DYNAMIC OPTICAL BREAST IMAGING

- A New Technique to Detect Breast Cancer at Early Stage -

RESULTS OF INVESTIGATIONAL USE OF DOBI COMFORTSCAN IN CHINA

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SUMMARY

A clinical study on Dynamic Optical Breast Imaging (DOBI®) modality was performed in Beijing to verify the safety and effectiveness of using DOBI Medical's ComfortScan® system in diagnosing malignancy in lesions of the breast. The ComfortScan® system is based on sensing and analysis of near infrared light penetration through the breast tissue and recording of the reaction of the tissue to a compression stimulus that induces changes in blood volume and metabolic rates associated with tumor angiogenesis in the breast. Preliminary results showed that the ComfortScan can help the performance and accuracy of clinical doctors through an In-Vivo, Non-Invasive, Non-Ionizing and Non-painful molecular vesicular Dynamical Optical Breast Imaging technology. However further evaluation of clinical significance for broad clinical applications is necessary.

1. INTRODUCTION

Methods contributing to the diagnostics of malignant tumors have been at the forefront of interest of physicians and researchers for many years. According to the American Cancer Society,[1] breast cancer is the most common cancer in women and is a leading cause of death among women worldwide. The latest statistics from the Health Ministry shows that breast cancer in China has a high incidence among women aged 30 to 54 years, which are earlier about 15 years than western countries. Currently, due to lack of preventive knowledge and ineffective early diagnosis, tens of thousands of Chinese women are still at risk of unknowingly developing the disease, and cancers are in advanced stage when they are found. The recent data from the Chinese Anti-Cancer Association (CACA) shows the incidence and death rates of breast cancer in China's major cities rose by 37 percent and 38.9 percent, respectively, over the last 10 years, while the death rate in rural areas rose by 39.7 percent. The death rate from breast cancer has been increasing by three percent annually in recent years.[2]

According to the Institute of Medicine,[3] early detection of breast cancer, or screening, has reduced breast cancer mortality by allowing intervention at an earlier stage of cancer progression. In clinics, more than 90 percent of early breast cancer patients can live 10 more years and their breast can be kept as much as possible. So undeniably, an advanced and special exam of breasts is needed for clinical diagnosis and early detection of breast cancer.

1.1 The Need for New Diagnostic Technologies

When it comes to diagnosing breast cancer, however, current methods are limited in their ability to differentiate between malignant and benign breast lesions. Diagnostic mammography has low specificity, the ability to detect a benign tumor. In addition, mammograms of women with dense breast tissue are difficult to interpret.[4] Women undergo more than 1 million biopsies each year in the U.S. (at an estimated cost of $1.7 billion) to determine whether cancer is actually present in suspect tissues. Up to 80 percent of these biopsies are benign – increasing medical costs and the pain and uncertainty of patients.[5] Furthermore, some adjunct technologies to mammography such as MRI and PET are expensive, or they cannot consistently detect microcalcifications (ultrasound and MRI) or, in the case of ultrasound, small tumors. What is needed in clincal breast cancer diagnosis is a noninvasive, cost-effective adjunct to mammography that can discriminate between malignant and benign lesions – thus preventing unnecessary biopsies.

In response to this need, on March 8, 2001, in a press release announcing the release of its comprehensive new study, ***Mammography and Beyond***, the National Academy of Sciences' Institute of Medicine issued a call to action for improvements in breast-imaging techniques. In addition to characterizing film mammography as the "gold standard" against which new imaging technologies will be measured, the press release states that "no single imaging technology is capable of accurately detecting all breast abnormalities" and that "ultimately, the best detection may come from using several different tools."[6]

Currently, breast cancer detection encompasses three stages. First, a physical examination or screening mammography identifies an abnormality in the breast tissue. Second, additional imaging modalities may be used to help decide if a biopsy is required. Third, if required, a biopsy is performed to diagnose the abnormality as either benign or malignant. Malignant abnormalities are further characterized biochemically and are staged according to the size of the tumor as well as the extent of invasion and metastasis in order to determine a prognosis and treatment.[7] The following sections review the utilization of mammography, ultrasound, MRI, PET and biopsy as diagnostic tools.

Mammography

Mammograms, x-rays of the breast, are generally categorized either as screening or as diagnostic. Screening mammography is used to check for breast disease in women who are asymptomatic. Diagnostic mammography is used to check for breast disease in women who experience new symptoms, or it is used to further explore a suspicious finding identified by a screening mammogram. Mammograms, however, do not detect cancer per se. Instead, they

help to identify tissue abnormalities, which in turn are subject to interpretation or additional testing such as ultrasound or, definitively, diagnostic biopsy.[8] Although most studies demonstrate a substantial reduction in death rates from breast cancer among women screened by mammography, women over age 50 benefit the most from screening mammography. Below age 50, the value of screening is less clear.[9] Since women in their 40s are generally premenopausal and therefore more likely to have greater breast density than postmenopausal women, it is more difficult to interpret mammograms – leading to some that are indeterminate. Mammograms for postmenopausal women on estrogen-replacement therapy are similarly difficult to interpret.[10] Because the specificity of mammogram testing is quite low, false-positive findings can have a detrimental effect on the screened population. As many as 80 percent of all breast lesions that are biopsied as a result of suspicious findings on a mammogram turn out to be benign.[11] Studies show that abnormal mammograms negatively affect a woman's psychological and emotional state and may impair daily functioning for 3 to 18 months.[12] Because the greater density of breast tissue in younger, premenopausal women renders mammography results more difficult to interpret, improved specificity and sensitivity in diagnostic methods would benefit younger women in particular.

Ultrasound, MRI and PET

Once an abnormality is identified through examination or mammography, the next stage in cancer detection can be utilization of an adjunct technology (such as breast ultrasound, MRI and PET) or, definitively, a biopsy. Ultrasound can help to determine if an abnormality that appeared on a mammogram is a cyst or a solid mass.[13] According to the National Cancer Institute, however, about half of cancers detected by mammography appear as a cluster of microcalcifications and ultrasound does not consistently detect microcalcifications nor detect very small tumors.[14]

As an alternative to ultrasound, MRI (Nuclear Magnetic Resonance Imaging) may eventually prove useful in a small number of cases for diagnosing breast lesions identified through screening mammography or clinical breast examination. MRI, however, remains an unproven technology for widespread use in breast cancer detection. Furthermore, it is an expensive diagnostic alternative and it cannot detect microcalcifications.[15]

Based upon the understanding that malignant tissue tends to metabolize glucose differently from tissue with benign abnormalities, positron emission tomography (PET) uses radioactive tracers such as labeled glucose to identify regions in the body with high metabolic activity.

PET scans, however, are an expensive alternative and are invasive in that they require the injection of a radioactive substance into the body.

Biopsy

According to the American Cancer Society, a biopsy is the only way to detect whether or not cancer is actually present. All biopsies remove a tissue sample for examination under a microscope. Biopsies include fine-needle aspiration (FNA) biopsy, core-needle biopsy (CNB) and surgical or excisional biopsy.[16] Surgical or excisional biopsies are the most traditional method of removing tissue for further study – they are also the most expensive and invasive. FNA biopsy requires insertion of a very thin needle on a syringe to remove either fluid from a cyst or clusters of cells from a palpable mass. CNB is more traumatic than FNA biopsy because it uses a larger needle with a special cutting edge to remove small cores of tissue. The tissue cores are usually large enough to enable pathologists to distinguish between invasive and noninvasive types of breast cancer.

Because 80 percent of breast biopsies are conducted on benign tissue – raising healthcare costs and causing pain, possible scarring and anxiety in patients – an adjunct technology that supplements mammography and reduces the large number of unnecessary biopsies would be of significant benefit to both patients and healthcare providers. Because the non-invasive DOBI technology is designed to identify the minute vascular changes associated with growing cancer in its earliest stages, it has the potential to provide a new screening tool, as well as DOBI ComfortScan has the potential to play a key role in improving current methods of breast cancer detection and treatment monitoring.

1.2 A New Technique to Detect Breast Cancer at Early Stage – Dynamic Opitical Breast Imaging

Physicians worldwide are looking for an innovative and inexpensive technology that provides further diagnostic information to complement current diagnostic data, thus allowing them to make a more complete and accurate diagnosis. Undeniably, a new screening, following up and monitering tool for breast carcer early detection and breast non-invasive treatment evaulation is increasingly paied great attention in the examination of the breast. The Dynamic Optical Breast Imaging (DOBI®) ComfortScan, while not intended to replace mammography, is a noninvasive, nonionizing medical imaging system designed to assist physicians in the diagnosis of breast cancer by providing new, image-based physiological information which mammography, ultrasound and physical exams cannot provide. The medical and scientific foundation of the DOBI technology is developed to image the body's

creation of new blood vessels (neovascularization) associated with the support of tumor development. This process, known as ***angiogenesis***, has been scientifically linked to the development and growth of most cancers and over 70 other human diseases. The ability for medical and scientific professionals to image angiogenesis in the human body in this manner is virtually non-existent. Thus, the ComfortScan system is designed to provide important physiology-based information not readily available to physicians today for determining the presence of abnormally vascularized lesions in the body.

The Role of Angiogenesis in New Breast Cancer Diagnostic Technologies

Since Judah Folkman's seminal hypothesis was published in 1971, the formation and growth of new blood vessels from preexisting blood vessels, called angiogenesis, has become widely recognized as a key biological process that occurs in both healthy and diseased tissues.[17] When properly regulated, angiogenesis is necessary for reproduction, embryonic development and wound repair. In such cases, the complex angiogenic process is maintained in careful balance by a variety of angiogenesis-stimulating growth factors, angiogenesis inhibitors, cell-bound molecules, the surrounding extracellular matrix (ECM) and other mediators. When this balance is tipped in favor of too much or too little angiogenesis, a variety of pathological conditions – such as cancer, rheumatoid arthritis and coronary artery disease – can be the result.[18,19] In particular, the role of angiogenesis in breast cancer has been documented.[20]

As in all cells, the cells of an incipient tumor require constant nourishment and oxygen as well as a way to remove waste products. As long as a tumor remains small – approximately one millimeter in diameter – the process of diffusion (through a cell membrane) can adequately provide nourishment and dispose of wastes. To grow beyond the "one-millimeter limit," the tumor cells must develop their own blood circulation system – mimicking the circulatory system of healthy tissue nearby, as shown in Figure 1. Normal cell tissue is interlaced with a dense network of capillaries. Constructed from endothelial cells, these capillaries supply nourishment and carry off wastes. When starved of oxygen, the cells of normal tissues are able to induce endothelial cell proliferation and the formation of new capillaries by releasing angiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). In imitation of normal cells, some of the cells in the tumor acquire the ability to secrete angiogenic growth factors – thereby attracting endothelial cells from nearby tissues and inducing these endothelial cells to multiply. By encouraging capillaries to grow into the tumor, tumor cells acquire direct access to oxygen-and-nutrient-rich blood as well as a way of removing waste products. This enables the tumor cells to grow explosively and spread widely. Some physicians use the presence or absence

of a dense capillary network in tumor samples to determine the stage of tumor development and predict its future course.[21]

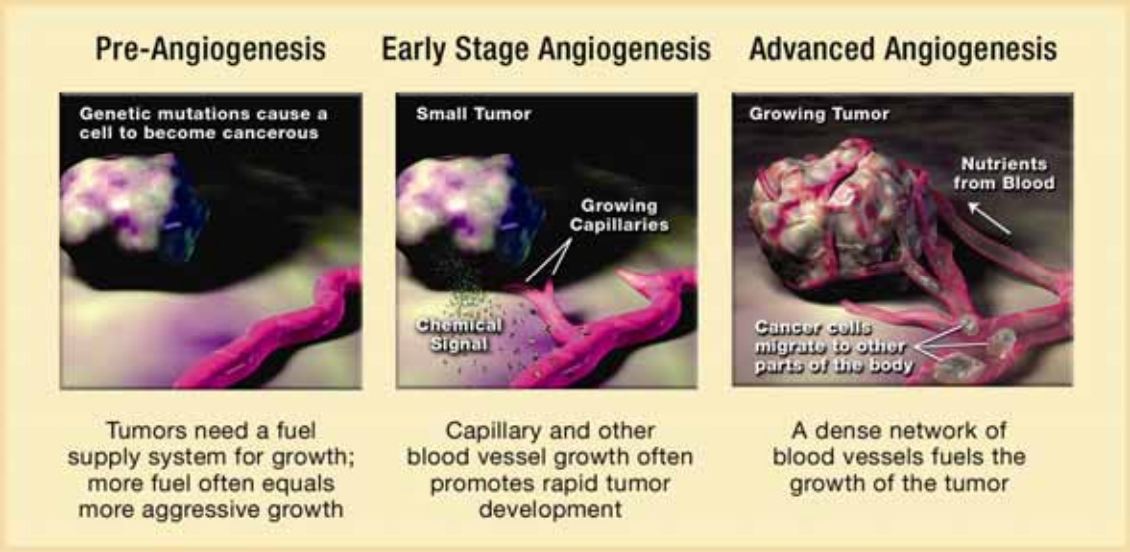

Figure 1. The Stage of Tumor Angiogenesis

Angiogenesis in tumors follows an orderly sequence of events:[22,23,24]

1. *Initiation*. The diseased tissue (tumor) produces and releases angiogenic growth factors that diffuse into the surrounding tissue.
2. *Proliferation and invasion by endothelial cells*. The angiogenic growth factors bind to receptors located on the endothelial cells of nearby blood vessels. Within an endothelial cell, signals are sent from the cell's surface to the nucleus and the cell begins to produce new molecules including enzymes. The enzymes dissolve tiny holes in the sheath-like basement membrane that surrounds the blood vessel. The endothelial cells begin to divide (proliferate) and they migrate out through the dissolved holes and toward the tumor. Specialized molecules, called adhesion molecules or integrins (αvβ3 and αvβ5), help to pull the sprouting tip of the blood vessel forward. Additional enzymes, called matrix metalloproteinases, or MMPs, dissolve the tissue in front of the sprouting blood vessel tip and, as the vessel extends, the tissue is remolded around the vessel. The sprouting endothelial cells roll up to form a blood vessel tube and the individual blood vessel tubes connect to form complete blood-vessel loops that can circulate blood.
3. *Maturation of blood vessels*. The newly formed blood vessel tubes are stabilized by the growth of specialized muscle cells, which provide structural support. Blood then begins to flow through the new blood vessels. These new blood vessels are the mechanism by which the tumor creates an oxygen-and-nutrient-rich environment in which to grow explosively and spread throughout the body. Without this environment,

the tumor would remain confined to the "one-millimeter limit" described earlier – starved for nutrients and choking on its own waste products.

The angiogenic blood vessels in malignant tissues share a number of observable characteristics. Together, these characteristics comprise a "unique vascular profile" or "angiogenic signature" that can be detected by the DOBI ComfortScan and can serve as diagnostic aids that indicate the presence or absence of malignant tissue. The unique tumor angiogenic signature is likely to be different than simple inflammation associated with benign conditions, as the following characteristics will show:

- *High density and high blood volume*. Blood vessels created to feed tumors are more numerous and dense than vessels in normal tissue.[25] The existence of differing vascularity in breast cancer is supported by Feldman[26] and Watt,[27] both of whom successfully imaged small groups of breast cancers using vascular imaging techniques. Wells found similar results using ultrasound,[28] as did Schoenberger[29] and Cosgrove.[30] This distinctive vascularity is also supported by Folkman,[31] who studied the mechanism of neoplasia, and by the empirical histology of Weidner,[32] who found that micro-vessel density (MVD) is greatest at the periphery of cancerous tumors, particularly metastatic tumors.
- *Resistance to blood flow*. Blood vessels created to feed tumors show greater resistance to the flow of blood than normal blood vessels in response to the application of gentle pressure.[33,34] Several theories have been proposed to explain this phenomenon.
- *Vessel collapse*. Blood vessels created to feed tumors show an increased likelihood of blood vessel collapse under external pressure. Again, several theories attempt to explain this phenomenon and its relationship to the resistance of blood flow. For example, since the blood-vessel wall in the tumor region has a high permeability,[35,36] the interstitial fluid pressure (IFP) in the tumor region is higher (20 mm Hg); in fact, it is close to and in equilibrium with the microvascular pressure (MVP).[37,38] This is in contrast to the IFP in normal tissue (0 mm Hg). In the region of a tumor, this leads to internal necrosis of the tumor and vessel collapse under external pressure.
- *High oxygen consumption and attenuated light transmission*. Since the oxygen requirements of a rapidly growing tumor are higher than in normal tissue, the blood vessels created to feed these tumors show evidence of oxygen depletion in the comparatively large quantities of blood that they carry. Furthermore, deoxygenated blood exhibits attenuated light transmission characteristics, which can be detected by various technologies.[34,39,40,41]

In addition to the observable physical characteristics cited in the previous section, research into the molecular basis of angiogenesis occurring in breast cancer patients indicates that integrin αvβ3 plays an important role in angiogenesis. The presence of high levels of integrin αvβ3 promotes angiogenesis and, conversely, low levels of integrin a αvβ3 are the most significant prognostic indicator of relapse-free survival in breast cancer patients.[42,43] Furthermore, clinical studies demonstrate that the degree of angiogenesis is correlated with the malignant potential of several cancers, including breast cancer. Researchers have also explored a novel approach to detecting angiogenesis *in vivo* using magnetic resonance imaging (MRI) and a paramagnetic contrast agent that is targeted to endothelial integrin αvβ3 via the LM609 monoclonal antibody. This new approach also enables the detection of angiogenic "hot spots" that are not observable by standard MRI.[44] These techniques – which focus on the molecular processes and vascular changes that accompany the development of breast cancer – have the potential to improve both the sensitivity and specificity of breast cancer diagnosis. They are also at the heart of the approach utilized by the DOBI ComfortScan.

As summary, a tumor requires a network of blood vessels to supply nutrients and oxygen and to remove waste products[45] to grow beyond the size of about 2 mm^3. The inherently complex process leading to the formation of these new vessels is known as tumor "angiogenesis." The increased vascularity associated with the growth of malignant lesions can be measured by microvessel density (MVD) count.[46] Tumor angiogenesis and its implication on clinical outcome have been intensively studied in breast cancer.[47] Numerous studies have documented that a high MVD correlates with the presence of nodal and distant metastasis,[18] establishing a relationship between the presence of angiogenesis and invasiveness in breast carcinoma.[48,49] These recent findings suggest that higher MVD in breast carcinoma is associated with the potential of the tumor to produce metastasis, and thus may be a prognostic indicator.[48] Gasparini suggests that breast cancer is an angiogenesis-dependent disease.[49] All solid tumors become clinically relevant once they develop a blood supply. Angiogenesis is the process by which growing tumors attract new blood vessels, allowing them to gain nutrients and eliminate waste. Recent developments in optical imaging technology and image processing make it possible to identify the minute vascular changes associated with growing cancer in its earliest stages. Once detected, these changes constitute a unique vascular profile that has the potential to indicate the presence of cancer before a cancerous lesion is discernable.

Dynamic Opitical Breast Imaging Technology in Early Breast Cancer Diagnostic

The imaging technology utilized in the DOBI ComfortScan is the product of over 80 years of development and experimentation in the field of optical imaging, which utilizes light in the visible spectrum to illuminate breast tissues. Max Cutler first introduced optical imaging of the breast in 1929.[50] He utilized a technique called diaphanography, which is the transillumination of breast tissue. This technique reveals a distinct difference in the transmission of red light through normal breast tissues and through the vascular angiogenic tissues adjacent to a carcinoma. While this early technology proved to be clinically ineffective and is no longer being used, it marks early attempts to utilize light.

More recently, Erterfai and Profio[51] utilized excised breast tissue to show that blood content (deoxyhemoglobin) affects transmittance (the absorption spectrum) in breast tissue. Profio et al[52] also noted that the contrast measured by a two-wavelength system correlated well with a model of oxy- and deoxyhemoglobin. They also reported previously unpublished data from the Santa Barbara Cancer Institute studying the vascularity of benign and malignant breast tissues. They found that the average concentrations of red blood cells were higher at the edge of a carcinoma and in the peripheral tissue next to the carcinoma than in normal tissue. The diaphanography results showed a "strong correlation between the contrast and the concentration of hemoglobin (red blood cells) in subgroups of the fibroadenomas and carcinomas." The absorption was observed in the 600-900 nm wavelength range. Peters[53] also investigated transmittance, reflectance, scattering and absorption across the spectral range of 500-1,100 nm and found that oxyhemoglobin and water content were the only reliable predictors of spectral differences.

It has been established that the vascularity associated with the growth of malignant lesions is inherently different from the vascularity seen in normal healthy tissue.[54] The DOBI ComfortScan™ system detects the differences by evaluating the light attenuation when an external pressure stimulus is applied over time. The Dynamic Optical Breast Imaging (DOBI) ComfortScan is sensitive to dynamic volumetric changes in blood and changes in deoxyhemoglobin. Both of these changes are commonly found in malignant tumors and result in a unique tumor angiogenic "signature." The ComfortScan System is able to measure these changes by applying uniform pressure to the breast. The change in pressure is believed to trap blood in the tortuous angiogenic structures that form around the tumor. This trapped blood becomes deoxygenated up to four times faster than normal tissue. The DOBI ComfortScan displays the effects of the changes in volume and/or the changes in deoxyhemoglobin over time. These changes appear as areas of low light level in the DOBI ComfortScan images because of greater light absorption. Normal or benign tissue, which

has normal vascular structures and a slower metabolic rate, does not absorb as much light. Consequently, it has a higher light level than malignant tumors.

In contrast to early unsuccessful transillumination techniques, the DOBI ComfortScan uses mechanical perturbation to create a dynamic signature. The DOBI ComfortScan's array of light-emitting diodes (LEDs) illuminates areas of vascular development in the breast that possess characteristics unique to malignant tumors. As described earlier, during the process of angiogenesis, a cancerous growth surrounds itself with a dense network of tiny blood-filled capillaries. These capillaries provide oxygen and nutrients to active tumors and they exhibit the unique physiological "markers" that the DOBI ComfortScan can detect. These physiological markers include dense vascularity, high blood-flow resistance, blood deoxygenation, attenuated light transmission and a greater likelihood of the blood vessels to collapse under external pressure.[34]

While other diagnostic imaging devices primarily detect static morphological (structural) changes, the DOBI ComfortScan is designed to detect dynamic (physiologic) changes, namely the dynamic flow, increased blood volume levels and depleted oxygen levels (deoxygenated hemoglobin) that are characteristic of malignancies. The currment ComfortScan system utilizes light from 127 light emitting diodes (LED), mounted on an illuminator plate inclined 30° from horizontal plane. The LEDs emit red light with a wavelength of 640nm for greater absorption and higher sensitivity of optical absorption of de-oxy-hemoglobin. Transmitted light is recorded by a Charge-Coupled Device (CCD) camera for approximately 45 seconds. As part of this process, the machine applies a slight amount of uniform pressure via a patented silicone membrane system – a pressure jump from 5mm Hg (setup pressure) to 10 mm Hg (analysis pressure) for about 30 seconds – to the breast, which already has been compressed lightly by the soft breast holder. When an external pressure stimulus is applied uniformly around the breast, the dynamics of blood redistribution, the capillary and vein collapse, and the oxygenated state of the blood as a function of time after the initial pressure stimulus in the area of abnormal vascularization will be different from those properties in normal areas of the breast tissue. The system collects the images of the breast before, during and after applying the pressure jump to record the changes as they occur.

Since a single static image alone does not reveal much information about abnormal vascularization because the light beams are heavily scattered and diffused by tissues resulting in very low spatial resolution, and only changes caused by re-distribution of blood volume and oxygenation level are detected, the dynamic response of the breast to pressure modulation is carried in the intensity variations among different images in the whole

sequence. The dynamic image sequence may be represented by I(x, y, t). The DOBI ComfortScan uses the first image after the pressure jump as a reference image, I_{ref}, after the first illumination cycle following the onset of the pressure step (breast shape has stabilized). This image is subtracted from the rest of the image sequence to represent the dynamic signature or response to the pressure at each spatial point (x, y):

$$DS(x, y, t) = (I(x, y, t) – I_{ref}) / I_{ref}$$

The vascular changes associated with cancerous lesions absorb more light than normal tissue and this creates areas of low light level on the image. As the light from the LEDs encounters the angiogenic tissue surrounding the tumor, the hemoglobin, which is trapped in the blood-filled capillaries near the malignancy, absorbs the red light more completely than in normal or benign tissue. Following each pressure jump, the system records the changes in light transmission at the red wavelength.[55] When compared with the abnormal regions, blood volume and oxygen saturation levels decrease at a different rate in the region with normal vascularity, normal interstitial fluid pressure, and normal oxygen consumption rate. The difference in dynamic signatures in normal and abnormal areas can be summarized as:

$$DS_a (x_a, y_a, t) \neq DS_n(x_n\ y_n\ t).$$

To process the images recorded by the camera, the DOBI ComfortScan utilizes proprietary computer algorithms that generate a graph of the changing light-transmission values for each location over time. Consequently, it visually displays the unique vascular profile of the angiogenic region of the breast that stands out in marked contrast to normal or benign portions of the breast. On the image, bright areas indicate normal or benign tissues and dark blue areas indicate a potential for malignancy. By displaying a contrasting appearance, the DOBI ComfortScan has the potential to confirm the presence of cancer and differentiate cancer from both benign lesions and normal tissue within the breast. The potential for the ComfortScan system as a diagnostic tool is to non-invasively differentiate between specific optical patterns of normal and abnormal vascularization areas and therefore to provide the physician with additional information as to the angiogenic status of the suspicious area. This information is intended to assist the physician in the diagnostic process, possibly in treatment recommendations and in regular screening or fullowup examination of breast cancer. Since vascular changes take place from the earliest stages of cancer development, the ability to image these changes can potentially lead to the detection of breast cancer and treatment of developing cancers at early stage – an important part of future uses for the DOBI technology.

2. MATERIAL and METHODS

2.1 ComfortScan Components and Description

In order to address the need for multiple, standardized imaging angles, the DOBI ComfortScan is designed to be mounted on an adjustable C-arm platform, which comprises soft breast holder, breast platform with LED array, digital-charged-coupled-device (CCD) camera, besides the system electronics and software and display monitor.[56] Descriptions of each of these items follow and can be viewed in Fig. 2.

Figure 2. DOBI ComfortScan System with its Components

Soft breast holder. It is necessary to compress the breast to achieve acceptable image contrast in the area of pathologic influence (API). The breast holder consists of a silicon membrane that provides a soft contact surface and an airtight seal over a pressure chamber. The pressure chamber can be inflated with low-pressure air. The silicon membrane gently compresses the breast between the silicon balloon on the camera side (top) and the flat breast platform (below) with its array of LEDs. The DOBI ComfortScan controls and monitors the rise, fall and maintenance of pressure in the pneumatic system with a custom-programmed microcontroller.

Breast platform with LED array. The DOBI ComfortScan utilizes a flat-plane array of 127 light emitting diodes (LEDs) that emit light in the single visible-red band (640 nm). The custom-programmed microprocessor precisely controls the optical exposure time and the intensity profile of the LED array, which enables versatile operation with breasts of different sizes and densities. The system supports independent control of the light intensity for each LED.

Digital CCD camera. The DOBI ComfortScan uses a 12-bit digital-charged-coupled-device (CCD) camera. The sensitivity of this camera is necessary because the changes in light intensity within the illuminated breast are small in amplitude in comparison to the amount of light emitted by the LEDs. Consequently, it is necessary to utilize a high-gain, low-noise device such as the CCD camera. The CCD camera employs an internal thermal-electric cooler and operates at a controlled low temperature of -20° C. This low temperature produces an extremely low dark-current output. The intrinsic spatial resolution of the camera is 768 x 512 pixels. The 5 x 5 pixel-binning mechanism increases the efficiency of photo collection. The final spatial resolution of the camera output is effectively 102 x 128 pixels. Gray-scale resolution of the signal from each pixel is up to 4,096 levels, which corresponds to 12 bits.

System electronics and software. The Controller is an electronic assembly that interfaces with the LED illuminator, the computer, the soft holder assembly and two pressure reservoirs located in the bottom of the base unit. Housed in the controller are circuit boards for lighting the LED, operating the pneumatic pump, sensing the pressure in the air chamber and interfacing with the computer. It houses also a microcomputer and a programmable read-only memory. The Computer System provides the main user interface, sending commands to the Controller and LED illuminator. Images are read from the CCD camera, processed and displayed. Data are stored and retrieved. The Computer System also monitors operation and alerts the operator to fault conditions. Unlike traditional transillumination methods, the DOBI ComfortScan applies a perturbation stimulus (pressure change) to the breast and facilitates observations of the change in transmission/absorption of red light by the breast. The system processes the measured incremental changes by using a variety of subtraction and contrast enhancement techniques to produce the diagnostic functional image. The control software for the instrument module is embedded in the microprocessor. The embedded microprocessor manages all modulation of the LED array intensity and the pneumatic pressure modulations of the breast holder in accordance with the specific protocol for each patient.

The DOBI ComfortScan system illuminates and senses light absorption properties of the

breast tissue during both static and dynamic conditions. In the dynamic acquisition phase, the ComfortScan compresses and decompresses the breast tissue, similar to the process available during conventional mammography, but with very low pressure.

The DOBI ComfortScan analyzes and compares light absorption across the static as well as multiple dynamic images for regions of extraordinary light absorption. Such regions are then more closely examined through a battery of digital processing techniques, and displayed as both scans and waveforms for the practitioner. These techniques involve digital subtraction of two or more of the images frames, spectral and temporal comparisons and intensity amplifications of the organized regions of the scans.

Current DOBI ComfortScan is intended for use on patients who have inconclusive diagnosis by mammography or other imaging tests or physical examination. The use of this device will provide the physician with dynamic functional information regarding abnormal vascularization in an area of interest in the breast. The dynamic functional information will be used to better characterize the lesion. A cluster version of current ComfortScan and the next generation of ComfortScan, ComfortScreen, have been under development and will be available in the near future for breast screening.

2.2 Use of the DOBI ComfortScan with a Patient

During an examination, the patient stands next to the machine and the DOBI System operator positions the patient's breast so that the inferior portion of the breast is in direct contact with the surface of the breast platform, which contains the array of red LEDs. The soft breast holder envelopes the top of the breast in a thin silicone membrane. In a computer-controlled sequence, the breast holder gently and uniformly compresses the breast to a pressure of less than 10 mmHg (less than 1/4 pound per square inch). The computer also controls the transmission of light through the breast while the digital CCD camera, located above the breast, records images in a sequence of several frames per second for approximately 45 seconds. The system accumulates the images in digital memory and the computer processes the minute, temporal variations in red-light intensity between benign and malignant tissues. The entire procedure requires approximately 5 minutes and the results are available immediately for display on the monitor.[56]

The clinical study of DOBI ComfortScan performed at the two hospitals in Beijing was conducted in accordance with The Provisions for Clinical Trials of Medical devices in SFDA Order No. 5. The enrolled patients are 18 years of age or older and have been considered the necessity of a breast biopsy after receiving mammography exasmination with BI-RADS 3

or 4. But in order to prove the product safety and effectiveness in normal condition by taking into account the current ComfortScan configuration and its intended use, following patient is excluded from this study:

- Subject has had any breast surgery in the ipsilateral breast (e.g., augmentation/ cancer/ reduction) within a year of the potential scan date.
- Subject has had a core or excisional biopsy in the ipsilateral breast within 3 months.
- Subject has undergone brachytherapy in the region of interest within the past 12 months.
- Subject is pregnant or lactating.
- Subject has accepted hormone replacement and/or oral contraceptives within the past 30 days.
- Subject has failed to keep fixed and persistent position during the examination.
- Subject has inflammatory skin disease (i.e., psoriasis, eczema)
- Subject has a known allergy to silicone

According to "Regulations for the Supervision and Administration of Medical Devices" and "Provision on Clinical Trial of Medical Device" of SFDA of China, the relevant data, such as study protocol, informed consent form, case report form etc., have been examined and approved by the Ethics Committees, in order to ensure this study is in accordance with ICH-GCP and the related medical administration regulations of China, and meet the requirements and principles of ethics.

2.3 ComfortScan Sanning Acquisition

After filling in all the data required (patient's name, age, breast size, technician's name, breast side, comments, etc.) the breast is positioned in a craniocaudal view (CC), similar to the mammographic one. The soft holder pressure is set to negative pressure to facilitate positioning, which is extremely important to ComfortScan scanning and readings. The breast should be centered on the breast support platform and all the rooms lights should be switched off. The camera will begin acquiring images in a preset rate. These images will be shown in both grayscale and color scale. To ensure a qualified scanning with proper LED patterns, the selected LEDs based on the breast size are placed automatically or manually according to the location of the lesion. After the selection of LED locations, the LED illuminator controls are now active. It is important to optimize the illumination settings by choosing either the manual control or the automatic intensity buttons. During this phase, you should set a marker using the mouse, by drawing a circle by means of the cursor, defining the region of interest. This region corresponds to the suspicious areas as been determined

by prior clinical or mammography findings. Once you have verified that the patient's breast is correctly positioned and that all the LED intensity and patterns are satisfactory, you can initiate the scan by clicking on the START button. The STOP button allows the scan interruption in case of problem. All the scans acquired are saved automatically on both the local disk and CD simultaneously.

2.4 ComfortScan Image Processing

The image data are processed to generate dynamic images of the superior and inferior portions of the breast in a cranial-caudal view. The images are displayed in gray scale or false color to reveal time-dependent changes in the transmitted light intensity caused by the pressure change. The images may be viewed as a cine loop to help visualize focal regions with different temporal behavior compared to surrounding tissue. In addition, the computer mouse may be used to mark and interrogate different areas of the image and to display the corresponding temporal curves. The temporal curves are displayed on a grid (% change in intensity v. time in seconds), which allows the shape and magnitudes of the curves to be characterized and quantified. As a diagnostic aid, the image processing software can classify the temporal curves for each image pixel and display an image of the breast in which regions with temporal curves typically associated with malignancy are displayed in dark blue and with temporal curves typically associated with normal tissue are displayed in green.

During pressure modulation, a serial of digital images are captured by the CCD camera and registered in the system memory. Currently, over one hundred frame images are collected and stored for each breast "scan". The first image is always recorded with no light exposure. This first image is referred to as the "dark-frame". In the data analysis, this "dark-frame" is then subtracted from the subsequent images. This subtraction eliminates the effects of any non-zero dark-current and other background noises of the CCD camera. An image normalization procedure is then performed. Through this normalization, any non-uniform intensity distribution collected from the camera is thoroughly compensated. Data analysis of this stage can be referred to as "preprocessing". After the "preprocessing", the system is ready to perform the pathology classification analysis described below using "dynamic signatures" and a "functional image".

Dynamic signatures are obtained from each local region (pixel) of the recorded images. Because dynamic responses from the API (area of pathologic influence) of the malignant region are quite different from those of the normal regions, contrast in the signatures can be recognized by the operator. Furthermore, for the ease of operator visualization and pathologic classifscation, a functional image is also constructed. A cross-correlation

algorithm is used for the generation of this functional image. In the cross-correlation process, a “reference signature” is selected from a normal breast region. Then a cross-correlation process is applied between the dynamic signatures from all regions of the breast with the reference signature. Because dynamic signatures from all normal regions are similar to the reference signature, a high level of correlation is obtained from these regions. On the other hand, dynamic signatures from the API are quite different from the reference signature; a low level of correlation is obtained from these regions. Consequently, the output from the correlation process produces a high-contrast functional image. On the functional image, bright intensities present normal areas, whereas dark intensities present in the API.

2.5 ComfortScan Image Interpretation

The interpretation of images is based in two separate physiological parameters: (1) the color range in color window and (2) the dynamic curves corresponding to each area selected. The blue or dark blue color is corresponding to areas of increased abnormal vascularisation, as this is estimated by analyzing the signal of LED emission by means of imaging functional programs incorporated into the computer system. The dynamic curves offer a plus sophisticated means of calculating the patterns of increased vascularisation, optimally permitting to predict the areas of neovascularisation.

There are two types of curves registered: (1) the progressive one that is correlated so far with the areas of increased abnormal vascularisation and (2) the fluctuating one that correlates with areas of 'normally' increased vascularisation, e.g. fibrokystic disease areas or florid fibroadenomas. The physiological explanation for these curves is based in the fluctuating rate of normal vascularisation, which is influenced by cardiac and respiratory rate, thus presenting smoothly curved up and down lines, in accordance with inspiration-expiration and systolic-diastolic rates. It is also worth mentioning the significant role of capillary vessels, which permit an 'elasticity' of hematogenous flow. On the contrary, areas of neovascularisation are typically characterised by the absence of capillary trichoid vessels, and blood is 'pooling' into abnormal arteriovenous shunts, not following the fluctuating cardiac and respiratory rate. This is represented by a progressive curve, without 'elasticity'. From DOBI ComfortScan preliminary study chosen to compare ComfortScan results with the findings of the considered-to-be the gold standard method for breast vascularisation, the breast MRI imaging with i.v. injection of gadolinium,[57] abnormal tumor vessels, especially the presence of arteriovenous shunts, are responsible for the rapid enhancement and the "wash-out" of malignant lesions.

2.6 Comparison with Mammography

Mammography utilizes x-rays to image the breast morphology for the breast screening or diagnostic, and is considered to be nowadays the gold standard for breast cancer examination. Mammogram is dependent upon the radiologist to interpret the morphology and then to infer the physiology and pathology of the breast. Mammography and palpation are currently the most used and accepted breast cancer screening tests. Although both provide important information, they are somewhat limited. Also, ultrasound (US) and magnetic resonance imaging (MRI) play a complementary role in the diagnostic process.

Mammography has detection rates that vary widely: Kolb reported overall sensitivity and specificity for screening mammography of 68% to 88% and 82% to 98%, respectively; however, in the same study, in the most dense breast tissue the reported sensitivity was 44%.[58] Mammography sensitivity rates are higher in women aged 50 years or older compared with those less than 50 years old. This can be explained with the decrease of breast density as a function of increasing age. Dense breasts (associated with a BI-RADS™ breast density scale of 3 or 4) are often seen in younger women and fatty breasts (e.g., BI-RADS density value of 1 and 2) are more common in the older women[59]. Kerlikowske also reported that age had a strong effect on mammography sensitivity, which was highest among women 60 to 69 years of age (87.0%) and lowest among women 30 to 39 years of age (67.9%).[60]

These findings suggest that there is a need to improve on the tools currently used to detect breast disease in younger women or those with more dense breasts. To demonstrate the DOBI ComfortScan is an improved tool for young woman breast examination and an useful tool for breast cancer diagnostic with addtional new physiological information, all the enrolled patients during the clinical study of DOBI ComfortScan in Beijing were performed mammography examinaitons but have inconclusive findings, which are catogrized as Breast Imaging Reporting and Data System (BI-RADS) 3 or 4. The results are shown in Table 1, 2, 3 and 4.

3. PATIENTS and RESULTS

A multi-center, Blinded Read Study to determine the sensitivity, specificity and safety of the ComfortScan System in detecting malignancy in lesions of the breast was conducted from year 2005 to 2006. All valid 62 women were examined with ComfortScan at Peking University People's Hospital and Capital Medical School Chaoyang Hospital in Beijing as

part of the present clinical study over a period of 6 months. The study included only age 18 or older women who had pathological findings, which are inconclusive on their previous mammography consisting of the presence of a circumscribed lesion or suspicion of circumscribed tumor process in the breast, i.e. BI-RADS 3 or 4. All these women underwent targeted excisional biopsy from the suspected site after mammography and DOBI ComfortScan evaluation. Images obtained with ComfortScan were evaluated through blinded readings by three independent doctors, who were trained by DOBI authorized technologist to use DOBI ComfortView software. To ensure a valid blinded reading, all the trainer and readers were blocked from the results of histology to prevent these results from affecting the evaluation of DOBI ComfortScan.

Among those 62 patients, the average age is 47.5, 90.3% patients have dense breasts: 10 very dense and 46 dense breasts separately, 54.8% and 37.8% patients have lesions with size less than 2 and 3 center meters respectively. Although the clinical trial protocol requests the patients, who should have BI-RADS 3 or 4 mammography, one BI-RADS 0, two BI-RADS 1, one BI-RADS 2 and three BI-RADS 5 are included within this study. Thus, only 88.7% patients are BI-RADS 3 or 4.

According to the clinical study protocol, table 1 gives the results of evaluation of mammogram before the ComfortScan image reading and ComfortScan reading before availability of biopsy. Because of the BI-RADS 3 and 4, some mammograms are still inconclusive (**I**ndeterminate), thus the statistic calculation could not performed even although the readers were requested to conduct either **M**alignant or **B**enign result for each mammogram. Table 2 shows the evaluation of DOBI ComfortScan by comparing with the results of histology results, which indicate the 50% prevalence rate of malignancy in this study, and the data on sensitivity, specificity and negative predictive value of DOBI ComfortScan have been calculated.

		ComfortScan Reading		Total
		M	B	
Mammogram Reading	M	**22**	**0**	22
	B	**2**	**14**	16
	I	**14**	**10**	24
Total		38	24	62

Table 1. Mammogram and ComfortScan Reading Results. Where M, B and I represent Malignant, Benign and Indeterminate because the inclusion criteria requests BI-RADS 3 or 4 mammography.

		Biopsy		Total
		M	B	
ComfortScan Reading	M	**26** (TP)	**12** (FP)	38
	B	**5** (FN)	**19** (TN)	24
Total		31	31	62
Sensitivity		SE	TP / TP + FN	**83.9%**
Specificity		SP	TN / TN + FP	**61.3%**
Negative Predicative Value		NPV	TN / TN + FN	**79.2%**
Youden's Index [-1,1]		YI	SE + SP - 1	**0.45**

Table 2. Evaluation of DOBI ComfortScan by comparing with the results of histology results, which indicate the 50% prevalence rate of malignancy in this study. But the evaluation of Mammography can not be conducted because its reading result consists of indeterminate outcomes even although the readers were requested to conduct either Malignant or Benign result for each mammogram.

In order to make a comparison between Mammography and DOBI ComfortScan, we have to select the 38 cases, which are 61.3% of the total studied cases and can be interpreted through mammogram reading. Thus, following table 3 demonstrates the evaluations and comparisons of the Mammogram and ComfortScan readings on sensitivity, specificity and negative predictive value. The results are compatible with ComfortScan clinical study in Czech Republic.[61]

	Read Out				SE	SP	NPV	YI
	TP	FN	FP	TN				
Mammogram Reading	**20**	**2**	**2**	**14**	**90.9%**	**87.5%**	**87.5%**	**0.78**
ComfortScan Reading	**21**	**1**	**3**	**13**	**95.5%**	**81.3%**	**92.9%**	**0.77**

Table 3. Evaluations and Comparisons of the Mammogram and ComfortScan for the 38 (61.3%) readable cases from total 62 valid Mammograms (study cases).

	Read Out				SE	SP	NPV	YI
	TP	FN	FP	TN				
Mammogram Reading	**29**	**2**	**17**	**14**	**93.5%**	**45.2%**	**87.5%**	**0.39**
ComfortScan Reading	**26**	**5**	**12**	**19**	**81.9%**	**61.3%**	**79.2%**	**0.45**

Table 4. Evaluations and Comparisons of the Mammogram and ComfortScan for all 62 cases by considering 24 indeterminate mammograms in Table 1 as malignant cases.

In general, the guildline of breast cancer diagnostic is “Don’t miss malignancies; but don’t seriously overcall the benigns”. Thus, if a common imaging diagnostic practice is applied to this study, the 24 (38.7%) indeterminate mammogram cases shoud be considered as “Malignant“ and then could be followed by further imaging or clinical study, or biopsy test. Under this clinical cretiera, the evaluations and Comparisons of the Mammogram and ComfortScan for all 62 cases is shown in Table 4 by considering the 24 inconclusive mammograms as malignances.

In comparison with the relatively balanced values of sensitivity and specificity with DOBI ComfortScan, the same parameters are clearly different with mammography as shown in Table 3 and 4. Sensitivity and specificity of the mammography in our sample were undoubtedly affected primarily by the relatively frequent results of mammography BI-RADS 3 and 4 (88.7% of all results in the BI-RADS 3 and 4 category) with dense breast structures. In our sample most of the women being examined (90.3%) had dense or very dense breasts. A very dense breast occurred in 16.1% of all women examined. Therefore the dense breast type was found in a total of 74.2% of women examined, while the involutional breast type was represented by 9.7%. With the dense breast type, logically, we register more frequently the result of indeterminate cases, or, of course, reduced specificity of the mammographic examination.

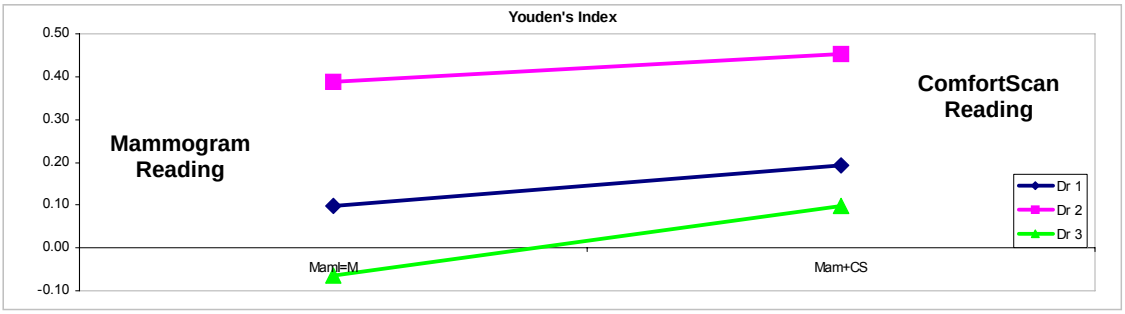

Figure 3. Accuracy Comparison of the Reading Results of the Mammogram and ComfortScan for all 62 cases from 3 independent readers. The Youden’s Index, accuracy, of the DOBI ComfortScan is higher than Mammography. The accuracies of all three independent readers are improved by comparing the ComfortScan reading with Mammogram reading. It also indicates that the poorer, less experience, reader is, the more improvement their reading will be.

Overall, the Youden’s Index, shown in Figure 3, summarizes the test accuracy by combining the clinical sensitivity and specificity into a single numeric value since the Receiver Operating Characteristic (ROC) curve shows the tradeoff between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity) and that the closer the curve follows the left-hand border (higher SP) and then the top border (high SE) of

the ROC space, the more accurate the test is. Figure 3 shows the Youden's Index, accuracy, of the DOBI ComfortScan is higher than Mammography.

4. DISCUSSION

The Dynamic Optical Breast Imaging (DOBI) technology of the ComfortScan is based on the characteristics, "nature signatures", of tumor angiogenesis: High microvessel density, Tortuous and leaky vessels and High rate metabolic load. Progressive formation of new vessels associated with the growth of malignant lesions differs from the vascular supply to benign lesions and normal breast tissue. Different behavior of pathological vascularization includes its reaction to the application of slight uniform pressure (approximately 10 mm Hg), which trap blood in the tortuous angiogenic structures that form around the tumor (blood verlume change) up to four times larger than tumor itself, over time, during which this trapped blood deoxygenates up to four times faster than normal tissue (different metabolic rate). The DOBI ComfortScan makes it possible to measure the transition of red light through the breast and records responses to changes in the volume of blood flow and the deoxyhemoglobin in the compressed tissue. Light absorption in the area around the malignant lesions over time is increased compared to that in benign or normal tissue. DOBI has been designed for the very purpose of detection of this difference, making it possible to differentiate between malignant and benign regions. It is used to study the dynamic behavior and optical properties of breast tissue, and discerns the contrast typical of malign lesions compared to adjacent normal breast tissue.

The results, which are demonstrated in table 2, 3 and 4, make it obvious that the difference in sensitivity and specificity between both methods under evaluation is small. It is necessary to be aware of the fact that the ComfortScan method is an entirely new approach, and in spite of the evaluating physician having received training in the method, it is not possible to compare these early experiences with the many years of experience with mammography. Moreover, the images are rather different from the conventional X-ray films. It is possible to describe the images obtained with ComfortScan as being more similar to those obtained in nuclear medicine. Also, the samples evaluated so far are very small, and there are some small studies in the current literature[57,61,62] with results similar to the Beijing study.

Through examining the benign readout, 16, 17 and 24, of mammograms, it notices that DOBI ComfortScan identifies one true malignancy for each reader respectively, as shown in Figure 4. This indicates that the combination of Mammography with ComfortScan can improve overall specificity, as this is an excellent method for differentiating benign lesions

from malignancy and for characterizing lesions depicted on screening mammograms. This has significant clinical effectiveness and meaningfulness to patients.

Mainly because of the density of breasts, over one third of the mammograms are indeterminate. By observing the blood volume change and the metabolic rate difference through transitted near infradred light over the uniformly compressed and modulated breast, the DOBI ComfortScan can conduct further diagnostic on those indeterminate mammograms. Figure 5, 6 and 7 demonstrate the results of the ComfortScan with respect to the indeterminate mammograms. This clinical application could significantly reduce the False Positive rate of Biopsy after a large scale clinical study.

As overall summary of this clinical study in Beijing, the Youden's Index, accuracy, of the DOBI ComfortScan is higher than Mammography. The accuracies of all three independent readers are improved by comparing the ComfortScan reading with Mammogram reading, as shown in Figure 3, which also indicates that the poorer, less experience, reader is, the more improvement their reading will be.

By comparing morphological imaging modality, such as Mammography, the DOBI ComfortScan displays boht spatial and temporal information of tumor angiogensis, namely functional or 4D imaging. The changes of blood volume and deoxygenation (the different metabolic rate) in tumor angiogensis are observed in spatial and temporal windows separately. Follwing figure 4, 5, 6 and 7 show the dynamic (functional) optical breast imaging method, which use both a dark blue area on the spatial view and a high metabolic rate on the temporal view to indicate the malignancy of a lesion. Otherwise, it could be benign. Through the observation of limited malignant cases, it is interesting to notice that the metabolic rate of most malignancies in this study is greater that 0.125, that is, the absorption of deoxy-hemoglobin is higher than 2.5% at 20 seconds. The clinical significance of this digital diagnostic approach needs to be approved through millions of case study. When a value were statistically determined through clinics to indicate all benign situation, a full digital imaging diagnosis would have great significance in clinical practice.

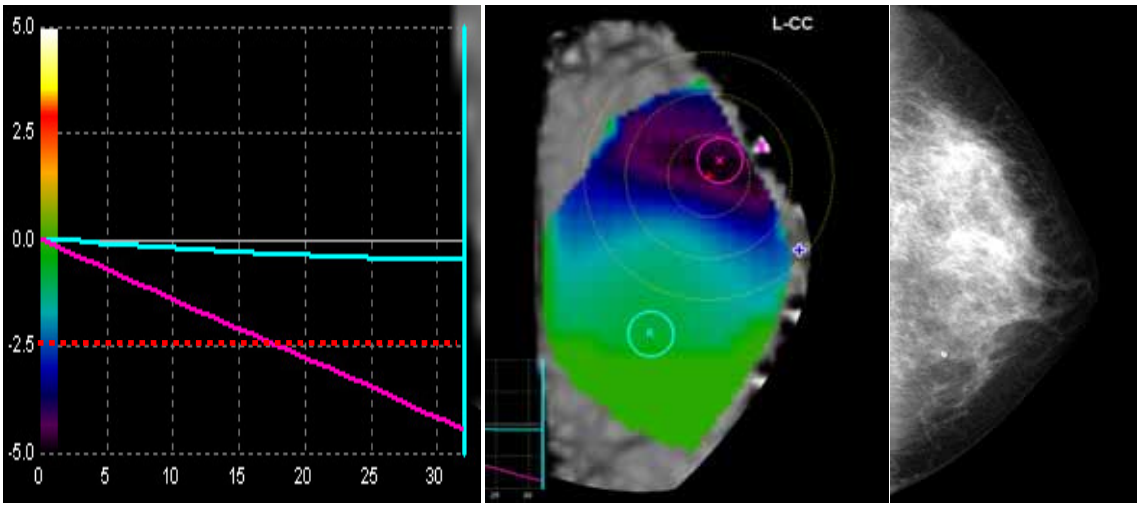

Figure 4. Case Study 116. A 66 year's old woman has 10mm BI-RADS 3 suspicious lesion. The mammogram readings by three readers are 2 benign and 1 indeterminate readouts respectively. But the ComfortScan indicates its malignancy because significant angiogenesis is presented by a dark blue area on the spatial view and a high metabolic rate on the temporal view separately. The biopsy result confirms that the lesion is malignant.

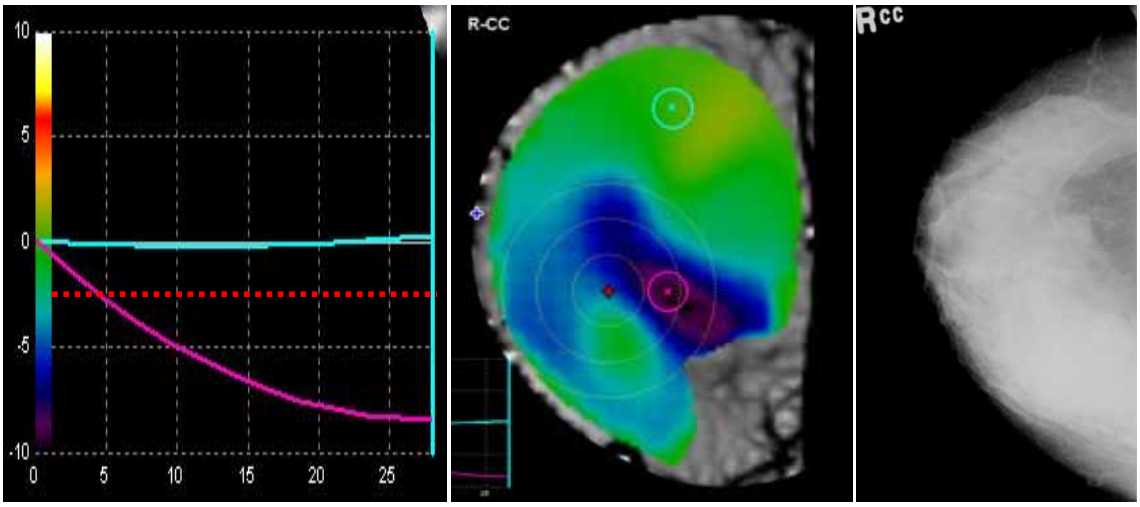

Figure 5. Case Study 201. A 61 year's old woman has 10mm BI-RADS 3 suspicious lesion. The mammogram readouts by two readers are inconclusive. But the ComfortScan indicates its malignancy because significant angiogenesis is presented by a dark blue area on the spatial view and a high metabolic rate on the temporal view separately. The biopsy result confirms that the lesion is malignant.

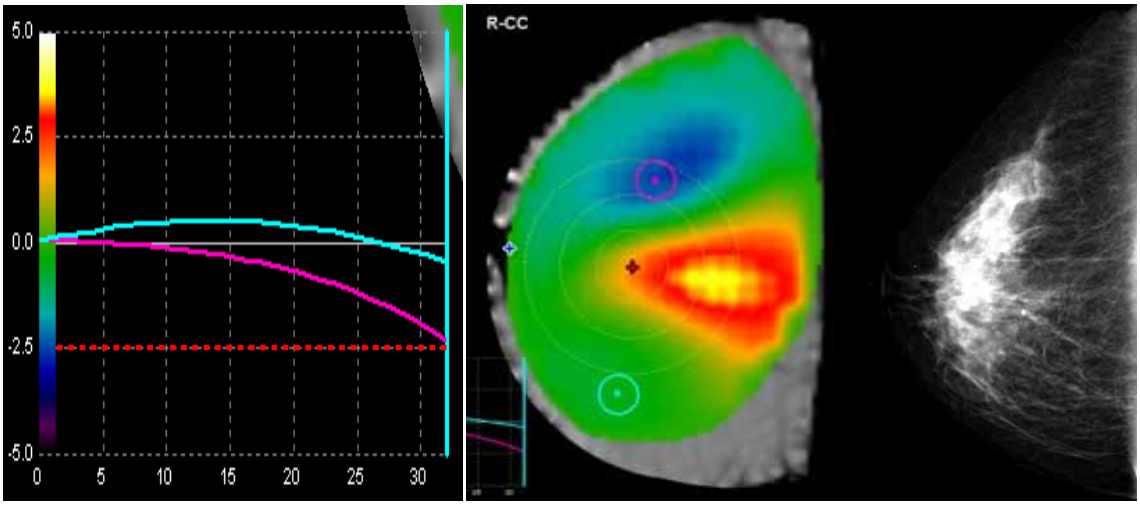

Figure 6. Case Study 121. A 48 year's old woman has 5mm BI-RADS 3 suspicious lesion. The mammogram readouts by two readers are inconclusive. But the ComfortScan indicates the benign because the tumor angiogenesis is not presented in both spatial and temporal views. The biopsy result confirms that the lesion is benign.

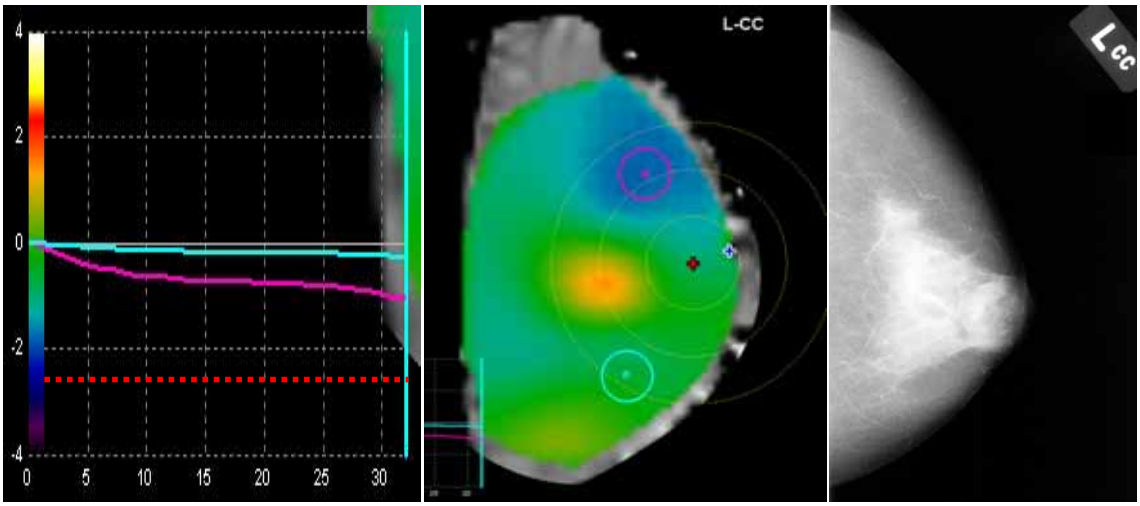

Figure 7. Case Study 209. A 63 year's old woman has 5mm BI-RADS 3 suspicious lesion. The mammogram readouts by all three readers are inconclusive. But the ComfortScan indicates the benign because the tumor angiogenesis is not presented in both spatial and temporal views. The biopsy result confirms that the lesion is benign.

As summary of the discussion, Mammography remains always the standard imaging procedure of control and all recent studies[63,64,65] support its value as a diagnostic and screening tool. However it is already known and proven that this "gold standard" is not an ideal screening tool. Potential radiation risk and diminished sensitivity in radiographically dense breasts represent the two main disadvantages of the technique, thus limitating its usefulness in high risk young women. It is well documentated in the study carried out by Kuhl CK et al[66] that gene carriers BRCA 1 and BRCA 2 are susceptible to have an increased radiosensitivity of breast parenchyma. Other clinical areas in which mammography is of

limited diagnostic value are: detection of lobular cancer, detection of ductal carcinoma in situ without associated microcalcifications, diagnostic work up of unknown primary presenting as axillary lymphadenopathy (these are usually small high grade lesions lodged in dense breast tissue), evaluation of multifocal disease and of locally advanced disease, not to mention its diminished sensitivity in post-treatment breasts.[67]

The addition of ultrasound to mammography can improve overall sensitivity, as this is an excellent method for differentiating solid from cystic lesions and for characterizing lesions depicted on screening mammograms. However it is not recommended as a first-line imaging method because of a variable false-negative rate, ranging between 3% and 47% as this is a highly operator dependant examination.[67]

The abnormal vascularity patterns of malignant lesions have been already well studied, with emphasis in the absence of normal capillaries and their replacement by the arteriovenous shunts pathologic basis, presented without exception in all cases of infiltrating tumors regardless of their histology, represents the physiological explanation of suspicious MRI enhancement. A full concordance was noted between negative MRI and normal DOBI scans. This could be of special interest in cases of patients who are BRCA 1 or 2 positive.[57] The study by comparing DOBI ComfortScan with MRI suggests that potential advantages of the ComfortScan include the facility of patient positioning, the rapidity of the exam (about 60 seconds of acqusition), a good tolerance, the absence of ionizing radiation and a high sensitivity, a reasonable cost and a very low breast compression, and DOBI modality could also be of theoretic value in cases of claustrophobic patients or in any other case of MRI contra-indication.[57]

Larger samples, evaluated over longer time periods, will undoubtedly tell more distinctly whether one can predict possible future use of DOBI ComfortScan as part of standard diagnostic investigation for malign breast gland lesions. This would bring distinct benefits, not only in terms of broader diagnostic possibilities, but also and more importantly in terms of radiation load, which is obviously zero in dynamic optical imaging, paving the way for future use as a method that is more suitable for mammographic screening for all ages.

5. CONCLUSION

The total of 62 scans have been acquired and interpreted by three independent blinded readers with encouraging results. This device could provide the physician with dynamic functional information regarding abnormal vascularization in an area of interest in the breast

and this information could be used to better characterize the lesion. ComfortScan can help the performance and accuracy of averaging, under averaging or less experienced doctors in their clinics most significantly. Dynamic optical breast imaging can be a promising complementary imaging modality for further investigation in cases of women with inconclusive mammography and/or physical examination. The study in Beijing comprised a small number of patients, but the preliminary results were encouraging enough, especially in cases of indeterminate mammographic cases. However further evaluation with a larger number of patients should be carried out.

Based upon its performance in clinical studies worldwide, the DOBI ComfortScan is a novel imaging technology that is appropriate as an imaging modality in diagnosing breast cancer at early stage. As a diagnostic tool of breast cancer, a large scale number of cases should be studied to charaterize different malignant and benign tumors at different stages respectively, different statues of patients, such as menopause stages with related nipple blue, and to statistically quantatize the metabolic rates of both malignant and benign tumors.

As a result, the ComfortScan system focuses on physiology-based dynamic functional imaging (i.e., what is occurring within the tissue in near real time) rather than a singular morphological image (i.e., a static anatomical snapshot showing physical details at a single point in time), such as those created by mammography. When combined with mammography or ultrasound, both of which provide simple morphologic images, the ComfortScan system's images of physiological changes in the breast is intended to provide physicians with a more complete data set to improve the physician's ability to provide an accurate breast cancer diagnosis.

With its negative predictive value of 98 percent and sepcificity of 87 percent,[68] the DOBI ComfortScan represents an opportunity to reduce the incidence and severity of invasive diagnostic intervention and, thus, to potentially reduce the number of unnecessary, painful and costly biopsies that are conducted on patients with healthy tissue. Furthermore, the safety profile, convenience, comfort and low comparative cost of the DOBI ComfortScan correspond closely to the call to action delivered by the National Academy of Sciences' Institute of Medicine.

Because it is an aid in detecting the minute vascular changes that accompany the process of angiogenesis during the earliest stages of malignant tumor growth, the DOBI ComfortScan could potentionally become a useful breast cancer screening tool if a full FOV (filed of view) cluster ComfortScan or DOBI ComfortScreen, next generation of the ComfortScan, could maintain a high negative predictive value, above 95%.

In addition to disease diagnosis, therapeutic monitoring of both pro- and anti-angiogenic drugs may also be a longer-term application of this technology and, since angiogenesis is found in many significant disease states (such as rheumatoid arthritis and adult blindness), the DOBI technology may have future applications in addition to cancer.

DOBI's dynamic analysis is a significant improvement over current static imaging. Breast density does not affect DOBI images, making DOBI especially important in the evaluation of dense breasts, as often seen in young women or those on Hormone Replacement Therapy (HRT). The initial results obtained with this rather new method, which is associated with no radiation load and well tolerated by women, hold promise for further development, particularly in the area of software development and standardization of evaluation parameters. Another important point to stress is the need for high-quality training of evaluating physicians which is, in our view, extremely important and affects the results of the investigation rather significantly.

DOBI ComfortScan is an Office, In-Vivo, Non-Invasive, Non-Ionizing and Non-painful molecular vesicular Dynamical Optical Breast Imaging modality. DOBI technology/modality will continue to improve as new features are added, much the same as other imaging modalities such as MRI, PET, CT, and digital mammography have evolved over time.

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