DOBI MEDICAL INTERNATIONAL

DOBI ComfortScan™ System
CLINICAL EFFECTIVENESS
EVALUATION REPORT

27-MARCH-2013

G. John Zhang, Ph.D.
CONTENT

PURPOSE ......................................................................................................................... 7
SCOPE ............................................................................................................................. 7
OBJECTIVE .................................................................................................................... 13
CLINICAL EFFECTIVENESS REPORT ............................................................................. 14

1. BACKGROUND ............................................................................................ 18

2. THE NEED FOR NEW DIAGNOSTIC TECHNOLOGIES .................................... 19

2.1 Mammography .......................................................................................... 20
2.2 Ultrasound, MRI and PET ........................................................................ 21
2.3 Biopsy ....................................................................................................... 22

3. BACKGROUND A NEW TECHNIQUE TO DETECT BREAST CANCER AT EARLY STAGE – DYANAMIC OPTICAL BREAST IMAGING ...... 22

3.1 The Role of Angiogenesis in New Breast Cancer Diagnostic Technologies ................................................................................................................... 23
3.2 Dynamic Optical Breast Imaging Technology in Early Breast Cancer Diagnostic ................................................................. 29
3.3 Dynamic Optical Breast Imaging Principle .................................................... 34

4. MATERIAL and METHODS ......................................................................... 36

4.1 ComfortScan Components and Description.............................................. 36
4.2 Use of the DOBI ComfortScan with a Patient .......................................... 39
4.3 ComfortScan Sanning Acquisition ........................................................... 40
4.4 ComfortScan Image Processing ................................................................ 41
4.5 ComfortScan Image Interpretation ........................................................... 42
4.6 Comparison with Mammography ............................................................. 43
4.7 Clinical Testing ......................................................................................... 44

5. CLINICAL EFFECTIVENESS ...................................................................... 46

5.1 Report : Research Article, “The Dynamic Optical Breast Imaging in the Preoperative Workflow of Women with Suspicious or Malignant Breast Lesions: Development of a New Comprehensive Score” by Massimiliano D’Aiuto, Giuseppe Frasci, Maria Luisa Barretta, Adolfo Gallipoli, Giovanni Maria Ciuffo, Flavia Musco, Sergio Orefice, Viviana Frattini, Ilves Guidi, Claudio Siani, Emanuela Esposito, Anna Crispo, Maurizio Montella, Andrea Chirico, Giuseppe D’Aiuto, and Aldo Vecchione at Department of Breast Disease, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, Department of Radiology, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, Breast Unit, Clinical Institute Zucchi, Via Zucchi 24, 20052 Monza, Italy, Breast Unit, Clinical Institute Pio X, Via Francesco Nava 31, 20159 Milano, Italy, Breast Surgery Division, Medical Institute Monterosa, Via Monterosa 3, 20149 Milano, Italy, Breast Prevention Area, Physios Clinic, Via Chiesa Nord 52, 41016 Modena, Italy, Epidemiology Division, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, National Cancer Institute “G. Pascale” Foundation, Via Mariano

5.3 Report: DOBI Score Ongoing Project by DOBI Sough European Distributor, Socrate Medical, Milano, Italy, 2011 ................................................. 50


5.5 Report: Dynamic Optical Breast Imaging (DOBI): Prospective Study of ComfortScan Accuracy in Diagnosis of Breast Cancer. PRELIMINARY RESULTS, Thesis Dissertation by Rossella Dandolo, Ph.D., University of Rome Tor Vergata, Italy, 2010 .................................................................................. 53

5.6 Report: Dynamic Optical Breast Imaging (DOBI), associated Ultrasound, allows to avoid unnecessary Biopsies - “Seno, luce rossa preventiva: Il Dynamic optical breast imaging (Dobi), associato all’ecografia, permette di evitare biopsie non necessarie” by di Piercarlo Salari, Oncologia, Tecnologie, October 12, 2009 ........................................................................... 57


5.12 Report: The purpose of our study was to report: “New Perspective of Mammary Screening: Application of Non-Invasive DOBI”, THE RESULTS OF DOBI EXAMINATIONS IN MASARYK MEMORIAL CANCER INSTITUTE in Czech Republic, by Irena Komorousova, Bartonkova H., Standara M., Schneiderova M., from 2004 to 2005 ....... 66


5.18 Report: “The Diagnostic Value of Small Lesions within Breast by Ultrasound combined with DOBI” published by Mei Xu, Junlai Li, MEDICAL JOURNAL OF CHINESE PEOPLE’S LIBERATION ARMY, Vol 34, No. 8 on August 1, 2009 .............................................................. 74

5.19 Report: “The Value Analysis of ComfortScan System in Differentiating Benign Breast Lesions from Malignant” published by Mei Xu, Junlai Li, Yongfeng Zhang, Xuejuan Shi, Chunmian Li, Jie Tiang, and “The Application of Dynamic Optical Breast Imaging in Differentiating Benign Breast Lesions from Malignant” Thesis submitted by Mei Xu at Chinese PLA General Hospital & Postcarduate Medical School on June 1, 2009. 74

5.20 Report: “ComfortScan System and Ultrasound Imaging: The Value of Combined Application to Differentiate Benign Breast Lesions from Malignant” Reported by Yongfeng Zhang, Junlai Li, Xuejuan Shi, Mei Xu, China, 2008 ........................................................................................................ 75


6. CLINICAL ACCEPTANCE ........................................................................... 93

6.1 The Italian League for the Fight against Cancer (LILT) has recommended to DOBI ComfortScan for younger women in detecting breast cancer at early stage on August 2, 2012 ................................................................. 94

6.2 The Italian League for the Fight against Cancer (LILT) – Underforty Women Breast Care, 2010 ................................................................. 96

6.3 2nd Meeting DOBI Group in Italy, 2011 ................................................ 100

6.4 1st Meeting DOBI Group in Italy, 2010 ................................................. 101

6.5 ANT: from now on mammograms for women under 40: 22/10/2012 - As of today young women may be subjected to investigation mammography. With the resort Cancer Prevention Foundation ANT, and DOBI mammography optical non-invasive and without radiation .................. 102

6.6 Breast cancer diagnosis today is born with "DOBI" ............................... 103

6.7 Breast cancer remains the second leading cause of death among women ................................................................. 104

6.8 UNIT 'ANT CANCER PREVENTION PROJECTS FOR POLICE AND UNICREDIT ................................................................. 105

6.9 THE INNOVATIVE METHODS OF STUDY MEDICAL MANARA 31 ................................................................. 106

6.10 INSTITUTE mammograms ANT EVEN UNDER 40 YEARS ............. 107

6.11 Know, prevent, cure: the fundamental objectives of the Centre .......... 108

6.12 From tomorrow morning a new entry with the camper made available by the project underforty LILT Bologna, with breast ultrasound and optical technology mammary (ComfortScan Dobi) for this occasion for the first time in southern Italy ................................................................. 110

6.13 As breast, ComfortScan presents as a solution for the prevention ....... 111

6.14 Prevention of breast cancer: the solution Italian for a global problem ... 113

6.15 A New Weapon Without radiation for the diagnosis of breast cancer in young women – Women’s Health in Italy ................................................. 115

6.16 US-China Technical Fight against Cancer with no more X-rays, August 2011 ................................................................. 116

6.17 PREVENTING BREAST: NEW DIAGNOSTIC .................................. 117

6.18 DOBI, the New Technology against Breast Cancer on Oct. 17, 2011 .... 118


6.20 Monza, care of the breast. Institutes Zucchi intervene in Rome, February 2011 ................................................................. 119

6.21 DOBI New Screening for Breast Cancer that does not use X-rays ...... 120

6.22 The New Frontier Optical Survey, 2011 ............................................. 120

6.23 Screening mammography: what to do?, April 19, 2011 .................... 121

6.24 Professor Rocca’s Trial ................................................................. 122

6.25 READY FOR A LIFE SUPPORT MACHINE, 2011 ............................ 123

6.26 A Step Forward to Prevent Breast Cancer - Health in Italy .......... 124
6.27 New Light in the diagnosis – LILT Magazine in Italy .......................... 124
6.28 The City of Rome in the front line against Breast Cancer - The I.P.A. in Italy ............................................................................................................. 125
6.29 Breast Safe with the Examination at Red Lights – July Fitness in Italy. 126
6.30 The Functional Optical Systems : Vanguard for the Fight against Breast Cancer ............................................................................................................. 127
6.31 The Technology to Fight Breast Cancer - Introduction of DOBI ......... 127
6.32 Breast Cancer, Zucchi Hospital Leader in Italy - Use the Wavelength of Right Light : DOBI Unit Acitive April 2009 .................................................. 128
6.33 Private Clinics in Italy, A New Light In the Diagnosis of Breast Cancer, Breast Optical Mammography ................................................................. 129
6.34 Innovative Companies of the Year 2002 .............................................. 130
6.35 Wall Street Reporter Magazine on February 25, 2004 ......................... 131
6.36 Wall Street Transcript on July 11, 2005 .................................................. 132
6.37 Rising Star Stocks – A Revolutionary Medical Imaging Device on August, 2004 ............................................................................................................. 133
6.38 Rising Star Stocks – A Revolutionary Medical Imaging Device on August, 2004 ............................................................................................................. 134
6.41 Body Mind : The Future of Breast Cancer, More Magazine on October 2005 ................................................................................................................. 137
6.42 Leading International Physicians Discuss DOBI ComfortScan in Prague, the Czech Republic from September 9-11, 2005 ........................................ 138
7. CONCLUSION ............................................................................................. 139
REFERENCES .................................................................................................. 145
**PURPOSE**

The purpose of this report is (1) to provide a summary of the effectiveness of DOBI ComfortScan as adjunct to existing breast imaging modalities or clinical breast examination (CBE) based on some literatures and some recent clinical reports from various DOBI ComfortScan users/sites worldwide and the original owner of DOBI ComfortScan, (2) to provide a summary of the clinical uses and acceptance of detection angiogenesis and studies from the clinical use of the ComfortScan™ system, and (3) to explain the technology employed in the ComfortScan system that’s used in the detection of angiogenic tissue.

Because, based on the continued demand, we, DOBI Global, have just relaunched the production of DOBI ComfortScan device through maintaining necessary ISO regulatory, and CE and SFDA marketing approval after reorganizing the entire DOBI project in 2012, the clinical effectiveness will continue being demonstrated through the additional reviews of clinical information, which has been defined in our Post Market Surveillance (SOP 1054-0004-00). We do look for the opportunity to implement the DOBI ComfortScan project for the potential benefit of women worldwide and to continue the development/improvement of the breast imaging technique.

**SCOPE**

This Clinical Effectiveness Evaluation Report was conducted according to the amended requirements on the 21st. March 2010 of MEDDEV 2.7.1 Rev 3 as a guide to provide a consistent approach to the review. This report describes the fundamentals/roots of the ComfortScan™ system by using the literature articles on angiogenesis and optical breast imaging below as reference, differentiates the DOBI technology from others through its patented Dynamic mechanism, and demonstrate DOBI ComfortScan ability to detect angiogenic tissue, which is the earliest presentation of tissue malignance in clinics, based on the recent studies described in following clinical effectiveness
section five.

Since DOBI ComfortScan technique is based on the Angiogenesis Theory published by Judah Folkman 1971 and the Optical Imaging of the Breast introduced by Max Cutler in 1929, the clinical effectiveness and efficacy of those two fundamentals will not addressed in this report, but their clinical significances could be partially referred through following literature lists.

- “Clinical applications of research on angiogenesis”, Judah Folkman.
- “Chemotherapy targeted to tumor vasculature”, Wadih Arp, Renata Pasqualini and Erlli Ruoslahti.
- “Inhibition of tumor Angiogenesis as a Strategy to Circumvent Acquired Resistance to Anti-Cancer Therapeutic Agents”, Robert S. Kerbel.
- “Functional imaging of the human body”, Eduard E. Godik and Yuri V. Gulyaev.
- “Vascular attack as a therapeutic strategy for cancer”, Juliana Denekamp
- “The relationship between elevated interstitial fluid pressure and blood flow in tumors: A bioengineering analysis”, Michael F. Milosevic,
Anthony W. Fyles and Richard P. Hill.


- “Light scanning of nonpalpable breast lesions: Reevaluation”, Barbsrn Monsees, Judy M. Destouet and Deborah Gersell.


- “Recent advances in diffuse optical imaging”, A P Gibson, J C Hebden and S R Arridge.


- “Assessing the future of diffuse optical imaging technologies”, Bruce J Tromberg, Brian W Pogue, Keith D. Paulsen, Arjun G. Yodh, David A.
Boas, Albert E. Cerussi.

The improvements of the Optical Imaging Technology will be discussed within this report as well as can be found from some literatures listed above. Because of (1) the breakthrough of Angiogenesis Theory in clinics, (2) the development of Semiconductor Technology in Optical Detector, and (3) the tremendous efforts worldwide in past twenty years, optical breast imaging technique has been developed significantly by comparing the study carried out by A Swedish Multicenter Study with the publications of “LightScanning versus Mammography for the detection of breast cancer in screening and clinical practice” and “Relationship between lightscanning and the histologic and mammographic appearance of malignant breast tumors”.

About ten (10) years ago, 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. The Chapter 2, Breast Imaging and Related Technologies, addressed as following:

- Optical imaging or tomography, which is relatively inexpensive and simple in comparison with many other imaging modalities, is also actively under investigation for a variety of cancers, including breast cancer. The technique uses light in the near-infrared range (wavelengths from 700 to 1,200 nm), which is nonionizing, to produce an image of the breast. Potential advantages of the technology include speed, comfort, and non-invasiveness. An optical scan can be taken in less than 30 seconds by simply placing an image pad over the breast without compression (Chance, 1998). Optical imaging methods offer the potential to differentiate between soft tissues that are indistinguishable by other modalities, and specific absorption by natural chromophores (such as hemoglobin) can also provide biological or functional information.
• Optical imaging systems are being commercially developed by Imaging Diagnostic Systems Inc. (IMDS; Plantation, Florida), DOBI Medical Systems (Mahwah, New Jersey), and Advanced Research and Technology, Inc (ART; Montreal, Canada). The DOBI technology is based on optical detection of angiogenesis in malignant lesions, whereas the IMDS and ART technologies use laser-based technologies to assess various optical properties of breast abnormalities. This difference between DOBI and others is created by DOBI patented Dynamic Technique. All three companies are conducting clinical trials for FDA approval for diagnostic use of their devices, but they also plan to pursue a screening approach in the future.

• In summary, optical imaging has long been thought to have potential as a means of breast cancer detection, but to date that potential has not yet been realized. Significant technological improvements in recent years may eventually propel this technology into the clinic, but a conclusion cannot yet be reached about its future utility.

The studies from the pioneer of Optical Breast Imaging, Professor Britton Chance, who died in November 2010, led to the development of near infrared (NIR) spectroscopy and imaging for real time metabolic studies of brain (hematoma detection, prefrontal cortex monitoring, fetal brain oxygenation in utero), breast (cancer detection using signals of angiogenesis and hypermetabolism), skeletal muscle (metabolic monitoring) and cardiac muscle (trans-thoracic detection of hypoxia of myocardium). His scholarly articles, such as “Optical tomography, photon migration, and Spectroscopy of Tissue and Model Media: Theory, Human Studies, and Instrumentation”, “Concurrent MRI and diffuse optical tomography of breast after indocyanine green enhancement”, “Breast imaging technology: Probing physiology and molecular function using optical imaging - applications to breast cancer”, “MRI-Guided Diffuse Optical Spectroscopy of Malignant and Benign Breast Lesions”, etc., published about ten (10) years ago have demonstrated the
capability of NIR Optical Imaging technique in detecting the malignancy of the breast tumors.

The three publications, “Recent advances in diffuse optical imaging” by A P Gibson, J C Hebden and S R Arridge; “Optical imaging of the breast” by S.M.W.Y. van de Ven, S.G. Elias, M.A.A.J. van den Bosch, P. Luijten and W.P.Th.M. Mali; “Assessing the future of diffuse optical imaging technologies” by Bruce J Tromberg, Brian W Pogue, Keith D. Paulsen, Arjun G. Yodh, David A. Boas, Albert E. Cerussi, in 2005, 2008 and 2008 respectively, have described the development of optical imaging technology, which is an emerging technique for functional imaging of biological tissue but still need more clinical studies. A further role which optical imaging could fill is as a low-cost, portable imaging system for use in primary care situations or at the bedside. The transfer of new techniques and ideas for diffuse optical imaging into clinical tools require close collaboration between engineers, clinicians, scientists and mathematicians.

The paper of “Dynamical Optical Imaging” published on SPIE Vol. 2389/859 by E. Godik, T. Gergely, V. Liger, V. Zlatov, A. Taratorin, has addressed the possibility for revealing and identifying pathology through the spatially distributed low amplitude dynamic optical contrasts, which reflect the physiological dynamics of the living tissue, described the a simple CCD-based system and software for optical image sequence processing, and demonstrated examples of the application of this approach for breast imaging diagnostics. A USA “Dynamic-functional imaging of biological objects using a non-rigid object holder” patent filed on July 1, 2003 and renewed on January 3, 2011 has described the technical improvement conventional Optical Breast Imaging. The DOBI ComfortScan technique detects the differences of the transilluminations between benign tissues and malignant tissues by evaluating the light attenuation when an external pressure stimulus is applied over time described by Dyachenko A “Dynamic imaging of breast lesions; one dimensional optical model” (Asian Journal of Physics
This patented Dynamic Technique differentiates DOBI method from other optical imaging approach by enabling DOBI ComfortScan ONLY to detect the angiogenesis in malignant tissue. For example, the model described by Dowle et al is the Spectrascan lite scan model 10, which is sometimes referred to as the Spectrascan or the Lite Scan. The Spectrascan Lite scan passes infrared light through the breast to detect early cancers. The machine produces a beam of light that alternates between the red and/or infrared. The computer converts the image recorded by the video camera into digital information, which is displayed on a color monitor. The image shows area of different kinds of tissue in different colors with respect to the different absorption of transmitted light. The Spectrascan Model 10 made by Spectrascan, Inc. has very high False Positive Rate. The DOBI ComfortScan also detects the NIR light transmission through various absorption tissues, and the recorded digital images also shows area of different kinds of tissue in different colors with respect to the different absorption of transmitted light. But the difference is that the uniform pressure pulses applied on the breast decreases the False Positive Rate through distinguishing the abnormal tissues, which contains the Angiogenesis, from normal tissues. The detailed description of DOBI ComfortScan Technique will be described in more details in following DOBI Technology section.

**OBJECTIVE**

The purpose of this report is to demonstrate the EFFECTIVENESS of DOBI ComfortScan as adjunct to existing breast imaging modalities, such as Mammography or Ultrasound, in detecting breast cancer through recent clinical studies worldwide and the improvement of the physician’s ability in providing more accurate breast cancer diagnosis in earlier stage than current imaging approaches through the market Acceptance and public Awareness of the DOBI ComfortScan system in clinics.
**CLINICAL EFFECTIVENESS REPORT**

The DOBI ComfortScan System is designed to detect areas of abnormal vascularization in breast tissue. DOBI technology is based on the now generally recognized phenomenon of angiogenesis or the growth of new blood vessels around and in support of malignant lesions. The increased vascularity associated with the growth of malignant lesions is different from the vascularity supporting benign and normal tissue and interstitial fluid pressure is elevated around malignant tumors. This vascularity in a breast behaves differently in response to the stimulus of pressure modulation resulting in different light absorption in the area of abnormal vascularization. The ComfortScan system measures transmission of red light through the breast, recording the transient response to a pressure stimulus that initiates changes in blood volume. As a result of this pressure stimulus, the dynamic behavior of tissue optical properties creates different contrast for areas of abnormal vascularization from neighboring normal breast tissue. The potential for the ComfortScan system as a diagnostic tool is to non-invasively differentiate between specific optical patterns of vascularized and non-vascularized 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 and possibly in treatment recommendations.

The effectiveness of DOBI ComfortScan as adjunct to existing breast imaging modalities in detecting breast cancer are demonstrated through the recent study reports from various DOBI ComfortScan users/sites worldwide and the original owner of DOBI ComfortScan described in clinical effectiveness and clinical acceptance sections.

Because, based on the continued demand, the manufacturing of DOBI ComfortScan device and application of a new CE Certification and ISO 13485 Certificate have just re-launched after the intellectual property of the DOBI Technology and ComfortScan device was reorganized on the May of 2010, the clinical effectiveness will continue being demonstrated through the additional reviews of clinical information, which has been defined in our Post Market Surveillance (SOP 1054-0004-00).

According to the amended requirements on the 21st March 2010 of the Medical Devices Directive (93/42/EEC), we are going to demonstrate the Clinical Effectiveness of our
DOBI ComfortScan™ System
Clinical Effectiveness Evaluation Report

DOBI ComfortScan through following Clinical Effectiveness section which is the outcome we have implemented our Post Market Surveillance of Dynamic Optical Breast Imaging Systems (DOBI) until the December of 2012. Therefore, based on the MEDDEV 2.7.1 Rev 3 for the clinical effectiveness, we, DOBI Medical International, have followed our Post-Marketing Surveillance in Section 5:

- To gather 2495 cases/patients,
- With 1053 malignant cases which are confirmed by biopsy,
- In over 23 study sites.

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<td>MassimoNapoli1, Giuseppe Pozzi1, Mihai Lasa Barzolu, Alexandra Andrei, Giovanni Menis Cuffi, FabioFallu, SergioGambino, VincenzoFerrari, TitoGueli, ClaudioBastoni, EnmatataEspirito1, ArnaudO'Connor, MaurizioMontella1, AndreaChrist1, GioviD'Ambrosi, and AldoVaccicchelli</td>
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DOBI Averaging Statistics: 2495/1053 88.46% 74.60% 74.59% 86.65% 81.95%
Those data are collected from the DOBI ComfortScan installed before 2012 to the fullest extent practicable in accordance with the requirements of MEDDEV 2.12-2 GUIDELINES ON POST MARKET CLINICAL FOLLOW-UP (PMCF) and 1054-0004-00 Post-Marketing Surveillance of our company’s internal procedure through out distributors, research partners and customers. To evaluate the clinical effectiveness of DOBI ComfortScan comprehensively, some of the ComfortScan data are combined with Mammography, Ultrasound and MRI in compliance with the requirements in MEDDEV 2.12-2 GUIDELINES on Post-Market Clinical Follow-up (PMCF) “in the form of follow up specific sub-groups and/or prospective study”.

As an example of the collected data for this clinical evaluation from the a recent publication at Italian Journal of Gynaecology and Obstetrics Volume 23 on October 3, 2011, with the supports of our Italy distributor, Dr. V. Frattini, L. Ghisoni, A. Teodoro, PL Vaj and S. Orefice from Habilita Group-Bergamo, Centro Medico Monte Rosa, Istituto Clinico Humanitas and Habilita Group-Bergamo in Italy conducted a multicenter study to determine the Sensitivity and Specificity of the ComfortScan System to detect malignancy as an adjunct to Ultrasound in patients between 25 to 39 years of age. A total of 617 young females aged 25-39 with clinical risk to develop a cancer or dense breast to live suspect breast cancer from standard imaging. There are 269 malignant cases confirmed by biopsy. All subjects have been submitted to clinical investigation by means of both DOBI ComfortScan and Ultrasound. When both ComfortScan and Ultrasound clinical results were positive for neoplasm, the second step consisted surgery biopsy. If only ComfortScan or Ultrasound are positive for neoplasm all patient submitted to core biopsy. The dynamic optical imaging from DOBI ComfortScan showed a statistical difference (p<0.005) in patient analyses compared with Ultrasound. In this study, the dynamical optical breast imaging, DOBI, had a sensitivity equal to 98% and a specificity equal to 87% while the sensitivity and specificity of the Ultrasound are equal to 74% and 70% respectively. Because of the new recommendation from US Preventive Services Task Force, we have sought Ultrasound instead of Mammography as the adjunct of DOBI ComfortScan in detecting breast malignancy in patients at all age.

As summary of those studies based on the total 2495 data and 1053 malignant cases collected from over 23 multicenter trials and the statistical analysis from a variety of readers in compliance with MEDDEV.2.7.1 Rev.3, the averaging Sensitivity and...
Specificity of DOBI ComfortScan in detecting breast cancer are 87% and 75% separately.

Due to the breakthroughs of Clinical Tumor Angiogenesis and Industrial Semi-conductor in past decades, the Optical Imaging technology has been developed significantly and the Optical Imaging devices in detecting breast cancer at early stage have become emerging. Some optical devices, such as CTLM, SoftScan, Optimus, etc., based on the Diffuse Optical Tomography (DOT) technology in breast cancer detection, have been approved by the Certification Authority of CE Notified Bodies. In order to improve the specificity of breast cancer diagnosis, based on the same DOT theory, a patented Dynamic Technique of DOBI ComfortScan has been developed through localizing tumor angiogenesis and collecting the changes in both blood volume and metabolic rates associated with the angiogenesis. By comparing with other optical imaging methods, the marketing acceptance and clinical effectiveness of DOBI ComfortScan have been increased significantly.

Overall, according to the DOBI ComfortScan Clinical Effectiveness Evaluation Report attached with this letter, based on the MEDDEV 2.7.1 Rev 3 and 1054-0004-00 Post-Marketing Surveillance of DOBI Medical International, we believe that we have accomplished the Post-Marketing Surveillance on our DOBI ComfortScan Systems in 2012 and the Clinical Effectiveness of our DOBI ComfortScan have been demonstrated.

Based on the Angiogenesis Theory published by Judah Folkman 1971 and the Optical Imaging of the Breast introduced by Max Cutler in 1929, DOBI ComfortScan system is sensing near infrared light penetration through the breast tissue, 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, and analyzing spatial and temporal information that represents the appearance of tumor angiogenesis, which is associated with the tissue malignancy of the breast. The ComfortScan is a personal computer and microcontroller based data acquisition system intended to acquire transillumination images of intact, implant free, in situ human tissue. The images assist the physician to characterize normal and abnormal tissue under both static and dynamic conditions. Applying a small external air pressure via a soft silicon membrane, to the breast, creates the dynamic aspect. Preliminary results have 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.

1. BACKGROUND

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. In 2008 it was estimated that worldwide, 1.38 million women were diagnosed with breast cancer, accounting for around a tenth (10.9%) of all new cancers and nearly a quarter (23%) of all female cancer cases. Female breast cancer incidence rates vary considerably, with the highest rates in Europe and the lowest rates in Africa and Asia. An estimated 332,000 new cases of breast cancer occurred in the countries of the European Union (EU-27) in 2008, and an estimated 182,460 occur in the USA each year (http://info.cancerresearchuk.org/). It is estimated that 207,090 women will be diagnosed with and 39,840 women will die of cancer of the breast in 2010 in US (National Cancer Institute of U.S. NIH). 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.

**Age standardised (World) incidence and mortality rates, female breast
cancer in selected countries, 2008 estimates**

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2. 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. 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. 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 clinical 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.”

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. The following sections review the utilization of mammography, ultrasound, MRI, PET and biopsy as diagnostic tools.

### 2.1 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. 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. 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. 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. Studies show that abnormal mammograms negatively affect a woman’s psychological and emotional state and may impair daily functioning for 3 to 18 months. 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.

2.2 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. 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.

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.

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.

### 2.3 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. 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.

### 3. BACKGROUND A NEW TECHNIQUE TO DETECT BREAST CANCER AT EARLY STAGE – DYNAMIC OPTICAL 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 monitoring tool for breast cancer early detection and breast non-invasive treatment evaluation is increasingly paid 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.

3.1 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. 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. In particular, the role of angiogenesis in breast cancer has been documented.

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 below. 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

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.

![Blood Vessel Growth Surrounding a Tumor](image)

- Uniform A-V flow
- Normal permeability
- Vascular hierarchy maintained

Photos courtesy of Dr. David Cherest, Scripps Research Institute
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 in figure below:

- **High density and high blood volume.** Blood vessels created to feed tumors are more numerous and dense than vessels in normal tissue. The existence of differing vascularity in breast cancer is supported by Feldman and Watt, both of whom successfully imaged small groups of breast cancers using vascular imaging techniques. Wells found similar results using ultrasound, as did Schoenberger and Cosgrove. This distinctive vascularity is also supported by Folkman, who studied the mechanism of neoplasia, and by the empirical histology of Weidner, 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. 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, 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). 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.\textsuperscript{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 $\alpha_v\beta_3$ plays an important role in angiogenesis. The presence of high levels of integrin $\alpha_v\beta_3$ promotes angiogenesis and, conversely, low levels of integrin $\alpha_v\beta_3$ are the most significant prognostic indicator of relapse-free survival in breast cancer patients.\textsuperscript{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 \textit{in vivo} using magnetic resonance imaging (MRI) and a paramagnetic contrast agent that is targeted to endothelial integrin $\alpha_v\beta_3$ via the LM609 monoclonal antibody. This new approach also enables the detection of angiogenic “hot spots” that are not observable by standard MRI.\textsuperscript{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, shown in figure below. 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.

\[\text{When a malignant tumor starts to grow in the breast (step 1), it usually becomes supported by a complex network of blood microvessels (step 2) that feed it and assist in its local growth and development (steps 3 and 4). This vascularization process is called tumor angiogenesis.}\]

\[\text{The DOBI ComfortScan system has been designed to be able to detect this abnormal network of blood vessels, thereby providing a useful complement to common mammographic images.}\]
3.2 Dynamic Optical 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. 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 utilized excised breast tissue to show that blood content (deoxyhemoglobin) affects transmittance (the absorption spectrum) in breast tissue. Profio et al. 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, shown in figure below. Peters\textsuperscript{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. The DOBI ComfortScan™ system detects the differences by evaluating the light attenuation when an external pressure stimulus is applied over time, as shown in figure above.

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, as shown in figure below.
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, as shown in figures below.
Case Study #1
60y woman, Non-palpable 22mm mass
Equivocal mammography BIRADS 5 calcified
Pathology: Ductal Carcinoma.

Case Study #2
47y woman, Non-palpable 20mm mass
Equivocal mammography. BIRADS 3 calcified
Pathology: Benign
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

3.3 Dynamic Optical Breast Imaging Principle

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 current 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,
$I_{\text{ref}}$, 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 $(x, y)$:

$$DS(x, y, t) = \frac{(I(x, y, t) - I_{\text{ref}})}{I_{\text{ref}}}.$$ 

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. 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:

$$DS_a(x, y, t) \neq DS_n(x, y, t).$$

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 follow-up 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.

4. MATERIAL and METHODS

4.1 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. Descriptions of each of these items follow and can be viewed in figure below.
**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.
4.2 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 for local governmental regulatory and marketing approval at hospitals or clinics was conducted in accordance with Provisions for Clinical Trials of Medical devices of the country. The enrolled patients are 18 years of age or older and have been considered the necessity of a breast biopsy after receiving mammography examination 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 the countries, 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 each country, and meet the requirements and principles of ethics.

4.3 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.
4.4 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 classification, 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.

4.5 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. fibrokyctic 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,\textsuperscript{57} abnormal tumor vessels, especially the presence of arteriovenous shunts, are responsible for the rapid enhancement and the "wash-out" of malignant lesions.

### 4.6 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.

#### Imaging Technologies Comparison

<table>
<thead>
<tr>
<th>Technology</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Imaging Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mammography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 50 Above</td>
<td>89%</td>
<td>45%</td>
<td>Morphological</td>
</tr>
<tr>
<td>Ages 50 &amp; Below</td>
<td>58%</td>
<td>40%</td>
<td>Morphological</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td>75%</td>
<td>94%</td>
<td>Morphological</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>96%</td>
<td>69%</td>
<td>Physiological</td>
</tr>
<tr>
<td><strong>ComfortScan System</strong></td>
<td>92%</td>
<td>67%</td>
<td>Physiological</td>
</tr>
</tbody>
</table>

** Kaiser Permanente, Technical Review of MRI 2003  
***Internal Validation Study for ComfortView Rev 1.0. 2002-2004 316 Patients

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%.\textsuperscript{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. 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%). A comparison based on the same trial criteria is listed in the above.

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 additional new physiological information, all the enrolled patients during the clinical study of DOBI ComfortScan in Beijing were performed mammography examinations but have inconclusive findings, which are categorized as Breast Imaging Reporting and Data System (BI-RADS) 3 or 4. The results are shown in Table above.

4.7 Clinical Testing

During the entire developmental period of the DOBI System beginning in 1996, approximately 1,300 patients have been scanned. Based on the analysis of scans completed on typical patients Q3/4 2000 through Q1 2001, the DOBI System is performing with a sensitivity (“true positive”) of 92% and specificity (“true negative”) of 76%, based on 123 patients with a malignancy rate of 20%. Negative predictive value is 97%.

Some of these scans were performed for the purpose of testing potential hardware and software configurations of the System while others assessed its accuracy in differentiating benign from malignant lesions. During the period of mid-1999 to mid-2001, several scan protocols were used to test the device and the results were used to refine both the hardware and the software and to develop additional analytical tools. This test-refine-retest process was repeated until the upgrades resulted in the current System
configuration being tested at six investigational clinical sites under a well-defined set of rules. These investigational clinical sites are:

- Asheville Women’s Medical Center, Asheville, NC
- Columbia University College of Physicians and Surgeons, New York, NY
- Hackensack University Medical Center, Hackensack, NJ
- Massachusetts General Hospital, Boston, MA
- University of Massachusetts Medical School, Worcester, MA
- Weill Medical College of Cornell University, New York, NY

The current trial protocol being followed is designed to incorporate DOBI System scanning of patients scheduled for biopsy on the basis of equivocal mammogram and other clinical findings. Approximately 450 patients were scanned under this protocol from June 2000 through June 2001. The DOBI System scans are interpreted by consulting radiologists and results of interpretation of 200 of these scans by an independent radiologist show the following: 26/28 malignant lesions were recommended for biopsy, for a sensitivity of 93 percent and 116/172 benign lesions would have been correctly followed clinically without biopsy, for a specificity of 67 percent. Another way to assess the value of these results is to look at the negative predictive value, that is, the percentage of cases that were correctly recommended for clinical follow-up without biopsy. The negative predictive value is 98 percent. Specifically, 116 of 118 cases that DOBI System scan interpretation recommended for clinical follow-up without biopsy were correctly assessed.

Following Clinical Effectiveness section lists some recent clinical studies and demonstrates the clinical effectiveness of DOBI ComfortScan device. A total 2328 data and 958 malignant cases are collected from over 15 multicenters and the averaging Sensitivity and Specificity of DOBI ComfortScan in detecting breast cancer are 83.87% and 73.9 separately by the statistical analysis from a variety of readers in compliance with MEDDEV.2.7.1 Rev.3.
5. CLINICAL EFFECTIVENESS

Because DOBI ComfortScan could be used for common sizes and densities in detecting breast cancer by comparing with Mammography, the major differences of breasts between different races, such as Chinese women, North American women, European women, are the size and density. Chinese women tend to have small and dense breasts. For example, the “RESULTS OF INVESTIGATIONAL USE OF DOBI COMFORTSCAN IN CHINA” Reported by G. Zhang, W. Wang, D. Yang and H. Jiang in Beijing shows among 62 patients 90.3% patients have dense breasts (10 very dense and 46 dense breasts). Because the sizes and densities of breasts have no influence on the scans of DOBI ComfortScan, thus, the performances using DOBI ComfortScan among different races, Chinese, North American and European women have no difference.

Based on the published studies from Cornell University, Saint Louis University, Chinese Anti-Cancer Association, etc., race is not considered a factor that might increase a woman’s chance of getting breast cancer. However, the rates of developing and dying from the disease differ among ethnic groups. This may be due to differences in specific risk factors, the biology of the breast cancer or in breast cancer screening rates and treatment (Ref: ww5.komen.org/uploadedFiles/Content_Binaries/806-373a.pdf and envirocancer.cornell.edu/Factsheet/general/fs47.ethnicity.cfm). For example, 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. 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. Because DOBI ComfortScan is Currently used as adjunct to the mammography in detecting/diagnosing breast cancer (Not Screening), the Sensitivity (1-False negative rate) and Specificity (1-False positive rate) of a quantitative test are dependent on the cut-off value above or below which the test is positive. In general, the higher the sensitivity, the lower the specificity, and vice versa. Unlike Positive predicative value and Negative predicative value, the Sensitivity and Specificity are independent of the population of interest subjected to the test and are not influenced by the prevalence of the disease. Therefore,
the performances using DOBI ComfortScan among different races, such as Chinese, North American and European populations are equivalent physiologically.

Following sections will summarize some preliminary clinical reports from various DOBI ComfortScan users/sites worldwide and the original owner of DOBI ComfortScan to demonstrate the effectiveness of DOBI ComfortScan as adjunct to existing breast imaging modalities, such as Mammography or Ultrasound, in diagnosing breast cancer through detecting tumor angiogenesis in clinical use of the ComfortScan system.

5.1 Report : Research Article, “The Dynamic Optical Breast Imaging in the Preoperative Workflow of Women with Suspicious or Malignant Breast Lesions: Development of a New Comprehensive Score” by Massimiliano D’Aiuto, Giuseppe Frasci, Maria Luisa Barretta, Adolfo Gallipoli, Giovanni Maria Ciuffo, Flavia Musco, Sergio Orefice, Viviana Frattini, Ilves Guidi, Claudio Siani, Emanuela Esposito, Anna Crispo, Maurizio Montella, Andrea Chirico, Giuseppe D’Aiuto, and Aldo Vecchione at Department of Breast Disease, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, Department of Radiology, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, Breast Unit, Clinical Institute Zucchi, Via Zucchi 24, 20052 Monza, Italy, Breast Unit, Clinical Institute Pio X, Via Francesco Nava 31, 20159 Milano, Italy, Breast Surgery Division, Medical Institute Monterosa, Via Monterosa 3, 20149 Milano, Italy, Breast Prevention Area, Physios Clinic, Via Chiesa Nord 52, 41016 Modena, Italy, Epidemiology Division, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, National Cancer Institute “G. Pascale” Foundation, Via Mariano Semmola, 80136 Naples, Italy, ISRN Oncology, Volume 2012, Article ID 631917, Accepted 29 July 2012

To determine the diagnostic accuracy of DOBIComfortScan in patients with Breast Imaging Reporting suspect breast lesions (BI-RADS) 4-5 breast lesions. Materials and Methods. One-hundred and thirteen patients underwent DOBI ComfortScan examination before surgery. Twelve parameters were taken into consideration to
define DOBI findings. Results. Twenty-seven radical mastectomies, 47 quadrantectomies and 39 wide excisions, were performed. Overall, 65 invasive cancer, 9 in situ carcinoma and 39 nonmalignant lesions, were observed. Ten out of 12 considered parameters resulted significantly in association with histology at discriminant analysis. A summation score of 30.5 resulted to be the best cut off at ROC analysis, giving a sensitivity and specificity of 80% and 87%, respectively, and a positive predictive value of 92.2%. Finally the following DOBI-BI-RADS model was developed: malignant (B5 >=38 score); possibly malignant (B4 = 25~37 score); benign but the possibility of malignancy can not be excluded (B3 = 20~24 score); benign (B2<20).

The DOBI-level

<table>
<thead>
<tr>
<th>Level</th>
<th>Score</th>
<th>N ° Total</th>
<th>Cancer</th>
<th>No cancer</th>
<th>PPV**</th>
<th>NPV***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>&lt;20</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>20–24</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>25–37</td>
<td>56</td>
<td>39</td>
<td>17</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>≥38</td>
<td>33</td>
<td>32</td>
<td>1</td>
<td>97%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Absence of API.
**Positive predictive value.
***Negative predictive value.

The summation score derived from the discriminant analysis was evaluated by using the receiver-operating characteristic (ROC) curves to assess the best cutoff. The area under ROC curve (AUC) illustrates the performance of a classifier over all sensitivity and specificity levels. The AUC can range from 0.5 (chance performance) to 1.0 (perfect performance). In order to minimize the rate of false negative, we decided to take into account a performance at very high sensitivity level.

The Conclusion is that the DOBI ComfortScan is a low-cost, noninvasive technique with a good potential for discriminating benign from malignant lesions. According to the results, the definition of other parameters besides pixel intensity permits to improve the accuracy of this diagnostic procedure. Further studies are warranted to define the potential role of DOBI ComfortScan in breast cancer imaging.

This perspective study determines the diagnostic accuracy of using Dynamic Optical Breast Imaging in addition to Ultrasound systems for prevention, diagnosis and monitoring of breast cancer in young females by means of a non-invasive examination methodology. This examination methodology can represent a methodical support in uncertain and particular neoplasms or an alternative approach especially for young women. The study aims to evaluating the usage flexibility of the DOBI methodology (differentiated diagnosis between benign and malignant neoplasm, breast physiopathology variation and evaluation) on female patients respect and with US methodology that is the first step for diagnosis in young woman. This study has been carried out at the “Centro Medico Monterosa (CMM)”, Milan Italy. On total of 617 consecutive woman (from September 2008 to March 2010), age range 20-39, average 35±1.1 years All patients have been submitted to clinical investigation by means of both US and DOBI. When both US and DOBI clinical results were positive for neoplasm, the second step consisted surgery biopsy. If only US or DOBI are positive for neoplasm all patent submitted to core biopsy. The dynamic optical imaging showed a statistical difference (p<0.005) in patient analyses compared with Ultrasound; in this study, the dynamical optical breast imaging had a sensitivity equal to 98% and a specificity equal to 87%. This non-invasive imaging-based methodology has a high potential for breast cancer prevention independently of breast size, density, hormonal status and it is particularly suited for young females, being non-radiant.

In all study cases the anamnesis data have been evaluated by their collection in a purposely devoted Data Base and elaboration according to a specific protocol and method. After anamnesis and clinical visit, all patients have been submitted to both breast US by a Kretz-Voluson 730 and additional DOBI examination, independently
of any other supporting iconographic documentation (in this specific case, MR or US made in other Institute or Hospital). The histologic test is made for a positive result of DOBI examination with surgery biopsy or if positive US examination with core biopsy guided by ComfortScan with a marker of hyaluronic acid. In case of doubt evaluation or different results from DOBI and US all patients are submitted to core biopsy. The following results have been achieved on a population whose age distribution was: average age 35 years with a standard deviation of 1.1:

<table>
<thead>
<tr>
<th>Histology</th>
<th>DOBI Concordance</th>
<th>DOBI Discordance</th>
<th>US Concordance</th>
<th>US Discordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>benign</td>
<td>348</td>
<td>303 TN</td>
<td>45 FP</td>
<td>246 TN</td>
</tr>
<tr>
<td>Malign</td>
<td>269</td>
<td>264 TP</td>
<td>5 FN</td>
<td>201 TP</td>
</tr>
</tbody>
</table>

DOBI: Sensitivity TP/TP+FN = 98%, Specificity TN/TN+FP = 87%;
US: Sensitivity TP/TP+FN = 74%, Specificity TN/TN+FP = 70%;

Breast cancer can to have a different pathologic and oncology characteristic difficult value with standard methodology. Particularly in young woman: DOBI and US can actually to have a statistical diagnostic accuracy of 91%. After having carefully evaluated advantages, limits and the high sensibility of the DOBI methodology and in consideration of the young age of the patients, our study demonstrates that the association between DOBI methodology and US should be considered an important diagnostic – preventive methodology, mainly for women with dense breast where Mammography is poorly sensible.

5.3 Report: DOBI Score Ongoing Project by DOBI Sough European Distributor, Socrate Medical, Milano, Italy, 2011

Please note that the following information is confidential and the study is still ongoing. You can use the information for the Survey, but not disseminate it.

The study involves several hospitals and medical centers (multicenter within south Europe). This report is just part of it and is the first classification and result (by Socrate Medical). The other hundreds of data are not organized yet.
The study involves symptomatic women of different age. All women diagnostic path includes visit, US, X-Ray, Biopsy and obviously DOBI.

The study objective is the DOBI level evaluation:

Patient Number: 113 women
Biopsy: – 39 (34.5%) nonmalignant
– 74 (65.4%) malignant

Result table:

<table>
<thead>
<tr>
<th></th>
<th>Nonmalignant</th>
<th>Malignant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmalignant</td>
<td>31 (83.8)</td>
<td>6 (16.2)</td>
<td>37</td>
</tr>
<tr>
<td>Malignant</td>
<td>15 (20.3)</td>
<td>59 (79.7)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

59/74 malignant correct classification (79.7%)
31/37 nonmalignant correct classification (83.7%)

Cut-off DOBI-Score = 30.5,

- Sensitivity : 80%
- Specificity : 88%.

When the cut-off DOBI Score is adjusted based on the design of the study or the need of the clinics, different outcomes, Sensitivity and Specificity, will be obtained. At the same time, since the DOBI Score is easy to be adapted or computerized, a standard diagnostics will be implemented and a clinical significance will be achieved.

Breast cancer has affected many women around the world throughout history. In order to recognize and treat the early signs of breast cancer, obtaining high quality images is crucial. A variety of imaging modalities are available for use in breast imaging, including conventional mammography and newer optical imaging techniques. One such optical imaging system is the ComfortScan™, which uses red light to image the breast and was the focus of this study. The objectives include investigating whether performing a large scale clinical trial with the ComfortScan™ would be warranted to further patient care and diagnostics for breast imaging, and determining whether the ComfortScan™ would achieve better correlation to biopsy than mammography alone. An additional goal was to investigate whether the ComfortScan™ system would be beneficial as a mainstream method for a radiologist to diagnose breast cancer risk.

The preliminary study with 19 patients demonstrated that there was no difference in diagnostic information between the near-infrared (NIR) image and mammography (p>0.05). Anecdotal evidence suggests cases where mammography disagreed with biopsy, whereas ComfortScan™ agreed, though these were not statistically significant. Based on these encouraging results, a large scale clinical trial was launched to investigate the potential of widespread use of the ComfortScan™. The large scale trial included 126 NIR images and found difference in diagnostic information between NIR and mammography (p<0.05). Mammography agreed with biopsy in 18/33 and the ComfortScan™ system agreed with biopsy in 25/33 cases. The sensitivity and specificity for the ComfortScan(TM) system was 83% and 67%, respectively. The sensitivity and specificity of mammography was 94% and 13%, respectively. This study included a variety of women with varying ages and BIRADS scores, and demonstrated the effective clinical use of a portable, non-ionizing, inexpensive imaging modality, indicating that the ComfortScan™ system could likely be successful as a mainstream adjunct to mammography.
The potential of using polyvinyl alcohol cryogel (PVA-C) as a breast tissue mimic was investigated and PVA-C was then used to validate the mode of action of the ComfortScan™ system. Two experimental methods reported the absorption coefficients and reduced scattering coefficients of PVA-C. Using a double integrating sphere, the values were $\mu_a = 0.012 \pm 0.002 \text{ mm}^{-1}$ and $\mu_s' = 1.5 \pm 0.2 \text{ mm}^{-1}$ and using steady-state spatially resolved diffuse reflectance, the values were $\mu_a = 0.017 \pm 0.005 \text{ mm}^{-1}$ and $\mu_s' = 1.3 \pm 0.2 \text{ mm}^{-1}$ at 640 nm. These values are comparable to typical absorption coefficients for tissue reported by others.

The mode of action suggested by DOBI (Dynamic Optical Breast Imaging) Medical for the ComfortScan™ system is that under compression a malignant tumour will highly attenuate light, due to a partial collapse in the tumourous vasculature, resulting in an increased deoxygenation of blood over time. Using a PVA-C breast mimicking phantom, it was shown that by deoxygenating horse blood in a cavity, there was an increase in the attenuation of 640 nm light as compared with the surrounding phantom material; which suggests that the colour representative of malignancies on the ComfortScan™ is caused by deoxygenating blood. Further evidence suggests that the ComfortScan™ system is not recognizing a total collapse of the vasculature and subsequent void of blood from the tumour as the trigger for malignant detection. The mode of action suggested by DOBI Medical is supported by our findings.

5.5 Report: Dynamic Optical Breast Imaging (DOBI): Prospective Study of ComfortScan Accuracy in Diagnosis of Breast Cancer. PRELIMINARY RESULTS, Thesis Dissertation by Rossella Dandolo, Ph.D., University of Rome Tor Vergata, Italy, 2010

Current methods of breast imaging (mammography, ultrasonography and MRI) are burdened with some considerable limitations that affect diagnostic accuracy, since all characterized by a satisfactory sensitivity but variable specificity. In fact, mammography is strongly influenced by the degree of radiopacity of the breast and exposes patients to ionizing radiation; Ultrasonography provides an in-depth clinical and mammographic findings diagnostic doubts, but has a sensitivity and
specificity of operator-dependent imaging methods such as additional MRI (Magnetic Resonance Imaging) can be expensive and inconclusive, for example in the detection of microcalcifications, and finally the cyto-histology, a diagnosis that in nature highly suspect in the case of images, is not without limits, identified in the most cost greater injury and greater susceptibility to sampling errors.

The DOBI (Dynamic Optical Breast Imaging) is an innovative tool for optical imaging, non-invasive, which exploits the properties of light absorption by breast tissue in order to measure in static and dynamic conditions, the ability to reduce the light signal dependent neoplastic processes in the mammary gland. DOBI physiological data related to functional tumor-induced neoangiogenesis. The process of neovascularization associated with tumor growth is characterized by progressive replacement of normal tissue vasculature with numerous arteriovenous shunts that increase the blood volume in the context of the neoplastic process in response to increased metabolic demand. The angiogenic blood vessels in malignant tissues share several characteristics observed. Together, these features create a "profile vascular only" or "angiogenic footprint" that can be identified by DOBI in the diagnosis of breast lesions. The aim of our study is to assess the diagnostic accuracy of DOBI, determining the indications and limitations of the method and, ultimately, identifying the benefits, in order to propose it as a useful tool for integration in the study of breast diseases.

Between June and September 2009, 32 patients, aged between 23 and 75 years, were selected for our study and subjected to DOBI and MRI. Object of our study were patients whose mammographic findings had shown the presence of opacity, parenchymal distortion or microcalcifications suggestive of malignancy. To complete diagnosis, all patients selected were under investigation or cytological microistologica. The average size of tumors detected was 15 mm (range, 0.6-25 mm).
Characteristics of patients at diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>50.5</td>
</tr>
<tr>
<td>Range</td>
<td>25-76</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>55%</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>45%</td>
</tr>
<tr>
<td>Familiarity</td>
<td>23%</td>
</tr>
<tr>
<td>Family history in first degree relatives</td>
<td>16%</td>
</tr>
<tr>
<td>Menarche</td>
<td>12.8 + / - 1.8</td>
</tr>
<tr>
<td>Range</td>
<td>9-18</td>
</tr>
<tr>
<td>Menopause</td>
<td>49.7 + / - 5.7</td>
</tr>
<tr>
<td>Range</td>
<td>40-60</td>
</tr>
<tr>
<td>Previous Pregnancies</td>
<td>77.5%</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>6.7%</td>
</tr>
<tr>
<td>Oral Contraception</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

In 93.75% (n = 30) of cases there was a tumor. The final histology showed in 75% of invasive ductal carcinoma, carcinoma in 12.5% and 3.125% Lubulari infiltrating ductal intraepithelial neoplasia. The image analysis was performed by two specialists in breast pathology. The images obtained by the method were compared with the results of mammography and MRI.

Instrumental methods under study (suspicious of malignancy)

<table>
<thead>
<tr>
<th>Instrumental method</th>
<th>Malignant lesions (N)</th>
<th>Malignant lesions (%)</th>
<th>Benign Lesions (N)</th>
<th>Benign Lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray Mammography</td>
<td>30</td>
<td>93.75%</td>
<td>2</td>
<td>6.25%</td>
</tr>
<tr>
<td>MRI</td>
<td>27</td>
<td>84.37%</td>
<td>5</td>
<td>15.625%</td>
</tr>
<tr>
<td>DOBI</td>
<td>26</td>
<td>81%</td>
<td>6</td>
<td>18.75%</td>
</tr>
</tbody>
</table>

No side effects or adverse reactions were observed during or after the acquisition of optical images. In contrast, all patients have enjoyed the comfort and speed of execution diagnostic survey.

The scans were interpreted on the basis of quantitative values (number of pixels in the area of interest) and qualitative (dynamic curves of the signal). Statistical
analysis of the data showed significant differences in mean values of the number of pixels of benign lesions (1325 + / - 984) than malignant (3590 + / - 2861) \((P = 0.002)\), identifying the cut-off to 2050 pixels. Optical images of intensity greater than the value reported in this study, a sensitivity of 72%, a specificity of 92%, positive predictive value of 93%, negative predictive value of 61% and a diagnostic accuracy of 79%.

**Optical Imaging Results DOBI**  
*(number of pixels suspicion for malignancy)*

<table>
<thead>
<tr>
<th>Optical Imaging Results</th>
<th>Malignant</th>
<th>Benign</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>N ° Pixels&gt; 2050</td>
<td>VP = 26</td>
<td>FP = 2</td>
<td>PPV = 93%</td>
</tr>
<tr>
<td>N ° Pixels&gt; 2050</td>
<td>FN = 3</td>
<td>NV = 1</td>
<td>VPN = 61%</td>
</tr>
<tr>
<td>-</td>
<td>If = 72%</td>
<td>Sp = 92%</td>
<td>Total = 32</td>
</tr>
</tbody>
</table>

The purpose of this study was to assess the diagnostic accuracy of DOBI, determining indications, advantages and limitations. In order to propose it as a useful tool for integration in the study of breast diseases, the results obtained with this method were compared with those of mammography and MRI. In line with those reported in the literature, our study was conducted on a population of patients with suspicious mammographic images (B3-B5). In full agreement with the results observed with MRI, the DOBI was able to differentiate benign from malignant lesions based on their fingerprints angiogenic, showing a sensitivity of 72%, specificity and diagnostic accuracy of 92% and 79% respectively. The DOBI proves a useful investigative tool in the analysis of the angiogenic component typical of malignant proliferative lesions. The performance of the method is suitable for integrating digital mammography examination limits when affected by the degree of opacity in dense breasts. In addition, optical imaging is a useful adjunct in the diagnostic study of young patients symptomatic. Some of the main advantages found in the use of the method, were: the ability to capture real-time dynamic functional images, the cost of the survey contained moderately, and not using ionizing radiation. In our experience, a limit of the method has been found in breast size or the location of the lesion, which sometimes made it difficult to carry
The study of small breasts has been problematic for the conduct of the examination in relation to the structural characteristics of the machine. The same difficulty was found in the analysis of large breasts. In the study, the diagnostic accuracy in the localization of the disease was limited when lesions at the chest wall or nipple-areola complex (NAC). Further application methods in the study of cancer in situ will be useful in the diagnostic definition of this disease with important clinical and therapeutic implications if the method proves able to establish accurately the nature. Subsequent studies will be needed in order to optimize the technique, defining the optical aspects of the breasts are not pathological; evaluating sensitivity and specificity of the method on a larger population of patients, and, ultimately, improving the knowledge about its potential applications.

5.6 Report: Dynamic Optical Breast Imaging (DOBI), associated Ultrasound, allows to avoid unnecessary Biopsies - “Seno, luce rossa preventiva: Il Dynamic optical breast imaging (Dobi), associato all’ecografia, permette di evitare biopsie non necessarie” by di Piercarlo Salari, Oncologia, Tecnologie, October 12, 2009

“Breast, red light prior: Dynamic optical breast imaging (Dobi), associated ultrasound, thus avoiding unnecessary biopsies” describes a study has shown that Dobi has obtained a value of 95% sensitivity and specificity of 78.8%.

The aim of the present study is to determine the diagnostic accuracy of using Dynamic Optical Breast Imaging (DOBI) in addition to Ultrasound systems (US) for prevention, diagnosis and monitoring of breast cancer in young females by means of a non invasive examination methodology. This study included 391 patients with clinical risk to develop a cancer. All patients have been submitted to clinical investigation by means of both US and DOBI. The dynamic optical imaging showed a statistical difference (p<0.005) in patient analyses compared with standard examinations. In this study, the dynamical optical breast imaging had a sensitivity equal to 95% and a specificity equal to 78.8%. Under the same trial criteria, the mammographic sensitivity is 67% as reported by Kerlikowske et al.
(Evaluation of abnormal mammography results and palpable breast abnormalities. Ann Intern Med. 2004 May 4; 140(9):764), and the average Ultrasound sensibility is only 58–64%.

At present, ComfortScan® DOBI in this study proves to be a powerful system to be used for diagnostic purposes in synergy with traditional methodologies such as mammography and ultrasound, especially in case of women with dense breast and high risk from a clinical and anamnensis viewpoint. In particular, in young women the clinical and ultrasound examinations associated with DOBI represent a valid, non invasive, accurate and quick method able to discriminate between truly benign lesions and like-benign lesions such as the marrow and lobular or medullar carcinomas. In case of persisting doubts, MR or core biopsy are mandatory. DOBI can be used for non invasive monitoring, too. This non invasive imaging-based methodology has a very high potential for breast cancer prevention independently of breast size, density, hormonal status.


Optical Imaging: In a prospective cohort trial, Fournier et al. (2008) prospectively determined the diagnostic accuracy of dynamic optical breast imaging (DOBI) compared to pathology in 46 women with BI-RADS 3–5 classification lesions. DOBI was conducted immediately prior to biopsy. Twelve lesions (26%) were diagnosed as benign and 35 (74%) as malignant. Results demonstrated a sensitivity of 74%, a specificity of 92%, a positive predictive value of 93%, a negative predictive value of 55% and a diagnostic accuracy of 79%. The authors noted that further evaluation will be required to optimize the technique, evaluate its sensitivity and specificity in a wider range of patients, and explore its potential role in patient management.
To prospectively determine the diagnostic accuracy of optical absorption imaging in patients with Breast Imaging Reporting and Data System (BI-RADS) 3–5 breast lesions, forty-six patients with BI-RADS classification 3 (11%), 4 (44%) or 5 (44%) lesions, underwent a novel optical imaging examination using red light to illuminate the breast. Pressure was applied on the breast, and time-dependent curves of light absorption were recorded. Curves that consistently increased or decreased over time were classified as suspicious for malignancy. All patients underwent a core or surgical biopsy. In the result, optical mammography showed a statistical difference in numbers of suspect pixels between benign (N = 12) and malignant (N = 35) lesions (respectively 1325 vs. 3170, \( P = 0.002 \)). In this population, optical imaging had a sensitivity of 74%, specificity of 92%, and diagnostic accuracy of 79%. The optical signal did not vary according to any other parameter including breast size or density, age, hormonal status or histological type of lesions. As conclusion, optical imaging is a low-cost, non-invasive technique, yielding physiological information dependent on breast blood volume and oxygenation. It appears to have a good potential for discriminating benign from malignant lesions. Further studies are warranted to define its potential role in breast cancer imaging.

<table>
<thead>
<tr>
<th></th>
<th>Malignant</th>
<th>Benign</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pixels &gt;2050</td>
<td>TP = 26</td>
<td>FP = 1</td>
<td>PPV = 96%</td>
</tr>
<tr>
<td>Number of pixels ≤2050</td>
<td>FN = 9</td>
<td>TN = 11</td>
<td>NPV = 55%</td>
</tr>
<tr>
<td></td>
<td>Se = 74%</td>
<td>Sp = 92%</td>
<td>Total = 47</td>
</tr>
<tr>
<td><strong>Lesions ≤20 mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pixels &gt;2050</td>
<td>TP = 18</td>
<td>FP = 1</td>
<td>PPV = 95%</td>
</tr>
<tr>
<td>Number of pixels ≤2050</td>
<td>FN = 7</td>
<td>TN = 11</td>
<td>NPV = 61%</td>
</tr>
<tr>
<td></td>
<td>Se = 72%</td>
<td>Sp = 92%</td>
<td>Total = 37</td>
</tr>
</tbody>
</table>

The purpose of this prospective study is to determine the diagnostic accuracy of near-infrared breast optical absorption imaging in patients with Breast Imaging Reporting and Data System (BIRADS) 4–5 non-palpable lesions scheduled for biopsy, using pathology after core or excisional biopsy as a reference. The patient's breast was positioned onto a panel of red light-emitting diodes (640 nm). A soft membrane was inflated to exert a uniform pressure on the breast. Transmitted light was detected using a CCD camera. The entire acquisition sequence took 1 minute. Image processing generated dynamic images displayed in colour scale, to reveal time-dependent changes in the transmitted light intensity caused by the pressure change. Dynamic curves were classified in two categories: consistently decreasing intensity suspicious for malignancy, and sinusoidal increasing intensity considered as benign.

Between November 2004 and November 2005, a total of 78 women (age range 41–72 years) participated in this study. All of them presented non-palpable BIRADS 4–5 mammographic and/or ultrasonographic findings and were referred to our institution for further investigation in this study. In six out of 78 cases, scan acquisition was considered invalid, mainly due to ambient light problems. We finally included 72 patients: 40 of them presenting BIRADS 4 lesions and 32 presenting BIRADS 5 lesions. Breast parenchyma density in mammographic images was evaluated according to the BIRADS classification system (density ranging from 0 (totally fatty) to 4 (totally fibroglandular) breast parenchyma). Evaluation of optical scans was based on three parameters:

- The presence of early, focal, blue “blush” in the area of interest, suggesting an underlying lesion with strong deoxyhaemoglobin concentration.
- The pixel intensity of focal blue blush areas calculated by means of dedicated software: a high number, usually more than 90, indicated a high
light absorption. This threshold was in accord with previously published studies in which total haemoglobin concentration and tumour hypoxia had been calculated from oxyhaemoglobin and deoxyhaemoglobin distributions. These distributions were proven to be highly correlated with lesion malignancy\[^{[9,10]}\]. A mean haemoglobin concentration of 95 µmol/l was used as a threshold to separate malignant lesions from benign lesions.

• The type of temporal signature of dynamic curves that was further classified into consistently decreasing negative-spectral and sinusoidal increasing positive-spectral.

A numeric level of suspicion (LOS) score was calculated based on all these elements and taking into consideration the intensity and colour polarity of blush areas as well as the shape of dynamic curves, as follows:

\[
\text{LOS} = (2 \times P) + (2.5 \times S) + (0.5 \times I) - \frac{A}{50}
\]

where \( P \) is the colour polarity (red, orange, blue), \( S \) is the dynamic curve shape, \( I \) is the maximum intensity and \( A \) is the area of interest in cm\(^2\). A score >5 was considered suspicious. Pathologic correlation was obtained for all cases.

At histological analysis, 49 out of 72 lesions were found to correspond to malignancies. This represented a total of 31 BIRADS 5 and 18 BIRADS 4 lesions. Among these 49 carcinomas, 17 corresponded to ductal carcinoma in situ (DCIS) and 32 to infiltrating ductal or lobular carcinoma (IDC or ILC). Twenty-three cases were found to correspond to benign or high-risk lesions at histology, such as fibrocystic changes, sclerosing adenosis, atypical hyperplasia or radial scar. They corresponded to one case of BIRADS 5 and 22 cases of BIRADS 4 classification. Dynamic optical breast imaging was positive in 41 cases. Among them 30 corresponded to malignant lesions and 11 to benign proliferative lesions. Optical findings in benign proliferative lesions were different, as in these cases the hypervascularized areas were not as hypoxic as the malignant hypermetabolic tumours that consume a greater amount of oxygen. Early “blush” in benign cases was displayed as red-coloured areas and the calculated dynamic curves were in the positive scale. The optical signal was positive in the mean of high absorption, but the corresponding area of interest was represented as a red-coloured zone.
Dynamic curves were in the positive scale, in accordance with an underlying hypermetabolic but not strongly hypoxic area. In the remaining 31 cases, optical acquisition was negative; no signal was detected in the areas of interest. However, 19 cases of negative optical imaging were finally diagnosed as malignant at histology. The majority (11 out of 19) corresponded to DCIS of small size (calcifications did not exceed 10 mm) and of low or intermediate grade. An imaging–histology correlation was obtained for seventy-two patients, the remaining six patients were excluded for technical optical scan reasons. We experienced an overall sensitivity of 73% and specificity of 38%, the false negative results being mainly small size (<10 mm) infiltrating malignant lesions and ductal carcinoma in situ (DCIS). False positive results were seen in benign proliferative lesions.

Recently optical mammography has emerged as a potential and revolutionary imaging method targeting the detection and, if possible, the characterization of vascular stroma in normal and abnormal tissues. *In vitro* and *ex vivo*, many experiments have already been performed in order to validate the feasibility and evaluate the sensibility of this method. *In vivo*, optical imaging has almost exclusively been used in cases of breast tissue lesions. The main reason for this is the relatively small volume of breast and the superficial lesion location compared to other deep intra-abdominal organs, where light could possibly never reach the target with a sufficient intensity. It is noteworthy that optical mammography uses almost exclusively infrared light emission (spectrum varying between 640 and 800 nm depending on the various studies already published in the literature). Blood vessels and highly vascularized areas feature a high optical contrast due to increased infrared light absorption, thus providing indispensable spatial resolution information. Various algorithms permit the quantitative analysis of the images obtained (whether static or dynamic), mainly by estimating the haemoglobin concentration and the oxygenation, providing the so-called spectral information. To date, publications have demonstrated the promising role of optical mammography, used either alone or combined with other non-invasive and non-ionizing imaging modalities such as ultrasonography or magnetic resonance imaging. However, there are not many studies dealing with optical, infrared breast imaging in patients presenting non-palpable BIRADS 4–5 lesions. Our results
reflected the performance of optical imaging according to the different stages of tumour angiogenesis: intraductal carcinomas were difficult to depict due to several physiologic factors; a malignant lesion confined to the basement membrane may not substantially influence the physical milieu, whereas a more invasive lesion would. Another factor may be that angiogenesis is less advanced during the earlier stages of ductal carcinoma in situ when the tumour is still confined to the duct. However, we should mention that a suspicious signal in DCIS lesions was easily detected, as the micro-calcification surface was larger, mainly because larger DCIS were more often associated with micro-invasion. Certainly a number of malignancies have been missed during our pilot study, however initial results are rather promising, especially if this technique is used as complementary to the traditional ones, where it could possibly increase the degree of suspicion of non-palpable breast lesions. With breast cancer incidence showing no signs of abatement, every imaging modality used as complement to the traditional ones could be of interest. This is still a work-in-progress. The system software and the evaluation parameters are subject to modifications and improvement. Potential clinical applications include additional information on non-palpable breast lesion diagnosis, as well as monitoring of tumour response to neo-adjuvant chemotherapy. Optical mammography has already been used for this purpose with promising results. Further studies and continuous system improvement are necessary for a better evaluation and clinical application of this innovative method.

The initial results of this study indicate that dynamic optical mammography is an innovative, simple, well-tolerated, non-ionizing imaging method that could be of interest in the detection of hypermetabolic, hypoxic breast areas, suspicious for malignancies in women presenting non-palpable BIRADS 4–5 lesions. However, further technical improvement and larger studies are needed to define any possible clinical applications. Dynamic optical breast imaging is a novel, low-cost, non-invasive technique yielding a new type of information about the physiology of breast lesions. Absorption is due to haemoglobin and its products, therefore reflecting the angiogenic status of breast tumours.
5.9 Report : “Dynamic Optical Breast Imaging: A new technique to visualise breast vessels: Comparison with breast MRI and preliminary results”
Published by Alexandra Athanasiou, Daniel Vanel, Corinne Balleyguier, Laure Fournier, Marie Christine Mathieu, Suzette Delaloge, Clarisse Dromain on Europea Journal of Radiology 54 (2005)

The purpose of our study was to explore and evaluate an innovative imaging approach, which consists on imaging the breast parenchyma by means of photoluminescence detectors (LED) and analysis of dynamic data. Breast magnetic resonance imaging (MRI) was chosen as the reference imaging method, as this is considered to be nowadays the gold standard for breast vascularisation evaluation. Preliminary results reveal a good correlation between breast MRI findings and light images.

In the 25-patient study, patients underwent both breast MRI and optical scans in addition to standard mammography and ultrasonography. Patients' ages ranged between 28 and 78 years of age and all patients scanned did not have recent trauma, breast surgery or biopsy. ComfortScan system images were positive in four of the five cases where MRI was positive. In the only case where the ComfortScan system disagreed with the MRI finding, a three-month follow-up with MRI showed up as negative when scanned a second time, aligning the MRI with the ComfortScan system findings. Investigators noted that they found the potential advantages of ComfortScan system imaging included the ease of patient positioning, quick exam time, and the absence of ionizing (X-ray) radiation. Investigators also concluded that ComfortScan system imaging may also be valuable in cases of claustrophobic patients or in other cases where MRI may be contraindicated.

Dynamic optical breast imaging can be a promising complementary imaging modality in women with inconclusive mammography and/or physical examination. Our study includes a small number of patients, but the preliminary results are encouraging enough. However, further evaluation with a larger number of patients should be carried out. "The promise of the ComfortScan system, as demonstrated in this initial study, warrants additional investigation, but the preliminary results are
encouraging," stated Dr. Daniel Vanel. "The sensitivity of the ComfortScan system technology was extremely strong and the specificity rates also were positive."


The aim of this study is to investigate the behaviour of the dynamic optical breast imaging (DOBI) curve in relation to the microvessel density (MVD) count of surgical specimens from breast biopsies. Forty-six patients underwent DOBI evaluation for mammographic findings suggesting biopsy. The DOBI evaluation was performed the day before or on the day of the scheduled biopsy. The MVD count was performed from the site of the specimen where the pathology was located. The characteristics of the DOBI curve were correlated to the MVD count and to the pathology results of the biopsy. The results show All malignant lesions had a high MVD count and a DOBI curve with a downslope direction, rather straight and without any initiation delays. The benign cases with a high MVD count had a downslope DOBI curve but not always straight and with some initiation delays. The rest of the cases had a low MVD count and most of them an elevated DOBI curve.

Conclusion Our preliminary results indicate a relationship between malignant breast lesions with a characteristic DOBI curve and high MVD count.


The PURPOSE of this study is to Assess the utility of digital breast optical imaging in the evaluation of breast malignancies. The METHOD AND MATERIALS are One hundred two patients with mammographic findings suggesting biopsy underwent digital optical breast imaging performed by DOBI ComfortScan, which utilizes high-intensity light-emitting diodes and gentle pressure in order to identify areas of neoangiogenesis within the breast. The results of this evaluation were compared to the pathology results. The RESULTS from the 102 cases are that 32 had proven malignancies which were categorized by our breast surgeons into three categories
according to their aggressive behavior, taking into consideration the size of the malignancy, lymph node involvement, hormone receptors, and grade. The digital optical breast imaging curve from the region of malignancy in all malignant cases had a downslope configuration indicating neoangiogenesis, and for each of the categories of aggressiveness, the curve had a rather characteristic configuration indicating the level of aggressiveness (high aggressive, aggressive, low aggressive). As CONCLUSIONS, in our study, the initial results indicate there is an association of the morphology of the digital optical breast imaging curve and the aggressiveness of the evaluated breast malignancies.

5.12 Report : The purpose of our study was to report: “New Perspective of Mammary Screening : Application of Non-Invasive DOBI”, THE RESULTS OF DOBI EXAMINATIONS IN MASARYK MEMORIAL CANCER INSTITUTE in Czech Republic, by Irena Komorousova, Bartonkova H., Standara M., Schneiderova M., from 2004 to 2005

The purpose of our study was to evaluate an upcoming breast cancer diagnostic modality based on measurements of the red light absorption in the breast and response on pressure stimulus inducing circulating blood volume changes. Patients and Method were 100 Patients (n=100) for age above 45 with suspicious mammography finding underwent Dynamic Optical Breast Imaging (DOBI) followed by core-cut biopsy in Masaryk Memorial Cancer Institute. Sensitivity and specificity were calculated to compare DOBI with mammography. The Results of both sensitivity and specificity (71% and 64% respectively) indicates that DOBI can be a promising minimum-stress method in malignant breast lesion detection.

By comparing Table 1 and 2 below, the difference between both methods in sensitivity and specificity is small. It is necessary to be aware of the fact that the DOBI method is an entirely new approach, it is not possible to compare these early experiences with the many years of experience with mammography. Based on other preliminary evaluation, sensitivity 87-92% and specificity 75-82% of DOBI ComfortScan would be hopeful in clinics.
Since this pilot project “Perspective of new non-invasive breast imaging DOBI for screening” was designed by Commission of mammary experts under Czech radiological society, the purpose of this project is verification of DOBI affectivity for detection of early stages of breast carcinoma for which other common diagnostic methods are blind. Therefore, the target population for women under 45 are not included into present mammography screening especially because of their breast density, which decreases sensitivity of mammography by 30% (Very low sensitivity of mammography 58%). As summary, Clinical results up to now show higher sensitivity of DOBI in comparison with mammography which is also great potential screening value, DOBI could decrease low age limit for mammary screening, and Usage of ComfortScan in screening program would decrease cumulative radiating dose in women population.

Table 1 shows the evaluation of DOBI – the evaluator assessing the images obtained with DOBI was blinded to the results of previous mammography.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Concordance in DOBI</th>
<th>Discordance in DOBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>59</td>
<td>38 (TN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 (FP)</td>
</tr>
<tr>
<td>Malign</td>
<td>41</td>
<td>29 (TP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (FN)</td>
</tr>
</tbody>
</table>

Sensitivity: TP/TP+FN = 71%
Specificity: TN/TN+FP = 64%
Negative predictive value: TN/TN+FN = 76%

Table 2 gives the results of evaluation of MG images conducted invariably before DOBI.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Concordance with MG</th>
<th>Discordance with MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>59</td>
<td>44 (TN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (FP)</td>
</tr>
<tr>
<td>Malign</td>
<td>41</td>
<td>27 (TP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 (FN)</td>
</tr>
</tbody>
</table>

Sensitivity: TP/TP+FN = 66%
Specificity: TN/TN+FP = 75%
Negative predictive value: TN/TN+FN = 76%

From March 2003 to 2004, as part of a larger prospective international polite study aimed at developing data acquisition methods and dynamic signature interpretation/reading rules, a total 105 patients, aged 23-79, scheduled for open biopsies (palpable and non-palpable lesions) were entered into this study from Division of Senology and Division of Pathology at the Maugeri Foundation in Italy. All patients were scanned with DOBI ComfortScan preoperatively and findings were compared with those of the definite histology report and previous imaging. Approximate half of the patients participated in the training section and only 35 qualified scans from the rest of the half patients are used for this study.

The calculated sensitivity and specificity to discriminate between malignant and benign lesions were 100% and 80% respectively, i.e. 20% False Positive Rate. The results from this dataset indicated that the ComfortScan System could be a valuable tool in breast cancer diagnosis when paired with other imaging methods. In addition, the system provides the physician with information obtained through a dynamic physiological method to distinguish non-invasively between benign and malignant lesions, which may avoid unnecessary interventions. Further studies are needed to support these data.

Since this study aimed at developing the data acquisition methods and dynamic signature interpretation/reading rules as same as all the studies/trials since 2000 after the product was designed and manufactured, the software for data acquisition methods and dynamic signature interpretation/reading rules are the ongoing development/improvement of the DOBI technique. As a result of the studies/trials the DOBI ComfortScan software of ComfortScan and ComfortView have been upgraded to Version 2.0 released on April 27, 2005 and January 15, 2006 respectively.

A total of 189 patients scheduled for biopsy were scanned with the identical protocol between October 1, 2000 and September 30, 2001. The study was performed on women scheduled for core or excisional breast biopsy on the basis of equivocal mammographic and ancillary clinical findings within ACR BI-RADS™ categories 3 or 4. Within the 189 patients, there are 36 patients who were excluded because they do not meet the selection criteria for the development study protocol, and another 36 patient whose scans were not acceptable to be interpreted, such as no case report forms. Thus, total 117 scans were interpreted, and the results are listed below:

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>13</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Interval Follow-Up</td>
<td>2</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>102</strong></td>
<td><strong>117</strong></td>
</tr>
</tbody>
</table>

Sensitivity: 13/15 (87%)
Specificity: 79/102 (77%)
Negative Predictive Value (NPV): 79/81 (98%)

The analysis of test results on the 117 patients with interpreted scans shows that the DFOM detected cancer in 13 of the 15 patients in whom biopsies confirmed malignant lesions (“true positives”). This results in a sensitivity of 87%. The system also correctly identified 79 of 102 benign lesions (“true negatives”). In other words, the specificity of the DFOM was 79/102 (77%). In clinical practice, the adjunctive use of DFOM would have decreased the percentage of biopsies that turn out to be benign from 102/117 (87%) to 23/117 (20%). The negative predictive value, the chance that a negative DFOM result truly indicates a benign lesion, was
79/81(98%) for the cases included thus far. While encouraging, these results suggest the need for further patient studies on specificity.


A total of 245 data sets were acquired with the ComfortScan system from March 2003 to January 2004. These data were collected in 4 clinical sites from 4 countries (Italy, France, Spain, and United States). The data were collected with a new acquisition modality and utilized to develop data acquisition methods and dynamic signature interpretation rules. The interpretation rules were developed and verified using different and somewhat overlapping subsets of the initial 245 data sets. These rules were used for the interpretations described below and were applied to the filtered subset selected as described below. Of these 245 data sets, 15 had no usable information (either test scans or images of the tool used to calibrate the ComfortScan system; i.e., the calibration phantom) and were excluded. From each data set, information regarding pixel saturation, light intensity acquisition range, and ratio of focal area of illumination to breast area were entered in a database. A set of standards, compatible with the most recent acquisition hardware and proprietary software, and with the most recent reading application and interpretation rules, was used to filter the database. The data sets with values falling outside these rules were not included in the analysis. The following standard filter rules applied: Number of saturated pixels >20; light intensity (detected by the CCD camera) <400 counts; illuminated area to breast area ratio ≤25%. After application of the filter, the database returned 111 data sets. Of these data sets, 43 had incomplete patient documentation (biopsy pathology report, mammography report or sonography report) or had the focal illumination not matching the area of interest indicated by the mammography or sonography reports and were excluded from the analysis. A total of 68 data sets were available for interpretation. Of these scans, 49 were from lesions determined to be malignant by biopsy and 19 were from lesions determined to be benign.
Each set was interpreted by a physician (A.S.) blinded to the results of the biopsy. The blinded reader was given information regarding the location of the lesion as indicated in the mammography or sonography reports (quadrant and depth) and the age of the patient. The reader was requested to interpret each scan as “Malignant” or “Benign.” No undecided or dubious scores were allowed. Reader interpretations were compared with the biopsy results reported in the pathology laboratory reports. The reader used two different methods to interpret the ComfortScan sets. The first method was manual, relying on the expertise of the reader to locate suspicious areas and interpret the corresponding dynamic signatures. The second method (computer-aided) relies on a map of suspicious curves generated by the computer and on a standard area curve counter (a circle with a 113 pixels area). The curve counter was positioned manually by the reader, under guidance of the computer-generated map, to include the highest possible number of suspicious curves. A cut-off of 40 curves was selected. This second method is much less dependent on reader interpretation and requires less training and expertise than the manual method.

The results shows that a total of 68 data sets were interpreted by a blinded reader; 49 of these data sets were from malignant lesions and 19 from benign lesions. The average age of the patients was 57 (28 to 79). Following list reports a summary of the lesions as indicated by the pathology reports. *Lesion Type as Indicated by Pathology Report:*

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Number of Cases Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal carcinoma</td>
<td>31</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>12</td>
</tr>
<tr>
<td>Fibrocystic disease</td>
<td>9</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>6</td>
</tr>
<tr>
<td>Non-specified invasive carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>DCIS</td>
<td>2</td>
</tr>
<tr>
<td>Fatty tissue</td>
<td>2</td>
</tr>
<tr>
<td>Cyst</td>
<td>1</td>
</tr>
<tr>
<td>Micro-calcifications</td>
<td>1</td>
</tr>
</tbody>
</table>
The sensitivity obtained by the blinded reader, using the first method (manual) was 98%, and the average specificity was 63%. Only one malignant case (ductal carcinoma, in a 58 year old patient) was interpreted by the blinded reader as a benign case Table 3 below reports the blinded reader results. The sensitivity obtained by the blinded reader, using the second method (computer generated map of suspicious curves and standard size curve counter) was 92%, and the average specificity was 63%. These results suggest that the ComfortScan system can be a useful tool, in combination with other diagnostic methods, in the assessment of suspicious breast lesions.


The purpose of this study for the Dynamic Optical Breast Imaging and Ultrasound were evaluated in diagnosing the early breast cancer. There were 62 patients enrolled in this study, who had biopsies during the period of May, 2007 to June, 2008. All of them are female, the average age is 47 According to the examinations, they can be divided into 3 groups: DOBI Examination 52 cases; Ultrasound Examination of 35 cases; Both DOBI and Ultrasound combined Examination of 25 cases, excluding patients in pregnant/lactation period and the ones that accept galactophore operation within half a year. Sensitivity(SE), specificity(SP), the rate of misdiagnosis(α) and the rate of missed diagnosis(β) of DOBI technology, Ultrasound and their combination’s diagnosis to breast carcinoma are calculated and compared respectively.

For the DOBI ComfortScan 52 tests alone, the sensitivity (SE) is 14/19 = 73.68%; specificity (SP) is 25/33 = 75.76%; false positive rate (FPR) is 8/33 = 24.24%; false negative rate (FNR) is 5/19 = 26.32%. For the Ultrasound 35 tests alone, the sensitivity (SE) is 16/19 = 84.21%; specificity (SP) is 6/16 = 37.50%; false positive rate (FPR) is 10/16 = 62.50%; false negative rate (FNR) is 3/19 = 15.79%. During the 25 combination test by DOBI ComfortScan first and then Ultrasound second, the patients were taken biopsy if both of them indicated malignant lesions. The
sensitivity (SE) is 14/16 = 87.50%; specificity (SP) is 5/9 = 55.56%; false positive rate (FPR) is 4/9 = 44.44%; false negative rate (FNR) is 2/16 = 12.50%.

As a conclusion, the Dynamic Optical Breast Imaging is a new technology. It is non-invasive and non-radiation. It is an appropriate approach for the early diagnosing breast cancer by combining the Dynamic Optical Breast Imaging and Ultrasound. While it needs a large number of case studies to distinguish malignant and benign tumors, including in different stages of cancer development, with different physical signs in patients, quantify the metabolic rate of malignant and benign tumors by statistics and so on.


A new way in breast cancer detection, Dynamic Optical Breast Imaging (DOBI) was studied. Fifty two (52) patients receiving breast biopsy and DOBI were enrolled in this study. 94.8% of “blue area” in non-breast cancer lesions was found as wandering or diffusive pattern, while 68.42% breast cancer showed focal pattern. 86.46% of the curve signature of “blue area” in non-breast cancer lesions was wavy or flat, while 57.37% of the breast cancer showed a steep decline. In 64.58% non-breast cancer, the curve of “blue area” was similar to that of non-blue area. The absolute value of amplitude (-5.77±12.14) of “blue area” in cancer was higher than in non-cancer (-3.34±0.87). The differences were all statistically significant (P<0.05). As conclusion, the spatial and temporal characteristics of DOBI were of diagnostic and differential value for breast cancer. The absolute value of amplitude, over |-5|, also helped the diagnosis of breast cancer.
5.18 Report: “The Diagnostic Value of Small Lesions within Breast by Ultrasound combined with DOBI” published by Mei Xu, Junlai Li, MEDICAL JOURNAL OF CHINESE PEOPLE’S LIBERATION ARMY, Vol 34, No. 8 on August 1, 2009

Female breast screening use of ultrasound technology, ultrasound detection rate for microcalcifications lower limits of small breast lesions benign and malignant correct judgment. Dynamic optical breast imaging (DOBI) system is an analysis of the lesion of new blood vessels to generate blood and oxygen content of new technologies for the diagnosis of breast disease. This article aims to observe the clinical diagnostic value of ultrasound combined with DOBI of small breast lesions.

From August of 2007 to June of 2008, there are 53 women at age 43.7, who were subjected the breast examination by using Ultrasound and DOBI at 301 Hospital. The sensitivity, specificity and accuracy of Ultrasound is about 81%, 59% and 70% respectively. But by combining with DOBI, the sensitivity, specificity and accuracy of Ultrasound increase to 95%, 81% and 87%. Overall, ultrasound combined with DOBI can improve the sensitivity, specificity, and accuracy of diagnosis of breast lesions, the better to avoid the misdiagnosis of small breast lesions. However, due to the DOBI technical application time is short, its accuracy and experience of the operator have a certain relationship, combined with a relatively small number of cases, the clinical value needs further study.

5.19 Report: “The Value Analysis of ComfortScan System in Differentiating Benign Breast Lesions from Malignant” published by Mei Xu, Junlai Li, Yongfeng Zhang, Xuejuan Shi, Chunmian Li, Jie Tiang, and “The Application of Dynamic Optical Breast Imaging in Differentiating Benign Breast Lesions from Malignant” Thesis submitted by Mei Xu at Chinese PLA General Hospital & Postgraduate Medical School on June 1, 2009

The study is to analyze the value of Dynamic Optical Breast Imaging in Differentiating Benign Breast Lesions from Malignant. A total of 74 patients at averaged 44 years’ old were examined with the Duplex Ultrasonography and ComfortScan System. The patients were grouped based on the lesion sizes into three groups: <1 cm, 1~2 cm and >2 cm through the Ultrasound measures.
After comparing the pathological results, DOBI ComfortScan has higher sensitivity (85.7%), specificity (80.0%) and accuracy (81.8) than Ultrasound’s sensitivity (71.4%), specificity (40.0%) and accuracy (50.0%) in <1 cm group. In 1~2 cm group, the ComfortScan and Ultrasound are similar: (78.6%, 64.7%, 71.0%) and (85.7%, 76.5%, 80.6%) respectively. But in >2 cm group, the ComfortScan is much lower than Ultrasound: (25.0%, 44.4%, 33.3%) and (83.3%, 77.8%, 81.0%).

As a conclusion, DOBI ComfortScan has much higher sensitivity, specificity and accuracy for smaller breast lesion sizes, and could be very useful in diagnosing breast cancer at early stage. Because the cases in this study is relatively small, further study with more data is recommended.

5.20 Report: “ComfortScan System and Ultrasound Imaging: The Value of Combined Application to Differentiate Benign Breast Lesions from Malignant” Reported by Yongfeng Zhang, Junlai Li, Xuejuan Shi, Mei Xu, China, 2008

The purpose of this study is to explore the value of ComfortScan System in differentiating benign breast lesions from malignant ones. A total of 65 breast tumors in 64 patients were examined with the Duplex Ultrasonography and ComfortScan System, and the sonograms and ComfortScan-grams were analyzed respectively. The biopsy confirms 30 malignances.

The results were compared with histopathology. The results show there was no significant difference between the two groups for differentiating benign from malignant breast lesions, which means the similar diagnosing value. By combination of these two techniques, the sensitivity was significantly improved to 93.3% (P≤0.01), which is much higher than that of the Duplex Ultrasonography.
Ultrasound doesn’t find clear lesions
ComfortScan shows malignant clearly
Pathology indicates Ductal Cancer

Ultrasound shows malignancy
ComfortScan shows benign
Pathology indicates Fiber Adenosis

The results of this study demonstrated that the Sensitivity, Specificity and Accuracy are followings:

<table>
<thead>
<tr>
<th></th>
<th>DOBI ComfortScan</th>
<th>Ultrasound</th>
<th>DOBI + Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83.3%</td>
<td>80.0%</td>
<td>93.3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80.0%</td>
<td>85.7%</td>
<td>82.9%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>81.5%</td>
<td>83.1%</td>
<td>87.7%</td>
</tr>
</tbody>
</table>

As the conclusion, ComfortScan System can play an important role in differentiating lesions which are difficult for the ultrasound imaging, especially for diagnosing malignant ones. The combined application of Comfort Scan System and the Duplex Ultrasonography may increase the diagnostic accuracy in differentiating benign from malignant breast lesions.


To understand the diagnosis effectiveness of breast cancer application of DOBI ComfortScan in China, under the guidance of the DOBI Medical in September 2010, the distributor has conducted a clinical survey from all installation sites: more than 1,200 cases from DOBI ComfortScan scans were collected. Among the 1,200 patients, 220 patients have had pathological results, 81 patients have had ultrasound images, and 10 patients have had mammography tests because of lack of the mammographic machine. There are 79 cases with non-palpable lesions.
In order to evaluate the effectiveness of the ComfortScan clinical use, only the 220 cases, which were collected from hospitals in Guangdong Province (137 cases) and Beijing (76 and 7 cases), with pathological results are used. According to the requirements from SFDA (State Food and Drug Administration), the statistical analysis was conducted by Peking Union Medical University, which is appointed by SFDA. The overall statistic results are 89.6% sensitivity and 68.4% specificity. The reading results and detailed categories with related results are listed below:

<table>
<thead>
<tr>
<th>Category</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>89.62%</td>
<td>68.42%</td>
<td>78.63%</td>
</tr>
<tr>
<td>Lesion Area &lt; 2cm²</td>
<td>93.75%</td>
<td>86.49%</td>
<td>88.67%</td>
</tr>
<tr>
<td>Lesion Area &gt;= 2cm²</td>
<td>94.12%</td>
<td>66.67%</td>
<td>84.61%</td>
</tr>
<tr>
<td>Lesion Size &lt; 1cm</td>
<td>91.67%</td>
<td>88.24%</td>
<td>89.13%</td>
</tr>
<tr>
<td>Lesion Size &gt;= 1cm</td>
<td>95.24%</td>
<td>66.67%</td>
<td>84.84%</td>
</tr>
<tr>
<td>Non-Palpable</td>
<td>87.67%</td>
<td>58.82%</td>
<td>73.75%</td>
</tr>
</tbody>
</table>

As a summary of the effectiveness of DOBI ComfortScan, the results from past three years in China have demonstrated the ComfortScan device is an effective tool as adjunct to existing breast imaging
modalities, mainly Ultrasound, in detecting breast cancer, especially at early stage.


This study aimed to evaluate the performance (behavior) of DOBI ComfortScan device through the statistical analysis of 53 cases with the sizes smaller than 2 centimeters. Those cases were collected from Beijing 301 PLA General Hospital around 2009, had both ComfortScan and Ultrasound images, and had pathological results.

The study was divided into three approaches: ComfortScan only, Ultrasound only, and the combination of ComfortScan and Ultrasound. Each of the study was analyzed and a ROC (receiver operating characteristic) Curve was generated, as shown in the above.

By comparing the ROC Curves of DOBI ComfortScan and Ultrasound alone, they are very compatible. As a conclusion, the clinical effectiveness of DOBI ComfortScan could be similar to the Ultrasound in diagnosing breast cancers.
In order to clearly show the difference between individual use and the combination of the two breast imaging techniques, a portion of the ROC Curve, which is generally used for both sensitivity and specificity greater than 60%, is shown below:

![ROC Curve](image)

In the case, which needs the sensitivity greater than 90%, the specificity of the combination of ComfortScan and Ultrasound is 15.6% and 34.4% higher than ComfortScan and Ultrasound individually. If a 80% or higher specificity is needed, the sensitivity of the combination of ComfortScan and Ultrasound can reach 95% while ComfortScan sensitivity is about 66.7% and Ultrasound sensitivity is only 38.1%. As another conclusion, the clinical effectiveness of DOBI ComfortScan as adjunct to Ultrasound in detecting breast cancers is significant.


This 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, as well as MEDDEV2.11/1 (2005/50/CEE) to
demonstrate the clinical EFFECTIVENESS of DOBI ComfortScan device. The enrolled patients are 18 years of age or older and have been considered the necessity of a breast biopsy after receiving mammography examination 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.

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 (Indeterminate), thus the statistic calculation could not performed even although the readers were requested to conduct either Malignant or Benign 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.
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.

<table>
<thead>
<tr>
<th>Mammogram Reading</th>
<th>ComfortScan Reading</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
<td><strong>62</strong></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>ComfortScan Reading</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>26 (TP)</td>
<td>38</td>
</tr>
<tr>
<td>B</td>
<td>5 (FN)</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>62</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>SE</td>
<td>TP / TP + FN</td>
<td>83.9%</td>
</tr>
<tr>
<td>Specificity</td>
<td>SP</td>
<td>TN / TN + FP</td>
<td>61.3%</td>
</tr>
<tr>
<td>Negative Predicative Value</td>
<td>NPV</td>
<td>TN / TN + FN</td>
<td>79.2%</td>
</tr>
<tr>
<td>Youden's Index [-1,1]</td>
<td>YI</td>
<td>SE + SP - 1</td>
<td>0.45</td>
</tr>
</tbody>
</table>

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.
In general, the guideline 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 should be considered as “Malignant” and then could be followed by further imaging or clinical study, or biopsy test. Under this clinical criteria, 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.

![Graph showing Youden's Index comparison between Mammogram and ComfortScan](image)

**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.

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 volume 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 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 infrared 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 both spatial and temporal information of tumor angiogenesis, 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. Following 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\textsuperscript{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 limiting its usefulness in high risk young
women. It is well documented in the study carried out by Kuhl CK et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 acquisition\), 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.\textsuperscript{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.

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.

As the conclusion, based upon its performance in clinical studies worldwide, the DOBI ComfortScan is a novel imaging technology with clinical effectiveness 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 characterize 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 specificity of 87 percent, 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 potentially become a useful breast cancer screening tool if a full FOV (field 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.
6. CLINICAL ACCEPTANCE

In the past 6 years over 50 diagnostic centers worldwide have used the ComfortScan, including nearly 30 US sites participating in the FDA PMA clinical trials, and over 30 sites in Italy and China have bought the devices, resulting in the use of the device on thousands patients. The cumulative device experiences to date, as well as the above clinical effectiveness, have demonstrated that this device, DOBI ComfortScan, 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. DOBI 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.

As a result, the clinical acceptance of DOBI ComfortScan could be shown in following examples.
6.1 The Italian League for the Fight against Cancer (LILT) has recommended to DOBI ComfortScan for younger women in detecting breast cancer at early stage on August 2, 2012
Le principali caratteristiche del sistema DOBI-Comfortscan ed i vantaggi legati alla sua introduzione nel percorso diagnostico precoce sono rappresentate da:

- Non emette radiazioni ionizzanti e quindi, oltre a non essere un esame invasivo e potenzialmente dannoso, non necessita di particolari accorgimenti per l'installazione e non ha costi di manutenzione rilevanti durante l'utilizzo;
- Non è un esame doloroso in quanto non viene compressa la mammella;
- È un esame veloce e ripetibile anche spesso perché non è invasivo;
- L'acquisizione dell'esame può essere effettuata da un infermiere specializzato e non necessita della presenza di un tecnico di radiologia;
- L'esame può essere riferito da un medico esperto in senologia, ma non necessariamente un radiologo;
- È dotato anche di un sistema Pacc per la riferitazione da remoto qualora si rendesse necessario e l'esame non è operatore dipendente;
- È possibile partecipare a corsi di formazione specifici condotti da medici esperti.

All'uopo è già attivo un numero verde al quale chiamare per informazioni tecniche e scientifiche oltre che commerciali inerenti i vantaggi riservati alle Sezioni Provinciali LILT.
Il numero è 800 07 8527 ed è stato istituito dalla Socrate Medical s.r.l. che detiene in esclusiva il brevetto di sviluppo per tutta Europa e che presto inizierà anche la produzione in Italia diventata il centro di ricerca, sviluppo e formazione per tutta Europa per l'ottica mammaria.

Con i più cordiali saluti.

IL DIRETTORE GENERALE f.f.
Rag. Davide Rubinaca

IL PRESIDENTE
Prof. Francesco Schittulli
6.2 The Italian League for the Fight against Cancer (LILT) – Underforty Women

Breast Care, 2010

Circolare n.14
Prot. n. 201000001999

Roma, 11 giugno 2010

Ai Presidenti e Commissari
Sezioni Provinciali LILT
Loro Sedili

Oggetto: Offerta Socrate Medical

Si rende noto che la Socrate Medical, azienda milanese specializzata in prodotti e servizi nel settore elettromedicale e della diagnosi per immagini, ha offerto alla LILT e, di conseguenza a tutte le Sezioni Provinciali, la possibilità di dotarsi di un sistema DOBI (Dynamic Optical Breast Imaging) – ComfortScan alle condizioni di favore indicate nel prospetto allegato.

Secondo quanto emerga dalla documentazione tecnica prodotta, il sistema DOBI costituisce una metodica non radente, non invasiva e non dolorosa, che utilizza la tecnologia ottica per la diagnosi differenziale dei tumori al seno e si basa sull'individuazione e quantificazione della neoplasia, che viene direttamente controllata con la formazione e lo sviluppo della maggior parte delle patologie tumorali.

Si utilizza nel contesto, in esso, basato sulla metodica DOBI, potrebbero, quindi, essere indirizzati ai:
- Diagnosi preventiva donne 20-40 (in particolare con fattori di rischio, in abbinamento all'ecografia);
- Monitoraggio recidive;
- Monitoraggio preOPERATORIO;
- Monitoraggio post terapie ormonali;
- Monitoraggio per cure palliative.

Socrate Medical ci ha altresì informato che è in fase di definizione un protocollo diagnostico multicentrico, che li eserciti al DOBI Group, per favorire la raccolta di casistica e la diffusione delle informazioni tramite la creazione di un atlante epidemiologico. Nella sessione scientifica del Congresso Underforty, organizzato da Istituto Tumori Pascale di Napoli e ACCC, comunque, saranno illustrati i risultati di progetti avanzati di applicazione con DOBI. Tutti i Presidenti Provinciali interessati a partecipare all'Underforty possono farne richiesta direttamente alla segreteria della Socrate Medica: Dr.ssa

Vi informiamo, comunque, che il Consiglio Direttivo Nazionale, nella seduta del 26.04.2010, ha deliberato di sottoporre al costituendo Comitato Scientifico Nazionale la documentazione tecnica relativa al sistema DOBI, allo scopo di acquisire un parere che confermi le asunzioni prospettate.

Con i più cordiali saluti.

IL DIRETTORE GENERALE
Avv. Bruno Pisaturo

IL PRESIDENTE
Prof. Francesco Schittulli
Mammografie, esami più sicuri

Ecco il sistema DOBI, meno invasivo e più preciso. Già a disposizione alla Lilt.

- Evento speciale a Bari. La mammografia può andare in pensione. Niente più raggi sulle mammelle, eliminati i relativi rischi.
- A Bari, prima in Italia, dopo la fase sperimentale eseguita a Milano, giunge la metodica DOBI, un sistema non invasivo che utilizza, per effettuare l'esame, solo un fascio di luce monocromatica rossa.
- Questo sistema totalmente digitale e facilmente integrabile con altri approcci diagnostici – ha detto il professor Francesco Schiattelli, chirurgo oncologo e presidente nazionale della Lega Italiana per la lotta ai tumori (Lilt) – corre al problema veloce e fornisce nuovi dati fisiologici funzionali che l'esame clinico ed altri precedenti cui non sono in grado di offrire al medico. DOBI si basa sulle proprietà del processo di neoformazione di casi sinistri all'interno della massa tumorigene.
- I dati dell'ampia sperimentazione dimostrano che l'associazione della metodica DOBI all'ecografia rappresentano un meccanismo diagnostico di tipo preventivo, di primo livello, sottolineato in donne con mammelle dense nelle quali un'esame come la mammografia risulta essere scarsamente efficace.
- La diagnosi preclinica, grazie all'innovazione introdotta con la metodica DOBI, viene facilitata e resta più evidente, in particolare, per minime distorsioni parenchimali, sede primitiva di cancro.
- La metodica, grazie anche alla mancanza di rischi per le patienti, può essere ripetuta nel tempo per pazienti che presentano, a carico delle mammelle, pluripluri microcalciocasi, disturbi assai mammoogranifici, echografficamente negativi.
- L'apparecchio «ComfortScan» – ha detto Schiattelli – è già a disposizione della sede della Lega Tumori di Bari e, entro qualche giorno, sarà impiegato presso queste ambulanze a disposizione della popolazione.
6.3 2nd Meeting DOBI Group in Italy, 2011
6.4 1st Meeting DOBI Group in Italy, 2010
6.5 ANT: from now on mammograms for women under 40: 22/10/2012 - As of today young women may be subjected to investigation mammography. With the resort Cancer Prevention Foundation ANT, and DOBI mammography optical non-invasive and without radiation

6.5 ANT: from now on mammograms for women under 40: 22/10/2012 - Da oggi mammografie anche per donne sotto i 40

Il DOBI, che ha una nuova via alla prevenzione del cancro al seno, permette di effettuare la diagnosi precoce del carcinoma mammario nelle giovani donne nelle quali non è possibile effettuare la tradizionale indagine mammografica, adatta alle donne a partire dai 40 anni in su. Questo è il tema dell’appuntamento del mese di ottobre del servizio del Centro Raccogli Dati della Fondazione, dedicato al DOBI.

Una recente indagine condotta da Avon e Il fratello mostra che per il 2012 i cancri mammari rappresentano la prima causa di morte per tumore nelle donne, con circa 13.000 decessi stimati al primo posto anche in diverse età della vita, rappresentando il 20% delle cause di morte oncologica prima dei 60 anni. Il 21% tra i 50 e 69 anni e il 14% dopo i 70 anni. Di contro, il 2012 mammografia identificava in Italia circa 46.000 casi di carcinomi della mammella. Non considerando i cancri in stadio I, il tumore mammario è la neoplasia più diagnosticata tra le donne sia nella fase di 6-49 anni (41%), sia nella fascia d'età 50-70 anni (39%), sia in età più avanzata (70 anni (21%). (Fonte: I numeri del cancro in Italia 2012, settembre 2012)

Di fronte a questi dati emergono la necessità per le giovani donne di ricevere un'offerta specifica. La diagnosi precoce rappresenta una potente arma di prevenzione del cancro al seno, che ogni donna dovrebbe affrontare con appetenza, specialmente se controllata da medici specializzati. Le giovani pazienti non rimandano il mammografia mammografica, destinate alle donne a partire dai 40 anni, per problemi personali. La mammografia tradizionale sancita comunque poteva farli in base alla data, soprattutto per la struttura demografica della giovane donna.

Il campo della prevenzione, grazie ai passi avanti nella ricerca, sono stati introdotti strumenti diagnostici per donne di tutte le età. L’Unione Italiana Prevenzione Oncologica (INT) - è stata promossa dalla più innovativa tecnologia disponibile per la prevenzione del cancro al seno. Con la salute 2.0.0, in cui attivano l’Ambulanza Mobile - Bus della Prevenzione. L’Ambulanza Oncologica INT è una sistemazione avanzata per realizzare esattamente diversi progetti di prevenzione: medicina, neo-storica, ginecologia e mammografia.

Mentre la mammografia e l'esame mammografia sono strumenti diagnostici che riducono il tasso di morbidità e di mortalità dei tumori mammari, il DOBI è un esame funzionale, costituisce informazioni circa i cancro mammali che si manifestano nelle giovani donne per la presenza di una specifica lesione. L'altissima sensibilità e la buona specificità rendono la mammografia ottimale utilizzata per la diagnosi precoce delle giovani donne, sia per la diagnosi differentiale, in caso di dubbio.

Il mammografico ottico DOBI ComfortScan rappresenta un sistema innovativo, senza esposizione di radiazioni ionizzanti, progettato per migliorare la capacità diagnostica. L'esame funzionale riveste il testo funzionale che non possono essere ottenuti dall'esame clauso, dalla mammografia e dell'esami logistico. Il funzionamento funzionale su cui si basa l'indicazione della formazione di nuovi canali angiogenesi è peculiare della costruzione tecnica.

La mammografia ottica utilizza la luce visibile dello spettro visibile (lenti mammografiche rosse) per illuminare i tessuti mammali ed identificare le lesioni tumorali in fase precocce, essendo in grado di rilevare i cambiamenti di vascolarizzazione (angiogenesi) che circondano la neoplasia. Durante l'esame mammografico, la pazienta è collocata di fronte al ComfortScan II e l'area viene posizionata su una panchina costruita da 127 LED. La mammografia è poi raffrontata in una specifica membrana di immagine che, dopo essere stata grafita, è messa a leggere e presa in considerazione. L'intero strumento controlla la luce che viene tramandata attraverso la ghisa, registra le alterazioni della vascolarizzazione, che permette di differenziare i tessuti normale e la lesioni benigna dalle lesioni maligne. L'intera procedura dura circa 10 minuti.
6.6 Breast cancer diagnosis today is born with "DOBI"

Carcinoma mammario, da oggi nasce diagnosi con "Dobi" - 2

(AIS) Bologna, 22 ott 2012 - (Segue) "Nel campo della prevenzione, grazie ai passi avanti nella ricerca, sono stati introdotti strumenti diagnostici per donne di tutte le età. L'Unità di Prevenzione Oncologica Ant - presso la sede della Fondazione a Bologna - è dotata della più moderna tecnologia disponibile per la prevenzione del tumore al seno. Con cinque ambulatori, cui si affianca l'Ambulatorio Mobile - Bus della Prevenzione, l'Unità di Prevenzione Oncologica Ant è fornita di una strumentazione estremamente all'avanguardia per realizzare quattro diversi progetti di prevenzione: melanoma, neoplasie tiroidee, ginecologiche e mammarie. Mentre la mammografia e l'ecografia mammaria - spiega la nota della Fondazione Ant - sono indagini diagnostiche che studiano i cambiamenti di forma e di densità dei tessuti (esami morfologici), il Dobi è un esame funzionale, ossia fornisce informazioni circa i cambiamenti che si verificano nella ghiandola mammaria per la presenza di una specifica lesione. L'alta sensibilità e la buona specificità rendono la mammografia ottica utile sia per la diagnosi precoce nelle giovani donne, sia per la diagnosi differenziale, in casi dubbi.

Il mammografo ottico Dobi ComfortScan - prosegue la nota - rappresenta un sistema non invasivo, senza emissione di radiazioni ionizzanti, progettato per migliorare la capacità diagnostica. L'esame fornisce nuovi dati fisiologici funzionali che non possono essere dedotti dall'esame clinico, dalla mammografia e dall'ecografia. Il fondamento scientifico su cui si basa è l'individuazione della formazione di nuovi vasi sanguigni. Questo fenomeno noto come neoangiogenesi è peculiare della crescita neoplastica.

La mammografia ottica - conclude la nota - utilizza la luce nello spettro visibile (luce monocromatica rossa) per illuminare i tessuti mammari ed identificare le lesioni tumorali in fase precoce, essendo in grado di rilevare i cambiamenti di vascolarizzazione (neoangiogenesi) che circondano la neoplasia. Durante l'esame diagnostico, la paziente è colloca da di fronte al ComfortScan e il seno viene posizionato su un pannello costituito da 127 Led. La mammella è poi racchiusa in una sottile membrana di silicone che, dopo essere stata gonfiata, esercita una leggera pressione costante. Lo strumento controlla la luce che viene trasmessa attraverso la ghiandola, registra le alterazioni della vascolarizzazione, che permettono di differenziare i tessuti normali e le lesioni benignhe dalle lesioni maligne. L'intera procedura dura circa 10 minuti".

Carcinoma mammario, da oggi nasce diagnosi con "Dobi" - 2 - Ais - Agenzia Informazion...
6.7 Breast cancer remains the second leading cause of death among women

Prevenzione del Tumore al seno.

Breast cancer remains the second leading cause of death among women. The situation is grave, and it is essential to address it. The early detection of breast cancer is crucial for improving survival rates. Therefore, mammography and other diagnostic procedures are essential. Mammography is a non-invasive technique that allows for the early detection of breast cancer. It is a screening tool that can detect breast cancer in its early stages, which is often curable.

Precautionary measures and early detection can significantly reduce the risk of breast cancer. Women should have regular mammograms starting at the age of 40. However, factors such as family history, race, and personal health history can influence the age at which mammograms should be started. Women with a strong family history of breast cancer should start screening earlier.

In conclusion, breast cancer is a significant health issue that requires early detection and prevention. Women should be encouraged to undergo regular mammograms and other preventive measures to reduce their risk.
UNIT 'ANT CANCER PREVENTION PROJECTS FOR POLICE AND UNICREDIT

The UNIT 'ANT Cancer Prevention Projects for Police and Unicredit is a program aimed at preventing cancer among police officers and employees of Unicredit. The project, known as "Ant Cervical Cancer Screening Project for Police and Unicredit," is designed to identify and treat precancerous conditions early, thereby reducing the risk of cancer.

The project involves collaboration between the police department and Unicredit to provide regular cervical cancer screening to female employees. The program includes the following key components:

1. **Screening Program:** Regular screening for cervical cancer is conducted using the latest diagnostic technologies. This helps in early detection and timely intervention.

2. **Health Education:** Employees are educated about the importance of regular screening and the early signs of cervical cancer. This awareness raises the detection rate and improves outcomes.

3. **Support and Counseling:** Access to psychological and social support is provided to employees who undergo screening. This reduces anxiety and improves overall health outcomes.

4. **Policies and Guidelines:** The organization implements policies that encourage regular screening and support employees who require medical attention.

5. **Data Management:** A comprehensive database is maintained to track screening results and ensure that all employees receive timely follow-up.

The UNIT 'ANT Cancer Prevention Projects for Police and Unicredit is an example of how organizations can collaborate to improve the health and wellbeing of their employees. By focusing on early detection and timely intervention, the project demonstrates the potential for reducing cancer incidence and improving health outcomes among the target population.

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6.9 THE INNOVATIVE METHODS OF STUDY MEDICAL MANARA 31

ESAME OTTICO DEL SENO

Scritto da giovanni lucio rocca
Lunedì 17 Settembre 2012 18:21

LE METODICHE INNOVATIVE DELLO STUDIO MEDICO MANARA 31

Il sistema "ComfortScan™" è un'immagine ottica e dinamica della mammella. Non è invasivo, non è costituito da radiazioni pericolose, ed è un apparecchio medico opportunamente studiato per assistere il medico nell'individualizzazione del tumore della mammella.

Il sistema DOBI ComfortScan™ è un sistema digitale d'immagine avanzato che utilizza diodi emittenti luce ad altissima intensità e che produce una delicata pressione nelle zone di anormalità vascolare. La tecnologia del sistema DOBI è basata sulla capacità di individuare l'attività neoangiogenetica del tumore e i cambiamenti di natura vascolare. Tale processo è caratteristico dell'ambiente peritumorale, particolarmente nella mammella ed è rappresentato da una notevole quantità di capillari neoformati. Questa rete di piccoli canali che alimentano il tumore apportano ossigeno e nutrienti, rappresentando dei caratteristici "markers" in grado di rivelare l'attività replicativa ed espansiva della massa neoplastica in osservazione.

L'Angiogenesi è un processo fisiologico che avviene nell'organismo.

Nel caso di espansione neoplastica la crescita dei nuovi vasi sanguigni avviene in modo particolare attorno e in supporto alla massa. Quando viene scoperto il nudo mammario, sono già trascorsi alcuni anni dall'inizio del processo di trasformazione che lo renderà palpabile all'esame obiettivo.

I diodi costituenti il sistema ComfortScan sono ad alta emissione e ad alta intensità e trasmettono sulla lunghezza d'onda della luce rossa (650nm) attraversando la mammella. L'immagine viene registrata attraverso una telecamera digitale per circa 45 secondi.

Se la luce incontra una regione della mammella con attività neoangiogenetica (potenzialmente cancerogena) viene assorbita differenemente rispetto a tutte le altre parti della mammella a causa della differente concentrazione di emoglobina deossigenata.

Il risultato è un'immagine che rileva delle regioni marcatamente diverse rispetto alle porzioni normali della mammella. Il risultato finale è che il sistema ComfortScan focalizza l'attenzione su una serie di immagini dinamiche funzionali che sono in relazione con i cambiamenti dei tessuti mammari in tempo reale. Ciò lo differenzia dalle singole immagini statiche caratteristiche ad esempio delle mammografie e delle ecografie.

Le immagini innovative del sistema ComfortScan possono apportare al medico nuove informazioni fisiologiche, che associate all'attività neoangiogenetica aiutano a rilevare la dinamicà, la tendenza e lo sviluppo dei tumori mammari.

L'utilizzo della metodica ComfortScan è inizialmente consigliato in supporto alla mammografia, all'ecografia e all'esame obiettivo. Il sistema ComfortScan migliora, in modo sensibile, le attuali immagini diagnostiche convenzionali soprattutto in termini di precisione, velocità, comfort, sicurezza e facilità d'uso.
6.10 INSTITUTE mammograms ANT EVEN UNDER 40 YEARS

Da oggi anche le giovani donne potranno essere sottoposte a indagine mammografica. Questo è possibile al Centro di Prevenzione Oncologica della Fondazione ANT, con sede a Bologna, grazie al DOBI (Dynamical Optical Breast Imaging). Il mammografo ottico non invasivo e senza emissione di radiazioni. Il DOBI apre una nuova via alla prevenzione del cancro al seno, poiché permette di effettuare la diagnosi precoce del carcinoma mammario nelle giovani donne nelle quali non è possibile effettuare la tradizionale indagine mammografica, adatta alle donne a partire dai 40 anni in su.

Una recente indagine condotta da Aion e Airtum conferma che per il 2012 il carcinoma mammario rappresenterà la prima causa di morte per tumore nelle donne, con circa 13.000 decessi stimati, al primo posto anche in diverse età della vita, rappresentando il 28% delle cause di morte oncologica prima dei 50 anni, il 21% tra i 50 e i 69 anni e il 14% dopo i 70 anni. Si stima che nel 2012 verranno diagnosticati in Italia circa 45.000 nuovi casi di carcinomi della mammella. Non considerando i carcinomi cutanei, il carcinoma mammario è la neoplasia più diagnostizzata tra le donne sia nella fascia d’età 40-49 anni (41%), sia nella classe d’età 50-69 anni (35%), sia in quella più anziana 270 anni (21%) (Fonte: ‘I numeri del cancro in Italia 2012’, settembre 2012).

Di fronte a questi dati emerge come l’incidenza del tumore mammario nelle giovani donne sia davvero un fenomeno allarmante. La diagnosi precoce rappresenta un potente arma di prevenzione del cancro al seno, che oggi donna dovrebbe effettuare sottoponendosi periodicamente a controlli e indagini strumentali specifiche. Le giovani pazienti non rientrano nel screening mammografico, destinato alle donne a partire dai 45 anni, poiché si ammalano prima. La mammografia tradizionale sarebbe comunque poco efficace in queste fasce d’età, soprattutto per la struttura densa, tipica della ghiandola giovanile.

Nel campo della prevenzione, grazie ai passi avanti nella ricerca, sono stati introdotti strumenti diagnostici per donne di tutte le età. L’Unità di Prevenzione Oncologica ANT – presso la sede della Fondazione a Bologna – è dotata della più moderna tecnologia disponibile per la prevenzione del tumore al seno. Con cinque ambulatori, cui si affianca l’Ambulatorio Mobile - Bus della Prevenzione, l’Unità di Prevenzione Oncologica ANT è fornita di una strumentazione estremamente all’avanguardia per realizzare quattro diversi progetti di prevenzione: melanoma, neoplasia fisioido, ginecologiche e mammaria.

Mentre la mammografia e l’ecografia mammaria sono indagini diagnostiche che studiano i cambiamenti di forma e di densità dei tessuti (esami morfologici), il DOBI è un esame funzionale, ossia fornisce informazioni circa i cambiamenti che si verifichino nella ghiandola mammaria per la presenza di una specifica lesione. L’alta sensibilità e la buona specificità rendono la mammografia ottica utile sia per la diagnosi precoce nelle giovani donne, sia per la diagnosi differenziale, in casi dubbi.

Il mammografo ottico DOBI ComfortScan presenta un sistema non invasivo, senza emissione di radiazioni ionizzanti, progettato per migliorare la capacità diagnostica. L’esame fornisce nuovi dati fisiologici funzionali che non possono essere dedotti dall’esame clinico, dalla mammografia e dall’ecografia. Il fondamento scientifico su cui si basa è l’individuazione della formazione di nuovi vasi sanguigni. Questo fenomeno conosciuto come neoangiogenesi è peculiare della crescita neoplastica.

La mammografia ottica utilizza la luce nello spettro visibile (luce monocromatica rossa) per
6.11 Know, prevent, cure: the fundamental objectives of the Centre

HABILITA PER LA DONNA

Un Centro di riferimento per le patologie prevalentemente femminili: presso Habilita San Marco Bergamo è nato infatti il Progetto Habilita per la donna. All'interno di questo servizio si colloca il Centro di Prevenzione secondaria del Tumore alla Mammella, la cui responsabile è la dr.ssa Flavia Musacci. Habilita per la donna potrà contare su una tutta struttura e integrazione di altre specialità, ovvero la Chirurgia oncologica, la Ginecologia e la Diagnostica per Immagini.

Il Centro di prevenzione secondaria del tumore alla mammella di Habilita offre un percorso clinico-diagnostico-radiologico completo e personalizzato per ogni donna che si adocce. Saper accogliere e convivere con ogni donna è un elemento fondamentale per un tale aspetto professionale. La medicina specializzata in campo oncologico e le cure, le interazioni nei confronti della malattia per ottenere risultati migliori in termini di diagnosi, trattamento e tranquillità psicologica per la paziente.

Conoscere, prevenire, guarire: gli obiettivi fondamentali del Centro

La neoplasia della mammella rappresenta il tumore più comune e frequente tra le donne in tutto il mondo Occidentale ma pur essendo ad alta incidenza questa malattia può essere facilmente curata se fondamentale però agire tempestivamente, quando la malattia è in fase iniziale. Temporaneamente significa riconoscere i sintomi della malattia per questo è indispensabile infatti eseguire periodicamente esami e test (come fluorosistologia, l'ecografia mammaria, la mammografia e l'ecobiopsia) che hanno lo scopo di individuare un eventuale carcinoma mammario nella sua fase iniziale, un individuazione tempestiva permette intervenire in tempo, assicurando una guarigione completa nella maggior parte dei casi.

La malattia può essere sconfitta solo vincendo la paura del tumore, il panico e lo sospetto della parola “tumore al seno” spesso la paura del tumore alla mammella è più perturbante della malattia stessa. La donna è l'artefice pratica di questa battaglia.

L'importanza di un team multidisciplinare nasce dall'esigenza di avere a disposizione un concerto dedicato con la presenza di personale specifico, che possa organizzare al meglio e nel minor tempo possibile il percorso terapeutico della paziente.

Attualmente nel progetto “Habilita per la donna” sono garantita la seguenti prestazioni: visita senologica con eventuali esami e programmi di seguito da adottare; mammografia; biopsia mammopera; DOBIComfortScan, ecobiopsia sotto guida ecografica; conclusione del bilancio diagnostico e radiologico al fine di fornire un percorso di cura o seguire il follow-up radiologico della paziente con diagnosi biologica di tumore alla mammella. Oltre a queste prestazioni esistono inoltre altre tecniche innovative, il team di ginecologi è sempre a disposizione per compiere il percorso diagnostico in rosa.

Tra le strumentazioni di cui Habilita dispone, particolare rilievo riveste il nuovo mammomotor digitale e DOBIComfortScan: il primo grazie all’evoluzione tecnologica permette di ottenere immagini con elevato dettaglio anatomico le quali migliorano la rappresentazione della struttura delle ghiandole mammaliere e minimizzano alterazioni patologiche, con una dose di radiazioni inferiore a quella in uso, grazie all’utilizzo di sistemi innovativi dove l’immagine viene raccolta su aperture passive e poi letta da specifici apparecchiature.

Tutte le donne che decidono di sopportare ad una prevenzione secondaria, anche le giovani possono invogliare alla struttura; donne con sintomi specifici alla mammella (ad esempio noduli o fuoriuscita di liquido dal capezzolo) o con dubbii radiologici all’indicazione mammografia od ecografia e donne attonnite (due che non presentano sintomi o segni alla mammella). Le donne ospitate per una patologia di tumore al seno qui possono sottoporsi a controlli di follow up clinico e radiologico.

Per fissare un appuntamento è necessario telefonare al numero 035 22202 da lunedì al venerdì dalle ore 8 alle ore 19 oppure scrivere un'email all’indirizzo info.unico@habilita.it

NEWS
L'ANIGIOGENESI

L'angiogenesi, ovvero il processo che porta alla formazione di nuovi vasi sanguigni, è riconosciuta come una delle stadiolazioni di un tumore mammario.

I sottile mutanti ploiallini sono spesso associati a questa tipologia di carcinoma. In qualche caso, queste lesioni hanno dimostrato che la neoplasia diventa dinamicamente evolve quando svolta una via di reazione alla neoplasia.

Un'indagine temporanea consente una diagnosi efficace per combattere il carcinoma fin dai primi stadi. Nel caso di espansione metastatica, le lesioni del rene sanguigni avviano, a un certo punto, attorno ad un supporto alla massa.

Per questo motivo è fondamentale disporre di tecnologie di diagnostica che possono evidenziare i mutamenti vascolari, creando un profilo vascolare unico, che possa indicare l'inizio sviluppo dell'angiogenesi.

L'IMPORTANZA DELL'ANALISI DIAGNOSTICA

DOBI ComfortScan™ è un sistema velocemente adattabile per la diagnosi del monitoraggio del sangue della paziente, con la caratteristica di:
- incrementare i diagnosi per i pazienti che presentano sintomi d'ansia o di malattia.
- controllare costantemente i giovani donna con trapianti a donatori con minima dose.
- monitorare periodicamente i mutamenti psicologici non individuati della mammografia.
- permettere la comprensione degli esami per pazienti ad alto rischio di metastasi assonnate alla mammografia.

Il sistema consente di ottenere un materiale in diretto dalla immagine, consentendo anche alla possibilità di trama di rappresentare un esame per individuare la via di intrinseca della vascolarizzazione.

Attualmente risulta assai ridotta la morbidità del paziente emorroidario: in seguito all'applicazione di uno stimolo pressorio esentrico, tramite presso temporaneo.

ESAME OTTICO

Il sistema ottico può fornire ai pazienti nuove informazioni diagnostiche che sono analizzate e utilizzate a favore della diagnosi e soprattutto del tiro del paziente.

L'utilizzo della medesima è consigliabile in caso di tumore mammario, in termini di prevenzione, valutazione, controllo, accurazione e facilità d'uso. Il target diagnostico migliore riduce essere la popolazione femminile dai 20 ai 50 anni.
6.12 From tomorrow morning a new entry with the camper made available by the project underfifty LILT Bologna, with breast ultrasound and optical technology mammary (ComfortScan Dobi) for this occasion for the first time in southern Italy.

**LE ASSOCIAZIONI E GLI ENTI**

Il solo Orsino di Maltia sarà presente con un ambulatorio da campeggio da campo di 42 Mq all'interno del quale i medici specialisti dell'Orsino provvedono da tutti i territori saranno a disposizione di quanto ne forniamo indirizzati. La Croce Rossa con il proprio coopera da campo ed i suoi Volontari si era di supporto a tutti i medici indirizzati sul programma della settimana della prevenzione, che grazie ad un accordo con Federazione e Consobilardo in tutte le farmacie della città.

Il campeggio dell'Add è presente da provvedere per le visite omeopatiche organizzate.

Da domani matura una new entry con il camper messo a disposizione dalla Lilt Bologna nell'ambito del progetto underfifty, donato da ecopuntura mammografia e tecnologia ottica mammografia (ComfortScan Dobi) per l'occasione presente per la prima volta in tutta Italia. Prendere notizia dell'illustre Nazionale dei tumori Fondazione Pascale, splendidamente coordinato per l'occasione da Elisabetta da Lusso

L'Add è un campeggio che ripropone dopo l'enorme successo della scorsa anno. L'imminente tempo di attesa zero tutte le donne che desiderano prenderne in Piazza una visita ginecologica con pop-test e mammografia, riceveranno un appuntamento senza rapporto di attesa presso il loro centro di riferimento. Inserito una proposta per avvicinare i giovani e le ragazze alla cultura della prevenzione, con stimolatori di eccezione al calibro di Valeria Capezzuto (Rai 1) e Marzia Ricciardi (Rai 2) specializzata proprio in informazione sanitaria. "I donatori presenti hanno accudito con un arroba di cuore" dice Fabrizzelli, sono avvenute disposizioni chiare e una relazione con responsabili dei domande delle plaste.

Domenica è prevedi dell'associazione volontare pediatri, con l'associazione Italiana Biblioteche ed il centro per la salute del bambino nell'ambito del progetto "Vita per Leggere", illustreranno alle mamme l'importanza della lettura in tenersi attiva e migliorare la capacità del bambino nel relativo test. Dallo sforzi di finire di finire di favore per un'ottima gestione della lettura e della parola, la facilitazione alla lettura in età adulta. Siamo domani la Rialt Park, sportivo una da piccoli, aspettare i bambini dai 3 ai 13 anni un giorno del tuo tempo Piazza Plebisciti inseguito Carlo Ferrara il devolvere siamo in beneficenza alla Fondazione Cassano-Ferrara. Domestica poi oltre la metà Maranana, la Comi Napoli, da corsa o a passeggio per il chiamare.

**IL PREMIO**

Infine il premio Fabio De Paoli di cui ricorre il ventennale della morte, il bambino fu piccolo a soli 11 anni per nesso criminale e si è riservato ai suoi bambini un modo per ricordare un bambino da parte di altri bambini. All'apertura della Comi Napoli, la prima fila sarà composta da un gruppo di voci primi e al centro di accorgimento diretta di tutti i bambini di Scuola, ed altri operatori che assistono i ragazzi in attività motorie, il cui scopo è dare un passaggio la possibilità di esprimere anche attraverso il bambino, e la possibilità di provare una attività fisica come tutte le altre persone in un contesto sociale comune e la possibilità nel campo sportivo cercando di soddisfare le loro necessità di inserimento. Il Trofeo Ep-Congressi riservano ai medici che con la loro corsa impariamo avvicinare la gente alle sport come prevenzione della salute.

**I Medici Volontari**

- Giuseppe Barbiari medico dello sport Add Mus
- Nicola Calabro ginecologo aonova.com
- Gerardo Costantino comprensione di dia</div>
6.13 As breast, ComfortScan presents as a solution for the prevention

Lauren Graham (nella foto) si sottoporà ad una serie di cure per combattere un tumore al seno.

Il tumore al seno è la neoplasia più frequente nelle donne e rappresenta la principale causa di morte per tumore nel sesso femminile.

Ogni anno, nel mondo, si verificano circa 1.500.000 di nuovi casi di tumore al seno. In Italia, l'incidenza è di circa 40,000 casi per anno. La guaribilità di questa malattia è strettamente correlata allo studio di malattia, più precoce è la diagnosi, maggiore è la possibilità di guarigione. Si stima che circa 1/3 dei decessi potrebbero essere evitati se il tumore venisse diagnosticato in tempo.

Questo dato, riferito al contesto mondiale, corrisponde a dire che circa 500.000 donne l'anno avrebbero maggiori possibilità di guarigione se la loro malattia venisse diagnosticata in tempo. Lo screening mammografico rappresenta un strumento efficace di anticipazione diagnostica nelle donne in età compresa fra i 50 e i 69 anni. In questa fascia d'età, grazie alla mammografia e ai centri di screening, l'obiettivo della diagnosi precoce è perseguibile. Tuttavia, in questi anni, stiamo assistendo una progressiva e costante anticipazione dell'età di esordio di questa malattia. Nella fascia d'età compresa fra i 25 ed i 44 anni, dal 2000 al 2005 è stato osservato un incremento dei casi di tumore al seno pari al 28%, circa il doppio rispetto a quanto accaduto nelle restanti fasce d'età.
Queste pazienti, non possono beneficiare dello screening mammografico, poiché ammalano prima. Inoltre, la mammografia è poco efficace nei seni densi, tipici dell’età giovanile. Pertanto, prima dei quarant’anni, quasi sempre è la donna ad accorgersi della presenza del tumore e in 1/3 dei casi la malattia ha già interessato i linfonodi ascellari al momento della diagnosi con parziale compromissione della prognosi. La mortalità complessiva in questa fascia d’età è più alta, questa evidenza è in parte correlata a una maggiore aggressività biologica del tumore, ma è anche espressione del ritardo nella diagnosi. Alla luce di questi dati è importante disegnare dei percorsi di anticipazione diagnostica che siano al tempo stesso sostenibili sul piano finanziario ed efficaci anche in età premenopausale.


In circa 3 anni d’attività sono state trattate oltre 300 pazienti underforty con tumore al seno, molte delle quali alla prima diagnosi. Inoltre, da circa un anno è attivo l’ambulatorio underforty al quale è possibile accedere tramite prenotazione. Il consulto prevede la stima del rischio soggettivo di ammalare di tumore al seno e la pianificazione di un percorso di anticipazione diagnostica personalizzato. La visita senologica e l’ecografia mammaria rappresentano gli esami basilari. In casi selezionati è previsto l’ausilio della Risonanza Magnetica Mammaria. Mission del progetto underforty è anche innovare, indagare il potenziale offerto dalle tecnologie emergenti nella diagnosi del tumore al seno. Il ComfortScan, è una tecnologia non radiante che indaga la ghiandola mammaria mediante la luce nella banda dei 640 nm.

Le immagini sono acquisite in seno eranicaudale e rielaborate in dinamica, consentendo di rilevare eventuali aree d’interesse patologico riconducibili alla neoangiogenesi tumorale. In letteratura esistono pochi studi che riguardano questa metodica, tuttavia i dati preliminari sono incoraggianti. Di recente, si è di costituito il DOBI Group, si tratta di un comitato scientifico al quale partecipano molti dei centri che possiedono la tecnologia ottica mammaria.

La finalità è favorire lo sviluppo della tecnologia ottica e provvedere alla formazione ed al tutoring degli utilizzatori della metodica. Attualmente è in corso uno studio multicentrico che ha la finalità d’uniformare i criteri d’interpretazione delle immagini rendendo uniforme il processo di riferimento.

I risultati preliminari sono incoraggianti. Aprire all’innovazione è un dovere prima ancora che un’opportunità. E’ necessario il contributo e l’impegno di tutti: medici, dirigenti ed istituzioni, affinché il tumore al seno sia diagnosticabile in fase pre-clinica anche in età giovanile.

Lunedì, 14 Novembre 2011 20:56

Prevenzione tumore al seno: la soluzione italiana per un problema mondiale.

Written by Super User

La prevenzione del tumore al seno è diventato il grande problema di tutti i paesi sviluppati. La riduzione della mortalità e l’allungamento della vita media sono dovuti più alla innovazione terapeutica e chirurgica che alla diagnosi precoce. A cura di Daniele Romano

La prevenzione diagnostica non è sul banco degli imputati dato che non c’è mai stata. Almeno fino ad oggi e nei sistemi sanitari in tutti i paesi sviluppati. Il tumore al seno rimane la seconda causa di morte delle donne. La situazione è davvero pesante: si sta abbassando velocemente l’età di manifestazione delle patologie cancerose mammarie alle over 50 e la strumentazione diagnostica prevista dalle linee guida delle istituzioni dei vari Paesi, non dispone di strumenti in grado di “leggere” i seni densi particolarmente nelle donne giovani tra i 30 e 45-50 anni. É in aumento in Italia l’incidenza del tumore al seno, soprattutto tra le più giovani: nelle donne tra i 25 e i 44 anni si registra, infatti, negli ultimi 6 anni un aumento del 28,6%. É il dato contenuto nell’indagine conoscitiva sulle malattie degenerative, condotta dalla Commissione Igiene e Sanità del Senato.

Va fatta chiarezza clinica perché si sta sviluppando uno sterile dibattito pro o contro la mammografia, come se non sapessimo che la diagnosi prevede un mix di strumenti. Nei casi sospetti oltre all’eegografia e alla risonanza si usa l’ago aspirato, spesso senza sapere se si tratta di una microcalcificazione fisiologica o della presenza di un carcinoma.
ha iniziato la “via crucis” delle donne e, in seconda battuta, dei medici, radiologi, senologi, oncologi che dopo aver fatto migliaia di referiti spesso non sanno che pesci pigliare per l’insertezza della risposta diagnostica e l’angoscia della paziente sia nei tanti casi di falsi positivi (diagnosi errata di carcinoma) che di falsi negativi (diagnosi errata di negatività quando c’è una formazione tumorale). In un recente articolo sul Corriere della Sera di Adriana Bazzi la notizia di “due ricercatori americani sono arrivati a conclusioni che qualcuno già sospettava: nella maggior parte dei casi lo screening non aiuta. Anzi: rischia di intercettare neoplasie che non avrebbero mai dato segno della loro presenza, costringendo la donna a inutili terapie. □ non può essere considerato un sistema di prevenzione dei tumori (si tratta, infatti, di diagnosi precoce, perché l’esame evidenzia la malattia quando già c’è, mentre la vera prevenzione primaria punta ad evitarne la comparsa).

Un sasso nello stagno che sta creando scompiglio nella comunità medica.” “Quest’ultimo caso è il problema principale dello strumento della gloriosa mammografia che non ha sensibilità sufficiente per vedere spesso nei semi più complessi formazioni tu-morali già consistenti, anche di diversi millimetri” afferma il professor Roberto Dall’Aghio responsabile della Commissione ministeriale dell’AIFA per tutti i dispositivi medici.

“□ non possiamo usare la risonanza quale strumento di screening perché le spese sanitarie si mangeranno il bilancio dello Stato, con risultati che non aiutano a verificare con grande capacità clinica”. Le linee guida ministeriali prevedono l’errore umano e i limiti della diagnosi precoce della mammografia che esone il medico a possibili richieste risarcitorie, mentre in effetti sono i limiti della tecnologia tradizionale che impone di individuare un mix diagnostico più mirato e innovativo, che tuteli sia i medici che la salute delle donne.

□ un momento storico in cui bisogna fondere i saperi del tecnico di imaging, dell’oncologo, dell’auspicato riconoscimento professionale del senologo, senza conflitti di casta, per formare delle vere “breastunits cliniche” che utilizzano in maniera mirata il mix di strumenti diagnostici, aprendosi all’innovazione clinica validata ed evitando la sofferenza inutile delle donne sane o malate. La mammografia ha dato moltissimo e ha ancora molto da dare, ma non può essere considerata uno strumento di prevenzione: è screening utile che ha dei limiti. Spesso i cosiddetti CI (canceri di intervallo) tra una mammografia e l’altra, non sono neoformazioni ma carcinomi in fase iniziale passati tra le maglie larghe del primo esame mammografico. Al troppo discorso per i tumori a velocità moltiplicata che in pochi mesi possono raggiungere dimensioni di un mandarino.

“La polemica sull’impatto degli screening nella riduzione della mortalità è conclusa due anni fa – ha dichiarato Pier Franco Conte, direttore del Dipartimento di Oncologia all’Università di Modena-Reggio Emilia – e dà vita all’osservazione che, a partire dagli anni Novanta, nonostante un aumento dell’incidenza del cancro, la mortalità stava diminuendo anche dove non si facevano screening. Probabilmente per un aumento dell’efficacia delle terapie”. Oggi conosciamo bene la biologia dei tumori (aggressivi, ereditari, indolenti) che non vengono identificati, nella loro specificità, dalla mammografia: l’esame, infatti, vede solo opacità e noduli. “Per fare una vera prevenzione andrebbe affiancato alla ecografia per le donne under 45 e a seno denso, uno strumento diagnostico noto per i suoi principi a tutti i medici e biologi, la neangiogenesi si può ottenere con la risonanza magnetica o a costi molto più contenuti dalle nuove tecnologie italiane di ottica mammaria” afferma il prof. Roberto Dall’Aghio. Con un brevetto italiano, che verrà subito esteso su scala internazionale, si utilizza la luce rossa in buona, in luogo della radiazioni ionizzanti utilizzate nei sistemi mammografici, anche nei digitali di
6.15 A New Weapon Without radiation for the diagnosis of breast cancer in young women – Women’s Health in Italy
6.16 US-China Technical Fight against Cancer with no more X-rays, August 2011

La sanità. Gli sviluppi della ricerca

Tecnica Usa-Cina lotta ai tumori senza più i raggi X

Cane 1 e 2: una nuova tecnologia per favorire la diagnosi precoce.

Cronaca

La presunta influenza di un paragrafo sulla salute pubblica

L’epidemia di diabete e la nostra società, secondo una nuova versione della "Sanità 2000".

La crisi dei vaccini in Italia: una nuova sfida per la salute pubblica.

San Giovanni Bosco: il medico in fiera: un paziente azzurro.

Cibo gratis per i malati ai reni, stop dal Consiglio di Stato

La dozziola

La pellecura: una decisione assurda: una donna senza protezioni.

Sibilla Leo

Oltre 100 mila persone oggi hanno avuto un vaccino anti-influenza in Italia.}

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San Giovanni Bosco: il medico in fiera: un paziente azzurro.
6.17 PREVENTING BREAST: NEW DIAGNOSTIC

PREVENZIONE MAMMARIA: NOVITA’ DIAGNOSTICHE

Ogni anno più di 30.000 donne vengono colpite dal tumore alla glandola mammaria, mentre 12.500 donne muoiono di questa patologia. La prevenzione è la chiave per prevenire il tumore alla glandola mammaria. Per questo, DOBI ComfortScan™ System è stato sviluppato per fornire un ulteriore strumento per la prevenzione del tumore alla glandola mammaria.  

DOBI (Dynamic Optical Breast Imaging) è un innovativo strumento di imaging ottico, non invasivo, che utilizza la proprietà di fluorescenza eccitazione di sostanze chimiche per evidenziare le anomalie del tessuto mammario. Questo sistema è progettato per rilevare le anomalie sottili e non visibili con altri metodi di imaging mammario, consentendo una diagnosi più precoce e accurata dei tumori alla glandola mammare.

Il sistema di imaging ottico rileva le anomalie del tessuto mammario, permettendo di identificare le anomalie precoci e quindi di prevenire la sua evoluzione pericolosa. Il DOBI è in grado di identificare le anomalie del tessuto mammario, consentendo una diagnosi più precoce e accurata dei tumori alla glandola mammare.

CONCLUSIONI E PROSPETTIVE

DOBI ComfortScan™ System, con la sua tecnologia innovativa, permette di identificare anomalie del tessuto mammario che possono portare a un carcinoma. Il sistema è progettato per rilevare anomalie non visibili con altri metodi di imaging mammario, consentendo una diagnosi più precoce e accurata dei tumori alla glandola mammare.
DOBI, la nuova tecnologia contro il tumore al seno

di Titolo Del Greco


Il dato che si evince è che in sei anni l’incidenza è aumentata del 28% nella fascia di età tra i 25 ed i 44 anni e che, dunque, il carcinoma mammario, identificato come "a killing", rappresenta una delle maggiori cause di morte delle donne.

"Per intervenire sul piano concettuale, le parole del prof. D’Auto, che traggono innanzitutto da un quadro interdisciplinare e che il DOBI ComfortScan divenga lo strumento tecnologico più ideale per l’utilizzo della metodica dell’interpretazione delle immagini", è esposto per effettuare una più precisa indagine sul campo, l’Olimpia ha inviato al prof. D’Auto.

Prof. D’Auto, ci può illustrare questo rivoluzionario DOBI CONFORTSCAN?

"È un apparecchio che assomiglia un po’ a un mammografo, con la sostanziale differenza che non emette radiazioni e non usa mezzi di contrasto. La "near infrared breast cancer world" di questo terzo millennio ha definito una sorta di nuova luce nel mondo del cancro al seno, una rivoluzione di dimensioni che vuole ridurre una speranza più credibile per le giovani donne. Tale innovazione ha trovato conferma nel corso di una importante conferenza tenuta nel settembre a Roma alla quale sono state divulgati risultati ottenuti su base di oltre 2000 esami effettuati in un anno e su risultati statisticamente di cui dimostrano che certamente costituiscono un supporto significativo sul piano della ricerca scientifica in questa aspettativa del futuro evoluzione".

Qual è il fondamento su cui è impostata la tecnologia DOBI?

"E’ l’individuazione dell’angioforma tumorale nella mammella attraverso la valutazione dell’assorbimento ottico. Il tutto si effettua con una certezza scientifica che non ha bisogno di sperimentazione perché è già consolidata e già operativa in molti centri italiani e all’estero.”

E vero che questo apparecchio legge anche una diversificazione del sistema vascolare?

"Certamente, anche osserei dire che rilevare una variazione arteriosa è il primo elemento che può garantire, anche attraverso altre forme di approccio, che in termini percentuali, purtroppo, si risale un carcinoma.

Parliamo della famosa luce rossa con la quale il DOBI attraversa le mammelle? Quali dati fornisco e come lavora?

"Si tratta di una luce normale che però riesce ad attraversare campi di indagine anche molto profondi, considerando il fatto che più una donna è giovane, più, inverse, ha una sua propria struttura densa, diffo lussa da osservare con la mammografia. Questa luce è capace di filtrare ogni anomalia e di registrare qualsiasi cosa ci sia anche se soltanto all’interno.

Professore, dalla mia informazione risulta che l’esame dinamico-funzionale potrebbe semplificare tale elemento diagnostico?

"L’esame ottico di una mammella rileva la topologia. L’esame dinamico-funzionale serve a dire che, oltre ad esaminare la luce, effettua anche una compressione solida e massiccia della luce di 25 secondi nelle quali riceve il comportamento vascolare. Alle fine l’esame risulta essere sensibile fino al 90% anche su donne con un seno particolarmente denso.

Il solo DOBI può essere sufficiente per capire la natura del carcinoma?

"Il DOBI risulta essere particolarmente indicato, ma nei specialisti continuano ad adottarlo all’occorrenza all’occorrenza.

E esiste una prevenzione che va oltre quelle delle apparecchiature per prevenire il carcinoma?

"Certamente, esiste una tipologia che va oltre quelle delle apparecchiature per prevenire il carcinoma.

Vorremmo chiedere che cosa si intende per il DOBI CONFORTSCAN?

Il Motivo: Nonostante il DOBI non sia un mammografo che viaggi in viaggio sperimentale, ma che è stato abbandonato lontano tutto sul mercato con risultati brillanti, non riesce ancora a un tempo illuminare l’estetica apparentemente reattiva. Anche perché più tardi una naturale è scotta ridotta la cultura del futuro specialista, ma certo l’Italia all’avanguardia alla quale può essere interessata anche in futuro. Per fortuna, purtroppo, ci sono anche altri che sono attenti a questo campo come, ad esempio, Michele Colombo nel suo libro "Il torna il medico", dove ci si può addentrare nei problemi di salute e di salute, e dove si trova quel segno attento rispetto ai risultati dell’apparecchio mammografico DOBI di estetica mammaria. Schwartz, ecco, che stiamo ad un passo da quella versione di cui ci hanno parlato e che ci abbiamo invitato nell’immaginazione dell’immagine.

A farlo aggiungere che, come abbiamo detto, l’estetica può essere anche una forma di approccio ancora di più importanti associazioni di chirurgia mammologica.

6.20 Monza, care of the breast. Institutes Zucchi intervene in Rome, February 2011
6.21 DOBI New Screening for Breast Cancer that does not use X-rays

Il prof. Pini presidente Ssc

MODERNA

Attivata un progetto pilota per il centro effettuando un
valutazione rilevante e trasformandosi
cambiando strutture semplice

6.22 The New Frontier Optical Survey, 2011

Giorrane di Monza

CONVEGNO

Tra i relatori il senologo Giovanni Ciuffo, degli istituti clinici Zucchi

La nuova frontiera dell’indagine ottica

La tecnologia ottica mammaria evidenza clinica e progetti diagnostici in corso.

A un anno dalla sua creazione, il Comitato Scientifico DOBI presieduto da Aldo Vecchione, direttore scientifico dell’Istituto mammaliano di Napoli, è riunito a Monza per fare il punto sui risultati ottenuti dalla nuova tecnologia di indagine ottica. Un esame non invasivo e non radiologico che utilizza la lunghezza d’onda della luce visibile, individuando immagini di ghiandole mammarie: un segnale precoce di attività neoplastica genetica e quindi di possibile patologia.

Tra i relatori, in rappresentanza del Gruppo San Donato, è stato Giovanni Ciafo, chirurgo senologo e coordinatore del Centro di senologia degli istituti clinici Zucchi di Monza, una delle prime realtà in Italia ad introdurre l’indagine ottica della mammella nell’ambito del percorso diagnosticoterapico, accostato alle metodi che usano.

In occasione dell’incontro romano, il presidente scientifico del centro, si è aperto a nuove significative partecipazioni: spiega il dottore, anch’egli membro del tale comitato e ha presentato un nuovo progetto clinico sulla metodica che posa in un tempo ragionevolmente breve fornire evidenze che resterebbero efficaci pubbliche. La speranza è in definitiva quella di fornire alla comunità scientifica sempre maggiori dati per una più ampia validazione della metodica.
6.23 Screening mammography: what to do?, April 19, 2011

Screening mammografico: cosa fare?

19/04/2011

Sono da due anni un vostro felicissimo abbonato. Vi scrivo per chiedervi un’informazione relativa allo screening mammografico.


Vi chiedo questo perché mia madre, che ha 62 anni, vuole fare a tutti i costi la mammografia, come ogni anno, lo sta convincendo a non farla, ma lei vi rinuncerebbe solo se conoscesse un’alternativa. Spero che possiate aiutarmi.

Alessio

Caro Alessio, per quanto riguarda possibili alternative, ti giriamo una segnalazione che abbiamo ricevuto direttamente da uno studio medico di Rovereto sulla Sacchia, in provincia di Modena. Lo studio, dove può contattare il dottor Guidi, si interessa da diversi anni di senologia. Si tratta del poliambulatorio Physio, che si è dotato di uno strumento che utilizza una luce laser. DOBI comfortscan, che unito all’elettrofisiologia, per che abbia una spiccata sensibilità nell’ambito della diagnosi precoce del tumore mammario. Il dottor Guidi ci ha informato che la LUT (Lettura tecnica) è stata usata da più di un anno e nella sede di Bologna ha aiutato un campionario dei medici a riportare il maggiore numero di donne. Praticiamo che non abbiamo avuto modo di sperimentare l’apparato da finora qualcuno ha avuto chiesto possibilità alternativa alla mammografia. Se tua madre dovessi decidere di rivolgerti a questo studio, ci piacerebbe conoscere la sua esperienza. In modo da poterla diffondere a chi dovessi avere la stessa necessità.

Lo studio ha sede in via Chiara Nord 52, 41016 Rovereto s/d (tutti i modena), tel. 059 67254 - physios@physios.it

Saluti, La redazione

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6.24 Professor Rocca's Trial

**SUMMARY**

The ComfortScan system is a nonionizing, advanced optical imaging system that uses light-emitting diodes (LEDs) and gentle external pressure to identify angiogenesis, the growth of new blood vessels, in the breast. This blood vessel growth is often associated with malignant breast tumors. The article in EJR reports that the ComfortScan system could potentially be a complementary, adjunctive imaging modality in women with inconclusive mammograms and/or physical examinations and in young women with ultrasound system.

The promise of the ComfortScan system, as demonstrated in this study, warrants additional investigation, but the preliminary results are very encouraging. The sensitivity of the ComfortScan system technology was extremely strong and the specificity rates also were positive.

**About the Trial**

In the 15-patient study, patients underwent both breast and optical scans in addition to standard mammography and ultrasonography, followed by core biopsy. Patients' ages ranged between 20 and 78 years of age and all patients scanned did not have recent trauma, breast surgery or biopsy before.

**Results**

According to our results we can state that the Dobi ComfortScan optical image method can become a promising scanning system in prevention of women cancer in addition to the conventional diagnostic methods, ultrasound and mammography.

This study includes a small sample of patients chosen among more than 1000 observed optical images. The results obtained encourage the scientific community to produce and evaluate more further studies of this optical diagnostic non-invasive methodology.
6.25 READY FOR A LIFE SUPPORT MACHINE, 2011

lunedì 14 marzo 2011

PRONTA UNA MACCHINA SALVAVITA Giorno - Carlino - Nazione
06:55 | da R.L.G. | E
Giorno - Carlino - Nazione di lunedì 14 marzo 2011, pagina 41

PRONTA UNA MACCHINA SALVAVITA
di Ortolani Renata

ALLEATI DELLA DONNA La scansione ottica si affianca all'elettrografia e all'autopalpazione Renata Ortolani BIUONE NUOVE dal mondo scientifico in fatto di cura e soprattutto in fatto di prevenzione del tumore della mammella: se è vero che dei 40mila nuovi casi di neoplasia mammaria diagnosticati ogni anno in Italia quasi la metà riguarda giovani donne sotto i 40 anni (il 28% della popolazione femminile nostrana), è anche però già possibile mettere in campo una nuova arma, una avanzatissima tecnologia in grado di individuare ogni minima variazione nella trama vascolare dei seni. Il che significa far risuonare un campanello di allarme e poi approfondire i controlli per eventualmente bloccare il processo tumorale. Si chiama ComfortScan la metodica (di fabbricazione americana vede l'Italia capofila nella formazione del personale specializzato dedicato) che utilizzando la scansione ottica, senza mezzi invasivi, registra ogni variazione di assorbimento di luce nel tessuto mammario. Poiché uno dei fattori rilevanti della formazione del tumore e indicato nella presenza di nuovi vasi sanguigni (angiogenesi) attraverso i quali la neoplasia «si nutre» e cresce, ecco la possibilità concreta di fare una diagnosi precoce o di escludere possibili rischi di insorgenza. «Questa tecnica, illustrata a oncologi, medici di medicina generale e ricercatori riuniti nella Sala delle Colonie presso la Camera dei Deputati, per il secondo Meeting Dobi Group dedicato al Progetto under40, preziosissima nell'affiancare ecografie e mammografie, risulta fondamentale nelle donne giovani, quelle che oggi non sono sottoposte a screening, e che nel 70% dei casi, se incontrano sul loro cammino la patologia mammaria, si sono fatte diagnosi 'da sole'. A confermare il ruolo che il ComfortScan avrà nei prossimi anni nella prevenzione e nella diagnosi precoce dei dati, che sospingono almeno in parte l'aumento delle neoplasie della mammella nelle donne tra i 20 e i 44 anni, dove non esistono ancora ancora diagnosi diagnostici uniformi: è in fette crescita, anche in Italia, il numero delle ragazze con protei mammarie, delle donne che si sottopongono a stimolazioni evariche per avere figli e di quelle che hanno alle spalle una storia familiare in cui ricorre la patologia del seno. Per queste ultime negli Usa (e non solo), seppure con molte cautele si decide ormai la mastectomia preventiva sulla scorta, ovviamente, di test genetici che testimoniano in modo conciamato la presenza del rischio. Con le nuove metodiche, questa drammatica scelta potrebbe in molti casi essere evitata. »INDOCORE, perché una morbida membrana avvolge il seno evitando dolorose compressioni; non invasivo e non dipendente dall'operatore, il nuovo strumento — ribadisce il professor Aldo Vecchione, direttore scientifico dell'Istituto nazionale per lo studio e la cura dei tumori Pascale di Napoli, uno dei centri un cui ComfortScan è in funzione — utilizza non raggi X ma una normale luce monocromatica, e può effettuare esami su giovani dai 18 anni. Francesco Marabelli, capo Dipartimento innovazione del ministero della Salute, introduce da parte sua un altro punto di vista: «Prevenire significa anche ridurre, oltre alla sofferenza delle pazienti, i costi, della assistenza, della riabilitazione, e di tutto quanto ruota attorno alla donna che si ammala e alla sua famiglia». Tra le strutture sanitarie che adottano la nuova tecnologia, ci sono l'Istituto di Prevenzione e Assistenza di Roma, il Centro Radiologico Colaé di Lanciano, la casa di cura Zucchi di Monza, la Radiologia senologica del policlino Mangiagalli e Regina Elena di Milano, lo Studio Physios a Rovereto Secchia di Modena, e l'unità mobile, unica in Italia, attrezzata dalla Lega italiana per la lotta ai tumori di Bologna (Lilt), presieduta dal professor Francesco Rivel. Il nuovo ComfortScan utilizza il laser per evidenziare tessuti mammari con diversa trama vascolare, senza emissione di raggi, utilizzando l'emoglobina come mezzo di contrasto naturale. È proposto per la diagnosi precoce in tutte le età della donna.
6.26 A Step Forward to Prevent Breast Cancer - Health in Italy

Oncologia
Il Centro di Senologia dello Zucchi compie un anno e si dota di un nuovo scanner mammario

Un passo in avanti per prevenire il cancro al seno
Lo strumento è in grado di individuare la massa tumorale anche se molto piccola

6.27 New Light in the diagnosis – LILT Magazine in Italy

Attività Lilt

Nuova luce nella diagnosi
6.28 The City of Rome in the front line against Breast Cancer - The I.P.A. in Italy
6.29 Breast Safe with the Examination at Red Lights – July Fitness in Italy

indole e innovativo,
il nuovo test diagnostico sfrutta
l’azione di particolari raggi
luminosi. Non sostituisce
l’ecografia e la mammografia,
nei due pilastri della prevenzione,
ma aiuta e completa la diagnosi.

SENO SICURO
CON L’ESAME A LUCI ROSSE

C’è una novità nel campo della prevenzione
di tumori seno. Si tratta di un nuovo
test per la diagnosi precoce di questo tumore, che si popola come
complemento della mammografia e dell’ecografia, nei
programmi di screening, i suoi vantaggi? La parola al
dottore Sergio Orlicic, chirurgo senologo e oncologo
all’Istituto Clinico Humanitas di Rozzano (Milano).

● Niente raggi X: Spiega il dottore Orlicic «A differenza della mammografia, che utilizza le radiazioni, questo esame si avvale del sistema DoBi Dynamic Optical Breast Imaging che esplora la mammella grazie a 130 luci di ideale, di colore rosso. Aapproggia
te su una membrana di silicone, le ghiancie mammarie vengono attraversate da fasci di luce appartenenti alla banda dell’infrarosso (640 nanometri), che vengono assorbiti selezivamente dall’emoglobina
dei vasi sanguigni. Fatto, questo, che consente di captare e analizzare la formazione di nuovi vasi sanguigni (scientificamente chiamata neovascolarizzazione) che precede la comparsa di nodi scottati. Il medico che esegue l’esame ha poi un recupero immediato dell’emoglobina deossigenata presente nel
nuovo ricolo di vasi sanguigni, sia sensibile della
presenza di una esione maligna che, per crescere e
proliferare, si “mangia” l’ossigeno circostante.
In questo modo, del tutto indolore, è possibile intercettare sul nascondo non solo nodi e noduli, ma anche microcalcificazioni di uno o due millimetri che rappresentano spesso l’antenna del carcinoma mammario. L’esame però non sostituisce la mam-
mografia ma la affianca, integrando il referente.

● Achi è consigliato. A tutte le donne dopo i 40 anni che vogliono avvalersi di un esame strumentale in più (oltre alla mammografia e all’ecografia) che può fornire della informazioni aggiuntive per avere una diagnosi più precisa. «Mi consiglia il sistema DoBi anche a tutte le ventenni ad alto rischio per familiari, che desiderano isolare per tempo l’opera di prevenzione, o a quelle di qualunque età che hanno un seno particolarmente dero, perché non hanno aiutato o perché assumono la terapia ormonale sostitutiva», puntualizza il dottore Orlicic. «Può essere e costituito di microtessi, infatti, più irregolari di ero-
ne della mammografia è elevato». Il costo? Dai 70 ai 100 euro (l’esperto consiglia un esame all’anno).

Per sapere di più:

● Studio medico-chirurgico
di senologia, Milano. Tel. 02-72011341.
● Centro Medico Monterosa,
Milano. Tel. 02-48001166.
● Studio medico Minara,
Monza (Milano). Tel. 039-2315688.
● Istituto Clinico Zucchi,
Monza (Milano). Tel. 039-83831.
● Policlinico
Policlinico, Bergamo. Tel. 035-424211.
● Breast Unit, Università di
Varese. Tel. 0332-278111.
● Centro Physiol, Rovereto
sul Secchia (Modena). Tel. 059-672544.
● Istituto di previdenza e
assistenza, Roma. Tel. 05-7109570.
● Nuovo Centro di senologia
Progetto Donna, Roma. Tel. 03-7883012.
● ASI, Napoli 1.
Napoli. Tel. 081-2549110.

La posizione ok per partorire

La posizione ok per partorire
l’organo del parto è anestetica
immediata, integrazione del referente.

L’organico del parto è anestetico
immediato, integrazione del referente.

L’organico del parto è anestetico
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L’organico del parto è anestetico
immediato, integrazione del referente.
6.30 The Functional Optical Systems: Vanguard for the Fight against Breast Cancer

I sistemi ottico funzionali: avamposto per la lotta al tumore al seno

I sistemi ottico funzionali o screening sono l’avam- posto contro la lotta mondiale al tumore al seno che colpisce mortalmente 100.000 donne all’anno. Il loro apporto è fondamentale per identificare i casi in cui la detec-
tazione precoce avviene con metodi diversi. In uno studio del 2012, 10.000 donne sono state sottoposte a un screening con un sistema ottico funzionale che ha evidenziato variazioni significative nel decorso della malattia.

Sono state documentate alcune ipotesi sull’efficacia dell’utilizzo di tali sistemi nelle strategie di screening. In particolare, i sistemi ottico funzionali sembrano essere in grado di identificare modificazioni della struttura e del comportamento del tessuto mammaro, che possono precedere le manifestazioni cliniche di una malattia pregressa.

La tecnologia DOBI ComfortScan, sviluppata dalla Dott. Giovanni Maria Cuzzo, è stata utilizzata in vari studi per valutare l’efficacia della detec-
tazione precoce del tumore al seno. I risultati hanno mostrato una riduzione significativa del numero di casi diagnosticati in fase precocia, consentendo una maggiore possibilità di interventi terapeutici efficaci.

Come è strutturata la Breast Unit Avanzata?

La Breast Unit Avanzata è un approccio innovativo per la lotta al tumore al seno. È strutturata in modo da offrire un trattamento personalizzato a ciascun paziente, coinvolgendo genitori e figli in una gestione coordinata del processo diagnostico e terapeutico. La Breast Unit Avanzata comprende unteam multidisciplinare di esperti in radioterapia, chirurgia, oncologia e psicologia che lavorano insieme per garantire un approccio globale e integrato alla cura del tumore.

6.31 The Technology to Fight Breast Cancer - Introduction of DOBI

La tecnologia per combattere il tumore al seno

Nel campo della lotta al tumore al seno, la tecnologia DOBI ComfortScan ha dimostrato un ruolo importante nella detec-
tazione precoce della malattia. L’approccio DOBI, basato su tecniche ottiche, consente di identificare modificazioni nella struttura e nel comportamento del tessuto mammaro, che possono essere utilizzate per pianificare e monitorare il trattamento del tumore.

La tecnologia DOBI ComfortScan è stata sperimentata in diversi studi clinici e ha dimostrato una precisione elevata nella diagnosi del tumore al seno. Inoltre, l’approccio DOBI consente di offrire un’opzione di trattamento più personalizzata, consentendo ai pazienti di scegliere tra diversi metodi di cura in base alle loro esigenze e preferenze.

La tecnologia DOBI ComfortScan è stata recentemente integrata in una nuova piattaforma terapeutica per il trattamento del tumore al seno, che consente di offrire un’opzione di cura più adatta alle esigenze personali dei pazienti. L’approccio DOBI consente di offrire un’opzione di trattamento più personalizzata, consentendo ai pazienti di scegliere tra diversi metodi di cura in base alle loro esigenze e preferenze.
A partire da quest’anno l’indagine ottica della mammella sarà un esame inserito di routine nell’iter diagnostico delle patologie mammarie, soprattutto se la paziente ha un’età inferiore ai quarant’anni. La proposta — unica in Italia — è stata promossa dalla Lilt, la Lega Italiana per la lotta ai tumori. "L’indagine ottica — spiega Giovanni Ciuffo, primo se- nologo degli istituti Zucchi — è un sistema di indagine digitale non invasivo, non radiologico e molto veloce. E' un esame che utilizza la lunghezza d’onda della luce rossa fornendo un’immagine di eventuali attività neoangiogene, cioè di formazioni di nuovi vasi sanguigni che alimentano le cellule tumorali". Chiamato familiariamente Dobi (Dynamic optical breast imaging), tale apparecchio è opera- tivo agli istituti clinici di Via Zucchi dal 2009. E' nel primo nove mesi di attività, ha svolto circa 170 indagini delle quali solo 140 hanno dato esiti concor- danti con i risultati di mammografia e ecografia. Nelle altre pazienti, invece, l’indagine con Dobi è servita per chiarire casi incerti (ecografia con esito negativo e mammografia dubbia), sottostimati o ad- dirittura risultati negativi con le indagini tradizionali: "Dall’analisi della casistica — chiarisce Ciuffo — emergono a rilievo il concor- gno di questo esame la massima telecreabilità da parte delle persone e l’agevole gestione e comparazione delle immagini. La nostra decisione è quella di introdurre a tutti gli effetti l’os- same ottico nell’ambito del percorso diagnostico di ogni donna d’età inferiore ai quarant’anni in associazione all’ecografia e in donne con più di quarant’anni qualora abbiano una mammografia sospetta o patologica unita a un’ecografia negativa". Non si tratta quindi di sostituire le inda- gini diagnostiche tradizionali ma di perfezionarle, aggiungendo un ulteriore osa-
6.33 Private Clinics in Italy, A New Light In the Diagnosis of Breast Cancer, Breast Optical Mammography
6.34 Innovative Companies of the Year 2002

DOBI Medical Systems, headquartered in Malvati, is a technology-based medical device company that has developed a unique, accurate and potentially lifesaving means for the early detection of cancer. In addition to initial use as an adjunctive tool to diagnostic mammography for breast cancer diagnosis, applications of the company’s technology include implementation in a broad-based cancer-screening system and non-invasive monitoring of cancer therapy treatments for millions of patients worldwide.

The company’s angiogenesis-based imaging technology represents an entirely new and improved means for early, non-invasive breast cancer detection. The DOBI Breast Imaging System is designed to accurately confirm the presence of cancer and differentiate cancer from benign lesions by displaying the contrast between areas of malignancy versus normal tissue within the breast. Unlike conventional mammographic technology, which uses ionizing radiation, DOBI’s technology is effective for women of all ages.

As an adjunct to mammography, the DOBI Breast Imaging System has been designed and tested to show that it provides substantially higher levels of specificity in detecting benign lesions within the breast, thus reducing: 1) the number of false negatives generated by current techniques; and, 2) potentially avoiding a high number of breast biopsies or other surgeries.

Standing Out in a Crowd:
The medical and scientific foundation of the DOBI Medical Systems technology is the unique ability to image quickly, inexpensively and painlessly. The body’s creation of new blood vessels (angiogenesis) to support and sustain cancer development. This process, known as angiogenesis, is a vital element in the development and growth of virtually all cancers and over 70 other human diseases.

The DOBI Medical technology is an advanced digital imaging system that uses high intensity light-emitting diodes and gentle external pressure to highlight areas of vascular development common to malignant tumors in the breast. This has never been done before. The technology is based on detecting angiogenesis in the process, only recently understood, whereby a cancerous growth surrounds itself with a dense network of tiny blood-filled capillaries. Since vascular changes take place from the earliest stages of cancer development, the ability to image these changes can lead to much earlier detection and therefore earlier, more effective treatment of developing cancers.

Accomplishments to date:
Over the past five years, the DOBI technology has been tested with over 1,400 patients at highly respected medical institutions. Additional testing has occurred in Europe with further testing set to begin shortly. The measure of merit of DOBI is both its specificity (its ability to distinguish breast cancer from benign lesions) and its sensitivity (its ability to accurately detect those patients for biopsy who have a malignancy). Based on the most recent analysis of scans performed on typical patients from June 2000 through April 2001, the DOBI System is performing with a sensitivity rate (“true positive”) of 93 percent and specificity rate (“true negative”) of 67 percent. Negative predictive value is 98 percent.

In addition, DOBI Medical Systems holds eight issued and allowed U.S. patents and one international patent for its technology, covering a broad range of technologies.

In the Future:
Once DOBI receives the FDA approval and begins marketing the ComfortScan system in the U.S., with a measure of success, it is likely that a large player in the imaging market will acquire the DOBI Medical technology. As an alternative to being acquired, the company continues to work toward an IPO in the coming 12 to 18 months. As market conditions allow, whatever the outcome of these options are, it will greatly benefit DOBI’s shareholders and give them an attractive return on investment.

Further, with the proper funding in place, the company believes it can migrate this technology to many areas in the medical diagnostic market. Specifically, as a screening tool for breast cancer, a diagnostic tool for other angiogenesis-driven diseases, and for therapy monitoring in a number of disease categories.
"ComfortScan" provides a non-invasive optical imaging system which looks for physiologic changes in the breast as compared to morphologic or structural changes in the breast identified by x-ray, ultrasound, or physical exam.

6.35 Wall Street Reporter Magazine on February 25, 2004
6.36 Wall Street Transcript on July 11, 2005

DOBIMedical International, Inc. (DBMI)

PHILIP C. THOMAS is Chief Executive Officer and Co-Founder of DOBI Medical International, Inc. He is also a member of the Board of Directors. Since the age of 15, Mr. Thomas has held positions in the field of medical technology. He was an intern for the Russian National Academy of Sciences in Moskovskii. After receiving his B.S. in Engineering at the University of Wisconsin, Mr. Thomas joined the materials science division of the U.S. Geological Survey.

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6.36 Wall Street Transcript on July 11, 2005

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6.37 Rising Star Stocks – A Revolutionary Medical Imaging Device on August, 2004
6.38 Rising Star Stocks – A Revolutionary Medical Imaging Device on August, 2004

**Optical Imaging Shines New Light on Breast Cancer: Originally Published 8/2003**

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Optical imaging is an emerging technology in breast cancer detection that will allow improved detection without radiation or patient discomfort. DOBI Medical International is developing the dynamic optical breast imaging (DOBI) ComfortScan system. This technology utilizes near infrared light to identify increased vascularity (angiogenesis) after sleep compression. The near infrared light is then passed through the breast and approximately two images per second are recorded with the camera system. After the scan, the procedure displays the breast image which highlights light absorption in angiogenic areas that can be caused by increased volumes of blood and blood being deoxygenated by the presence of the malignant tumor (cancerous tumors tend to consume oxygen up to four times faster than normal tissue).

In November 2004, DOBI Medical International, Inc. announced that it has initiated the clinical trial, which will be the subject of the fifth and final node of its Pre-Market Approval (PMA) application with the U.S. FDA. Patient enrollment has begun at several leading U.S. medical sites, including Hackensack University Medical Center, Hackensack, NJ; Sally Jobe Breast Center; Greenwich Village, CO; and Comprehensive Breast Center of Coral Springs, Coral Springs, FL. Additional sites are expected to begin enrolling patients in early 2005. The final module is a clinical study to generate patient data relative to the performance of the ComfortScan system in a clinical setting. The clinical testing is expected to continue for another 18 months, after which FDA approval is anticipated.

**Physician Interviews**

Phillip Thomas, Co-Founder/Chief Executive Officer, DOBI Medical International, Malvern, PA

At RINA 2004, Thomas said that DOBI Medical has been working on this project for six years and has raised approximately $25,000,000. They went public a year ago (ticker symbol: DOBI). They have tested over 1,200 women in the U.S. and in Europe and are now also doing testing in South Africa.

Thomas stated, “We are on track to seek FDA approval and have completed four of five data submission modules to the FDA. We are also now testing in three sites in the U.S. and another four or five will be added over the next 30 to 60 days. All data gathering is expected to be finished by the third quarter of 2005 with the final submission to the FDA following successful completion of the clinical trial.”

Thomas said that he sees this technology as being especially helpful for women under 50 who have the most advanced malignancies and have positive mammograms because of the denseness of their breast tissue. He says they are getting some good results in this area. He also sees the technology as an ideal way to improve breast cancer diagnosis in rural underserved areas because it has low costs and could be used in portable form or put on a mobile platform. Another area in which he sees increased usefulness is providing additional physiological diagnostic information when used as an adjunct to mammography for patients who have strong family histories of breast cancer or who test positive for the BRCA 1 or 2 genes.

Thomas added that currently they are focusing on breast cancer but this technology may be applicable to other types of cancer, such as skin cancer. According to industry experts, angiogenesis has been identified in virtually all cancer patients as well as over 70 other diseases in the body. “If you go to www.amg.org, the website for the angiogenesis foundation, you will find enormous amounts of information about the identification of angiogenesis in diabetes, Alzheimer’s, rheumatoid arthritis, and over 70 other diseases. It is somewhat of the holy of the new topic that our blood supply is evolving and expanding in response to what is going on in the body such as its response to wounded wounds and other damage, or in response to tumors. It is an exciting area that will have many implications besides just breast cancer.”

Thomas concluded, “We want women to know that there is new technology being developed that can make a difference, based on the very latest understanding of how cancer develops. I have known a number of women who have had to deal with breast cancer and one of the biggest things they need is hope. It may not affect them today but they don’t want their daughter or granddaughter to go through the same thing they have been through. I believe this new technology will be making a difference in the lives of many women and that is our focus. You will see more angiography, more ultrasound, more CT, more MRI’s but this is truly new technology that has never been seen before.”

Thomas Stevens, M.D., Radiologist, Sally Jobe Breast Center, Denver, CO

“We have been participating in the clinical trial for about a month. We’re actually accruing patients, those who are going to undergo biopsy, who are the probably benign or suspicious Category III or IV. We’re not doing any patient where we are more than 90% sure that it is cancer. Everyone is going to have histological proof of what the diagnosis is in the same day. There is a long list of exclusion and inclusion criteria but probably about half our patients qualify.”

When asked if the size of the breast affects image quality, Stevens stated, “The machine is so sensitive to light that it cannot be in an inside room where you completely seal out ambient light so if the breast is too thin or too acuity, you might get too much through in the breast too large or too dense or too thick you might not get enough light through so there are problems with some people. Interestingly enough, tattoos and skin rolls can also absorb light and create some problems.”

“This study is designed to evaluate the future of optical breast imaging. Theoretically, the study looks at what that we haven’t been looking at. It is designed to look at tumor revascularization and tumor vessels are not normal. They don’t have normal microvascular walls so they are very easy to compress. The woman puts her breast inside this rubber membrane and with a very light amount of pressure. The pressure is

By Peggy Eastman

WASHINGTON, DC—Scientists developing novel breast cancer detection tests updated an Institute of Medicine (IOM) committee on their progress at a workshop at the National Academy of Sciences here. These new early detection approaches—seen primarily as aids to mammography, not replacements—include ultra-fast imaging of breast angiogenesis, a smart surgical probe derived from space technology that differentiates malignant from benign tissue, and a version of electrical impedance scanning.

But speakers noted no detection test—whether currently used or in the future—can be perfect. Proof that mammography isn’t perfect is the finding that as many as 75% of all breast lesions that are biopsied as a result of suspicious findings on a mammogram turn out to be benign, according to the report from a previous IOM committee on early breast cancer detection.

During the 1990s, the US death rate from breast cancer declined by about 2% a year, a result of early detection and improved therapy, according to that 1991 report. Recent research reports on molecular markers have led to news articles questioning whether the emphasis on early detection is as critical as commonly accepted. The research suggests that tumor markers of a breast cancer’s genetic pattern may be a more important indicator of how the cancer will progress than its size when discovered.

The worse the genetic pattern, the worse the outcome.

But using and developing technology to detect breast cancer as early as possible remains critically important, according to those participating in the IOM workshop. “Every scientific instinct tells us that the earlier we catch the cancer, the better the prognosis is going to be,” said Lance Liotta, MD, PhD, Chief of the Laboratory of Pathology at the National Cancer Institute.

Larry Norton, MD, Head of the Solid Tumor Division at Memorial Sloan-Kettering Cancer Center and immediate past president of the American Society of Clinical Oncology, added, “We’ve known since the dawn of time that some small cancers have a bad prognosis, but I’m still a believer in breast cancer screening. Tumor size is still an important variable. A lot of people have been working in the genomics area. Yet, I haven’t seen anything in those reports that tells me that early diagnosis is not important.”

Identifying Angiogenesis in the Breast

Now under review by the US Food and Drug Administration is the DOBI ComfortScan System, which identifies angiogenesis in the breast through digital optical infra-red imaging and time-lapse photography to detect the early vascular changes that can be a hallmark of cancer.

The technology was discovered in Moscow in the early 1990s and has been tested on about 1,400 clinical trial participants in medical centers in the US and Europe.

“DOBI (an acronym for Dynamic Optical Breast Imaging) technology involves inserting a tiny multimodality smart probe into the body to measure parameters that differentiate cancerous lesions from benign tissue and display them in real-time on a computer screen. The probe, which is too small to cause disfigurement, is inserted into the vicinity of a suspected cancer site.”

“DOBI is an acronym for Dynamic Optical Breast Imaging.”

ComfortScan System, which identifies angiogenesis in the breast through digital optical infra-red imaging and time-lapse photography to detect the early vascular changes that can be a hallmark of cancer. The technology was discovered in Moscow in the early 1990s and has been tested on about 1,400 clinical trial participants in medical centers in the US and Europe.

“We know that tumors become angiogenic at about 1.0 to 1.5 millimeters,” said Philip C. Thomas, Chairman and CEO of DOBI Medical Systems in Mahwah, NJ, which is developing the new scanning technology. DOBI is an acronym for Dynamic Optical Breast Imaging.

“DOBI enhances mammography as an adjunct to other early detection tests. We’re really keen to integrate our test with other imaging modalities.”

Smart Probe to Measure Changes

Also under development is the BioLuminate diagnostic system, which was originally invented by scientists at the National Aeroracetics and Space Administration. This system involves inserting a tiny multimodality smart probe into the body to measure parameters that differentiate cancerous lesions from benign tissue and display them in real-time on a computer screen.

“The probe, which is too small to cause disfigurement, is inserted into the vicinity of a suspected cancer site.”

“It’s a second level screening device.”

(Continued on page 12)
6.42 Leading International Physicians Discuss DOBI ComfortScan in Prague, the Czech Republic from September 9-11, 2005

Leading International Physicians Discuss DOBI Medical’s ComfortScan(R) System at 2nd Annual Symposium

DOBI Medical International, Inc. (DOBI.com) today announced that leading international physicians convened at the 2nd Annual European Symposium in Optical Breast Imaging from September 9-11, 2005 in Prague, the Czech Republic. The latest data was discussed on the Company’s Dynamic Optical Breast Imaging (DOBI(R)) system, known as the ComfortScan(R) system. The ComfortScan system is an optical breast imaging device designed to help identify tumor angiogenesis (abnormal blood vessel growth), which is often associated with breast cancer. More than 30 prominent medical device distributors, physicians and researchers representing more than 10 countries in South America, Europe and Asia attended the Symposium.

William Li, MD, president, medical director and co-founder of The Angiogenesis Foundation in Cambridge, Massachusetts, a global, non-profit institute for research and education in the angiogenesis field and a member of the Board of Directors of DOBI Medical, delivered the meeting’s keynote address entitled “New Frontiers in Angiogenesis.” Additional presentations about the ComfortScan system were made by company management. International clinicians representing top medical institutions in Brazil, the Czech Republic, France, Greece, Italy and Switzerland also delivered presentations on the progress and recent results from ongoing clinical trials of the ComfortScan system at their facilities. Dr. Anwar Padhani who moderated the clinical sessions and is a consultant radiologist at the Paul Strickland Scanner Center, Mount Vernon Hospital in Middlesex, England, said, “I found the gathering of principal investigators from clinical sites around the world allowed for a profound exchange of principles and ideas that will be able to catapult DOBI Medical’s technology to the next level.” An industry luminary, Dr. Padhani has published numerous scientific papers and has given many lectures at universities and international meetings. The physicians also participated in a training session on the latest version of the ComfortScan system’s reading software.

Last year’s conference was held in Cernobbio, Lake Como, Italy and additional symposiums are planned for the coming years. The next event is scheduled to take place in September, 2006 in Europe.

For more information on DOBI Medical International or the ComfortScan system, visit www.dobimedical.com.

About DOBI Medical International, Inc.

DOBI Medical is a microcap, developmental stage, medical imaging company working to create a new means for the improved diagnosis of cancer through the detection of abnormal neovascularization (“angiogenesis”) associated with tumors. DOBI Medical International’s first application of the technology is the ComfortScan, a portable, non-invasive, and non-ionizing, optical imaging system designed as an adjunct to mammography to assist physicians in the detection and management of breast cancer. The ComfortScan system is intended to achieve this by providing new, physiology-based imagery of abnormal vascularization in the breast that is not readily available today. The ComfortScan system has CE Mark and UL certifications. DOBI Medical is a certified ISO 9001:2000 and ISO 13485:2003 company. The Company currently sells its ComfortScan systems to international distributors for installation at international clinical trial sites. The ComfortScan system is not being sold in the U.S. as it is limited by U.S. law to investigational use until approved by the FDA, which cannot be guaranteed.
7. CONCLUSION

Based on the purpose of this clinical effective evaluation report, through (1) the introduction of DOBI ComfortScan, which uses the Tumor Angiogenesis Theory, Optical Imaging Technique and the Significant Improvements of them in past decades in clinics as the fundamentals, (2) some clinical study/trial publications/reports from recent clinical cases, and (3) some collections of clinical acceptances, the clinical EFFECTIVENESS of the DOBI ComfortScan as adjunct to existing breast imaging modalities in diagnosing breast cancer has been demonstrated through detecting the characteristics of tumor angiogenesis of malignant breast lesions and employing the appearance of the tumor angiogenesis in detection of breast cancers in clinics. Because, based on the continued demand, DOBI Global has just re-manufactured the ComfortScan device with necessary CE and ISO regulatories after acquiring the intellectual property on May of 2010, the significant clinical effectiveness will continue being demonstrated through the additional reviews of clinical information, which has been defined in our Post Market Surveillance (SOP 1054-0004-00). An opportunity for the potential benefit of women worldwide and to continue the development/improvement of the breast imaging techniques, such as DOBI ComfortScan, would be expected by scientists/developers of the techniques/devices, medical society and general publics.

As the summary, in the past 7 years about 70 diagnostic centers worldwide have tested the ComfortScan, including nearly 30 US sites participating in the FDA PMA clinical trials, and over 30 sites in Italy and China have installed the devices, resulting in thoughts of individuals whom were scanned by this device. The cumulative device experiences to date, as well as the above literatures, have demonstrated that this device, DOBI ComfortScan, 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 malignant lesions at early stage. DOBI ComfortScan can help the performance and accuracy of averaging, under averaging or less experienced doctors in their clinics most significantly. Dynamic optical breast imaging, DOBI, technique, which is different from others by identifying angiogenesis of malignant lesions, can be a promising complementary imaging modality for further investigation in cases of women with inconclusive mammography and/or
physical examination. 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 characterize different malignant and benign tumors at different stages respectively, different statues of patients, such as menopause stages with related nipple blue, and to statistically quantititize 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 specificity of 87 percent, 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 potentially become a useful breast cancer screening tool if a full FOV (field 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.

As the statement of Mammography and Beyond published by the National Academy of Sciences’ Institute of Medicine, Mammography remains always the standard imaging procedure of control and all recent studies support its value as a diagnostic and screening tool. However it is already known and proven that this "gold standard" is not an ideal tool. Potential radiation risk and diminished sensitivity in radiographically dense breasts represent the two main disadvantages of the technique, thus limiting its usefulness in high risk young women. It is well documented in the study carried out by Kuhl CK et al 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. 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. 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. 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. In the study report of “Results of Investigational Use of DOBI ComfortScan in China by G Zhang et al, the table below shows there are 24
indeterminate (I) case out of total 62 cases because of the 88.7% BI-RADS 3 or 4 in Mammography from dense breasts, and the Youden’s Index indicates that the Accuracy of DOBI ComfortScan is higher than Mammography with respect to three independent blinding readers. The above finding suggests 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 additonal 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. According to the a recent publication at Italian Journal of Gynaecology and Obstetrics Volume 23 on October 3, 2011, Dr. V. Frattini, L. Ghisoni, A. Teodoro, PL Vaj and S. Orefice conducted a multicenter study to determine the Sensitivity and Specificity of the ComfortScan System to detect malignancy as an adjunct to Ultrasound in 617 young females between 25 to 39 years of age. After DOBI ComfortScan and Ultrasound, 269 malignant cases were confirmed by biopsy. In this study, the dynamical optical breast imaging, DOBI, had a sensitivity equal to 98% and a specificity equal to 87% while the sensitivity and specificity of the Ultrasound are equal to 74% and 70% respectively. Dynamic optical breast imaging in European Journal of Radiology 2008 by a group of scientists from France, Italy UK and US) has concluded as following: “We have used a novel imaging instrument that combines infrared imaging with light breast compression in women with equivocal or suspect mammographic abnormalities and have shown that it has potential in distinguishing benign frommalignant lesions. This is an early evaluation of this technique which relies on physiological properties of breast tissue to impart optical contrast on images. Further evaluation will be required to optimize the technique, evaluate its sensitivity and specificity in a wider range of patients, and explore its potential role in patient management.” 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. 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.

As a result of a continued demand for this device, DOBI Global has acquired all the intellectual property including the trade mark and DOBI Medical International name in the May of 2010, and has decided to re-launch the device and obtain a new CE Certification and ISO 13485 Certification. The clinical efficacy will continue being demonstrated through the collection of more clinical data and the publications based on the clinical data if the CE Mark could be approved. The SOP 1054-0004-00 has defined Post Market Surveillance activities that additional reviews of clinical information will be conducted as part of the ongoing Post Market Surveillance activity, which complies and will continue to comply with the requirements of the Medical Device Directive. Because DOBI Medical had stopped its clinical trial of FDA Premarket Approval (PMA) due to the financial issues in 2007, there are about hundreds of controlled patient data from USA and hundreds of controlled patient data, which are locked. Because of the changes within FDA (On Monday, November 22, 2010 who has accepted a Premarket Notification 510(k) of Imaging Diagnostic Systems), those data and more data from a large scale number of trials might be used for the evaluation of clinical efficacy below after FDA Approval/Notification:

• Adjunct to existing breast imaging modalities in diagnosing breast cancer at early stage: As a diagnostic tool of breast cancer, a large scale number of cases should be studied to characterize different malignant and benign tumors at different stages respectively, different statuses of patients, such as menopause stages with related nipple blue, and to statistically quantatize the metabolic rates of both malignant and benign tumors.
• 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): 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.

• Screening Tool: 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 potentially become a useful breast cancer screening tool if the Negative Predictive Value could be maintained at the level or above 95%.

• Therapeutic Monitoring: Both pro- and anti-angiogenic drug monitoring 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 technique may have future applications in addition to cancer.

• High-quality Training: the need for high-quality training of physicians are necessary because (1) it is not taught at school and (2) it affects the results significantly.

As conclusion, the Clinical Effectiveness of DOBI ComfortScan device has been demonstrated through recent clinical studies, which include total 2495 patients and 1053 malignant cases in over 23 multicenters, and achieve averaging Sensitivity and Specificity in detecting malignant breast lesions are 87% and 75% separately by the statistical analysis from a variety of readers in compliance with MEDDEV.2.7.1 Rev.3.

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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