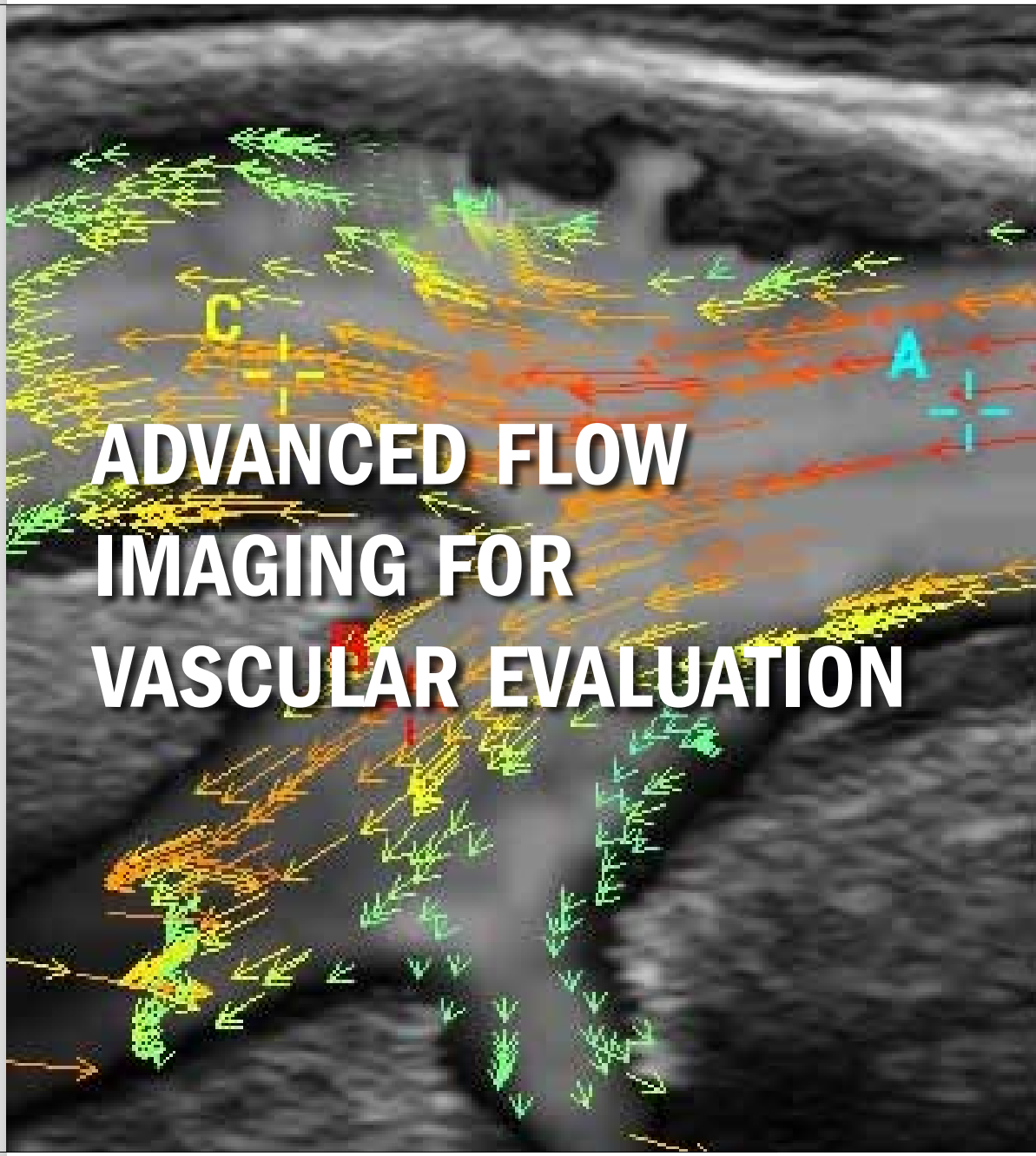
Breast Imaging



Automated density maps for local breast density assessment

DIAGNOSTIC IMAGING EUROPE



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BY ALAN BARCLAY, Ph.D.

Radiomics – the brave new world of clinical imaging?

One of the cherished objectives of the much-touted campaigns for "personalized medicine" in the treatment of cancer is that detailed characterisation of a patient's tumor will allow the selection of exactly the appropriate therapeutic approach that would optimise the chances of a successful outcome and minimise the impact of otherwise debilitating side-effects. The theory behind this is that knowledge of the genomic composition of a tumor would, for example, be able to predict the susceptibility of the cancer to a particular dose of a specific chemotherapeutic agent or avoid the administration of other agents which would anyway have had no effect on the particular tumor. A few successful examples of translation of the genomic information obtained from tumor biopsies into clinical applications have been reported, but, as pointed out in a recently published seminal paper on radiomics (*Grossman P et al defining the biological basis of radiomic phenotypes in lung cancer Elife. 2017 Jul 21;6. pii: e23421. doi: 10.7554*) these approaches have certain inherent limitations, such as the invasive nature of biopsies or sampling artefacts caused by intra-tumor heterogeneity.

It is here where it is postulated that medical imaging can step into the breach, since in contrast to biopsies, imaging is non-invasive (if we ignore the exposure to radiation in modalities such as CT) can be carried out longitudinally and crucially can give information about the entire visible tumor volume. The hope is that by detailed characterization of the phenotype of a tumor, radiomics may fill the gap.

Traditional imaging approaches such as X-rays, CT, MRI and PET allow extraction on a semi-quantitative basis of the two-dimensional anatomical and morphological features of tumors. Typically, characteristics such as gross shape, contrast enhancement, and size can be established using the traditional imaging modalities. As described by Chen (*Chen B et al Development and clinical applications of radiomics in lung cancer Radiation Oncology 2017;12:154*), the aim of radiomics is to decode the intrinsic heterogeneity, genetic characteristics and other phenotypes of a lesion and so generally involves the extraction of a large number of image features from images. Such features cover the fields of texture, advanced shape modeling, and heterogeneity. In practice, the image analysis involved in radiomics generally uses computer algorithms to process the data collected by various medical imaging modalities.

As pointed out by O'Connor in his comments on the Grossman *et al* paper, the fundamental strength of this use of the quantification of the radiographic phenotype via radiomics is that it recognizes that digital images aren't just images — they are also complex data (*O'Connor JPB. Rethinking the role of clinical imaging, eLife 20178; 6: e30563*). However, extracting such data from images is not as simple as it may sound: several obstacles still have to be overcome. For example, as described by Limkin and the group from the Institut Gustave Roussy from Paris, significant statistical problems can arise from the analysis of the "big data " that are involved in radiomics (*Limkin EJ et al. Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology. Ann Oncol. 2017 Jun 1;28(6):1191-1206*). Thus, "over-fitting" can lead to relationships being discovered when in fact there are none, underlying the importance of replicating any discovery of relationships via prospective studies. In addition, there is as yet no generally accepted standardised terminology to describe the derived image features, which makes it difficult to compare results and data between studies. As emphasised by O'Connor, biomarkers can only become fit for guiding clinical decision-making when they become fixed in their acquisition, analysis and quality assurance process, all defined clearly in standard operating procedures (SOPs). Even the traditional PACS systems which, although generally taken for granted by radiologists, in fact currently play a vital role in the storage and communication of radiology images will have to be adapted to be able to handle the radiomics algorithms so that widespread clinical use can be achieved.

Although the dynamism in the field can be gauged from the dramatic increase in the number of recent publications dealing with radiomics, until the current challenges are successfully addressed, the dream of radiomics-based personalized cancer treatment remains just that— a dream.

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OCTOBER 2017

The Front Cover image shows part of a Vector Flow (V Flow) image of the carotid bifurcation acquired by the Resona 7 ultrasound system from Mindray. The system measures the speed and direction of all blood cells flowing through every point of the ROI in a short space of time. The color and size of the arrows allow visual quantification of the flow behavior. Images courtesy of Dr A Goddi, Varese, Italy.

FEATURE ARTICLES

IMAGING NEWS

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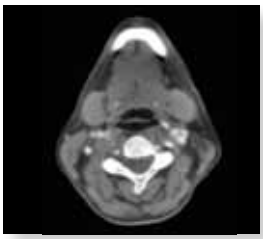
ADVANCED VECTOR FLOW IMAGING IN VASCULAR EVALUATION 18

A new technique for non-invasive evaluation of flow dynamics in human vessels may allow earlier detection of abnormal vascular conditions. The main advantages of the new method, known as Vector Flow Imaging (VFI), are the independence of the method on beam-flow angle and the ability to assess multi-directional blood flow. ..... **by Dr Alfredo Goddi**

REPORTS



Radiopaque 3D printing is an easy to use method for printing realistic phantoms using standard office equipment

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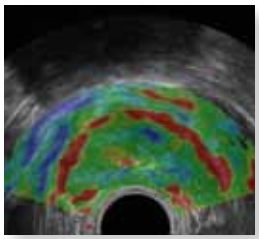

The importance of ultrasound in modern diagnostic and interventional radiology. Prof G. Bizzarri talks about his experiences with modern ultrasound imaging

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BREAST IMAGING SPECIAL

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COMING IN THE NEXT ISSUE:
MRI special

Early termination of trial of endovascular therapy after imaging evaluation of ischemic stroke

The DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trial is a prospective randomized phase III multicenter controlled trial of patients with acute ischemic anterior circulation strokes due to large artery occlusion treated between six and 16 hours of stroke onset with endovascular thrombectomy therapy plus standard medical therapy versus standard medical therapy. The purpose of the trial is to assess the safety and efficacy of thrombectomy in carefully selected patients

in this extended time window. In the study, patients who met the inclusion criteria underwent either CT perfusion/CT angiography (CTP/CTA) or MR diffusion weighted imaging/perfusion weighted imaging/angiography (DWI/PWI/MRA) studies prior to randomization. These images were processed with an automated image analysis platform to identify patients with salvageable brain tissue (Target Mismatch Profile). Patients who had evidence of an internal carotid artery (ICA) or middle cerebral artery (MCA) M1 occlusion and a Target Mismatch Profile were randomized in a 1:1 ratio to treatment with one or more approved thrombectomy devices plus standard medical therapy versus standard medical therapy alone. The first interim analysis was scheduled to be conducted at 200 patients and the next at 340 patients. But, as announced by Dr Joseph Broderick, who is the principal investigator of the NIH StrokeNet National Coordination Center, after a review of the available DEFUSE 3 data by the Data Safety and Monitoring Board, the trial was terminated in July due to the high likelihood of benefit in the mechanical thrombectomy group.

DEFUSE 3 is not the first trial of its kind to be terminated at the interim analysis due to the high likelihood of benefit in one arm. More recently, the DAWN trial, which used the same automated perfusion software (RAPID) as DEFUSE 3 to select patients who were likely to have salvageable tissue in an extended time window, was terminated at its interim analysis and later declared positive.

Dr Gregory Albers, Principal Investigator of the DEFUSE 3 trial said "Only time will tell how the results of DEFUSE 3 will compare to DAWN and how both of these trials will ultimately impact clinical practice. Two positive late window trials should have a major impact on how ischemic stroke patients who present between six and 24 hours are assessed and treated.

As both trials relied on perfusion imaging to identify patients, it is likely that perfusion imaging will become the standard for imaging late-window stroke patients"

www.nihstrokenet.org/clinical-trials/acute-interventional-trials/defuse-3

Smokers who undergo a CT scan of their lungs more likely to quit

New research from a UK group has found that smokers who undergo a CT scan of their lungs are more likely to quit smoking (*Brain K et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. Thorax. 2017; 72: 912*). Lung cancer is one of the most common and serious types of cancer and has the highest mortality of all cancers. Around 44,500 people are diagnosed with the condition every year in the UK. Similar, proportional statistics apply in the rest of Europe. The smoking cessation analysis of the UKLS trial involved 4,055 participants aged 50 to 75. The group was split into those who underwent low-dose CT screening for early detection of lung cancer and a control group who did not undergo screening. Of the smokers who took part in the screening, 10 per cent had successfully quit after two weeks, and 15 per cent had quit after two years -- both higher than the 5% rates found in the control group. The UK Lung Cancer Screening pilot trial is the first to assess the feasibility, cost-effectiveness and behavioral impact of lung cancer screening, using

a single low-dose CT screen on a high-risk population in the UK. Professor John Field, University of Liverpool's Clinical Professor of Molecular Oncology, Chief Investigator of the UK Lung Cancer Screening Trial and Principal Investigator of the Liverpool Lung Project, said: "Lung cancer continues to be the leading cause of cancer mortality worldwide.

"The findings of this study dispute the belief that a negative screening result offers a "licence to smoke". Engaging with lung screening can give smokers an opportunity to access smoking cessation support -- at a time when they are likely to be more receptive to offers of help."

Dr Kate Brain, from Cardiff University, said: "Our trial shows that CT lung cancer screening offers a teachable moment for smoking cessation among high-risk groups in the UK. "We now need evidence about the best ways of integrating lung cancer screening with stop-smoking support, so that services are designed to deliver the maximum health benefits for current and future generations."

https://tinyurl.com/Brain-et-al-trial

Study shows MRI is safe for patients with wide variety of pacemakers, defibrillators, even non-conditional devices

Magnetic resonance imaging appears to be safe for patients with cardiac implantable electronic devices (CIEDs), even for chest imaging, according to a new study by researchers from the Intermountain Medical Center Heart Institute in Salt Lake City. In the past, MRIs have been considered dangerous for patients who have CIED devices. However, a new study found that MRI imaging can be safely performed on patients with such devices (*Mason S et al. Real world MRI experience with non-conditional and conditional cardiac rhythm devices after magnaSafe. Cardiovasc Electrophysiol. 2017 Sep 28. doi: 10.1111/jce.13351*).

"MRI has become very popular," said Jeffrey L. Anderson, MD, senior study author and cardiologist at the Intermountain Medical Center Heart Institute. "It's excellent for looking at soft tissue changes. But it involves very high-strength magnetic fields, which means that if a patient has any implanted metal devices containing iron, it could potentially cause harm."

Researchers at the Intermountain Medical Center Heart Institute evaluated 212 MRI studies in 178 patients with a cardiac implantable electronic device between February 2014 and August 2016. They didn't find a single problem requiring remediation in the entire series, which involved a total of 418 implanted leads. "That's a pretty big number of leads exposed to these very strong MRI fields. You would think that if there was even a 1 percent chance of having a problem, it would have shown up," Dr. Anderson said. "Not even one generator or lead needed more than a minor adjustment, if any at all."

In the past, MRIs have been considered risky because of the fear that the generator circuits of a pacemaker or defibrillator device could be disrupted, or that its metal leads could be pulled out of place by the magnetic field, or that the lead tips could become hot and scar surrounding tissues, interfering with pacing and defibrillating function.

To address such possibilities, some newer devices have been specifically made and tested to be safe for use with MRIs, under certain test conditions in magnetic fields. Devices in this category are referred to as "conditional CIEDs"), and have been approved for MRI use under imaging conditions implemented by the FDA.

However most people who have implantable defibrillators and pacemakers don't have these newer, more expensive conditional devices, but instead they have standard non-conditional devices. In patients with non-conditional devices who have a medical need for imaging, MRI usually hasn't been used, despite the fact that MRI may have been deemed the most desirable diagnostic tool. Alternatively, the non-conditional devices and leads have been removed and replaced with conditional devices and leads beforehand.

Imaging decision-making for those with cardiac implantable electronic devices has started to change with the publication this year of a large multicenter study called the MagnaSafe Registry study, which showed that non-conditional devices can be safely imaged by MRI, if proper precautions are observed (*Russo RJ et al. Assessing the Risks Associated with MRI in Patients with a Pacemaker or Defibrillator. New Engl J Med. 2017; 376: 755).*

The NEJM study was limited in that it looked at the safety of MRIs only in parts of the body not in direct proximity with the implantable cardiac rhythm devices, which are typically in the chest under one of the collarbones.

The new Intermountain Medical Center Heart Institute study directly builds on the MagnaSafe study, validating findings of the main MagnaSafe cohort of 1,500 patients, and expanding that group of patients to include those who need an MRI of their lungs, heart or other organs within the chest.

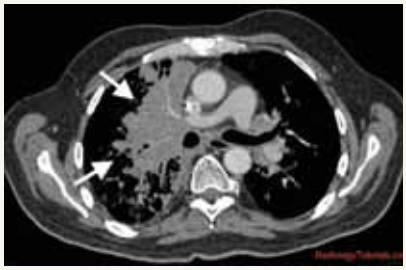
In addition, the new study includes many patients with conditional devices, providing a side-by-side comparison of the two types of devices.

https://tinyurl.com/Mason-et-al-paper
https://tinyurl.com/Russo-et-al-paper

Role of CT in NSCLC post-surgery follow-up questioned

The optimal follow-up protocol for patients with completely resected non-small cell lung cancer (NSCLC) remains elusive after results of the IFCT-0302 trial, presented at the recent ESMO 2017 Congress in Madrid did not show a difference in overall survival (OS) between patients who received CT scans as part of their follow-up, and those who did not. Indeed, the findings suggest regular CT scans, which many guidelines recommend, may not be necessary. "Because there is no difference between arms, both follow-up protocols are acceptable," said study investigator Prof. Virginie Westeel, from Besançon, France. "A conservative point of view would be to do a yearly CT-scan, which might be of interest over the long-term, however, doing regular scans every six months may be of no value in the first two post-operative years," she said. The suggestion is a departure from standard clinical practice, since the majority of medical societies and clinical practice guidelines (2) recommend follow-up visits in which chest CT is considered appropriate

every three to six months in the first two years after surgery. The multicenter study included 1775 patients with completely resected stage I–II-IIIA NSCLC who completed follow-up visits every 6 months for the first two years, and yearly until five years. Patients were randomized to a control follow-up, that included clinical examination and chest X-ray (CXR), or an experimental follow-up group that included the control protocol with the addition of thoraco-abdominal CT-scan plus bronchoscopy (optional for adenocarcinomas). After a median follow-up of eight years and 10 months, overall survival (OS) was not significantly different between the groups at a median of 99.7 months in the control arm and 123.6 months in the experimental arm. Three-year disease-free survival rates were also similar, at 63.3% and 60.2% respectively, as were eight-year OS rates at 51.7% and 54.6%, respectively. Commenting on the study, ESMO spokesperson Dr. Floriana Morgillo, from the University of Campania Luigi Vanvitelli, Naples, Italy, said that although the study does not demonstrate a significant benefit with CT-based follow-up, the trend towards better survival in the CT arm suggests longer follow-up may eventually reveal a benefit of this approach. However, in the meantime, she says CT-based surveillance is still an appropriate option because of its potential for impacting second primary cancers. "A significant proportion of patients with early stage NSCLC develop second cancers between the second and fourth year after surgery, and early detection of these with CT-based surveillance beyond two years could allow curative treatment," Morgillo said, adding that patients must also be informed of the radiation exposure risks with CT



https://tinyurl.com/Westeel-ESMO-congress-2017

Risk score may safely reduce need for imaging and hospital admission in suspected appendicitis

The role of imaging in the diagnosis of appendicitis is controversial. A newly published prospective interventional study and nested randomized trial analyzed the impact of implementing a risk stratification algorithm based on the Appendicitis Inflammatory Response (AIR) score, and compared routine imaging with selective imaging after clinical reassessment (*Andersson et al. Randomized clinical trial of Appendicitis Inflammatory Response score-based management of patients with suspected appendicitis. Br J Surg 2017; 104: 1451*) .

The results indicate that a classification system based on patient symptoms and basic lab tests might reduce the need for diagnostic imaging, hospital admissions, and surgery in patients with suspected appendicitis.

The system is based on the Appendicitis Inflammatory Response (AIR) score, which includes the following parameters: pain in right iliac fossa, history of vomiting, rebound tenderness or muscular guarding, body temperature, white blood cell count, proportion of neutrophil granulocytes, and C-reactive protein concentration.

The study included 1068 patients presenting with suspicion of appendicitis who were randomized to routine diagnostic imaging or in-hospital observation with selective diagnostic imaging after repeat AIR-scoring. The researchers concluded that the AIR score-based risk classification can safely reduce the use of diagnostic imaging and hospital admissions in patients with suspicion of appendicitis

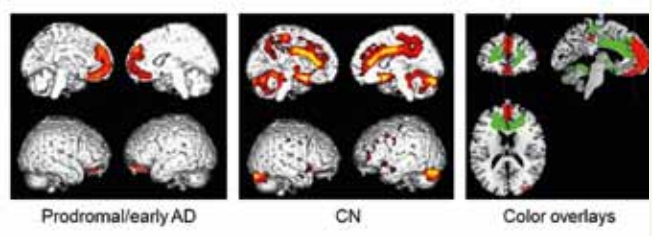
https://tinyurl.com/Andersson-et-al-paper

Association between nutritional status and Alzheimer's brain changes shown by multimodal imaging

A newly published study from the Multimodal Neuroimaging for AD Diagnosis (MULNIAD) group, shows that hypometabolism in the medial prefrontal areas is specifically associated with Alzheimer's disease-related nutritional problems, and that decrease in fat mass may have a key role. (*Sugimoto T et al. Decreased Glucose Metabolism in Medial Prefrontal Areas is Associated with Nutritional Status in Patients with Prodromal and Early Alzheimer's Disease. J Alzheimers Dis. 2017; 60: 225*).

Nutritional problems, especially weight loss, are commonly seen in individuals with Alzheimer's disease (AD); however, the underlying mechanisms are not well understood. This current study is the first to clarify the associations of nutritional status with AD-related brain changes comprehensively by using multi imaging modalities including amyloid-β (Aβ)- PET, ^{18}F-FDG-PET, and structural MRI. In the trial, subjects were 34 Aβ-positive individuals with mild cognitive impairment or early AD (prodromal/early AD), and 55 Aβ-negative cognitively normal (CN) subjects. The associations between nutritional status (body mass index, waist to height ratio, fat mass index, and fat-free mass index) and brain changes were examined by multiple regression analysis using statistical parametric mapping. In the prodromal/early AD group, nutritional status was significantly positively correlated with regional cerebral glucose metabolism (rCGM) in the medial prefrontal cortices, while different topographical associations were seen

in the CN group. Aβ deposition and gray matter volume were not associated with nutritional status. Sub-analysis in the prodromal/early AD group demonstrated that fat mass index, but not fat-free mass index, was positively correlated with rCGM in the medial prefrontal areas.



Overlay of significant posituve correlation of regional cerebral glucose metqabolism (rCGM) with Waist to Height ration (WHtR)in prodromal AD (red overlay) and CN (green overlay) groups

"These results suggest that hypometabolism in the medial prefrontal areas is specifically associated with AD-related weight loss, and decrease in fat mass may have a key role. However, this cross-sectional study provides preliminary results, so we need further longitudinal investigation considering the fat tissue metabolism including adipokines to deepen our understanding of AD related weight loss", says Dr. Takashi Sakurai. After adjusting for cognitive function, the significant link between fat-mass index and rCGM was preserved. The study findings of decreased glucose metabolism in medial prefrontal areas in Aβ-positive individuals may explain the underlying mechanism of weight loss in AD.
https://tinyurl.com/Sugimoto-et-al-paper

Study shows plateau in the use of CT in emergency department for children with abdominal pain as ultrasound increases

Abdominal pain is a common pediatric complaint to emergency departments (EDs), and clinicians often rely on imaging for diagnosis. Studies demonstrated a dramatic increase several years ago in the use of computed tomography (CT) in this population despite the associated risk of radiation-induced problems. Following the widely publicized emphasis on the need for radiation reduction, a group of researchers from the University of California, San Francisco set out to evaluate recent national trends in the United States on CT use among pediatric patients presenting to EDs with abdominal pain. In a recently published study (*Fahimi J et al. Computed Tomography Use Plateaus Among Children With Emergency Visits for Abdominal Pain. Pediatr Emerg Care. 2017 . doi: 10.1097*) the researchers described their use of data from 2008 to 2011 in the National Hospital Ambulatory Medical Care Survey system. They carried out a cross-sectional analysis of ED patients 18 years or younger whose chief complaint was abdominal pain Outcome measures included annual proportions of visits with x-ray, ultrasound, or CT, as well as diagnosis of appendicitis and hospital admission. It was found that of 32,304 ED visits, 2120 (6.6%) were for abdominal pain. And the proportions of visits using CT, ultrasound, and plain x-ray were 16.0%, 10.5%, and 23.4%, respectively. For all outcome measures, including imaging, hospital admission, and diagnosis of appendicitis, there was no change from 2008 to 2011. However considering previous data, there was a significant rise in ultrasound use from 5.4% in 1998 to 12.1% in 2011. Multivariate analysis of CT use found the strongest predictor to be increasing age. Females, black children, and those with Medicaid insurance had lower

odds of having a CT.

The group concluded that, in contrast to the earlier dramatic increase in CT use for pediatric patients with abdominal pain, CT usage remained constant between 2008 and 2011. There was no associated change in the rate of diagnosis of appendicitis or hospitalization; however, the use of ultrasound is increasing.
https://tinyurl.com/Fahimi-et-al-paper

Structural, functional, and metabolic brain markers differentiate collision versus contact and non-contact athletes

There is growing concern about how participation in contact sports affects the brain.

People who play contact sports show changes to their brain structure and function, with sports that have greater risk of body contact showing greater effects on the brain, according to the results of a newly published study from a group of Canadian researchers (*Churchill NW et al. Structural, Functional, and Metabolic Brain Markers*

The study compared the brain images of players of sports where body contact takes place but is not purposeful (e.g . football shown above) with sports such as American football where body contact is intentional and yet other sports where no body contact takes place.

Differentiate Collision versus Contact and Non-Contact Athletes. Front Neurol. 2017; 8: 390).

The group from St. Michael's Hospital in Toronto performed pre-season brain scans of 65 varsity athletes — 23 from collision sports (with routine, purposeful body-to-body contact), 22 from contact sports (where contact is allowed, but is not an integral part of the game) and 20 from non-contact sports.

They found that the athletes in collision and contact sports had differences in brain structure, function and chemical markers typically associated with brain injury, compared to athletes in non-contact sports.

Lead author Dr. Nathan Churchill, from St. Michael's Neuroscience Research Program, said there was growing concern about how participation in contact sports may affect the brain.

Most of the research in this area has focused on the long-term effects for athletes in collision sports, such as football and ice hockey, where players may be exposed to hundreds of impacts in a single season. Less is known about the consequences of participating in contact sports where body-to-body contact is permitted, but is not purposeful, such as soccer, basketball and field hockey.

In sports such as American football where body contact/collision is intentional

This study looked at both men and women in a variety of sports, and found progressive differences between the brains of athletes in non-contact, contact and collision sports.

This included differences in the structure of the brain's white matter - the fibre tracts that connect different parts of the brain and allow them to communicate with one another. Athletes in sports with higher levels of contact also showed signs of reduced communication between brain areas and decreased activity, particularly within areas involved in vision and motor function, compared to those in non-contact sports, such as volleyball.

However, these differences do not reflect significantly impaired day-to-day functioning, said Dr. Tom Schweizer, head of the Neuroscience Research Program and a co-author of the paper, noting that the athletes in this study did not report significant health problems and were all active varsity athletes. He said that the study fills an important gap in understanding how contact affects healthy brains, as a step toward better understanding why a small number of athletes in contact sports show negative long-term health consequences. The findings indicate persistent differences in brain physiology for athletes participating in contact and collision sports, which should be considered in future studies of concussion and subconcussive impacts https://tinyurl.com/Churchill-et-al-paper

A picture of burnout: case studies and solutions toward improving radiologists' well-being

The syndrome of physician burnout is a response to chronic job-related stress characterized by emotional exhaustion, de-personalization, and a diminished sense of accomplishment that is becoming an increasingly recognized healthcare issue. This is particularly problematic in radiology, where one-half of radiologists report symptoms of burnout. In fact radiologists rank 10th out of 25 surveyed specialties. Physician burnout is associated with outcomes of significant public interest including higher rates of medical error, lapses in professionalism, faculty turnover, and suicidal ideation. In 2016, the American College of Radiologists Commission on Human Resources issued a report providing 10 recommendations for the prevention and treatment of physician burnout. Many of these remedies require cooperative engagement of both the individual physician and the healthcare organization. Additionally, implementing the American College of Radiologists recommendations, such as reducing the isolation of radiologists, restoring work-life balance, and reducing prolonged stress, may require not only organization support but culture change. Negative aspects of the culture of medical practice that have the potential to limit interventions aimed at alleviating burnout include perfectionism, a culture of "blame and shame, and ineffective outdated leadership paradigms.

Current studies in the United States suggest that 75% of all physicians are now employed by large organizations including academic medical centers, Health Maintenance Organizations, large practice groups, and hospitals. This shift in workplace dynamics from private practices creates an environment where individual physician autonomy, and therefore personal ability to control drivers of burnout including productivity expectations and organizational culture surrounding work-life balance, may be limited.

A recent review (*Restauri N et al. A Picture of Burnout: Case Studies and Solutions Toward Improving Radiologists' Well-being.Curr Probl Diagn Radiol. 2017; 46(5): 365.*) integrates current evidence surrounding physician burnout with fictional case vignettes in an attempt to depict how an individual physician experiences drivers of burnout (lack of autonomy and control, absence of meaningful or value- aligned work, and poor physician leadership) as a complex and interrelated function of medical culture and healthcare organizational leadership. Case

vignettes provide a vehicle to paint a tangible picture of individual burnout while examining evidence- based solutions. It is clear that patients, individual providers, and the healthcare system as a whole suffer when a physician becomes burned out; therefore, solutions to this wide-spread problem must occur on both the individual and the organizational level.

Though challenging, addressing these complex causative factors will be necessary to maintain the physician workforce required to provide safe and effective care to our patients.
https://tinyurl.com/Restauri-et-al-paper

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Radiopaque three-dimensional printing of realistic patient phantoms

By Dr F B Schwarz & Dr P Jahnke

This article gives a brief overview of the current limitations of phantoms used in the quality control of in computed tomography and radiation therapy and the disadvantages of commercially available 3D printing approaches for individual phantoms. Radiopaque three-dimensional printing is presented as a solution to these issues — radiopaque 3D printing is a novel and easy to use method designed for printing realistic phantoms using only readily available standard office equipment.

INTRODUCTION:

Ensuring that the performance characteristics of CT imaging and radiation therapy (RT) systems are maintained at the highest level is of vital importance in modern healthcare. For this reason the regulatory authorities in many countries have introduced regulations requiring regular checks of CT and RT systems. The increasing complexity and performance of modern CT and RT devices mean that phantoms are becoming ever more important to allow practical verification of system properties. Thus, calibration and quality assurance are routinely performed with geometric phantoms. However, geometric phantoms cannot realistically simulate the individual patient exposure to ionizing radiation.

Anthropomorphic phantoms are designed for a more realistic representation of the human body. Traditional anthropomorphic phantoms such as the Alderson phantom (RSD, Long Beach, Calif) consist of a limited number of tissue-simulating materials, typically bone, lung and soft tissue, with an average human shape [1]. Alderson-type anthropomorphic phantoms are manufactured in a complex and highly manual production procedure, which restricts the possible level of detail and results in elevated costs. While such phantoms do allow approximation of radiation attenuation of the human body, detailed simulation of human tissue characteristics is not possible.

As an alternative, animal models could be used for research purposes [2]. However, animals cannot directly simulate the human body and animal studies are limited by ethical concerns, challenges in procurement and maintenance and associated costs.

To overcome these limitations, anthropomorphic phantoms that faithfully mimic both the anatomy and radiation absorption characteristics of individual patients would be highly desirable.

3D printing may provide the necessary technologies to produce such phantoms. Based on medical 3D data sets derived from CT or MRI scans, printable 3D computer models can be generated through data postprocessing. Most 3D printed phantoms have been realized by other groups using material extrusion or photopolymerization technology [3-12]. For instance, Ehler *et al.* [3] created a 3D printed head phantom for dosimetric measurements in radiation therapy using a fused deposition modeling (FDM) 3D printer. The outer shell of the head was printed using an ABS (acrylonitrile butadiene styrene) plastic and was filled with a homogeneous polymeric mixture with a mass density mimicking soft tissue. Interesting material developments in FDM now provide ABS bismuth composite filaments with stronger radiation attenuation than native ABS. These were used by Ceh *et al.* [4] to print a head phantom with soft tissue and bone mimicking ABS types on a dual extrusion FDM printer. A multi-material PolyJet 3D printer was used by Mayer *et al.* [5] to combine two materials with different absorption characteristics in a thorax phantom, where soft and bone tissue could be distinguished.

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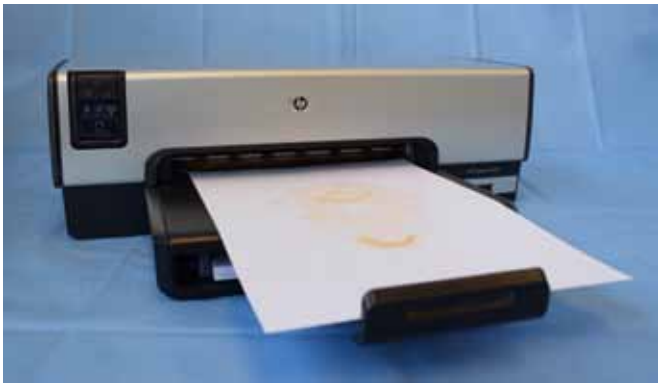

Figure 1: Standard HP Deskjet 6940 (Hewlett Packard, Palo Alto, Calif) office inkjet printer used for radiopaque printing with iodine enhanced ink.

The advantage of these approaches is that commercial, ready-to-use technology can be applied for 3D printing individual phantoms. However such commercial 3D printing technologies were not designed for printing 3D objects with precise radiation attenuation. FDM 3D printers can only create homogeneous objects, which limits their use for production of advanced phantoms. FDM printed phantoms often combine a 3D printed part (e.g. outer shell or bone mimicking part) with additional manually crafted materials like a casted homogeneous polymer part. Advanced photopolymerization printers allow the combination of multiple materials within one model (e.g. the Stratasys PolyJet, Eden Prairie, Minn), but are very expensive. In addition the very complexity of these machines and materials limits the development or modification of specialized materials with distinct radiation attenuation properties. While the examples published up till now are promising steps on the way towards implementable 3D printed phantoms, they still represent phantoms with only simplified anatomy and/or significant deviations in attenuation characteristics from the original patient and remain quite complicated and expensive.

"... Our results show that standard office equipment can be used to create realistic anthropomorphic phantoms of individual patients..."

To address these issues, we initiated a study [13] with the aim of developing a 3D printing method specifically designed for creating anthropomorphic phantoms with the anatomy and attenuation properties of individual patients. Our design objectives were that the method should be easy to use, universally applicable and inexpensive. In addition the phantoms should display the original anatomy at high resolution and have realistic radiation attenuation properties faithfully representing the patient. We hypothesized that conventional ink jet printers could be used together with radiopaque ink to transfer grey scale encoded CT images to standard office paper at high resolution and that a stacking of such printed sheets could generate 3D objects that would display the original patient anatomy with realistic radiation attenuation properties.

RADIOPAQUE THREE-DIMENSIONAL PRINTING:

In our study, radiopaque printing was carried out with a standard desktop printer (HP Deskjet 6940; Hewlett Packard, Palo Alto, Calif), using the black ink cartridge (HP 339) that allows printing for an accurate reproduction of anatomic details at high resolution. The printer was modified for radiopaque printing with iodine-enhanced ink by replacing the original black ink in the cartridge with an aqueous solution of potassium iodide (0.60 g/mL). Standard office paper (80 g/m^2, 0.1 mm thickness) was used as substrate.

Standard soft-tissue kernel CT images of a patient were grey scale inverted to achieve high printer deposition of attenuating ink in areas of high patient attenuation such as bone and vice versa for low attenuating tissues such as fat. 100 printed paper sheets were stacked and examined in our CT scanner. The first feasibility test already showed the patient anatomy at a surprising level of detail. However, Hounsfield units deviated significantly from the original patient.

We continued with analysis of the relationship between print template gray scales, printer deposition and Hounsfield units by 1) printing square templates with gray scales ranging from 0% (white) to 100% (black) and measuring Hounsfield units and 2) determining printer deposition by weighing printed sheets. These experiments revealed a linear correlation between printer iodine deposition and Hounsfield units. However, there was an exponential correlation between template gray scales and Hounsfield units, This correlation could be described by a mathematical equation derived using a curve fitting procedure.

Using this a correction procedure was developed to reproduce the Hounsfield units of the original patient in the printed model. The curve fit equation was inverted and applied to the square templates for verification. Results showed that the gray scale correction procedure now gave a linear correlation between template gray scales and Hounsfield units.

Using the same correction procedure for the patient CT data set from the first feasibility test, the patient CT images were printed again, stacked and examined in our CT scanner. Results showed that the preceding gray scale correction procedure allowed correction of any deviation in Hounsfield units in the patient model, which now displayed both detailed anatomy and Hounsfield units closely matching the original patient.

SIGNIFICANCE AND FUTURE APPLICATIONS:

Our results show that standard office equipment can be used to create realistic anthropomorphic phantoms of individual patients. Only slight modifications of an ink jet printer are required for radiopaque printing and standard office paper can be used as substrate. In order to realize realistic Hounsfield units a calibration procedure is necessary to take the

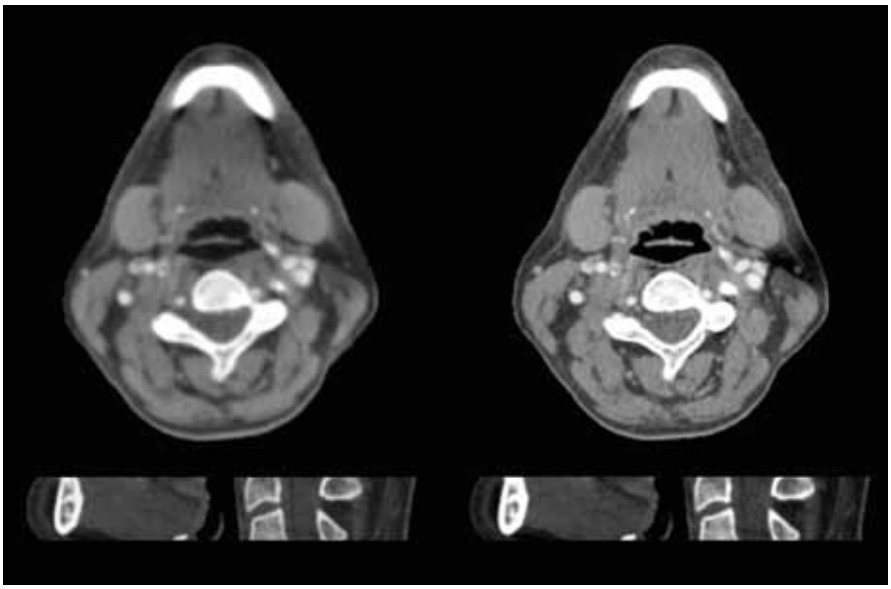

Figure 2: Left Panel : CT images of a head and neck phantom . Right Panel: the original patient. Axial view in the top row, sagittal view in the bottom row.

characteristics of the printer deposition into account.

In contrast to previous approaches using commercial 3D printers, radiopaque three-dimensional printing produces detailed and highly realistic phantoms through separation of build material (standard paper) and attenuating material (iodine enhanced ink) which can be deposited at high resolution. The necessary printing equipment is easily available, inexpensive and familiar to any user with even basic experience in operating desktop printers for standard office applications.

In a recent study, radiopaque printing with iodine-enhanced ink was used to create realistic breast phantoms for 2D and 3D x-ray imaging by printing with a mixed ink consisting of clinical contrast agent and regular pigmented ink [14]. In a modified approach, a similar approach has been proposed for validation of brain SPECT analysis by printing MRI images with 99mTc pertechnetate-enhanced ink on paper and alternating stacking with an FDM printed head shell [15].

With its focus on computed tomography our study shows that the phantom printing should first be preceded by characterisation of the printer and – if necessary – the use of a calibration step as proposed in our work. This calibration should focus on the relationship between template gray scales and printer deposition which can easily be analyzed by measuring resulting Hounsfield units. This calibration process should be performed rigorously and thoroughly to precisely create the desired Hounsfield units in the final phantom.

In addition to traditional phantom applications, realistic phantoms created with our method may broadly be used for any purpose where actual patients would be desirable test objects, e.g. in protocol optimizations, dosimetric investigations, device testing, calibration, quality assurance, training and demonstration. In contrast to traditional phantom manufacturing, such individuality does not represent a challenge but is automatically part of the method, providing means for exposure optimization for individual patients.

CONCLUSION:

We present a novel and easy-to-use method requiring only standard office equipment for the creation of realistic patient individual phantoms. Starting from standard CT data sets, conventional desktop ink jet technology can be used to print patient data with iodine-enhanced ink on standard office paper. Paper stacking results in 3D objects with detailed patient anatomy and realistic radiation attenuation characteristics. Phantom printing should be preceded by printer characteristic and a calibration procedure. Possible future applications of these phantoms range from general investigations in imaging and dosimetry to optimization of individual radiation exposure in computed tomography and radiation therapy.

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1. Data on file and from public sources, 2017. **2.** Results from Friedewald, SM, et al. "Breast cancer screening using tomosynthesis in combination with digital mammography." JAMA 311.24 (2014): 2499-2507; a multi-site (13), non-randomized, historical control study of 454,000 screening mammograms investigating the initial impact of the introduction of the Hologic Selenia® Dimensions® on screening outcomes. Individual results may vary. The study found an average 41% increase and that 1.2 (95% CI: 0.8-1.6) additional invasive breast cancers per 1000 screening exams were found in women receiving combined 2D FFDM and 3D™ mammograms acquired with the Hologic 3D™ Mammography System versus women receiving 2D FFDM mammograms only. **3.** In an internal study comparing Hologic's standard compression technology to the SmartCurve™ system (18 x 24cm).

The role of the imaging department and its workflow in acute ischemic stroke

By Dr C Zerna, Dr Z A Assis, DrAlmekhlafi & Dr M Goyal

INTRODUCTION

Six positive trials of mechanical thrombectomy for anterior circulation acute ischemic stroke due to large-vessel occlusion established endovascular therapy as a standard of care for such patients. These trials (MR CLEAN, ESCAPE, SWIFT-PRIME, EXTEND-IA, REVASCAT and THRACE) each enrolled 70-500 previously-independent subjects with varying eligibility regarding age, stroke severity, treatment time window, intravenous (IV) recombinant tissue plasminogen activator (rtPA) treatment, and additional extracranial occlusions [1-6]. Imaging techniques to determine the site of occlusion and the presence/ extent of salvageable brain varied and included (multiphase) computed tomography angiography (CTA), CT perfusion and diffusion-weighted magnetic resonance imaging (MRI). A meta-analysis of these trials showed that patients who received endovascular therapy had significantly lower disability at 90 days compared with those who received standard medical treatment (OR 2.49, 95% CI 1.76–3.53; P <0.0001). The long-term follow-up results of the MR CLEAN and REVASCAT trials show a similar degree of superiority of endovascular therapy over standard medical treatment to the 90 day results [7]. The more recent DAWN trial showed that mechanical thrombectomy (with the TREVO device) when initiated between six to 24 hours of stroke onset in selected patients with proximal anterior circulation occlusion leads to better clinical outcomes at 90 days compared to standard medical management [8]. The trial was stopped early for crossing a pre-specified predicted probability threshold for superiority and publication of the results are underway. All these trials have proved the critical role of imaging-based patients' selection for endovascular therapy.

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IMPORTANCE OF IMAGING DEPARTMENT REORGANIZATION IN THE NEW STROKE ERA

Many of these recent endovascular trials have published metrics on their workflow and further established the well-known paradigm "time is brain" by showing that faster treatment leads to higher odds of favorable outcome [9]. To meet the ever increasing demand for faster workflow within the imaging department, the following recommendations may be considered:

"...Non-contrast CT remains the primary imaging technique for stroke syndrome presentations and helps to quickly differentiate ischemic and hemorrhagic stroke..."

• *Efficiency*

Parallel processing and team work are key factors of fast treatment with the majority of activity during an acute stroke protocol takes places in the imaging department. Including the CT technical staff and the on-call (interventional) radiologist in the "heads up" team notification (e.g. paging system) for an incoming acute stroke patient ensures availability of the CT scanner, rapid image acquisition and interpretation.

• *Standard and simple image acquisition protocols*

Non-contrast CT remains the primary imaging technique for stroke syndrome presentations and helps to quickly differentiate ischemic and hemorrhagic stroke and to measure the extent of early ischemic changes using the Alberta Stroke Program Early CT Score (ASPECTS) [10]. To locate the site of occlusion, all endovascular trials have used CTA. Uniform imaging protocols for non-contrast CT and CTA of head and neck vessels should be available for CT technologists

across a regional stroke network to make image acquisition and interpretation as easy as possible.

Because acute ischemic stroke treatment is time sensitive, front-line physicians, including stroke neurologists, general neurologists, emergency room physicians, and trainees have important roles in imaging interpretation which is why multiphase CTA, even when used by relatively inexperienced readers and even when occlusions are distal, is advantageous [11, 12]. Multiphase CTA has been found to improve diagnostic accuracy for detection of anterior circulation intracranial occlusion and can measure collateral status by assessing backfilling pial arteries distal to the intracranial occlusion compared to the unaffected contralateral hemisphere [12, 13]. It is therefore helpful for involved front-line physicians, other than a trained radiologist, to make a decision regarding possible endovascular treatment.

• *Implications on radiology training*

In instances where round-the-clock availability of a neuroradiologist is not feasible, the staff radiologist on duty must be capable of rapidly aiding interpretation of ischemic changes on the non-contrast CT, identify the vascular occlusion site on CTA, and assess collateral status and endovascular access (e.g. arch tortuosity) if necessary. Acute stroke imaging and interpretation should be introduced early in the radiology residency training programs to ensure that trainees are capable of performing these tasks.

"... A well-organized imaging department contributes to fast, safe, and successful treatment of acute ischemic strokes..."

• *Hub for acute stroke management*

In addition to image acquisition, the imaging department will now also become the new site for acute stroke treatment. Not only image acquisition and interpretation but also treatment decision making, consent taking and discussion with family members will be taking place within or in the vicinity of the CT scanner. Further, increasing number of centers initiate IV rtPA in the CT area after acquisition of the non-contrast CT (and exclusion of clinical contraindications) which has been shown to be associated with faster treatment times [14].

If a large vessel occlusion and salvageable brain are detected, the patient should directly be transferred to the angiography suite from the CT area. By involving the on-call (interventional) radiologist early in the acute stroke protocol process, the angiography suite should be ready to receive the patient immediately. In Calgary, we found it ideal to have a prearranged stroke tray (BRISK: Brisk Recanalization Ischemic Stroke Kit) ready for use with all the necessary devices set up in the order they would be needed during the procedure [11]. New generation stent retrievers have been used in the majority of the above discussed randomized controlled trials and although different centers prefer different techniques, it is advisable to adhere to a standardized institutional protocol as much as possibly to avoid confusions among team members and additional delays [11]. Cross-training x-ray and CT technicians to help in the angiography suite may speed up endovascular treatment during nights or weekends [10].

• *Quality control within imaging department*

Using iterative feedback and aggressive time metric goals to challenge existing workflows at regular time intervals will further enhance the acute stroke protocol process [11].

FUTURE DIRECTIONS AND CONCLUSION

Imaging-based selection paradigms based on site of occlusion and extent of core infarct will likely serve as a new biomarker for acute stroke decision making and will help extend the current evidence by fostering research in regards to the appropriate treatment of more distal intracranial occlusions, proximal intracranial occlusions with mild or no neurological symptoms, and "wake-up" or late-presenting acute strokes.

A well-organized imaging department contributes to fast, safe, and successful treatment of acute ischemic strokes resulting in higher odds of favorable outcome. Critical steps for workflow efficiency include early notification, simple imaging acquisition and interpretation protocols, parallel processing, team work and feedback.

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Advanced Vector Flow Imaging in vascular evaluation

By Dr Alfredo Goddi

A new technique for non-invasive evaluation of flow dynamics in human vessels may allow earlier detection of abnormal vascular conditions.

INTRODUCTION

Hemodynamics play an important role in the pathogenesis of atherosclerosis. Thus, vessel walls that are exposed to a steady blood flow and with a higher level of wall shear stress (WSS) remain essentially disease-free. In contrast, areas of blood vessels that are affected by disturbed or turbulent flow, which in turn results in a low level of shear stress, become prone to atherosclerosis [1]. Disturbed flow usually occurs in vessel dilatation, branching regions or in case of adverse pressure gradient and significant flow decelerations [2].

Consequently, the ability to analyze WSS hemodynamically and to measure it accurately is an essential basis for the assessment of the atherosclerotic risk in the general population.

Color Doppler imaging (CD) and Spectral Doppler or Pulsed Wave analysis (PW) can provide a real-time direct imaging visualization of flow and the measurement of blood velocities, respectively. The methods have been used to characterise patterns of flow velocity [3.4,5] and correlate them with variations in WSS [1].

However, such conventional Doppler modalities measure only one-dimensional blood velocity components, namely those parallel to the direction of the UltraSound (US) beam. The techniques are therefore dependent on angle and vessel geometry which can cause variability in the results [4,5].

Moreover, line-by-line US transmission provides a limited CD frame rate of about 20 to 30 Hz, thus permitting only low temporal resolution. This characteristic reduces the possibility of the detection and display of the dynamics of any transient phenomena. PW has a higher temporal resolution than CD and provides a complete spectrum of velocities, but it displays information generated in only a small sample volume.

The accuracy of PW depends on the precise estimation of the angle between the ultrasound beam and the flow in the vessel. This angle is difficult to estimate correctly particularly when streamlines differ from the vessel course, even when using CD as a guide. The assumption that the flow velocity vectors are axial at bifurcations and curves and in the presence of plaques has been shown to be incorrect [3]. Moreover, because of their pulsatile nature, flow components frequently vary temporally over a cardiac cycle.

All these limitations explain why, in routine clinical practice, a precise quantification of disturbed flow, which by definition is multi-directional, is not achievable with conventional ultrasound systems.

To overcome these limitations, a new method of multi-dimensional estimation of flow velocity vectors, known as Vector Flow Imaging (VFI), has been developed [6]. This proposed vector Doppler method is based on the estimation of at least two of the three components (namely the x, y, and z-axis) which, in physics describe a velocity vector. In practice, VFI is carried out by measurements taken in two or more independent directions using multiple US transmitters and receivers [7]. The independent velocity so estimated can then be used to reconstruct the true flow vector and the velocity magnitude at each site [7].

The main advantages of VFI are the independence of the method on beam-flow angle and the ability to assess multi-directional blood flow, thus displaying the real flow characteristics.

VECTOR FLOW IMAGING

Various VFI methods, based on several different measurement principles have been proposed, but only a few have been implemented in commercial systems. Whatever the principles of measurement, the methods can be categorized into two groups. The first category, based on conventional line-by-line acquisition, evaluates the flow pattern complexity in real-time at a relatively low frame rate, whereas the second group, being based on plane-waves and parallel receiving, achieves a higher frame rate during a short period of acquisition, thus allowing a better depiction of the complex flows [8,9].

In plane wave imaging (PWI), a series of single

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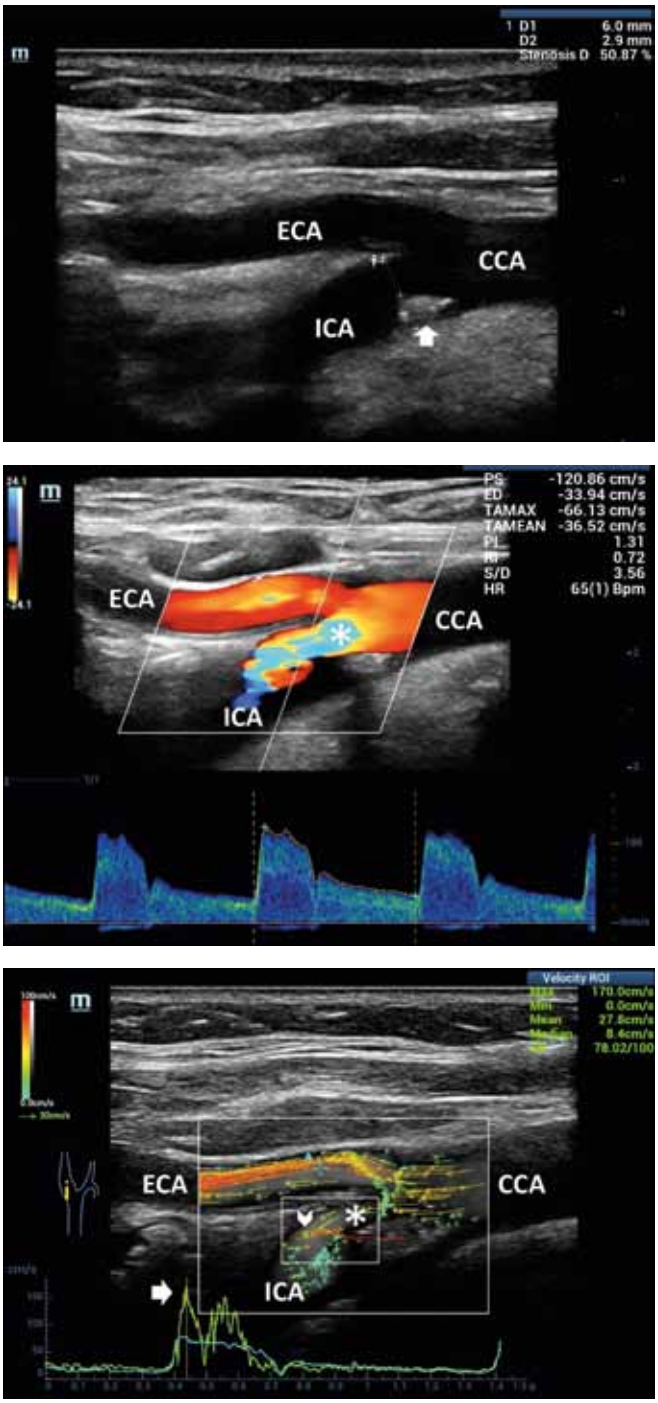

Figure 1 Top Panel. B-mode image of the carotid bifurcation (CB) shows a calcified plaque (arrow) causing a nearly 50% stenosis (degree defined by NASCET).
Middle Panel. The mosaic of colours (*), a consequence of aliasing. PW measures a 120 cm/s PSV value, consistent with a nearly 50% stenosis; spectral broadening highlights turbulence.
Bottom Panel. A VFI frame extracted from the 900 images of the cine loop acquired in 1.5 seconds shows mainly laminar velocity vectors in CCA and ECA and turbulent flow in the ICA. The automatic detection of the maximum velocity vector point (arrowhead) – coincident with the red arrows moving back due to aliasing – in the selected ROI and the related yellow velocity curve below (arrow) allows the recognition of an instant PVS of 170 cm/s, higher than the PW finding, thus grading a 50% to 60% moderate stenosis. The instant SD value of 78/100 also quantifies a high level of turbulence.

unfocused beams, oriented in different directions over a wide area of the field of view, are transmitted and allow parallel retrospective beamforming upon reception [10]. The number and angulations of the transmitted plane waves and the retrospective beamforming, performed from multiple angles, affect the spatiotemporal resolution of PWI [11].
Several PWI-based VFI methods have been developed, but only one of them, using a new vector computation algorithm known as vector projectile imaging (VPI), generates a significantly high frame rate of 416 Hz.
VPI derives the true velocity vectors (i.e., each velocity component) at any location from the multidirectional transmission and reception of plane waves. Tested *in vitro* on an anthropomorphic phantom simulating carotid bifurcation, VPI has been shown to enable adequate tracking of spatiotemporal flow variations [12].

HIGH FRAME RATE VECTOR FLOW

High frame rate VFI, known as V Flow, and currently commercially available only on **Mindray's Resona 7** system, represents one implementation of the VPI method and generates a frame rate of 400-600 Hz, thus allowing a detailed characterisation of flow patterns and simultaneous high-resolution B-mode images by interleaving focused waves with multi-directional Doppler transmission [13].
With V Flow, the flow within a selected region of interest (ROI) is analyzed by the system at a pulse repetition frequency (PRF) of 15 kHz and an extremely high frame rate for 1.5 seconds, thereby allowing the examination of at least one cardiac cycle. V Flow measures the speed and direction of all blood cells flowing through every point of the ROI in a short space of time. The data are reprocessed automatically by the system, generating a sequence of 900 images displayed at a frame rate of 25Hz. The flow is represented by several colored arrows showing the different velocity, magnitude, and direction at every point of the vessel. Green arrows represent low velocities, yellow and orange arrows medium velocities, and red arrows depict high velocities. The longer the arrows, the faster the flow. The color and size of the arrows thus allow visual quantification of the flow behavior. The high acquisition frame rate results in a detailed visualization of the flow, with even otherwise uncaptured transitory events, which can occur during a cardiac cycle, being able to be assessed. The approach also allows the distinction of the different flow components and their extension and duration [11]. The flow characteristics can be evaluated visually, frame by frame, to assess the flow pattern (e.g., laminar and helical flow, recirculation, counter eddy, vortex, and turbulence) by considering the vectors' directions and lengths. Such detailed analysis is particularly helpful whenever the hemodynamics become extremely complicated, as in vessel bifurcations or when plaques develop [Figure 1].
For numerical quantitative flow evaluation, a package of

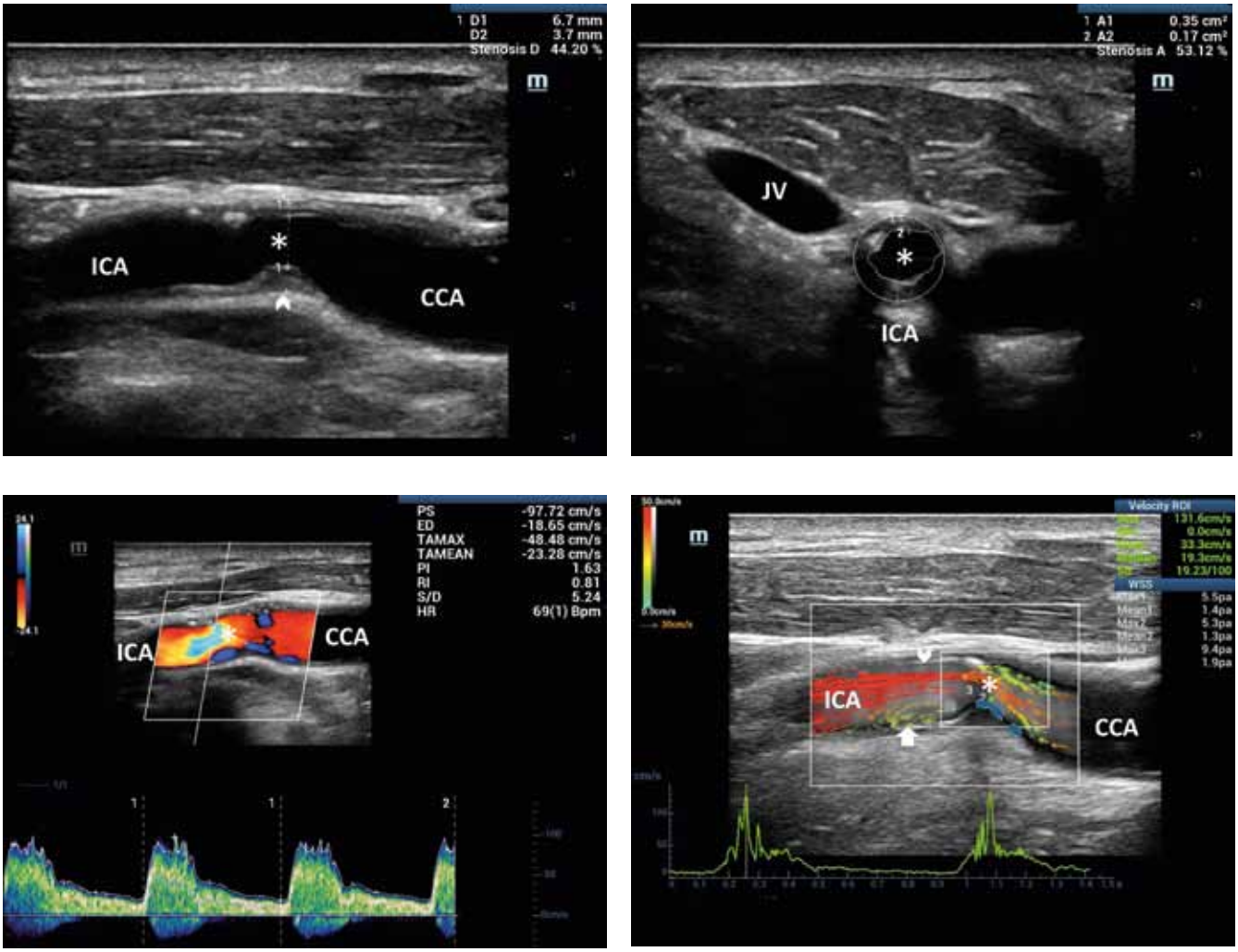

Figure 2. Top Left and Top Right. B-mode longitudinal and transverse views show a low-to-moderate degree stenosis at the entrance of the ICA, quantified as 44.2% in diameter and 53.1% of the area.
Bottom Left. CD shows increased velocities in the ICA (*), coded in blue as a consequence of the aliasing artefact. Spectral Doppler rules out an increased velocity (PSV 97.7 cm/s) and highlights flow disturbances through the spectral broadening and bidirectional flow.
Bottom Right. The VFI frame, extracted at the systolic peak, shows a narrow high-velocity streamline (long red vectors) shifting toward the anterior wall of the ICA (arrowhead) at the stenosis level (*). Distally to the stenosis (arrow), the separation of the layers develops a slow fluid movement upstream (short green vectors). The automatic detection of the point of maximum velocity vector in the selected ROI allows the recognition of an instant PVS of 131 cm/s, higher than the PW finding, thus grading the stenosis as moderate (50-60% – NASCET). The high WSS value (max 9.4, mean 1.9 Pa) at the stenosis level (blue dot #3) is related to the impact caused by the plaque on the hemodynamics.

easily applicable tools and measurement parameters have been developed. These comprise: multiple user-defined vector velocity curves, which show the variation of flow velocities in subsequent cardiac cycles; the automatic detection of the maximum velocity vector point, combined with the circular variance for the angles of vectors in a specific selected area, thus allowing the characterization of non-laminar flow; measurements of volume flow and wall shear stress (WSS) at different locations, which are useful for the study of the hemodynamics of complex flow [Figure 2].

CLINICAL APPLICATIONS OF VFI

A comprehensive assessment of blood flow should be the ultimate goal of every ultrasound evaluation, which means that the hemodynamic characteristics of the flow should be displayed. Because local hemodynamic variations have a strong influence on the WSS and are a major factor in the development of atherogenesis, the practical clinical applications of V Flow relate to each change in vessel direction or bifurcations and changes in the vessel wall itself (e.g. plaque and vessel diameter), which greatly affect the profile of the blood streams.

Due to its anatomical position and strategic clinical role the carotid bifurcation has been the vessel most thoroughly investigated in detail by VFI, ever since the early development phase of the technology.

In such studies, VFI has been able to identify a vortex in the carotid sinus during the deceleration phase after peak systole, no matter which estimation method was used [14,15,16,17]. In addition, thanks to the combination of higher spatial and temporal resolution, V Flow has been shown to be able to clearly outline flow behaviour in vessel enlargement and kinking, together with variations in the

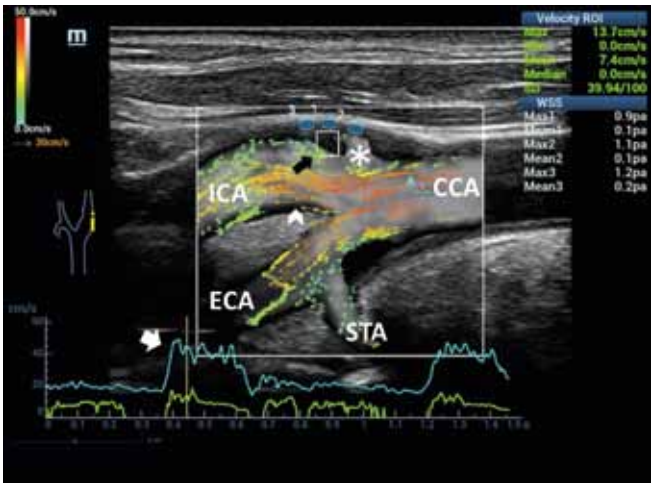

Figure 3. VFI of the Carotid Bifurcation. In the enlarged ICA sinus, the maximum velocity streamline (red vectors) flows along the side of the divider (arrowhead); a wide area of recirculation (*) is well delineated by the VFI on the opposite side. The vector point in the selected ROI (black arrow) inside the disturbed flow area shows low velocities (instant velocity of 13.7 cm/s) during the descending systolic phase (white arrow on the velocity curve below) and apparently moderate turbulence (instant SD 39.9/100). However, the WSS measurement in three locations near to the turbulence area indicates a weak shear stress (0.1-0.2 Pa), resulting in higher risk for the development of atherosclerosis.

shape of the carotid bifurcation [17]. In such conditions, some measurement parameters, such as the circular variation of the vector angles in a selected region of interest allow the instant characterisation of any flow disturbances and thus provide a deeper understanding of possible effects on plaque formation, so enabling a stratification of the patient's risk [Figure 3].

Analysis of the relationship between disturbed flow patterns and atherosclerosis has shown that V Flow has the potential to improve the understanding of turbulence [17]. The possibility, via the V Flow method, to estimate WSS at a precise location among different flow patterns, as well as in vessel stenosis, can be an important adjunct in the assessment of overall clinical value.

Another emerging clinical application of V Flow is the evaluation of arteriovenous fistulae (AVF) used hemodialysis [18].

This current brief review has mainly focused on the current clinical applications of the high frame rate of VFI, but it should be noted that the vector Doppler technique can also be applied in other vascular areas, such as in femoral arteries [19], as well as in the cardiology field [20].

CONCLUSION

VFI technology provides an intuitive representation of flow in all directions, independent of the vessel geometry. V Flow has been shown to be able to visualize complex flow patterns, thus providing new information on flow behaviour and allowing for a quantitative evaluation of turbulence. The benefits of the high frame rate in VFI are even more evident when the technology is used for WSS measurement, an important parameter associated with vascular function and atheroma growth.

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ABBREVIATIONS.

CCA: Common carotid artery; *CB*: Carotid Bifurcation; *CD:* Color Doppler; *ECA:* External carotid artery; *ICA*: Internal carotid artery; *PW*: Pulsed wave or Spectral Doppler; *STA:* Superior thyroid artery; *PWI:* Plain wave Imaging; *ROI:* Region of Interest; *US:* UltraSound; *VFI:* Vector Flow Imaging; *WSS:* Wall Shear Stress; *V Flow:* the high frame rate VFI system available on Mindray's Resona 7 system.

DISCLOSURE:

Dr Goddi is a consultant for Esaote; GE Healthcare,; Shenzhen Mindray Bio-Medical Electronic Co;, Supersonic Imagine.

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Cardiovascular risk assessment in women: association between breast arterial and coronary artery calcification

By Dr T Datta, Dr AJ Ryan, Dr BG Choi, Dr JF Lewis & Dr AD Choi

In this article we present a summary of the current status and clinical implications of the association of breast artery calcification (BAC) with coronary artery calcium scoring (CACS). We briefly introduce the epidemiology of cardiovascular disease in women, explore the role of coronary artery calcium scoring in cardiovascular risk stratification and further discuss the findings and limitations that exist in various studies that have been carried out thus far on this topic. Lastly, we establish the clinical implications of these conclusions in light of current breast screening guidelines and suggest future directions for clinical utility.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN WOMEN

Cardiovascular disease (CVD) remains the leading cause of death in women today [1]. Specifically, for women <50 years of age, coronary heart disease has become the primary etiology of premature mortality, and — unlike in men — these mortality rates are not declining [2, 3]. Moving forward, it is estimated that almost 45% of women will be living with some form of CVD by the year 2035 and the associated burden of cost with this evolving disease process will approach approximately $500 billion per year in the US alone [4]. A number of factors encompass this inequality including symptom recognition delay, anatomic, physiologic, and genetic factors, as well as possible underutilization of diagnostic tests and treatments. Furthermore, clear disparities in cardiovascular risk factors exist not only in women compared to men but also in African American women compared to white women based on lifestyle, diet, and socioeconomic background [3]. For these reasons, exploring female-specific risk factor stratification tools is useful in clinical screening to identify CVD in women

Mammography represents a potentially important alternative screening modality to identify CAD risk in women. In the United States, given the roughly 40 million mammograms already performed, identification of cardiovascular risk by demonstrating an association between BAC and CAD may enable a gender-specific methodology to identify women at increased risk from CAD.

> ***" ...demonstrating an association between BAC and CAD may enable a gender-specific methodology to identify women at increased risk from CAD..."***

ROLE OF CORONARY ARTERY CALCIUM SCORING IN CARDIOVASCULAR RISK STRATIFICATION

Traditional risk assessment tools such as the Framingham Risk Score (FRS) used to determine the 10 year absolute risk of coronary heart disease (CHD), underestimate coronary artery disease risk in women resulting in potential misclassification of women with subclinical disease as low risk [5]. Coronary artery calcium scoring (CACS) by computed tomography (CT) has come to light as a potential means to improve this risk stratification process. Specifically the Multi-Ethnic Study of Atherosclerosis (MESA) showed that the presence of coronary artery calcification (CAC) in women considered to be at low risk based on the FRS was predictive of future CHD and CVD events [6, 7]. CACS is mainly accomplished by visualizing CAC and

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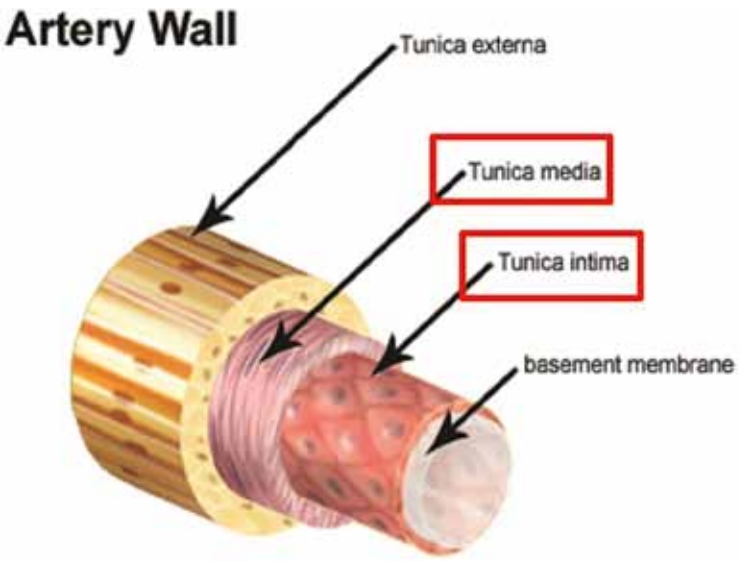

Figure 1: Intima (affected breast artery calcification) versus media (affected by coronary artery calcification) layers of artery wall.

calculation of the Agatston score that is used as a marker of subclinical heart disease [8]. Agatston scores can be categorized by risk prognostication ranging from 0 to >400; corresponding to non-identifiable disease to severe disease [7]. A CACS score >400 suggests that a patient is 7X more likely to have a cardiac event compared to those without any CAC [5]. This CACS is a class IIA recommendation based on the 2010 American college of Cardiology Foundation/American Heart Association guidelines for assessment of CV risk in asymptomatic adults and guides clinical decisions in medical management with pharmacotherapy and aggressive lifestyle modification [9, 10]. The European Society of Cardiology 2016 guidelines classify coronary artery calcium scoring a Class IIb recommendation as a risk modifier in cardiovascular risk assessment, though these guidelines do not account for newer studies in low radiation dose scanning [11]. Several recent studies have shown comparative CAC imaging with minimal radiation doses, mitigating potential concern associated with radiation exposure [9, 10].

PATHOPHYSIOLOGY OF BREAST ARTERY CALCIFICATION

Breast artery calcification and coronary artery calcification have differing histologic and anatomic patterns of calcium deposition but may be linked by a common inflammatory cascade. In coronary artery calcification, it is the arterial intima that is affected while in breast artery calcification, the medial layer of the artery is most involved [Figure 1]. This breast artery calcification in the intimal layer is termed Mönckeberg calcification and the process of its development involves degeneration of elastin fibers seen mainly in small- and medium -sized arteries. To set apart malignant calcific lesions from those seen as a part of ductal calcification, interpretation takes into account the morphology, size, and distribution. The overall prevalence of BAC is about 29.4% however can have ethnic variation [12].

Although the anatomic location of calcification differs in BAC and CAC, they are both governed by an inflammatory cascade interaction with smooth muscle cells leading ultimately to arterial stiffening [12]. This suggests in part that BAC may not be a purely benign finding but rather hold implications for cardiovascular risk stratification as in the clinical example shown in Figure 2.

EVIDENCE TO DATE ON BREAST ARTERIAL CALCIFICATION AND CORONARY CALCIFICATION

Pechhi *et al.* conducted a prospective study in 74 Italian postmenopausal women under age 65 and found a modest correlation of BAC with the presence of CAC using 4-slice multidetector cardiac CT [13].They found that BAC had a positive predictive value for CAD of 95% with a sensitivity of 70% and specificity of 86% [13]. Maas *et al.* examined postmenopausal women aged 49-70 years and found that BAC showed a strong correlation to CAC using 16-slice multidetector CT. However the prevalence of BAC in this population was much lower than previously reported [14].

In 2013 Matsumura *et al.* performed a case control study showing that BAC presence was not predictive of CAC score >0, but in an age-adjusted model, BAC presence did demonstrate a statistically significant correlation with high-risk calcium score (Agatson score >400)[15]. In 2014, a group of 150 Iranian women undergoing screening

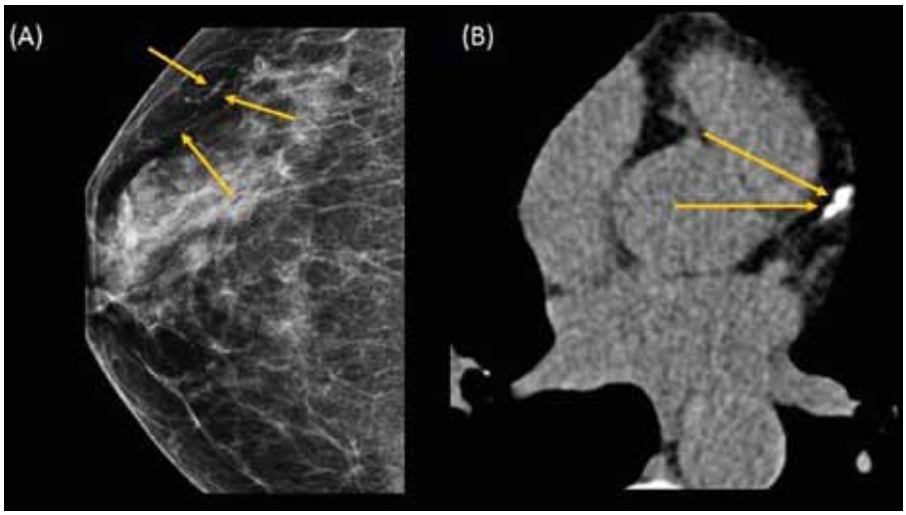

Figure 2: 69-year-old woman a former smoker who underwent (A): mammography which demonstrated breast arterial calcifications. (B): Coronary artery calcium scan which showed moderate coronary calcification with an Agatston Score of 260. Several years after her mammogram she had a myocardial infarction and is currently on optimal medical therapy for secondary prevention of coronary artery disease.

	Year	N	Age	Sensitivity	Specificity	PPV	NPV	Accuracy
Pecchi et al. [13]	2003	74	<65	70%	86%	95%	40%	73%
Maas et al. [14]	2007	499	49-70	17%	94%	76%	51%	54%
Matsumura et al. [15]	2013	202	30-90	91%	54%	12%	99%	56%
Moradi et al. [16]	2014	150	>40	57%	80%	23%	95%	78%
Newallo et al. [17]	2015	195	46-59	67%	85%	40%	95%	88%
Margolies et al. [19]	2016	292	39-92	63%	76%	70%	69%	70%

Table 1: Summary of Studies Assessing Accuracy of Breast Arterial Calcification in Predicting Coronary Artery Calcium on Mammography vs Non-Contrast Chest CT. Abbreviations: N=Number; PPV = Positive Predictive Value; NPV = Negative Predictive Value

mammography after coronary CTA were studied in a cross-sectional analysis by Moradi *et al.* who suggested that the severity of BAC had no significant correlation to CAC severity [16]. Newallo et al, examined African American women for varying relation of BAC to CAD; in this study population, BAC prevalence was 21% and 11% had CAC > 100 [17]. The authors found that women with BAC were 7X more likely to have CACS>100 when compared to those women without BAC [17].

Recently, Chadashvili *et al.* performed a retrospective analysis of 145 women referred for coronary CT angiography within a year of mammography and found BAC association with CAC > 11 [18]. Lastly, in 2016 Margolies *et al.* investigated the relationship of BAC with incidentally found CAC in women without known CAD who have undergone noncontrast chest CT [19]. Rather than an Agatston score in this non-gated CT scan, the study derived a systematic scoring system to quantify the degree of calcification in the four main coronary vessels. There was a high statistical significance in the association between BAC score, the number of calcified breast vessels, BAC length and density and CAC score, and furthermore greater extent of BAC was superior in predicting CAC presence compared with the standard risk factors (age, HTN, hyperlipidemia, diabetes, smoking, and chronic kidney disease) [19].

Limitations to the above mentioned studies include limited sample size and, with the majority of women recruited for these studies already had been referred for CT, the potential for selection bias. Variation in methods used for measuring CAC and BAC is also of note as is the generalizability of the data given that subject recruitment was mostly from limited geographic and ethnic backgrounds.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

American recommendations as to the age of initiation and duration of testing for breast cancer screening vary depending on the professional body iussuing the guidelines (e.g. The United States Preventive Services Task Force; The American Cancer Society; The American College of Radiology and the Society of Breast Imaging). The European Guidelines for Quality Assurance in Mammography Screening recommend specifically to initiate screening at age 50 [20]. Nevertheless, there is awidespread use of screening mammography in most women starting between the ages of 40-50 [21]. With this in mind, the identification of breast arterial calcifications as a potential marker for cardiovascular risk factors, and for detection of asymptomatic coronary artery disease presents a unique approach to improved risk stratification in women.

In summary, while BAC is typically reported as a benign finding, multiple studies have demonstrated modest association of BAC with the development of CAD. This may enable BAC to be a gender-specific tool to predict CAD risk in asymptomatic women. Moving forward, larger randomized prospective trials are necessary to both validate and assess long term outcomes in determining the relationship between BAC and CAC. Given current breast cancer screening guidelines for mammography, the potential implications of further research are broad-ranging.

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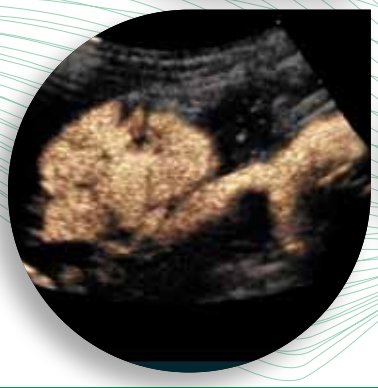

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SUMMARY OF PRODUCT CHARACTERISTICS 1. NAME OF THE MEDICINAL PRODUCT SonoVue 8 microlitres/mL powder and solvent for dispersion for injection **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of the dispersion contains 8 µL sulphur hexafluoride microbubbles, equivalent to 45 micrograms. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** Powder and solvent for dispersion for injection. White powder. Clear, colourless solvent. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** This medicinal product is for diagnostic use only. SonoVue is for use with ultrasound imaging to enhance the echogenicity of the blood, or of fluids in the urinary tract which results in an improved signal to noise ratio. SonoVue should only be used in patients where study without contrast enhancement is inconclusive. **Echocardiography** SonoVue is a transpulmonary echocardiographic contrast agent for use in adult patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation. **Doppler of macrovasculature** SonoVue increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries in adult patients by improving the Doppler signal to noise ratio. SonoVue increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment in adult patients. **Doppler of microvasculature** SonoVue improves display of the vascularity of liver and breast lesions during Doppler sonography in adult patients leading to more specific lesion characterisation. **Ultrasonography of excretory urinary tract** SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4 and 5.1. **4.2 Posology and method of administration** This product should only be used by physicians experienced in diagnostic ultrasound imaging. Emergency equipment and personnel trained in its use must be readily available. **Posology** *Intravenous use* The recommended doses of SonoVue in adults are: B-mode imaging of cardiac chambers, at rest or with stress: 2 mL. Vascular Doppler imaging: 2.4 mL. During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician. **Elderly Patients** The dose recommendations for intravenous administration also apply to elderly patients. **Paediatric Patients** The safety and efficacy of SonoVue in patients under 18 years of age has not been established for intravenous administration and use in echocardiography and vascular Doppler imaging. *Intravesical use* In paediatric patients the recommended dose of SonoVue is 1 mL. **Method of administration** For instructions on reconstitution of the medicinal product before administration see section 6.6. *Intravenous use* SonoVue should be administered immediately after drawing into the syringe by injection into a peripheral vein. Every injection should be followed by a flush with 5 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. *Intravesical use* After introduction of a sterile 6F-8F urinary catheter into the bladder under sterile conditions, the bladder is emptied of urine and then filled with saline (normal sterile 0.9% sodium chloride solution) to approximately one third or half of its predicted total volume [(age in years + 2) x 30] mL. SonoVue is then administered through the urinary catheter. Administration of SonoVue is followed by completion of bladder filling with saline until patient has the urge to micturate or there is the first slight sign of back pressure to the infusion. Ultrasound imaging of the bladder and kidneys is performed during filling and voiding of the bladder. Immediately following the first voiding, the bladder may be refilled with saline for a second cycle of voiding and imaging, without the need of a second SonoVue administration. A low mechanical index (≤ 0.4) is recommended for imaging the bladder, ureters, and kidney during ultrasonography of the urinary tract with contrast. **4.3 Contraindications** Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. Intravenous use of SonoVue is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure > 90 mmHg), uncontrolled systemic hypertension, and in patients with adult respiratory distress syndrome. SonoVue must not be used in combination with dobutamine in patients with conditions suggesting cardiovascular instability where dobutamine is contraindicated. **4.4 Special warnings and precautions for use Hypersensitivity reactions** In the event of an anaphylactic reaction, beta blockers (including eye drop preparations) may aggravate the reaction. Patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions. *Intravenous use* **Patients with unstable cardiopulmonary status** ECG monitoring should be performed in high-risk patients as clinically indicated. It is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the administration of SonoVue. Use extreme caution when considering the administration of SonoVue in patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders because in these patients allergy like and/or vasodilatory reactions may lead to life threatening conditions. SonoVue should only be administered to such patients after careful risk/benefit assessment and a closely monitoring of vital signs should be performed during and after administration. It should be emphasised that stress echocardiography, which can mimic an ischaemic episode, could potentially increase the risk of SonoVue utilisation. Therefore, if SonoVue is to be used in conjunction with stress echocardiography patients must have a stable condition verified by absence of chest pain or ECG modification during the two preceding days. Moreover, ECG and blood pressure monitoring should be performed during SonoVue-enhanced echocardiography with a pharmacological stress (e.g. with dobutamine). **Chronic obstructive pulmonary disease** Caution is advised when SonoVue is administered to patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease. **Other concomitant diseases** Caution is advisable when administering the product to patients with: acute endocarditis, prosthetic valves, acute systemic inflammation and/or sepsis, hyperactive coagulation states and/or recent thromboembolism, and end-stage renal or hepatic disease, as the numbers of patients with those conditions who were exposed to SonoVue in the clinical trials were limited. **Patients on mechanical ventilation or with unstable neurological diseases** SonoVue is not suitable for use in ventilated patients, and those with unstable neurological diseases. **Interpretation of voiding urosonography with SonoVue and limitations of use** False negative cases can occur with voiding ultrasonography with SonoVue and have not been clarified (see section 5.1). **Technical recommendation** In animal studies, the application of echo-contrast agents revealed biological adverse reactions (e.g. endothelial cell injury, capillary rupture) by interaction with the ultrasound beam. Although these biological side effects have not been reported in humans, the use of a low mechanical index is recommended. **Excipients** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. **4.5 Interaction with other medicinal products and other forms of interaction** No interaction studies have been performed. **4.6 Pregnancy, lactation, and fertility Pregnancy** No clinical data on exposed pregnancies are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical safety data). As a precautionary measure, it is preferable to avoid the use of SonoVue during pregnancy. **Breastfeeding** It is not known if sulphur hexafluoride is excreted in human milk . However, based on its rapid elimination from the body via the expired air, it is considered that the breastfeeding can be resumed two to three hours after administration of SonoVue. **Fertility** No clinical data are available. Animal studies do not indicate harmful effects on fertility. **4.7 Effects on ability to drive and use machines** SonoVue has no or negligible influence on the ability to drive and use machines. **4.8 Undesirable effects Adult population-Intravenous use** The safety of SonoVue after intravenous administration was evaluated in 4653 adult patients who participated in 58 clinical trials. The undesirable effects reported with SonoVue after intravenous administration were, in general, non-serious, transient and resolved spontaneously without residual effects. In clinical trials, the most commonly reported adverse reactions after intravenous administration are: headache, injection site reaction, and nausea. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < /100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reactions Frequency Category		
	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Not known Cannot be estimated from available data
Immune system disorders		Hypersensitivity*	
Psychiatric disorders		Insomnia	
Nervous system disorders	Headache, paraesthesia, dizziness, dysgeusia	Sinus headache	Vasovagal reaction
Eye disorders		Vision blurred	
Cardiac disorders			Myocardial infarction** Myocardial ischemia**
Vascular disorders	Flushing	Hypotension	
Respiratory, thoracic and mediastinal disorders	Pharyngitis		
Gastrointestinal disorders	Nausea, Abdominal pain		
Skin and subcutaneous tissue disorders	Pruritus, rash		
Musculoskeletal, connective tissue and bone disorders	Back pain		
General disorders and administration site conditions	Chest discomfort, injection site reaction, feeling hot	Chest pain, pain, fatigue	
Investigations	Blood glucose increased		

*Cases suggestive of hypersensitivity may include: skin erythema, bradycardia, hypotension, dyspnoea, loss of consciousness, cardiac/cardio-respiratory arrest, anaphylactic reaction, anaphylactoid reaction or anaphylactic shock. **In some of the cases of hypersensitivity, in patients with underlying coronary artery disease, myocardial ischemia and/or myocardial infarctions were also reported.

In very rare cases, fatal outcomes have been reported in temporal association with the use of SonoVue. In all these patients there was a high underlying risk for major cardiac complications, which could have led to the fatal outcome. **Paediatric population - Intravesical use** The safety of SonoVue after intravesical administration was based on evaluation of published literature involving use of SonoVue in over 6000 paediatric patients (age range 2 days to 18 years). No adverse reactions were reported. **Reporting of suspected adverse reactions** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **4.9 Overdose** Since there have been no cases of overdose reported to date, neither signs nor symptoms of overdose have been identified. In a Phase I study doses up to 56 mL of SonoVue were administered to normal volunteers without serious adverse events being reported. In the event of overdose occurring, the patient should be observed and treated symptomatically. **5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties Pharmacotherapeutic group: Ultrasound contrast media. ATC code: V08DA05.** Sulphur hexafluoride is an inert, innocuous gas, poorly soluble in aqueous solutions. There are literature reports of the use of the gas in the study of respiratory physiology and in pneumatic retinopexy. The addition of sodium chloride 9 mg/mL (0.9%) solution for injection to the lyophilised powder followed by vigorous shaking results in the production of the microbubbles of sulphur hexafluoride. The microbubbles have a mean diameter of about 2.5 µm, with 90% having a diameter less than 6 µm and 99% having a diameter less than 11 µm. Each millilitre of SonoVue contains 8 µL of the microbubbles. The intensity of the reflected signal is dependent on concentration of the microbubbles and frequency of the ultrasound beam. The interface between the sulphur hexafluoride bubble and the aqueous medium acts as a reflector of the ultrasound beam thus enhancing blood echogenicity and increasing contrast between the blood and the surrounding tissues. *Intravenous use* At the proposed clinical doses for intravenous administration, SonoVue has been shown to provide marked increase in signal intensity of more than 2 minutes for B-mode imaging in echocardiography and of 3 to 8 minutes for Doppler imaging of the macrovasculature and microvasculature. *Intravesical use* For ultrasonography of the excretory urinary tract in paediatric patients, after intravesical administration, SonoVue increases the signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis, and facilitates the detection of reflux of fluid from the bladder into the ureters. The efficacy of SonoVue for detection/exclusion of vesicoureteral reflux was studied in two published open label single centre studies. The presence or absence of vesicoureteral reflux with SonoVue ultrasound was compared to the radiographic reference standard. In one study including 183 patients (366 kidney-ureter units), SonoVue ultrasound was correctly positive in 89 out 103 units with reflux and correctly negative in 226 out of 263 units without reflux. In the second study including 228 patients (463 kidney-ureter units), SonoVue ultrasound was correctly positive in 57 out of 71 units with reflux and correctly negative in 302 out of 392 units without reflux. **5.2 Pharmacokinetic properties** The total amount of sulphur hexafluoride administered in a clinical dose is extremely small, (in a 2 mL dose the microbubbles contain 16 µL of gas). The sulphur hexafluoride dissolves in the blood and is subsequently exhaled. After a single intravenous injection of 0.03 or 0.3 mL of SonoVue/kg (approximately 1 and 10 times the maximum clinical dose) to human volunteers, the sulphur hexafluoride was cleared rapidly. The mean terminal half-life was 12 minutes (range 2 to 33 minutes). More than 80% of the administered sulphur hexafluoride was recovered in exhaled air within 2 minutes after injection and almost 100% after 15 minutes.In patients with diffuse interstitial pulmonary fibrosis, the percent of dose recovered in expired air averaged 100% and the terminal half-life was similar to that measured in healthy volunteers. **5.3 Preclinical safety data** Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and toxicity to reproduction. Caecal lesions observed in some repeat-dose studies with rats, but not in monkeys, are not relevant for humans under normal conditions of administration. Intravesical local tolerance for SonoVue was also assessed. A single-dose study and a repeat-dose study, both followed by a treatment-free period, were performed in female rats with local toxicity evaluated through macroscopic and histopathological examination of both kidneys, ureters, the urinary bladder and urethra. It did not reveal any test item-related lesions in any of the examined organs, in particular in the urinary bladder, in both the single-dose and the repeat-dose studies. It was therefore concluded that SonoVue is well tolerated in the urinary tract in the rat. **6. PHARMACEUTICAL PARTICULARS 6.1 List of excipients Powder:** Macrogol 4000, Distearoylphosphatidylcholine, Dipalmitoylphosphatidylglycerol Sodium, Palmitic acid **Solvent:** Sodium chloride 9 mg/mL (0.9%) solution for injection. **6.2 Incompatibilities** This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. **6.3 Shelf life** 2 years. Once reconstituted, chemical and physical stability has been demonstrated for 6 hours. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user. **6.4 Special precautions for storage** The medicinal product does not require any special storage conditions. For storage conditions after reconstitution of the medicinal product, see section 6.3. **6.5 Nature and contents of container** Type I colourless glass vial containing 25 mg of dry, lyophilised powder in an atmosphere of sulphur hexafluoride closed with a grey butyl rubber stopper and sealed with an aluminium crimp seal with a flip-off disc. A transfer system (MiniSpike). Type I clear glass pre-filled syringe containing 5 mL sodium chloride 9 mg/mL (0.9%) solution for injection. **6.6 Special precautions for disposal** Before use examine the product to ensure that the container and closure have not been damaged. SonoVue must be prepared before use by injecting through the septum 5 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to the contents of the vial. The vial is then shaken vigorously for twenty seconds after which the desired volume of the dispersion can be drawn into a syringe as follows: **1** Connect the plunger rod by screwing it clockwise into the syringe. **2** Open the MiniSpike transfer system blister and remove syringe tip cap. **3.** Open the transfer system cap and connect the syringe to the transfer system by screwing it in clockwise. **4** Remove the protective disk from the vial. Slide the vial into the transparent sleeve of the transfer system and press firmly to lock the vial in place. **5** Empty the contents of the syringe into the vial by pushing on the plunger rod. **6** Shake vigorously for 20 seconds to mix all the contents in the vial to obtain a white milky homogeneous liquid. **7** Invert the system and carefully withdraw SonoVue into the syringe. **8** Unscrew the syringe from the transfer system. Do not use if the liquid obtained is clear and/or if solid parts of the lyophilisate are seen in the suspension. SonoVue should be administered immediately by injection into a peripheral vein for use in echocardiography and in vascular Doppler imaging in adults or by intravesical administration for use in ultrasonography of the excretory urinary tract in paediatric patients. If SonoVue is not used immediately after reconstitution the microbubble dispersion should be shaken again before being drawn up into a syringe. Chemical and physical stability of the microbubble dispersion has been demonstrated for 6 hours. The vial is for a single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. **7. MARKETING AUTHORISATION HOLDER** Bracco International B.V. Strawinskylaan 3051 NL - 1077 ZX Amsterdam The Netherlands **8. MARKETING AUTHORISATION NUMBERS** EU/1/01/177/002 **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 26 March 2001 Date of latest renewal: 24 April 2006 **10. DATE OF REVISION OF THE TEXT** 24/08/2017

The importance of ultrasound in modern diagnostic and interventional radiology

Imaging in general is an indispensable part of modern medicine, with ultrasound playing a particularly important role. Thanks to continuing technological innovations, many modern ultrasound systems now contain advanced features which previously were limited to top-of-the-range models.This has contributed to the expansion of applications of the technique, now in routine use in many Point-of Care applications. Other recent advances involve fusion of real-time ultrasound images with datasets from other 3D imaging modalities such as MRI, CT & PET — an approach which is having a significant impact in interventional radiology.

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Prof. Giancarlo Bizzarri talks about his experiences with modern ultrasound imaging and the future potential of the technology

Q *In your opinion just how important is ultrasound in today's radiology departments and what are the main ta+sks that are best carried out by ultrasound imaging ?*

Well, let's remember first of all that ultrasound is a powerful medical imaging technology that does not involve the use of ionizing radiation, so it is safe, has no side effects, and offers an unmatched real-time imaging capability. It is a complete diagnostic tool with clinical applications in all medical fields, and is particularly suitable for diagnostic use during pregnancy, in neonates, pediatrics and in adults. The technology can be used to examine the thorax, abdomen, heart, soft tissue, musculoskeletal structures, blood vessels, and the brain.

Figure 1. The power of ultrasound has been significantly increased over the last decade by the development of several new technologies such as color Doppler, contrast-enhanced ultrasound (CEUS), harmonic imaging and elastography.

Over the last decade, the power of ultrasound has been significantly increased through the introduction of several technical developments, such as color-Doppler, contrast enhanced ultrasound, harmonic imaging, and elastography [Figure 1].

Nowadays, many medical specialists other than radiologists make regular use of ultrasound in their daily practice. For example, ultrasound is frequently used outside radiology departments as "point of care" or "bed-side" ultrasound while, thanks to its flexibility and ease-of-use, ultrasound has been successfully introduced in emergency departments.

But we have also to remember that such diagnostic applications are just one side of the ultrasound coin — the real-time nature of ultrasound has resulted in its increasing use to guide interventional procedures.

For example, in our department of Interventional and Diagnostic Radiology, although the number of diagnostic ultrasound examinations has been reducing over time, 90% of all interventional procedures are now performed with the exclusive or combined use of ultrasound.
In terms of overall usage of ultrasound, the reduction in the number of ultrasound examinations carried out in the radiology department has been compensated by the increase in ultrasound in Point-of-Care applications. It should be noted however that the use of ultrasound in the radiology department has the advantage of cost-efficiency since it is possible to justify specific accessories necessary for particular applications e.g. software,, probes, etc., around a single central system that would not be possible in several different POC systems.

Figure 2. Modern ultrasound systems are intuitive and easy to use, with the result that the ultrasound specialist can focus on the patient, rather than on manipulating the system itself.

Q *You mentioned ease-of-use of modern ultrasound systems. Just how important is this?*

The constant requirement for increased productivity in hospitals, diagnostic centers and private practices has been one of the main driving forces behind the simplification of the practical use of ultrasound systems. The need for reduced costs and optimization of the available resources has been a huge stimulus to the development of ultrasound instruments, one example being that advanced features which used to be only available on large top-of-the-range systems can now be found on compact and portable devices.
The widespread and growing use of ultrasound has caused industry to focus on design, ergonomics, and ease of use of systems[Figure 2]. The development of intuitive and simple user interfaces has allowed the operator to focus on the patient rather than on manipulating the system itself, with the result that diagnostic confidence has also been increased. In addition, the introduction of purely digital scanners makes it possible to produce easy-to-use, self-adjusting equipment, which has stimulated the main semiconductor manufacturing companies to begin large-scale production of integrated circuits specially for ultrasound systems.
This has resulted in a further reduction of costs and equipment miniaturization, which in turn has led to more widespread use of advanced diagnostic technology in fields which until a few years ago were considered exotic, such as in ambulances and rescue vehicles, in playgrounds, in military applications and even in space stations.

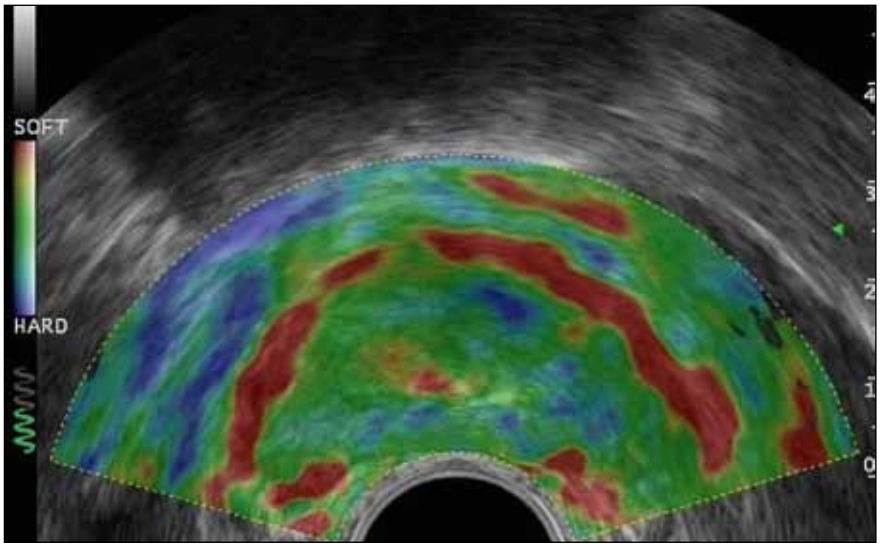

Figure 3. Strain elastography or shear wave techniques are highly promising for the characterization of thyroid, breast, musculoskeletal, prostate, and hepatic lesions

Q *So looking forward now, what are the main emerging developments which are likely have an impact on everyday clinical practice?*

Diagnostic ultrasound is a varied and complex field, and some approaches are more effective than others at providing high-tech answers to current requirements in radiology. Highly promising developments include:

- Non-invasive measurement of tissue elasticity using strain elastography or shear wave techniques is highly

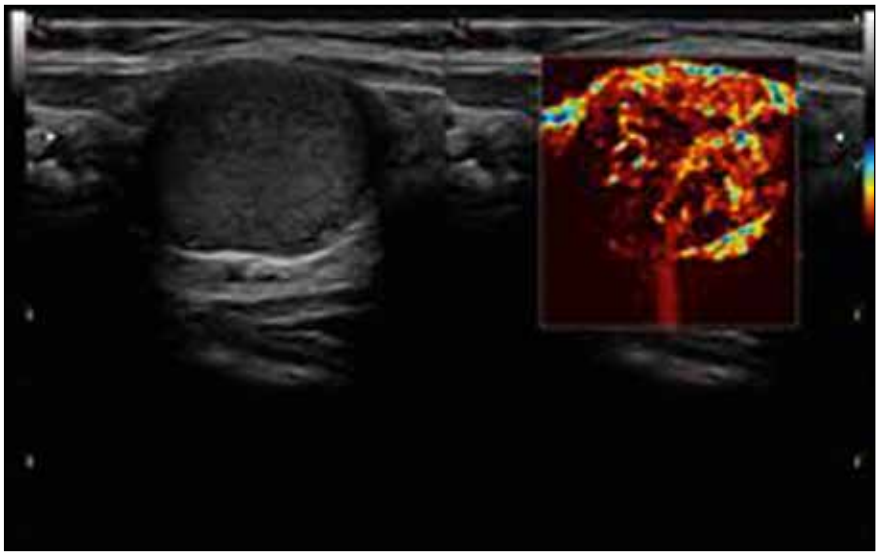

Figure 4. New algorithms for advanced hemodynamic evaluation such as Esaote microV allow the detection of low-velocity blood flow and microvascularisation, for example in thyroid lesions, breast cancer, or in the early diagnosis of degenerative rheumatic disease.

useful for the characterization of thyroid, breast, musculoskeletal, prostate, and hepatic lesions [Figure 3].

• The introduction of new algorithms for color Doppler in advanced hemodynamic analysis allows the detection of low-velocity blood flow and microvascularization, for example in the presence of thyroid lesions, breast cancer, or in the early diagnosis of degenerative rheumatic disease. [Figure 4].

• Contrast-enhanced ultrasound (CEUS) has high sensitivity, deep penetration and high resolution. In addition, in the near future tissue-specific contrast media agents are likely to be available for a wide range of clinical applications. Speaking of contrast agents, it should be noted that there are no issues with the safety of ultrasound contrast agents. This is in contrast to the current debate on the significance of recent findings showing the deposition in the brain of gadolinium from Gadolinium Based Contrast Agents used in MRI

• Real-time image fusion techniques allow ultrasound to be spatially co-registered with multiple image diagnostic modalities, such as those from MRI, CT, PET, and scintigraphy, to create a virtual environment that maximizes anatomic localization and lesion characterization [Figure 5]. This advanced multimodal imaging has applications in both diagnostics and, more importantly, in minimal-invasive surgery techniques and interventional procedures involving organs such as the liver, prostate, neck, spine, and even the lungs and head, thus increasing diagnostic and localization accuracy and reducing radiation doses, time, and costs.

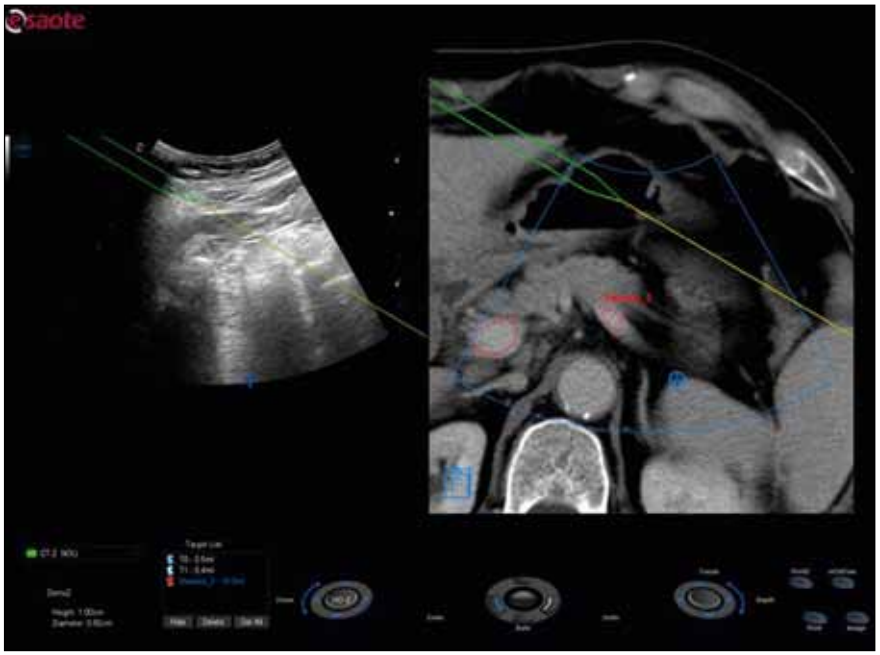

Figure 5 Real-time image fusion techniques allow ultrasound to be spatially co-registered with multiple volumetric image diagnostic modalities, such as those from MRI, CT, PET, and scintigraphy,

Q *This multimodal, real-time approach combining ultrasound and MRI, PET, and CT datasets seems to be a very hot topic nowadays. Just exactly what are the main benefits of this approach?*

As I said, we can combine the top performance and exclusive solutions of ultrasound systems with the specific information offered by MRI, PET, CT, and scintigraphy. Specifically developed for interventional imaging, fusion imaging technology provides additional clarity and precision when ultrasound-guided interventional procedures are required [Figure 6].

Interventional radiology (IR) requires dedicated features and solutions to allow the optimal management of many kinds of clinical problems. In radiology, we have access to various types of imaging techniques such as MRI, CT, PET, fluoroscopy, nuclear medicine imaging, etc., but in order to provide the best patient care, it is often not enough to use just one of these techniques. Image fusion merges real-time ultrasound data such as Doppler, CEUS, and Elastosonography with the functional 3D information from other systems.

In this way, we can combine the advantages of real-time ultrasound imaging with the benefits of the other modalities, not only in the abdominal area (especially for the liver and kidneys), but also in a whole-body radiology approach that can offer benefits in pain management medicine, neurology, urology, and even endocrinology.

By merging information from different modalities, fusion imaging technology

Figure 6. Specifically developed for interventional imaging, fusion imaging technology provides additional clarity and precision when ultrasound-guided interventional procedures are required.

can also provide a real-time, accurate, low-cost, and radiation-free solution in the field of research and teaching.

Q *So this three-dimensional approach seems to becoming increasingly accepted in IR, but what about two-dimensional images?*

The cognitive localization of lesions with real-time ultrasound while still making use of secondary 2D technology represents a significant challenge in everyday clinical practice.

Recently, an advanced technique has been developed that makes it possible to precisely locate a lesion or other anatomical landmark on real-time ultrasound via co-registration of the probe position with a 2D secondary modality, instead of simply guessing the correct position of the probe in a cognitive way. In our experience, the use of these body mapping technologies with x-rays and scintigraphy can result in a high level of accuracy, with very easy matching and precise real-time tracking. These new 2D mapping techniques provide significant support in the accurate diagnosis and proper planning of surgical and interventional procedures [Figure 7]

Figure 7. New 2D mapping techniques provide significant support in the accurate diagnosis and proper planning of surgical and interventional procedures

Q *So could this become more of a "point of care approach", not strictly related to classical radiology?*

Because techniques such as BodyMap 2D virtual navigation, 3D fusion imaging, and virtual biopsy can increase the diagnostic confidence in different parts of the body, there are countless possible applications in urology, endocrinology, pneumology and hepatology, gynecology, and many more fields, each having its dedicated interface and tools.

Simplified and automatic fusion technologies and customized protocols will reduce the learning curve for the operator, and will thus help to make all these techniques more widespread.

Multipurpose equipment, oriented to the productivity of cross-functional departments, and of application in fields as varied as lung biopsy, back pain, renal ablation to name but a few, will make it possible to provide a real shared ultrasound service, as we already see in interventional radiology today.

Q *What about new developments in this innovative approach and likely future impact?*

Nowadays, the main efforts in the field of medical imaging are being directed towards prevention, diagnosis, selection of optimal (i.e. personalized) local or systemic therapy, guidance in local treatment, assessment of the result of therapy, both local or systemic, and monitoring of disease progression. All these objectives require information to be not only archived and communicated, but also co-registered and processed by fusion and virtual reality software algorithms.

In the near future, these new technologies will be integrated into all imaging and diagnostic modalities, PACs, Oncology Information Systems, and Hospital Information Systems, thus going beyond the simple radiological environment and spreading throughout all diagnostic and therapeutic fields.

Agfa considers making its HealthCare IT unit a stand-alone entity to focus growth

Radiologists mostly know of Agfa through its extensive range of analogue and digital imaging systems and IT solutions for the healthcare sector, but the company also develops and markets a range of imaging products designed for the printing industry. as well as for specific industrial applications.

Now, in an announcement issued at the end of August' Agfa confirmed that the company's board of directors has asked the management to study how to organize the HealthCare IT activities into a stand-alone legal entity structure and organization within the Agfa-Gevaert Group

Increasing the independence of the HealthCare IT activities would be a natural progression in the continued transformation of the group. In such a set-up, HealthCare IT would be able to increase its focus on the large and attractive markets in which it is already present. The main part of the Agfa-Gevaert Group, which would consist of Agfa Graphics, Agfa Specialty Products and Agfa HealthCare's Imaging business, would also be better positioned to pursue growth, profitability and new opportunities.

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Filling the gap in European ultrasound training

FUJIFILM SonoSite continues to attach a lot of importance in ultrasound training and education, helping clinicians to develop and maintain their practical skills in a variety of ultrasound disciplines. Learning a new ultrasound procedure or technique can be challenging – particularly if the participant feels not to have adequate understanding or training – and it remains a barrier to clinicians making the transition to using ultrasound in everyday practice.

That's why FUJIFILM SonoSite established its education centre in Luton, UK: to provide expert training and instruction to support the learning needs of doctors, nurses and practitioners across a broad range of disciplines.

Every month, people from all over Europe take part in the ultrasound courses, delivered and designed by point-of-care specialists from the medical industry, with, for example backgrounds in regional anaesthesia, EMED, critical care and musculoskeletal treatment. The course attendees, often with little or no experience of daily ultrasound use, are provided with expert tuition and plenty of opportunities to ask questions, and gain confidence and experience using ultrasound carried out on the Blue Phantom ultrasound training model.

Recently, as part of its drive to continually improve and expand its educational services, FUJIFILM SonoSite hosted a complete ultrasound-guided regional anaesthesia education (CURE) course at its training centre. The two-day event featured a new extended format that provided more extensive, in-depth ultrasound training than ever before, delivered by experienced, friendly consultants. The well-received course, taught through a mixture of mini lectures, video presentations and practical sessions, described the use of point-of-care ultrasound for regional anaesthesia – including brachial plexus, lumbar plexus and truncal blocks – and beginning with a review of the anatomy and indications for each type of block. Participant numbers were deliberately limited to ensure maximum hands-on time, and the practical sessions featured a mix of live model scanning and ultrasound-guided needle placement in phantoms, with an emphasis on individual tuition and feedback from course tutors.

Anyone who missed the last CURE course, is warmly invited to attend the next course scheduled for the 30th of October 2017, which qualifies for CPD credits from the Royal College of Anaesthetists, and counts towards the European Diploma in Regional Anaesthesia and Acute Pain Management (EDRA).

Throughout October and November, FUJIFILM SonoSite will be running further courses in ultrasound-guided venous access, Level 1 emergency medical ultrasound, and scanning techniques for musculoskeletal soft tissue and joints. The company has also teamed up with USabcd to offer a one-day course aimed at critical care physicians and surgeons exploring focused intensive care echocardiography (FICE).

To register for upcoming courses, and to learn more about other FUJIFILM SonoSite educational initiatives, visit:
www.sonositeeducation.com

Siemens Healthineers' visualization experts in cinematic rendering nominated for the highly prestigious German Future Prize 2017

Dr Robert Schneider(left), Dr Klaus Engel (centre) , of Siemens Healthineers and Prof. Franz Fellner of the Kepler University Hospital in Linz are nominees for the 2017 German Future Prize. Photo copyright Deutscher Zukunftspreis

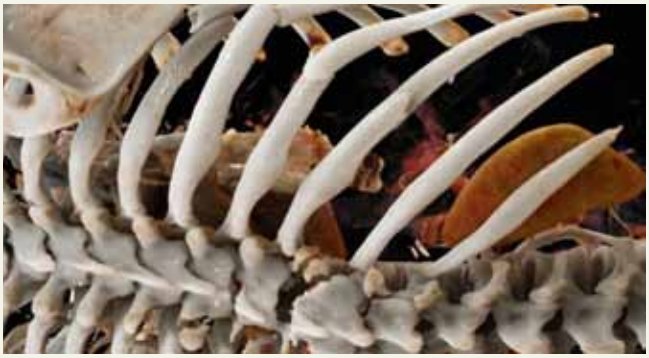
Dr. Klaus Engel and Dr. Robert Schneider from Siemens Healthineers are members of three research teams put forward for the highly prestigious German Future Prize award. Together with Dr Engel and Di Schneider is Professor Franz Fellner, MD, head of the Central Radiology Institute at Kepler University Hospital in Linz. The three nominees are jointly responsible for developing the medical visualization technology known as Cinematic Rendering, which allows photorealistic representations of clinical image data The technology facilitates communication between patients and referring physicians, supports surgeons in the choice of surgical strategies and opens up new opportunities in medical training.

The German Future Prize is awarded by the President of Germany, Dr. Frank-Walter Steinmeier, and is one of the country's highest distinctions for technology and innovation.

Cinematic Rendering technology, developed by the two visualization experts and their clinical partner, generates photorealistic three-dimensional representations of the human body from the output of CT and MRI scans. Using the radiological software Syngo.via and Syngo.via Frontier, the technique enables previously unseen levels of clarity. These striking new images simplify communication between physicians and patients or between radiologists and referring clinicians, help surgeons select the most appropriate surgical strategy, and open up new horizons in medical training.

The German Future Prize will be awarded on November 29, 2017. "The nomination for the German Future Prize of two of our leading visualization experts and one of our clinical research partners is a great honor for our company – and a testament to our sustained investment in innovation," said Dr. Bernd Montag, CEO of Siemens Healthineers. More than 12,500 patents have been registered to Siemens Healthineers employees, while in the 2016 business year alone the company invested around a billion euros in research and development – a field in which it employs some 7,500 people. Siemens Healthineers also draws on a collaborative network comprising over 4,200 research partners all over the world. "Time and again, our close collaboration with clients and research partners has enabled us to pioneer groundbreaking innovations in countless areas of medical technology and quickly bring them to market, benefiting users and boosting efficiency in healthcare systems worldwide, but above all increasing patient well-being. For many people, Cinematic Rendering offers the first real insight into what is going on inside their body. This example highlights the broad range of opportunities originating from the digitalization of healthcare," Montag explained.

Inspired by film technology and the physics of light Klaus Engel and Robert Schneider developed the new visualization technology taking inspiration from film technology, and refined it in collaboration with Franz Fellner. Cinematic Rendering provides unprecedented photorealistic clinical images by leveraging the physics of light. A specially developed algorithm simulates the complex interactions of elementary light particles (photons) with patient data from CT or MRI scans. Unlike animations in the film industry, where only the light reflected off the surface of the character's body is calculated, the algorithm developed by the researchers from Siemens Healthineers also takes into account the light which penetrates the subject's tissue, where it is scattered in different directions. This results in hyper-realistic representations of fractures, organs or the structure of the finest blood vessels.



An example of the astonishing images produced by Cinematic Rendering. The above image shows fractures of the thoracic vertebrae and ribs

Since early 2017, users of the imaging software Syngo.via have been able to create photorealistic images from any CT or MRI scan. These images can be used for instance to explain a planned operation to a patient, but also between radiologists and referring physicians. The photorealistic images can vividly illustrate the course of a fracture line or the growth of a tumor. The creation of the images does not involve any additional radiation exposure, as rendering takes place entirely in the postprocessing stage with just a few mouse clicks.

The German Future Prize was founded in 1997 by the then German President Dr. Roman Herzog, and has since come to symbolize the country's scientific potential and innovative spirit. Besides excellence in research, the main selection criteria used by the jury include the development's patentability and market viability of the technology development being considered.

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New editor-in -chief of European Radiology

The European Society of Radiology (ESR) has announced that Prof. Yves Menu of the Hôpital Saint Antoine, Paris, has been appointed as the new Editor-in-Chief of its scientific journal European Radiology. Menu will take over from Prof. Maximilian F. Reiser, from Munich, who steps down from the position in late 2017.

The ESR is "very happy and pleased to appoint such an outstanding and well-respected leader and friend of the ESR to this prestigious position," said Prof. Paul M. Parizel, Chair of the ESR Board of Directors. Following an application procedure and a thorough review process, Prof. Yves Menu was unanimously appointed by the ESR Executive Council and he will officially assume his position as Editor-in-Chief as of 2018. The January issue of European Radiology will contain Menu's selection of manuscripts. A gradual handover of duties between the current and future Editor-in-Chief has already started in autumn 2017.

Prof. Yves Menu is an outgoing Professor of Radiology at the Saint Antoine Hospital and University Pierre & Marie Curie, Paris. "It is an honour to follow in the footsteps of such prominent editors. I have had the pleasure of working with Prof. Reiser before, and I am looking forward to taking over from him and to this new and exciting endeavour," stated Menu.

Menu is a long-time member of the ESR and is well known within the radiological community in Europe and beyond.

During his initial term of three years, Prof Menu will focus on further establishing the journal as Europe's number one general journal for clinical radiology. His editorship will focus on optimising workflows and editorial procedures, as well as strengthening the Impact Factor, which is currently 3.967 for the year 2016, and enhancing compliance with international publishing and research standards. "Competition in scientific publishing is high, and there are a lot of new publications on the market; we must make sure that we maintain our ESR brand and stay at the forefront of quality and science in order to serve our community," said Menu.

www.european-radiology.org

Guerbet streamlines its contrast media portfolio

Partly as a result of the recent decision by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) to withdraw the licence to market for certain linear gadolinium-based contrast agents GBCAs, and also partly as a result of its acquisition of Mallinckrodt's contrast media & delivery systems, Guerbet, the French-based company specialised in contrast products and solutions for medical imaging, has announced that it has taken measures to streamline its brand portfolio. It will phase out sales throughout the world of two products: Hexabrix (meglumine and sodium ioxaglate) and Optimark (gadoversetamide). In 2015, the company already announced the withdrawal in the US of Hexabrix, an iodinated contrast medium for X-ray imaging that has the same indications as two other Guerbet products, namely Optiray (ioversol) and Xenetix (iobitridol). Now Hexabrix sales in Europe, Asia and Latin America will progressively be phased out, to be completely removed from the market by the end of 2019 at the latest. Guerbet markets Optiray and Xenetix in more than 70 countries.

Guerbet's decision to phase out Optimark is also part of its product portfolio prioritization. Optimark and Dotarem (gadoteric acid) are both gadolinium-based contrast agents (GBCAs) and have similar indications for MRI. Optimark is a linear agent and faces decreasing worldwide demand, while Dotarem, a macrocyclic and ionic GBCA agent, has seen worldwide demand increase. This move to streamline its gadolinium-based contrast agent portfolio through a focus on Dotarem is consistent with recent recommendations of the PRAC committee to withdraw the licence to market of linear GBCAs but not macrocyclic GBCAs.

www.guerbet.com

New president & CEO of GE Healthcare Europe appointed

Catherine Estrampes has been announced as President & CEO for GE Healthcare Europe, effective as from 1 October 2017' Estrampes will report to Kieran Murphy, GE Healthcare CEO. "Catherine brings strong experience from her career with GE Capital and more recently managing GE Healthcare's U.S. Central Zone. Her vision and leadership skills will be key assets as we continue to grow our business in the region, providing the best solutions and services to help improve outcomes for Europe's healthcare systems and patients," said Kieran Murphy. Catherine began her career at GE Healthcare in France in 1988 where she held business and marketing leadership positions for the Cardiology/Interventional and CT product lines. She moved to the U.S. in 1999 with GE Capital where she held several General Manager positions. Catherine then returned to GE Healthcare in 2010 in the position of General Manager in Mid America. In 2013, her responsibilities were expanded to General Manager U.S. & Canada Central Zone with responsibilities spanning the GE Healthcare portfolio. Catherine returned to the Europe organization earlier this year as Imaging Leader.

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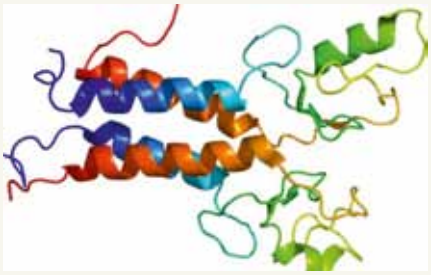
1. Data on file and from public sources, 2017.

U.S. guidelines for management of hereditary breast and ovarian cancer syndrome updated

BRCA1 and *BRCA2* mutations account for 4% of breast cancer cases and up to 24% of epithelial ovarian cancer cases, making these mutations the most common cause of hereditary breast and ovarian cancer syndrome. The estimated risk for breast cancer by the age of 70 is 45% to 85% (*BRCA1* or 2) and, for ovarian cancer, 39% to 46% (*BRCA1*) or 10% to 27% (*BRCA2*). The prevalence of *BRCA* mutations is relatively high in certain populations (e.g., 1 in 40 among Ashkenazi Jews of European



The BRCA1 protein shown above is expressed by the *BRCA1* gene and is involved in the repair of DNA. Mutations in the gene mean that DNA repair is adversely affected

ancestry). Now, the American College of Obstetricians and Gynecologists (ACOG) has updated its guidance for assessing and managing hereditary breast and ovarian cancer. The key recommendations are:

- Genetic counseling should be offered to all women with epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer).
- Genetic testing should be offered when counseling indicates an inherited cancer syndrome.
- In *BRCA* mutation carriers and women with personal or family histories of ovarian cancer, routine screening with CA 125 measurement or transvaginal ultrasound is not recommended.
- Breast cancer surveillance for mutation carriers is age-dependent.

i) 25–29: clinical breast examination every 6 to 12 months and breast imaging annually (optimally MRI with contrast).

ii) ≥30: annual mammography and MRI, alternating every 6 months.

- *BRCA* mutation carriers should be offered risk-reducing bilateral mastectomy and bilateral salpingo-oophorectomy (the latter is recommended at age 35–40 for *BRCA1* or age 40–45 for *BRCA2*).

Dr Andrew Kaunitz, professor and associate chair of the OB/GYN department at the University of Florida College of Medicine in Jacksonville, FL, USA commented on the guidelines as follows. "*ACOG advises that genetic counseling should precede genetic testing. Such counseling should include pedigree and risk assessment and, to guide informed consent, information about benefits, harms, and possible outcomes of genetic testing. In addition, counseling should address the implications of disclosure or nondisclosure of results to family members. Clinicians without the required expertise in cancer genetics should refer patients to a genetic counselor (as I do in my practice). If in-person counseling is not available, qualified telephone-based services represent another good option* "
www.acog.org

Study shows MRI effective in detecting postpartum cancers

Pregnancy-associated breast cancer, which is rare but often aggressive, was detected with MRI in 98% of cases reviewed according to a recently published article (*Myers KS et al. Imaging Appearance and Clinical Impact of Preoperative Breast MRI in Pregnancy-Associated Breast Cancer. AJR Am J Roentgenol. 2017; 209: W177*)

The study reviewed cases of patients who had given birth within the previous 12 months. Breast MRI showed a sensitivity of 98% and changed the surgical management for 28% of those patients. The study's authors, led by Kelly S. Myers of the Department of Radiology

at Johns Hopkins Hospital, said breast MRI may play an important role in the management of pregnancy-associated breast cancers.

The study included 53 women, nine of whom presented during pregnancy and 44 during the first year postpartum. The sensitivity rate of MRI was 98%, or 52 of the 53 patients. The authors said the study markedly expands on the current literature regarding breast MRI for patients with pregnancy-associated breast cancer. Although the study covered only 53 patients, the authors said it is to their knowledge the largest series of breast MRI examinations performed in the setting of pregnancy-associated breast cancer, showing that further research is warranted.

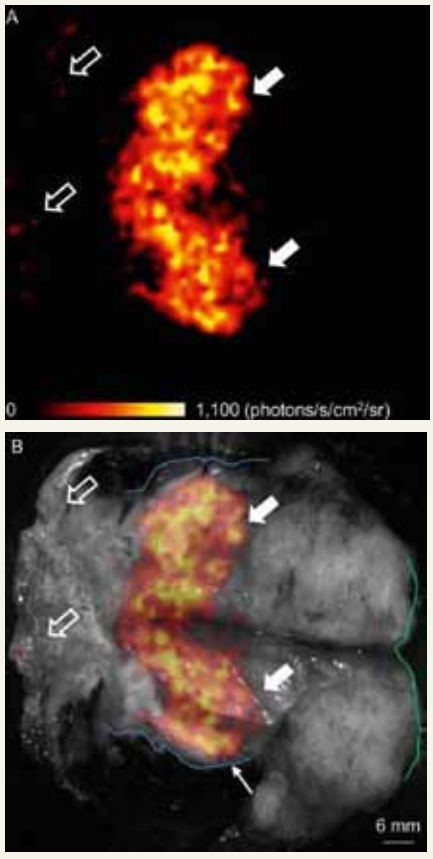
"Preoperative planning is especially important for patients with pregnancy-associated breast cancer because of the often aggressive nature of these cancers," the study said. "In contrast to the previous assumption that breast MRI would be of limited utility in this population, we found that it showed a pathologically proven larger tumor size or greater extent of disease in 23% of patients."
https://tinyurl.com/Myers-et-al-paper

Combined optical and molecular imaging could guide breast-conserving surgery

Breast-conserving surgery (BCS) is the primary treatment for early-stage breast cancer, but more accurate techniques are needed to assess resection margins during surgery to avoid the need for follow-up surgeries. Now, in a first-in-human study, British researchers have provided a possible solution using Cerenkov luminescence imaging (CLI), which combines optical and molecular imaging by detecting light emitted by the PET radiotracer ^{18}F FDG. (*Grootendorst MR et al. Intraoperative Assessment of Tumor Resection Margins in Breast-Conserving Surgery Using ^{18}F-FDG Cerenkov Luminescence Imaging: A First-in-Human Feasibility Study. J Nucl*

Med. 2017; 58:891)

CLI's high-resolution and small-sized imaging equipment make it a promising technology for assessing tumor margins during breast tumor surgery. ."Currently, approximately 1 in 5 women who undergo breast-conserving surgery, (also known as lumpectomy), require repeat surgery due to inadequate excision of the tumor during the initial surgical procedure," explained Prof A Purushotham, of King's College London, UK. "By accurately assessing tumor resection margins intraoperatively with CLI, surgeons may be able to completely clear the cancer with a single operation, thereby reducing the number of breast cancer patients requiring a second, or even third, surgical procedure. Ultimately this could lead to improved patient care and reduced healthcare costs if confirmed in larger clinical studies."



Top Panel. A Cerenkov image; Bottom Panel Grey-scale photographic image overlaid with the Cerenkov signal. An increased signal from the tumor is visible (white arrows); mean radiance is 871 ± 131 photons/s/cm2/sr, mean TBR is 3.22. Both surgeons measured the posterior margin (outlined in blue) as 2 mm (small arrow); a cavity shaving would have been performed if the image had been available intraoperatively. The medial margin (outlined in green) measured >5 mm by both surgeons. Pathology ink prevented assessing the lateral margin; a phosphorescent signal is visible (open arrows)

This study included 22 patients with invasive breast cancer. ^{18}F FDG was injected 45-60 minutes before surgery. Immediately after the excision of tumors, specimens were imaged intraoperatively in an investigational CLI imaging system. The first 10 patients were used to optimize the imaging protocol; the remaining 12 were included in the analysis dataset. Ten of the 12 patients had an elevated tumor radiance on CLI, and agreement among raters on margin distance was good. Sentinel lymph nodes, which used technetium-99m to facilitate identification, were successfully detected and biopsied in all patients. ^{18}F-FDG CLI is, therefore, a promising, low-risk technique for intraoperative assessment of tumor margins in breast-conserving surgery. A randomized controlled trial will evaluate the impact of this technique on re-excision rates.

Purushotham points out, "The feasibility of intraoperative CLI as shown in this study, in combination with the wide applicability of ^{18}F-FDG across a range of solid cancers, provides a stepping stone for clinical evaluation of this technology in other solid cancer types that also experience incomplete tumor resection due to close or involved margins." He also notes, "CLI offers the ability to image clinically approved and widely used PET tracers intraoperatively by using small-sized imaging equipment, thus expanding the field of traditional nuclear medicine."

https://tinyurl.com/Grootendorst-et-al-paper

Breast cancer patients largely find radiation therapy experience better than expected

A new survey presented at the recent ASTRO meeting has found that the actual radiation therapy experience that breast cancer patients underwent largely exceeded their expectations. The survey, which addressed the fears and misconceptions regarding radiation therapy for breast cancer, found that more than three-fourths of the breast cancer patients surveyed found their experiences with radiation therapy, including overall and specific long-term and short-term side effects to be less "scary" than expected.

"Radiation oncologists know firsthand that our patients come in with fears and sometimes misconceptions. Unlike many other treatments and fields of medicine, it is very hard to imagine what radiation therapy is like," said Dr N Shaverdian, MD, lead author of the study from the David Geffen School of Medicine at the University of California, Los Angeles (UCLA). "Still, it is surprising to find that upwards of 90 percent of women surveyed agree that if future patients knew the reality of the radiation therapy experience, they would be

less afraid of treatment. "Advances in radiation therapy technologies over the past several decades and the increased use of hypofractionation--where radiation is given in larger doses across fewer sessions--have afforded patients more convenient treatment options, as well as lower toxicity rates in many situations," said Dr. Shaverdian.

"Our study shows that women who received modern breast radiation therapy overwhelmingly found the treatment experience far better than expected. The negative stories out there are frightening and pervasive, but they generally are not reflective of the actual experience," added Dr Susan McCloskey, Director of the Breast Service at UCLA Radiation

Oncology and senior author of the study.

Surveys were sent to all patients who received treatment for breast cancer at a UCLA-affiliated multidisciplinary breast cancer clinic between 2012 and 2016. Eligible patients had six or more months of follow-up and were without tumor recurrence. Sixty-five percent of these 502 patients returned surveys, and study findings are based on these 327 responses. The median age of survey respondents was 59 years (range 28-89 years). Patients represented various disease stages; 18 percent had stage 0 breast cancer; 38 percent stage I; 34 percent stage II; and 9 percent stage III. Eighty two percent underwent breast conserving surgery, 13% had axillary dissection, 37% received chemotherapy, and 70% received endocrine therapy. All patients received radiation therapy (RT), delivered as either standard whole-breast RT with or without regional nodal coverage, hypofractionated whole-breast RT, post-mastectomy RT, or partial breast RT.

Patients completed the survey a median of 31 months (range 6-61 months) after completing radiation therapy. Survey questions assessed fears and beliefs about breast cancer treatment and side effects, as well as how the actual experience compared to initial expectations. Specifically, patients were asked if the treatment experience, short-term side effects and long-term side effects were as expected, worse than expected or better than expected.

Nine in ten patients (90%) found the actual experience of breast radiation therapy to be "less scary" than anticipated. Overall short-term and long-term side effects of radiation were better than expected or as expected for 83 percent and 84 percent of respondents, respectively. Patients also reported that side effects were less severe than or as expected for short-term breast pain (75%), skin changes (61%) and fatigue (78%), as well as for long-term appearance changes (85%), breast pain (79%), breast size changes (73%) and breast textural changes (70%).

More than two-thirds (68%) of these breast cancer patients reported that they had little to no prior knowledge of radiation therapy at the time of their diagnosis, yet nearly half (47%) also shared that they had previously read or heard "frightening" stories of serious side effects from radiation therapy. Nearly all women surveyed (94%) responded that they were initially fearful of receiving radiation therapy. The most common initial fears related to radiation therapy were concerns about damage to internal organs (40%), skin burning (24%) and becoming radioactive (7%). Very few patients found confirmation for these negative stories during treatment, however; among 327 respondents, eight women (3%) found the negative stories they previously read about radiation therapy to be true and six women (2%) found the negative stories they heard from family and friends to be true. The trend of finding negative stories to be largely untrue was even more pronounced among patients who underwent breast conservation therapy. Nine in ten survey respondents agreed that "After treatment, I now realize that radiation therapy is not as bad as they say it is," and/or that "If future patients knew the 'real truth' about radiation therapy, they would be less scared about treatment."

"We hope that these data, which reflect the voices of past breast cancer patients, can help to counsel future patients and their physicians on the actualities of the modern breast radiation therapy experience," said Dr. Shaverdian. "Patients who have received this treatment provide the most credible account of its actual impact, and their accounts show that outdated, negative stereotypes of breast radiation are almost universally found to be untrue." http://www.astro.org/annualmeeting.

Study of over 15,000 Asian women shows large variation in compression used in mammography

Current force-standardized protocols used in mammographic examinations have largely been optimized for Caucasian women and thus, Asian women,who generally have smaller breasts, may be being subjected to protocols that aren't suitable for them. A group of researchers from Malaysia have carried out a study to investigate the variability of mammographic compression parameters used in breast imaging in Asia. (*Lau S et al. Mammographic compression in Asian women. PLoS One. 2017 18;12(4):e0175781.*).

The Sensitive SigmaPaddle from the Dutch company Sigmasceening is the first pressure based compression paddle providing real-time pressure information of the whole mammographic breast compression procedure, which can considerably improve compression reproducibility with the aim of arriving at an evidence-based pressure target; similar for all women

The group analysed 15 818 raw digital mammograms from 3772 women who had undergone screening or diagnostic mammography at the University of Malaya Research Imaging centre in Kuala Lumpur. The mammograms were processed by the volumetric breast density (VBD) measurement software (Volpara) to assess compression force, compression pressure, compressed breast thickness (CBT), breast volume, VBD and Mmean glandular dose (MGD) against breast contact area. In a parallel study the group studied the effects of reducing compression force on image quality and MGD based on studies on 105 Asian women, as well as using the RMI156 Mammographic Accreditation Phantom and polymethyl methacrylate (PMMA) slabs. It was found that compression force, compression pressure, CBT, breast volume, VBD and MGD correlated significantly with breast contact area.

It was found that compression parameters including compression force, compression pressure, CBT and breast contact area varied significantly in the women. Although the mean compression

force in the Malaysian study was comparable to previous reported studies, the compression pressure was generally higher than those reported in Caucasian women This is possibly because the breast contact area of Asian women in the Malaysian study is generally smaller than Caucasian women

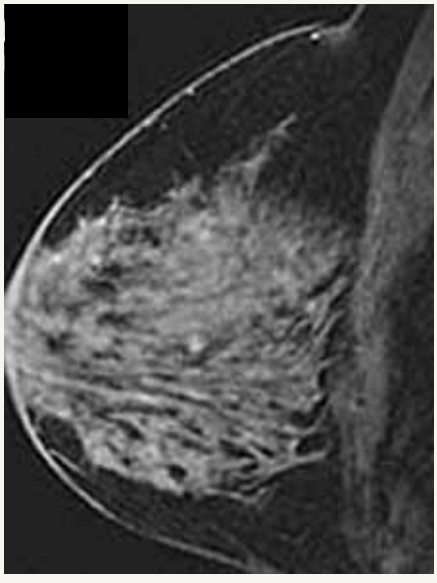
The authors concluded that force-standardized protocols led to widely variable compression parameters in Asian women and that, based on the phantom study, it may be feasible to reduce compression force by up to 32.5% with minimal effects on image quality and MGD.

Commenting on the results, Monique van Lier, Clinical Application Scientist at Sigmascreening, the Dutch medical technology company said "at Sigmascreening we have developed a breast compression system (the Sensitive SigmaPaddle) based on the automatic measure of the pressure used in compression (i.e. the force applied to the breast divided by the surface contact area of the breast on the paddle which is measured in real time). The Sensitive SigmaPaddle is the first pressure based compression paddle providing real-time pressure information of the whole mammographic breast compression procedure, which can considerably improve compression reproducibility with the aim of arriving at an evidence-based pressure target;, similar for all women. If this were to be used in Asia, we would expect more optimal breast compression, which could improve specificity of tumor detection and at the same time prevent unnecessary discomfort and pain, which may contribute as well to a higher breast cancer screening compliance of women. In other words, the use of this technology would protect women — especially those with smaller breasts — against excessively high compression pressures while potentially improving the results of the test. This Malayasian study underpins the importance of taking breast size into account and is in accordance with Sigmascreening's concept of the Sensitive Sigma Paddle, which applies pressure guidance during mammography. As a result of this, extremely high or low pressures, as observed in this study, should disappear almost entirely by the use of the Sensitive Sigma paddle. It optimizes compression for every individual breast, by taking breast size and stiffness into account, for the most optimal screening result while reducing unnecessary and often extreme pain.

In Europe, over 10,000 patients have already experienced the more woman-friendly way of carrying out mammograms while clinicians are starting to recognize the improved sensitivity and specificity of the pressure technology. The technology is already in use in the United Kingdom, Norway, France, Germany, Sweden, The Netherlands, Belgium and Switzerland.
https://tinyurl.com/Lau-et-al-paper

Breast cancer screening with mammography plus ultrasonography or MRI in women 50 years or younger at diagnosis and treated by breast conservation therapy

A recently published paper from a team of Korean researchers describes the results of their study to determine whether younger women (aged ≤50 years) who have undergone breast conservation therapy may benefit from breast MRI screening as an adjunct to mammography (*Cho N et al. Breast Cancer Screening With Mammography Plus Ultrasonography or Magnetic Resonance Imaging in Women 50 Years or Younger at Diagnosis and Treated With Breast Conservation Therapy. JAMA Oncol. 2017. doi: 10.1001*). The researchers set out to assess the screening yield and tumor characteristics detected by combined mammography and magnetic resonance imaging (MRI) or ultrasonography in women diagnosed at 50 years or younger who had undergone breast conservation surgery and radiotherapy for breast cancer. A total of 754 women underwent 2065 mammograms, ultrasonography, and MRI screenings. Seventeen cancers were diagnosed, and most of the detected cancers (13 of 17 [76%]) were stage 0 or stage 1. Overall cancer detection rate (8.2 vs 4.4 per 1000; P = .003) or sensitivity (100% vs 53%; P = .01) of mammography with MRI was higher than that of mammography alone. After the addition of ultrasonography, the cancer detection rate was higher than that by mammography alone (6.8 vs 4.4 per 1000; P = .03). The specificity of mammography with MRI or ultrasonography was lower than that by mammography alone (87% or 88% vs 96%; P < .001). No interval cancers were found., MRI screening detected 3.8 additional cancers and ultrasonography detected 2.4 additional cancers, most of which were stage 0 or stage 1, per 1000 women and increased sensitivity over mammography alone.



The authors conclude that after breast conservation therapy in women 50 years or younger, the addition of MRI to annual mammography screening improves detection of early-stage but biologically aggressive breast cancers at an acceptable level of specificity. Results from this study can be used to help informed patient decision-making regarding screening methods after breast conservation therapy. In younger women who have undergone breast conservation therapy, the addition of MRI screening or ultrasonography to mammography should therefore be considered.
https://tinyurl.com/Cho-et-al-paper

Patient control of breast compression during mammography

The Gustave Roussy Institute (IGR) in the south of Paris is one of the most prestigious European centers for the diagnosis and therapy of cancer. The IGR breast cancer unit is particularly active, conducting numerous research projects and performing thousands of breast imaging exams annually.

The unit has recently carried out a trial to evaluate the effect of enabling patients to control the level of breast compression themselves during their mammography examinations. Preliminary results of this trial are now available.

Morgane Cousin (Left Panel) is senior radiographer of the breast cancer unit at the French Institut Gustave Roussy. Dr Corinne Balleyguier (Right Panel) is senior radiologist and head of the department.
emails:
morgane.cousin@hotmail.fr;
corinne.balleyguier@gustaveroussy.fr

We spoke to Morgane Cousin, Senior Radiographer of the Breast Cancer Unit and Dr. Corinne Balleyguier, Radiologist and Head of Department.

Q *Before we get on to the recent trial itself, please give us a brief overview of the breast cancer unit at the Institut Gustave Roussy. How many patients do you see each year and what breast imaging modalities do you have available ?*

Thanks in part to the reputation of the Institut Gustave Roussy, we see more than 12,000 patients per year in our breast imaging service. However we are well equipped to deal with this number of patients. We have three mammography systems, including the latest General Electric model, the Pristina mammograph — this is the one with the so-called self-compression module and which we used in our study — as well as a stereotactic macrobiopsy machine, three ultrasound scanners, and two MR imaging systems. We carry out all the procedures necessary for the complete diagnosis, treatment and follow-up of our patients. Thus, we can carry out standard mammography, tomosynthesis, contrast mammography, ultrasound guided-microbiopsies stereotactic biopsies, fine needle aspirations and MRI-guided biopsies as well as pre-operative patient management.

Q *Let's now focus on the Pristina mammography system. This includes a device that allows women undergoing the mammography examination to have some control, under the supervision of the technician, over the process of breast compression which itself is necessary for optimal image acquisition. In practice, how do you use this feature?*

The radiographer begins the examination in exactly the same way as in standard mammography, i.e. by positioning the breast carefully on the paddle and by applying a standard compression force of 3 decaNewtons (daN), which is the minimum force necessary for acquisition of images of acceptable quality. The greater the compression, the better the quality of the images, but the problem is of course that greater compression can be more uncomfortable or even painful for the patient.
After the radiographer has applied the minimum 3 daN force to immobilise the breast, the patient can either leave the control of compression to the radiographer or take control of it herself, through means of a self-compression control device which she holds in her free hand. In appearance, the device looks like a typical TV remote controler. By simply pressing the + button on the controller, the patient can increase the compression, up to whatever level she considers sufficient. It is at this stage that we then begin the acquistion of the images.

We've had the auto-breast compression mammography system for nearly a year now so our radiographers have

Using a remote control device (similar to a TV remote control), in the Pristina system, the patient can herself increase the breast compression force from the minimum set by the radiographer to a level at which the patient can still accept

become familiar with the technique. We have now accumulated a lot of experience with it and have been able to assess patient reaction to the system.

Q *So could you explain the rationale and design of the study you carried out to evaluate the reaction of the women to the system and the quality of the images?*

The aim of our study was simple, namely to evaluate the advantages — and any disadvantages — that the self compression system provides compared to standard mammography where the compression force is set only by the radiographers.
To do this, we studied 100 women in whom one breast was compressed using the new self-compression system whereas the other breast was compressed only by the radiographer, i.e. in the standard method. In both cases, we recorded the final force used for the breast compression and, of course, we monitored the quality of the mamograph images in both groups.
In addition, we noted the reactions that the women expressed regarding the new system and whether or not they would prefer the new system in future mammography examinations Finally we compared the length of time that the new examination system took compared to the standard system, and the reaction of the radiographers to the new system.

Q *Now, can you describe the preliminary results and their implications?*

The most striking finding of our trial was that when women used the self-compression method for one breast they tended to apply more compresson force to that breast than in the other breast where the radiographer alone set the compression force. In addition, there was a clear psychological effect on the women in the self-compression group in that the patients felt more "in control" of the examination and consequently were less stressed or put off by the procedure.

As for image quality, in any case a minimum of compression is applied for the acquisition of good quality images. which is why the acquisition of the images is only carried out beyond 3 daN. Of course, the thinner the breast being imaged, the better the image quality and/or the lower the radiation dose needed. Thus, the increased compression used when women self-compressed had the effect of reducing the thickness of the breast and so enabled us to acquire an image of equivalent quality but at lower radiatron dose. Quality images with lower dose is one of the principal goals in our unit.
Regarding the comparative time the examinations took, we did not find any significant difference in the duration of the examination with or without self-compression.
Of the patients who used the self-comporession system for one breast, more than three-quarters told us that they would be more at ease and ready to have their next mammogram if they had the self-compression.
Thus, overall, our first experience with the self-compression system in our breast unit has been very satisfactory, both from our point of view and — more importantly — from the patients' point of view. We are encouraged, and intend, to continue with the new system.

" .... the patients felt more "in control" of the examination and consequently were less stressed or put off by the procedure...."

Q *All your patients underwent "diagnostic imaging". Can you speculate on how non-symptomatic women (e.g. those following screening programs) would react?*

We also carry out mammograms in women who are neither symptomatic, intermediate-risk nor high-risk of breast cancer, and they have reacted to the new system exactly in the same way as the women described above. So we consider objectively that there will be no difference between symptomatic women and others.

Q *How do you consider developing your study and how do you envisage the future ?*

We want to include more patients to validate the initial results. At the same time, we would like to inform all our referring breast physicians about this new way of carrying out mammography, so that we can offer it routinely to all our patients.
We also intend to investigate new compression materials, with the objective of trying to make mammography more acceptable to women and thus encouraging more women to take part in breast screening programs, with fewer drop-outs.

Mammographic compression and diagnostic performance

By Prof. K Grimbergen & Prof. A den Heeten

One of the factors dissuading women from continuing participation in breast screening mammography programmes is the pain and discomfort caused by the compression of the breast necessary to optimize the quality of the mammographic image. Recently a new system for breast compression has been developed based on the use of pressure (i.e. the force applied to the breast divided by the contact area of the breast with the paddle).

This article reviews the question of breast compression in mammography in general and discusses the significance of two recently published articles on the relation between breast compression and the performance characteristics of mammography. If an optimal compression pressure, namely approximately 10kPa, is applied in screening mammography, then an increase of 5% in one-year sensitivity may be achievable.

Mammography is typically carried out in two situations, either as a screening tool or as a clinical/diagnostic tool. Of these two situations, the majority of investigations, — at least 150 million per year — are carried out in either an organized or non–organized setup for screening purposes [1].

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In Western Europe, one in eight women will develop breast cancer in her lifetime, of whom more than 75 % are detected after the age of 50 [2]. Every year breast cancer kills more than 500000 women and recently it has become one of the leading causes of morbidity and mortality in low- and middle-income countries (LMICs), where 60% of the world's total of new cases are currently diagnosed [3, 4]. In LMICs the 5 years survival rate varies between 10 and 40%, in contrast to a survival rate of 80% in countries with better healthcare organization and low threshold mammographic breast cancer screening.

Since mammography — together with other factors such as the development of new therapeutic treatments — has undoubtedly played an important role in the improvement of the survival rate of breast cancer patients [5], we thought it useful to take a closer look at the future relevance of the modality and possible future innovations and improvements. In particular, in this article we focus on the recent insights in the importance of mammographic compression.

Over the last few years, there has been a significant technology innovation with the introduction of tomosynthesis, which, as a variant of mammography still requires breast compression as an essential element.

COMPRESSION IN MAMMOGRAPHY:

The term "compression" is misused in mammography. In almost every other technical discipline, such as engineering, physics and computer science, the term compression is used to describe the process involved in making something smaller in volume. In mammography the only reduction is in the thickness of the breast after deformation, but this barely relates to the actual volume of the breast itself. Thus in this context, the word "compression" should perhaps be replaced by the word "flattening", which is a better description of the clamping of the breast between two flat parallel plates, the paddle and the bucky plate. The flattened breast is at right angles to the x-ray source, thereby minimizing the differences in distance travelled by the x-rays in the breast tissues, which would not be the case in a round or oval breast without flattening.

However one important question has never been satisfactorily answered, namely at which point in time is breast flattening sufficient? Put another way, when is it optimal to stop increasing the force used to flatten the breast?

Such simple, but in practice extremely important, questions are impossible to answer without some basic physics background. Breast flattening is caused by a combination of the pressure and the flexible (but not compressible) nature of the breast. In mammography systems this flattening is a result of an applied force generated by a motor. The force will instantaneously be distributed over the contact area, and a mean pressure between the breast and the paddle will be felt by the woman

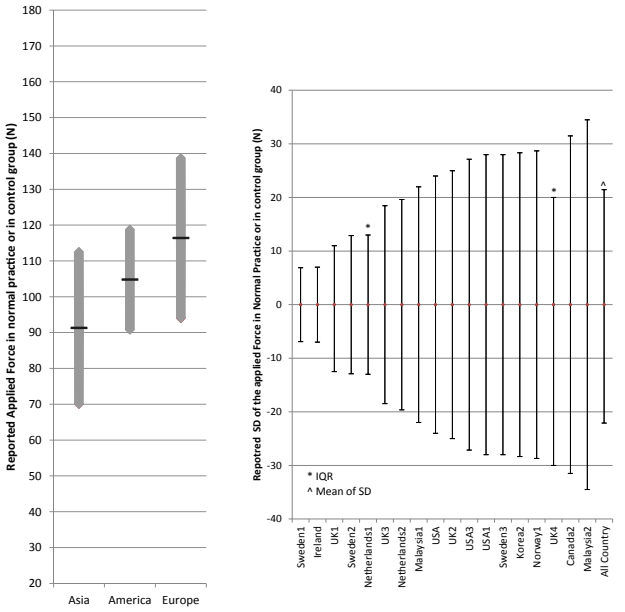

Figure 1. Mean compression forces and standard deviations in newtons applied throughout the world; left panel per continent and right panel per country. [7]

involved. At the same time an identical reaction force is generated by the bucky plate. When the motor is exposed to a counter force, the force it generates increases from 0 daN (1 decanewton (daN) is close to 1 kilogram of force) to a maximum of 20 daN [6].

The mean pressure which will ultimately be reached in manual mammography, i.e. without the intervention of a pressure sensor, is dependent on the individual properties (volume, stiffness) of the woman's breasts, her personal pain threshold and on the skill and experience of the technician (awareness, empathy, training, and guidelines).

In pressure-guided compression all four independent parameters influencing the patient's experience are grouped into one factor, and can be managed in a simple way by monitoring only this single physical parameter, namely the mean pressure. In this way, the flattening procedure stops at a reasonable point and this is — in most cases — below the pain threshold of women.

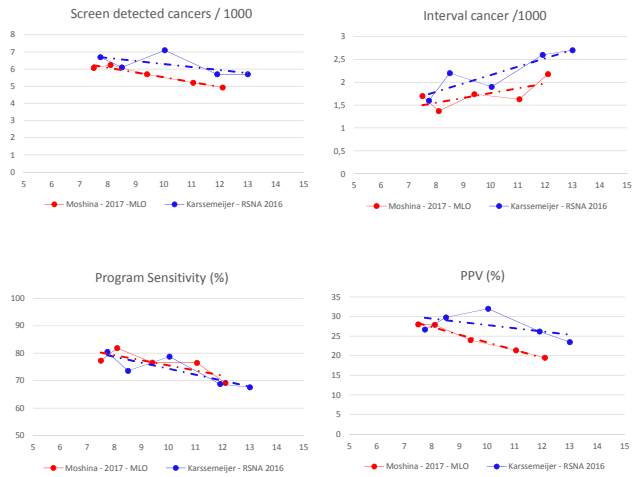

Figure 2. Comparison of the performance measures versus mean pressure in kPa of the Norwegian study and the Dutch study (the dots indicate the median values of the 5 pressure groups in both studies).

GUIDELINES

When a woman undergoing mammography asks the technician: "When will you stop compressing my breast?" the most frequent answer is : "When the skin is taut". While the breast compression is progressing, the technician generally uses her finger to probe the skin and so estimate its tautness. At some indeterminate point the technician then simply decides the compression is sufficient and stops. Other — so-called — guidelines suggest aiming for a force between 12-18 daN. In fact, the only absolutely clear guideline is that provided on page 76 of the European guidelines, namely "there is no optimal value known for the force" [6]. Figure 1 illustrates the consequences of this lack of guidelines and lack of consistency in practice which leads to a wide variation in the compression forces typically used in different countries and continents.

EFFECT OF PRESSURE ON SCREENING PERFORMANCE.

An important question arising in this respect is whether the level of pressure applied could influence the efficacy of mammography in its primary role, namely the detection of cancers. The possibility of analyzing this aspect further depends on the availability of large, accurate and continuously monitored databases, which can be found in organized breast cancer screening programs in countries with national cancer registers. A second important condition is that the mammographic images are stored in a "for processing format" so that a new generation of software can be used that opens up the possibility of datamining the large datasets generated by screening mammography. Such software is provided by the Volpara company and enables a reliable estimate to be established of the contact area of the breast on the paddle, based on the mammography image and other important parameters such as the volume of the breast. We have validated this specific method for contact area measurement [8]. Once the breast contact area has been determined the mean contact area pressure at the moment of exposure can be easily calculated simply dividing the applied force (which is stored in the DICOM header), by the estimated contact area.

THE NORWEGIAN EXPERIENCE

A first peer-reviewed paper on the relation between compression force, pressure and the performance of screening mammography, was published by the group of Solveig Hofvind of the Norwegian Cancer Registration in Oslo [9]. They investigated the relation between compression force and pressure at the time of the mammographic screening examination with early performance measures in a population-based breast cancer screening program. In this context, the term "early performance measures" is taken to cover all performance parameters except mortality (e.g. recall rate, rates of screen detected and interval breast cancers, positive predictive value of recall (PPV), screening sensitivity and specificity, and histopathologic characteristics of screen-detected and interval breast cancers). The number of mammograms available for analysis totaled 261,641 examinations with follow-up data, in

• CC & MLO	• MLO
• 50-69 years	• 50-75
• Subsequent rounds	• First rounds and subsequent rounds
• GEE, Odds ratios (crude and adjusted for confounding)	• General estimated equations for confounders (GEE)
• Interval cancers 2 years	• Interval cancers 1 and 2 years
• Mean Breast Volume 964 cm^3 (MLO)	• Mean Breast Volume 973 cm^3 (MLO)
• Mammographic machines of different vendors.	• Mammographic machines only Hologic Selenia.
• Cut off values pressure bins MLO: <7,5; 7,5-8,7; 8,8-10,0;10,1-12.0; ≥ 12,1	• Cut off values pressure bins MLO: ≤7,74; 7,75-9.26; 9,27-10.80; 10,81-13; ≥13,01
• Recall in subsequent rounds 2,4%	• Recall in subsequent rounds 2,5%

Some relevant similarities and differences between the Norwegian study and the Dutch study

93,444 subsequently screened women. The study period was 2007–2015.

The exams were categorized into three equal sized groups. For those who are not familiar with the use of force and pressure and potential confounders, the main conclusions of the paper, as expressed in the abstract, perhaps should be explained because they appear to be in mutual disagreement. The authors concluded that high compression force and low compression pressure were associated with more favorable early performance measures in the screening program, a finding which may be, for many people, a counter-intuitive result. The relation between high forces and favorable early performance measures lies directly in the tendency of technicians to apply more force to large breasts. It may be thought that low pressure is related to low force, but a relatively high force applied to an even larger contact area will result in a lower pressure. A second source of misunderstanding is the assumption that ongoing higher forces will result in a thinner breast, lower dose and better image quality. In fact, the contrary can be the case.

For these reasons it is more sensible not to focus on force but on the results based on pressure groups and compare them with results reported earlier by the group of Karssemijer in the Netherlands, [10,11].

DUTCH EXPERIENCE

The establishment of a relation between compression pressure and screening performance in the Netherlands was performed in a series of 113,464 screening exams [10]. These examinations were carried out in the former Prevention Center (now the Midden West region) because in this screening center "for processing images" that are essential for the analysis were generated, in contrast to other Dutch screening centers. These exams were categorized into five equal groups of increasing applied pressure, in such a way that each group contained 20 % of the exams. Pressure thresholds between the groups were 7.7, 9.2, 10.7 and 12.8 kPa. Measures of screening performance were then determined for the exams in each group. It was found that PPV and the cancer detection rate varied significantly within the five groups. There was a clear indication that the group with a moderate pressure (around 10 kPa) had an overall better screening performance than those in the lower and higher pressure categories. However, in such large studies important confounders could apply and should be addressed. In a follow-up study [11], the data were supplemented with an extra year's data to reach 132,801 examinations with follow-up of the screening performance parameters. In this extended study, the level of interval cancers was known so the sensitivity and specificity of the screening program could be calculated. It is important to note that a distinction was made between one-year sensitivity and two-years sensitivity. Another important point is that in both studies the statistical technique known as Generalized Estimating Equations, (GEE) was applied to correct for confounders, such as examinations of the same women, the breast volume and the density. Thus the statistical approach differs from that used by the Norwegian group, since in the Norwegian study crude and adjusted odds ratios were calculated. It should also be noted that only the MLO projections were used in the Dutch study due to historic guidelines restricting the use of CC to first round clients, and mainly patients with more dense tissue. Thus an analysis of a mix of MLOs with CCs could skew and bias the results. For this reason when comparing the results of the Norwegian study and the Dutch study we focus solely on the MLO results of the study as presented in the addendum table A 2 2.3. of the Norwegian study.

In all the important performance parameters the trends appeared to be the same [Figure 2].

DIFFERENCES AND SIMILARITIES BETWEEN THE NORWEGIAN AND DUTCH DATA.

Despite their differences, the data from these two studies seem suitable for comparison. The most striking similarity, which could have a direct significance, is the general finding of decreasing performance parameters in the higher pressure compressions. It can be seen that the level of screen-detected cancers, the positive predictive value, the program sensitivity, and interval cancer rate all have the same trends in both studies. However, the Dutch data indicate an optimal performance in the middle group 3, i.e. around 10 kPa.

It could be expected that screening performance will be negatively affected by very low pressures as can be seen in the Dutch data and also, but less obvious in the Norwegian data. There is a trend towards worsening performance parameters for the groups with the lowest pressures. In this respect it should be noted that an important parameter is missing from the Norwegian data, namely the one-year interval cancers.

ONE-YEAR INTERVAL CARCINOMA VERSUS TWO-YEARS INTERVAL CARCINOMA.

The reason that we want to stress the value of one-year program sensitivity is because we are evaluating neither the Norwegian nor the Dutch screening performance data, but simply looking for signs of the influence of compression pressures on the performance of mammography as a diagnostic test. So metrics that come close to the pure mammographic performance (and not to the performance of organized screening as such) are the most informative. There are well known proxies for mammographic performance in the monitoring and evaluation of screening programs, one of which is one-year sensitivity [12]. Here the assumption is that interval cancers detected in the first year (almost always because they

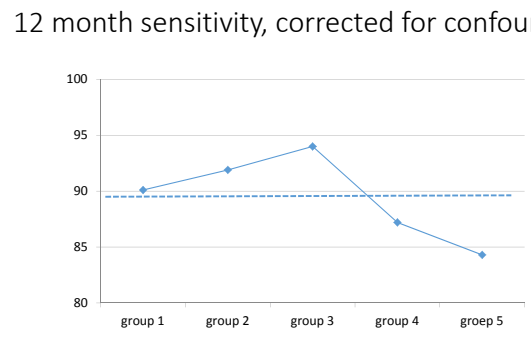

Figure 3. One year program sensitivity (%) in the Dutch study for the 5 different pressure groups. Dotted line indicates the average.

became symptomatic) were already present at the time of screening and were simply not detected at that time. So the question is: "do we see in the one-year sensitivity a similar or even more pronounced trend" — the answer is clearly yes.

BREAST VOLUME:

With the current method used for breast compression, women with the smallest breast volumes (<500mL) are clearly prone to receive the highest pressures. If in the Norwegian data we analyze the interval cancer rates plotted against volume, it can be seen that not only have these women a much higher chance of suffering from severe pain and discomfort [1], but they also have a 30% higher likelihood to be confronted with an interval carcinoma compared to women with larger breasts in group 4 and 5. A similar trend can be seen in the Dutch data.

CONCLUSION:

The many complaints from women undergoing mammography regarding pain and discomfort from breast compression together with misunderstanding and misconceptions of the mechanics of breast compression in mammography, was the main driver behind our proposal, made five years ago, of a new approach to compression [13]. We modified the mammographic compression procedure through the use of a transparent and radiolucent pressure measurement tool fitted to the compression paddle. In addition we investigated a more rational way of determining when breast compression was sufficient in the light of the set criteria, namely immobilization, sufficient image quality, and as low as reasonable radiation dose.

The research in the two papers on compression and performance discussed above, was made possible because of the existence of a datamining tool from the Volpara company that enables a reliable measure of the breast contact area duing mammography [8]. As the force value is available in the DICOM header, a retrospective calculation of the mean pressure at exposure is simple. The reported data indicate that women who received the highest pressure not only suffered from significantly more pain and discomfort, but also seemed to be subjected to a less optimal test.

Despite the fact that there are important similarities in the results of both the Norwegian and the Dutch studies, some differences cannot be explained away. The near absence in the Norwegian study of a performance decline at the low pressure end of the spectrum which was obvious in the Dutch data, deserves a closer look.

We recently discovered that mammography systems produced by different companies might differ in their force measurements by more than 10% (also within the same brands). In new studies, it is important that all mammography systems be calibrated and documented, since this can have a significant effect on the reported pressure. Another interesting point in the Norwegian data is the exclusion of women who participate in the first round (in the Netherlands such women have more dense breasts and a higher tumor detection rate), at the cost of a much lower positive predictive value.

We can conclude that the pressure used during mammographic exposure plays an important role and if the proper pressure can be reached with most patients in screening (according the Dutch data around 10 kPa), then an increase in 5% in the one-year mammographic sensitivity, might be achieved. This could be even more important than the complete effect of digitization of the breast cancer screening program in the Netherlands as a whole.

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Improving the detection of breast cancer through artificial intelligence

By Prof. Nico Karssemeijer

The reading by radiologists of the mammograms generated in current breast screening programs is an extremely time-consuming process, a situation which is likely to be exacerbated by the increasing use of digital breast tomosynthesis systems in the future. In addition, even with the currently recommended process of using double readers, there are still a significant number of breast cancers which are not identified in screening mammography. Several years ago, it was thought that the use of Computer-Aided Detection (CAD) systems could address these issues, but in practice such CAD systems failed to live up to expectations.

The advent of extremely powerful algorithms generated by Deep Learning technology and massive training processes is now revolutionizing the field.

This article describes the performance of a new, commercially available system developed using Deep Learning and designed to provide focussed decision support to breast radiologists. Initial evaluation data are presented which demonstrate the potential of the approach, for example in the use of such Artificial Intelligence systems as "second readers".

Breast cancer screening programs have adopted international quality assurance guidelines with the aim of maximising the chances of achieving the main objective of screening mammography, namely the early detection of breast cancer. These guidelines cover all aspects that have an impact on screening outcomes, and have resulted in excellent technical quality control of imaging equipment, which is one of the fundamental and critical factors in screening. However, it is well established that, even when working with high performance equipment under optimal conditions, radiologists can still fail to detect breast cancer. The quality of human interpretation of mammograms appears to be one of the most difficult factors to control —indeed it can be argued that this is the single most important factor in the whole screening process. Extensive audits of breast cancer screening programs reveal that over 50% of cancers in screened populations were already visible on previous mammograms when it is known where to look. This holds for both screen-detected and interval cancers detected in between screening rounds. This figure has not changed over the years, not even after the introduction of digital mammography. The crucial question is whether these missed cancers could have been detected earlier, without leading to an unacceptable increase in false positives. Some decades ago researchers thought the answer to this question was simply yes: Computer Aided Detection (CAD) systems were designed to identify potential abnormalities in mammograms. The idea was that if radiologists were to carefully inspect locations marked by CAD they would not overlook cancers marked by the system. However, this turned out to be an illusion. Radiologists still miss cancers, even when they are marked by a CAD system. The assumption that radiological errors in screening are due to radiologists not looking in the right place was wrong. Therefore, it is not surprising that despite widespread use of CAD in practice, there is mounting evidence that current CAD technology is not fulfilling its promise [1].

To design a better system to support radiologists in screening, we, with radiologists, investigated in detailed experiments the causes of screening errors. We found that the biggest difficulty is not the actual detection of suspicious regions, but rather their assessment. Since many regions in mammograms can look somewhat suspicious, the hard part for the radiologists is the decision on which ones they should act and how. This led to the conclusion that the key to improve the reading of screening mammograms is to help radiologists with decision-making. The potential benefit of this approach is great, as was demonstrated in a study where we assessed the best achievable performance in detecting malignant soft tissue lesions in mammograms. We used a large series of screening mammograms in which breast cancer had been missed, mixed in with normal exams. By using a panel of radiologists independently interpreting the mammograms we found that assessment by the panel was much better than that of any of the individual radiologists. The sensitivity of the individual radiologists ranged from 15% to 48%, at a recall rate of 5%. With a panel of 8 radiologists, sensitivity at the same recall rate increased to 61% and the results suggest that with more readers this could increase even further. The hope is that by using smart Artificial Intelligence techniques this 'best achievable performance' can become within reach of screening programs, for the benefit of all women participating in screening.

"... even when working with high performance equipment under optimal conditions, radiologists can still fail to detect breast cancer..."

DEEP LEARNING

Remarkable advances in machine learning have resulted in a breakthrough in the field of computer image analysis over the

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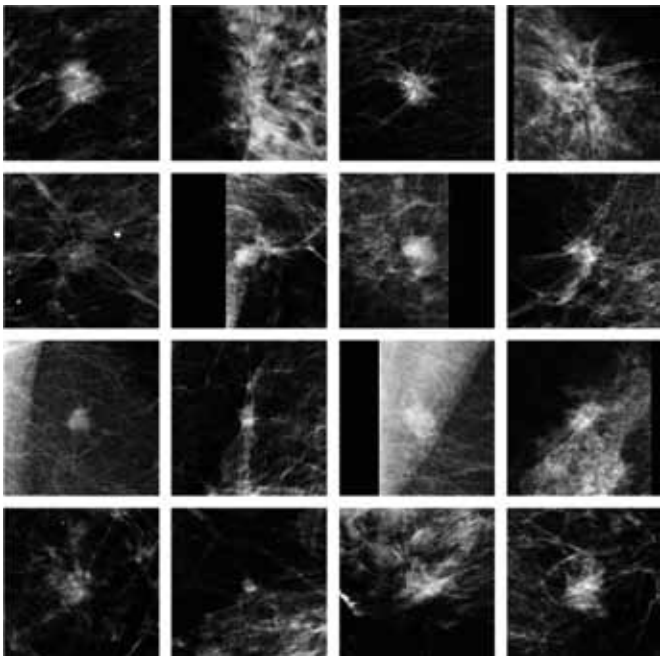


Figure 1. Deep learning systems are trained with small patches containing suspicious regions and learn to distinguish cancers from normal tissue or benign lesions. In one experiment 400 patches were interpreted by four experienced radiologists and by the deep learning system, a Convolutional Neural Network (CNN). The performance of the automated system was better.

last few years. Using the technique known as deep learning, artificial neural networks can be trained to recognize patterns in the same way as human beings. It is only a matter of time before such artificial networks outperform humans for certain specific tasks. The reading of screening mammograms is one task where conditions are ideal for the application of deep learning: the reading of mammograms is a repetitive task for which large amounts of reliable data are available for training. In addition, the imaging procedure itself is highly standardized.

The basic principle behind the deep learning approach is that the computer will learn to directly recognize features in images without the intervention of an expert who has previously "taught" the system what the features of interest are. In the training phase, literally millions of examples are presented to the system. Typically, these examples are sub-images (patches) of images containing a target (e.g. cancer) or a non-target pattern. After training, the system can distinguish the two types of patches. The more examples that are provided in training, the better the system learns the task.

In a recent study, we trained a deep learning system to recognize cancer in patches of 5x5 cm^2 extracted from mammograms [2]. Only soft tissue lesions were included. Typical examples are shown in Figure 1. Over one million patches were used to train the system. The performance of the system was subsequently compared to that of four experienced screening radiologists using a set of 400 patches that had not been seen by the system during training. It turned out that the deep learning system had a higher performance than the radiologists [3]. Even though this study had limitations — in practice the reading of mammograms is more complex than judging small regions of interest — this result nevertheless demonstrates the potential of the whole approach of the new machine learning technology.

DECISION SUPPORT

To assist radiologists with the interpretation of suspicious regions, we designed an interactive approach in which radiologists can select regions in mammograms for a second opinion provided by an AI system. In an experimental evaluation of this approach, we asked nine screening radiologists to read 200 exams with and without the support of a system for automated detection of malignant soft tissue lesions. The series contained 80 mammograms with cancer, 20 false positives, and 100 normal exams. The algorithms used in this study were developed at the Radboud University Medical Centre. Both the "classical" CAD approach and the interactive decision support approach were evaluated in the study. It was found that the use of the interactive decision support was highly effective, while results confirmed that just showing CAD marks — as is done in the classical CAD approach — in fact did not help the readers [4].

Given the rapid development of deep learning techniques in general, especially when coupled with massive training, it is now possible to produce much more powerful algorithms than were possible at the time of the Radboud study cited above. The remarkable progress made in the field over the past few years is shown in Figure 2. Using the same series of test exams as in the above-mentioned reader study, (which of course had not been used for the training process, so the algorithms had not previously "seen" the images), we compared the stand-alone performance of the system used in the earlier reader study with that of Transpara, a new system developed using deep learning by ScreenPoint Medical.

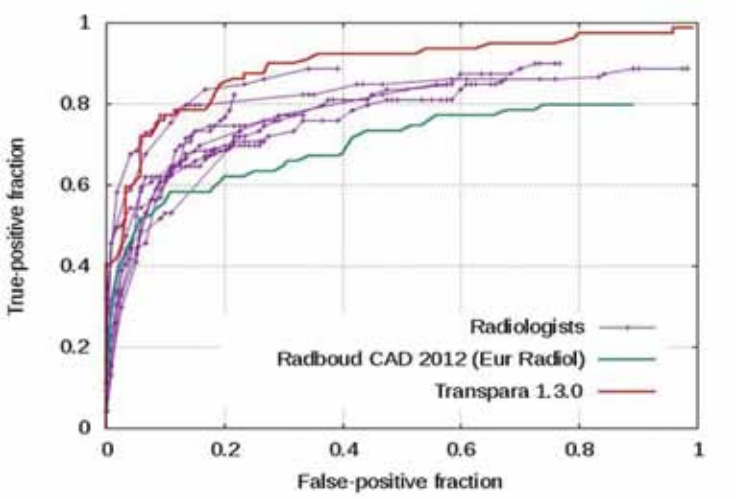
"... the detection performance of the new Transpara system .. for soft tissue lesions appeared to be as good as that of the best reader in this study..."

At the time of the earlier study the AI system developed at Radboud University still performed worse than the radiologists. In contrast, the detection performance of the new Transpara system (V 1.3.0) for soft tissue lesions appeared to be as good as that of the best reader in this study.

INCREASING PRODUCTIVITY

Breast cancer screening is a demanding and time-consuming task for radiologists. With the aim of improving quality, European Guidelines currently recommend independent double reading of screening mammograms by two radiologists. However, with increasing shortages of skilled screening radiologists, in practice such double reading may not be sustainable in the future. In fact, the problem of manpower/resources is likely to become significantly worse when breast screening programs transition to digital breast tomosynthesis, for the simple reason that it takes longer to accurately interpret all slices of a 3D tomosynthesis dataset than it does to read a mammogram. Artificial Intelligence may provide a solution to this problem, since when computers read mammograms or tomosynthesis data as well as radiologists the computers are serving as a second reader, thus potentially removing the need for double human reading.

To investigate the feasibility of this approach, we applied the deep learning system Transpara 1.3.0 to a series of 4,600 screening mammograms acquired using imaging systems from four different



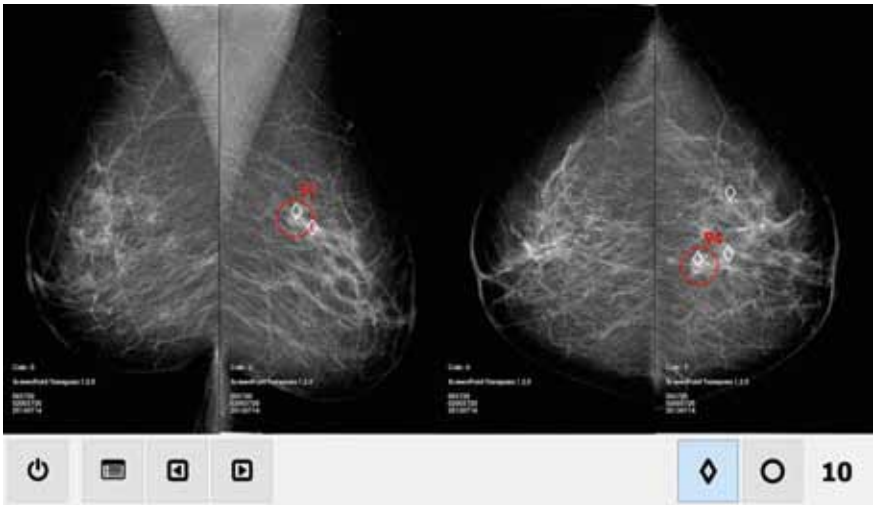


Figure 2: A conventional CAD system (Radboud CAD 2012) for detection of malignant soft tissue lesions was compared with the results of nine radiologists (Bottom Panel). While this conventional CAD system by itself performed less well than the radiologists, it helped them to improve detection [1].
The rapid progress of machine learning can be seen in the results of the Transpara deep learning system from ScreenPoint Medical, Nijmegen. The Top Panel shows the comparative ROC of the radiologists, the conventional CAD system and the Transpara system which can be seen to perform as well as the best radiologist reader in this test.

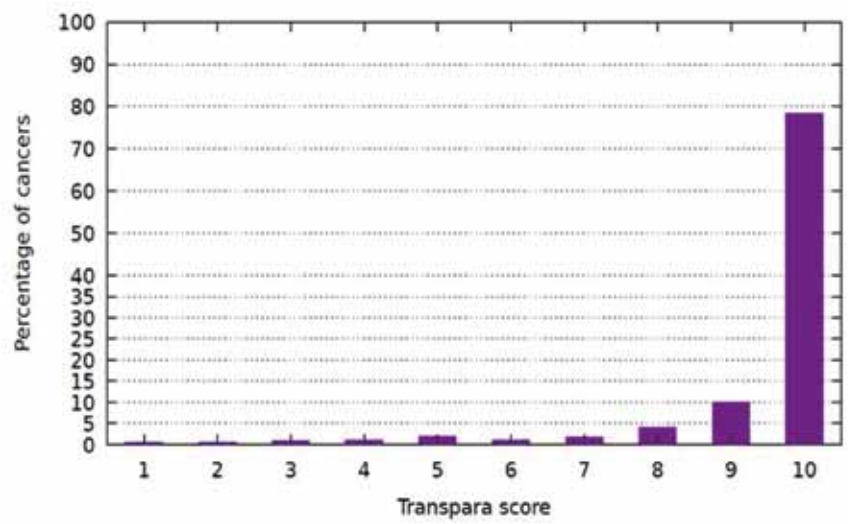


Figure 3. The Transpara deep learning system generates a score indicating the probability that breast cancer is present and detectable in a mammogram. In screening practice, the number of mammograms in each category is approximately equal. The figure shows the expected percentage of cancers in each category: 78% of exams with screen-detected cancers fall in category 10, while very few are in the lowest categories.

vendors, and including a representative series of 600 screen-detected cancers. The Transpara system combines suspicious findings in each screening study and categorizes the study (four mammographic views) according to its overall level of suspicion, attributing a score which reflects this level of suspicion. The scoring system ranges from 1 to 10 and was developed so that approximately 10% of the mammograms fall into each category. Results are shown in Figure 3. In the lower scoring categories very few cancers occur, whereas most exams with cancer fall into the highest scoring category. Thus, a higher score means a higher probability of cancer. It is expected that radiologists will increase their productivity through use of such a system, since it allows them to focus on the most relevant exams. For example, double reading of exams in the lower categories is probably not cost-effective or justifiable, given that the prevalence of cancer in exams in these categories is extremely low.

DISCUSSION

Breast cancer is a leading cause of death in women. In the EU more than 420,000 women are diagnosed with breast cancer each year and 130,000 women die of the disease. While early detection by screening is an effective way to reduce breast cancer mortality, it may not be possible to ensure the continued quality of screening programs in the future, due to the scarcity of skilled radiologists. Even with a sufficient number of experienced radiologists and the use of double reading, the quality of mammographic interpretation remains far from optimal. The fact is that the reading of screening mammograms is hard for humans. It is likely that in the near future computers will outperform radiologists. The use of AI is expected to reduce cost, increase the quality of screening programs, and reduce variability in the detection process.

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Automated Breast Ultrasound improves breast cancer screening outcomes

By Dr Ian Grady

Breast cancer is the most prevalent cancer in women within the European Union. In 2012, almost 460,000 women were diagnosed with breast cancer and just over 132,000 women died from breast cancer. The incidence of breast cancer is higher in Europe than it is in any other area of the world [1].

Of course, premature death is not the only outcome of breast cancer. The treatment of breast cancer patients results in significant costs to national health programs throughout the Union. Lost productivity in women who suffer from breast cancer results in further cost. These costs are ultimately born by all the citizens of the Union, through their tax payments.

The greatest negative outcome of breast cancer is arguably the tremendous burden of human suffering caused by this disease. This is, needless to say, beyond measure.

The magnitude of all of these outcomes depend, more than on anything else, on the stage at which each breast cancer is diagnosed. Mortality, despite advances in treatment, is still significantly higher in women who have advanced stage breast cancer [2].

Cost also depends upon stage. The cost of treating women with advanced cancers (stage 2 or greater) is more than double the cost of treating women with early stage cancers [3]. Suffering defies quantization, but clearly women with advanced cancers suffer more with radical surgical procedures and toxicity from extensive chemotherapy and radiation.

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MAMMOGRAPHIC SCREENING

Because breast cancer outcomes depend so heavily on the stage at diagnosis, the screening of asymptomatic women for early stage breast cancer has become the basis of breast cancer control worldwide [4]. The idea behind screening, of course, is to detect breast cancers in asymptomatic women before they reach an advanced stage. All the benefits of screening come from this reduction of stage at diagnosis [5].

Mammographic screening has been shown, in particular, to decrease stage at diagnosis and, therefore, mortality. Between 1963 and 1991, a series of clinical trials were performed to evaluate the effect of an invitation to screening mammography [4, 6]. With the exception of the Canadian National Screening Studies, these trials showed a significant reduction on mortality in all age groups studied [Table 1]. Accordingly, since the 1970s, the mammographic imaging of asymptomatic women has been the primary technology used for breast cancer screening.

Trial	Year	Mortality (OR)	Advanced CA(OR)
HIP	1963	0.76 (NR)	0.82 (0.66-1.00)
Two-County	1977	0.69 (0.56-0.85)	0.69 (0.61-0.78)
Malmö 1	1976	0.82 (0.67-1.00)	0.83 (0.68-1.00)
Edinburgh	1978	0.79 (0.60-1.05)	0.87 (0.73-1.04)
Canadian 1-2	1980	1.05 (0.85-1.30)	1.27 (1.02-1.57)
Stockholm	1981	0.91 (0.65-1.27)	0.82 (0.67-1.01)
Gothenburg	1982	0.76 (0.56-1.04)	0.80 (0.61-1.04)
Age Trial	1991	0.83 (0.66-1.04)	0.89 (0.72-1.10)

Table 1 – Early mammographic screening studies showing significant mortality reductions in the screened populations. [4, 6]

However, it is well known that mammography does not detect all cancers in asymptomatic women. Up to 20% of women will have their breast cancer missed on mammogram alone. Most of these women have either increased breast density or are at high risk of developing breast cancer.(7)

Supplemental screening has been proposed as a method of detecting early stage breast cancers that would otherwise be missed on mammogram alone in women with increased breast density or elevated risk of breast cancer. This involves the use of an additional method of imaging in women at risk of having a cancer missed on mammogram.

Several imaging technologies have been proposed for use in supplemental screening including tomosynthesis, ultrasound, magnetic resonance, molecular breast imaging, and contrast-enhanced spectral imaging. However, most of the literature on supplemental screening involves the use of ultrasound.

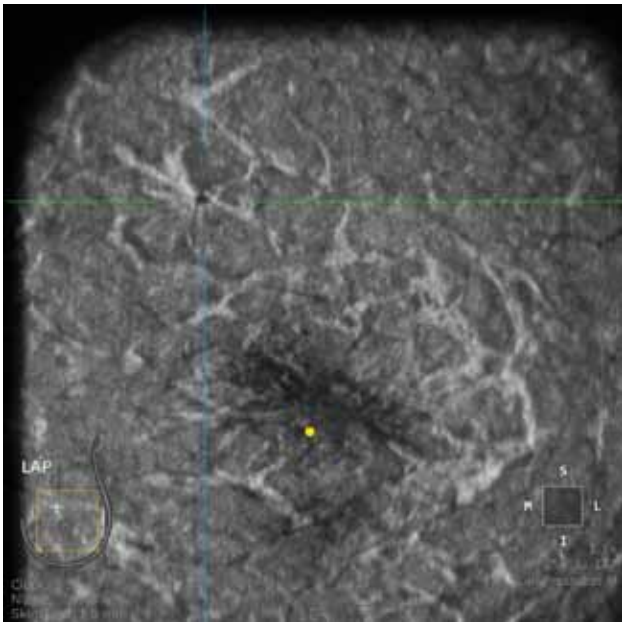

Figure 1 – A 6mm invasive ductal carcinoma seen on automated breast ultrasound in a 72-year-old asymptomatic female. The lesion was not seen on screening mammogram due to increased breast density.

NEW SCREENING STRATEGIES BASED ON ULTRASOUND

Ultrasound, compared to other imaging technologies, is inexpensive, fast, contrast-free, and radiation free. Automated breast ultrasound techniques involve the use of a scanner that acquires a volume of ultrasound data. This can be read as a series of transverse images (SonoCine, Tractus, or CapeRay systems) or reformatted into the coronal plane for review as a tomographic image (General Electric, Siemens, Hitachi-Aloka, or Delphinus systems). Unlike hand-held ultrasound, the entire examination can be saved and used in the review of future studies.

Automated breast ultrasound has been shown to detect early stage breast cancers not seen on mammogram. Several series have shown that early stage breast cancers can be detected with automated breast ultrasound in up to 7.7 women per 1,000 asymptomatic women screened that were not seen on mammogram. [Table 2].

The efficacy of new screening strategies can be evaluated based on the number of advanced breast cancers that they prevent. The lower the proportion of advanced cancers diagnosed, the lower is breast cancer mortality.(4) This relationship is shown in figure 2.

Trial	Year	Screened	Yield
Kelley et. al	2010	6,425	3.6
Giuliano et. al.	2013	3,418	7.7
SOMOINSIGHT	2014	15,318	1.9
EASY	2016	1,668	2.4
ASTOUND	2016	3,231	4.0
Grady et. al.	2017	7,451	4.2

Table 2 – Supplemental screening studies using automated breast ultrasound imaging. Yield is expressed as the number of detected cancers per 1,000 asymptomatic women screened that were not seen on mammogram.(8-13)

In the early mammographic screening trials, women who were not invited to screening served as the control population to which mortality and the prevalence of advanced cancers was compared. This type of trial is no longer possible, but control populations can be derived from either women who present with symptomatic cancers or women who participate in conventional mammographic screening.

To evaluate potential new ultrasound screening strategies, we reviewed our screening experience using mammography and ultrasound. From 2011 to 2016, we had 7,451 screening events in 3,435 women in women with increased breast density or increased risk. We identified 122 cancers in this population. Women who had symptomatic cancers, 36 of the total, served as the control group. For each asymptomatic cancer, we recorded each imaging modality on which it was seen. From this, advanced cancer odds ratios for each imaging strategy were derived [13].

With the advanced cancer odds ratios, we can rank potential imaging strategies using the method of Tabar *et. al.* These results are shown in Figure 3.

First, all of the potential strategies that we studied are better than the combined results from the early screening trials and far superior to no screening. Mammographic screening now is significantly better at preventing advanced cancers than it used to be. This, of course, reflects the progress in imaging technology that has occurred since the screening trials were completed.

"... the best imaging strategy, in terms of mortality, is a combination of mammographic and ABUS imaging. This combination significantly outperforms screening mammography alone..."

Note that the best imaging strategy, in terms of mortality, is a combination of mammographic and ABUS imaging. This combination significantly outperforms screening mammography alone.

Surprisingly, ABUS alone is also a very good imaging strategy, outperforming the early clinical trials. In our study, there was no significant difference between mammographic screening and ABUS alone screening [13]. This result has significance in particular for resource-limited regions where

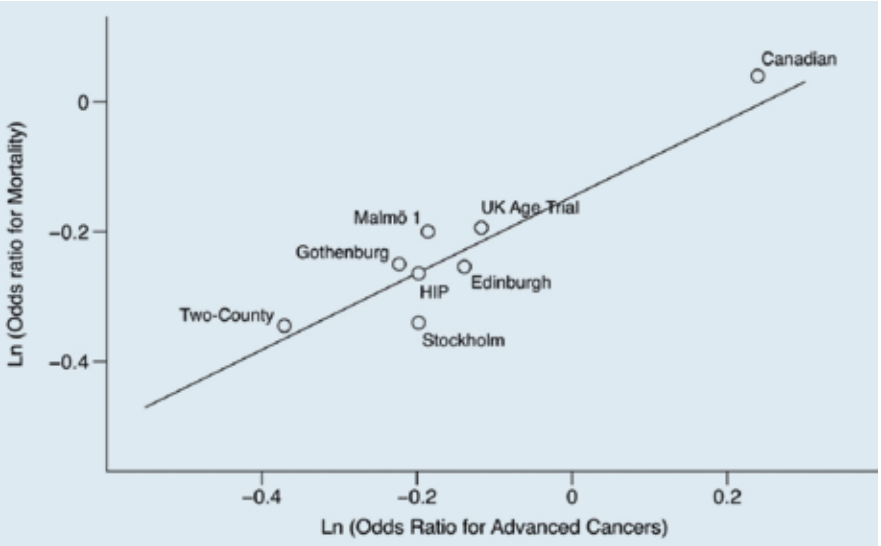

Figure 2 – Relationship between odds ratio of advanced cancer prevention versus odds ratio for mortality in the early mammographic screening trials. The linear regression function can be used to evaluate the efficacy of new screening strategies [4].

breast density is prevalent, such as Asia.

FUTURE RESEARCH

These results are limited in scope and will have to be confirmed eventually with a prospective, preferably multicenter study. Larger numbers would help to elucidate the magnitude of any differences between mammographic and ABUS alone screening.

A prospective study in an Asian population comparing ultrasound versus mammographic imaging would be very helpful in defining the role of ultrasound only screening in this population.

The method of comparing different screening strategies, originally described by Dr. Tabar, [4] can be used to explore other supplemental imaging methods such as tomosynthesis, magnetic resonance, molecular breast imaging, and contrast-enhanced spectral mammography.

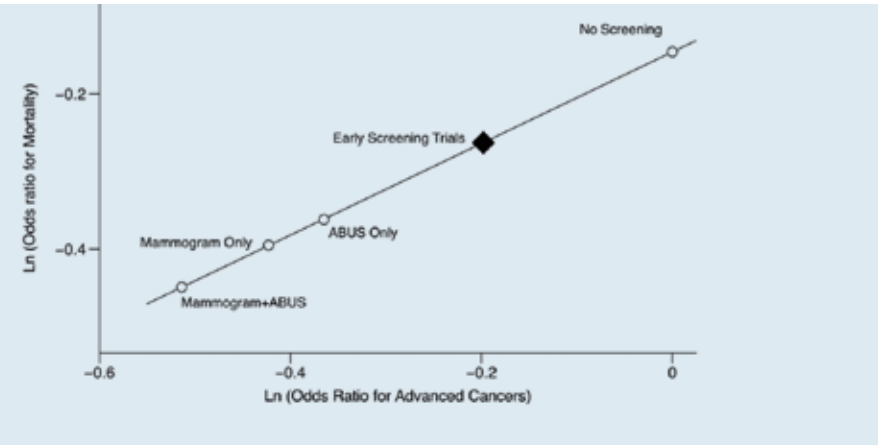

Figure 3 – Ultrasound-based screening strategies compared to an aggregate of the early mammographic screening trials and to no screening.[13)].

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Digital breast tomosynthesis in screening - does it reduce the recall rate?

By Dr A J Maxwell

Digital breast tomosynthesis (DBT) has rapidly been adopted by the breast screening community as a useful adjunct to, and possibly even a replacement for, conventional 2D digital mammography. Its superior sensitivity to 2D mammography for cancer detection is now well established but the evidence for its effect on screening recall rates is less consistent.

This article summarises the results of a recent randomised UK trial of DBT in screening the most challenging group, the younger women at increased risk. The study demonstrated no significant difference in recall rates between those who were screened with 2D mammography only and those screened with 2D plus DBT.

There was, however, evidence of a radiologist learning curve in reading screening DBT examinations. The potential future role of DBT in screening is discussed.

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DIGITAL BREAST TOMOSYNTHESIS

Since its commercial introduction several years ago, digital breast tomosynthesis (DBT) has quickly become established as an essential tool in many breast centres. During the DBT examination the x-ray tube of the mammography machine performs a series of low dose exposures of the compressed breast as it swings through an arc, and these are then reconstructed into a series of 1mm thick slices. It is not a true 3D technology, as the appearances on each slice are influenced by the composition of the tissues in the adjacent slices. The radiation dose is similar to that of a conventional 2D mammogram, which can additionally be performed under the same breast compression as the DBT. This dual examination therefore uses double the radiation of a single examination, and dose considerations have led to the development of software enabling reconstruction of a synthetic 2D mammogram from the DBT dataset as a potential replacement for the conventional 2D mammogram.

DBT has been shown to be at least as accurate as focal compression views in the assessment of screen detected abnormalities [1, 2, 3] and is useful in the assessment of symptomatic women [4, 5]. It provides a better assessment of the extent of malignancy than 2D mammography [6] and is increasingly used for image-guided biopsy [7].

DIGITAL BREAST TOMOSYNTHESIS IN PRIMARY SCREENING

Large studies of DBT in population screening such as the Oslo [8], Malmo [9] and STORM [10, 11] studies have shown a significantly higher sensitivity for the combination of 2D mammography and DBT compared to 2D mammography alone. The Oslo study reported a 27% higher cancer detection rate. As there was no increase in the detection of *in situ* disease, this equated to a 40% increase in invasive cancer detection. Similar findings have been seen in observational studies performed following the service introduction of DBT [12, 13].

Routine screening using DBT is now undertaken in an increasing number of centres in the USA and in some European countries. It is commonly performed together with 2D mammography, particularly as microcalcifications can be difficult to judge on DBT. There is now reasonably robust evidence that DBT plus synthetic 2D (S2D) mammography is diagnostically equivalent to DBT plus

conventional 2D mammography [11, 14], and the lower overall dose has led to S2D replacing 2D for screening in some centres.

"...The study showed no significant difference in either the overall recall rates between the groups .... or in the false positive recall rates..."

Composite densities are a common cause of false positive 2D mammograms. The ability of DBT to resolve these should, therefore, result in a reduction in the number of false positive recalls from screening, and indeed some studies have shown this to be the case [15, 16]. Other studies, however, have suggested that the recall rate is not affected by the addition of DBT, or may even increase [9] [11]. We have performed a study focusing on recall rates in perhaps the most challenging group of women undergoing screening, namely the younger, higher risk women.

DIGITAL BREAST TOMOSYNTHESIS IN SCREENING YOUNG HIGHER RISK WOMEN

This study [17] was performed in women aged 40 to 49 attending family history services and referred for, or currently undergoing, annual mammographic screening in two UK breast centres. These women are often particularly anxious because of their increased risk. Furthermore, their breast density is on average higher than that of older women, and this increases the likelihood of composite densities which may result in recall for further assessment.

The study was designed to compare false positive recall rates with 2D mammography alone and 2D plus DBT and is, to our knowledge, the first published prospective randomised controlled trial of DBT in screening. Mammography was performed on Hologic Selenia Dimensions equipment. Eligible and consenting women undergoing incident (second or subsequent round) screening were randomised to undergo either 2D mammography alone or 2D plus DBT. A year later those who remained in the study received the alternate examination, i.e. those who had 2D the first time then had 2D plus DBT, and *vice versa*. All examinations were double read by two radiologists with experience of DBT in screening assessment. Disagreement between the radiological opinions was resolved by consensus discussion, with arbitration by a third radiologist if necessary. Recruitment of women undergoing prevalent (first round) screening also took place but this was halted part way through the study due to a below target recruitment rate.

A total of 1227 women undergoing incident screening were recruited, and of these 1170 had 2D only and 1175 2D plus DBT examinations. The study showed no significant difference in either the overall recall rates between the groups (2D 2.8%; 2D plus DBT 2.7%) or the false positive recall rates (2D 2.4%; 2D plus DBT 2.2%). One interesting finding was that in the first year of the study there were significantly more 2D plus DBT examinations which were scored as abnormal by one or both readers but were judged to be normal at consensus/arbitration (and the women therefore not recalled) than in the second year. This suggests an initial lack of confidence in reading DBT screening examinations (particularly in dismissing benign asymmetric densities) which then improved with experience.

The findings suggest that, at least in our practice, there is little or nothing to be gained by adding DBT in terms of reducing recall rate in these younger women. As recall rates tend to be lower in older women due to their lower breast density, one would expect the same conclusion to hold true for women in the UK's population screening age group (50 to 70 years), although this does require confirmation with further research. Centres with higher recall rates may obtain some reduction from the addition of DBT, although arguably double reading with robust consensus/arbitration (as in our centres) could achieve the same goal. The recall rates in this study were surprisingly low, even for the 2D only examinations. Most of our population screening is carried out using mammography machines from another manufacturer, and it is possible that 2D false positive rates vary according to the machine used.

UNANSWERED QUESTIONS ABOUT DBT IN SCREENING

Although DBT is being increasingly used in population screening, there remain a number of unanswered questions about its role, in particular whether there are defined subgroups of women that would benefit from its use and about its cost effectiveness.

The sensitivity of mammography is inversely related to breast density due to the masking effect of fibroglandular tissue [18]. Although the sensitivity of DBT has been reported to be higher than 2D mammography in breasts of all densities, there is evidence to suggest that women with denser breasts are most likely to benefit [11]. DBT may therefore have a role for screening these women in a stratified screening programme.

There has been almost universal disregard among the authors of the published DBT studies of the prevalent/incident screening status of the women studied. This is of fundamental importance, as women undergoing screening for the first time have a substantially higher false positive recall rate than those being screened for the second or subsequent time (7.9% v. 3.0% in the UK population screening programme) due to the absence of previous mammograms for comparison. DBT may be more useful in reducing false positive recalls in this group than in previously screened women. Furthermore, the workload resulting from screening only prevalent women with DBT (predominantly the longer reading times) would be much easier to manage than

if DBT were used for screening all women. This limited additional workload may be offset to a certain extent by a reduction in false positive recalls for assessment, thus also addressing one of the harms of screening.

"...There has been almost universal disregard among the authors of published DBT studies of the prevalent/incident screening status of the women studied..."

The cancer detection performance for women undergoing repeat screening with DBT remains to be seen. The high detection performance reported in many of the large DBT studies is almost certainly due to some extent to the 'prevalent screen effect', whereby the first use of the higher sensitivity new technology detects additional cancers that wouldn't have been detected with the standard technology. The detection rate for DBT may then drop towards the pre-DBT level for subsequent rounds, although there may be an overall downshift in the size of screen-detected cancers. One would hope to see fewer interval cancers in women screened with DBT, but robust data on interval cancer rates are not yet available.

"... The high detection performance reported in many of the large DBT studies is almost certainly due to some extent to the 'prevalent screen effect'..."

The high sensitivity of DBT for the detection of small spiculate masses (typically low grade invasive cancers) has raised the question of whether screening with DBT increases overdiagnosis. This may be an argument for concentrating DBT usage in younger women, in whom slow growing cancers would otherwise eventually present symptomatically and would therefore not be overdiagnosed.

The multicentre PROSPECTS study (Prospective Randomised Trial of Digital Breast Tomosynthesis (DBT) Plus Standard 2D Digital Mammography (2DDM) or Synthetic 2D Digital Mammography (S 2D) Compared to Standard 2D Digital Mammography in Breast Cancer Screening) will randomise 100,000 women undergoing population screening in the UK and will hopefully provide answers to some of these important questions.

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Evaluating automated density maps for local breast density assessment

By Dr A Oliver

In this article we summarize our recent study where we evaluated the consistency of the spatial glandular volumetric tissue distribution provided by Volpara software. To that end, we used repeated pairs of mammograms, which were acquired in a slightly changed position of the breast. We found that the Volpara Density Maps tool is reliable in estimating the local glandular tissue distribution, being robust to small variations of the acquisition angle and in the beam energy, although divergences may arise due to different breast compression conditions.

INTRODUCTION

Volumetric breast density has been shown to have a high correlation with the risk of the development of breast cancer [1, 2]. This has motivated the investigation of strategies for the stratification of women in screening programmes based on breast density [1]. Several software tools have been developed to estimate breast density from X-ray mammographic images, including systems from Volpara [2], from Hologic (Quantra) [3] and from the University of Toronto, Canada (CumulusV) among others.

Global density measures provided by the Volpara system have been validated against MRI [3] and CT images [4]. The reliability of the system has also been investigated in a favorable comparison versus a standard two-dimensional area-based reference method [5].

In contrast to global measures, local density measures aim to provide localized information of the parenchymal distribution. Although as yet there is no clear clinical application, it is expected that this kind of measurement will provide a better risk assessment and local characterisation of disease development and parenchymal changes [6, 7].

The software from Volpara which has recently been approved by the FDA was originally described by Highnam *et al.* [8]. Intuitively, Volpara starts by looking for the region of lowest intensity in the inner area of the mammogram, which is considered as a region where no dense pixels have been traversed in the acquisition. Subsequently, knowing the intensity of the rest of the mammogram and applying some physics of light acquisition, the software is able to provide the thickness of the glandular tissue at each point of the mammogram, obtaining what is known as a density map [Figure 1]. To generate the map, some key acquisition parameters (e.g. kVp, X-ray tube anode material, filter material, compressed breast thickness located in the DICOM header) need also to be extracted from the meta-data of the image [9]. The validation of the spatial distribution of the glandular tissue identified by local measures is a challenging task. Several factors, such as the breast compression or temporal changes (aging, involution, hormonal interactions) [10], can modify the appearance of the mammogram as well as the automatic density measures. In our work [11], we evaluated the repeatability of the glandular tissue measures provided by Volpara Density Maps. Specifically, we used repeated mammograms for quantitative assessment of the variation of the density maps. To our knowledge, our study was the first to analyze the results of Volpara Density Maps using mammograms of the same breast acquired in a short period of time (only a few minutes). In such a case, there is no change in the glandularity of the breast.

EVALUATION OF THE DENSITY MAPS

To evaluate the similarity of the density maps we used 99 pairs of mammograms (198 FFDMs in total), comprising 56 pairs of CC and 43 pairs of MLO projections. Each image pair corresponded to mammograms that had been repeated due to a suspicious area prompting the radiologists to slightly change the position of the breast. Since the mammograms were acquired within a very short time interval, we assume that the only changes in the mammograms are due to the acquisition itself, e.g. different anode/cathode material, different breast compression, and different position of the breast (the breast can be a bit rotated

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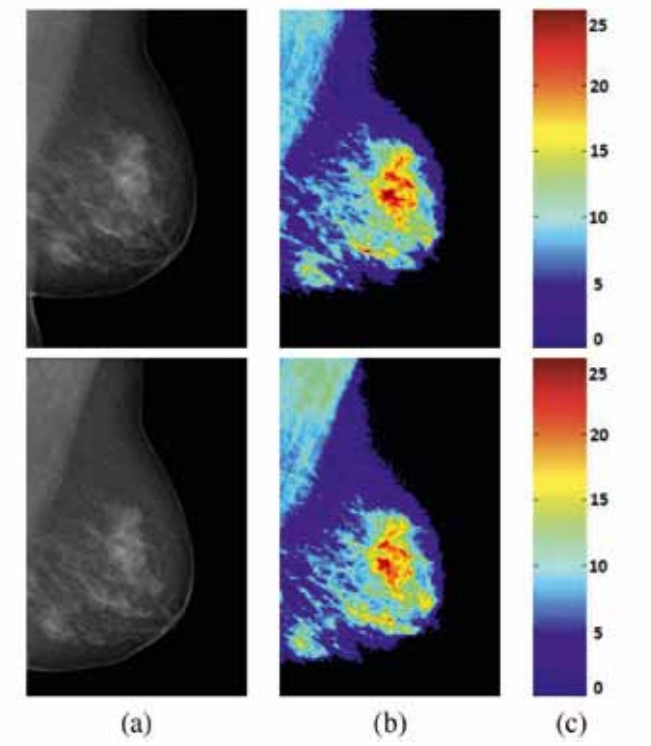
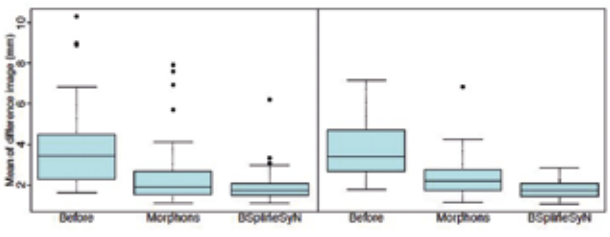


Figure 1. First column (a) shows an example of a mammogram pair studied in the work. The mammograms are very similar, although there are small changes due to differences in compression and patient's placement between the two acquisitions. The second column (b) corresponds to the respective density maps, being blue the less dense areas and red the densest parts of the breast. The color scale (c) shows the amount of glandular tissue in millimetres.

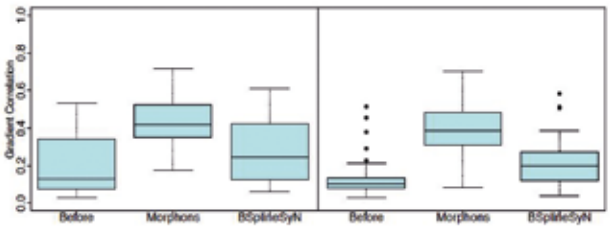
between the two explorations). Therefore, this dataset allows a quantitative evaluation of the robustness of density maps generated by the software.

A common way to assess the similarity between two images is to subtract them, so that the same structures in the same position cancel each other. In contrast, small variations in location result in a repeated presence of the structure (i.e. the positive and the negative location). Our dataset inherently corresponds to the second case, i.e. where the structures do not necessarily appear in the exact same position in both density maps. In order to minimise such differences we needed to use a deformable registration algorithm that allows local deformation of the images, making them more similar. For this, we used the morphons [12] and the B-Spline SyN [13] algorithms. Once the density maps were registered, the similarity between them was analyzed by statistics, namely the mean and the standard deviation computed on small regions extracted from the difference image on the one hand and on the other, the correlation between gradients of the two density maps. In this latter case, the gradient images were obtained convolving each image with a Sobel filter and the statistic using the normalised cross-correlation. These statistics allowed us to evaluate the structural similarity of the local tissue distribution: the more similar, the lower the measures. This allowed us to objectively measure the glandular tissue deformation: the closer the similarity, the higher the gradient correlation.

We analyzed the similarity of the density maps according to different parameters. We mainly evaluated how differences in anode/filter and breast thickness affected the results. Figure 2 shows the mean of the difference image and the gradient correlation results before and after registration according to the anode/filter used. Significant differences were found between the use or not of the registration algorithm. However a similar behavior was observed independently depending on whether the anode/filter was changed or not in the second acquisition. There was a difference in the behavior of the registration algorithms, in that B-Spline SyN outperformed the morphons algorithm with the intensity-based measure while the reverse was true with the gradient-based measure. This shows the necessity of using different deformable registration algorithms. On the other hand, Figure 3 shows the similarity of the obtained density maps depicted for different breast thickness between acquisitions. It can be seen that in this case, when no registration algorithm was used , there was a relationship between breast thickness and the mean of the difference image. The larger the differences in compression, the larger the mean difference, which indicated a bigger difference in the local glandular tissue (in the density map). Notice, however, that when using either morphons or B-Spline SyN registration, the final result was almost independent of the breast compression. A similar trend was observed in the gradient correlation, although, for this measure, the use of morphons registration again provided better results than using the B-Spline SyN combination. Additionally, we also analyzed the effect of the angle of view and end point energy. No significant differences were found in both cases, although mammograms pairs had

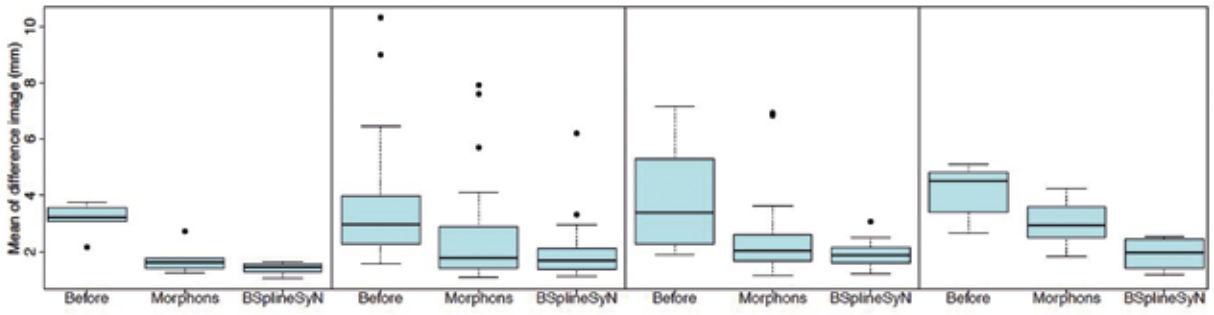


(a) Mean of Difference Image.

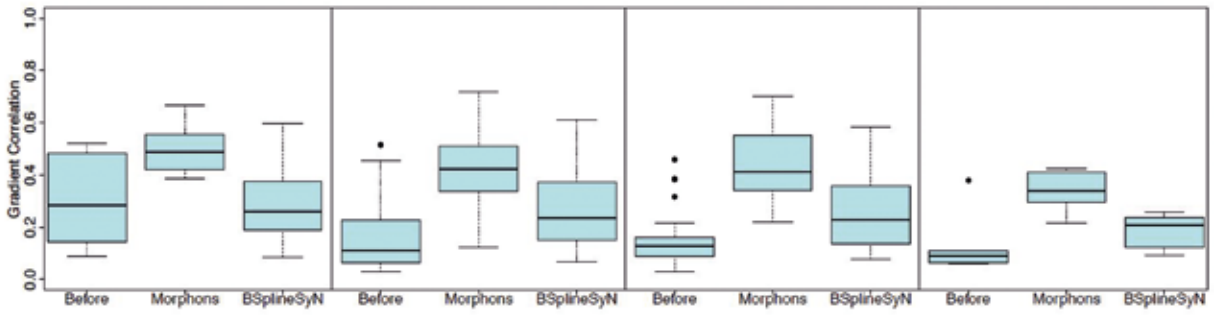


(b) Gradient Correlation.

Figure 2. (a) Mean of the difference image and (b) gradient correlation between density maps without registration and after use of the morphons and B-Spline SyN registration algorithms for different breast thicknesses between acquisitions. The left box shows the results obtained when both density maps came from images acquired with the same anode/filter composition whilst the right box shows the result when the anode or the filter changed between acquisitions.



(a) Mean of Difference Image.



(b) Gradient Correlation.

Figure 3. (a) Mean of the difference image and (b) gradient correlation between density maps. The first box (left) corresponds to the reference level (0 - 1 mm). The rest of them are: small (2 - 5 mm, centre-left), medium (6 - 10 mm, centre-right) and large (10 - 19 mm, right) difference.

differences in angle acquisition from 1 to 3 degrees and in end point energy of the spectrum between 1 and 4 keV.

DISCUSSION

In this work, the objective was to evaluate the repeatability of the local glandular tissue density map generated by the Volpara Density Maps software. An ideal dataset for such an evaluation would consist of duplicate mammograms with totally identical acquisition conditions. However, obtaining such an ideal dataset would involve (i) ensuring that the patient's positioning was exactly the same and (ii) subjecting the patients to an extra dose of radiation purely for data quality purposes.

To avoid this in practice we obtained images retrospectively from a real clinical scenario, where mammograms were repeated to allow further investigation of suspicious findings. Mammograms which were repeated due to artifacts within the image, a bad placement of the breast resulting in misalignment or even in part of the breast lying outside of the mammogram, were discarded in our study.

Therefore, in the pairs of mammograms we used, both images were in perfect conditions to be studied using the Volpara software. Direct comparison between the density maps obtained from the two acquisitions was not feasible, due to the different positioning and acquisition parameters. We were able to get round this issue by using deformable registration algorithms, which allowed us to artificially move the structures present in the density maps to similar locations, thus obtaining a statistically significant improvement in the similarity. When analyzing the robustness of the density maps according to the acquisition parameters, our results show that the output of the Volpara software was not affected by the change of the anode and filter material, the end point energy, and (small) difference of point of view between the first and second acquisition. However, breast thickness had a clear impact on the glandular tissue distribution. A posterior deformable registration between the density maps showed that discrepancies can be minimized.

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The cost-effectiveness of a population-based mammographic screening program in Lower Silesia, Poland

By Dr Bartlomiej Szynglarewicz and Prof Rafal Matkowski

In this article, we present a summary of our recent analyses of the cost-effectiveness of the organized and population-based breast cancer screening program in the Polish region of Lower Silesia, which has a population of 3 million people [1-3]. We show that the cost of cancer detection through high quality mammographic screening is relatively low, which makes the program applicable in other health care systems, even those in emerging economies.

The potential benefits of mammography screening need to be carefully balanced against the financial burden for the state in countries which have a national health care system [4]. In many high-income economies, mammographic screening has been widely implemented; various improvements in breast cancer outcomes, such as decreases in mortality have been attributed to such screening mammography programmes [5-7].

However, in countries with emerging economies and which are in the process of introducing nation-wide programs, the cost-effectiveness of population-based screening has to be particularly taken into account. Although Poland is ranked by the World Bank among the high-income countries (*http://data.worldbank.org/country*), the gross national income (GNI) per capita of 13 730 USD remains considerably lower than that in Western Europe, and is in fact just slightly above the borderline value of 12 616 USD. The country's economic situation has resulted in a severely limited health care budget. There are mixed data on the economic attractiveness of screening mammography in low- and middle-income countries but the evidence base on this is still too small to generalize the findings or draw and extrapolate any significant conclusions [8].

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BREAST CANCER SCREENING IN POLAND

Population-based breast cancer screening in Poland has been fully operational since the 1st of January 2007 (after a pilot phase in 2006) under the auspices of the Polish National Health Fund. This nation-wide program targets women aged 50-69 who are not undergoing treatment or being followed-up for breast cancer. Personal invitation letters are issued centrally by the National Health Fund using its population register.

Two-view (namely cranio-caudal and oblique) screen-film mammography is used as the standard screening test. The usual length of a round of the program is two years. All women with suspicious findings on imaging are recalled for assessment. The second level diagnostic tools that are used are breast clinical examination, additional imaging, and invasive investigations if needed. Following further assessment women with benign lesions are referred for mammography at the routine round duration of the program, while women with lesions of uncertain potential of malignancy are referred to a short-term follow-up after 6 months. Women in whom breast cancer has been detected are referred for treatment — image-guided biopsy (core-needle or vacuum-assisted). During the initial (2007-2008) and first subsequent (2009-2010) rounds

Expenses	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016
Screening mammograms	4 104 338	5 524 312	5 842 888	5 312 698	4 510 567
Recall and further assessment	209 860	211 453	186 383	165 742	178 262
Invitation letters and leaflets	137 431	146 196	190 576	146 770	118 661
Regional coordinating center	342 275	240 113	349 290	352 294	319 723
Total expense	4 793 904	6 122 074	6 569 137	5 977 504	5 127 213
Cancers detected[1]	1 049	987	1 312	1 070	1 009
Expense per cancer detected	4 570	6 203	5 007	5 586	5 081

[1] invasive cancers and ductal carcinomas in situ

Table 1. Detailed cost of breast cancer screening in the region of Lower Silesia in the years 2007-2016 presented round-by-round and expressed in 2016 USD

of screening, the technical recall rate in the programme was 0.27% and 0.1% respectively the whereas further assessment rates were 6.2% and 4.5%, respectively. The cancer detection rates, both invasive and ductal carcinoma in situ, were 6.6/1000 and 5.5/1000 while the cancer detection rate expressed as a multiple of the expected breast cancer incidence rate was 3.8 and 3.3, respectively [9.10].

The general assessment using early indicators reveals that the diagnostic service conforms to the European standards at an acceptable or even desirable level [11].

Data for our investigation were collected in a prospective manner using the SIMP computer system (the official electronic system for the monitoring of prophylaxis programs), as well as the databases of the regional branch of the National Health Fund and the Lower Silesia Cancer Registry. The amount of expenses incurred was obtained from the Regional Coordinating Center for Screening Programs for each year that was analyzed. The number of screen-detected cancers comprises both ductal carcinomas *in situ* and invasive breast cancers. The costs of invasive investigations are included in the costs of the further assessment, with the exception of vacuum-assisted biopsy that is reimbursed separately. Costs were measured, converted into US dollars (USD), and expressed in 2016 USD using the comparison of purchasing power of money calculated using the Consumer Price Index (CPI). Financial calculations were calculated using the database of the Polish National Bank (*www.nbp.pl*) to determine exchange rates and the MeasuringWorth service to measure the value of amounts in USD over time (*www.measuringworth.com*).

The analysis of cost-effectiveness is presented round-by-round in detail in Table 1.

To summarize, the total expenses for the screening program in the initial (2007-2008) and subsequent rounds (2009-2010, 2011-2012, 2013-2014, and 2015-2016) were $4 793 904, $6 122 074, $6 569 137, $5 977504, and $5 127 213 USD while the numbers of cancers detected were 1049, 987, 1312, 1070, and 1009. The cost-effectiveness ratio obtained in the program for each round was $4570, $6203, $5007, $5586, and $5081 USD per cancer found.

During the 10 years of the population-based program, the total expense for screening expressed in USD was 28,589832 and the number of detected cancers was $5427. Thus the average cost of each breast cancer detected in the screening program in the region of Lower Silesia in the period of 2007-2016 was $5268 USD.

As we have pointed out elsewhere, it is difficult to compare the costs and effects among different screening programs [2]. In general, organized and centralized programs tend to increase the cost-effectiveness of mammographic screening, mainly because of better organization, attendance rate, the use of extended invitation scheme covering a large part of the eligible population and comprehensive quality assurance procedures [4]. Published cost-effectiveness ratios may differ tremendously, and are often the result of different methods of calculation, different time periods being considered, and the inclusion or exclusion of downstream cost.

The impact of a screening programme depends on many factors, such as the epidemiology of the disease, the health care system, the quality of program, and the costs of health care [12].

Analysis using a computer model has shown that these marked differences make it impossible to set up one uniform policy for all countries [4,12].

When we evaluate the cumulative expense for mammographic screening with regard to the number of cancers found, our program looks favorable. If we compare the same period at the start of the program in other countries, the reported cost of cancer detection expressed in 2016 USD varied from $11544 in Italy, (1991-1992) to $13106 in Spain, (1995-1996) [13,14]. Our screening seems to be much more cost-effective but the limitations of such comparisons should be kept in mind.

However this difference is in any case hard to explain. It could have been influenced by many factors, since the number of cancers detected is the result of screening sensitivity, incidence of breast cancer in the eligible population, and the percentage of women screened [15]. In addition, lower reimbursement rates and salary levels in the Polish health care system compared to those in Western Europe are among other possible explanations. Some performance indicators can reflect the cost-effectiveness of screening program. Taking all this into consideration, our service seems to work well. The recall rate is acceptable, minimal-invasive biopsy rate (core-needle and vacuum-assisted) is at a desirable level (95%) while the cancer-to-biopsy ratio is very high (72%) [9,10].

The main disadvantage of our studies is the fact that since vacuum-assisted biopsy is reimbursed separately so its cost is not included in the total expense for the screening program. For the convenience of the women undergoing mammography more than 90% of screening mammograms are carried out in many small services outside our hospital, although still adhering strictly to high quality standards. In contrast however, the vast majority of vacuum-assisted procedures in the region of Lower Silesia and almost all biopsies for screen-detected abnormalities are in fact performed in our institution. Hence, some conclusions regarding biopsy costs can still be drawn. The reimbursement rate for vacuum-assisted procedure in Poland during the 2007-2008 period was approximately $1000 USD. This type of biopsy offers a lot of advantages but because of limited budgets it was generally reserved for microcalcifications (under stereotactic guidance) and for very small mass lesions (ultrasound-guided). In 2007 the number of cancers found in screening program was 543. As we reported elsewhere, in the same year a minimal-invasive biopsy rate was 95% while a benign-to-malignant ratio was 1:2.55, which gives a cancer-to-biopsy ratio as high as 72% [16]. To confirm the malignant histology of screen-detected lesions the total number of core-needle and vacuum-assisted biopsies performed in the year was 254 and 462, respectively. If we include the additional cost of vacuum-assisted procedures ($462000 USD) in the total expense for the screening program the cost of cancer detection in 2007 will rise up to $4936 USD, which however still remains relatively low.

CONCLUSION

Our findings indicate that, because of the low cost per cancer detected, a population-based mammographic screening conforming to the European quality standards is cost-effective for emerging economies. Such screening programmes should be an important part of the public policy even in countries with tightly limited health budget.

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CONFLICTS OF INTEREST

None declared

Detecting early breast cancer by integrating full-field digital mammography and automated breast ultrasound

By Prof. Christopher L Vaughan

Screening for breast cancer using full-field digital mammography (FFDM) has benefited many women over the past two decades, despite the poor sensitivity of this imaging modality in dense breast tissue. This has led more recently to the development and application of automated breast ultrasound (ABUS) as an adjunctive modality to reduce the incidence of false negative findings.

In this article, we review the studies that have sought to integrate FFDM and ABUS in a single platform, and then summarise our own research findings obtained with our dual-modality Aceso system.

There is compelling evidence that screening with FFDM – digital X-ray images of cranio-caudal (CC) and medio-lateral oblique (MLO) views of both breasts – has been successful in diagnosing healthy women for the early detection of breast cancer [1], despite some recent reports to the contrary. Although FFDM has reduced mortality, the imaging modality performs poorly in women who have dense breast tissue — often the case for premenopausal women younger than age 50 — and sensitivity drops to less than 50% [2]. The problem is that dense fibro-glandular tissue often masks underlying tumours and the resulting false negative finding at screening can have devastating consequences for the woman concerned: a poorer prognosis and more costly treatment.

Despite its poor spatial resolution, ultrasound is able to distinguish very well tissues of different density and has therefore been employed as an adjunct to mammography. Because hand-held ultrasound suffers from repeatability problems and is time-consuming, automated breast ultrasound (ABUS) devices — where the patient lies supine on a bed and her breasts are naturally compressed under gravity — have been developed and introduced over the past decade [2]. With this approach, the radiographer locates the transducer assembly on the patient's breast and a B-mode ultrasound probe scans across the breast in the frontal plane, gathering multiple 2D images that may be combined to produce 3D volumetric data of the underlying tissue.

Strong evidence to support the use of FFDM followed by ABUS as a screening tool was reported by Giuliano and Giuliano [3]. They studied 3,418 women with mammographically dense breasts and reported that when ABUS was added, their detection rate was 12.3 breast cancers per 1,000 women screened compared to 4.6 per 1,000 by FFDM alone. Brem *et al.* [4] showed that FFDM plus ABUS produced an additional 1.9 detected cancers per 1,000 screened, although there was a concomitant increase in false positive findings. In a study of 185 asymptomatic women with dense breasts (BI-RADS c or d), Giger *et al.* [5] reported that when ABUS was added to FFDM, sensitivity increased from 58% to 74%, while specificity was statistically unchanged.

Although there are clear-cut benefits of employing FFDM followed by ABUS as a screening strategy, this approach has three distinct drawbacks.

First, the breast is in a different orientation and degree of compression for the two modalities, which complicates the interpretation and co-registration of the X-ray and ultrasound images.

Second, the time required to prepare the patient and gather separate images is at least 30 minutes, compared with just 10 minutes for FFDM alone.

Third, there is the considerable capital expense to acquire separate FFDM and ABUS systems.

All this begs the obvious question: is it possible to integrate the two modalities into a single platform? The potential for combining the modalities was hinted at over thirty years ago during the analogue imaging era by Novak [6].

Ideally, a dual-modality platform should include the following five functional attributes:

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(1) the breast to be in same orientation and degree of compression when FFDM and ABUS images are obtained;
(2) images to be acquired simultaneously, thus minimising the time the woman's breast is held stationary;
(3) ABUS images of the whole breast to be obtained in a single scan;
(4) radiation dose exposure to the woman to be minimised;
(5) the design to accommodate acquisition of both X-ray and ultrasound images in 3D.

A review of the field of dual-modality imaging – combining X-rays and ultrasound to detect breast cancer – shows that there are four basic design concepts that have been described in the literature.

• In **design one**, FFDM images are captured by a flat panel X-ray detector located underneath the breast while an ultrasound probe, located on top of the compression paddle, moves under automated control [7].
• In **design two**, researchers from the USA [8] and Germany [9] have adapted design one by replacing FFDM with digital breast tomosynthesis (DBT), the technique that enables 3D X-ray images of the breast to be reconstructed. Although the clinical results were encouraging, enabling lesions to be co-registered on the DBT and ABUS images, the design had a major drawback: the images were gathered sequentially rather than simultaneously because the ultrasound scanner had to be moved out of the X-ray field of view, meaning that the patient's breast was compressed for too long.
• **Design three** employs a slot-scanning approach to acquire FFDM images, with an X-ray camera scanning beneath the breast, and an ultrasound probe moving in parallel to the camera [10], enabling both FFDM and ABUS images to be acquired simultaneously. However, because the researchers were unable to acoustically couple the probe to the breast, they could not gather clinical images.

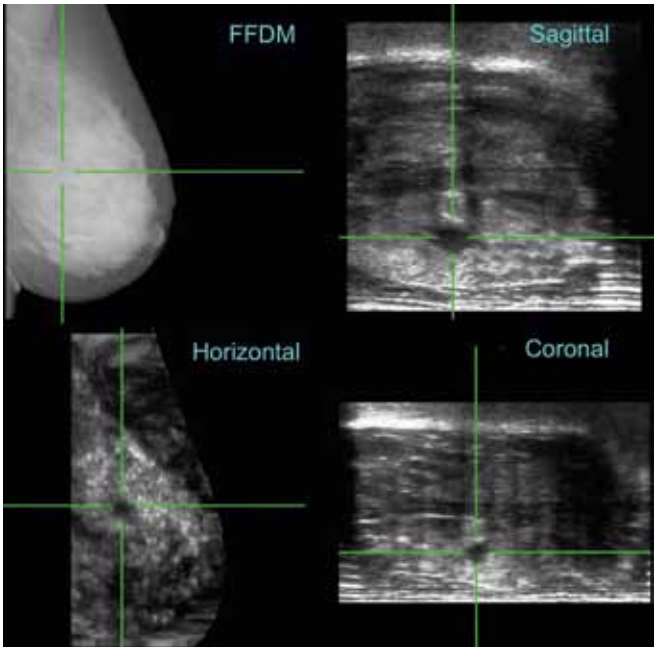

Figure 2. Co-registration of the FFDM in the horizontal plane and the ABUS images in the horizontal, coronal, and sagittal planes for a 42-year-old volunteer [14]. A lesion (benign cyst) has been highlighted by green crosshairs in the ABUS views, but the lesion is occult in the FFDM image. Note that for the ABUS images, the sagittal plane view is the acquired image, whereas the coronal and horizontal plane views have been reconstructed.

• In **design four,** the patient lies prone on her stomach with her breast protruding through an opening in the bed [11]. Both the X-ray and ultrasound systems are located beneath the support and rotate around the breast through 360 degrees, enabling 3D images to be gathered for both modalities. To date, this design has not been built and clinically tested.

Figure 1. The Aceso dual-modality breast imaging system, showing the digital X-ray camera (right) and the linear ultrasound probe (left) immersed in mineral oil in a hermetically sealed breast platform [13, 14].

DUAL MODALITY ACESO SYSTEM

Named after the Greek goddess of healing, our dual-modality Aceso system is based on design three, in which FFDM is accomplished via a slot-scanning geometry, while ABUS is implemented by positioning a linear ultrasound probe parallel to the X-ray camera [12]. As illustrated in Figure 1, acoustic coupling is enhanced by locating both the probe and camera in a hermetically sealed breast platform filled with mineral oil [13]. Two clinical trials have been conducted on 83 women – 65 healthy volunteers and 18 patients referred by clinicians at Groote Schuur Hospital – and the findings have demonstrated the potential of an integrated dual-modality system to detect breast cancer [14, 15].

The average time spent by the 83 women in the imaging room for the radiographer to acquire a full set of dual-modality images – FFDM and ABUS of both breasts in CC and MLO views – was just 10 minutes. This is comparable to standard screening mammography times and considerably less than the 30 minutes required when the two modalities are performed sequentially. While the FFDM image is gathered in the horizontal plane (parallel to the breast platform), the ABUS images are acquired in the sagittal plane and multiple slices may be reconstructed to form a 3D data set. Because the FFDM and ABUS data have a common origin and coordinate system, and are acquired simultaneously with the breast in the same orientation and degree of compression, co-registration of the images is straightforward.

CLINICAL EXAMPLES

Some of the subjects in our first clinical trial had extremely dense breasts (BI-RADS d) and here we feature a 42-year-old healthy volunteer with no prior history of breast pathology [14]. The FFDM image for the left LMO view confirmed no evidence of pathology. However, when the ABUS images in the sagittal plane were viewed as a video clip, the animation revealed the brief appearance of a dark well-defined lesion close to the breast platform. As seen in Figure 2, the four views illustrate the co-registration of the FFDM and ABUS images, while the green crosshairs identify the location of

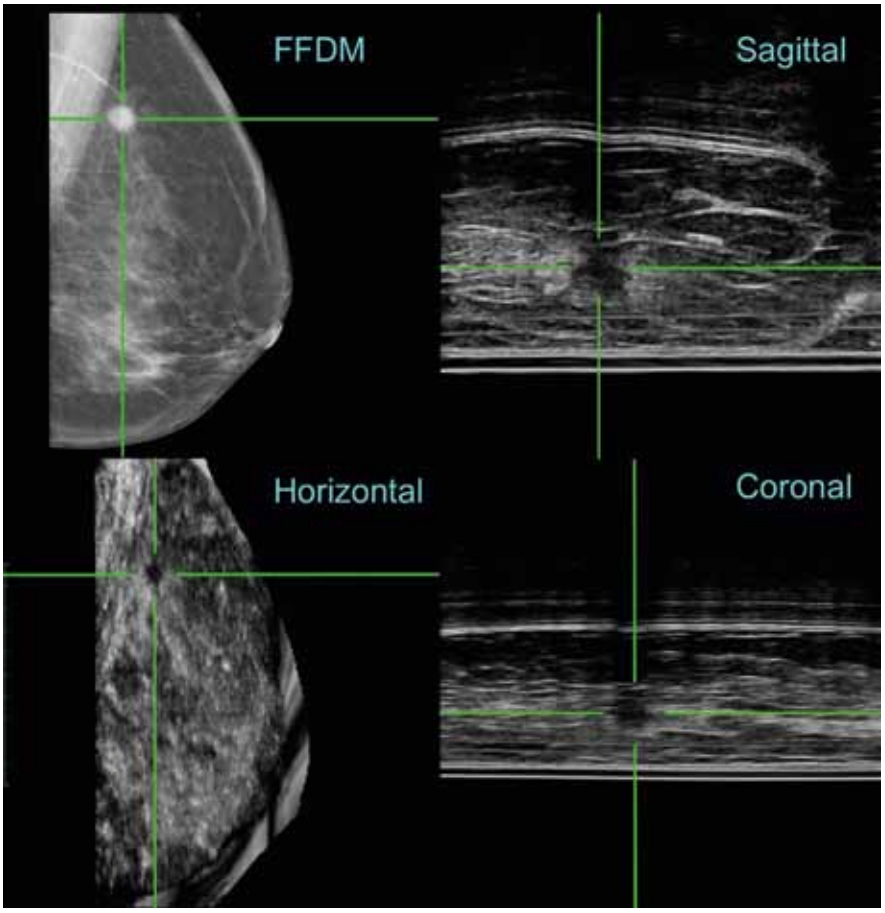

Figure 3. Co-registration of the FFDM in the horizontal plane and the ABUS images in the horizontal, coronal, and sagittal planes for a 61-year-old patient [15]. A malignant lesion has been highlighted by green crosshairs in the ABUS views and is clearly co-registered in the FFDM image. Note that for the ABUS images, the sagittal plane view is the acquired image, whereas the coronal and horizontal plane views have been reconstructed.

the lesion that is clearly occult in the FFDM image. Follow-up evaluation revealed a benign cyst. Since the ABUS images were not of sufficient quality, we developed a custom linear ultrasound probe – 192mm long, 0.5mm element pitch, 6.5MHz centre frequency for our second clinical trial [15].

Our second clinical example is a 61-year-old woman who presented with a four-week history of a painless left breast lump [15]. There was no familial history of breast cancer, she had not used hormone replacement therapy, and when examined clinically, a 2cm suspicious, hard, irregular mass was palpated. The FFDM image for the left MLO view revealed a spiculated lesion in the outer quadrant. The 3D location of the lesion, identified by the green crosshairs in Figure 3, is highlighted by co-registration of the FFDM and ABUS images generated by Aceso. An invasive ductal carcinoma was confirmed following needle biopsy, cytology and histology. The patient underwent breast preservation surgery and axillary node clearance, followed by adjuvant radiotherapy and hormonal therapy. As can be seen by comparing the ABUS images in Figures 2 and 3, the quality of the ultrasound was significantly improved in the second clinical trial [Figure 3].

CONCLUSION

Although FFDM may still be considered the gold standard for early detection of breast cancer, if a woman has dense breast tissue, lesions are often mammographically occult. A false negative finding can be devastating because a later diagnosis will inevitably lead to more expensive treatment and a poorer prognosis. Although other imaging modalities such as digital breast tomosynthesis (DBT) have demonstrated success in women with dense breasts, even DBT misses some lesions. Our second-generation Aceso system, with its improved quality FFDM and ABUS images [15], has proven its potential as a screening system for early detection of breast cancer in a busy clinic.

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DISCLOSURE

Dr Kit Vaughan is a board member and shareholder in CapeRay.

Contrast-Enhanced Spectral Mammography compared to breast MRI for evaluation of the extent of disease in newly diagnosed breast cancer

By Dr S A Lee-Felker

This article summarizes the results of a recent study comparing the diagnostic performance of MRI and Contrast-Enhanced Spectral Mammography (CESM) for the detection of index and secondary cancers in women with newly diagnosed breast cancer. The results indicate that, in such patients, CESM has a sensitivity equal to that of MRI and a PPV greater than that of MRI,

Breast cancer is the most common non-cutaneous malignancy among women in the United States and worldwide, with an incidence of 233 per 100,000 in the United States and 362 per 100,000 in the European Union [1].

While mammography and breast ultrasound are considered as gold standards for the initial detection and diagnosis of breast cancer, dynamic contrast-enhanced breast magnetic resonance imaging (MRI) has the highest overall sensitivity for detecting breast cancer, with a reported sensitivity of 90% [2]. MRI depicts both lesion morphology and perfusion behavior and is well suited for identifying multifocal (more than one cancer site within the same quadrant), multicentric (more than one cancer site among different quadrants), and contralateral breast cancer. Accordingly, MRI is the imaging modality of choice for evaluating newly diagnosed breast cancer [3, 4]. In our practice, women with dense breasts, mammographically occult breast cancer, and invasive lobular carcinoma are referred routinely for MRI to evaluate the extent of disease for treatment planning.

However, the specificity of MRI is limited [5], as both benign and malignant lesions can enhance [6]. Additional sequences such as non-fat saturated T1, T2 or short tau inversion recovery (STIR), and diffusion weighted imaging have been added to MRI protocols to help improve lesion characterization, with nevertheless imperfect specificity and additional trade offs of longer scan times, lower throughput, longer interpretation times, and overall higher costs. For the patient, the limited specificity of MRI is especially problematic for treatment planning, since additional suspicious enhancing lesions detected on MRI warrant targeted biopsy to confirm malignancy prior to any change in management, often resulting in delayed treatment [7-9].

Recently, a few studies have evaluated bilateral contrast-enhanced spectral mammography (CESM) as an alternative to MRI, citing its similar ability to depict lesion morphology and perfusion, while doing so with faster imaging acquisition, equal sensitivity for detecting index cancers [10, 11], superior specificity [10], and lower cost. CESM has been used both for screening and diagnostic indications, including evaluation of newly diagnosed breast cancer.

The purpose of our retrospective study was to compare the diagnostic performances of MRI and CESM for detection of index and secondary cancers in women with newly diagnosed breast cancer, using histology or imaging stability as the reference standards.

We studied a cohort of women with newly diagnosed breast cancer who underwent both MRI and CESM as part of routine clinical evaluation between March 2014 and October 2015 (n = 52). The majority of these women first underwent MRI and were subsequently referred for CESM as part of "second look" diagnostic imaging in conjunction with targeted breast ultrasound (n = 46). The minority of these women were diagnosed with breast cancer at outside institutions without prior imaging available; they first underwent CESM as part of diagnostic imaging in conjunction with targeted breast ultrasound prior to MRI (n = 6).

MRIs were performed in the prone position without breast compression on a 1.5 Tesla scanner (Siemens

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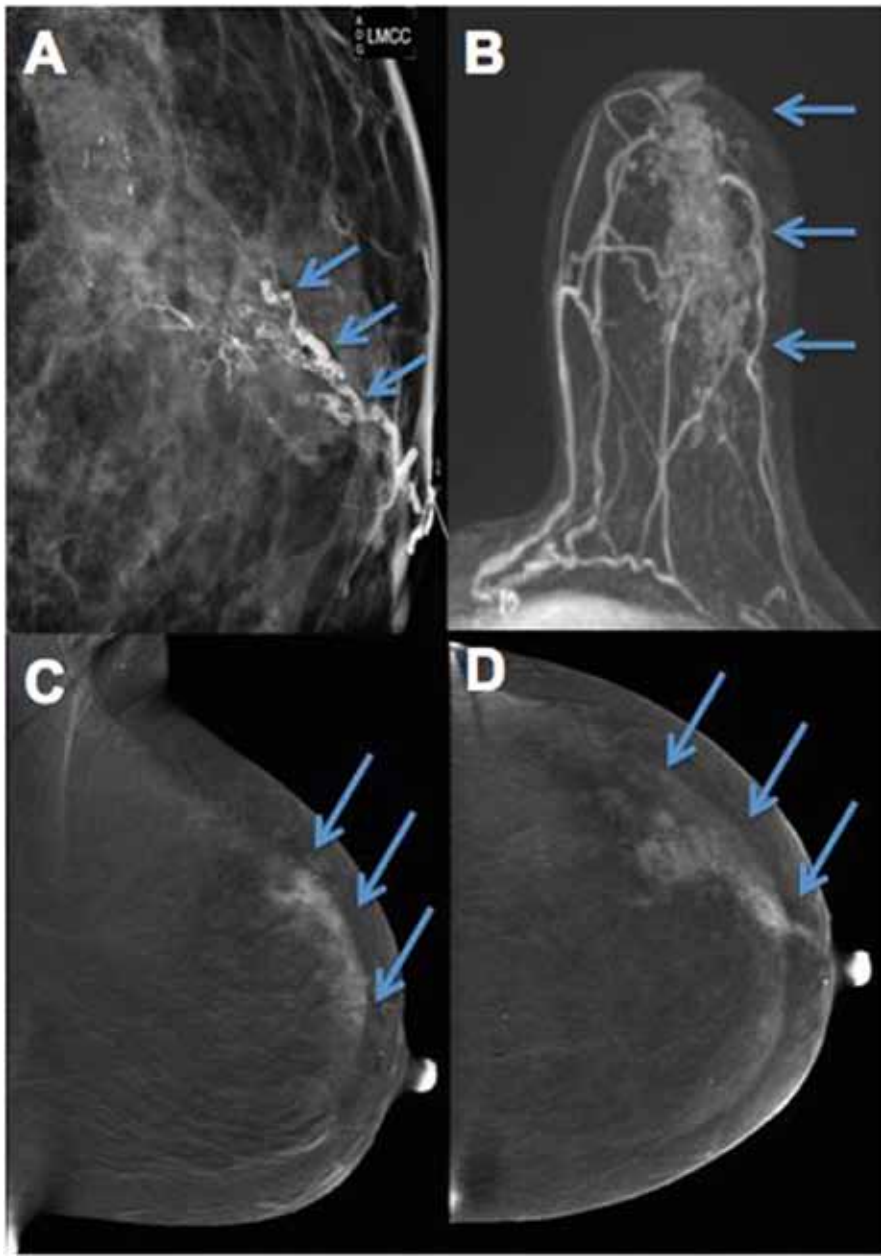

Figure 1. A 43 year-old woman presented for spontaneous bloody left nipple discharge. After inconclusive diagnostic imaging evaluation including mammography and breast ultrasound (not shown), ductography showed multiple irregular filling defects within medium-sized ducts (A, arrows). The patient underwent contrast-enhanced breast MRI and spectral mammography. Both MRI (B, arrows) and CESM (C and D, arrows) show clumped non-mass enhancement in a segmental distribution in the upper outer quadrant of the left breast. MRI-guided core needle biopsy showed ductal carcinoma in situ.

Avanto, Erlangen, Germany) using a dedicated 16-channel breast coil. The following axial sequences were performed: three-plane localizers, non-fat saturated T1, STIR, and pre- and four post-contrast fat saturated T1 at 90 second intervals after intravenous injection of 15 mL gadolinium contrast (Magnevist, Bayer, Leverkusen, Germany) using a power injector at a rate of 2 mL/sec followed by a 20 mL saline flush. Images were reviewed on a dedicated workstation (CADstream, Merge Healthcare Inc., Chicago, IL).

CESMs were performed on a dual energy digital mammography (SenoBright, GE Healthcare Inc., Chicago, IL). Within seven minutes, standard craniocaudal and mediolateral oblique mammographic projections of each breast were obtained at 90 second intervals after a two minute delay following intravenous injection of 90 cc iodinated contrast (Omnipaque 350, GE Healthcare Inc., Chicago, IL) using a power injector at a rate of 3 mL/sec followed by a 10 mL saline bolus. The peripheral intravenous line was disconnected from the injector prior to image acquisition. High and low energy images of each projection were obtained and post-processed automatically for subtraction images by the digital mammography unit. Images were reviewed on a dedicated workstation (GE Healthcare Inc., Chicago, IL).

Clinical MRI reports interpreted in consensus by two of five breast radiologists with two to 17 years of experience with MRI were compared to blinded interpretations of CESMs (both low energy and post-contrast subtraction CESM images) performed independently by two of five breast radiologists with 2.5 years of experience with CESM.

Index cancers were identified based on the presence of a dominant suspicious enhancing mass, non-mass enhancement (NME), or enhancing focus. Suspected secondary cancers were identified based on the presence of additional suspicious enhancing masses, NME, or enhancing foci in the other three quadrants of the ipsilateral breast or in any quadrant of the contralateral breast, with "second look" diagnostic imaging consisting of CESM and targeted breast ultrasound and/or biopsy requested for further evaluation.

When breast conserving treatment was desired, additional suspicious MRI findings were pursued with CESM and targeted breast ultrasound. If CESM and/or ultrasound collaborated the MRI finding as suspicious, targeted biopsy followed. If CESM and/or ultrasound revealed a benign or no correlate for MRI finding, such as a complicated cyst, imaging follow up ensued (MRI for MRI only findings and ultrasound for sonographic correlates). MRI findings, CESM findings, histology results, and/or imaging follow up were recorded.

52 women with 120 lesions were included for analysis (mean age 50 years, range 29 to 73 years). 11 women had one lesion each, 19 women had two lesions each, 17 women had three lesions each, and five women had four lesions each.

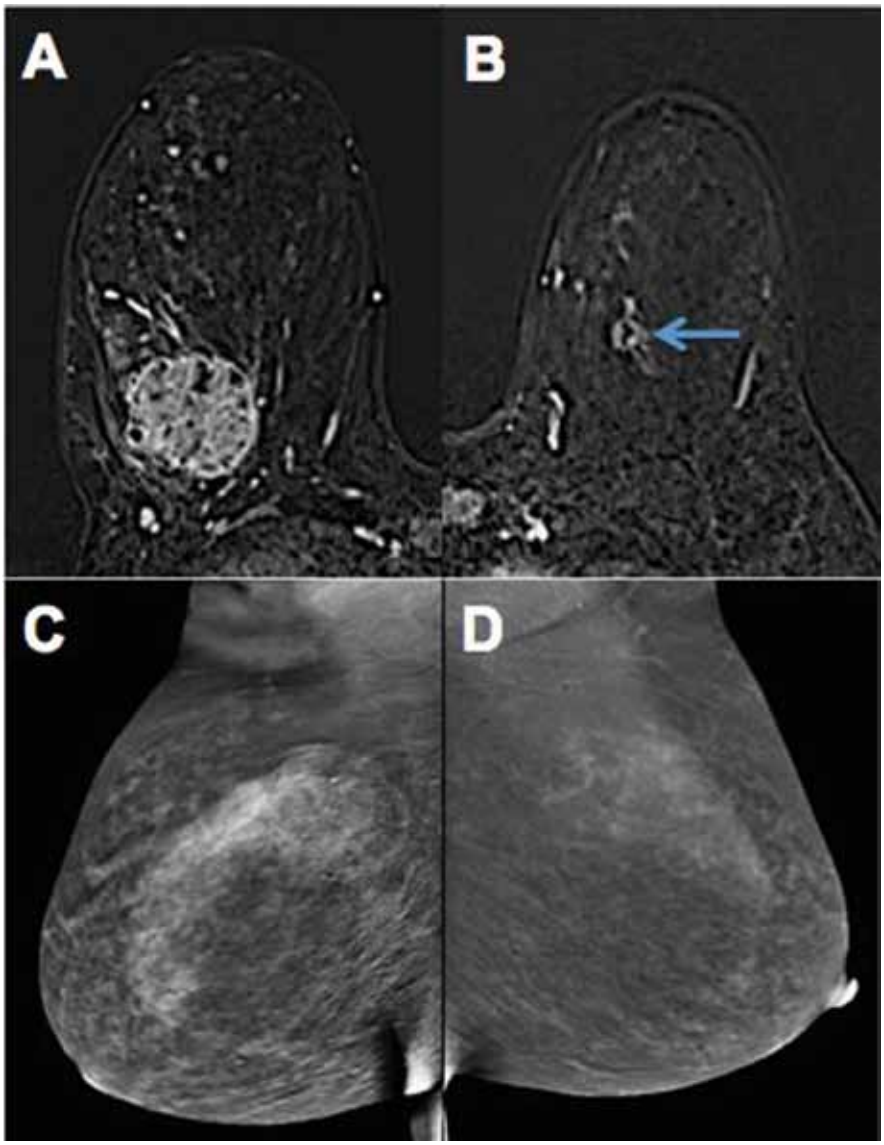

Figure 2. A 46 year-old woman presented with a right breast palpable abnormality at the 9:00 position. After diagnostic mammography and breast ultrasound showed a suspicious 4.5 cm mass at the 9:00 position of the right breast (not shown), ultrasound-guided core needle biopsy yielded invasive carcinoma of no special type. Contrast-enhanced breast MRI showed the biopsy-proven cancer at the 9:00 position of the right breast (A), as well as a rim-enhancing mass at the 11:00 position of the left breast (arrow, B) without correlate on CESM (C, D) or targeted second look breast ultrasound. MRI-guided biopsy yielded fibrocystic change.

In our study, CESM had similar overall sensitivity (94% (66/70) versus 99% (69/70)), significantly higher PPV (93% (66/71) versus 60% (69/115), $p < 0.001$), and significantly fewer false positives than MRI (five versus 45, $p < 0.001$) for overall cancer detection. These MRI false positive lesions resulted in 21 additional core needle biopsies, one surgical excisional biopsy, and ten prophylactic contralateral mastectomies. The excisional biopsy and prophylactic contralateral mastectomies did not result in additional cancer diagnosis. CESM also had similar secondary cancer detection compared to MRI (100% (11/11) versus 91% (10/11)).

CONCLUSION

CESM is a promising imaging modality with the potential to depict lesion morphology and perfusion with faster imaging acquisition, equal sensitivity [Figure 1], superior PPV for cancer detection [Figure 2], and lower cost compared to MRI. The superior PPV of CESM may help expedite treatment planning for women with newly diagnosed breast cancer. CESM can be integrated into routine diagnostic imaging and is valuable for extent of disease evaluation in women with newly diagnosed breast cancer. If these findings are confirmed, more women will have a high quality diagnostic option when MRI is not available or when contraindications for MRI exist.

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Breast ultrasound from the patient's perspective

How the clinical advantages of high-definition imaging with elastography support compassionate care.

By Dr Kamilia Kozlowski

Knowing that modern mammography can miss cancer in dense breast tissue, my colleagues and I at the Knoxville Comprehensive Breast Center have been performing ultrasound screening since 1983 for dense breasts and indeterminate mammographic clinical findings. We recently helped pass a breast density notification law here in Tennessee. Currently in the United States, more than half of the individual states have passed legislation which requires radiologists to inform women if it is found that they have dense breasts.

In addition to advocating effective breast cancer screening, I also strongly encourage my peers to use state-of-the-art ultrasound technology. At my practice, we have used an ultrasound system (Aixplorer, SuperSonic Imagine) with real-time elastography technology, ShearWave Elastography (SWE) for eight years. We now have ten units and recently upgraded to a new higher-resolution transducer with 256 elements and a bandwidth of 5 to 18 MHz (the SuperLinear SL18-5). The system gives us high-resolution images, as well as the SWE color-coded map and analysis of tissue stiffness, a key parameter in diagnosing lesions.

When ultrasound technicians come from other hospitals, they are astounded at the resolution of our ultrasound, as well as the added benefits of SWE. Which makes me wonder why more facilities aren't using this technology. It is well established, and the distinct clinical advantages of SWE allow us to detect cancer more definitively, reducing both false positive and false negative results. High-technology ultrasound with elastography also has the important advantage of making a very stressful patient experience more tolerable.

COMFORT AND EDUCATION

Years ago, when my mother had a thyroid biopsy, the surgeon told her "It went well." I realized that he meant from his perspective, the procedure went well. My mother was positive for lymphoma, and I was left to tell her. Thus, when I started my independent breast center, I knew it was important to inform my patients openly about their findings. They arrive at the office to find out the number one question on their mind, "Do I have breast cancer?" To send them out of the office to have their results given to them in time through the referring doctor's office is unwarranted and only increases anxiety for the women. This is unthoughtful of the woman's psyche.

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The clinical breast radiologist's interaction with patients during the workup is extremely valuable. Breast ultrasound is an inherently stressful experience for patients who are worried they may have cancer or already know they have the disease and are bracing themselves to hear the details. The entire breast imaging visit from the time a woman walks through the front door of the office is an inherently stressful visit. My staff is very well aware that it is important for every department of the office — from check-in, mammography, breast ultrasound, breast MR and any biopsies that may follow — to work on alleviating the woman's fears.

"…. the distinct clinical advantages of SWE allow us to detect cancer more definitively, reducing both false positive and false negative results…."

If a patient is referred after a positive mammogram or MRI, I begin by asking, "What is your understanding of the findings from the previous test?" They usually say, "I don't know. They told me I need a biopsy."

I explain that a biopsy is a possibility, but first we will do some additional high-tech imaging. I counsel patients

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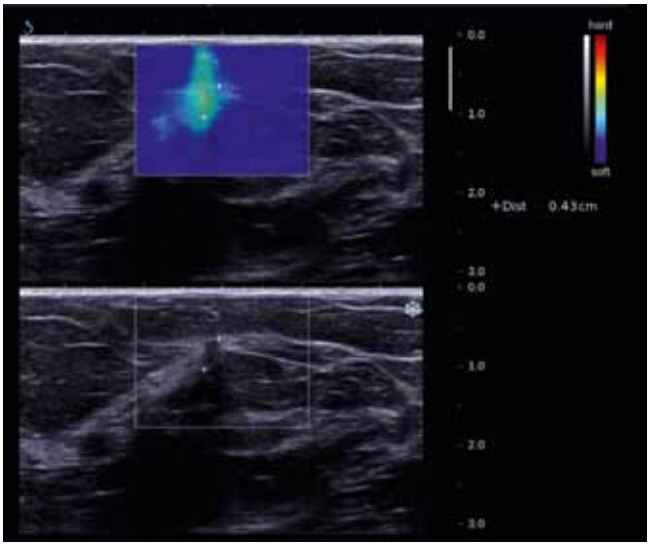
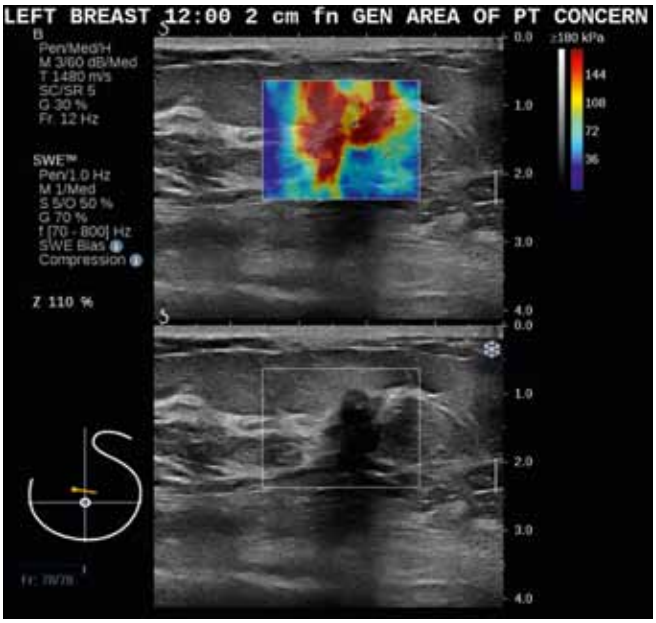


Shearwave elastography, performed using the Aixplorer Multiwave Ultrasound System colorizes non-palpable masses on the basis of their elasticity. The above image shows a malignant breast lesion, with a hard shell. Stiff tissue is indicated in red, soft tissue in blue.

through the entire workup, keeping them apprised of what I am doing and seeing. I explain that breast ultrasound allows me to evaluate the breast tissue's physical properties through sound absorption and transmission. As a result, I can actually see anatomy of the breast which is not the case with 2D or 3D mammography. I can review the images with the patient, point out the anatomy of the breast tissue, as well as findings of importance that are occult on mammography or relate to a mammographic finding.

Depending on the reason for the ultrasound, I might explain that the ultrasound is allowing me to get good images through their dense tissue or that it is telling me a lot about the mass detected in mammography. I can show them what I'm looking



Invasive ductal, grade 2 cancer-palpable, mammographic mass that is non vascular on Doppler US, Stiff on SWE.

at on the screen – healthy breast tissue or the lesion size, borders and stiffness. I want to give patients information rather than leave them in the dark, and they appreciate that. Our ultrasound system also allows us to get images and data very quickly, which helps minimize physical and psychological discomfort.

CONFIDENCE AND RESULTS

Using SWE to evaluate breast tissue alongside high-definition ultrasound images gives us a very strong confidence in our conclusions. This confidence is projected to our patients. Patients feel they can trust us and feel reassured that our findings will be the ultimate, verified diagnosis.

"…. Our ultrasound system also allows us to get images and data very quickly, which helps minimize physical and psychological discomfort…."

Patients are at the breast center for an answer. If we suspect cancer, we are very open and detailed about what we see, what that means, and what comes next in their work-up . Patients need and want to know. We explain that they will need a biopsy and what to expect from that procedure.

I always tell patients what I am doing and seeing throughout the visit – for example, I tell them that I see on the ultrasound the lump detected in mammography, that its shape suggests it might be cancerous, and that the tissue firmness shown on SWE is also suspect. In this way patients do not have a surprise waiting for them at the end of the work-up.

Even if there is something of concern, they feel reassured by the process and my openness.

Every woman dreads hearing that she has breast cancer, but we can present the news compassionately to avoid shock or a sense that this is a death sentence, which breast cancer typically is not. Many of these patients have already been through the ominous experience of having a doctor say she feels something or the mammogram shows a suspicious lump. They are very scared. When they hear the news that everything is OK, their facial expressions changes completely to smiles and tears of joy. I explain the benign lump and any other steps ahead.

Thanks to the ultrasound images and SWE technologies , along with Doppler to access vascularity, we are able to determine with much greater confidence whether a lesion is benign or malignant and as a result perform fewer needle biopsies.

From the patients' perspective, instead of waiting, terrified, for another appointment and enduring a biopsy, they can know immediately that they do not have cancer.

It is another important example of how using the latest technology enables us to excel clinically while helping improve the patient experience.

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While targeted radiotherapy can be effective, uncertainties throughout the process – from imaging to planning to treatment – can impact the quality of care. These uncertainties, combined with growing caseloads, higher patient throughputs and increasing pressure on resources, all present a challenge to providing efficient care. With innovations that can reduce these uncertainties, improve accuracy, and enhance the ability to assess therapy response and adapt treatment plans if necessary, radiation oncologists can confidently deliver consistent, high-quality care.

RTdrive MR Prostate enables radiation oncologists to generate high-quality treatment plans for prostate cancer with fewer manual steps by harnessing the power of the Ingenia MR-RT platform, MR-only simulation, Auto-Contouring and Pinnacle^3 Auto-Planning. Due to this breakthrough in intelligent automation, radiation oncologists can create treatment plans more quickly with less effort, saving valuable time and contributing to a better patient experience.

"Oncology care teams strive to increase precision, accelerate time to treatment, improve patient care and enhance patient satisfaction," said Ardie Ermers, General Manager of Radiation Oncology at Philips. "Delivering on our commitment to provide meaningful innovations for patients and care providers, we have focused on developing solutions in radiation oncology to streamline workflows from start to finish."

With integrated tools, systems and software that span from imaging to treatment planning, Philips' radiation oncology solutions streamline processes and workflows to improve radiotherapy planning and delivery.

This year, Pinnacle3 16 has a refreshed user interface and an overall improved look and feel. New features include Deformable Image Registration (DIR) incorporated into the Dynamic Planning module, and Intensity Modulated Proton Therapy (IMPT), which integrates Proton Photon planning into the Pinnacle3 16 Proton Planning environment.

PHILIPS HEALTHCARE
EINDHOVEN, THE NETHERLANDS
www. www.philips.com

Fuji Sonosite POC ultrasound is a hit in pediatric intensive care

Ultrasound technology is helping the Pediatric Intensive Care Unit (PICU) at King's College Hospital, London, UK to rapidly obtain vascular access in critically ill patients. Dr Akash Deep, Director of the PICU, explained: "PICU treats patients ranging in age from just a few days old to 18 years, effectively young adults. In many of these patients, for example a child in septic shock, vascular access must be obtained without delay, and we rely on ultrasound for this procedure. Until recently, this was performed using a hand-held system that was quite old, so we could not always obtain the image quality we needed."

"Our theatres are now equipped with point-of-care ultrasound systems. We used one of these for a PICU patient where vascular access was proving particularly difficult, and were amazed by the difference it made; within minutes, an arterial line was in place. I am convinced this contributed to better management of the patient's septic shock by helping us to rationalise inotropes and vasopressors, and we simply could not have done this with our other ultrasound instrument. This played a large part in our decision to obtain a system specifically for the PICU. We are also the largest liver transplant centre in Europe, and use continuous renal replacement therapy a great deal. Vascular access is difficult in many of these patients, and the system has proved a real boon for us. We've

had it for a few months now, and I see the satisfaction on the registrars' faces when they use it. They are absolutely ecstatic."

FUJIFILM SONOSITE
BOTHELL, WA, USA
www.sonosite.com/

One Less thing for OR staff to worry about during breast cancer surgery

KUBTEC announced that it has developed a unique solution to a potential problem faced by OR staff when treating patients for breast cancer.

The Automatic Specimen Alert (ASA), now available on the Mozart System, KUBTEC's proprietary intraoperative 3-D Tomosynthesis system, eliminates the possibility that OR professionals may forget to remove the excised specimen from the system once imaging is complete.

With checklists in place in most ORs, this happens infrequently; but when it does, it can have serious

downstream consequences, as the specimen must be fixed in formalin within 60 minutes from the time of excision in order to be considered viable by Pathology. Older systems currently in use have a small window through which the technician can see into the specimen chamber. For this to be beneficial, it requires the operator to be close to the instrument and to remember to look inside despite handling many other responsibilities simultaneously.

"We thought that a more elegant, convenient solution would be to proactively alert the user on the rare occasions when the specimen is not removed in a timely fashion. And that's what we've developed," remarked Vikram Butani, CEO at KUBTEC. "We conceived that an active alert is superior to a passive, old fashioned window for these infrequent yet potentially serious situations."

After 10 minutes of inactivity, the MOZART System's ASA feature flashes a very clear indication on the system's monitor screen if a tissue sample remains inside the cabinet. "With Automatic Specimen Alert the technician can see from across the OR that an action is needed. We would not be surprised if the window feature eventually becames obsolete after medical professionals discover how much safer and more efficient things are this way," Butani concluded.

KUBTEC
STRATFORD, CT USA
http://kubtec.com.

Integrated ultrasound and angiographic imaging for navigation during structural heart disease interventions

Siemens Healthineers has introduced TrueFusion, an application on the new Release 5.0 of the ACUSON SC2000 cardiovascular ultrasound system that integrates ultrasound and angiography images. These integrated images can be used to guide cardiac teams when administering treatment for structural heart disease.

Fused imaging for structural heart evolving rapidly. Increasingly, these minimally invasive procedures involve multimodality imaging and multidisciplinary clinical teams. To reliably diagnose structural heart disease and perform these complex interventions, clinical teams need detailed, real-time imaging information – specifically, real-time soft tissue and blood flow information from echocardiography as well as 2D imaging information from fluoroscopy – to be visible in one view for common orientation. Addressing the need for fused images, the new TrueFusion application sends anatomical and functional markers as well as valve models from the ACUSON SC2000's True Volume transesophageal echocardiography (TEE) transducer to an Artis with PURE angiography system, overlaying ultrasound information with live fluoroscopy images to navigate structural heart procedures. By directly and seamlessly integrating co-registration of Artis fluoro and

ACUSON SC2000 echo into the workflow via machine learning-based probe detection and automated registration updates, TrueFusion enables clinical teams to identify soft tissue-based structures that are provided directly from the integrated ultrasound system. With the system, not only can echocardiographers and interventionists better communicate and achieve more intuitive anatomical orientation during challenging procedures, but clinical teams potentially can reduce contrast usage and procedure time as well as patient and clinician X-ray exposure. "With one of the industry's broadest portfolios for diagnosis, therapy, and follow-up of cardiovascular disease, Siemens Healthineers supports patient care along clinical pathways to improve outcomes," says Philipp Fischer, General Manager of Siemens Healthineers Cardiology. "For the high innovation pace of novel procedures and devices in structural heart disease, we provide data and image integration for clinical decision support and real time therapy guidance."

SIEMENS HEALTHINEERS
ERLANGEN, GERMANY
www.siemens.com/healthineers.

Approval of innovative medical device for cTACE procedures

Guerbet, the specialist in contrast products and solutions for medical imaging, has announced that it has obtained the CE mark for its innovative conventional Trans-Arterial Chemo-Embolization (cTACE) mixing and injection system, Vectorio. Designed in collaboration with interventional radiologists worldwide, Vectorio is a unique set of Lipiodol resistant medical devices including syringes, patented stopcock and sampling devices. Lipiodol Ultra Fluid (ethyl esters of iodized fatty acids of poppyseed oil) was initially developed for diagnostic radiology in indications including liver lesion diagnosis, lymphography and hysterosalpingography, and then used in interventional radiology for cTACE. This latter is a minimally invasive procedure which consists of mixing Lipiodol Ultra Fluid with an anticancer drug and injecting this treatment trans-arterially in the liver as a loco-regional targeted chemotherapy.

The Vectorio system is designed for mixing and delivering Lipiodol Ultra Fluid & anticancer drugs during cTACE procedures in adults with known, intermediate-stage hepatocellular carcinoma (HCC) which is the most common primary liver cancer and is the second biggest cause of death due to cancer worldwide. The medical device offers multiple

advantages for healthcare professionals, such as 24 hours Lipiodol resistance; a patented 3-way stopcock with 4 connections offering possibility of "On-table mixing" (interventional radiologists have the possibility of remixing without disconnection from the micro-catheter, thus maximizing the safety during the intervention).

"Vectorio has been developed in collaboration with international interventional radiologists to match their medical needs for accurate, user-friendly and safe solution during cTACE procedures. The development of these image-guided procedures is a top priority for Guerbet's interventional franchise. We have a worldwide commitment to improving the prognosis and quality of life of patients with liver cancer" said Yves L'Epine, CEO of Guerbet.

GUERBET,
VILLEPINTE FRANCE
www.guerbet.com .

Demonstrations of multi-modality diagnostic displays

Barco, a global leader in healthcare imaging, will use NeoLogica's RemotEye Suite universal viewing solution software to enrich and simplify radiology and breast imaging display demonstrations in the United States and Canada. The software allows all types of patient images – including 3D mammography – to be displayed in one, easy-to-use application.

With the growing demand for patient imaging, it is essential to develop solutions that help radiologists manage the increased workload by enhancing their productivity and working comfort during long days. Barco offers a rich portfolio of diagnostic display systems designed to boost clinician's diagnostic confidence and workflow efficiency in radiology reading rooms.

The NeoLogica RemotEye Suite will allow Barco to easily and efficiently demonstrate these benefits using a single viewing application that showcases its diagnostic display capabilities in the best light. The software offers full DICOM compliance, a web-based architecture, cross-platform compatibility, and support for a wide variety of devices. Simply put, any DICOM image can be displayed anytime, anywhere, on any device.

"We are pleased to partner with NeoLogica to support our sales team with this innovative solution to power our diagnostic imaging demonstration systems," comments Kurt Deyoung, VP Sales, Hospital Accounts. "The RemotEye Suite allows us to easily display datasets of all types, offering cross-modality support, flexible image-hanging options, and a rich toolset that enables our team to effectively demonstrate the unique capabilities of Barco's display solutions."

Barco will utilize the RemotEye Suite software to demonstrate the complete line of Coronis and Nio display systems – featuring the award-winning, multi-modality Coronis Uniti and Coronis Fusion 6MP – educating radiologists on the wide array of diagnostic features for viewing a multitude of patient image types.

NeoLogica designs and develops advanced software solutions in the medical imaging field, with the RemotEye Suite its flagship product.

"We are proud to have established this partnership with Barco, which is globally recognized as the reference within the industry when it comes to the quality of medical displays. I am sure our RemotEye Suite product, and more specifically our RemotEye Viewer software module, together with the dedication and professional-

ism of our technical staff, will provide all the support Barco needs to showcase the full and impressive potential of their latest medical display solutions," Marco Sambin, CEO and co-founder of NeoLogica.

BARCO
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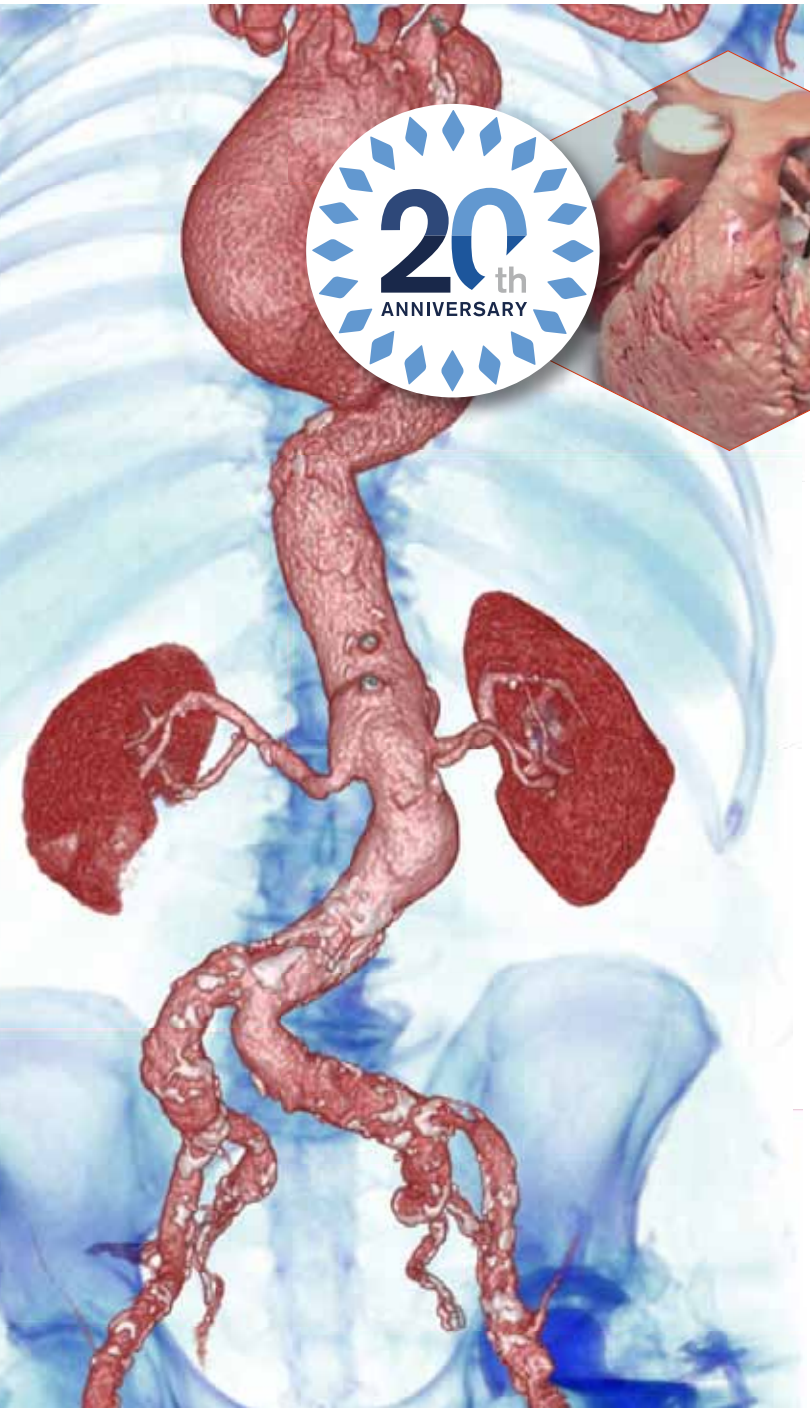

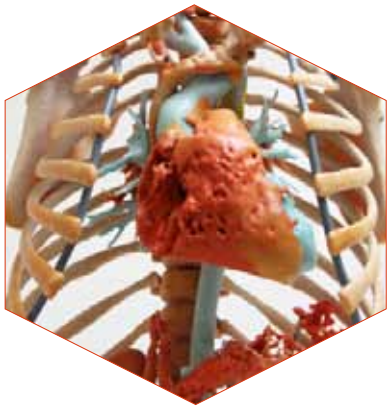

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